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Allergology and Clinical Immunology

A case of arthritis of a rare origin

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BML is a 38-year-old male coming from Senegal; he has lived in Italy in the last years and he has been in good health up to September 2009: since then, BML developed a non-traumatic painful swelling of the third finger of the left hand, accompanied by low-grade fever (up to 38°C). The dactylitis was self-limiting and was followed by febrile arthritis with functional impairment, first of the right elbow, then of the right knee. The migrant arthritis seemed to resolve after a cycle of low-dose prednisone therapy (5 mg per day for 1 month, on December 2009). On April 2010, BML is admitted to the local hospital because, in the last 3 days, he has suffered of a painful swelling and functional impairment of the right knee, accompanied by fever (at home up to 40°C) without chills. The patient has no history of trauma, recent travels abroad, rash, risky sexual intercourses, insect bites. BML has not significant family history of disease with the exception of diabetes mellitus. He is married with two healthy children, has never smoked and does not consume alcohol; he complains of episodic headache (resolving with NSAIDs), sporadic emesis after prolonged fasting and very rare episodes of self-limiting normochromic diarrhea without abdominal pain, fever or weight loss. The physical examination reveals a young man in good general conditions; his vital signs (temperature, blood pressure and respiratory rate) are normal except for a pulse rate of 100 bpm. BML has signs of arthritis of the right knee (tumor, dolor, calor and functio laesa), mild hepatomegaly. The remainder of the physical examination is within normal limits. Routine laboratory investigations (including a complete blood cell count, blood creatinine and electrolytes, TSH, uric acid in blood and urines, urinary tests including 24 h proteinuria, fecal occult blood on three occasions) are normal, with the exception of a transient mild elevation of transaminase (on therapy with NSAIDs) and inflammatory markers (ESR and CRP are, respectively, two and 24 times higher than the normal values; serum proteins electrophoresis reveals a mild polyclonal elevation in gamma-globulins, with a normal count of IgG, IgA and IgM). An arthrocentesis of the right knee is performed, obtaining 50 ml of torbid, golden yellow fluid, containing many leukocytes and some needle-like crystals; cultures of sinovial fluid are negative. Blood tests for autoimmune diseases (autoantibodies: ANA, ENA, ANCA, anti-CCP, antibodies for celiac disease; C3, C4, CH50; cryoglobulins; rheumatoid factor; HLA-B27) are negative, as well as many tests for infectious diseases (antibodies for Chlamydia, Treponema, Borrelia, Parvovirus B19, HCV and HIV, TAS, procalcitonin; stool cultures and throat swab). The markers for viral hepatitis indicate a chronic HBV infection (positivity of HBsAg, anti-HBe, anti-HBc IgG; negativity of Anti-HBs, HBeAg, Anti-HBcIgM, HBV-DNA). Repeated stool analyses for fecal parasites are positive for *Strongyloides stercoralis* (at a larval stage of development). There is a mild elevation of total IgE and of IgE for Ascaris and Anisakis (the antibodies for Strongyloides are ongoing). Many instrumental tests give a normal result: the X-rays of right knee, right elbow, chest and pelvis, the examination of eyes and retinas, the ultrasound examination of the abdomen and lower limbs' deep veins; the trans-thoracic echocardiogram does not reveal signs of endocarditis. An esophagogastroduodenoscopy with biopsy is performed, revealing a hiatal hernia and a chronic gastritis on the base of an infection by *Helicobacter pylori* (treated with antibiotics on discharge). The patient starts a therapy with ketoprofen, but in the meanwhile he develops arthritis of the right elbow, so he is switched to indomethacin; he is also treated with albendazole to eradicate the intestinal parasitosis. During this therapy BML shows a progressive clinical improvement (reduction of pain and signs of arthritis) and is discharged. He is now on follow-up by the Hepatologist (for a possible future therapy for HBV infection, not indicated at the moment), the Specialist in Tropical diseases (to evaluate the necessity of a second line treatment of the strongyloides infection) and the Rheumatologist. This case could represent a peculiar form of reactive arthritis, secondary to a bowel colonization by *Strongyloides stercoralis*; this parasite usually remains within the bowel (giving only a mild diarrhea) unless its pathogenicity is favoured by an immunodeficient state (as on steroidal therapy, even at a low-dose); sepsis can occur because intestinal bacteria follow the parasitic spread in the body (with a possible involvement of lungs, central nervous system, sierosas). A review of the literature has shown rare cases of reactive arthritis associated with this parasitosis; the absence of HLA B27 and of eosinophilia (as in our case) cannot exclude the diagnosis. In this case, the possible pathogenetic relevance of HBV infection cannot be excluded at the moment, and could be reinforced in case of relapse of arthritis after the complete eradication of the *Strongyloides stercoralis*.

A simple rheumatoid arthritis case?

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AP, a 72-years-old man with hypertension, alcohol abuse and a previous tubercular pleurisy, is admitted to the local hospital because of a 2 weeks continuous fever (up to 38°C) with chills, cough, dispnea on mild exertion, asthenia; in the last 5 months he has had a weight loss of 8 kg, pain in both his arms with functional impairment, and a progressive swelling and stiffening of his fingers. Before hospitalization, AP has transient vomit and diarrhea, followed by syncope with sphincter incontinence.

On admittance, AP is in poor general conditions; he is pale and feverish, slightly lethargic, but he has not other signs of meningitis. His physical examination reveals some rales at the lung bases and a itchy rash on his back, swelling of both hands and fingers (with associated calor, rubor and functio laesa), a moderate swelling of both ankles. AP has a mild neutrophilic leukocytosis (WBC 10,800 mcl^{-1}, 85% neutrophils), a moderate normocytic anemia (Hb = 10 g/dl, MCV = 89 fl) with iron deficiency (iron = 12 mg/ml, nv = 60–160; transferrin saturation = 6%) but with high ferritin (699, nv = 15–300 ng/ml); the inflammatory markers are elevated (CRP and ESR, respectively, 30 times and 2 times higher than the normal range); albumin is reduced (2,73 g/dl), gammaglobulines are slightly elevated while immunoglobulines are within normal range; renal and thyroid function are within the normal limits; hepatic function tests are normal with the exception of cholinesterase, moderately reduced; proteinuria (1 g/day) is initially found, but this urinary abnormality resolves (leaving only a mild proteinuria of tubular kind) after stopping the NSAIDS that AP used for pain relief. The chest X-ray shows a previous left pleurisy; hands and wrists X-ray reveal multiple fingers arthrosis; meningitis is ruled out by a neurologic examination and by head CT (showing a chronic vascular encephalopathy). A negative result is obtained for many tests for infectious diseases (antibodies for HBV, HCV, treponema, leptospira, parvovirus B19; Widal Wright; Weil Felix; urinary antigens of Streptococcus and Legionella; stool, urine and sputum cultures extended to mycobacteria; throat swab; procalcitonin), for autoimmune diseases (ANA, ENA, ANCA, cryoglobulins, haptoglobin), cancer (CA125, CA19.9, CEA, PSA, urinary cytology). The fecal occult blood is positive more than once. The Mantoux test is slightly positive; two of multiple blood cultures are positive for *Staphylococcus* species (non aureus). Anti-CCP and rheumatoid factor are markedly positive (respectively, ten times and two times higher than the normal limits), while the complement fractions are only slightly reduced. Among the instrumental tests performed, the EEG, the Holter ECG are normal; the ENT district is normal at endoscopy. Trans-thoracic echocardiogram shows a mild left ventricular hypertrophy and no signs of vegetations; the EMG reveals a sensory-motor neuropathy of arms and legs. Repeated blood pressure measurements show a symptomatic orthostatic hypotension. An ultrasound abdominal examination shows a fatty liver and little gallbladder stones; the echocolor doppler of the legs excludes a deep venous thrombosis and reveals a moderate atherosclerosis. To rule out endocarditis, a trans-esophageal echocardiogram is performed, and a severe atherosclerosis with complicated plaques all along the thoracic aorta is revealed. This finding is confirmed by a thoracic and abdominal CT, which shows ulcerated plaques all along the aorta, a thyroid cystic lesion, a group of microcystic lesions in the head and a 2 cm cyst of the tail of pancreas. During the hospitalization, AP develops a bloody diarrhea (requiring a blood transfusion), so a colonoscopy is performed and seven colonic polyps (ranging from a few mm to 2 cm) are removed (the histology is still ongoing). The bloody diarrhea resolves with oral vancomycin. AP receives a prolonged multiple systemic antibiotic therapy (first piperacilline-tazobactam, then levofloxacin and imipenem, followed by vancomycin) but he continues to be feverish and suffering until high dose prednisone (50 mg/day) is started: fever resolves immediately, and a progressive remarkable reduction of articular swelling, rigidity and functional impairment is noted; the reduction of prednisone dosage is followed by a transient rise in the temperature curve. The complex clinical history of AP, in our opinion, could be explained by a diagnosis of rheumatoid vasculitis, in a patient affected by alcoholic liver disease with neuropathy; the cysts in the head and tail of the pancreas have not been still characterized (but they have a CT aspect, respectively, suggesting benign neoplasms and the consequences of a previous pancreatitis). A TC PET will be performed (eventually followed by a MNR of the biliary tract, in case of uncertain results); together with the ongoing tests, the TC PET scheduled should rule out cancer and check if our hypothesis is correct. AP is now on treatment with prednisone 30 mg/day with a fairly good clinical result; if the tests and the clinical development will confirm the diagnosis, the patient will start azathioprine. In the meanwhile, AP is on close follow-up by specialists in rheumatology and internal medicine.

Erythema multiforme mayor during levofloxacin therapy in an old woman with multiple pathology

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Introduction: Adverse skin reactions to drugs are frequent; for many commonly used drugs, rates exceeding 1% are reported. Erythema multiforme (EM) is an acute mucocutaneous inflammatory and hypersensitivity reaction characterized by skin eruption, with symmetric erythematous edematous or bullous lesions of the skin and mucous membranes; EM is classified as major when 2 or more mucous membranes are involved. More than half the cases have no known cause, while half are caused by medications, infections, immunotherapy, or illnesses. Quinolones have sometimes been associated with EM but only one case has been reported after levofloxacina. We describe a case of EM major developed during levofloxacina therapy in an old woman with multiple pathology.
Case report: An 83-year-old woman was admitted for a generalised skin rash with mucosal involvement of the mouth and vagina. She referred an history of appendectomy, cholecystectomy, quadrantectomy for breast cancer, obesity, type 2 diabetes mellitus and mixed dyslipidemia. She was on chronic therapy with metformin and fibrates. Diarrhoea for about 4 weeks and a therapy with levofloxacina 500 mg once daily in the last 2 days for an infected malleolar skin ulcer were also reported. Physical examination showed an erythematous skin rash of the trunk, abdomen, and limbs, with a cockade-like aspect; mucosal ulcers of the mouth and vagina were also present. Laboratory investigation documented CRP 201 mg/l, WBC 27,790 μl^{-1}, PLT 702,000 μl^{-1}, Hb 10.6 g/dl, urea 180 mg/dl, creatinine 8.6 mg/dl; urine examination was positive for hematuria with traces of proteins. She was treated with methylprednisolone, antihistamines, systemic antibiotics, and, after detection of Cl. difficile toxin in faecal samples, metronidazole with the regression of skin rush, mucosal ulcers, and diarrhoea. The patient was then discharged, 23 days after, asymptomatic and with normal laboratory findings.
Discussion: Quinolones are an uncommon cause of EM; for our patient, skin reaction was probably elicited by levofloxacina therapy. Multiple pathology, both chronic and acute, is a typical feature for patients in internal medicine wards. The severe renal failure described for our patient was probably caused by sepsis and dehydration, but a tubulo-interstitial nephropathy related to antibiotic therapy cannot be excluded.

Role of arterial blood gas analysis in first evaluation of obese patients

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Introduction: Obesity is a worldwide epidemic condition and rapresents a major risk factor for some cardiovascular, metabolic and osteoarticular disorders. Moreover, obesity predisposes to serious respiratory diseases, like obstructive sleep apnea syndrome (OSAS) and obesity hypoventilation syndrome (OHS), which are

under-recognized and so under-treated. OSAS, consisting in recurrent upper airway occlusions associated to transient hypoxemia and hypercapnia during sleep, predisposes to metabolic syndrome and cardiovascular diseases, in particular systemic hypertension. OHS, defined as daytime hypercapnia ($PaCO_2 > 45$ mmHg) associated to obesity, is characterized by high morbidity and mortality. Arterial blood gas analysis (ABG) is actually required to make diagnosis of OHS, identifying hypercapnia usually associated to elevated bicarbonates concentration ($[HCO_3^-]$) (compensated respiratory acidosis). On the other hand, ABG may show isolated elevated $[HCO_3^-]$, indicating a possible sleep respiratory disorders, like sleep alveolar hypoventilation that preceeds OHS or severe OSAS.

Patients and methods: From April 2009 to May 2010, 80 patients, consecutively referring to our Obesity Unit for first evaluation, were screened for the presence of hypercapnia or isolated elevated $[HCO_3^-]$, using ABG taken with patients sitting and breathing room air. We also evaluated body mass index (BMI), abdominal and neck circumferences (AC and NC), mean percentage of fatty mass (MPFM) using bioelectrical impedance technique, smoking habit, presence of diabetes and systemic hypertension, Epworth Sleepiness Scale score (ESS), Mallampati classification of oropharynx (MC), and history of habitual snoring and sleep apnea. Relationships between variables describing obesity severity (BMI, AC, NC and MPFM) and PaCO2 and $[HCO_3^-]$ were examined by Pearson correlation. We have then divided patients in 2 groups, with normal and high $[HCO_3^-]$, which were compared by Student t test for continuous variables, after checking for normal distribution, and by the χ^2 test for nominal variable.

Results: The ABG sampling has been successfully obtained for 44 of 80 (55%) patients (18 males and 26 females, aged 49 ± 14 years, BMI of 38.2 ± 5.3 kg/m^2, AC of 123.1 ± 11.0 cm, NC of 41.5 ± 4.3 cm and MPFM of 43.1 ± 6.6%). The failure in performing ABG was due to patient refuse, technical limitations (availability of blood gas analyzer) and anatomical limitations (artery inaccessibility due to periarterial tissue). No statistically significant correlation was found between variables describing obesity severity and PaCO2 and $[HCO_3^-]$. We found $PaCO_2 > 45$ mmHg in 3 over 44 patients (7%) and $[HCO_3^-] > 26$ mmol/L in 33 over 44 patients (75%). The only difference we found between patients with increased and patients with normal $[HCO_3^-]$, was the prevalence of systemic hypertension (0 vs. 39%, respectively; $p = 0.013$).

Conclusions: In this study we have shown high prevalence of OHS and of isolated elevated $[HCO_3^-]$, which suggests a possible sleep respiratory disorder, in ambulatory patients at first evaluation for obesity. We have also found that the variables normally used to describe obesity severity are unable to predict presence of hypercapnia or elevated $[HCO_3^-]$. Moreover, we have found higher prevalence of systemic hypertension in obese patients with elevated $[HCO_3^-]$ when compared with obese patients with normal $[HCO_3^-]$, suggesting a relationship between hypertension and the respiratory disorder. We conclude that ABG should be considered for a complete first clinical evaluation of obese patients.

Sudden behaviour alterations in a lively man

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A 73-year-old diabetic man was hospitalized for poor glucose control. His family referred he didn't take on his antidiabetic therapy (repaglinide 0.5 mg bid and metformina 500 mg bid) for 2 weeks, when he began to show slight amnesia and poor capacity of focusing his attention on. For 1 week, according to his family, the man showed gait disorders, characterized by shuffling and posture instability. According to the neurologist they had consulted, this onset of a shuffling gait was the manifestation of an extrapyramidal disorder, such the Parkinson disease. At admission he was confused. Clinical examination revealed just right inguinal hernia—it did not require surgical treatment—and left leg edema (the patient referred small saphenous chronic venous insufficiency). Romberg negative, no cranial nerves deficit, no force deficit. BP 120/80 mmHg, HR 86 bpm, RR 16 min^{-1}. No fever, rash, sore were found. Laboratory test showed mild chronic kidney failure (creatinine clearance 50 ml/min/1.73mq), anaemia (Hb 10.6 g/dl, MCV 86 fl, MCHC 34%, ferritin 104 ng/ml), glycemia 190 mg/dl. Urinalysis was normal and he had a urine output of 50 ml/h. The patient got back his antidiabetic theraphy and added on telmisartan 80 mg/day, ticlopidine 250 bid and atorvastatin 20 mg/day. Next morning, the patient behaved in a strange way: we assisted to an uncontrived urination wherever he was, even dressed in living room. Mini Mental Test and neuropsychological test were performed, then we put diagnosis of ADD-Attention Deficit Disorder. CT scan showed ventriculomegaly, due to a normal pressure hydrocephalus, confirmed by an MRI. We made lumbar puncture in order to analyse CSF. We drained 50 cc of liquor. After this diagnostic procedure, we could observe the return to correct gait. Normal Pressure Hydrocephalus (NPH) results from the gradual blockage of the CSF draining pathways in the brain. The ventricles enlarge to handle the increased volume of CSF, and the compression of the brain from within by the fluid-filled ventricles destroys or damages brain tissue. The term "idiopathic adult hydrocephalus syndrome" may be more accurate, because intracranial pressure is not always normal in NPH. When trauma, hemorrhage, infection, mass lesions, or acqueductal stenosis contribute to hydrocephalus, it is considered as secondary form of NPH. NPH can occur with varying combinations. The classic clinical triad first described by Hakim and Adams (1965) was gait disturbance, urinary incontinence, and dementia. Although no one feature is pathognomic of the gait disturbance in NPH, the most common descriptors include "shuffling", "magnetic", and "wide based". Disequilibrium and slowness of gait (due to short steps and gait apraxia) are common. Frontal and subcortical deficits (psychomotor slowing and impaired attention, executive, and visuspatial disfunction, difficult dealing with routine tasks and short-term memory loss) can be the earliest cognitive signs of NPH. The bladder symptoms of NPH are directly caused by detrusor overactivity, which can result in urinary frequency and urgency in mild cases. Brain imaging study demonstrates non obstructive ventricular enlargement disproportionate to cerebral atrophy. Lumbar puncture can serve the dual purpose of adding to diagnostic certainty and assisting in prognostication about response to the treatment. CSF shunting procedures can lead to significant clinical improvement in NPH symptoms in approximately 60% of NPH patient. Our patient didn't need any shunting procedures, he undergoes to periodical clinical control, but he had never shown neurological signs. We decided to report this case to underline how it is important to put attention on trivial and missed clinical manifestations, which are often expression of organic disease. The diagnosis is difficult because the dementia symptoms of NPH can be similar to those of Alzheimer disease, while the walking problems are similar to those of Parkinson disease. Unlike these diseases, NPH can be reversed in many people, but first it must be correctly diagnosed.

An unusual case of acrocyanosis

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Introduction: We describe here a 34-year-old man who came presenting acrocyanosis in the upper-lower limbs, nose, ears, zygomas and knees. Familial history was negative to autoimmune diseases. Physiological history was norm, not pollens, drugs and food allergy. Remote history only positive for exantema diseases except for varicella.
Clinic history: Fifteen days before the hospitalization he suffered a typical infection of varicella treated at home with aciclovir and antihistamines drugs to reduce pruritic symptomatology. Three days after the end the antiviral therapy there was a change of the stain cutaneous on the limbs by the rose to red-blue coloured for variable time on 5–10 min. Two days later, when he was in the open a low temperature, he came presenting stain cutaneous red-blue on the nose, zygomas and knees. To persist this symptomatology he went to an Emergency Department and admitted in our hospital with diagnosis of acrocyanosis.
Objective examination: Neurological, cardiac, abdominal and superficial lymphatic examination were normal and so also the thorax auscultation. In the cutaneous examination there were scabby pustules on the scalp and trunk. The peripheric pulses were present and Adson, Wright, Mc Gowen manouvers were normal. There were not signs of deep vein thrombosis to the lower limbs, hypothermia on the hands and feet without nail injures. Positive Lavaignel–Lavastine mark with hyperhidrosis of cutaneous tissue, cyanosis stain of the upper-lower limbs, knees, ears, zygomas and nose.
Laboratory, instrumental and medical examinations: Laboratory tests revealed LDH: 650 (range 240–480), GOT: 54 (range 0–50), Coombs direct test: positive, Coombs indirect test: negative, present cryoagglutinins with level of 1,024. Antibodies of treponema, B, C and A hepatitis markers, tumoral markers, cryoglobulins were negative. ANA, anti-DNA, ENA, ANCA, C3, C4, blood cultures, erythrocyte sedimentation rate (ESR), rheumatoid factor, C-reactive protein (CRP), serum immuno-globulins (IgG, IgA, IgM, IgE), anti-streptolysin titre, blood count test, thyroid hormones were normal. Chest-X-ray, arterial and veins color-coded duplex ultrasonography, laser Doppler hands and feet, abdomen ultrasound, nephrologist and oculistic examinations were normal. The nailfold hands video microscopy was positive for architecture alterations of capillaries.
Clinic course: During the hospitalization the patient was treated with combined therapy: saline solution 250 ml 0.9% NaCl + pentoxifillina 100 mg (two dose/day), diosmina 500 mg (two dose/day), prednisone 12.5 mg/day. On the dimission the prednisone was reduced to 6.5 mg/day for others 3 weeks. After 2 months to ambulatory check the patient had reduced acrocyanosis only on the limbs but the laboratory tests revealed still hight level of cryoagglutinins with value of 1,024. For this thing the patient began methotrexate 2.5 mg (5 mg + 5 mg dose a time in a week for 3 months). On the following check acrocynosis and cryoagglutinins were absence.
Discussion and conclusion: This clinic situation can arise during an infective disease [1], to give a drugs, tumours (especially Hodgkin lymphoma) or autoimmune diseases (systemic lupus erythematosus). Others causes are: virus (Coxackie virus, Cytomegalovirus, mononucleosis virus, HIV, influenzal virus, varicella-zoster virus), bacterias (Klebsiella, mycoplasma pneumoniae), drugs (quinidina, alphamethyldopa, penicillin, acetylsalicylic acid, some analgesic, sulphonylureas). The antigen reaction can cause an agglutination antigen–antibodies with polymeric aggregation development [2]. This aggregation causes a reduction of blood velocity in the microcirculation and the subsequent erythrocytes peripheral stasis. In addition there is arteriole and venous plexus subpapillary vasospam caused by a low temperature with development of acrocyanosis and red-blue cutaneous stain [3, 4]. For this clinic course has been formulated acrocyanosis diagnosis by cryoagglutinins. The phenomenon has been ascribed to the varicella-zoster infection which in adult age can bring to immune phenomenons how that described.

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Stress, emotions and memory

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The brain is the key organ of the response to stress because it determines what is threatening and, therefore, potentially stressful, as well as the physiological and behavioral responses which can be either adaptive or damaging. Stress involves two-way communication between the brain and the cardiovascular, immune, and other systems via neural and endocrine mechanisms. Acute and chronic stress are detrimental for human body, particularly for brain. Cognitive performance, in elderly people is impaired by stress. Stress causes morphological and functional dendrities alterations in several brain regions involved in the cognitive processes. Several studies shown that chronic stress causes retraction and simplification of dendrites in the CA3 region of the hippocampum and prefrontal cortex and affects hippocampum-dependent spatial ability. Furthermore chronic stress enhances dendrities arbors in the amygdala and facilitates also amygdala-dependent emotions such as fear: these important reactions to salient events, seems to involve different brain regions functions. More recently, convergent evidence in animals and humans demonstrate that stress specifically impairs working memory, concerning the management of information in order to obtain a correct executive feedback to the perceived stimulus. Human Pet imaging experiments also indicate that the subjects who received adequate maternal care during childhood are less vulnerable to stress even in adulthood. There are also variations in dendrities morphology and function between individuals: in post-traumatic stress memory disorders are more relevant in men than in women. Animal and human experiments also indicate finally highlight that emotional functions are also impaired by acute and chronic stress. Stress influences negatively brain functioning in different ways: it is able to induce psychiatric and neurological symptoms in people without history of psychopathology or neurological disease playing the role of primary causal factor or of triggering factor. Attention has been recently focused on work-stress related diseases, such as the symptoms and signs present whenever work-related demands exceed worker's ability and resources. In vivo electrophysiology has identified cellular correlates of extinction learning and memory in the brain structure, in particular, in the basolateral nucleus of the amygdala. Moreover interesting is the link between chronic stress and cortical rhythms with a decreasing of electroencephalographic coherence. Even if the newest

technologies confirm that stress impairs brain, many questions still challenge investigators. Further studies on the brain coherence are essential for to discover new targets to contrast stress-induced damage.

Regulation of T and B cell immune responses in systemic lupus erythematosus (SLE) patients: role of mesenchymal stromal cells from lymph nodes

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Lymph node microenvironment is the site where immune response in autoimmune diseases could take place. This microenvironment is characterized by different populations of accessory stromal cells as lymph node mesenchymal stromal cells (LMSC) that interact with healthy or autoreactive T and/or B cells. LMSC may strongly influence the outcome of immune response. We have analyzed whether LMSC can exert an inhibiting effect on T lymphocyte activation and proliferation while saving B cells from apoptosis. LMSC displayed a fibroblast-like morphology and were characterized by the surface expression of CD73, CD90, CD146 antigens. On the other hand, they did not express several surface markers typical of different leukocyte subpopulations as CD45, CD14, CD15, CD3, CD16, CD33, CD34. LMSC can differentiate in adypocytes or osteoblast under appropriate culture conditions. LMSC secreted SDF-1 and IL8 but not regulatory cytokines as IL10. This cytokine was secreted in co-culture with healthy peripheral blood lymphocytes suggesting that a microenvironment where regulatory T cells can be derived is determined during LMSC-lymphocyte co-cultures. Importantly, LMSC Inhibited T cell proliferation to polyclonal stimuli as phytohemagglutinin (PHA) or anti-CD3 monoclonal antibodies (mAbs). This inhibiting effect was dependent on the ratio between LMSC and lymphocyte and on LMSC-lymphocyte direct contact. Indeed, at the LMSC-lymphocyte ratio of 1:5 a 50–85% of inhibition was detected while at 1:25 ratio this inhibiting effect was still evident only for stimulation of T cells with anti-CD3 mAbs (50% of inhibition). LMSC could inhibit lymphocyte proliferation also to oligoclonal stimuli as staphylococcal bacterial toxins as SEB or in mixed lymphocyte reaction. Importantly, IL2 was produced by T cells also during co-cultures with LMSC but this T cell growth factor was not consumed to induce proliferation of T cells. This finding would suggest that IL2 interaction with its receptor and consequent signalling is impaired by LMSC. In addition, we observed that during LMSC-lymphocyte co-cultures the up-regulation of the surface expression of the NKG2D activating receptors of cytolytic effector cells was strongly impaired. This upregulation may be mediated by IL2, thus further supporting the idea that IL2-mediated signalling is affected by LMSC. Importantly, the NKG2D-mediated activation of CD8 + T cells was defective in T lymphocytes as the killing of target cells due to NKG2D–NKG2D ligand interaction was strongly reduced in T cells harvested from LMSC-lymphocyte cocultures. Noteworthy, LMSC were able to prolong survival of healthy and systemic lupus erythematosus (SLE) B cells in the absence of addition of exogenous growth factors. This effect was linked to the LMSC-dependent increment of Bcl-x_L/Bax ratio. This protective effect was impaired by the treatment of LMSC with therapeutic doses of corticosteroids. Indeed, 10^{-6} to 10^{-7}M concentrations of dexametasone strongly reduced the levels of Bcl-x_L/Bax ratios in B cells co-cultured with LMSC and this correlated with the increment of mitochondrial-dependent apoptosis of B cells. In some instances, also the up-regulation of CD38 and the alpha chain of IL2 receptor was detected co-culturing LMSC with B cells. In this context, we found also that LMSC can express high levels of messenger RNA coding for stromal derived factor 1 alpha (SDF1) and B lymphocyte activating factor of the tumor necrosis factor family (BAFF) indicating that these cytokines can be responsible for promoting survival and activation of B cells. In conclusion, our present data would support the idea that LMSC can be a relevant cellular player in regulating T cell-mediated immune response in lymph node and B cell survival and activation. Thus, we propose that LMSC can be considered as a new target for therapy in some autoimmune diseases as SLE where subversion of immune tolerance and expansion of B cell compartments are relevant in the pathogenesis of the diseases.

Allergic diseases in the elderly:new epidemiological insights

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Immunosenescence is a pathophysiological event in the aging process which probably represents the greatest danger to the individual; dysregulation of immune functions and alteration of cytokines and thymic hormone levels lead to an increased susceptibility to infections, autoimmunity and more frequent neoplastic events and allergic reactions. In fact, there is a state of inflamm-ageing in senescence with a consequent increase of type 1 (IL 2, IFNγ, TNF α) and type 2 (IL 4,IL 6, IL10) lymphokines which has been rarely reported. The aim of this study was to investigate the incidence of allergic manifestations in subjects referred to our Allergology Unit over a three-month period in early 2008, demonstrating that 15% of these manifestations were found in elderly patients, 51.8% of whom were suffering from allergic reactions to drugs. Urticaria and eczema, such as skin manifestations, accounted for 71.4% of these symptoms, but a diagnosis for an allergic reaction and the allergen responsible was individuated in only 13.8% of these patients; it was possible to hypothesize an allergic dermatitis in 18% by means of patch testing. Rhinitis was present in 16.8% of subjects and food allergies in 8%. In fact, non-specific factors, such as a reduced mucus production, vasomotor aspects, and gastroesophageal reflux, seem to be responsible for rhinitis in the elderly without allergic sensitization. Regarding food allergies, the most frequent allergen was Anisakis due to consumption of raw fish. In addition, the quality of life in this patients resulted significantly reduced. As far as Further studies are

necessary to better understand the pathogenic mechanisms involved in the development of allergic manifestations and to assess the true incidence of respiratory, food and drug allergies in the elderly population.

Coronary artery disease and-or cerebral non-fatal ischemic stroke following retinal vein occlusion: a 8-year follow-up

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Fourty-five consecutive subjects (26M, 19F; mean age 54 ± 14) with a diagnosed retinal vein occlusion (RVO), were followed-up for 8 years. As many as 145 sex-age- and blood pressure-matched individuals (78M, 67F; mean age 54.4 ± 13.5), that did not experience any vascular event, served as controls. At the time of the RVO, controls and subjects did not differ as to hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, smoking habits, inherited/acquired thrombophilia. At the follow-up completion, they differed as to statin consumption ($p = 0.016$). During the 8-year follow-up, in the control population, 11 out of 145 (7.6%) subjects had experienced a major vascular event (8 coronary artery disease; 3 cerebral non-fatal ischemic stroke). In contrast, of the 45 subjects with a history of RVO, as many as 10 (22.2%) had experienced a major vascular event: 4 coronary artery disease; 4 a cerebral non-fatal ischemic stroke; 2 a cardiovascular + cerebrovascular event ($p = 0.012$). A prolonged antiplatelet treatment, prior to the major vascular event, was found in 5/45 cases (11.1%) versus 23/145 (15.9%) controls ($p = 0.63$). In contrast, a long-lasting administration of antihypertensive drugs, to achieve a control of blood pressure, was found in 83.4% of controls and only in 46.7% of cases ($p < 0.0001$). In conclusion, in a 8-year follow up, coronary artery disease and/or non-fatal ischemic stroke were more common in subjects with a history of RVO than in a large setting of subjects comparable for cardiovascular risk factors. These data also argue for RVO as a vascular disease in which aggressive antihypertensive therapy to prevent stroke and/or myocardial infarction is needed.

Cardiac failure in long-term department

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Introduction: Cardiovascular failure is a clinical syndrome characterized by signs and symptoms and evidence of cardiac changes both structural and functional at rest. According to European data the majority of the general population is between 2 and 3% and is increases for those over 75 years of age, reaching 10–20% for those between 70 and 80. Italian studies have shown the frequency in older subjects with a greater number of co-morbidities.
Aim: Observe the characteristics of patients hospitalized in our C.O.U. from March 2009 to February 2010.
Materials and methods: 81 patients with an average age of 86 years have been examined. Of these, two patients died during hospitalisation and three patients had to be hospitalized a second time. The co-morbidities more present were FA for 58.3% of the cases, hypertensive cardiopathy for 54.1%, COPD for 41.6%, Alzheimer for 16.6%, diabetes for 20.83%, CHD for 20.80%. As for negative prognostic factors IRC was found in 12.5% of the cases and anaemia in 12.0%. 6% is located in IV class NYHA. At the moment of hospitalization they were under poly-pharmacotherapy: diuretics, digitalis, anti-aggregates, ACE-inhibitors, nitrates. At discharge from the hospital the drug most prescribed was Furosemide, followed by Sartani or ACE-inhibitors, cardio-selective beta blockers. Some patients had to undergo anticoagulant therapy, while those for whom that was not possible were treated with Indobufene. Digitalis was prescribed only for subjects with atrial fibrillation.
Conclusion: The not so high prevalence of CHD is to be ascribed to the fact that this pathology predominantly regards subjects hospitalized in cardiology. The higher age range of the hospitalized subjects is due to the aging of the population and the improvement of ischemic cardio-pathological therapies, which represent a very frequent cause for cardiac insufficiency. Our experience has highlighted the necessity to involve persons like professional nurses and/or caregivers in order to promote a more efficient domicile administration of the patients.

Increased oxidant stress and recidivant atrial fibrillation after electrical cardioversion

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Previous studies gave evidence for increased oxidant stress in patients with atrial fibrillation (AF). The aim of this study is to evaluate in AF subjects submitted to electrical cardioversion if the degree of oxidant stress could identify patients with recidivant AF at 3 months from electrical cardioversion. The oxidant stress was studied in 60 patients (37 males, 23 females, aged 52–80 years, 19 paroxismal, 41 persistent AF), behind GP91phox (ELISA kit performed and validated in our laboratory), a catalytic core of NADPH oxidase, and Urinary PGF2alfa-III (Tema Ricerca, Bologna, Italy), as markers of oxidative stress. After 3 months from electrical cardioversion, 47 (29 males, 18 females, 14 paroxismal, 33 persistent AF) mantained sinusal rhythm, while 13 subjects (8 males, 5 females, aged 52-78 years, 4 paroxismal and 9 persistent AF) showed AF at ECG. The two subgroups didn't differ from sex, age, paroxismal or persistent AF, pharmacological treatment with antiarrhitmic drugs or statins. No patient used antioxidant drugs. GP91phox (36.16 ± 3.95 vs. 26.10 ± 6.34 pg/ml; $p < 0.0001$) and Urinary PGF2alfa-III (544.12 ± 210 vs. 324.88 ± 114 pg/mg creatinine; $p < 0.002$) levels, evaluated immediately before the cardioversion, were significantly higher in patients with recidivant AF at 3 months respect to patients who maintained sinusal rhythm. In addition GP91phox and Urinary PGF2alfa-III were significantly correlated each other ($r = 0.62$; $p < 0.0001$). Atrial dimension did not identify patients at risk of recidivant AF. The study shows that increased oxidative stress identify AF patients at risk of recidivant atrial fibrillation after electrical cardioversion. This confirms a role of oxidant stress in the pathogenesis of atrial fibrillation. Interventional studies could be useful in these patients to modulate oxidant stress and influence recidivant AF after electrical cardioversion.

A man from Altamura with recurrent fever and abdominal pain

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A 32-year-old caucasian patient was presented with recurrent episodes (5 in the last months) of fever (max 38.5°C) and abdominal pain, bloating and severe constipation. Symptoms start 3–4 days before the fever and persisted about 1 week. On admission the patient looked ill, there was no fever, but diffuse abdominal pain, positive blumberg sign, and hypertympanism were shown on physical exam. Blood analyses, stool cultures, autoimmunity, viral serology etc. were normal except for CRP (15× UNL). Abdominal ultrasound showed splenomegaly (134 mm). Colonoscopy was normal. The clinical diagnosis of Familial Mediterranean Fever (FMF) was hypothesized, due to the recurrent type of pain-fever attacks (8, 4, 1, and 2 weeks), acute abdominal symptoms but otherwise totally healthy periods in between each attack. While starting therapy with colchicines (1 g/day p.o.), the genetic analysis was undertaken (University of Bari and Genoa Medical Schools). Following therapy with colchicines, no other attack has ever reported by the patient, so far. Genetic analysis confirmed the diagnosis, with mutation of exon 2 (c.442 G>C) and of exon 10 (c.2282 G>A) of MEFV gene ("*Marenostrina*").

Discussion: Suspect of FMF was supported by negativity of laboratory, except PCR, by the geographic origin of the patient (Apulia), by clinical manifestations, and by the absence of symptoms in between acute attacks. In particular, clinical diagnosis of FMF was probable by demonstrating the presence of 1 major plus 1 minor Tel-Hashomer criteria (major criteria: recurrent episodes of fever and serositis, amyloidosis type AA with no other predisposing condition, positive response to colchicine; minor criteria: recurrent episodes of fever, erysipelas-like erythema, a first degree family member with FMF). Genetic test confirmed the clinical diagnosis. Differential diagnosis with FMF was: acute appendicitis, peritonitis, acute pancreatitis, acute cholecystitis, inflammatory bowel diseases, infectious origin fever (included gastroenteritis and endocarditis) and others periodic fevers. Of note, the patient was original from an area west to Bari: Altamura where several other cases of FMF are being followed up at our referral center.

Conclusions: FMF (ICD9: 277.31) belongs to the group of rare diseases (Italian Ministry of Health RC0242) and symptoms can be easily confused with other frequent conditions (some simulating acute abdomen with potential surgical implications). The diagnosis of FMF needs to be established since colchicines can prevent further attacks and screening should be reserved to other family members and other members originating from the same geographical area.

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Hematology

Endocrine and bone disease in appropriately treated adult patients with beta-Thalassemia major

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The natural history of beta thalassemia major (TM) has significantly changed during the last two decades. At present TM patients survive over their 30s and 40s, but they have considerable morbidity. Bone demineralization is an important cause of morbidity in older patients; the etiology is multifactorial and partially unknown. We examined cross-sectionally 111 adult TM patients (66 females and 45 males, 32.6 ± 6 years), regularly transfused, properly chelated and replaced for endocrine defects. Bone demineralization was detected in 92.7% of patients, with different severity according to gender and site: osteopenia was the prominent finding at the femur, osteoporosis at lumbar spine ($p < 0.001$), more evident in males. The femoral site was more influenced by biochemical and clinical factors; despite adequate replacement, femoral *T* score was lower in the hypogonadic than in the eugonadic group ($p = 0.047$). A significant correlation was found between bone mass and body mass index (BMI), alkaline phosphatase (ALP) and pre-transfusional Hb levels. Multivariate analysis indicated as significant regressors ALP, BMI and hypoparathyroidism (*T* score: $p = 0.005$, 0.035, 0.002; *Z* score: 002, 0.009, 0.003, respectively) at femur, only ALP at lumbar spine ($p = 0.008$ and 0.045 for *T* and *Z* scores, respectively). Statistical significance was reached more frequently by *T* score, while *Z* score demonstrated to have a lower sensitivity. Despite best care facilities, bone demineralization in thalassemic patients remains a challenge; further exploration of the relationships between bone loss and endocrine, biochemical and hematologic variables is warranted to find effective measures to reduce bone pain and fracture risk.

Table Statistic results (mean ± standard deviation and *p* value) of comparisons between clinical/biochemical dicotomic variables and *T* or *Z* scores at femoral and vertebral sites

	T score (mean ± DS)		*Z* score (mean ± DS)	
	Femur	Lumbar spine	Femur	Lumbar spine
Gender				
Males	−1.58 ± 0.746*	−2.44 ± 1.119	−1.50 ± 0.830*	−2.28 ± 1.196
Females	−1.90 ± 1.018*	−2.12 ± 1.267	−1.87 ± 0.967*	−2.04 ± 1.219
Hypogonadism				
Yes	−1.46 ± 0.772*	−2.20 ± 1.095	−1.65 ± 0.744	−2.12 ± 1.098
No	−1.85 ± 0.952*	−2.26 ± 1.250	−1.73 ± 0.975	−2.15 ± 1.247
Hypoparathyroidism				
Yes	−1.87 ± 0.855*	−2.36 ± 1.116*	−1.82 ± 0.850*	−2.21 ± 1.126
No	−1.31 ± 1.130*	−1.71 ± 1.527*	−1.20 ± 1.118*	−1.79 ± 1.547
Calcium therapy				
Yes	−1.64 ± 0.819*	−2.05 ± 1.160*	−1.68 ± 0.795	−2.01 ± 1.192
No	−1.93 ± 1.030*	−2.49 ± 1.247*	−1.75 ± 1.081	−2.31 ± 1.224
Bisphosphonate therapy				
Yes	−1.67 ± 0.905*	−2.09 ± 1.190*	−1.66 ± 0.928*	−1.99 ± 1.184*
No	−2.35 ± 0.674*	−3.23 ± 0.634*	−2.14 ± 0.823*	−3.16 ± 0.614*

* $p < 0.05$

Non-langerhans cell histiocytosis associated with progressive neurological syndrome

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Introduction: Non-Langerhans Cell Histiocytosis include a wide variety of uncommon and overlapping diseases. They are generally benign proliferative disorders, classified according to immunohistochemistry. Clinically they can be divided into three major groups, those that predominantly affect skin, those that affect skin but have a systemic component and those that primarily involve extracutaneous sites.
Case report: In 1996 a 49-year-old man presented with fever, asthenia, night sweats, joint pain and purple papules on chest and legs. Skin biopsy of the papules was consistent with a diagnosis of Multicentric Reticulohistiocytosis. A bone scan revealed abnormal uptake at almost all skeletal segments and X-ray showed multiple areas of bone loss. Treatment with corticosteroids and methotrexate was discontinued after 4 months for lack of response and side effects. A treatment with non-steroidal anti-inflammatory drugs improved joint pain. Four years later the patient developed a progressive neurological syndrome with vertigo, ataxia, dysarthria and dysphagia. Brain Magnetic Resonance showed multiple areas of altered signal first interpreted as brain vasculopathy. The patient began acetylsalicylic acid but in the following years the neurological symptoms worsened and a resonance imaging performed 2 years later revealed extensive signal alterations in the brainstem, cerebellar vermis and periaqueductal gray areas, and showed hyperintense focal lesions in T2-weight sequences in subcortical white matter. Cerebrospinal fluid analysis revealed some oligoclonal bands but no atypical cells. These findings were interpreted as vasculitis and a course of i.v. immunoglobulin was tempted, without results. So a new course of corticosteroid based treatment and methotrexate was adopted, but neurological symptoms progressed and resonance imaging performed in 2007 confirmed multiple focal lesions of white matter suggestive for gliotic-demyelinating damage. The patient died 1 year later.
Discussion: Central nervous system involvement has never been reported in Multicentric Reticulohistiocytosis, differently than in other non-Langerhans cell histiocytosis. Intracranial Rosai–Dorfman disease typically presents as meningioma-like dural-based mass, whereas central nervous system involvement in Erdheim–Chester disease appears to be a result of pathological histiocytic proliferation or a demyelination process. The neurologic alterations here reported have been radiologically described as diffuse vasculitic damage which could be an unusual manifestation of the disease. Therefore, not only the histiocytic infiltration itself, but even an autoimmune process could be implicated in the central nervous system involvement of histiocytic disorders. On the other hand, autoimmune diseases are frequently associated with Multicentric Reticulohistiocytosis.

A case of dendritic-cell lymphoma with rapid development

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A 71-year-old man was admitted to our Department because of suspected pneumonia and diffuse bone pain on May 2010. The patient had been well until June 2008, when palpable, non-itchy skin lesions developed on the back. Shortly after, a skin biopsy was performed and pathological findings were suggestive of dendritic-cell lymphoma. A total-body CT scan showed multiple enlarged lymph nodes in the left lateral cervical and inguinal regions. Moreover, the disease also involved the pharynx and the right axillary lymph nodes on PET scan. Then, examination of specimens from a bone marrow biopsy and aspiration revealed the malignant process. The patient underwent partial remission receiving hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), alternated with courses of high-dose methotrexate and cytarabine, together with CNS prophylaxis. Subsequently, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen was performed, followed by radiotherapy to the neck and the pharynx. Due to the occurrence of a skin relapsing, first etoposide, cyclophosphamide, doxorubicin, and prednisone according to the EPOCH regimen, then modified DHAP protocol (dexamethasone, cytarabine, and cisplatin) were administered with partial improvement of skin lesions. The last cycle was on April 14, 2010. On May 2, 2010 the patient was examined for cervical and femoral pain at our haematological outpatient clinic; cervical and lumbar radiographs disclosed no lesions but chest radiography showed a suspected pneumonia at the left basis; then, he was referred to our ward. On physical examination, the patient complained of cough and dyspnoea; a large haemorrhagic blister on the mucous membrane lining the right jowl was detected. Laboratory tests showed platelets 22,000 μL^{-1}, white cells 16,000 μL^{-1} with 54% of blast cells, and LDH 8,252 UI/L. We started broad-spectrum antibiotic therapy with piperacillin/tazobactam and vancomycin and performed a total-body CT scan, which revealed an ischemic area into the spleen and multiple small nodular images into the lungs. In 10 days the patient developed liver and pulmonary failure and required blood and platelet transfusions almost every day for a really serious bleeding diathesis. Despite these measures, the patient developed a severe, persistent headache associated with vomiting; rapidly, bilateral miosis developed; given the unfavourable clinical evolution, we decided to begin palliative sedation with morphine sulphate. CD4+ CD56+ malignancies (dendritic cell malignancies) are really rare haematological neoplasms; at diagnosis, most patients have cutaneous nodules that had appeared a few weeks to a few months previously; when not initially involved, bone marrow infiltration occurs rapidly in the course of the disease. Median follow-up after beginning of chemotherapy is 15 months; the median time of relapse is 9 months. Unfortunately, our patient showed us the quickness of worsening of dendritic-cell lymphoma in blastic phase, as literature reports.

Evaluation of cardiac function and glucocerebroside accumulation in Gaucher patients

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Introduction: Gaucher disease (GD), the most common inherited lysosomal storage disorder, is a multisystemic disease due to an autosomal recessive defect of the gene encoding glucocerebrosidase enzyme, responsible for accumulation of glucosylceramide into reticuloendothelial cells, particularly in liver, spleen and bone marrow. GD is a clinically heterogeneous disorder and it is classically

classified in type 1 (non-neuronopathic disease), types 2 and 3 (acute and chronic neuronopathic disease, respectively). The manifestations and the clinical progression of GD are highly variable between affected patients as well as age, features of clinical presentation and organ involvement. Each patient needs an accurate initial multisystemic assessment, staging different organ damages and the burden of the disease, followed by periodical evaluation. Cardiac disease is reported as a rare complication including restrictive cardiomyopathy and progressive calcifications of heart valves and aortic arch.

Objective: To assess the evidence of cardiac disease with CMR in GD patients.

Materials and methods: Consecutive patients were recruited at the Policlinico Foundation, University of Milan. In all patients, the diagnosis of GD was previously confirmed by enzymatic assay as well as by mutation analysis. Medical history of cardiac disease and the presence of cardiovascular risk factors were surveyed by direct interview. Patients were scanned with a 1.5 Avanto Siemens using a comprehensive cardiovascular evaluation protocol including morphologic T1 and T2-weighted sequences as well as functional cine sequences and inversion-recovery turbo-flash sequences to evaluate early and late-enhancement after gadolinium contrast media (Magnevist 0.03 mmol/kg). Phase-contrast sequences were used to assess transvalvular velocities.

Results: Six patients were investigated, age 43 (range 29–60), male, all received enzyme replacement therapy for a median of 8.5 years (range 1–18). Five of six patients showed bi-atrial enlargement (left atrium 4,5 cm, area 26 cm^2), one patient showed moderate aortic stenosis (VENC = 3.3 m/s) in bicuspid valve with mild aortic dilatation and one patient showed moderate mitral regurgitation (2/4). No evidence of myocardial enhancement was evident after gadolinium contrast media.

Conclusion: Although cardiac disease in GD is considered rare, in the present series we have found 2 valvular disease and mild to moderate bi-atrial enlargement in 5 of six patients, with a moderate increase of LV myocardial mass index and no evidence of DE. Further study to evaluate the prognostic value of these findings is warranted.

Reduced genomic DNA methylation in peripheral mononuclear cells as an index for the occurrence of cancer disease

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Genomic DNA hypomethylation is a common epigenetic finding in cancer tissues as well as cancer precursor cells. However, it is still unknown if genomic DNA methylation status can reflect the presence of cancer or is a biomarker of impending cancer. From a Northern Italian cohort we selected 68 subjects, who had a cancer at the enrollment or developed cancer disease during a follow-up, along with same number of age-and sex-matched control subjects, and determined the genomic DNA methylation status in peripheral mononuclear cells using an LC/MS method. Subjects affected by cancer showed reduced genomic DNA methylation compared to controls [(% methylation: 4.39 (95% CIs 4.25–4.53) vs. 5.13 (95% CIs 5.03–5.21)]. Furthermore, a clear cut-off value for DNA methylation (4.53%) was identified for higher risk of cancer for affected vs. controls. Furthermore, only patients with hypofolatemia (folate levels below 12 nmol/L) and homozigosity for MTHFR 677 C > T, had DNA hypomethylation compared to controls. The presence of MTHFR 1298 A > C does not influence DNA methylation. Using a quantitative LC/MS method is possible to indentify a cut off DNA methylation value (4.53% mCyt) under which there is the presence of neoplastic disease. We conclude that genomic DNA methylation status, especially under 4.53%, in peripheral mononuclear cells can be a predictor of harboring or developing cancer disease.

Acute renal failure and hypercalcemia as onset in splenic lymphoma

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A 34 years old Caucasian woman with general malaise, abdominal fullness, and nausea was admitted to our hospital. She also reported of a 3 kg weight loss during the previous 4 months. She didn't take any drugs. A blood sample revealed microcytic hypochromic anemia (haemoglobin of 8.5 g/dL) with erythrocyte sedimentation rate (ESR) of 30 mm/h. Biochemistry tests showed acute renal failure with serum creatinine of 1.9 mg/dL (normal range 0.6–1.4 mg/dL) and creatinine clearance of 39 mL/min, hypercalcemia (Ca^{++} 13.5 mg/dL, normal range 8.6–10.2 mg/dL) in association with normal phosphate levels, LDH 933 UI/L (normal range 285–540). Urinalysis showed low proteinuria with increased urinary excretion of calcium. Serologic tests for hepatitis C virus (HCV) was positive with normal liver function; serology was negative for hepatitis B virus (HBV), Cytomegalovirus and Epstein Barr virus. The physical examination was normal except for marked splenomegaly. The patient was treated with hydration and furosemide for hypercalcemia without improvement of symptoms and renal function. Biochemistry tests revealed that serum intact PTH (i-PTH) levels were decreased compared to normal ranges, while serum $1,25(OH)_2$ and parathyroid hormone related protein (PTHrP) levels were normal; thyroid hormones and bone alkaline phosphatase levels were normal. Abdominal ultrasound showed a vascularized no well-defined mass (13 cm in diameter), with hypoechoic density between spleen and left kidney. We ordered a total body computed tomography CT that confirmed a huge irregular lesion in relation to the spleen with several calcifications and fibrosis; this lesion did not become enhanced after an injection of contrast medium. Moreover the CT revealed a lymphadenopathy in the para-aortic area. Bone marrow examination was negative for blasts or mononuclear cell infiltration. Because spleen tumor was suspected, a splenectomy was performed. Histological examination of the spleen showed neoplastic proliferation with diffuse large B cell components. The diagnosis was high grade non-Hodgkin's lymphoma large B cell (B-NHL). After surgical removal of the spleen, laboratory analysis showed hypocalcemia (Ca^{++} 7.1 mg/dL), an impairment of renal function (creatinine 0.7 mg/dL) within 24 h. In our patient with B-NHL we have found to be associated with hypercalcemia and acute renal failure at presentation. Hypercalcemia of malignancy (HM) is a syndrome in which hypercalcemia occurs in the absence of bone metastases. Hypercalcemia is a relatively frequent metabolic disorder recognized in tumors such a breast cancer, multiple myeloma, adult T cell leukaemia, renal cell carcinoma and non small cell lung. In contrast to solid tumor disease and T cell malignancies HM is less common in B cell lymphoma. The mechanism of hypercalcemia in patients with malignancy may include the increased production of 1,25 dihydroxivitamin D ($1,25(OH)_2$), i-PTH or PTHrP Vitamin D-dependent hypercalcemia is due to increased calcium and phosphate absorption from the intestine and to decreased excretion of calcium. PTHrP have a similar activity to PTH; this is secreted by the

cancer cells and promotes osteoclastic bone resorption causing hypercalcemia. Generally high serum calcium levels in patients with B cell lymphoma are dependent to the secretion of $1,25(OH)_2$ from lymphoma adjacent macrophages as often revealed by immunohistochemistry. Because of dramatic recovery of renal function and hypercalcemia after splenectomy, we can speculate that main mechanism of hypercalcemia is related to vitamin D production from neighboring lymphoma macrophages.

AL amyloidosis and acquired factor X deficiency: a case report

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A 54-year-old Caucasian man was admitted to our Hospital for left gluteal haematomas occurred immediately after intramuscular NSAID injection for abdominal pain. He referred no complain until the last year, when he developed easy bruising after minor traumas and a similar episode few months ago. No major bleeding after surgery or tooth extraction was mentioned. Family history of bleeding was negative. Laboratory investigations performed at the admission showed a normocytic-normochromic anemia (Hb 7.2 g/dl) that required red blood cells transfusions and an isolated prolonged Prothrombin Time (PT) (ratio 1.35, normal range 0.85–1.15). An abdomen ultrasound revealed severe hepatosplenomegaly with increased splenoportal axis calibre. The patient was discharged and referred to our Haemostasis and Thrombosis Centre. Coagulation tests performed in our laboratory confirmed a prolonged PT (ratio 1.47) associated with a prolonged activated Partial Thromboplastin Time (aPTT) (ratio 1.52, normal range 0.85–1.15) that were both corrected by normal plasma, suggesting the absence of circulating coagulation inhibitors. Supposing a deficiency of coagulation factors, we investigated the coagulation pathway, finding isolated low factor X plasma levels (23%, normal range 66–126%). Factor X deficiency was supposed to be acquired on the basis of his negative bleeding history in the past. Therefore, the patient underwent subsequent investigations in order to identify secondary causes of his acquired coagulation disorder. Liver function tests were normal. Serum proteins electrophoresis showed the presence of an IgG kappa monoclonal component (0.7 g/dl), associated with renal failure (glomerular filtration rate 30 ml/min) and proteinuria in nephrotic range (0.5 g/24 h). Abdominal ultrasound confirmed the previously reported abnormalities. A cardiac ultrasound showed a left ventricular wall slight thickened with sparkling appearance in the presence of preserved systolic function, compatible with amyloidosis. To confirm this diagnosis a periumbilical subcutaneous adipose tissue biopsy, after infusion of fresh frozen plasma to correct the coagulation disorder, was performed showing amyloid deposits. No other criteria for multiple myeloma were satisfied and the patient was diagnosed to be affected by primary AL amyloidosis with secondary factor X deficiency. A treatment with melphalan and high doses dexamethasone for an overall seven courses was prescribed. After the second cycle hemorrhagic symptoms disappeared and when the fifth cycle was completed a disease remission was achieved. Nevertheless, two additional cycles were administered to consolidate the results. After 4 years the patient is in complete hematological remission, with no signs of organic damage caused by AL amyloid and with normal factor X activity. The table below shows the laboratory values at diagnosis, during chemotherapy and at present. Primary amyloidosis with acquired factor X deficiency is well described in literature. The underlining mechanism is not well understood but it has been proposed that factor X binds to amyloid fibrils primarily in the liver and spleen. Although rarely, amyloidosis can present itself with isolated hemorrhagic disorder. So, in case of factor X deficiency particularly attention should be payed to rule out amyloidosis and monoclonal gammopathy, because these are the two disorders most frequently associated with the acquired coagulation defect, and without a specific treatment of the underlined disease the hemorrhagic diathesis is not well controlled.

	Diagnosis	Second cycle	Fifth cycle	End of chemotherapy	Present
Serum protein electrophoresis					
Monoclonal protein IgG κ (g/dl)	0.7	0.3	Undetectable	Undetectable	Undetectable
Proteinuria (g/24 h)	0.5	0.06	0.05	<0.05	0.17
Urine immuno -fixation	IgG k	Undetectable	Undetectable	Undetectable	Undetectable
Serum free light chains					
κ (mg/l) (nr < 19.4)	251	60.1	28.9	26.2	38.9
λ (mg/l) (nr < 26.3)	27.4	20.9	16.6	17.4	17.2
κ/λ (nr 0.26–1.65)	9.16	2.88	1.74	1.51	2.20
Factor X (%) (nr 70–120)	26	36	45	49	69
Creatinine (mg/dl) (nr < 1.3)	2.56	2.38	2.60	2.80	2.14

Monoclonal gammopathy and pericardial effusion: a likely association

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Pericardial effusion is a rare complication of lymphoproliferative diseases, that usually manifests in the advanced or terminal stage of the disease. There is a long pre-diagnostic phase in the natural history of some of these lymphoproliferative diseases, and in a large percentage of cases the pericardial effusion is difficult to fit into the clinical picture. Aim of this study was to assess a possible relation between the presence of monoclonal gammopathy, as a marker of the pre-clinical stage of lymphoproliferative disease, and idiopathic pericardial effusion. The study included all patients admitted to the Department of Internal Medicine "C. Frugoni", at Bari University Hospital between 2008 and 2009 with a diagnosed monoclonal component (MC) of the disorder, compared with a control group consisting of all patients admitted to the same Department during the same period, with no monoclonal component. Pericardial effusion was demonstrated by echocardiogram and/or chest CT. Patients with autoimmune, neoplastic or infectious diseases, in which a pericardial

effusion could occur, were excluded from the study. Monoclonal proteins were present in 28 patients (age range 50–80 years), 7 (25%) of whom had a pericardial effusion of varying severity. The characteristics of the latter group of patients (sex, medical history, typing and titres of the monoclonal component, BJ, hemoglobin values and ESR, as well as effusion volume) are shown in the Table. A total of 1,759 patients admitted to the same Department during the same period, with no monoclonal component, were the controls; of these, 35 patients (2%) had an idiopathic pericardial effusion. In the 7 patients with a monoclonal component as well as pericardial effusion, in the tests done to identify the etiology of the effusion, cultures and serological tests excluded viral and mycobacterial infections; dosages of tumoral markers and a search for autoantibodies were negative, as were instrumental analyses. Renal function parameters and calcium values were within normal limits, no osteolytic lesions were present and bone marrow biopsy showed a percentage of plasma cells <10%. Therefore, the monoclonal component was diagnosed as MGUS. The prevalence of pericardial effusion was significantly higher in the group with a monoclonal component than in the control group (25 vs. 2%; OR 16.419; 95% CI 6.55–41.14; $p < 0.0001$), causing us to hypothesize that there is a likely association between pericardial effusion and monoclonal gammopathy.

Sex	Medical history	MC	MC dosage (mg/dl)	BJ	Hb (g/dl)	ESR	Echocardiogram (effusion volume in cc)
♀	Hypertension, anemia	IgMλ	–	–	8.6	106	<200
♀	Dilated cardiomyopathy	IgMλ	IgM 445	–	12.3	21	<200
♂	Ischemic heart disease, peptic ulcer	IgGκ	IgG 1,080	κ	7.4	21	<100
♀	Thyroiditis, ischemic heart disease, metabolic syndrome	IgGκ	IgG 1,470	–	12	96	>500
♀	Heart failure, HCV infection	IgMκ	–	–	–	–	<100
♂	Diabetes mellitus, colonic polyposis	IgMκ	–	–	12.9	57	<100
♂	Ischemic heart disease, diabetes mellitus	IgGκ	–	–	–	–	<100

Folic acid effects on *S*-adenosylmethionine, *S*-adenosylhomocysteine and DNA methylation in patients with intermediate hyperhomocysteinemia

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Background: The effect of folic acid (FA) supplementation resulting from homocysteine (tHcy) lowering purposes is so far unexplored for its effects on DNA methylation as well as plasma *S*-adenosylmethionine (AdoMet) and *S*-adenosylhomocysteine (AdoHcy) concentrations. Since impaired folate status has been associated with altered DNA methylation in *MTHFR677TT* genotype, it is of critical interest to evaluate whether high dose FA may modify this fundamental epigenetic feature of DNA. The homocysteine lowering effect induced by FA restores impaired DNA methylation in end-stage renal disease (ESRD) patients, although observations are not univocal in all studies. Yet, whether this effect is mediated through modifications of AdoMet or AdoHcy concentrations is unknown.

Aim of the study was to investigate the effect of FA supplementation on AdoMet, AdoHcy, and DNA methylation in hyperhomocysteinemic subjects without ESRD.

Methods and results: We recruited seven hyperhomocysteinemic, *MTHFR677TT* patients (tHcy > 30 mmol/l) with adequate renal function, to evaluate the effect of 8 weeks 5 mg FA/day supplementation. FA supplementation induced a decrease in tHcy (51.1 ± 21 vs. 26.1 ± 27 mmol/L before and after folate supplementation, respectively, $P < 0.01$), with a parallel increase in plasma AdoMet concentrations, and a decrease in AdoMet/AdoHcy ratio ($P < 0.05$). After FA supplementation global DNA methylation was unchanged.

Conclusions: Supraphysiologic FA supplementation can modulate biochemical markers in one-carbon metabolism such as tHcy, AdoMet and AdoMet/AdoHcy ratio in hyperhomocysteinemic subjects. The reduced homocysteinemia and the increased methyl compounds availability solely by vitamin supplementation do not affect genomic DNA methylation.

Bevacizumab as a new pharmacological possibility for hereditary hemorrhagic telangiectasia (HHT): preliminary results

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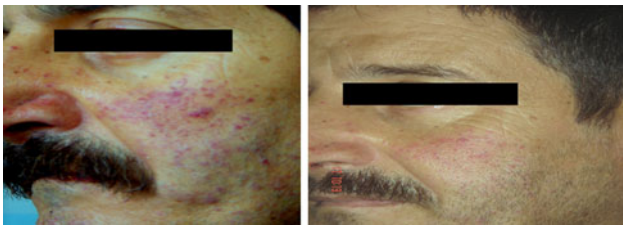
Bevacizumab, a monoclonal anti-VEGF antibody, has been reported to be effective in anecdotal cases of HHT [1–3], a genetic disease with multiorgan arteriovenous vascular malformations [4, 5]. As we have already noted an increased level of VEGF in the serum of HHT patients and its implication in the severity of epistaxis episodes [1], we immediately realized that the use of this anti-angiogenic drug might present a valid treatment which, at present, is lacking for these patients.

Methods: For this reason, we initiated an independent prospective pilot study (drug was furnished by our hospital to avoid any conflict of interest), with an experimental design considering three arms to evaluate different dosages of bevacizumab: 6 patients treated with 1 mg/kg, 6 patients with 2.5 mg/kg, and 6 patients with 5 mg/kg, with one i.v. injection every 3 weeks for 3 months. All HHT patients enrolled presented severe bleeding episodes, epistaxis and/or GI hemorrhaging, provoking hemoglobin values ≤10.0 gr/dl. Once enrolled, the patient data base included: frequency and severity of epistaxis, gastrointestinal bleeding, values pertaining to hemoglobin, hematocrit, serum iron, VEGF, echocardiography, rhinoscopy, video capsule endoscopy and total body CT. Our protocol calls for monitoring with clinical-chemistry laboratory tests for 5 month before treatment, every month during treatment and 1 month after suspension, in addition to the basal evaluation every 3 months and 1 year after treatment suspension. The study was approved by the local ethics committee.

Results: The first 3-month follow-up of the first arm (lowest dosage) has been completed and the impressive outcome encouraged us to report these preliminary results. Administration of bevacizumab

determined a reduction of epistaxis frequency from an average of 3 pretreatment episodes daily to a maximum of 1 episode daily. A dramatic decrease in transfusions was also noted: from an average of 13 blood transfusions and 26 iron transfusions/month to 4 and 6, respectively. The mean cell hemoglobin concentration improved from 6.9 gm/dl (range 4.5–9.6) to 9.0 gm/dl (range 6.3–14.5; Wilcoxon test $p < 0.05$) at the end of treatment. Moreover, in the 3/6 patients with facial telangiectases, we observed a surprisingly distinct regression of this sign (Fig. 1). During therapy, all patients reported an improvement in their quality of life and returned to their daily activities. No adverse side effects were observed, possibly due to the low dosage. However, 3 months after suspending treatment we observed a return to pretreatment values. We have now initiated the second study arm (2.5 mg/kg).

Comments: The use of low dose Bevacizumab for 3 months improved dramatically the clinical conditions and quality of life of our first series of severe HHT patients. The fact that patients in this study returned to pretreatment conditions after drug suspension demonstrates the efficacy of the drug even if its effects reasonably disappear, once suspended, in this chronic genetic disease. Our preliminary results are very promising in that they not only could establish the efficacy of a new drug class used for a rare disease without a systemic drug therapy, but also demonstrate the effective use of Bevacizumab at the lowest dosage, thus decreasing the probability of long-term side effects.



Thrombosis and Hemostasis

Two year outcomes of venous thromboembolism in elderly patients: results of the MASTER registry

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Background: Little information exists on the long-term clinical outcome of venous thromboembolism (VTE) in elderly patients.
Aim of the study: To prospectively compare the long-term clinical outcome of VTE in a cohort of elderly patients aged >75 years and in a cohort of patients aged ≤75 years enrolled in a large, multicenter registry and to identify independent predictors of clinical outcomes in the elderly.
Patients and methods: Consecutive patients with symptomatic, objectively confirmed, acute VTE were included in the MASTER registry in 25 Italian centers. Patients were followed-up for 24-months. Major clinical outcomes were death, recurrence of VTE and major bleeding. Cox regression analysis was used to assess major determinants of outcomes.
Results: A total of 2,119 patients (49.8% males) were enrolled in the study, of whom 440 (20.8%) were >75 years and 1,679 (79.2%) ≤75 years. Information on mortality at 2 years was available for 2,021 patients (413 > 75 years and 1,608 ≤ 75 years) and information on VTE recurrence and bleeding events was available for 1,988 patients (404 > 75 years and 1,584 ≤ 75 years). The 2-year cumulative incidence of mortality was 13.1% in patients >75 and 7.0% in patients ≤75, hazard ratio (HR) 1.52, 95% CI 1.09–2.13. Cancer (HR 3.44, 95% CI 1.94–6.09) was the only independent predictor of mortality in the elderly. The 2-year cumulative incidence of recurrent VTE was 6.4% in patients >75 and 6.2% in patients ≤75 (HR 1.05; 95% CI 0.67–1.63). The 2-year cumulative incidence of bleeding was 4.0% in patients >75 and 2.2% in patients ≤75, Odds Ratio 1.84; 95% CI 0.97–3.50.
Conclusions: As expected, long term mortality rates after acute VTE are significantly higher in patients >75 years than in younger patients. Rates of recurrent thrombotic events were similar between the two groups, whereas bleeding events were nearly twice more frequent in the elderly.

Intermittent flushing with heparin versus saline for maintenance of peripheral intravenous catheters in a medical department: a cluster-randomized controlled study

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The majority of patients admitted to hospital require intravenous catheterization for hydration, feeding and/or the administration of drugs. However, these devices may be responsible for morbidity and discomfort, since they frequently need early replacement as results of occlusion or superficial phlebitis. Several studies examined the efficacy of flushes with heparin in preventing these complications, and three meta-analyses concluded that the effect of intermittent flushing with heparin at low concentration (10 U/mL) was equivalent to that of 0.9% sodium chloride flushes. The latest meta-analysis investigated also safety and efficacy of heparin concentrations of 100 U/mL used as an intermittent flush, but no firm conclusion was reached because of limitations of the few available studies. Based on the literature evidences, our hospital substituted sodium chloride for heparin a few years ago, but we got the feeling that this change was responsible for an increased rate of catheter-related phlebitis. On these bases, we decided to perform a cluster-randomized, open controlled trial.
Objective: To ascertain whether flushing peripheral intravenous catheters with 3 mL of a 100 U heparin/mL solution instead of saline improves the outcome of infusion devices.
Participants: 214 medical patients without contraindications to heparin: 107 allocated to heparin and 107 to saline flushes (control group).
Main outcome measure: Catheter occlusion and catheter related phlebitis.
Results: Flushes with heparin instead of saline halved the number of patients that experienced catheter occlusion (from 47 to 23, $p < 0.03$) and catheter related phlebitis (from 56 to 28, $p < 0.001$). Similar results were obtained when the analysis was based on catheters. Flushing with heparin did not cause either heparin induced thrombocytopenia or bleeding tendency.

Conclusions: Substituting heparin for saline in the maintenance of peripheral venous catheters advantaged both patients and the health system, in that it reduced the number of catheter related phlebitis and the number of catheters per patient. Flushing with heparin did not produce side effects. However, this study did not enrol subjects with platelet or coagulation defects, and, therefore, physicians or nurses must exercise caution when prescribing this type of catheter maintenance for patients at risk of bleeding. Moreover, although none of the 107 patients receiving heparin flushes developed thrombocytopenia, this study cannot exclude for certain that this treatment poses a low risk of heparin induced thrombocytopenia.

Antibodies to tissue-type plasminogen activator (t-PA) in patients with acute myocardial infarction treated with the recombinant protein: characterisation and clinical correlations

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Percutaneous coronary angioplasty is the treatment of choice in acute myocardial infarction with ST elevation (STEMI), but thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) is also widely and successfully used. However, re-occlusion follows rt-PA treatment in up to 30% of patients within 1 year. Anti-t-PA antibodies, previously described in patients treated with rt-PA, could play a role in this event. In this paper we characterised anti-t-PA antibodies in patients with STEMI treated with rt-PA. We collected plasma samples from 30 STEMI patients (20 treated and 10 not treated with rt-PA) at baseline and 15, 30, 90 and 180 days after treatment, and from 40 healthy subjects, and used immunoenzymatic methods to detect anti-t-PA antibodies. An increase in the plasma titre of anti t-PA antibodies was observed 15 days (IgM, $p = 0.0001$) and 30 days (IgG, $p = 0.0001$) after rt-PA treatment. Six patients had a particularly high increase of anti t-PA IgG which bound to the catalytic domain of t-PA (two cases) or the kringle 2 domain (four cases) and were of IgG1 or IgG3 subclasses. Clinical follow-up after 1 year showed ischemic re-occlusion in four of these patients and in none of the other 14 treated patients**.** The infusion of rt-PA may induce the production of specific antibodies that can bind active sites of the t-PA molecule, thus potentially increasing thrombotic risk. The finding of ischemic complications in four out of six patients with high levels of anti-t-PA antibody further supports this view.

Incidence and prognosis of asymptomatic distal deep vein thrombosis in medical in patients: the IMPACT study

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Background: Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism, is the third cause of mortality. DVT of the lower limbs is the more frequent clinical manifestation of VTE and can involve proximal or distal veins (dDVT). dDVT is often asymptomatic and data about its incidence and prognosis are scanty, especially in high risk medical inpatients. Therefore, there is a lack of consensus on the value of detecting and treating them.
Aim: To prospectively evaluate incidence, characteristics and prognosis of asymptomatic isolated dDVT in an internal medical setting.
Study design: Consecutive patients hospitalized for acute medical illnesses, in whom VTE was not the admission diagnosis, underwent Doppler Ultrasound (US). Clinical evaluation of lower limbs, Ddimer (DD) measurement, and hereditary and transient VTE risk factors assessment were also performed. When a dDVT was found, US characteristics (number of dDVTs, distance from popliteal cavity, dDVT diameter and length) were recorded. For all patients with dDVT a standard 6-week treatment with therapeutic doses of low molecular weight heparin or fondaparinux was planned. Follow-up visits were scheduled at 1, 6, and 12 weeks.
Preliminary results: Until now 97 patients (45 males, 52 females), mean age 77 ± 14 (range 19–104) years, admitted to our internal medicine unit were enrolled. Eleven asymptomatic dDVTs were found (11.3%). A non statistically significant difference in the incidence of dDVT was found according to sex ($p = 0.093$) and age ($p = 0.159$). Clinical signs of DVT and difference in legs diameter were not related to dDVT. Immobilization was significantly associated to dDVT ($p = 0.024$). Finally, increased DD levels were not associated with dDVT.
Conclusions: We found a high incidence of clinically silent dDVTs in medical inpatients. Among risk factors, only immobilization is a strong risk factor for dDVT. The study is still ongoing and no prospective data are available yet.

Activation of coagulation in eosinophil-related inflammatory skin diseases

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Background: An increased risk of thrombosis has been described in patients with hypereosinophilic syndromes. It has been shown that eosinophils are a source of tissue factor (TF), the initiator of blood coagulation. TF is embodied within eosinophil granules and exposed during their activation. The aim of this study was to evaluate the local and systemic activation of coagulation in eosinophil-related skin diseases as compared to other inflammatory cutaneous disorders.
Methods: We studied 63 patients with bullous pemphigoid (BP), 20 with chronic urticaria (CU), 14 with atopic dermatitis (AD) and 6 with cutaneous drug reactions (CDR), as eosinophil-driven diseases, and 20 with psoriasis, 4 with dermatitis herpetiformis and 5 with primary cutaneous T-cell lymphoma, as non eosinophil related disorders, as well as 40 healthy controls. The markers of coagulation prothrombin fragment F1 + 2 and D-dimer were measured by ELISA in plasma of all subjects. TF was evaluated immunohistochemically in skin specimens from the patients and in 20 normal skin samples. We also performed in situ hybridization to evaluate TF m-RNA and immunofluorescence studies with laser scanning confocal microscopy to demonstrate the colocalization of TF with a classic eosinophil marker (CD 125).
Results: F1 + 2 and D-dimer plasma levels were higher in BP, CU, AD and CDR patients than in controls ($p = 0.0001$), whereas were normal in all the non eosinophil-driven conditions. As demonstrated

both by immunohistochemistry and in situ hybridization, TF was hyperexpressed only in skin specimens from the eosinophil-related diseases, mainly in BP. Colocalization experiments confirmed eosinophils as a source of TF.
Conclusions: The coagulation cascade is activated in association with skin expression of TF in BP and to a lesser extent in other eosinophil-mediated disorders but not in noneosinophil-driven conditions. The hypercoagulability may contribute to inflammation, tissue damage and possibly to thrombotic risk.

Natural history of cerebral vein thrombosis: a large multicenter study

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Background: Cerebral vein thrombosis (CVT) has been considered, until a few years ago, an uncommon disease with significant long-term morbidity and high mortality rate. New non-invasive diagnostic techniques have increased the frequency with which this disease is diagnosed. Only a few study with a relatively short follow up have evaluated the natural history of CVT.
Methods: In a multicenter study (19 centers) we evaluated the long term prognosis of a large cohort of patients with a first episode of CVT. Only patients with a objectively diagnosed CVT and with a follow up of at least 6 months were considered. Patients were contacted locally by each center. Information was collected in a computerized database. End points were recurrent CVT, other venous thromboembolic events (VTE) and mortality.
Results: 512 patients (73% female) with CVT were included. About 40% of patients were idiopathic. Patients were followed for a total follow up of 2,218 patients year. Mean follow up was 4.3 years (range 6 months, 21 years). At the end of follow up 12 patients died (2.3%). Almost all patients were treated with oral anticoagulation, the mean duration of treatment was 12 months, and the mean time of follow up after anticoagulation discontinuation was 3.2 years. CVT recurred in 17 patients (3.3%), and 32 patients (6.3%) had an other clinical manifestation of VTE for an overall incidence of recurrence of 22.1 events/1,000 patients year. Many events occurred after anticoagulation discontinuation for an incidence of recurrence in this group of 29.1 events/1,000 year patients.
Conclusions: In this large retrospective multicenter study with a very long follow up, the risk of CVT recurrence and of incidence of other venous thromboembolic events appear to be low. Further analyses will explore if some subgroups have a higher risk of recurrence.

Prevalence of arterial and venous thromboembolic events in diabetic patients with and without the metabolic syndrome: a cross sectional study

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Background: Metabolic syndrome (MS) is associated with an increased risk of cardiovascular events. Recent studies have found a higher prevalence of the MS in patients with idiopathic venous thromboembolic events (VTE) compared to controls suggesting a role of the MS in the pathogenesis of VTE. The presence of MS was shown to further increase the risk of arterial cardiovascular diseases (CVD) in diabetic patients. Conversely, there are no studies that have compared the risk of VTE in diabetic patients with and without the MS.
Methods: A cross sectional study comparing the prevalence of arterial cardiovascular events and VTE in diabetic patients with and without the MS was conducted
Results: Nine hundred and fifty three patients were included in the study; 85.7% of patients had MS. Patients with the MS had an increased prevalence of CVD as compared with those without (23.4 vs. 11.8%; OR 2.28, 95% CI 1.33, 3.95%; $p = 0.0024$) and the MS was an independent predictor of CVD in diabetic patients (OR 3.16, 95% CI 1.78, 5.59) after multiple logistic regression analysis. The prevalence of VTE was higher in patients with the MS in comparison to patients without the MS, but this association was not statistically significant (3.43 vs. 1.47%; OR 2.38, 95% CI 0.56, 10.10%).
Conclusion: Our study confirms the role of MS as an adjunctive cardiovascular risk factor in patients with diabetes and suggests that MS could be considered an adjunctive risk factor for VTE in these patients. Further studies are necessary to confirm these preliminary findings.

Seasonal and monthly variability in the incidence of venous thromboembolism: a systematic review and a meta-analysis of the literature

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Background: Many studies showed that the occurrence of cardiovascular and cerebrovascular events exhibits a seasonal and monthly variation. On the other hand, evidences on the existence of a seasonal and monthly variation in the incidence of venous thromboembolism (VTE) are more conflicting. Therefore, we conducted a systematic review and a meta-analysis of the literature to assess the presence of an infradian rhythm of this disease.
Methods: MEDLINE and EMBASE databases were searched up to January 2010. Monthly and seasonal variation in the incidence of VTE were analyzed.
Results: Seventeen studies for a total of about 35,000 patients were included in our systematic review. Twelve studies (23,469 patients) analyzed the seasonal variation and 10 studies (22,825 patients) the monthly variation of VTE. Our results showed a significantly increased incidence of VTE in winter in comparison to the other seasons (chi-square 146.04, $p < 0.001$). Thus, in winter there is a RR of VTE of 1.143 (99% CI [1.141, 1.144]) in comparison to the other seasons.
Furthermore, our analysis showed a significantly increased incidence of VTE in January in comparison to the other months (chi-square 232.57, $p < 0.001$). The RR of VTE in January is 1.194 (99% CI 1.186, 1.203), in comparison to the other months. Subgroup analyses including only idiopathic venous thromboembolic events confirmed the results of principal analyses.
Conclusions: Our data support the presence of a infradian pattern in the incidence of venous thromboembolic events, with a significantly higher risk in winter and in January. Future studies are needed to better clarify the mechanisms behind this pattern.

Post-partum onset of severe bleedings in a woman with disregarded classic type Ehlers–Danlos syndrome

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Introduction: Ehlers–Danlos syndrome (EDS) is a heterogeneous group of inheritable connective tissue disorders associated with variable inheritance patterns and biochemical defects and characterized by skin hyperextensibility, joint laxity, tissue fragility, easy bruising, and poor wound healing. The clinical manifestations can vary according to the sub-type of disease.
Case report: A.M, 60-years-old woman came to our attention for severe chronic vaginal bleeding. In pediatric age, tonsillectomy, adenoidectomy and dental avulsions were performed without bleeding complications. Since childhood, she had frequent and recurrent joint dislocations. At the age of 30 years, she had a vaginal delivery, complicated by extensive vaginal lacerations with hematoma formation and subsequent perineal wound dehiscence. Since then, hemorrhagic diathesis and skin bruising from minimal trauma appeared, associated to severe meno-metrorrhagia, which was completely absent before the childbirth. At the age of 58 years, she underwent hysterectomy, bilateral salpingectomy and anterior vaginoplasty because of the onset of hystero-cystocele. The operation was complicated by hematoma of the vaginal vault that was treated by surgical drainage and vaginal repair. Since this surgical operation, the patient had presented significant vaginal bleeding, more abundant after Valsalva maneuver. The coagulation parameters always proved normal and no lack of primary or secondary hemostasis was identified. Finally, diagnosis of Classical Type EDS was made, according to clinical criteria of Beighton, and it was then confirmed by biochemical demonstration of collagen type V deficiency.
Discussion: Classical EDS, unlike Vascular type EDS, is usually characterized by mild bleeding diathesis which generally occurs only during surgery, dental avulsion or childbirth. In the case described, even though the patient had presented skin hyperelasticity and joint hypermobility since she was born, she never experienced major bleeding diathesis until the age of 30 years. Instead, after delivery, very frequent and sometimes severe bleeding began. In literature have been described many cases of aggravation or first onset of hemorrhagic diathesis in asymptomatic patients affected by EDS, but in most of these cases an additional trigger can be identified (acquired deficiency of FVIII, vWF, thrombocytopenia). Conversely, the cases in which an acquired bleeding cause can't be identified are very rare. Early diagnosis of EDS is extremely important because, even though there are no specific therapy nowadays, there are many surgical recommendations which can effectively reduce the immediate and late surgical complications. In particular, in Obstetrics and Gynecology, is now possible to prevent maternal and neonatal delivery complications.

High prevalence of some components of the metabolic syndrome in patients with idiopathic venous thromboembolism

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Background: Although patients with idiopathic VTE are at higher than normal risk of asymptomatic atherosclerosis and of cardiovascular events, the impact of cardiovascular risk factors on VTE is poorly understood.
Objective: to assess the prevalence of the metabolic syndrome and of its components in patients with juvenile idiopathic VTE.
Methods: As many as 323 patients referred to our Thrombosis Ward for a recent (<6-months) juvenile idiopathic venous thromboembolism (VTE), were compared with 868 gender- and age-matched subjects, in whom a history of venous thrombosis had been excluded, referred during the same period time to our Ward. All had undergone a clinical assessment for smoking habits and for the presence of the components of the metabolic syndrome.
Results: The metabolic syndrome was detected in 76/323 cases (23.5%) and in 81/868 controls (9.3%) ($p < 0.001$; OR: 2.990; 95% CI: 2.119–4.217). Smoking was more common in patients with idiopathic VTE than in controls. In addition to the metabolic syndrome as a whole, its major individual determinants (arterial hypertension, impaired fasting glucose plasma levels, abdominal obesity, hypertriglyceridemia, low HDL-cholesterol) significantly correlated with idiopathic VTE (p always <0.05). The prevalence of thrombotic events was lower in females than in males ($p = 0.000$; OR: 2.217), the latter being most often hypertensives, smokers, hypertriglyceridemics, carriers of a metabolic syndrome and of impaired fasting glucose than females. In a multivariate analysis, arterial hypertension, impaired fasting glucose, abdominal obesity, and hypercholesterolemia independently predicted idiopathic venous events.
Conclusions: Both metabolic syndrome as a whole and its major components individually considered, independently predict juvenile idiopathic VTE.

Lack of change in insulin levels as a biological marker of PAI-1 lowering in GH-deficient adults on r-HGH replacement therapy

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Background: Adults with growth hormone deficiency (GHD) are at risk of vascular events. Abnormally high circulating levels of PAI-1 may contribute to such risk.
Aims: To prospectively evaluate whether changes in insulin and/or insulin-like growth factor-1 (IGF-1) levels, following recombinant human GH (r-HGH) replacement in GHD adults, explain changes in PAI-1. To measure PAI-1, t-PA, insulin and IGF-1, at baseline and after 6-month r-HGH replacement in 60 GHD adults.
Results: Insulin and IGF-1 level changes following r-HGH replacement did not show a significant intercorrelation. Percent change (%Δ) of PAI-1 and %Δ t-PA correlated with %Δ insulin (both $r = 0.41$, $p < 0.001$), but not with %Δ IGF-1. Insulin enhancements above the upper limit of the method variability (13%) occurred in 36 out of the 60 individuals (57%). PAI-1 and t-PA did not change in them. In contrast, in the 24 subjects with %Δ insulin $\leq$13%, PAI-1 ($p = 0.019$) and t-PA antigen ($p = 0.009$) decreased significantly. Analysis by quintiles of %Δ insulin was consistent with this finding. Fat body mass decreased independently of %Δ insulin. In multivariate regression analyses, %Δ insulin was the strongest correlate of %Δ PAI-1 and of %Δ t-PA ($\beta = 0.32$ and 0.39 respectively, $p < 0.05$).
Conclusions: Regardless of %Δ IGF-1, lack of change in insulin levels during r-HGH replacement, independently predicts PAI-1 and t-PA changes in adults with GHD.

Thromboembolic prophylaxis in patients with acute and/or chronic heart failure in a department of internal medicine

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Heart failure is a disease more common in internal medicine (as already shown by the study Themistocles), so that the DRG relative to it is in first place for number of admissions in the departments of Internal Medicine. Has long been recognized that the heart failure is characterized by abnormalities of blood flow, vascular wall components and whole blood. These changes induce a state of hypercoagulability and thus a high risk of thrombosis. Recently, inflammatory markers were identified, as IL-6 and PCR, which, in combination with other markers such as D-dimer or thrombin-thrombomodulin complex, lead to measurable and demonstrable hypercoagulability. A study published in Chest in 2006, on autopsy findings, reported that in 25% of patients hospitalized for heart failure, the cause of death was attributed to pulmonary embolism. Moreover, 75% of patients hospitalized in Internal Medicine for heart failure suffer from multi-organ or systemic diseases or are suffering from more diseases. These diseases are combined with thromboembolic risk factors commonly found as older than 40 years, obesity, bed rest, ejection fraction less than 20% and membership in NYHA class 3 or 4. The above results in a series of clinical problems summarized in the following three questions:

1. Which items are most relevant to the prognosis?
2. Which patients should be treated and for how long?
3. Which therapeutic approach to use?

From the above it is clear that all patients hospitalized for acute or chronic heart failure are considered at high risk of thromboembolic disease, and then was treated pharmacologically: in fact all the trials that related to thromboembolic prophylaxis showed a statistically significant reduction of events with the use of low molecular weight heparin (LMWH), even higher than unfractionated heparin and safer. The optimal duration of thromboprophylaxis is 10–12 days and is the average time of hospitalization of these patients. Was however noted that a certain number of patients experiencing thromboembolic events up to 110 days after admission (EXCLAIM study, with patients older than 75 years with a history of venous thromboembolism, acute and hypomobility). For this reason, patients were randomized to continue treatment with LMWH or placebo for 28 days. In this way has been demonstrated beyond doubt the efficacy of treatment in reducing the thromboembolic risk for the price of a modest increase in bleeding events. Subgroup analysis showed that in patients with heart failure, the effectiveness of prolonged prophylaxis is greater than the total population of the study. This means that high-risk situation thromboembolic benefit most from extended prophylaxis. In conclusion, the thromboembolic risk of patients hospitalized for heart failure in Internal Medicine is, by definition, high; this risk increases if there are additional risk factors (age, immobilization, comorbidities, etc.) far from rare in these patients. Therefore, further research aimed at highlighting a category of patients at increased risk between them (with instrumental examinations or diagnostic tests) is actually irrelevant to determining the appropriateness of thromboembolic prophylaxis: It must be practiced, unless strong contraindications, to all these patients.

Inherited thrombophilia and cerebral venous thrombosis in a child with nephrotic syndrome: a case report

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In October 2009 a 13-year-old boy visited our Emergency Room because of fever, productive cough and vomiting. His parents reported recurrent effusive otitis media treated with trans-tympanic drainage. Laboratory tests showed a relapse of nephrotic syndrome (third episode; the first in 2003 and the second in 2006). He was admitted at the Nephrology Unit and started prednisone. On day 2, the patient showed a rapidly progressive clinical deterioration and developed neurologic symptoms. A cranial magnetic resonance imaging (MRI) showed an extensive cerebral vein thrombosis (CVT) of transverse, straight and the posterior third of posterior sagittal sinuses. Cerebral damage in the left temporal cortex and a concomitant left otomastoiditis were also reported. The patient needed to be transferred to the Pediatric Intensive Care Unit, underwent endotracheal intubation and started treatment with intravenous unfractionated heparin. Antimicrobial therapy was also given, because of Pseudomonas aeruginosa at an ear swab. Despite disagreement of the hematologist of our Thrombosis Center, an attempt to selective lysis of thrombus during angiographic procedure was done by neuroradiologists, without success. Thereafter, systemic fibrinolysis (rt-PA 0.3 mg/kg/h for 6 h) was started with a prompt improvement of neurological symptoms. MRI angiography following systemic fibrinolysis showed a complete recanalization of all the previously involved venous sinuses. Endotracheal tube was removed and intravenous heparin was replaced with therapeutic doses of subcutaneous low-molecular-weight heparin. On day 10 the patient returned to the Nephrology Unit, the acute phase of nephrotic syndrome was over, and on day 12 he was discharged and referred to our Thrombosis Center for the continuation of treatment and thrombophilia screening. The latter showed quantitative (type I) protein S deficiency, one of the natural anticoagulant proteins [(protein S functional: 34% (normal range 79–183%), protein S antigen: 56% (normal range 75–177%)]. The same deficiency was diagnosed in the father, in 4 out of 5 brothers/sisters and in the paternal grandmother. According with the patient and his parents, we decided not to give oral anticoagulant therapy (warfarin) but to continue therapeutic doses of low-molecular-weight heparin. Although a single episode of deep vein thrombosis in the presence of inherited protein S deficiency indicates long-term anticoagulant therapy, because of the young age of the patient and the presence of circumstantial risk factors (otomastoidite and relapse of nephrotic syndrome) at the time of thrombosis, we decided to discontinue low-molecular-weight heparin after 6 months. In the future, antithrombotic prophylaxis with low-molecular-weight heparin is mandatory in case of infections, relapses of nephrotic syndrome and high risk situations (surgery, trauma, leg plastering, immobilization).

Conclusions: nephrotic syndrome in childhood is associated with a hypercoagulable state and thromboembolic diseases. CVT, a rare but life-threatening thrombotic manifestation, should be considered in patients with nephrotic syndrome and neurologic symptoms. Its early diagnosis and prompt anticoagulant treatment, other than treatment of nephrotic syndrome, are essential to ensure a good prognosis and a successful outcome. In our patient the presence of inherited thrombophilia, such as protein S deficiency, represented a strong additional risk factor for thrombosis.

Acquired haemophilia A: three different presentations of the same disease

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Acquired haemophilia A (AHA) is a rare autoimmune bleeding disease caused by the presence of autoantibodies directed against clotting factor VIII (FVIII), that partially or completely suppress FVIII procoagulant activity. It is characterized by severe and often life-threatening spontaneous or post-traumatic haemorrhages in patients without a prior history of bleeding disorder. Laboratory diagnosis includes isolated prolonged activated Partial Thromboplastin Time (aPTT) that is not corrected mixing patient and normal plasma, reduced FVIII levels and evidence of FVIII inhibitor in the serum using the Bethesda assay. The aim of management is to control haemorrhages as well as to eradicate FVIII inhibitor. The treatment of bleeding episodes depends on the titer of the FVIII inhibitor: patients with a low inhibitor titer (<5 BU/ml) can be treated with high doses of human FVIII concentrates and/or desmopressin, whereas patients with a higher titer are generally treated with by-passing agents, as activated prothrombin complex concentrates or activated recombinant factor VII (rFVIIa). Immunosuppressive drugs, mainly steroids and cyclophosphamide, alone or in combination, are used for eradication. We report three different clinical presentations of patients with AHA, successfully treated.

Case 1: On January 2010, 1 month after an uncomplicated vaginal delivery, a 33-year-old woman presented with prolonged menstrual bleedings and spontaneous ecchymoses. Laboratory tests revealed mild anemia, a prolonged aPTT (ratio 1.25, normal range 0.85–1.15) not corrected by normal plasma, a decreased FVIII activity (1%, normal range >50%) and the presence of FVIII inhibitor (30 BU/ml). A rFVIIa (90 μg/kg) bolus was administered and repeated after 3 h with cessation of bleeding. Despite prednisone (1 mg/kg/day) was immediately started, 2 months after cyclophosphamide (2 mg/kg/day) was added following the resumption of the haemorrhages and an increase of FVIII inhibitor levels (60 BU/ml). After 3 weeks of treatment the FVIII inhibitor disappeared and immunosuppressive therapy was tapered.

Case 2: On November 2009 a 63-year-old man presented with lower back pain, haematuria and left leg haematomas. Abdominal computed tomography scan showed the presence of left iliopsoas haematomas (14 × 16 cm) which dislocated ipsilateral ureter and revealed a renal neoplasm. Laboratory tests showed moderate anemia, a prolonged aPTT (ratio 2.31) not corrected adding normal plasma, a FVIII activity of 6% and a FVIII inhibitor titer of 200 BU/ml. Immunosuppressive therapy with prednisone 1 mg/kg/day was started and activated prothrombin complex was administered with a reduction of back pain and with an apparent cessation of bleeding (stable haemoglobin levels and haematomas dimensions at ultrasounds follow-up). Four weeks later FVIII inhibitor was 5 BU/ml. Eight weeks later the haematomas was healed and the inhibitor was not detected, activated prothrombin complex was stopped and steroid therapy began to be reduced.

Case 3: On November 2008 a 78-year-old man presented with gluteal haematomas immediately after an intramuscular NSAID injection for recurrent lumbar back pain. A previous haematomas of the left arm occurred 2 weeks before after a vaccination. The patient had a history of parzial gastrectomy for neoplasm. Laboratory tests showed severe anemia and a mild prolonged aPTT (ratio 1.21). The concentration of factor VIII was 5% and the titer of inhibitor was 8 BU/ml. Red blood cells transfusions were required due to anemia and the persistent haemorrhagic status. The patient was successfully treated with subcutaneous desmopressin therapy (0.3 μg/kg/day for 5 days, with FVIII activity increased to 48% after 1 h) and immunosuppressive therapy (prednisone 1 mg/kg/day). After 2 months of treatment the FVIII inhibitor disappeared and after 9 months prednisone was stopped. Investigations for conditions most frequently associated with AHA led to exclude malignant recurrence or autoimmune diseases.

Conclusions: In patients with a sudden bleeding diathesis AHA must be ruled out, as diagnostic delays or inadequate treatments are associated with high mortality rates. Diagnosis should be considered in any patient who presents with unusual and unprovoked haemorrhages and an isolated prolonged aPTT not corrected adding normal plasma and not related to lupus anticoagulant antibodies. When AHA is diagnosed, the possible coexistence of an underlying disease (postpartum, malignancies, autoimmune diseases) responsible for this immunologic complication should be suspected and intensively searched for, but about half of the cases are apparently idiopathic.

Pregnancy or thrombosis in liver transplantation: that is the question?

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Case report: We report a case of two successful pregnancies in a patient with a prior diagnosis of essential thrombocytemia with secondary portal vein thrombosis and portal hypertension. A 19-year-old woman affected by undefined thrombocytosis (platelets count 650,000 mmc^{-1}) since 1990 was admitted to our department in May 1995 for severe abdominal pain and hepatosplenomegaly. History was negative for smoking or autoimmune disorders and laboratoristic exams showed a slight increase of leukocytes, erythrocytes, hemoglobin, transaminases, bilirubin, and decreased PT. Portal hypertension secondary to inferior vena cava thrombosis was confirmed by Doppler evaluation that revealed the presence of a complete splenoportal occlusion. Ultrasonographic assessment showed also severe hepatosplenomegaly and presence of ascites. Thrombolytic therapy with urokinase was started within 3 h from the admission. She underwent to diuretic and beta-blocking therapy, with gradual remission of the presenting clinical features and progressive reperfusion of the vessel. Recanalization of the portal axis was documented by ultrasound and subsequent MRI with contrast medium. Bone marrow aspiration and biopsy resulted highly suggestive for essential thrombocytemia (ET), and the cause of the clinical epiphenomena were referred to this chronic myeloproliferative syndrome. A course of interferon-alpha, according to literature, was started and subsequent follow-ups showed a stability of clinical and laboratoristic data. Two years later, the patient was admitted again for the occurrence of ascites, subcutaneous venous collaterals and acute bleeding of oesophageal varices. She

underwent to endoscopic band ligation in the emergency department. CT scan and subsequent MRI with arteriographic evaluation of splancnic arteries and veins were highly suggestive of Budd-Chiari syndrome with subsequent portal and splancnic hypertension. Imaging suggested the presence of hypervascular nodules in the liver, narrowing of the vena cava and left hepatic vein occlusion. Liver biopsy showed areas of nodular hyperplasia. Oncocarbide was started, and patient was put in list for liver transplantation. Orthotopic liver transplantation was performed in November 1998, with a regular clinical course. Serial clinical and laboratoristic controls were in the normal range. In the following years patient continued her therapy with interferon-alpha. Despite her clinical history, she had two uncomplicated pregnancies after withdrawal of oncocarbide. Currently both the patient and her children are doing well.

Discussion: Essential thrombocythemia (ET) is an acquired myeloproliferative disorder with a prolonged clinical course and a near-normal life expectancy [1, 2]. It is characterized by a sustained elevation of platelet number with an increased risk for thrombosis and hemorrhage. Whereas most of the patients with ET are asymptomatic, some may experience vasomotor, thrombotic, or hemorrhagic disturbances. Arterial and venous thromboses, as well as platelet-mediated transient occlusions of the microcirculation and bleeding, represent the main risks for ET patients. This pathology has been described to complicate pregnancy with recurrent abortions, intrauterine death, and fetal growth retardation due to placental infarctions [3]. However, pregnants affected by ET have often a favourable outcome. An increased risk for thrombosis is always present among pregnants, and it can be increased in the ET subgroup. On the other hand, hemorrhagic risk is low, except in patients with acquired Von Willebrand's disease [4]. Many pregnancies in ET have a successful outcome with minimal therapy. Cytoreductive treatment should preferably be avoided, especially during the first trimester [5]. Moreover, none of these has a product license for use in pregnancy. Interferon use has been associated with a higher live birth rate, whereas ASA treatment didn't affect any major outcome [2]. IFN-α does not cross the placental barrier, and represents a potential therapeutic solution when platelet reduction is required for high risk patients. Reducing the platelet count using IFN-α might improve the chance of a successful outcome in subsequent pregnancies [5].

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Oxidative stress and platelet activation in subjects with moderate hyperhomocysteinemia due to MTHFR 677 C → T polymorphism

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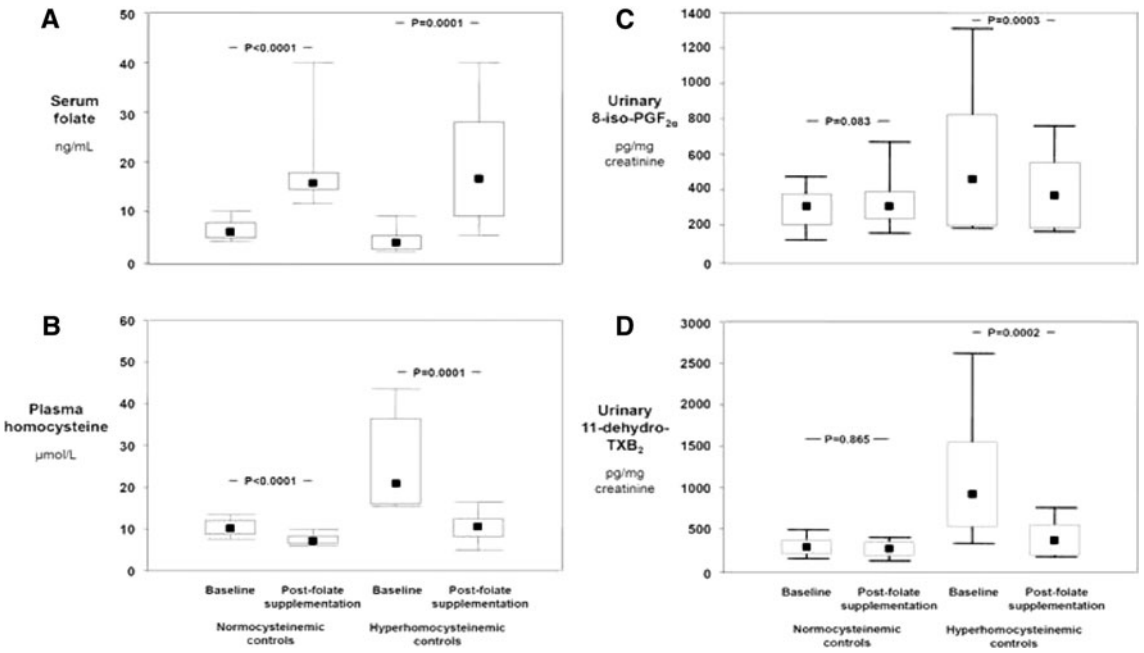
Background: Mild to moderate elevation of plasma total homocysteine (tHcy) is an independent risk factor for cardiovascular disease in both men and women. Randomized clinical trials of the effects of tHcy lowering with folic acid in patients with and without vascular disease showed a 18–27% reduction in plasma tHcy, but no statistically significant change in the risk of major cardiovascular events. However, baseline levels of tHcy and folic acid were in the normal range in these trials and the presence of MTHFR 677 C → T polymorphism was not investigated. We speculated that increased oxidant stress associated with mild hyperhomocysteinemia would induce enhanced generation of the F2-isoprostane 8-iso-prostaglandin(PG)$F_{2\alpha}$ and other biologically active isoeicosanoids and that these compounds would in turn contribute to persistent platelet activation in this setting.

Methods: In order to investigate the short-term effects of tHcy lowering on urinary 8-iso-$PGF_{2\alpha}$ and 11-dehydro-thromboxane $(TX)B_2$ excretion, folic acid supplementation was performed in the 23 hyperhomocysteinemic carriers of the polymorphism and in 18 controls without hyperhomocysteinemia, who were given 5 mg/d folic acid for 8 weeks.

Results: In the 23 hyperhomocysteinemic individuals carrying the MTHFR 677 C → T polymorphism, folic acid supplementation caused a statistically significant increase in serum folate levels [from 4.4 ± 2.5 to 20.0 ± 13.9 ng/mL ($P = 0.0001$)]. These changes were associated with statistically significant reductions in plasma tHcy [from 25.6 ± 11.8 to 10.8 ± 3.9 μmol/L ($P = 0.0001$)], as well as in urinary 8-iso-$PGF_{2\alpha}$ and 11-dehydro-TXB_2 excretion [from 593 ± 429 to 414 ± 249 pg/mg creatinine ($P = 0.0003$), and from 1,171 ± 814 to 760 ± 425 pg/mg creatinine ($P = 0.0002$), respectively].

Conversely, in the 18 control subjects no statistical significant changes were recorded in either urinary 8-iso-$PGF_{2\alpha}$ or 11-dehydro-TXB_2 excretion [from 301 ± 116 to 268 ± 98 pg/mg creatinine ($P = 0.083$), and from 302 ± 125 to 352 ± 195 pg/mg creatinine ($P = 0.865$), respectively] despite a statistically significant increase in serum folate levels [from 6.6 ± 3.0 to 18.1 ± 8.3 ng/mL ($P < 0.0001$)] and a significant reduction in plasma tHcy [from 10.3 ± 2.0 to 7.5 ± 1.2 μmol/L ($P < 0.0001$)].

Discussion: The baseline level of Hcy, resulting from the variable interaction between the genotype and the folate content in the diet, is a major determinant of the extent of inhibition of the biochemical indexes of lipid peroxidation and platelet activation. Thus, inclusion of subjects with Hcy in the normal range in clinical trials is likely to



dilute the benefit of folate supplementation and might explain the largely negative results of these trials. Our findings identified subjects with the MTHFR 677 C → T polymorphism, Hcy levels >15 µmol/L and low folate status, as the ideal candidates for trials designed to test the efficacy of folate supplementation on clinical endpoints.

Soluble CD40L in Mediterranean Spotted Fever: relation to oxidative stress and platelet activation

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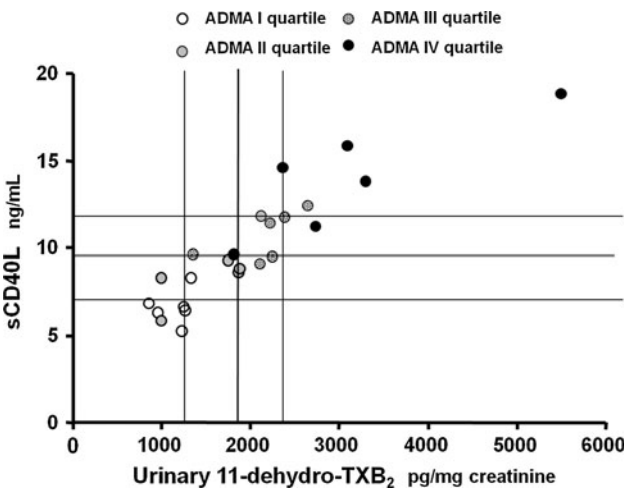
This paper is dedicated to the memory of Serafino Mansueto, whose research allowed us to achieve significant progress in understanding the clinical and pathogenic aspects of rickettsial infections.

Introduction: In the present study, we tested the hypothesis that *Rickettsia conorii* infection increased in vivo lipid peroxidation with generation of 8-iso-prostaglandin (PG)$F_{2\alpha}$ and other biologically active iso-eicosanoids and that these compounds would in turn contribute to endothelial dysfunction and platelet activation in the setting of Mediterranean Spotted Fever (MSF). Moreover, consequent augmented release of soluble CD40 ligand (sCD40L) by activated platelets would be able to promote further inflammation and endothelial activation.

Materials and methods: We measured in 24 patients with MSF, in the acute stage and at follow-up (after day 21), plasma C-reactive protein (CRP), sCD40L, asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, as a marker of endothelial dysfunction, and the urinary excretion rates of 8-iso-$PGF_{2\alpha}$ and 11-dehydro-thromboxane (TX)B_2. Twenty healthy subjects were also studied as controls.

Results: Plasma levels of CRP, sCD40L, ADMA and urinary metabolites excretion were significantly higher in MSF patients in the acute phase than at recovery ($p < 0.0001$), or compared with healthy controls ($p < 0.0001$). When concentrations of ADMA of the entire sample at baseline were divided into quartiles, the excretion rate of 11-dehydro-TXB_2 as well as plasma sCD40L significantly increased from the first to the fourth quartile (by Kruskal–Wallis test; H 15.9; $p < 0.001$ and H 16.7; $p < 0.001$, respectively). Moreover, there was a direct correlation between time-related changes in plasma sCD40L and changes in 11-dehydro-TXB_2 excretion (Rho 0.47, $p = 0.033$) or in 8-iso-$PGF_{2\alpha}$ (Rho 0.45, $p = 0.028$) throughout the observation period in the 24 patients.

Conclusions: Thus, our study supports the idea that systemic inflammation, platelet activation and endothelial dysfunction are common features of MSF, with several feed-forward mechanisms sustaining enhanced sCD40L shedding and amplifying the relationship between inflammation and platelet activation.



The pain of a young men

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Introduction: Malformations of the inferior vena cava (IVC) are relatively uncommon in general population, with a reported prevalence of 0.07–8.7%. However, in patients with lower-extremity deep venous thrombosis (DVT) the incidence of these anomalies appears to be greater. It is necessary to suspect in young persons with DVT but without clinical or historical risk factors (coagulopathy, trauma, surgery, some medication, cancer, chronic diseases cardiovascular or respiratory).
Case report: A man 34-year-old got in Emergency Room showing slight fever, limping gait, low back pain radiating to the right thigh and to the lower abdomen, edema and pain at the legs. Examination results for chest and heart were normal, abdomen and legs were tender to palpation. Homans' sign was positive. DVT was suspected. A Doppler Ultrasound revealed thrombosis of both iliac and both femoral veins. Normal ECG, lumbo-sacral back bone and chest radiographs, room air oxygen saturation, but high value of D-dimer (1,360 ng/ml), leukocytosis (21.230 mmc^{-1}, 88% neutrophils), patient seriously suffering. Contrast-enhanced CT scans of the thorax, abdomen and pelvis excluded pulmonary embolism and revealed hypoplasia of the IVC. The patient was referred to our Medical Division for more accurate investigations and suitable therapy. Laboratory investigations included blood cell count, liver and renal function tests, plasma lipid, urinalysis, coagulation studies (prothrombin time, INR, partial thromboplastin time, fibrinogen, protein S, protein C, antithrombin III, antiphospholipid antibody, factor V Leiden, omocistein), inflammation and autoimmunity studies (VES, PCR, RA test, ANA, anti-ds DNA, anti-ENA). These tests yielded normal results except for high value of PCR (12.70 mg/dl). Negative tests for the infectious or neoplastic associated diseases. Magnetic Resonance Angiography demonstrated "interruption of IVC in subhepatic tract with paravertebral, azygos and hemiazigos veins collateral circles. Ectatic bilateral ilio-femoral veins with massive thrombosis. Thrombosis in the subdiaphragmatic azygos". The adopted therapy was anticoagulation with Enoxaparin 8.000 U.I. every 12 h, and further an oral dose of 4 mg of Acenocumarol, with target INR of 2.5 (range 2.0–3.0). General discomfort, slight fever, abdominal pain, legs pain, low back pain persisted along some days. Analgesic therapy took no place. An antibiotic therapy (Levofloxacin 500 mg/day i.v.) together with Prednisone 20 mg^2/day i.v. produced a slight amelioration of symptoms and PCR value lowering, but persisting slight fever and discomfort. Adjunctive therapy with Ceftriaxone 2 g/day i.v. produced disappearing of fever and the patient general health improvement. The patient was dismissed from the Hospital with anticoagulant therapy (Acenocumarol in oral dose/day according to range INR 2.0–3.0) and follow up at 6 month. At follow up the Doppler Ultrasound showed a persistent thrombosis of femoral veins mostly supported by superficial veins. Magnetic Resonance Angiography showed a marked reduction of ilio-femoral veins enlargement, probably explanation of partial recovery of clinical situation. No other variations were recorded.
Discussion: The congenital inferior vena cava malformation represents a predisposition to deep-venous thrombosis in spite of well-developed collateral circulation and must be suspected in young patients with DVT, without triggering factors or defects of coagulation predisposing to thrombophilia. Low back pain is a symptom caused by overloaded and enlarged venous structures with potential spinal nerves compression. In our patient this pain radiating to thigh and lower abdomen was the initial symptom but also the more persistent. No association with infectious diseases was ascertained, but antibiotic therapy improved the symptoms. The long-life anticoagulant therapy is under discussion: not recommended—because the patient had no other convincing and permanent risk factors for thrombosis; recommended—because the anticoagulant therapy indefinitely reduces the risk of recurrent events, including life-threatening or fatal pulmonary embolism. On the basis of registered follow-up indefinitely anticoagulant therapy we decided for our patient.

The effect of subclinical hypothyroidism on vitamin K stability and sensitivity

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Introduction: The effect of vitamin K antagonists (VKAs) is potentiated in overt hyperthyroidism and attenuated in overt hypothyroidism. Data on subclinical thyroid dysfunction and anticoagulation are lacking, in particular on subclinical hypothyroidism. The aim of this study is to explore the effect of subclinical hypothyroidism on VKAs sensitivity and stability.
Methods: Among 996 patients followed at the Anticoagulation Clinic of the Department of Clinical Medicine of the University Hospital of Varese, Italy, patients with subclinical hypothyroidism occurring during VKAs treatment, who were treated with L-thyroxine and achieved an euthyroid state still on VKAs, were included in the study. VKAs sensitivity was calculated as median weekly dosage in mg. VKAs stability was measured as time spent in the therapeutic range (TTR). Weekly dosage and TTR were calculated during 6 and 12 weeks before objective diagnosis of subclinical hypothyroidism, during the first 6 and 12 weeks after L-thyroxine treatment was began, and during the first 6 and 12 weeks after objective euthyroidism has been reached.
Results: Twenty-six patients (8 males; median age 72.1 years) became subclinical hypothyroid during VKAs treatment. Half of the patients had a Hashimoto's thyroiditis and half an iatrogenic cause of subclinical hypothyroidism. Main indication for anticoagulation was atrial fibrillation and two third of the patients had a target INR of 2.5. During a 6 weeks time interval, mean weekly dosage was 29.9 mg [$\pm$12.1 standard deviation (SD)] in subclinical hypothyroidism and 26.8 mg [($\pm$12.1 SD) in euthyroidism ($P < 0.05$); median TTR was 61% (33–91 interquartile range [IR]) in subclinical hypothyroidism and 81% (51–100 IR) in euthyroidism (median difference = 13.5%; 95.2% confidence interval -8.5 to 30.5%). During a 12 weeks time interval, mean weekly dosage was 30.8 mg ($\pm$12.4 SD) in hypothyroidism and 27.0 mg ($\pm$12.7 SD) in euthyroidism ($P < 0.05$); median TTR was 54% (36–82 IR) in subclinical hypothyroidism and 65% (55–79 IR) in euthyroidism.
Conclusions: Data of our pilot study suggest that subclinical hypothyroidism may affect both VKAs stability and sensitivity. Given the high prevalence of thyroid disorders in the anticoagulated population, larger studies are urgently warranted.

The effect of thyroid autoantibodies on warfarin stability

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Introduction: An influence of overt thyroid dysfunction on the sensitivity to oral vitamin K antagonists has been described. Data on the effect of thyroid dysfunction on warfarin stability are currently sparse and not conclusive. To our knowledge, no data have ever been published on the interaction between thyroid antibodies and warfarin. The aim this study was therefore to test the hypothesis of an effect of thyroid autoantibodies on warfarin stability.
Methods: A retrospective inception cohort study was carried out in a population of 100 consecutive adult outpatients with provoked or unprovoked deep venous thrombosis followed at the Anticoagulation Clinic of the Department of Clinical Medicine of the University Hospital of Varese, Italy, and treated with warfarin to achieve therapeutic range of the international normalized ratio (INR) between 2.0 and 3.0. Thyroid autoantibodies, i.e. anti-thyroid peroxidase (AbTPO), anti-thyroglobulin (AbTg), and anti-TSH receptor antibodies (AbTR), were measured in all patients. We compared warfarin stability in patients with elevated antibodies levels to those with antibodies within the normal range. Stability of oral anticoagulation was evaluated during a period of 3 months, before or after the date of antibody measurement, and presented as the percentage of time in range and the standard deviation (SD) of the mean INR values.
Results: Overall, 36 patients, 12 with elevated antibody levels (5 women; mean age 71.0 years) and 24 with normal antibody levels (10 women; mean age 66.5 years) with available INR values were analysed. Eight patients had elevated AbTPO levels (one also elevated TrAb), four elevated AbTg, and none isolated elevated TrAb. Percentage of time in range was slightly lower, although not significantly, in patients with elevated antibodies (61.9 vs. 70.1%, $p = 0.16$), whereas the SD of the INR values was higher in patients with elevated antibodies (0.83 vs. 0.65, $p = 0.05$), suggesting that thyroid autoantibodies may be responsible for the instability of the INR control.
Conclusions: The presence of thyroid autoantibodies may be associated with an increased instability of the INR control and, therefore, deserves further investigation in prospective clinical trials.

Pulmonary embolism in patient with deep venous thrombosis and past AMI

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Name: R.S.
Age: 50
Medical history positive for cardiovascular illnesses and diabetes mellitus.
Heavy smoker, great eater and drinker, regular alvo and diuresis.
For long dyslipidemia and altered liver enzymes.
Six years ago inferior AMI. Obese.
Last June trauma and gluteal abscess from a car accident.
A month ago thrombophlebitis of the right lower limb, treated with EBPM.
Ten days agoappearance of dispnoea. Three days ago greater dispnoea. The patient reaches the Emergency Department.
He is intensely dyspneic, tachycardiac, pale, sweaty, with right lower limb edema.
O.E. thorax: whistles and hisses through the whole lung.
EGA: hypoxia and hypocapnia. Respiratory alkalosis.
ECG: Sinus tachycardia. Past inferior AMI.
Cardiac enzymes in norm, D-dimero 5517. Glycemia 217 mg/dl.
Venous Ecocolour-doppler: incompressible right popliteal vessel with a thrombotic ipo-isohecogen formation inside it.
TC Chest: right pulmonary artery filling defect, with morphological lengthening which extends to the principal ramifications of the inferior and superior lobes. Presence of left pulmonary artery filling defect of the superior and inferior lobes.
Practiced therapy: calcic nadroparina 0.9 ml × 2; metiprednisolone 20 mg × 2; levofloxacina 500 mg ev; omeprazolo 20 mg; O_2; insulin then metformina. To follow warfarin according to INR.
On the third day the patient shows a reduction in dispnoea and tachicardia, arterial pressure in the normal range.
EO thorax: negative. After some days a clean improvement of the clinical picture is reported and the patient is discharged from the hospital following from the diagnosis of Pulmonary Embolism. Thrombosis of the right poplitea. Diabetes Mellitus type 2. Obesity. Tabacism. Past AMI.
Therapy at discharge :valsartan, metformina, bisoprololo, rosuvastatina, warfarin.

Managing the double haemorragic and thromboembolic risk in patients with acquired haemophilia

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Introduction: Most patients with acquired haemophilia (AH) are in the elderly age and carry thromboembolic risk factors or history of vascular disease, requiring antithrombotic therapy.
Case reports: We report three cases of AH patients in whom the coexistence of bleeding and cardiovascular risk influenced clinical choices. A 80-year-old man, with a history of coronary artery disease on oral anticoagulation because of atrial fibrillation and ventricular tachiarrhythmias, was diagnosed with AH because of severe post-traumatic haematomas, in spite of cessation of warfarin. Because of cardiovascular risk, a severe iliopsoas haematoma and massive haemothorax were treated with rFVIIa at lower doses (60 μg/kg every 4 h for 5 days). Inhibitor disappeared within 6 weeks of steroid treatment. This patient suddenly died probably because of arrhythmic complications. A 59-year-old man with a history of multiple myeloma and a recently onset bleeding tendency leading to diagnose AH, showed a severe haematoma of the arm, treated with desmopressin and rFVIII concentrate. During eradication treatment, unstable angina occurred, treated only with anti-ischemic drugs, as the coagulation abnormality led to deferral of coronary angiography and antithrombotic treatment. Inhibitor was negative after 8 weeks. The patient undergone coronary angioplasty and stenting, and started low-dose aspirin with frequent clinical and laboratory follow-up. AH was diagnosed in a 70-year-old man with previous myocardial infarction on antiplatelet treatment, evidence of a kidney mass and a history of recurrent bleeding (melena,

hematuria; hematomas). Clopidogrel was stopped and a single 90 μg/kg rFVIIa infusion controlled a post-traumatic gluteal haematoma. During eradication treatment, when FVIII levels became >30%, prophylaxis with low-molecular weight heparin was introduced.

Conclusions: Management of AH patients requires an accurate evaluation of coexisting cardiovascular risk factors/disease. In particular, inhibitor eradication should be obtained as early as possible in order to minimize bleeding risk and to adopt antithrombotic strategies when needed.

Clinical Epidemiology

News on thrombocytopenia and thrombocytosis from the study of sardinian genetic isolates

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The availability of clinical, laboratory and genetic data on 12,517 inhabitants of 10 villages in a secluded area of Sardinia (Ogliastra) allowed us to address the theme of the prevalence of thrombocytopenia in general population, a matter that has never been extensively investigated. High density SNPs analysis and genealogical records demonstrated a high genetic differentiation among such villages. We observed a platelet count lower than 150×10^9 L^{-1} in 3.2% of females and 4.8% of males, with a mean value of 3.9% in the entire population. Thrombocytopenia was mild ($100–150 \times 10^9$ platelets/L), asymptomatic and not associated with other cytopenias or overt disorders in most cases. Its prevalence was quite different in different villages, with values ranging from 1.5 to 6.8%. Interestingly, it was negatively correlated with the prevalence of a mild form of thrombocytosis, which ranged from 0.9 to 4.5%. The analysis of platelet counts in different villages revealed that their distribution curves were roughly Gaussian, and that they were shifted to the left in the populations with the highest prevalence of thrombocytopenia and the lowest of thrombocytosis, while they were shifted to the right in those with opposite characteristics. Analysis of platelet counts in different classes of age revealed that platelet number progressively decreased during ageing. As a consequence, thrombocytopenia was nearly absent in young people and its prevalence regularly increased during the lifetime. The opposite occurred for thrombocytosis. Given the high genetic differentiation among Ogliastra villages with "high" and "low" platelet counts and the substantial heritability of this quantitative trait (54%), we concluded that the propensity to present mild and transient thrombocytosis in the youth and to acquire mild thrombocytopenia during ageing are new genetic traits. Further investigation is required to ascertain whether this conclusion applies also to populations other than those of Ogliastra.

Prevalence of celiac disease during Ehlers-Danlos syndrome

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The Ehlers–Danlos syndrome (EDS) is a clinically variable and genetically heterogeneous group of inherited connective tissue disorders, characterized by varying degrees of tissue fragility of the skin, ligaments, blood vessels and internal organs and articular hypermobility. According to the Villefranche nosology of 1997, EDS is classified in six subtypes, based on clinical characteristics, mode of inheritance, and biochemical and molecular findings. We described in a recent paper regarding a pilot study performed on 21 patients affected by hypermobility type (HT) of EDS some gastrointestinal problems. The problems highlighted were: recurrent/chronic dyspepsia/gastritis (66.7%), gastro-esophageal reflux (57.1%), and manifestations of irritable bowel disease, including recurrent unexplained abdominal pain (61.9%) and constipation/diarrhea (33.3%), abdominal hernias (4.8%). Three patients underwent double contrast colon study because of recurrent abdominal pain and X-ray revealed the dolichocolon presence. One patient had colonic diverticula. Reviewing our data base that actually include 30 EDS patients we noted that three patients had coeliac disease too and that they were treated with glutin free diet. Two of these three women were sisters. Three other women showed signs and symptoms suggestive for celiac disease. For this reason all three women were underwent to serological test for antibody antitransglutaminase (IgG- and IgA-tTG) and antigliadin (IgG-, IgA-AGA). Our result showed: one patient with high values of anti tTG-IgA (36 U.A./ml; n.v. > 16 U.A.), high value of IgG-AGA (62 U.A./ml.;n.v. > 50 U.A./ml), the second one with high levels of IgA-tTG (30.60 U.A./ml; n.v. > 11 U.A./ml), high levels of IgA-AGA (93.30 U.A. n.v. > 30) while the third patient showed a high level of IgG-AGA (<100 U.A./ml; n.v. > 50 U.A./ml). The results obtained by serological tests together with clinical signs and symptoms lead us to add these three woman to the previous three already knwn to be affected by celiac disease. Currently, therefore, of the 30 patients with EDS, 6 are also affected by celiac disease. All these 6 patients are woman, rancing age from 20 to 50 years, mean age 34.50 ± 4.41 years whit hypermobility type of EDS. It is well know that celiac disease has, in general population a prevalence of 1.0–1.5%. Finland has one of the highest recorded rates, with a prevalence of 2%. Our EDS patient's population show a prevalence of celiac disease much higher than reported in the general population. In fact, our data show a prevalence of 20%. This is the first time someone describes this phenomenon. We do not known the current state of knowledge, provide any explanation. However, it seems important to add to the already rich clinical picture of EDS too surprising epidemiological aspect.

Impact of chronic versus episodic migraine on disability and health-related quality of life in Italy

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Objective: To compare the impact of chronic migraine (CM) to episodic migraine (EM) on headache-related disability and health-related quality of life (HRQoL) in Italy.
Methods: Cross-sectional data were collected via web-based survey. Respondents were classified as having CM $\geq$ 15 headache days/month or EM $\leq$ 14 headache days/month. Demographic and clinical characteristics were assessed. Migraine Disability Assessment Questionnaire (MIDAS) and Migraine-specific Quality of Life Questionnaire v2.1 (MSQ) assessed headache-related disability and HRQoL, respectively. Higher MIDAS scores indicate greater headache-related disability, whereas MSQ domain scores (Role Functioning-Preventive, Role Functioning-Restrictive, Emotional Functioning) range 0–100, where higher scores demonstrate better functioning. Analysis of variance (ANOVA) models compared HRQoL/disability by migraine group.
Results: Of 7,692 Italian panelists contacted, study sample comprised 976 completers who met migraine criteria; 6% CM ($n = 55$), 94% EM ($n = 921$). Demographic features were similar in this predominantly female (CM = 91%; EM = 81%) midlife (mean age 37) sample. CM reported more severe headache pain (100 vs. 78%) and more comorbid health conditions than EM. CM had significantly higher MIDAS scores, indicating greater disability (CM: mean $\pm$ SD 86.7 $\pm$ 62.1 vs. EM: 19.2 $\pm$ 18.9, $p < 0.0001$). Lower MSQ scores for CM than EM indicated worse HRQoL and negative impact on overall functioning (restrictive: 43.9 $\pm$ 18.3 vs. 54.0 $\pm$ 21.1, $p < 0.001$; preventive: 56.5 $\pm$ 23.2 vs. 67.7 $\pm$ 21.8, $p < 0.001$; emotional: 52.2 $\pm$ 22.6 vs. 69.4 $\pm$ 23.7, $p < 0.0001$).
Conclusions: CM was associated with greater headache related-disability and worse HRQoL compared to EM, supporting the substantial impact of CM on Italian sufferers. Adequate treatment to reduce frequency of migraines may positively impact patient ability to work, participate in family and social activities, and reduce disability.
Study supported by: Allergan Inc.

Table 1 Mean (SD) of MIDAS, MSQv2.1 by Migraine group (total), Italy

	CM ($n = 55$)	EM ($n = 921$)	Total sample ($n = 976$)	*P* value*
MIDAS score	86.7 (62.1)	19.2 (18.9)	23.0 (28.2)	<0.0001
MSQv2.1 scores				
Role functioning preventive	56.5 (23.2)	67.7 (21.8)	67.1 (22.1)	0.0002
Role functioning restrictive	43.9 (18.3)	54.0 (21.2)	53.4 (21.2)	0.0006
Emotional functioning	52.5 (22.6)	69.4 (23.7)	68.4 (23.9)	<0.0001

* *P* value from 2-sample *t*-test comparing CM and EM groups

High prevalence of undiagnosed peripheral artery disease and clinical significance of ankle brachial index to predict adverse outcome in patients hospitalized in an internal medicine ward

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Peripheral artery disease (PAD) is frequently underdiagnosed in clinical practice, leading to a lack of opportunity to detect subjects at a high risk for cardiovascular events and death. The measurement of ankle-brachial index (ABI) represents a noninvasive, objective way to diagnose PAD and to predict adverse outcome in patients with both clinical and subclinical PAD or with previous coronary and cerebrovascular events. We investigated the prevalence of unrecognised PAD in patients hospitalized in an Internal Medicine Ward and prospectively evaluated the outcome of these patients with respect to ABI values. We measured ABI, by hand-held 8-MHz Doppler probe (Stereodop 448-S Ultrasomed) in 707 patients (46% men), aged 50 years or older (mean age 74.7 $\pm$ 10.23 years). Patients were categorized according to ABI values as normal ($\geq$0.90 and $\leq$1.40) or pathologic (<0.90 or >1.40). All causes and cardiovascular deaths were prospectively evaluated during a follow-up period of at least 1 year. Only 8% of the total population were diagnosed of having a symptomatic PAD while we recorded a prevalence of 29% of patients with a low ABI value (<0.90); older age, male sex, smoking habit, hypertension, previous CHD and stroke, significantly increase the risk of having an ABI < 0.90. An high ABI value (>1.40) were detected in 8% of the patients, while 63% of the patients had a normal ABI value. Patients with ABI < 0.90 and ABI > 1.40 showed a significantly higher all-cause mortality risk at the univariate analysis ($p = 0.05$), while only high ABI independently predicts all-cause mortality ($p = 0.019$), together with age, increased creatinine and systolic BP and reduced total cholesterol values and concomitant neoplasm or cardiovascular events. A simple ABI measurement revealed a large number of subjects with unrecognized PAD among those hospitalized in an Internal Medicine ward and may independently predict all-cause mortality risk.

Prevalence of metabolic syndrome (MS), carotid lesions and fatty liver in the San Lazzaro metabolic study (SLMS): an interim analysis of a population-based survey

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Aim: To determine the prevalence of the MS, which has worldwide diffusion of 20–30% in adults, and its association with carotid lesions and fatty liver in the general population of San Lazzaro di Savena, a stable population 30,000 inhabitants Emilia Romagna's town located

in a geographic area with high prevalence of obesity, cardiovascular and cerebral diseases [1].
Methods: A sample of the adut population (age 20–85) was randomly selected using as strata sex, age and education level (elementary, intermediate, high, university) as a surrogate of the economic level from the Ufficio Anagrafe of San Lazzaro di Savena. After population sensibilization on the study by media and general practitioners, starting from October 2008 subjects were recruited by letter and phone call and invited to present on appointment at the local Health District. During the visit each subject underwent to: anthropometric measurements; blood pressure evaluation; administration of a questionnaire on lifestyle habits (semiquantitative measures of nutritional and alcohol intake and of physical activity) and family/personal history of diseases; blood and urine sample for biochemical tests; carotid and liver ultrasound for evaluation of intima-media thickness (IMT, Mannheim consensus, 2006) and of hepatic steatosis [2]. Presence of MS was defined according to NCEP-III [3].
Results: The final sample consisted of 2,611 subjects (99% confidence, 2.5% precision) and we report here on the results of an interim analysis on the first 238 subjects recruited into the study. The response rate was 92% (238/258 contacted) with a F/M ratio of 1.03 and a balanced distribution of subjects in all seven age strata as well as in four educational levels. The overall prevalence of the MS was 30%, fatty liver was found in 37.4% of the subjects and carotid IMT mean value measured was 0.93 ± 0.4 mm (range in european general population 0.63–0.84, increasing by age and number of cardiovascular risk factors).
Conclusions: If these ad interim data will be confirmed on the whole sample of the study we may conclude that: (a) in San Lazzaro di Savena the prevalence of MS is higher with respect to other areas of Emilia Romagna, and (b) the large proportion of subjects with fatty liver and high IMT values may be a determinant for the high risk of developing cardiovascular and liver diseases in this population.
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Gastroenterology and Hepatology

Hepatic decompensation after transarterial chemoembolization for hepatocellular carcinoma: predictive value of MELD and MELD-Na

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Background: Transarterial chemoembolization (TACE) is the method of choice in patients unsuitable for surgery and ablative treatment. However, its severe side effects continue to limit its use and the role of prognostic variables able to predict clinical decompensation post-TACE is controversial. On the other hand, MELD has been already associated with survival in HCC patients undergoing TACE.
Aim: To evaluate the prognostic value of MELD and its modified form (MELD-Na) on the occurrence of hepatic decompensation after TACE.
Methods: Thirty-five consecutive HCC patients undergoing 65 sessions of TACE were included in the study. Before TACE was carried out, MELD and MELD-Na were evaluated. After treatment patients underwent clinical, hematologic and ultrasonographic assessments in order to identify the occurrence of hepatic decompensation (ascites or encephalopathy) or post-embolization syndrome (fever, nausea and right upper quadrant pain). One month after TACE a CT scan was performed to assess tumor response.
Results: Acute hepatic decompensation occurred in 15 out of 65 treatments (23%), with 7 cases of ascites, 8 cases of encephalopathy and none irreversible complications. Post-embolization syndrome was observed after 21 TACE (32%). Approximately, a complete response was obtained in 20% of sessions, partial response in 54%, no response in 26%. Mean MELD/MELD-Na scores were 10.7 ±4.4 and 11.6 ±5.7, respectively, in all patients enrolled. Patients who developed hepatic decompensation had higher pre-TACE MELD ($P = 0.009$), and MELD-Na ($P = 0.015$) scores compared with those without complications. No differences were found as concerning the development of post-embolization syndrome and the response to treatment.
Conclusion: High level of MELD and MELD-Na are predictive of hepatic decompensation after TACE and may help in selecting patients suitable for treatment. However, larger studies are needed to better establish the prognostic value of these scoring systems in HCC patients undergoing TACE.

Ursodeoxycholic acid and simvastatin in patients with nonalcoholic fatty liver disease and metabolic syndrome

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Background and aims: Nonalcoholic fatty liver disease (NAFLD) is a common condition in Metabolic Syndrome (MS). No effective medical therapy is available for all patients with NASH. Ursodeoxycholic acid (UDCA) has been suggested to be of benefit based on open label clinical studies. Many patients with NAFLD and MS have hyperlipidemia, their elevated serum aminotransferase levels make physicians wary about prescribing statins. However, the benefits NAFLD and MS patients from statin therapy would most likely outweigh any theoretical risk of liver injury. Combination of Ursodeoxycholic acid (UDCA) and Simvastatin is perspective for the treatment dyslipidemia and NAFLD.
The aim was to assess the efficacy of UDCA and Simvastatin in MS patients with NAFLD and dyslipidemia.
Methods: We examined 80 MS patients, 46 male (mean age 48 ± 13 years; BMI = 33.4 ± 4.9 kg/m^2; waist circumference = 113.2 ± 11.1 cm) and 34 female (mean age 45 ± 10 years; BMI = 33.2 ± 3.9 kg/m^2; waist circumference = 93.4 ± 9.2 cm) with clinical and ultrasound features proven NAFLD and laboratory proven dyslipidemia. Liver biopsy was performed in 68 patients with elevated liver function tests and showed histological findings of non-alcoholic steatohepatitis (NASH). All patients received UDCA at the

dose of 600 mg/day and simvastatin at the dose of 40 mg/day over a period of 6 months.
Results: In the NASH group the mean serum AST levels decreased from 82.2 ± 26.4 to 38. ± 11.2 IU/l, serum ALT levels from 95.9 ± 24.4 to 31.9 ± 16.3 IU/l at the end of the treatment period ($p < 0.0003$). After 4 weeks we had no one case of increasing AST or ALT levels in the UDCA and simvastatin therapy; 95.5% patients ($n = 65/68$) with NASH reached normal liver function tests. All 80 patients decreased total cholesterol levels from 248 ± 38.6 to 171 ± 23.3 mg/dl, triglycerides from 263.7 ± 121.6 to 162 ± 49 mg/dl, LDL from 150.9 ± 49.7 to 92.8 ± 24 mg/dl, increased HDL from 40 ± 14 to 48.2 ± 10 mg/dl at the end of the study ($p < 0.000006$).
Conclusions: A significant improvement in the levels of aminotransferases and lipids was obtained with combination of UDCA and Simvastatin in NAFLD patients. These results reveal that UDCA and Simvastatin may be considered an effective treatment in patients with NASH and MS. Thus, lipid-lowering agents and UDCA should be prescribed for patients with NAFLD unless contraindicated, with careful monitoring of transaminase levels during therapy.

Sustained virological response reduces insulin resistance in patients with genotype 1 chronic hepatitis C

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Background and aims: Chronic hepatitis C (CHC) has been associated with an increased prevalence of type II diabetes and insulin resistance (IR). Recently, a genotype-specific association between HCV genotype 1 and IR has been proposed. However, it remains unclear whether this is a causal relationship. The present study investigated the association of sustained virologic response (SVR) with IR in patients with genotype 1 Chronic Hepatitis C.
Methods: Thirty-five treatment-naïve non-diabetic patients with genotype 1 CHC were enrolled received combination therapy with peginterferon alfa-2a plus ribavirin for 48 weeks. IR was measured at week 0, 12, 24, or 48, and post-treatment week 12 using the homeostasis model for assessment of IR (HOMA-IR). Clinical evaluation by a single pathologist included age, gender, race, body mass index (BMI), HCV viral load, alanine aminotransferase, gamma-glutamyl transpeptidase, total cholesterol, HDL, LDL-cholesterol, triglycerides, and baseline liver biopsy for steatosis, METAVIR inflammatory grade, and fibrosis stage. IR was considered categorically, setting a threshold of HOMA-IR > 3. Change in HOMA-IR post-therapy was considered as a continuous variable; HOMA-IR data were log-transformed for analysis as a continuous variable.
Results: Matched pre- and 12 week post HOMA-IR measurements were available from 35 non-diabetic patients with genotype 1 CHC. SVR rates were 60% in genotype 1 CHC patients. SVR was associated with a reduction in prevalence of IR ($P < 0.001$). This was independent of changes in BMI, alanine aminotransferase, gamma-glutamyl transpeptidase, and lipid levels. HOMA-IR did not change in non-responders.
Conclusions: SVR was associated with a reduction in HOMA-IR in patients with genotype 1 CHC. The results suggest that HCV genotype 1 can play a causal role in the development of IR, which may be reversed by viral eradication.

On-treatment serum HBsAg decline during telbivudine therapy in naive chronic hepatitis B: case report

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Background: HBsAg clearance is the ultimate goal of antiviral treatment in Chronic Hepatitis B (CHB). Telbivudine (LdT) is a new nucleoside analogue with antiviral activity specific for HBV. The long-term data on the drug efficacy, obtained from the GLOBE trial and the 2,303 extension study, showed rapid and powerful antiviral efficacy. In this case report, in agreement with data in literature, LdT showed rapid and efficacy reduction of HBV-DNA levels, persistent (>2 years) PCR negativity, ALT normalization, and HBsAg serum levels decline. Furthermore LdT did not demonstrate side effects and nephrotoxicity.
Aim: To demonstrate the efficacy and safety of LdT to induce reduction of ALT serum levels, to promote a rapid HBV-DNA PCR negativization and a progressive reduction of quantitative HBsAg.
Methods: 52-year-old Caucasian patient with naive chronic hepatitis HBV-related (CHB) HBeAg negative. In 2004 patient has been diagnosed as HBV positive with increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels (1.5–2 × ULN). In December 2007 patient attended our Hepatology Unity for the first time. A complete clinical and virological evaluation was performed and then long-term suppressive treatment by Telbivudine (LdT) at the standard dose of 600 mg daily was started. On-treatment monitoring: ALT every month, HBV-DNA and HBsAg serum levels (Abbott Architect®, Abbott Laboratories) at week 12, 24 and 48 were performed. Follow-up monitoring: monthly ALT serum assay, HBV-DNA and HBsAg index every 3 months.
Results: Rapid virological suppression and HBV-DNA PCR negativity were achieved (Fig. 1). Persistent PCR HBV-DNA negativity and progressive decline of HBsAg were recorded at week 72 (Fig. 1).
Conclusions: Long-term suppressive treatment by Telbivudine has a rapid and powerful antiviral efficacy. Pharmakodynamic and kinetics of Ldt suggest that it may represent a viable therapeutic option for patients with CHB and it should now be granted a large space in the therapeutic landscape.

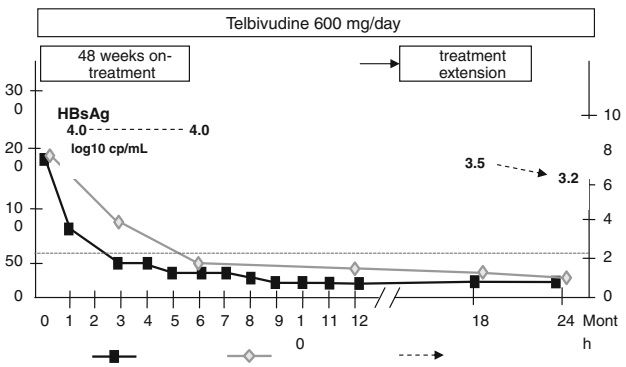

Fig. 1 Virological and biochemical course on Telbivudine to date

On-treatment serum HBsAg level is predictive of sustained off-treatment virologic response to telbivudine in HBsAg-negative chronic hepatitis B patients

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Background: Effective management of chronic hepatitis B infection is still very challenging, despite of decades of clinical research. Telbivudine is one of the most frequently used antiviral drug at the current stage, but its long-term effectiveness, particularly off-treatment, is still unclear.
Objectives: To assess on-treatment HBsAg kinetics in patients treated with telbivudine for 2 years, and to predict sustained virologic response (SR) 2 years off-treatment. STUDY DESIGN: Serum HBV DNA/HBsAg levels were assessed from 12 HBeAg negative patients treated with telbivudine 600 mg/day for 104 weeks, at baseline, weeks 24, 52 and 104, as well as during off-treatment follow-up. HBsAg serum levels were quantified by the Architect® HBsAg assay (Abbott Laboratories); HBV-DNA was assessed by COBAS Amplicor® (Roche Diagnostics).
Results: on-treatment HBsAg levels <2 log(10)IU/ml at week 104 were highly predictive of SR (i.e., HBV DNA < 300 copies/ml or undetectable, ALT normalization) at 2 years off-treatment (positive predictive value [PPV], 93%; negative predictive value [NPV], 100%). HBsAg levels consistently declined from baseline only in patients achieving SR during 2 years off-treatment. At weeks 24 and 52, HBsAg decline rate was a better predictor of off-treatment response than HBV-DNA decline rate. On-treatment HBsAg decline rates >0.8 and >1 log(10)IU/ml at weeks 24 and 52 were predictive of SR (PPV, 75%; NPV, 86% at week 24; PPV, 75%; NPV, 86% at week 52).
Conclusions: Serum HBsAg levels < 2 log(10)IU/ml at week 104 on-treatment are highly predictive of SR to telbivudine at 2 years off-treatment. On-treatment HBsAg decline rate at weeks 24 and 52 from baseline were also more predictive of SR than HBV-DNA decline rate.

Combination therapy with pegylated interferon and ribavirin determines a decrease in squamous cell carcinoma antigen (SCCA)-immunoglobulin m (IgM) complex (SCCA-IgM IC) serum levels in patients with HCV-related liver cirrhosis

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Background: Aberrant squamous cell carcinoma antigen (SCCA) expression is an early event in hepatocarcinogenesis, and increasing serum levels of SCCA variants IgM immune complexes (SCCA-IgM IC) have been found in cirrhotic patients who develop hepatocellular carcinoma (HCC). SCCA-IgM can also be detectable at low percentages in patients with chronic hepatitis. About 30% of patients with chronic hepatitis develop a progressive liver disease and one of the most intriguing issues is the detection of non-invasive markers for fibrosis stage and disease progression.
Aims: To determine if patients with compensated cirrhosis treated with peg-interferon and ribavirin, responders to treatment, show a reduction of fibrosis and serum levels of SCCA-IgM complexes.
Methods: We longitudinally evaluated a cohort of cirrhotic patients with hepatitis C virus infection (HCV) who underwent pegylated interferon (PEG-IFN) and ribavirin treatment. SCCA-IgM IC levels were assessed in the sera of 13 cirrhotic patients with HCV (8 males and 5 females; median age 58 years) before, at the end, at 6-month and 1-year of follow-up after treatment with Peg-IFN and ribavirin. ELISA assay (Hepa-IC XG003 XEPTAGEN) was used to determine the presence of SCCA-IgM complexes. SCCA-IgM IC serum levels (arbitrary units/mL, AU/mL) were evaluated according to treatment outcome: sustained virological response (SVR) versus non-response (NR).
Results: Overall, 6 patients obtained a SVR to antiviral therapy (46%). There was no significant difference in baseline SCCA-IgM IC serum levels between SVR and NR patients. When compared to baseline (252.2 AU/mL), SVR patients showed a significant decrease in median SCCA-IgM IC serum levels at the end of treatment (156.8 AU/mL, $P = 0.013$) and at both 6-month (76.8 AU/mL, $P < 0.001$) and 1-year follow-up (42.4 AU/mL, $P < 0.001$), while no significant modification was observed in NR patients.
Conclusions: In patients with HCV-related liver cirrhosis, successful antiviral therapy is associated with a significant decrease in SCCA-IC serum levels. Because of the pathophysiological correlation between SCCA and liver carcinogenesis, it is hypothesized that in patients with liver cirrhosis, SVR may be accompanied by a decreased proliferative stimulation.

A comparative study of terlipressin and albumin for type-1 hepatorenal syndrome (HRS) in patients with cirrhosis and spontaneous bacterial peritonitis (SBP) vs. cirrhosis alone

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Background and aims: Hepatorenal syndrome (HRS) is the development of renal failure in patients with advanced chronic liver disease, occasionally fulminant hepatitis, who have portal hypertension and ascites. Estimates indicate that at least 40% of patients with cirrhosis and ascites will develop HRS during the natural history of their disease. Relevant studies include those implicating the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and the role of renal prostaglandins (PGs). Strong associations have been reported between spontaneous bacterial peritonitis (SBP) and HRS and the use of vasopressin analogues with volume expanders in the management and prevention of HRS. Despite some encouraging studies of new pharmacological therapies, the development of HRS in people with cirrhosis predict a poor prognosis because renal failure is usually irreversible unless liver transplantation is performed. Patients with renal failure and active bacterial infections (without septic shock) are currently considered as having type-1 HRS according to the new diagnostic criteria reported in 2007.

Methods: Twenty-one patients with cirrhosis and serum creatinin >2.5 mg/dL diagnosed between 2009 and 2010 were included in the study. Patients were classified into 2 groups according to the precipitating factor of HRS found at diagnosis. Ten patients developed HRS induced by SBP (group 1) and 11 patients, neither had SBP at admission to the hospital nor developed SBP during development of HRS (group 2). Patients receive terlipressin (1–2 mg/4 h iv) and albumin (1 g/kg followed by 20–40 g/day). The end points of the study were improvement of renal function and survival at 3 months. Improvement of renal function was defined as a decrease in serum creatinin to a value <1.5 mg/dl (complete response).
Results: Both groups were similar with respect to renal function at enrolment. However, the impairment in MELD score was more marked in group 2 versus group 1 (32 ± 6 vs. 24 ± 6 points; respectively, $p < 0.004$). Reversal of HRS occurred in 7/10 patients (70%) in group 1 compared to only 4/11 patients (36%) in group 2 ($p = 0.012$). Independent predictive factors of response to therapy were baseline serum bilirubin, and SBP precipitating factor for HRS. There were significant differences between group 1 and group 2 in terms overall survival at 60 days 54 versus 23%, respectively; ($p = 0.042$). However, survival at 3 months was not significantly different between the two groups. Reversal of HRS was associated with a prolonged survival (median survival 147 days) versus 13 days in patients with no improvement of renal function ($p < 0.001$). Independent predictive factors of survival were baseline MELD score and response to therapy. There were no significant differences between the two groups with respect to the overall frequency of side effects.
Conclusion: Non-selective V1 vasopressin agonist (Terlipressin) has similar vasoconstrictor potency to ornipressin but a lower incidence of ischemic complications. Inactive by itself, it is coverted into a biologically active form (lysine–vasopressin) by the action of tissue endopeptidases and exopeptidases. Due to its longer half-life (2–10 h) compared to ornipressin, it may be administered as a bolus. It has lower incidence of adverse ischemic effects. The plasma volume expanders are indicated for the correction of abnormal haemodynamic parameters in HRS and albumin is useful for plasma volume expansion and cardiac output maintenance. In our study Terlipressin and albumin were significantly more effective for HRS type-1 and spontaneous bacterial peritonitis than HRS type-1 without active bacterial infections.

Safety and efficacy of low dosage of fondaparinux in cirrhotic patients with portal vein thrombosis

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Background and aim: Portal Vein Thrombosis (PVT) is a well known risk of liver cirrhosis (LC) despite the longer coagulation times. Patients with advanced liver disease have an increased risk of bleeding because of coagulopathy and portal hypertension. The aim of our study was to assess the efficacy and safety of low dosage of fondaparinux in patients with advanced LC and with PVT.
Methods: We screened for hepatocellular carcinoma 26 cirrhotic patients by ultrasound doppler. Twelve patients presented PVT without hepatocellular carcinoma. Three patients with portal cavernoma were excluded from the study. Only six patients with recent PVT entered the study and, after informed consent, received 5 mg/day of fondaparinux subcutaneously for at least 4 months. An endoscopic examination and Computed Tomography (CT) was performed in all the patients. A follow up by ultrasound with Doppler examination was done every month while CT was done at fourth month.
Results: The aetiology of cirrhosis was: HCV infection in three patients, HBV in two and alcoholic in one; four patients were in class A Child Pugh and two in class B. Four patients presented class F1/F2 esophageal varices, two patients with F3 class and the evidence of red cherry spots were previous submitted to band legation. PVT was occluding in one patients and incomplete in five patients. Extension to portal branches was noted in two patients while extension to splenic and superior mesenteric vein was disclosed respectively in two and one patients. Complete recanalization of PVT occurred in four patients ($4/6 = 66\%$) (one of whom with a total PVT), while partial recanalization was seen in two patients (33%). No significant side effects were noted in all the patients.
Conclusion: In cirrhotic patients without hepatocellular carcinoma and with PVT anti-thromboembolic therapy with low dosage of fondaparinux (5 mg/day subcutaneously) seems to be safe and effective as treatment. Further studies, on more patients, will be needed to confirm our results.

A prospective and multicentre study upon gluten-free diet compliance score

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Background: A dietary interview performed by expert personnel is the current gold standard to check whether patients with coeliac disease (CD) follow a strict gluten-free diet (GFD). However, a straightforward and objective method to perform such a dietary interview is currently lacking. We previously developed a questionnaire based on four fast and simple questions, that can be administered even by non expert personnel [1].
Aims: To prospectively verify the efficiency of our questionnaire.
Methods: The questionnaire results on five level score (0–4). From March 2008 to April 2010, the questionnaire was administered to 93 CD patients (74 females, mean age 39.6 ± 13.8 years) on a GFD (median 22 months, 25th–75th percentile 15–64, range 11–254), who were undergoing their first routine clinical re-evaluation. To avoid any influence, both on patient and doctor, the questionnarie was administered by an operator, who was not aware of the results of the clinical re-evaluation. The score obtained was compared with persistence of both villous atrophy (VA) and endomysial antibodies (EMA) tested on monkey oesophagus.
Results: The questionnaire was fulfilled in less than 1 min. The table shows that patients scoring the lowest results were more frequent among the patients with persistence of VA (Fisher's exact, $p < 0.0001$; test for trend, $p < 0.0001$). They were also more frequent among patients with persistence of positive EMA but statistical significance was not reached (Fisher's exact, $p = 0.052$; test for trend, $p =$ ns). A patient scoring 0 died because of refractory CD.

Conclusions: Our questionnaire is a reliable and simple method to verify compliance to a GFD.

Score	0–1	2	3–4
Pts with persistent VA on a GFD: *n* (%)	6/13 (46)	1/4 (25)	3/76 (4)
Pts with positive EMA on a GFD: *n* (%)	7/13 (54)	0/4 (0)	19/76 (25)

Reference

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Italian translation and validation of "coealic disease questionnaire" in adult patients with coeliac disease on a gluten-free diet

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Introduction: To confirm the reliability and validity of the Coeliac Disease Questionnaire (CDQ) [1] in its Italian version. Cultural adaptation of such an instrument to assess quality of life of patients with coeliac disease is a major challenge.
Methods: The instrument was translated according to the translation algorithm and was administered to 119 patients (55 at home and 64 in the out-patient clinic).
Results: Completeness was optimal. Item internal consistency was satisfied for 100 and 97% of patients for the specific and generic part, respectively. Discriminant validity was satisfied for all the patients. Cronbach's α coefficient was >70% in all cases. While assessing the responsiveness (external discriminating validity) of CDQ, we found lower scores (worse emotion and gastrointestinal worries) in females. The general CDQ was higher in patients reporting subjective well being. The worry score was better in patients with a longer history of coeliac disease, in those without symptoms and in patients living alone. The emotion score was higher for males and patients reporting subjective well being. Finally, the social score was higher in patients found to be affected by coeliac disease diagnosed through serological screening of another disease.
Conclusion: The Italian translation of CDQ sounds natural, is easy to understand and reduces possible cultural biases to a minimum. A field test gave results comparable to the original validation, supporting the use of CDQ in cross-national surveys.
Reference

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Enteropathy in patients with common variable immunodeficiency

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Background: Patients affected by common variable immunodeficiency (CVI) complain very often of gastrointestinal symptoms and a villous atrophy is frequently found in them. Although this can be due to Giardia lamblia and other microbial pathogens, the ethiology of the flat mucosa is not clear in patients without intestinal infections. Some case reports suggest an association between CVI and coeliac disease (CD).
Aims: To investigate the causes of enteropathy in patients with CVI.
Patients: 10 patients (F 2, age 40.4 $\pm$ 9.5 years) affected by CVI and subtotal villous atrophy were studied by means of duodenal biopsy before and after a gluten-free diet (GFD), HLA typing, and coeliac antibodies.
Results: Histological response to a GFD (2 pts) or positive IgA endomysial antibodies (1 pt) allowed a diagnosis of CD in three patients. In the remaining seven patients the lack of an histological response to a GFD (7 pts) or HLA typing (3 pts) excluded the diagnosis of CD. One of these patients was affected by recurrent giardiasis.
Conclusions: Although we found CD in 33% of the patients with CVI without intestinal infections, the flat mucosa is not gluten-sensitive in the majority of these patients and needs further investigations. The diagnosis of CD must be based on the demonstration of a flat duodenal biopsy improving while on a GFD; HLA can have a relevant diagnostic role while coeliac antibodies have no role in most of the patients.

Multimodal personalized strategy on allocation of patients with HCC to TACE

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Background: BCLC (Barcelona Clinic Liver Cancer) represents today the gold standard for allocation of patients with Hepatocellular Carcinoma (HCC) to treatment. According to BCLC, Trans-Arterial-Chemo-Embolization (TACE) is reserved to intermediate stage (or B stage), but several concerns to this approach are emerged. Aim of this study is to evaluate the effect of a multimodal personalized strategy on allocation of patients to TACE.
Methods: All patients with newly diagnosed HCC were jointly managed in a multidisciplinary team including hepatologist, oncologist, radiologist, pathologist, interventional radiologist, interventional ecographist, surgeon and transplant surgeon. Each patient was discussed collectively and each therapeutic procedure competed against

others, in a different manner respect to BCLC-approach. This patients were compared with a retrospective cohort of patients treated with TACE between 2003 and 2007.

Results: From November 2008 to May 2010, 326 patients were consecutively managed in our multidisciplinary group. 89 (27%) of them were allocated to TACE as a first treatment. Compared with historical cohort (Table), patients allocated according to multimodal personalized strategy were treated at lower score of CLIP. Notabily, less than 50% of our patients were classified as BCLC-B. 55 (61,7%) patients allocated according to multimodal personalized strategy received one or more treatments than TACE.

Conclusions: When multimodal personalized strategy is employed, TACE appears as an integrate tool than a single approach, and not seem limited to the intermediate stage of BCLC classification.

	Group 2003–2007 ($n = 97$)	Group 2008–2010 ($n = 89$)	p value
Mean age (years)	68 ± 9	65 ± 9	NS
Male sex (%)	73.2	83	NS
Child A/B/C (%)	60.4/33.3/6.3	73.3/25.6/1.2	NS
MELD (score)	10 ± 3	11 ± 3	NS
BCLC A/B/C/D (%)	43.3/37.1/17.5/2.1	38.4/48.8/ 11.6/1.2	NS
CLIP 0/1/2/3/4–6 (%)	12.8/35.1/28.7/ 11.7/11.8	19.7/50/27.3/ 3/0	0.004
Single nodule (%)	30.9	33.3	NS
2–3 Nodules (%)	36.2	43.2	NS
≥4 Nodules (%)	33.0	23.5	NS
Portal vein thrombosis (%)	11.6	7.6	NS
Combined treatments (%)	47.4	61.7	NS

Altered paraoxonase expression in patients with genetic haemochromatosis

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Background: Genetic haemochromatosis is a common heritable disorder characterized by the progressive accumulation of iron. The liver is usually the main target of the iron overload-related tissue damage. Iron-induced oxidative stress is known to play a pivotal role in the onset and development of liver disease during haemochromatosis. Serum paraoxonase (PON1) is a pleiotropic, antioxidant enzyme synthesized by the liver. Previous studies have suggested a role of PON1 in the regulation of oxidative stress and fibrosis in chronic liver disease.

Materials and methods: Serum PON1 activities were measured in 74 subjects with genetic haemochromatosis (81.1% males; mean age 46.5 ± 13.6 years). Most of them were carriers of classical HFE genotypes (78.4%). None of them were clinically cirrhotic at enrolment. For 19 subjects tissue samples from liver biopsy were available for immunostaining with antibodies against PON1, as well as PON2 and PON3.

Results: As compared with samples from normal liver, hemochromatosis liver samples showed a clearly increased staining with all PON antibodies, basically in the perivenular areas that are known to be primarily involved in iron accumulation. As regards to PON1 activity levels in serum, after exclusion of 20 patients who were already under phlebotomy therapy at enrolment, we found that ferritin level was a significant predictor of PON1 activities with negative coefficients in linear regression models adjusted for sex, age, and HDL concentration (standardized beta coefficient −0.525, $P = 0.005$, −0.337, $P = 0.051$ and −0.422, $P = 0.024$ for paraoxonase, TBB-Lase, and DEPCyMCase activity, respectively).

Conclusions: Our results suggest that PON expression is altered in subjects with genetic haemochromatosis and that in such patients iron overload may be associated with an impairment of PON1 serum activities.

Acute drug-induced hepatitis due to "natural product" used for weight loss

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Aesthetic canons conveyed by mass media induce particularly in female gender the introjection of a canon of beauty consisting in having the body as lean as possible, achieved sometimes to the danger of health. This shape of beauty is pursued not only by increasing physical activity and with an often unbalanced diet, but also by making an unjustified use of drugs and products marketed as "natural." The Authors describe a case of severe acute hepatitis in a young woman who was taking a weight loss "natural product".

Case report: A 22-year-old woman from Ghana, living in Italy since 5 years, presented to Emergency Room with a seven-day history of nausea, epigastric and right upper quadrant pain. She reported pale stools and dark urine. There was no history of foreign travel. She denied recent or regular use of drugs and she did not drink alcohol. On physical examination there were a mild overweight (BMI 26 kg/m^2), scleral icterus, right upper quadrant and epigastric tenderness but no palpable organomegaly. Initial blood work showed a serum total bilirubin measuring 11 mg/dL (0.2–1.0), direct bilirubin 9 mg/dL (0.0–0.3), Aspartate Aminotransferase (AST) 3,150 UI/L (10–30), Alanine Aminotransferase (ALT) 2,949 UI/L (10–36), Lactate Dehydrogenase (LDH) 1,041 UI/L (140–480), normal haematological, electrolytes, renal function, amylase, C-reactive protein and international normalized ratio of prothrombin. Abdominal ultrasound revealed only mild hepatomegaly with hepatic steatosis and minimal perihepatic and pericholecystic fluid. During hospitalization she received intravenous hydration and proton-pump inhibitor drug. Extensive viral serology and auto-immune antibodies serology were negative. Gamma glutamyl-transferase (GGT) and alkaline phosphatase (ALP) plasma levels were 78 UI/L (5–36) and 139 UI/L (32–104), respectively. On further questioning, the patient volunteered that 2 weeks before admission she had started, in order to lose weight, a

herbal product containing wakame, opuntia, glucomannan, green tea and banaba extracts; taurine and chromium picolinate; ruscus extracts. These substances would promote adipose tissue catabolism, limit fat absorption, help control hunger (especially the craving for sweets) and have diuretic action. This "natural" product, available in various formulations and to be taken with main meals and before sleeping, is currently purchased over the internet, by phone and in many Health & Beauty Store and in some drug store. Because on the 6th day of hospitalization, serum enzyme tests were as follows: AST 3,133 UI/L, ALT 2,819 UI/L, LDH 953 UI/L, total bilirubin 18.8 mg/dL, direct bilirubin 15.3 mg/dL, the patient was moved to a hepatologic referral Center with facilities for liver transplantation. Here liver biopsy was performed, that revealed severe acute hepatitis with punctiform necrosis indicative of toxic-pharmacological damage. Intravenous methylprednisolone 40 mg daily was started with prompt improvement of serum bilirubin and liver enzyme tests. Nine months later, while the patient was taking prednisone 2.5 mg daily, ALT, bilirubin and GGT values were 50 UI/L, 1.0 mg/dL and 16 UI/L, respectively.

Conclusions: This case report highlights:

1. The importance of inquiring into alternative medicine and herbal remedies in cases of acute hepatitis;
2. That although there are many reports in literature of hepatotoxicity induced by herbal products to lose weight (by direct toxicity or for the presence of contaminants), the awareness in the general population and health-care personnel remains poor;
3. The need of more knowledge of individual products and greater responsibility of companies that market them in indicating the possible side effects;
4. The need of more rigorous studies both before and after marketing of the product, in addition to the sporadic reports of suspected adverse reactions.

Gastric-protection in patients in therapy with antiplatelet drugs

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The association of PPI (Protonic Pomp Inhibitor) and Thienopyridine is often used to reduce the risk of gastrointestinal bleeding built in the anti-aggregating therapy, even if several studies explain that the PPI can cause a reduction of anti-aggregating effect of clopidogrel, probably because the PPI inhibit the CYP2C19, an hepatic P450 enzyme which converts clopidogrel in its active form. Nevertheless the TRITON-TIMI 38 study with 136,08 patients shows that there are not more thrombotic events in patients in therapy with prasugrel or clopidogrel in association with PPI than in patients treated only with the antiplatelet drugs. In any case a Controlled and Randomized Clinical Trial (CRCT) is necessary. Currently the data don't prove the reduction of clopidogrel effect so we think the doctors can administrate this association, if necessary. In fact there is a high risk of ischemic events in patients suffered from coronary disease, above all the patients over 75 years with renal insufficiency and in therapy with several drugs. Nevertheless the same patients in therapy with antiplatelet or anticoagulants drugs have a high risk of bleeding too. Furthermore there is a close correlation between bleeding and ischemic events, because the haemorrhage causes the suspension of antiaggragant/anticoagulant drugs and the blood loss reduces the oxygenation of tissue with an increased risk of ischemic damage. The risk factors of haemorrhage can be divided in two classes:

1. Unchangeable: age, sex, race, renal insufficiency
2. Editable: anemia, choice of antiplatelet therapy, choise of gastroprotective therapy

The "good clinical practicum" shows that the increase of the haemorrhagic risk in therapy with ASA (75-300 mg) is low (O.R. 1,3), except for patients with history of gastropathy (Ulcer, IBD) or chronic use of FANS or steroids. But the risk of bleeding with the association ASA + tienopiridin/heparin or antiplatelet + anticoagulant is higher, so in these cases it's useful to start a gastroprotective therapy (the most effective is the therapy with PPI, 20 mg/day).

Delayed puberty in a boy with abdominal pain

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Luca, 16 years old, weight 31 kg, height 139 cm: in this way came to our observation, 3 years ago, in June 2007, this young boy with a clinical history "greater" than him, began at age of 13 when he had frequent bloody diarrhea with mucus or pus, so he practiced blood-chemical tests that showed: thrombocytosis (>1,000,000 mm^{-3}), neutrophilic leukocytosis, increased indices of inflammation (SER, CRP, fibrinogen) and iron deficiency anemia (Hb 6.86 g/dl). In addition to the low weight-height development, performed hormone assays showing low levels of testosterone and screening tests for celiac disease, with negative result. For the persistence of fatigue, weight loss, urgency to defecate, Luca was hospitalized. Upper digestive endoscopy was negative, with normal duodenal biopsy and then colonoscopy showed at histological biopsy found "active colitis, probable inflammatory bowel disease in dormant state". He practiced Rx hand and wrist, with detection of bone age of 13 years and 6 months and brain MRI with a regular volume of cable sella and pituitary parenchyma. It was diagnosed "Inflammatory bowel disease. Severe iron deficiency anemia. Hypogonadism ipogonadotropo". Luca began therapy with corticosteroids and mesalazine (400 mg^2/day) with mild improvement in clinical symptoms and laboratory indices. On admission to our Medical Division, laboratory tests confirmed thrombocytosis (888,000 mm^{-3}), iron deficiency anemia (Hb: 7.6 g/dl, iron 9 μg/dL), reduction in testosterone levels: 9 ng/dl (nv 271–965) and gonadotropins LH: 0.2 IU/L (vn 1–8.4) and FSH: 0.4 IU/L (vn 1–10.5), normal GH, cortisol, ACTH and thyroid hormones, positive ANA (1:80) with a nucleolar pattern, negativity of ASMA and AMA and antiendomysial and antigliadin Ab negative. It was practiced a scintigraphy with labeled leukocytes, the result was Crohn disease (small severity), with extensive involvement of the large intestine, terminal ileum and some jejunal loops. We decided to begin monoclonal antibodies therapy (infliximab 5 mg pro kg with an induction phase at time 0, 2, 6, and then every 8 weeks, in association with mesalamine (400 mg^2/day). Already the fourth cycle of infusion therapy, the patient reported: discrete improvement of clinical conditions, diarrheal episodes less frequent, obvious increased in height-weight (weight 38.400 kg and height 150 cm), increased muscle tone and tropism, increased in the pubic and axillary hair. Laboratory data showed Hb 11.3gr/dl, serum iron 11microg/dl, ESR 15 mm/h and increased levels of testosterone 145 ng/dl, LH 3.6UI/L, FSH 2.2 UI/L. Three years have passed. Now Luca is 19, weighs 50 kg, his height is 160 cm, infuses infliximab 300 mg i.v. every 8 weeks. The laboratory indices show: Hb 11.4 dl^{-1}, ESR 26 mm/h, Sideremia 9microgr/dl, with bowel function characterized by two evacuations per day with stools of normal colour and consistency. The lack of growth

associated with delayed puberty is a rare presentation of Crohn's disease, but common in children. The etiology is multifactorial. The main determinant is the inflammatory process itself, with the release of proinflammatory cytokines (TNF-, IL-1). Moreover, poor appetite, avoidance of eating because of pain or discomfort, and poor absorption of nutrients by the damaged intestines, prolonged use of corticosteroids contribute to significant reduction of the height in almost one in five children. Recent data from a large prospective study with infliximab (Remicade) in patients with moderate to severe Crohn's disease showed a significant recovery of growth during the first year of regular infusions. For decades, many patients with Crohn's disease required prolonged courses of corticosteroids, repeated surgeries, or both, despite treatment with 5-aminosalicylic acid (mesalamine) or immunomodulators such as azathioprine. The introduction of biological treatments dramatically improve life quality of patients with chronic inflammatory bowel disease, proving efficacious in patients whose condition was resistant to conventional treatment.

Cardiovascular diseases

Anemia: risk factor for outcomes in elderly patients with atrial fibrillation without left ventricular dysfunction

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Background: Anemia is a pathological condition frequently present in the elderly population and is a widely recognised cause of an increased risk of morbility and mortality in many cardiovascular and non-cardiovascular pathologies. Atrial fibrillation is considered the most common of the cardiac arrhythmias and presents a high prevalence in elderly patients, even in the absence of clear cardiovascular pathologies.
Aim of our study: To verify the prognostic impact of anemia on mortality and re-hospitalization in elderly patients with permanent AF and left ventricular systolic function preserved.
Materials and methods: 187 patients, with an average age of 78.9 ± 5 years, were included in our study. 81 were males and 106 females. All subjects were patients in our University Department between February 2007 and February 2009 and presented permanent atrial fibrillation without left ventricular systolic dysfunction. Anemia was defined in accordance with the WHO criteria as a level of concentration of hemoglobin less than 13 g/dl for males and less than 12 g/dl for females. As an indicator of miocardiac performance the left ventricle ejection fraction was determined in accordance with the modified Simpson's biplane analysis in apical four- and two-chamber views The average value of the EF was $55 \pm 4\%$. The average value of the dimensions of the left atrium was 42 ± 3 mm. The average value of the hematocrit was 39.4%.
Results: The reduction in the concentration of Hb was significantly connected with the outcomes of rehospitalization and mortality, after adjustments are made for co-morbility and pharmacological treatments ($p < 0.001$) for values of Hb greater than 11.7 in males and 10.3 in females. The correlation between anemia and mortality was significantly more evident in males. The presence of anemia increased the incidence of rehospitalization by 31% compared to subjects with normal levels of Hb.
Conclusions: Anemia represents a predictive factor independent of rehospitalization and mortality in an elderly population with permanent atrial fibrillation. Further observations are necessary particularly for the purpose of evaluating if the correction of the anemic state modifies the risk of these outcomes.

Serum uric acid, but not rs7442295 polymorphism of SCL2A9 gene, predicts total and cardiovascular mortality in severe coronary artery disease

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Background: High levels of serum uric acid (SUA) have been associated with cardiovascular events in several studies, but the role of hyperuricemia as independent prognostic predictor of cardiovascular mortality is still matter of debate. The aim of the current study were: (1) to examine the predictive value of SUA for mortality in the setting of secondary prevention of coronary artery disease (CAD); (2) to evaluate possible associations between mortality and rs7442295 polymorphism of SCL2A9 gene, that has been related to SUA in recent genome-wide association studies.
Methods: A cohort of 703 patients with angiographically proven CAD was prospectively followed for a median period of 57 months. The large majority of them (92.5%) underwent coronary revascularization.
Results: During the follow-up, 116 (16.5%) out of 703 patients died, with 83 events (11.8%) attributed to cardiovascular causes. After adjustment for all the other predictors of mortality at univariate analysis (i.e. age, myocardial infarction history, ejection fraction, diabetes, hs-CRP and creatinine, statin, β-blockers, and allopurinol therapy), elevated SUA levels ($\geq$0.41 mmol/l—the 75° percentile) significantly predicted both total and cardiovascular mortality (HR for total mortality 1.87 with 95% CI 1.05–3.34; HR for cardiovascular mortality 2.09 with 95% CI 1.03–4.25). Although rs7442295 was an independent predictor of SUA (standardized β-coefficient for the G allele -0.100, $P = 0.008$ by adjusted linear regression), it was not associated with total or cardiovascular mortality.
Conclusions: basal concentrations of SUA levels $\geq$0.41 mmol/l in CAD patients independently predicted total and cardiovascular mortality, whereas no association was found between rs7442295 polymorphism and mortality.

Renal tubulo-interstitial involvement in hypertensive patients with metabolic syndrome

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Background: Renal resistive index (RRI) are influenced by both renal (tubulo-interstitial damage) and extra-renal (arterial stiffness and atherosclerosis) determinants. Patients with hypertension and/or diabetes mellitus (DM) show stiffened arteries and high RRI values.

Recently, increased RRI were associated with metabolic syndrome (MS) in patients with DM. We investigated RRI and renal volume-to-resistive index ratio (RV/RRI) in hypertensives with MS, but with neither DM nor impair fasting glucose.

Methods: We studied 40 hypertensive patients (58 ± 11 years; M/F = 25/15) in chronic antihypertensive therapy. MS was diagnosed by the presence of at least two of increased waist circumference, high triglycerides and low HDL-cholesterol. RRI ≥ 0.70 or >95% upper confidence limit expected for the age decade were considered pathologic. Decreased RV/RRI was defined for values below the median, i.e. <187 mL m^2/kg. A bivariate logistic regression analysis was performed to evaluate the predictive value of MS and of its components for pathologic RRI and/or decreased RV/RRI, adjusting for age, gender, IMT and hsCRP.

Results: Patients with MS ($n = 8$) showed lower RV/RRI values (171 ± 19 vs. 190 ± 23 mL m^2/kg, $P = 0.03$) and a higher prevalence of decreased RV/RRI (7 out of 8 vs. 13 out of 32, $P = 0.04$) compared to patients without MS ($n = 32$). The presence of MS resulted a predictor for both pathologic RRI (crude O.R. 5.4, 95% CI 1.00–29.05, $P = 0.049$) and decreased RV/RRI (crude O.R. 10.2, 95% CI 1.12–93.34, $P = 0.039$), even after adjustment. Low HDL-cholesterol and increased waist circumference resulted significant independent predictors respectively for pathologic RRI and decreased RV/RRI.

Conclusions: In our hypertensive patients, MS was associated with increased RRI and decreased RV/RRI, despite normal glucidic metabolism. MS-related tubulo-interstitial involvement seems mediated by HDL-cholesterol and abdominal fat, and independent of atherosclerosis and low-grade inflammation.

Seasonal variation in heart failure hospitalization and mortality

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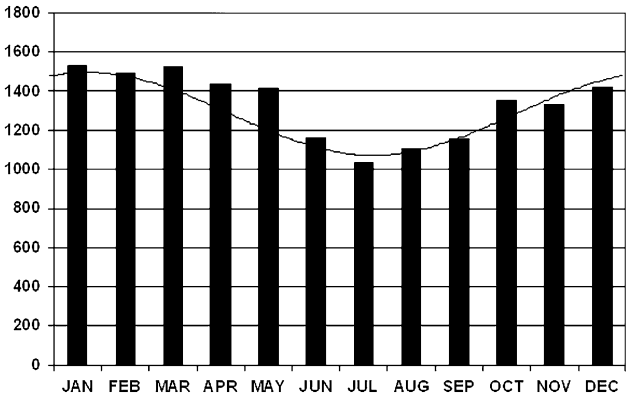
Background: A seasonal variation has been reported for occurrence of acute cardiovascular events, such as myocardial infarction, sudden death, stroke and transient ischemic attack, rupture/dissection of aortic aneurysms and pulmonary embolism [1–3].

Hypothesis: The aim of this study was to determine whether a seasonal variation exists also for hospitalizations and deaths due to heart failure (HF), and to examine possible contributors to such variability.

Methods: The study included all consecutive cases of HF admissions to Ferrara Hospital between January 2002 and December 2009. The day of admission was categorized into seasonal intervals, and twelve 1-month intervals for seasonal and circannual analysis, respectively. The sample was divided into subgroups by gender, age, presence of major cardiovascular risk factors (arterial hypertension, diabetes mellitus), patients' outcome, and order of ICD-9 codes (first diagnosis, accessory diagnosis). The statistical analysis was performed by χ^2 test goodness of fit (seasonal analysis) and partial Fourier series (circannual analysis) on total cases and considered subgroups.

Results: The database included 15,954 with the ICD-9-CM codes of HF (420–429), mean age 77.7 ± 10.5 years). Hospital admissions for HF were most frequent in Winter (28.4%) and least in Summer (20.4%, Chi-square = 214.16, $p < 0.001$). Chronobiological analysis yielded a significant peak in January for total cases and all subgroups considered. No differences were found considering subgroups by gender, age, fatal cases, presence of hypertension and diabetes mellitus, patients' outcome (dead during hospitalization, discharged alive, transferred to other department), and order of ICD-9 codes (first diagnosis, accessory diagnosis).



Conclusions: A seasonal periodicity for HF deaths and hospitalization is demonstrated, characterized by a peak in winter months, independent of gender, age, major cardiovascular risk factor, and outcome. These data could be useful for practitioners to improve causative prevention measures, therapeutic management, and educational strategies.

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Residual risk in type 2 diabetic patients treated with lipid lowering drugs

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Cardiovascular disease is the main cause of morbidity and mortality in type 2 diabetic patients. Control of risk factors for atherosclerosis, such as high low density lipoprotein cholesterol (LDL-C) level, has been proved to be useful in prevention of cardiovascular events, bringing about an average 25–30% reduction of cardiovascular risk. This means an unacceptably high residual risk of 70–75%. Studies with high doses of statins demonstrated that further lowering of LDL-C is associated with an increased protection against cardiovascular disease. On these basis, guidelines of the international scientific societies suggest that in high risk patients, such as type 2 diabetics, LDL-C must be less than 100 mg/dl and optionally less than 70 mg/dl.

However, residual risk remains high even if the therapeutic goal is reached, suggesting that other risk factors may operate. Among other risk factors, low HDL-C (<40 mg/dl in male and <50 mg/dl in female) and/or high triglycerides (>150 mg/dl), which are frequently seen in diabetic population, might play an important role.

Aim of our study was to investigate in a group of type 2 diabetic patients how many of them reached the LDL-C target and were also at goal for HDL-C and/or triglycerides.

The study was carried out on 401 type 2 diabetic patients (234 males and 167 females), age range: 34–82 years (mean 67.4 ± 10.04). Mean Hba1c was 7.03 ± 1.05%, total cholesterol 175 ± 32.62 mg/dl, LDL-C 97.0 ± 27.71 mg/dl, HDL-C 51.1 ± 15.35 mg/dl and triglycerides 134.8 ± 65.0. Of the 401 patients, 234 were on hypolipidemic drugs (207 on statins, 4 on simvastatin plus ezetimibe, 1 on statin plus fenofibrate and 22 on fibrates). Of them, only 61 patients (26.1%) had LDL-C <70 mg/dl, 84 (35.9%) had LDL-C between 70–99 mg/dl, 72 (30.8%) between 100–129 mg/dl and 17 (7.3%) ≥ 130 mg/dl, 77 (33%) had HDL-C < 40 mg/dl (males) or <50 mg/d (females) and 86 (37%) had serum triglycerides >150 mg/dl.

Of 61 patients with LDL-C <70 mg/dl, 31 (51%) had low HDL-C and/or high serum triglycerides.

	N	%
Males with LDL cholesterol <70 mg/dl		
HDL-C <40 mg/dl and/or TG >150 mg/dl	16	43.2
HDL-C >40 mg/dl and/or TG <150 mg/dl	21	56.8
Females with LDL cholesterol <70 mg/dl		
HDL-C <50 mg/dl and/or TG >150 mg/dl	15	62.5
HDL-C >50 mg/dl and/or TG <150 mg/dl	9	37.5

In our series of type 2 diabetic patients, 42% were not treated with lipid lowering drugs, 74% of those treated did not reach the therapeutic goal. Half of the patients who reached LDL-C level <70 mg/dl remained at theoretical high risk because of low HDL-C and/or high serum triglycerides.

Correlation between Carotid artery ultrasound and CHD in our environment patient

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Background: Atherosclerosis is a systemic process, involving multiple arterial districts at the same time. Carotid doppler ultrasound is an easy and non-invasive test, able to evaluate the layers of the neck arteries and the involvement of this district in the atherosclerotic process. Carotid intima-media-thickness (IMT) is known to be a marker of the systemic atherosclerotic process. Dopper ultrasound could become useful, allowing a correct risk stratification in the systemic involvement by the atherosclerotic process. Moreover, it could be functional, in association with the other already-validated rulers, in targeting the best therapeutic choice for acute coronary heart disease [6]. An increase of IMT or the presence of atherosclerotic plaque in asymptomatic patients have been associated to an increased risk for coronary heart disease (CHD) in large, perspective studies [1–4]. On the other hand, a recent meta-analysis [5] showed that neither the presence of an increased IMT neither the presence of a plaque were discriminatory enough to be considered a reliable screening test among patients with symptomatic CHD. Aims of the study: To evaluate a correlation between carotid arteries ultrasonographic pattern and coronaric pathology extension among symptomatic CHD patients living in our region.

Materials and methods: In the period 01/2007–01/2008, we enrolled 100 consecutive patients admitted to our Internal Medicine Department for acute coronary syndrome (ACS). For each patient, we evaluated the classical risk factors (familiarity, known CHD, diabetes mellitus, dyslipidemia, hypertension, smoke and obesity), the extent of the atherosclerotic pathology (cerebrovascular events, peripheral arteries pathology and CHD) and the therapy at the moment of the admission. Every subject underwent to doppler ultrasound: IMT, presence of carotid plaque and degree of stenosis were evaluated. Coronarographic assessment evaluated the number of arteries with significant obstruction, the total coronary score (TCS), the site and the degree of stenosis. We performed the statistical analysis with SPSS 13.0 package for Windows systems.

Results: The absence of a previous history of CHD and a negative carotid ultrasound (normal IMT, no evidence of any plaque) were the strongest protective factors for multiple-vessel coronary disease (CHD: OR = 0.132; 95% CI 0.027–0.628, $p < 0.05$; Negative US: OR = 0.223; 95% CI: 0.067–0.742, $p < 0.05$). Lower percentages of stenosis were associated to lower TCS as detected at coronarography (0–30% stenosis at US: OR = 6.76 [95% CI: 19.25–2.37, $p < 0.05$] of obtaining a low TCS) with a decrease of the risk of low TCS with proportional to the increase of carotid stenosis.

Discussion: In this small, retrospective analysis we correlate a normal carotid ultrasonographic pattern with a low risk of multiple-vessel involvment at coronarography. Moreover, in this population of symptomatic patients, we correlate the percentage of carotid stenosis with a proportional increase of the risk of an higher TCS at coronarography. These data suggest that among high-risk, symptomatic patients, carotid ultrasound and doppler evaluation can be a reliable indicator of the extent of coronary pathology.

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Pulmonary arterial hypertension associated with the use of interferon beta for multiple sclerosis

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The interferons (IFNs) are a complex group of proteins that act as immunomodulators. Different forms of IFNs have been evaluated and are nowadays widely used in many diseases. Among side effects there are: flu-like symptoms, neuropathies, neuropsychiatric effects, bone marrow depression, liver and renal and heart failure, cardiac arrhythmias, hypo- and hypertension, Raynaud's phenomena. Pulmonary arterial hypertension (PAH) is a very rare side effect and it has been only recently described. Herein is described the case of a patient with multiple sclerosis (MS), who developed progressively severe PAH since 1 year after introduction of IFN beta-1a. Discontinuation of IFN and treatment with sildenafil resulted in dramatic clinical improvement.

Case report. A 59-years-old woman was diagnosed MS in 2001. In 2005 she started IFN beta-1a, administrated 3 times a week. After a year there was the first evidence of electrocardiographic abnormalities indicative of right ventricular (RV) strain. The transthoracic Doppler-echocardiography confirmed RV strain with an estimated pulmonary arterial systolic pressure (PASP) of 70 mmHg. The subsequent right heart catheterization (RHC) was performed and it revealed a pulmonary arterial systolic, diastolic and mean pressure of 80, 36, 41 mmHg respectively. Testing of pulmonary vasoreactivity with adenosine was negative. Then she started only warfarin treatment. Thereafter a progressive worsening of physical capacity occurred (NYHA functional class II–III $\rightarrow$ IV) and she was referred to our Center in November 2009 with a clinical picture of overt right-sided heart failure. The ecocardiography showed dilated right atrial and RV chamber, RV severe hypokinesia with tricuspid annular plane systolic excursion (TAPSE) of 6 mm, pericardial effusion, severe tricuspid regurgitation (TR) with an estimated PASP of 87 mmHg. At RHC pulmonary arterial systolic, diastolic and mean pressure were 98, 51, 69 mmHg, respectively. With the usual treatment of congestive heart failure a moderate improvement was obtained. No clear cause of PAH was indentified. Then we decided to discontinue IFN beta-1a and to start sildenafil 40 mg t.i.d. Subsequently the patient showed a dramatic and progressive improvement of functional capacity (NYHA II) associated, 3 months later, to an improvement of all the ecocardiographic RV findings. In particular the TR resulted moderate (with an estimated PASP of 58 mmHg) and TAPSE 10 mm.

Then glatiramer acetate therapy for MS was started.

Conclusions:

1) The case presented is the first description of PAH associated with IFN beta-1a in a patient with MS; in literature at present there are only 1 analogous case report in a woman treated with IFN beta-1b and 10 cases in patients treated with IFN alfa.
2) In our patient discontinuation of IFN beta-1a and administration of sildenafil resulted in an impressive improvement.
3) We think that greater attention should be directed to the association between IFNs use and PAH, because this side effect of IFNs is perhaps underestimated and because it could be diagnosed only when PAH has become irreversible, as it has been very recently reported in some cases.

A case of congestive heart failure in patient with primary (AL) amyloidosis at initial presentation

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Amyloidosis may be defined as the extracellular deposition of the insoluble fibrillar protein amyloid in one or more organ. The natural history of amyloidosis is poorly understood, and the clinical diagnosis is often not made until the disease is far advanced. The accumulation of amyloid deposits in the heart is the main prognostic factor, with a median survival of 4-6 months for patients with congestive heart failure at diagnosis. There are multiple different forms of Amyloidosis; Primary or AL Amyloidosis is the most common and arguably the most aggressive and lethal form of systemic amyloidosis, leading to organ failure and death. This disorder results from plasma cell dyscrasia in which amyloid deposits are derived from monoclonal immunoglobulin light chains. Amyloid deposits can be reabsorbed and organ function restored if the amyloid-forming precursor light chain is eliminated by suppressing the underlying plasma cell dyscrasia, while using supportive measures to sustain organ function. We describe the case of a 53-year-old Bulgarian male, previously asymptomatic and without cardiovascular risk factors (body mass index = 24.4, waist circumference = 94 cm, denied hypertension, diabetes, dyslipidemia, and smoking) who reported since few months asthenia and progressive exertional dyspnea, and recent lower limbs edema. Basal electrocardiogram showed atrial fibrillation 86 min^{-1}. and low-voltage QRS complex, while the standard thoracic radiographs highlighted cardiomegaly, interstitial edema and bilateral pleural effusion. The patient was subjected timely to trans-thoracic echocardiogram, that showed: symmetric thickening of left ventricular wall and interventricular septum, with diffuse hyperrefractile granular sparkling and ejection fraction of 38%; dilation of the right ventricular with pulmonary systolic arterial pressure of 40 mmHg; minimal posterior pericardial effusion and restrictive filling doppler pattern. The abdominal echography revealed hepatomegaly and thin ascites. 24 h-blood pressure monitoring recorded a normotensive profile; no lesions were displayed in carotid and peripheral arterial-venous vascular echo-doppler. NT-proBNP plasma levels were raised (3.148 pg/ml), instead cardiac enzymes, and D-Dimer levels, and all the standard laboratory parameters were in the normal range, except for the presence of monoclonal peak (27.2%) in the gammaglobulin fraction of serum protein electrophoresis. Radial immunodiffusion showed increase in IgG concentrations (1.890 mg/dl) and serum immunofixation confirmed the presence of an IgG-λ monoclonal protein; Bence-Jones proteinuria was absent and $beta_2$-microglobulinaemia was 2.95 mg/l. There were no abnormalities in the peripheral blood smear, and nor osteolytic lesions in the standard skeletal radiographs. In the well grounded suspicion of Amyloidosis, the patient was undergone an abdominal subcutaneous fat radial biopsy, that was positive for Thioflavin T amyloid deposits. A bone marrow biopsy, carried out contemporaneously, were negative for malignant B-cell (IgA^+ plasma cells $< 5\%$), and revealed only inversion of k/λ ratio. The patient was treated with high-dose Furosemide, Potassium canrenoate 50 mg/daily, Valsartan 40 mg/daily, and Enoxaparin 6.000 U.I. $\times$ 2/daily (then oral anticoagulation therapy; INR-target 2.5), achieving improvement of clinical picture and gradual regression of

symptoms, ascites, and pleural-pericardial effusion. NT-proBNP plasma levels also decreased (371 pg/ml), and the patient undertaken treatment with Carvedilol 2.5 mg × 2/daily. After 21 days, the patient was transferred to the Haematology Care Unit, where he was treated by combination of oral Melphalan and Dexamethasone (treatment in progress at present).

Unfortunately, in future the patient could need heart transplantation; this is currently the only established surgical approach to the treatment of refractory heart failure. Finally, we suggest currying out immediate haematological and cardiological tests on young and middle-age patients presenting with congestive heart failure in absence of cardiovascular risk factors, in order to rule out a possible underlying Amyloidosis.

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Hypocalcemia may determine heart failure? A case report

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It's discussed the case of a 88-year-old woman presented with severe myocardial dysfunction and a history of pulmonary oedema and congestive heart failure due to hypocalcemia related to moderate renal failure. Althought in animal experiments hypocalcemia has been shown to lead to cardiac decompensation, the occurrence of congestive heart failure resulting from hypocalcemia is quite rare in clinical practice. Calcium plays a key role in cardiac muscle contraction and metabolism and it is also apparently involved in the mechanisms of the direct positive inotropic effect of digitalis. Many reports suggest that heart failure due to hypocalcemia is reversible. In the present case, the left ventricular ejection fraction was low and ECG showed a long QT interval when the serum calcium level was decreased, and they improved as the serum calcium level increased. This is direct evidence that serum calcium is necessary for cardiac muscle contraction and hypocalcemia is an underestimated precipitating factor of heart failure. The role of vitamin D and parathyroid hormone in determining cardiovascular risk is discussed as well. The aim of this work is to remind physicians that hypocalcemia, if recognized, can be treated pharmacologically, and this may improve heart failure.

Improvement of left ventricular geometry and function after alcohol withdraw: a case report

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A 52-year-old man presented to our hospital for dyspnea and palpitations. He reported 7 years history of the ingestion of more then 2 l of wine per day and one previous admission to the hospital for confusion due to ethanol abuse. He was conscious, and physical examination showed PA 140/90 mmHg, FC 88 bpm with several extrasystoles, at chest pulmonary rales in lower lobes, slightly peripheral oedema and at abdomen hepatomegaly and splenomegaly. His laboratory evaluations revealed Hb 12.1 g/dl, MCV 105 fl, platelets 115,000 g/dl, AST 88 U/L, ALT 61 U/L, GGT 257 U/L. Antibody for hepatitis A, B, C was performed on blood sample, and all were negative. His electrocardiogram showed sinus rhythm, some ventricular extrasystoles and nonspecific T-wave abnormality. A subsequent chest X-ray revealed cardiomegaly and basal congestion. The echocardiographic exam showed moderate global left ventricular (LV) systolic dysfunction, with an ejection fraction (FE) of 35% by modified Simpson's biplane method. The LV end-diastolic dimension (EDD) was 6.10 cm, EDD/height was 3.69 cm/m; LV mass (LVM) 199.04 g, LVM/height 51.49 g/$m^{2.7}$, relative wall thickness was 0.26; as eccentric LV hypertrophy. Right ventricle was dilated (right ventricular outflow tract diameter at subpolmonary region = 4.1 cm), with normal systolic function. Left atrium was dilated (left atrial volume was 56 ml). Color Doppler flow revealed moderate mitral regurgitation and moderate tricuspid regurgitation with systolic pulmonary pressure (PAPs) 45 mmHg. PW mitral flow showed a restrictive filling pattern. The patient was treated with furosemide, canrenone, bisoprolol, ramipril and after 1 week he was discharged asyntomatic. A subsequent dypiridamole stress test was negative for myocardial ischemia. After 12 months of abstaining from alcohol, at control visit he was asyntomatic, PA 120/80 mmHg, FC 70 bpm, sinus rhythm, with normal lung sounds and without peripheral oedema. A repeat echocardiogram revealed a significant improvement of LV systolic function, with FE 50%. EDD 5.4 cm, EDD/h 3.27 cm/m, LVM/h 49.50 g/$m^{2.7}$. Color Doppler showed reduction of severity of mitral and tricuspid regurgitation, with reduced PAPs (35 mmHg). PW mitral flow showed an impaired relaxation filling pattern.

Discussion: High dose of alcohol intake is a known risk factor of myocardial depression, and of dilated cardiomyopathy (ACM). Thus, between 3–36% of all cases of dilated cardiomyopathy are thought to occur because of excessive ethanol intake. Patients consuming >90 g of alcohol a day for >5 years are at risk for the development of asymptomatic ACM, clinically expressed as an impairment of left ventricular function (non-symptomatic stage). Patients who continue to drink may become symptomatic and develop sign and symptoms of heart failure (HF). Similar to other dilated cardiomyopathies ACM is characterized by an increased LV mass, dilation of the ventricles, wall thinning, and ventricular dysfunction, in absence of ischemic heart disease or nutritional deficiencies. In absence of complete alcohol abstinence, the 4 year mortality for ACM is estimated about 50%. A short duration of symptoms of HF and abstinence from alcohol are the two factors associated with favourable outcomes. Results from studies that compared long-term outcome of alcoholic and idiopathic dilated cardiomyopathy are discordant, but there is some evidence that suggest that complete withdrawal of alcohol is necessary and migh improve prognosis in alcohol-mediated cardiomyopathy.

Conclusion: In patients with alcoholic dilated cardiomyopathy, the mainstay and the goal therapy is abstinence from alcohol, in addition to recommended HF pharmacotherapies. Alcohol adverse effects on LV function can be reversible, while the persistent alcohol abuse is correlated with a worse prognosis.

High-density lipoprotein cholesterol and tryglicerides: markers of residual cardiovascular risk

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Residual cardiovascular risk consist in a higher incidence of major cardiovascular events despite the achievement of therapeutic goal in low-density lipoprotein cholesterol (LDL-C) lowering by the use of aggressive statin therapy in patients with dyslipidaemia, and expecially among those with metabolic syndrome and insulin resistance. This residual risk has been attributable to lower high-density lipoprotein cholesterol (HDL-C) and higher tryglicerides (TG) levels despite the achievement of LDL-C to target levels. Accordingly, a recent post hoc analysis of the "Treating to New Target" trial has demonstrated that high-density lipoprotein cholesterol (HDL-C) is a strong, independent, inverse predictor of risk of coronary disease. Thus, even among patients with LDL-C <70 mg/dl, those in the lowest quintile of HDL-C exhibited an increased risk of major cardiovascular events compared to those in the highest quintile ($P = 0.03$). Thus, for every 1.0 mg/dl increase in HDL-C, cardiovascular risk was reduced by 2–3%. Hypertryglyceridaemia is a strong predictor of coronary heart disease. PROVE-IT trial evaluated the role of intensive statin therapy in patients with acute coronary syndrome. After 2 years of follow up, significantly lower events occurred in treatment group with LDL-C < 70 mg/dl and TG < 150 mg/dl, compared to the group with LDL-C < 70 mg/dl and TG > 150 mg/dl. Thus, mixed dyslipidaemia including hypertriglyceridaemia, low HDL-Col levels, a preponderance of small, dense LDL particles and an accumulation of cholesterol-rich remnant particles has a significant role, in addition to and indipendently of LDL-Col in the risk cardiovascular disease. The anti-atherogenic effects of HDL-C may be a result of reverse cholesterol transport (RCT), the pathway in which cholesterol in peripheral tissues is transported to the liver for the elimination in bile. The cholesteryl ester transfer protein (CEPT) facilitates the exchange of TG from VLDL particle for cholesterol esters from HDL-Col and LDL-C. The endogenous plasma activity of CETP is modulated by the magnitude of triglyceridaemia. Hypertriglyceridaemia, promotes formation of atherogenic small dense low-density lipoprotein. Small, dense LDL-C are especially prone to oxidation and thus more likely to be taken up by macrophages in the artery wall, leading to further progression of the atherosclerotic plaque. HDL-C contrasts atherosclerosis directly, by removing cholesterol from foam cells, by inhibiting the oxidation of LDL-C, by inhibiting expression of adhesion molecules with decreased binding of inflammatory cells. Low HDL-cholesterol has been shown to correlate with elevated PAI-1 in humans, with increased platelet aggregation. Raising HDL-C can be achieved by both pharmacological therapy and lifestyle changes, expecially by smoking cessation, aerobic exercise, weight loss and dietary manipulation. Although statins are the initial drugs of choise, combination therapy may be a necessary strategy to reach complete lipid goal in addition to LDL-C target. Therapeutic strategies includ omega-3 fatty acids, niacin, fenofibrates and bile acid sequestrants. Thus, raising HDL-C and reducing TG represents an important strategy for reducing residual cardiovascular risk.

Beta-blockers plus conventional therapy in diastolic heart failure

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Diastolic heart failure (DHF), also referred to as heart failure with preserved ejection fraction, currently accounts for more than 50% of all heart failure patients. Arterial hypertension is the most common risk factor for heart failure in general population and miocardial infarction, and LV hypertrophy (LVH) and valve heart disease represent predictors of subsequent heart failure in hypertensive patients. Moreover in absence of a clinical history of heart failure, impaired left ventricle (LV) early diastolic relaxation, detected by pulsed Doppler echocardiography, is predictive of an higher incidence of major cardiovascular events both in general population and in hypertensive patients, independently of age, gender, and ambulatory blood pressure. There are no specific recommendations for treating diastolic heart failure, but general suggestions should target symptom reduction, pathological causes and underlying mechanism that are altered by the disease processes. Beta-blockers have many potentially useful effects. Beta-blockers reduce heart rate, with a prolongation of LV filling time, allowing to counterbalance the resistance to the diastolic inflow of a stiffened left ventricle. The volume overload, such to induces episodes of acute DHF, can be prevented or reduced by hypo-saline diet or also by a moderate diuretic administration. ACE-inhibitors and angiotensin-inhibitors can exert a beneficial effect on DHF, since they reduce both afterload and preload, induce regression of LVH and decrease of myocardial interstitial fibrosis. Also low dose of spironolattone and canrenone, are able to reduce myocardial fibrosis, antagonizing the cardiac fibrotic effects of aldosterone without significant additional antihypertensive effects, with an improvement of diastolic function. Beta-blockers vary with regard to several pharmacologic properties, including beta1/beta2 selectivity, intrinsic sympathomimetic activity, and, with the newest beta-blockers, vasodilatation. The SWEDIC study investigated the effects of carvedilol into double blind multi-centre study, in additional to conventional treatment. Four different diastolic function variable were evaluated by Doppler-Echocardiography: mitral flow E:A ratio, deceleration time (DT), isovolumic relaxation time (IVRT) and the ratio of systolic/diastolic pulmonary venous flow velocity. At the end of study there was a statistically significant improvement in E:A ratio in patients treated with carvedilol versus placebo ($P < 0.05$). Another studies compared the effects of administration of atenolol or nebivolol on resting and exercise hemodynamic parameters and maximal exercise capacity, in patients with normal systolic function (ejection fraction >0.50 and an end-diastolic diameter < 32 mm/m2) and diastolic dysfunction (E/A < 1.0, pulmonary wedge pressure > 12 mmHg at rest and >20 mmHg at peak of exercise). After 6 month therapy, nebivolol much more atenolol induced increase of both E/A ratio ($p < 0.004$) and cardiac index and reduction of wedge pressures, both at rest and during exercise. The differences observed between the two beta-blockers may be ascribed to the peripheral vasodilatatory action and nitric oxide (NO) release associated with nebivolol administration. Moreover, increased NO release in the vessels of skeletal muscle may increase their dilatatory capacity and thus allow better muscle perfusion during exercise. Lastly, NO is one of the most powerful endogenous lusitropic agents.

Another study (SENIORS), was successful in demonstrating that nebivolol reduces the composite risk in all-cause mortality and cardiovascular hospital admission, regardless patients with DHF. In conclusion, new beta-blockers have a beneficial effect in patients with diastolic heart failure, in additional to diuretics, ACE-inhibitors and low dose of aldosterone antagonists. Preventive strategies directed toward an early and aggressive blood pressure control are likely to offer the greatest promise for reducing the incidence of diastolic heart failure.

Lacking evidence of left cardiac sections involvement in patients with chronic viral hepatitis

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Background and aims: Myocardiopathy has been described secondary to a wide range of viral infections, including hepatitis B (HBV) and C (HCV) viruses. It is not clear whether the heart is compromised in patients with HBV and/or HCV related chronic hepatitis. The purposes of the present study were to evaluate some morphological and functional aspects of cardiac left sections in a large cohort of patients with HBV and/or HCV related chronic hepatitis by means of conventional and newer ecocardiohraphic techniques.
Methods: For this aims, 142 Patients with HBV and/or HCV related chronic hepatitis and 168 healthy controls received clinical, biochemical, and hemodynamic evaluations, conventional Doppler echocardiography, and myocardial tissue Doppler imaging study for measurements of cardiac left sections, diastolic and systolic function of left ventricle (LV), and mitral valve structure and function.
Results: In patients with chronic hepatitis, biochemistry, hemodynamics (heart rate, blood pressure, and systemic vascular resistance), ecocardiographic measures of left sections, standard ecocardiographic indices of LV diastolic and systolic function (the E/A ratio, isovolumic relaxation time and deceleration time of the E wave; LV ejection fraction and cardiac output, respectively), and myocardial tissue Doppler values of LV diastolic and systolic function (myocardial early diastolic velocity, early peak diastolic mitral annular velocity and LV filling pressures; myocardial peak systolic velocity, respectively), and frequency of mitral valve calcification and regurgitation were not statistically different when compared with controls.
Conclusions: Conventional Doppler echocardiography and tissue Doppler imaging study did not show any abnormality in both dimensions and function of cardiac left sections in patients with HBV and/or HCV related chronic hepatitis.

Subclinical impairment of right ventricular diastolic function as an early sign of cardiac involvement in patients with pre-SSc. Results of a TDI study

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Background: Scleroderma (SSc) is an autoimmune disease, clinically expressed by skin, lung, oesophagus and heart fibrosis. Myocardial fibrosis affects negatively the outcome of patients with SSc, secondary to abnormalities in right (RV) and left (LV) ventricular function. It has recently been recognized a new clinical condition, so-called pre-SSc, which is characterized by Raynaud phenomenon, absence of fibrosis of skin and/or other organs, and evidence of serum anti-topoisomerase I or abnormalities at capillaroscopy. The aims of the present study were to evaluate geometry and function of RV and LV in a small population of patients with pre-SSc by means of traditional ecocardiography and tissue doppler imaging (TDI) study.
Subjects and methods: 13 females pre-SSc patients (age: 43 ± 13 years, mean $\pm$ SD), were enrolled on the basis of the results of: routine biochemical and autoimmune tests, thoracic radiography and HRTC, oesophageal manometry and radiography and capillaroscopy. 12 healthy subjects constituted the control group. Each patient was subjected to: 12-lead ECG, traditional echocardiography and TDI study. The statistic analysis was performed by ANOVA method; were considered significant p values < 0.05.
Results: Both diameters and thickness of LV and of RV in pre-SSc were not significantly different as compared with those in controls; both systolic and diastolic function of LV and of RV examined by traditional echocardiography did not reveal any difference by comparing the two groups; TDI study of RV revealed in pre-SSc E' values significantly ($p < 0.05$) higher than controls and an inverted E'/A' ratio; in pre-SSc, TAPSE and PAP were significantly ($p < 0.05$) higher than those in the control group.
Discussions and conclusions: TDI, a modern echocardiographic technique devoted to the study of myocardial intrinsic properties, could identify some mechanic functional abnormalities which, sometimes, the conventional echocardiography could fail to reveal early during natural history of some chronic diseases. In conclusion, in pre-SSc patients: (a) both systolic and diastolic function of the LV are normal; (b) systolic function of the RV is preserved; (c) RV diastolic function is abnormal when examined by TDI. These abnormalities could represent an early marker of myocardial involvement in pre-SSc patients.

Elevated levels of cardiac troponin : strong predictor of worse prognosis in patients with decompensated heart failure

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In general elevated cardiac troponin levels reflects irreversible myocardial cell necrosis. However, several conditions, abnormal values have been described not related to acute coronary disease, like myocarditis, pulmonary embolism, acute heart failure, septic shock, tachycardia with haemodynamic compromise, renal insufficiency, cerebrovascular accidents as well as after therapeutic procedures like PTCA, electrophysiological ablations, or electrical cardioversions.
Objective: To evaluate the prognostic significance of elevated levels of cardiac troponin T (TnT) of outcomes in patients with decompensated heart failure.
Methods: A total of 95 consecutive patients(41 males and 54 females, with an average age of 72 ± 4 years, hospitalized due to decompensated HF, with left ventricular systolic dysfunction (EF $< 45\%$,) were included in the study. Exclusion criteria patients using intravenous inotropic agents, as well as those with, pulmonary thromboembolism, acute coronary syndrome, patients with ICDs,creatinine levels > 2.2 mg%, liver failure, or neuromuscular diseases. Patients were followed for 12 months.

Results: High levels of TnT (>0.02 ng/ml) were detected in 46 patients (48.4%). The global mortality was 35.4%. In the groups with high TnT and low TnT levels (<0.02 ng/ml) there were, respectively, 23 versus 10 deaths ($p = 0.001$), 14 versus 9 patients needed IV inotropic agents ($p = 0.26$) and 16 versus 12 patients were re-hospitalized ($p = 0.10$). Also patients with elevated troponin had a lower systolic blood pressure. Mean troponin levels were significantly higher in those individuals who died ($p = 0.004$). The need for intravenous inotropic agents and the persistence of the third sound showed to be independent predictors of death; however, we observed a higher tendency towards mortality for patients presenting high TnT when compared to those with low troponin levels ($p = 0.07$).
Conclusion: The presence of elevated levels of troponin is associated with significantly increased overall mortality and predicts adverse events. These findings suggest that routine assessment of troponin concentrations in HF patients is warranted. It remains possible that troponin measurements have greater prognostic value such as those with more advanced HF or lower ejection fraction. Maybe a combination of biomarkers, including BNP and perhaps hsTnT, could be used for guiding in the management of patients with heart failure.

HbA1c risk factor in patients with heart failure and left ventricular dysfunction

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Background: There is a constantly increasing number of indications in literature that suggest an increased cardiovascular and global risk in all conditions with an altered glycid metabolism. HbA1c is considered as the gold standard in the assessment of glycemic control in diabetics patients; it reflects the mean blood glucose level during the 6–8 weeks preceding the test. Recent data would seem to indicate that increases in HbA1c, even slight, are associated with an increase in cardiovascular risk.
Aim of our study: To verify the prognostic impact on mortality of levels of HbA1c in non-diabetic patients with left ventricular dysfunction.
Materials and methods: We studied 152 non-diabetic patients with chronic heart failure. 84 were females and 68 males, with an average age of 69 ± 4 years. 69% of these patients (45.3%) presented left ventricular systolic dysfunction (defined as an ejection fraction less than 45%). In 55.2% of the patients examined (84 patients) the value of HbA1c was greater than 3.8% (normal value 2.8–3.8%).
Results: 15% of the patients with systolic dysfunction had values of HbA1c greater than 4% and presented a risk of cardiovascular mortality two times greater than the group with normal levels of HbA1c. The risk remains high even after adjustments are made for age and concomitant diseases. After 1 year the mortality in the group with elevated values of HbA1c was 26% compared with 12% in the group with normal levels of HbA1c.
Conclusions: Our data confirm that dysglycemia represents an independent risk factor for the progression of heart failure and that levels of HbA1c are strongly associated with a worse prognosis even in non-diabetic subjects. That being so, the routine evaluation of HbA1c as an indicator of cardiovascular risk would be desirable.

Supervised training improves endothelial function measured during induced ischemia in peripheral arterial disease

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Introduction: Favorable effect of training on cardiovascular pathology is well documented in literature. Mechanisms evoked are the following: increased NO availability for reduction of oxidative stress, inflammation decrease, improvement of glucidic and lipidic metabolism, resetting of neuro-endocrine balance. These mechanism are also involved in the improvement of patients with peripheral arterial disease (PAD) treated with training. PAD is a model of inducible ischemia, in fact claudication is a condition in which ischemia/reperfusion phenomenon is present when walking is conducted till maximum pain. This phenomenon may produce a great amount of radical oxygen species with possible consequence on endothelium function. Xanthine oxidase is one of the most relevant enzyme involved in this process. Different types of training are proposed for PAD patients and there is not a consensus whether the ischemic pain should be reached during exercise. So we aimed to verify if maximal treadmill test (till pain) causes endothelial dysfunction, if oxidative stress is acutely aroused and if xanthine oxidase is involved. Therefore, we aimed to verify if a training performed under the onset of ischemic pain can improve endothelial function ether at rest and after maximum tolerated exercise.
Patients and methods: We enrolled 20 patients with PAD (16 males, 4 females, aged 65–77). Endothelium dependent dilation (EDD) was measured at humeral artery by ultrasound method, before and after maximal treadmill test (speed 3.2 km/h; slope 10%). We administered allopurinol 600 mg the day before and 600 mg 6 h before a new treadmill test. Serum uric acid and lactate were determined throughout the study. Afterwards patients performed supervised training under pain onset for 20 days with physiotherapist overview. Every 7 days a new treadmill test was performed for updating training distance. At the end of the training period EDD was measured before and after a maximal treadmill test. Furthermore microcirculatory endothelium dependent dilation was measured at the skin of the forefoot by means of laser-Doppler (LD) after iontophoretic acetylcholine administration.
Results: Maximal treadmill test acutely reduced EDD (6.1 ± 0.7 vs. 9.2 ± 0.9%; $p < 0.05$). Allopurinol improved EDD (10.1 ± 0.3 vs. 9.4 ± 0.6%; $p < 0.05$) with a reduced fall after maximal test (delta decrease −21.3 ± 2.2 vs. −33.2 ± 1.2%; $p < 0.05$). Training increased pain free walking distance (131 ± 12 vs. 66.6 ± 21 m; $p < 0.05$) and absolute walking distance (275 ± 15 vs. 125.8 ± 40 m; $p < 0.05$). EDD improved after training period (11.3 ± 0.7 vs. 9.2 ± 0.9; $p < 0.05$). The fall in EDD, observed during maximal treadmill test at the end of training period, was smaller than the one measured before training (delta decrease −15.5 ± 2.4 vs. −33.2 ± 1.2%; $p < 0.005$). Microcirculatory endothelium dependent dilation measured with LD increased after training (Table).

Table Microcirculatory flux with LD after iontophoretic acetylcholine

Acetylcholine 0.10 mA	10 s	20 s	40 s
T 0 (% incr)	35 ± 9	70 ± 15	120 ± 15
T 20 (%incr)	147 ± 38*	182 ± 22*	470 ± 54*

* $p < 0.005$ T20 vs. T0

Conclusions: We demonstrate that walking through maximal pain causes impairment of EDD, this is caused by oxidative stress and can be reduced by inhibition of xanthine oxidase. Aerobic training improves EDD and microcirculatory endothelial function, furthermore training reduces the drop of EDD during maximal exercise and increased oxidative stress. As a consequence these results suggest the training should be performed under the maximal pain.

Carnitine improves endothelial function and microcirculation in patients with critical limb ischemia

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Introduction: L-propionyl carnitine (LPC) improves walking distance in intermittent claudication due to peripheral obstructive arterial disease. LPC is involved in beta oxidation of fatty acids acting on coenzyme-A, so improving energetic supply to tissues. Critical limb ischemia is a severe terminal stage of atherosclerosis of lower limb arteries, characterized by rest pain and severely decreased flow to the foot with initial ischemic sufferance. In the study protocol we aimed to analyze the modifications induced by LPC infusions on microcirculation and endothelial function in patients with critical limb ischemia.
Material and methods: 14 patients (aged 68–78 years) with CLI underwent microcirculatory study with laser Doppler (Periflux PF3, Perimed, Stocholm, Sweden) at the forefoot. At the same site we analyzed transcutaneous oxygen and carbon dioxide pressure (TcPO2 and TcPCO2). We measured these parameters at rest and after 3 min of ischemia induced by a cuff inflated at the calf. We also measured endothelial dependent and independent dilation at brachial artery with ultrasound methodology. Therefore, patients underwent infusions with L-propionyl carnitine (600 mg in 250 cc saline solution) twice for 15 days. Pain score was calculated with an analogical scale.
Results: therapy with LPC increased microcirculatory hyperemia detected with laser Doppler (before LPC: 47 ± 25 vs. 30 ± 12%, ns; after LPC 75 ± 23 vs. 28 ± 14%, $p < 0.05$), we also measured an improved TcPO2 (39 ± 7 vs. 22 ± 5 mmHg, $p < 0.05$) and a decreased TcPCO2 (75 ± 9 vs. 93 ± 10 mmHg: $p < 0.05$). Endothelial dependent dilation increased after therapy (11.1 ± 4.9 vs. 6.2 ± 3.5% : $p < 0.05$), endothelial independent dilation was unchanged. At the end of LPC administration, pain scale values were reduced (5.5 ± 0.6 vs. 9 ± 1.4% $p < 0.05$).
Discussion: the results reveal an improvement in microcirculatory hyperemia probably trough an increased endothelial function. A better oxidative metabolism may be a great advantage in ischemia resistance of tissues. An improvement of endothelial function may be due to antioxidant properties of LPC, this aspect may be of great interest for the prognosis of this disease.

Plasma vascular endothelial growth factor levels in mild hypertension

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Vascular endothelial growth factor (VEGF) is a multifunctional glycoprotein which is a mitogenic for endothelial cells. It has a high affinity with endothelial cells in the macro and microvascular vessels. It is the most important regulator of pathological or physiological angiogenesis and additionally leads to increased vascular permeability. VEGF is one of the most potent angiogenic factors known and is thought to function as a endogenous regulator of endothelial integrity. Several studies indicate that inflammation plays a pivotal role in the pathophysiology of essential hypertension. Vascular endothelial growth factor (VEGF) is currently discussed as a possible mediator of inflammation. Animal studies have revealed that VEGF promotes endothelial regeneration and induces migration and activation of monocyte through induction of chemokines such as monocyte chemoattractant protein (MCP)-1. However, there is still a debate over the vasculoprotective versus pro-inflammatory effect of VEGF. We performed this study to investigate the hypothesis that VEGF and MCP-1 play a role as inflammatory mediators in essential hypertension. Thirty never treated patients with mild hypertension and 30 healthy controls were examined; serum levels of VEGF and MCP-1 were measured via commercially available enzyme linked immunoassay (R&D System). Hypertensive showed increased plasma levels of VEGF ($p < 0.05$) and MCP-1 ($p < 0.05$). VEGF positively correlated with mean arterial pressure/$r = 0.46$, $p < 0.05$); multivariate analysis demonstrated VEGF to be an independent predictors of MCP-1 levels. In this study, we observed increased plasma levels of VEGF and MCP-1 among patients with mild uncomplicated hypertension, who were free of target organ damage; stepwise multivariate analysis suggest that elevated VEGF levels contribute to the elevated MCP-1 levels. This study suggest that in mild hypertension, inflammatory pathway have already been activated. In conclusion, the present study seems to suggest new insights into the pathophysiological mechanisms in essential hypertension linking inflammation and vascular endothelial growth factor.

Nephrology

Heart and kidney: if one's diseased, better keep a close eye on the other

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In November 2009 a 53 year-old white man with 2 years history of stage I primary arterial hypertension was admitted to our hospital because of oliguria.

On clinical history, he receveid diagnosis of mild kidney disease with reduced GFR (chronic kidney failure stage 2—creatinine clearance 60 ml/min/1.73 m^2) 2 months before.

Two weeks prior to this admission, laboratory investigations (blood cell count, serum biochemistry and urinalysis) didn't show meaningful alterations. He referred for 5 days bad control of his blood pressure (on therapy with low salt diet, telmisartan + HCT 80/12.5 mg/day, nifedipine 30 mg/day and furosemide 25 mg every 48 h) and progressive oliguria, without prodromal symptoms (fever, rash, diarrhea, urinary symptoms or sore throat). On examination, he was afebrile, his blood pressure was 90/60 mmHg, he had faint heart sounds and bilateral mild leg pitting edema. No thoracic pain, no neurological signs, no evidence of blood loss. He was not compliant to monitoring its diuresis so we put on urinary catheter (urine output 25 ml/h); abdominal US didn't revealed urinary tract obstruction. Rapid urinalysis revealed proteinuria (++) and microhematuria. The chest radiogram showed enlargement of cardiac silhouette. His ECG showed sinus tachycardia with inverted T waves only in aVL and mild antero-lateral ST segment elevation, no significative alteration of PR segment, T waves and QT segment. Serum biomarkers of myocardial necrosis were absent. Laboratory tests disclosed a leukocyte count of 12,400 mm^{-3} with normal differential, hemoglobulin 15.4 g/dl, HCT 44%, platelet count 507,000 mm^{-3}, BUN 312 mg/dl, creatinine 21.41 mg/dl (it was not an errour!!! we reapeated test three times), serum albumin 3.4 g/dl, C-reactive protein 4.6 mg/dl, LDH 906 U/l, phosphore 20 mg/dl, sodium 132 mmol/l and potassium 6.26 mmol/l. ANA, tine test, TORCH study, tumoral markers were negative. Moderate posterior pericardial effusion without hemodynamic alterations was confirmed by echocardiography and the patient suddenly received intensive hemodialysis to relieve uremic symptoms. Three days later was seen improvement in renal function, which definitively settled within 10 days (creatinine clearance 48 ml/min/1.73 m^2). Acute pericarditis presentation may be subtle. Thoracic pain is the most common symptom but is absent in many cases. Fever, malaise, and non productive cough are frequent. Viral and bacterial pericarditis usually present with dramatic symptoms, but uremic and tuberculous pericarditis often go unnoticed by the patient. To direct a specific treatment, it is important to be aware of the causes of pericarditis. Uremic pericarditis has become very rare nowadays. It results from inflammation of the visceral and parietal pericardium and correlates with the degree of azotemia (BUN $>$ 60 mg/dl) has a good response to dialysis. Therefore, chronic dialysis can cause stubbornly recurrent pericarditis, called "dialysis pericarditis", in up to 13% of patients on maintenance haemodialysis. In uremic patients, also during tamponade, autonomic impairment allows heart rate to remain slow (60–80 beats/min), despite fever and hypotension. The ECG does not show the typical diffuse ST/T wave elevations observed with other causes of acute pericarditis due to the lack of the myocardial inflammation. If the ECG is typical of acute pericarditis, intercurrent infection must be suspected. Most patients with uremic pericarditis respond rapidly to haemo- or peritoneal dialysis with resolution of symptoms, without requiring chronic maintenance hemodialysis, as our patient.

A proteinuria that should not be underestimated

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A 73-year-old man was admitted to hospital because of newly onset of nephrotic proteinuria and peripheral edema. He did not reported—fever, dysuria, hematuria, joint pain or new drugs assumption. He had a past history of benign prostatic hyperplasia, previous HBV infection, and arterial hypertension. Three months before hospital admission, evidence of bilateral lung consolidations with pleural effusion investigated with bronchoalveolar lavage and thoracentesis (fluid cytologies and microscopic and cultural examination including tuberculosis negative), Computed Tomography(CT) and Positron Emission Tomography (that revealed mild increased tracer uptake suggestive of inflammatory nature)—The patient was treated with unspecified antibiotics. A new -CT scan was-l performed 15 days before admission revealed improvement in lung consolidations. Medications included finasteride and amlodipina. Physical examination -did not show any pathological condition—except for the presence of peripheral edema. Arterial blood pressure, pulse rate and respiratory reate were normal. Irbesartan, simvastatin and furosemide were administered with weight loss and reduction of peripheral edema. Laboratory tests showed—proteinuria (6 g/24 h) with low levels of total serum proteins (5.2 g/dL) and albumin (2.9 g/dL) associated with—mild normocytic anemia, high erythrocyte sedimentation rate, increased levels of ferritin (serum iron and transferrin levels within normal range), hypercholesterolemia and low levels of IgG. All the other tests—were normal (immunoglobulins, creatinine, urinary sodium and potassium, glicemia, liver and thyroid function, ANA, ENA, anti-DNA antibodies, c-ANCA, p-ANCA, C3, C4, rheumatoid factor and tumor markers such as CEA, CA19-9, PSA and alphafetoprotein). No monoclonal peak was found on protein electrophoresis. Serologic tests showed previous HBV infection and was negative for HCV infection. Urinary sediment revealed mild microhematuria, and hyaline, hyaline-granular and granular-fatty casts with lipiduria. A diagnostic procedure with renal biopsy was performed and histological examination revealed membranous nephropathy (MN) with atypical features. Patient's age and the absence of autoimmune or infesctious disease, suggested the hypothesis of a malignancy-associated MN. In order to investigate the presence of a neoplastic lesion, an esophago-gastro-duodenoscopy and a colonoscopy were performed and resulted negative. CT scan of the chest, abdomen and pelvis revealed an improvement in lung consolidations and showed a liver lesion suggestive for (?) hepatocarcinoma so the patient was referred to surgical evaluation. Membranous nephropathy (MN) is one of the most common causes of the nephrotic syndrome in nondiabetic adults. Although the most of MN are idiopathic (approximately 75%), 25% of cases

have been associated with hepatitis B antigenemia, hepatitis C virus (rare), autoimmune diseases (systemic lupus erythematosus), thyroiditis, use of certain drugs (such as penicillamine and nonsteroidal anti-inflammatory) and malignancies. In fact, up to 5–20% of adults with MN, mostly those over the age of 65 years and with atypical pattern on renal biopsy, have been reported to have a malignancy, commonly a solid tumor. The risk of malignancy in a patient with MN can vary from 2 to 12 times higher than that observed in the general population after adjustment for age and gender. The interesting aspect of this case lies in the mode of presentation of the disease. In the cases of nephrotic proteinuria where the etiology is not immediately apparent and particularly in the presence of a histological pattern of membranous nephropathy with atypical features in an elderly patient, the possible presence of a neoplastic lesion should always be considered and then investigated.

Recurrence of kidney calcium stones: calcium intake or calcium restriction? Current recommendations

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About 10% of people will experience nephrolithiasis in their lifetime, and about 70% of those will have recurrences. About 80% of stones are calcium based, and about 80% of those are calcium oxalate stones. Both genetic and environmental factors contribute to stone formation, but the genes responsible for the heritable aspect of stone formation have not been delineated definitively. Hypercalciuria is the most common trait associated with calcium stones, yet its cause in most patients remains unclear. It is still often referred to as "idiopathic hypercalciuria". Many patients with hypercalciuria have increased intestinal absorption of calcium. A low-calcium diet is recommended to prevent recurrent stones in these patients Recently, the efficacy of a low-calcium diet has been questioned, and greater emphasis has been placed on reducing the intake of animal protein and salt. For several reasons, a calcium-restricted diet is not advised for patients with idiopathic hypercalciuria. Dietary calcium restriction can put the patient into negative calcium balance. Further, it is thought that with less calcium to bind to dietary oxalate, more unbound oxalate can be absorbed in the colon and eventually excreted in the urine. This increase in urinary oxalate can be to the point of supersaturation, even though urinary calcium levels remain unchanged. This, in turn, increases the likelihood of stone formation. Several studies showed that a higher intake of dietary calcium is actually associated with fewer calcium stone events in both men and women. A study in 120 Italian patients with hypercalciuric calcium oxalate stones concluded that a diet that is normal in calcium, low in sodium, and low in animal protein was associated with a lower frequency of calcium stones than a low-calcium diet. During 5 years of follow-up, cumulative incidence of stone recurrence was 20% in the normal-calcium group and 38% in the low-calcium group: a significant difference. Urinary calcium levels dropped in both groups, but urinary oxalate levels decreased in the normal-calcium group and increased in the low-calcium group. Thus, calcium-oxalate saturation in the urine was significantly lower in the normal-calcium group than in the low-calcium group (Borghi L. et all). Calcium intake should not be restricted unless there are very strong reasons because of the inverse relationship between dietary calcium and calcium stone formation. The minimum daily requirement for calcium is 800 mg and the general recommendation is 1,000 mg/day. Calcium supplements are not recommended except in cases of enteric hyperoxaluria, when additional calcium should be ingested with meals to bind intestinal oxalate. The absorption of calcium from fortified beverages is generally less than that of milk and cannot be considered a reliable source of bioavailable calcium. Mineral water, on the other hand, appears to be a good source of bioavailable calcium and should be considered a calorie-free alternative to carbonated beverages. An inverse relationship between high fluid intake and stone formation has been demonstrated. The general recommendation for calcium stone formers is to maintain a high urine flow with a generous intake of fluids. The aim should be to obtain a 24-h urine volume of at least 2 L. Randomized trials show also that reduced intake Na and Cl could play a role in reducing urinary calcium concentrations and urinary urate levels; restriction of animal protein reduces the synthesis of endogenous oxalate. The clinical evidence suggests that a diet rich in fruits and vegetables decreases calcium and increases citrate excretion with affecting on the solubility of other crystals and prevent recurrence of kidney stones.

Cystatin C as "troponin-like" marker for acute kidney injury in an hospitalized popolation

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Preface and aim of the study: The Acute Kidney Injury is currently defined and stratified according to the AKIN diagnostic criteria (Acute Kidney Injury Network), and its diagnosis would be eased by the location of a troponin-like biomarker for Kidney Injuries. The aim of this study is to evaluate the effectiveness of the usage of cystatin C as a "troponin-like" marker for Acute Kidney Injuries.
Materials and methods: Each patient hospitalized betwen 02 May 2008 and 01 July 2008 has been examinated. The main targets were: the evaluation of cystatin C as biomarker of Acute Kidney Injury; the determination of an appropriate treshold value for clinical application; the determination of mortality rates during hospitalization and the time of average confinement. To evaluate the area under the curve(AUC) the dates have been showed using the Receiver Operating Characteristic (ROC).
Results: Out of 206 examinated patients, 57 (27.7%) presented an Acute Kidney Injury, 32 (56.1%) were in AKI class 1, 8 (14.1%) in class 2, 17 (29.8) in class 3. The average levels of cys C were 1.2 and 2.45 mg/l in AKI patients. The area under the curve resulted 89 $\pm$ 2.8 confirmig cystatin C effectiveness in predicting AKI.
Conclusions: This study has confirmed Cystatin C quality as a "troponin-like" marker in relation to AKI (AUC-ROS 89% vs creatinine 70%). In the future the disease will likely be analysed according an "AKI panel" that will take consideration of many different markers. Because of its characteristics, and because of its reliability in an early and sensitive diagnose of the Acute Kjdney Injury, Cystatin C should be considered as a future part of this panel.

Correlation between contrast enhanced ultrasonography (CEUS) and histological grading in chronic glomerulonephritis: preliminary data

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Background and purpose of the study: In nephrology, Contrast Enhanced Ultrasonography (CEUS) allows the study of kidney focal

lesions and vascular diseases and is safely employed in patients with contraindications for the use of Magnetic Resonance and Computed Tomography contrast agents (EFSUMB Study Group, Ultraschall Med 2008, 29: 28–44). To date, CEUS is not employed for renal parenchymal diseases evaluation. We looked for a correlation between time/intensity (t/i) curves derived from CEUS and histological parameters in patients with chronic glomerulonephritis and preserved renal function.

Methods: 31 patients with biopsy-proven glomerulonephritis and glomerular filtration rate >60 ml/min underwent to CEUS. t/i curves were obtained, and derived parameters were correlated with a histological grading developed by two blinded pathologists and based on activity and chronicity indices scores (Table 1). Statistical analysis was performed by Spearman's rank correlation.

Results: Comparing t/i curves with the histological grading, we found that wash-out profile was correlated with disease activity indices: wash-out signal intensity, area under the curve during wash-out, wash-out slope (respectively: $\rho_s = 0.46$, $p = 0.03$, $\rho_s = 0.43$, $p = 0.01$, $\rho_s = -0.36$, $p = 0.03$). The histological element that appeared to be correlated with CEUS was mesangial hyperplasia.

Conclusions: Present data seem indicate that active glomerular lesions characterized by mesangial hyperplasia impair the regular contrast agent wash-out in patients with still preserved renal function. Our data suggest a possible role for CEUS in the evaluation of disease activity in patients with early stages of glomerulonephritis and in their follow-up during therapy.

Table 1 Histological grading

Activity	Chronicity
Mesangial hyperplasia	Glomerular sclerosis
Subendothelial deposits	Fibrotic crescents
Cellular crescents	Tubular atrophy
Fibrinoid necrosis	Interstitial fibrosis
Leucocyte infiltrate	
Interstitial infiltrate	

Miscellanea

An unusual evolution in a common intraabdominal infection

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We report the case of a 78-year-old man admitted to our ward complaining fever (up to 39°C), shiver, abdominal pain and dysuria since 5 days. At home he had been treated with amoxicillin clavulanate for the last 4 days. He was affected by hypertension, chronic renal failure, diabetes mellitus, benign prostatic hypertrophy. On arrival, clinical examination revealed mild hypogastric pain, with normal bowel sounds. His blood pressure was 140/70 mmHg, his pulse rate was 60 bpm and he was apyretic. Laboratory tests showed mild leukocytosis (13,000 mm^{-3}), elevated creatinine (1.9 mg/dl) and elevated CRP (245.6 mg/L). Chest X-ray and Abdomen X-ray were negative. The following day his body temperature raised (38°C), so blood and urine cultures were performed. He was then treated with systemic antibiotic therapy (Ceftriaxone i.v.). Abdominal ultrasound (US) revealed echogenic material, corresponding to incomplete portal vein thrombosis, hepatic steatosis and colelitiasis. Absence of enhancing seemed to exclude a neoplastic thrombosis. Tests for neoplastic markers were actually negative. A differential diagnosis was made between venous thrombosis and pylephlebitis (infective suppurative thrombosis of the portal vein). Suspecting pylephlebitis Metronidazole was added to Ceftriaxone and anticoagulation with Low Molecular Weight Heparin (LMWH) was started (enoxaparine 3,000 U twice day), a lower dose adjusted for renal function. Abdominal US was repeated after 3 days; a mild hypoechogenic lesion with a small colliquated area was found out, consistent with an infective lesion. Cytoaspiration of such lesion was done, resulting in hematic material, fine needle biopsy was then performed and the histological examination was consistent with hepatic phlegmon. Persisting abdominal and epigastric pain, esophagogastroduodenoscopy was done, showing chronic antral gastropathy. After 2 weeks antibiotic therapy, there was no more abdominal pain and fever, inflammatory markers were also normalized. Colonoscopy was performed revealing a pattern consisting with recent diverticulitis. Abdominal US was then repeated and it showed complete resolution of hepatic phlegmon and 2 months later the thrombus was no more visible. Pylephlebitis is a rare condition that might complicate any intraabdominal or pelvic infection; it is often secondary to diverticulitis, appendicitis, biliary tree infection or inflammatory bowel disease. Our patient actually developed two complications of diverticulitis: pylephlebitis and hepatic phlegmon. Broad spectrum antibiotics are the major treatment approach to pylephlebitis. The role of anticoagulation therapy is still controversial, as there are no prospective randomized controlled studies and no consensus on its use. Diagnosis and treatment of pylephlebitis are difficult because there are no specific clinical signs, symptoms and laboratory features. Pylephlebitis is a serious condition with significant morbidity and mortality, raising up to 32%. Early diagnosis and immediate adequate treatment are the most important determinants for the prognosis.

Temporal arteritis: report of a case starting with a permanent loss of vision

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We report the case of a 81-year-old woman admitted to our hospital complaining epigastric and thoracic pain, irradiated to the neck and lower jaw; the patient also reported a modest occipital headache whose onset dated back few weeks before. The case history of the patient highlighted a permanent pace-maker implantation for recurrent syncope, chronic atrial fibrillation, aphasic transient ischemic attack, aortic and carotid atherosclerosis, percutaneus coronary

intervention for angina pectoris, glaucoma. The patient was on treatment with: Bisoprolol 5 mg 1 cp, Spironolactone 50 mg 1 cp, Transdermic nitrate 10 mg, Frusemide 500 mg ¼ cp, Warfarin 5 mg, Omega-3 fatty acids 1,000 mg 1 cp, Simvastatin 20 mg 1 cp. At the admission to our ward, the patient was apyretic and clinical examination revealed bilateral carotid bruit. Blood tests showed normal renal and liver function, normal haematological values, increased erythrocyte sedimentation rate and alpha 2 globulins. Troponin I serum levels were within normal limits, ECG showed no sign of cardiac ischemia, ecocardiographic examination revealed the presence of a moderate concentric hypertrophy of the left ventricle. Thoracic X ray was negative. Myocardial scintiscan showed the presence of a normal cardiac perfusion. Because of the persistence of epigastric pain, a EGDS was performed, demonstrating the presence of an acute gastritis. During hospitalization the patient complained of a severe headache, dyplopia and amaurosis fugax. For these reasons, a CT scan of the brain (chronic vascular encephalopathy with no acute ischemic lesions) as well as a Doppler ultrasound examination of carotid arteries (no significant stenosis) were performed. An ophthalmologic examination was also performed; it did not demonstrate any alteration of fundus oculi. Two days after, because of the relapse of amaurosis, a new ophthalmologic evaluation was repeated, now demonstrating the presence of a left ischemic optic neuropathy resulting in substantial visual loss. Because of the persistence of visual symptoms and the onset of bilateral pain in the temporal regions, tongue and scalp, claudicatio of the jaw, difficulty in swallowing and hearing loss with increased C– reactive protein (CRP) plasma levels, the presence of a temporal arteritis was suspected. This hypothesis was supported by a visible, enlarged and thickened temporal artery. So we started a high dose steroid therapy (methylprednisolone 125 mg i.v. 3 times a day) with a rapid improvement of headache and temporal pain. The visual problems remained stable, with a stability of the ophthalmologic test. Simultaneously, a biopsy of the temporal artery was performed, which confirmed the diagnosis of temporal arthritis. Abdominal ultrasound examination was also performed in order to exclude the presence of an aneurysm of the abdominal aorta (possible complication of this type of vasculitis). The patient continued the treatment with high dose of steroids: methylprednisolone 125 mg 3 times a day in the first 5 days, then 125 mg each day for 7 days. Then, blood examination showed reduction of CRP to almost normal levels, with a further improvement of jaw claudicatio and swallowing. Patient was discharged with methylprednisolone 75 mg each day to tapered progressively once the disease had been adequately controlled, low doses aspirin in addition to the oral anticoagulant therapy, and calcium, vitamin D and biphosphonate (prevention of osteoporosis). In conclusion, the case reported focuses on the possible misinterpretation, at least in the beginning, of a temporal arteritis in the presence of misleading signs and symptoms (history of cardiopathy and thoracic pain, absence of visual problems and headache). The timely use of a steroid therapy, after the first appearance of claudicatio of the jaw and of visual problems, allowed to limit permanent visual damage to the controlateral eye. Therefore, an in-depth clinical investigation might allow a correct diagnosis despite a misleading clinical presentation.

POEMS syndrome: when the internist can help the neurologist

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A 43-year-old woman was admitted to the hospital because of bilateral pitting edema of the lower extremities, mild pleural and pericardial effusion (revealed by a recent chest radiography and echocardiography) developed during the last month. She was suffering from 12 months history of demyelinating polyneuropathy (motor involvement was predominant) with multiple lesions of the cerebral white matter; oligoclonal spikes had been disclosed by protein electrophoresis in the cerebrospinal fluid (CSF).

Laboratory test results were remarkable for a monoclonal IgA—lambda component found out at the serum protein electrophoresis, as well as for antinuclear antibodies (showing a weak dotty pattern); folic acid and vitamin B12 were slightly decreased. The patient was taking, at home, Pregabalin 150 mg/day, she had recently received intravenous immunoglobulins (at high dose) with no clinical improvement. The failure of such treatment and the CSF analysis showing a normal protein content left out the "possible" diagnosis of chronic inflammatory demyelinating polyneuropathy. The general examination, at admission, showed normal blood pressure and heart rate, no fever, leg edema and a mild systolic murmur. The neurologic exam revealed a distal leg weakness and lower limb hypoesthesia with absent deep tendon reflexes. First level blood tests showed normal blood count (except for mild thrombocytosis), erythrocyte sedimentation rate, glucose, renal and liver function and confirmed a monoclonal IgA lambda component with Bence Jones' protein in the urine. Second level blood tests were also found mostly negative: serologies for hepatitis C, B, and cardiotropic viruses, rheumatologic tests, antinuclear antibodies, thyroid function. Echocardiography showed a small pericardial effusion (<300 ml) with a mild mitral insufficiency and precluded the hypothesis of a cardiac origin of the edema. Arterial and venous ultrasonography of the lower limbs was negative too. Mild splenomegaly but no ascites were found on abdominal and pelvis ultrasound. Electromyography reported decreases in evoked motor responses and absent sensory responses, as compeared with a previous study. Such features seemed to exclud hepatic, renal, immunologic and cardiovascular etiology of the edema. Amyloid neuropathy was also excluded on examination of a biopsy specimen of a fat pad. Amyloidosis in fact, may also be associated with neuropathy, as the result of deposits of abnormal light chains in the nervous tissues. A diagnosis of POEMS syndrome was then predicated on the following: polyneuropathy and monoclonal plasma cell proliferative disorder as well as pleural effusion, legs edema, splenomegaly. Such diagnosis actually requires the presence of at least two major criteria (the presence of sclerotic bone lesions, which is also a major criterion, was also found in this patient at the omeral and sacral standard radiography) and the fulfillment of at least two other minor criteria. Thrombocitosis and low vitamin B12 levels were also present and this association is often described. Magnetic

resonance imaging of the brain also revealed multiple enhanceing focal lesions of the white matter, as actually described in other patients with POEMS syndrome. We can then conclude that in presence of many features we can commonly found in our internistic ward (as those linked to extravascular volume overload), when associated to a demielynating polyneuropathy and monoclonal plasma cell proliferative disorder we must not miss to recognise a possible POEMS syndrome.

Unusual etiology in a case of pulmonary hypertension

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A 60-year-old woman, affected by IgG lambda monoclonal gammopathy of undetermined significance (MGUS) diagnosed in 1987, that switched into MGUS/multiple myeloma in 2006, presented with progressive dyspnoea, dry cough, and a 6-month history of unilateral recurring pleural effusion. Pulmonary and pleural biopsy showed non-specific chronic inflammation. Respiratory function tests revealed a restrictive pattern, while CT scan showed a ground glass opacification in the superior pulmonary lobes, bilateral diffuse pleural thickening, enlarged mediastinal lymph nodes. Moreover, the patient progressively developed severe pulmonary hypertension. At presentation we observed tachycardia, dyspnoea with hypossic hypocapnic respiratory failure, easily corrected with oxygen therapy, right massive pleural effusion, and minimal contra lateral effusion. A CT scan performed to rule out pulmonary embolism confirmed pulmonary ground glass opacities with enlarged mediastinal lymph nodes. An echocardiography showed left ventricular concentric thickening with "sparkling" appearance of the myocardium, slight right ventricular diastolic dysfunction, and pulmonary hypertension (estimated pulmonary arterial pressure 53 mmHg, similar to previous data). As the echocardiographic results were suggestive of amyloid cardiomyopathy, we performed Congo red staining on the pulmonary specimen obtained during the previous thoracoscopy, demonstrating the presence of AL amyloid deposits. Treatment with melphalan and prednisone associated to bortezomib courses was initiated first on an inpatient basis. The diagnosis was made 8 months ago and the patient is still alive. The cough disappeared after the first administration of prednisone while the lung effusion still persists. The clinical presentation in AL amyloidosis depends on the number and nature of the organs affected. The major sites of clinically important amyloid deposition are in the kidneys, liver, and heart. Although it has long been known that primary systemic amyloidosis has a propensity to involve the lung, cases have been infrequently reported. Pulmonary interstitial involvement with amyloid has been recognized in both AL and AA types; persistent pleural effusions develop in 1–2% of patients with systemic amyloidosis, and appear to be caused by pleural infiltration with amyloid deposits. Pulmonary hypertension with right-sided cardiac failure is a rare complication of amyloidosis and its natural history is non-well defined.

Subdural hematoma in intracranial hypotension syndrome: indications and results of surgical treatment

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Spontaneous intracranial hypotension syndrome is a rare physiopathologic entity. This can be due to various causes. Treatment of spontaneous intracranial hypotension syndrome is often conservative, but cases not responsive to medical treatment have to be treated with an epidural blood patch. This procedure stimulates the scar formation in the cerebrospinal fluid fistula site. However the clinical corse of patiets affected by spontaneous intracranial hypotension syndrome can be complicated by a subdural hematoma. This complication occurs in the 10% of patients. Aim of this paper is to analyze all cases of subdural hematoma in patients affected by spontaneous intracranial hypotension syndrome reported in the literature, included four personal cases, and to analyze the outcome related to the hematoma features and of treatment.

Chronic heart failure management program

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Clinical background: Chronic Heart Failure (CHF) is one of the most remarkable health problem for prevalence (until 2% in west countries), morbidity and mortality. CHF is a disease of the elderly: approximately 80% of the patients hospitalized with CHF are more than 65 years old. CHF has strong impact in terms of social and economic effects: very frequent hospital admissions and significant increase of medical costs. CHF elderly patients demand for an effective and integrated disease management program, because in this patients are present: Poor self-care, High prevalence of comorbidities (COPD, diabetes, hypertension, anaemia, renal dysfunction, cancer), High prevalence of diastolic heart failure, Polypharmacy, Physical and cognitive limitations (Difficult transfers to the hospital), Inadequate social support and social isolation, Depression and anxiety, High incidence of precipitating factors, Poor education, Poor compliance to therapy (pharmacological and not), Need of frequent reassessments.
Management program*:* Patients Elderly and with concomitant diseases (the patient himself and his family are considered as active users). Personnel Multidisciplinary team providing specialized follow-up: Nurse (responsible of education and follow-up), Specialist (internist, geriatrician, cardiologist), Dietician, psychologist, social assistant. Primary care physician: Telephone follow-up and improved communication.

Methods: Home assistance, Improved communication (Easy and frequent telephonic contacts).
Interventions: Patients and family education, Diet counseling, Therapy adjustment, Increase in compliance to diet and therapy, Intensive follow-up for early detection and treatment, Episodes of WHF, Concomitant diseases (e.g. infections).
Aims: Reduction in the incidence of hospitalizations, Improvement in the clinical course/quality of life, Reduction in management costs.

Migraine is associated with impaired norepinephrine-induced vasoconstriction

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Several studies have postulated an association between migraine and an increased risk of cardiovascular events, such as stroke and coronary artery disease. Recently, it has been demonstrated that patients with migraine studied during the interictal period show an abnormal vascular reactivity due to a distinct defect of the vascular smooth muscle cells to vasodilate in response to nitric oxide. However, it is unclear whether the vasoconstrictory response is preserved. To clarify whether in patients with migraine the vasoconstrictory response is impaired, we studied 11 patients with migraine (M) during the interval between the headache attacks and compared them with 11 healthy controls (C). We measured forearm blood flow (FBF) by strain-gauge plethismography during intra-brachial, graded infusion of norepinephrine (NE, 140–560 ng/l/min). Basal FBF was similar in M and in C (2.46 ± 0.36 and 3.06 ± 0.23 ml/dl/min, respectively). During NE infusion, FBF decreased by 1.59 ± 0.21 ml/dl/min in C and by 0.40 ± 0.28 in M, $p = 0.003$. The slope of the dose response curve was -2.5 ± 0.3 in C and -0.8 ± 0.5 µl/dl/min/ng in M, $p = 0.006$. In conclusion: in patients with migraine studied in the interval between the attacks, the vasoconstrictory response to norepinephrine is severely impaired. The data suggest that migraine is characterized by a complex vasomotion disturbance that involves both the vasodilatory as well as the vasoconstrictory ability of the resistance vessels.

Quality appraisal of syncope guidelines

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Background: In 2009 the European Society of Cardiology (ESC) published a new version of Guidelines for the diagnosis and management of syncope [1]. A standardized-care pathway developed in strict adherence to ESC Guidelines recommandations has previously shown to improve significantly the overall diagnostic yield and to reduce hospital admissions, resource consumption and global costs of syncope management [2]. However, no studies attempted to evaluate guidelines methodological quality. AGREE (Appraisal of Guidelines for Research and Evaluation) is an international board of researchers who seek to improve the quality and effectiveness of clinical practice guidelines by establishing a shared framework for their development, reporting and assessment. A validated, general methodology has been proposed as a tool to evaluate clinical guidelines in any disease area. The aim of our study was to assess the methodological quality of ESC Syncope Guidelines (version 2009) by using the AGREE Instrument.
Methods: The ESC syncope guidelines were assessed independently by four appraisers. The AGREE Instrument [3] consists of 23 key items organized in six domains: scope and purpose (items 1–3), stakeholder involvement (4–7), rigour of development (8–14), clarity and presentation (15–18), applicability (19–21), and editorial independence (21–23). Each item is rated on a four point scale, ranging from 4 ("strongly agree") to 1 ("strongly disagree"), that measures the extent to which the item has been fulfilled. Domain scores were calculated by summing up all the single scores of each item contained in a domain and by normalizing the total as a percentage of the maximum possible score for that domain. The number of high rated [3, 4] items and the balance between the domains were finally used to determine the overall assessment of the guideline (guideline should/should not be recommended for use in practice) [4].
Results: The guideline rated high [3, 4] on 62% of the items considered.
Conclusions: According to our appraisal, ESC Syncope Guidelines showed a sufficient overall quality and could be recommanded for use in clinical practice. Indeed, in accordance with AGREE instructions, they rated high on the majority of items and most domains scores were above 60% (4). Nevertheless they showed weaknesses in the fields of stakeholder involvement and rigour of development. This could be partially due to the lack of high quality studies on syncope investigation and treatment. Low scores could also be explained by bad reporting, because when no information is provided about an assessment item, the resultant domain score will be lower. Our findings suggest that further efforts are required to ensure the highest possible quality for clinical recommandations in syncope management.

Table 1 The overall assessment scores for each of the six domains evaluated

Domain	Score (%)
Scope and purpose	78
Stakeholder involvement	41
Rigour of development	54
Clarity and presentation	77
Applicability	64
Editorial independence	75

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Internal medicine, graded care hospitals and the heterogeneity of patients at admission

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Health care organizations are at a crucial crossroad in the challenge to provide improved patient care quality and services in an environment of complex rapid changes and constrained resources. In this context, the so-called model of "graded care hospital" is being proposed to enhance efficiency and efficacy of the patient-centered care. A first requirement is the correct allocation of the patient at admission, which must take into account the severity of the disease, the presence of comorbidities, and the nursing care needs. To identify the parameters to be used in internal medicine to distinguish different grades of intensity of care, our institution is partecipating in a multicentric prospective study promoted by the Health Councillorship of the Lombardy Region. A first step was to describe the population of internal medicine patients using a comprehensive and interdisciplinary approach. Here we present some preliminary data concerning the first series of our patients, consisting of 100 subjects consecutively admitted to our ward, through emergency, in January 2010 (a second series is now under recruitment); 52 were females; the age ranged 18–99, with a median of 78 years. To identify patients at risk of deterioration, we applied the Modified Early Warning Score (MEWS), a tool for bedside evaluation based on five physiological parameters: systolic blood pressure, pulse rate, respiratory rate, temperature and AVPU [Alert, Reacting to Voice, Reacting to Pain, Unresponsive] score; scores $\geq$5 are associated with increased risk of death [1]. To measure comorbidity and severity we used the Cumulative Illness Rating Scale (CIRS), structured in 14 organ systems; it rates the presence and the severity of a disease for each system according to operationalized criteria on a 5-point scale (ranging from 0 = no impairment to 4 = extremely severe); the comorbidity index (CI) is defined as the number of organ systems with a rating $\geq$2; the severity index (SI) is defined as the mean of points [=points for all items except psychiatric/13] [2]. The nursing care needs were quantified by an Intensive Care Nursing Index (ICNI), which rates the needs of 10 functions (physiological and related to diagnostic/therapeutic procedures) according to a 4-point scale (from 1 = no need to 4 = completely dependent).

At admission to our ward, after having initially been treated in the emergency ward, our patients had the following mean values ($\pm$ SD): MEWS 1.42 $\pm$ 1.39; CIRS-CI 4.35 $\pm$ 1.64; CIRS-SI 0.94 $\pm$ 0.35; ICNI 2.21 $\pm$ 1.24, with the following distributions:

Population aging and the internal medicine, what role for a continuity of care service, our experience in the province of Lecco

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A trend towards the aging of the population and an increase in life expectancy in industrialized countries, associated with the increase of chronic diseases, are critical for today's Health Services being responsible for an uncontrolled health spending and also for the overcrowding of Emergency Rooms and wards, particularly the Departments of Internal Medicine. Some interesting studies are focused on the characteristics of the patients admitted to a ward of Internal Medicine, highlighting the prevalence of patients aged 65 or more, with many comorbidity and the high rates of hospital readmission, length of hospitalization and inappropriate recovery. Currently only 18–20% of patients have assisted discharge despite the high rates of patients with functional impairment. Medical errors often occur when patients move between care settings. Effective transitional care processes, linked with strong home care programs can reduce re-hospitalization by a third in some less intensive models and by half or more in some more intensive models. These data suggest that improving the relationship between hospital and Territorial Services is crucial to assure appropriateness of patient care and optimal use of a Specialistic division, in fact Hospital discharge planning is aimed to decrease length of stay in hospitals as well as to ensure continuity of health care. Our "Frailty Department" operates throughout the province of Lecco providing quality home care for geriatric and frail patients through the coordinated work of multidisciplinary teams comprising medical specialists, nurses, rehabilitation therapists, dietitians, psychologists and social workers, in collaboration with General Practitioners. Since 2007 we have also been directly involved in the Continuity of Care within the Hospital of Lecco, playing the role of Care Management and Governance of the Network during the transition between Hospital care and Territorial Services. We present here the work of the last 3 years. From 2007 to 2009 our Continuity of Care Service has received over 3,000 requests of protected discharge from Hospital, every patient has been evaluated and 2,788 of these had receives continued care at home followed by our teams, with different intensities of care depending on the underlying diseases. Of these patients 53% are 75 years or more and 36% were discharged from Internal Medicine Department. A careful analysis of our data highlights the great importance of the relationship between Hospital and Territorial Services, so we think that every acute care hospital should adopt a well structured transitional care service dedicated to the Management of Continuity of Care for older and frail patients, able to reduce the hospital stay,optimize the appropriateness of care, and not least allowing to reduce healthcare costs and the proper use of a Specialistic Division such as Internal Medicine.

Serological effects of temporary interruption of imiglucerase (Cerezyme) therapy in three adult patients with stable Gaucher disease type 1

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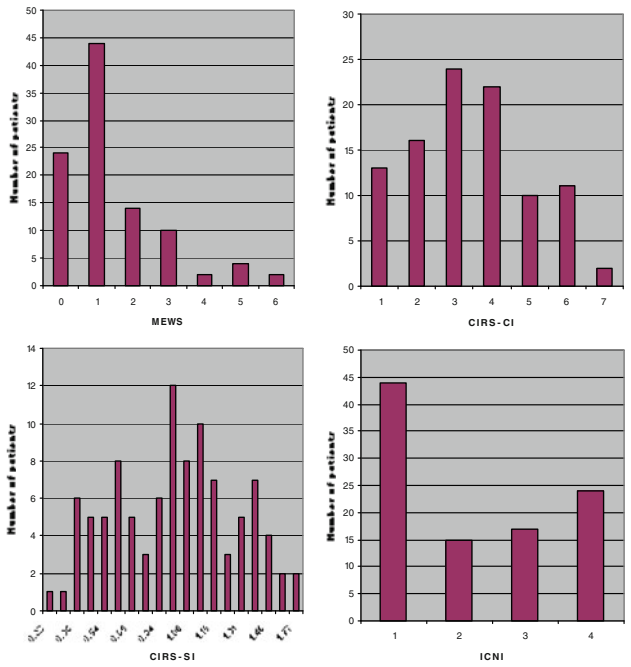
Introduction: Gaucher disease is an autosomal recessive lysosomal storage disorder, in which a deficiency of the enzyme glucocerebrosidase leads to the accumulation of glucocerebroside in the mononuclear phagocyte system, predominantly in liver, spleen and bone marrow. The type 1 is the most frequent and non-neuronopathic form, characterized by cytopenia and involvement of spleen, liver and bone marrow. Enzyme replacement treatment (ERT) with imiglucerase (Cerezyme®) is the standard of care for the treatment of patients with Gaucher disease type 1. In June 2009 an acute shortage of imiglucerase has occurred as a result of viral contamination of the production facility. The clinical implication of temporary interruption of treatment was not easy to predict.

Cases and results: Three adult patients with stable Gaucher disease type 1, who were in low frequency administration treatment schedule with usual monthly cumulative dose (respectively 60 U/kg/4 weeks for two patients and 56 U/kg/4 weeks for the last one), were followed during the period of imiglucerase therapy's acute lack. We recorded

changes from baseline in haemoglobin, platelets, chitotriosidase, liver enzymes, ferritin and ACE (angiotensin-converting enzyme) levels. Accordingly to the severity of the disease, two patients required enzyme replacement therapy after 4 months of interruption, nevertheless at the minimum dosage available (20 U/kg/4 weeks), the third one after 6 months (25 U/kg/4 weeks).

Conclusions: Our experience of abrupt withdrawal of treatment in 3 adult patients with type 1 Gaucher disease demonstrated the usefulness of enzyme replacement therapy even in older age and clinically stable patients. A close monitoring allowed only a temporary suspension of ERT, because the prevalent haematological involvement of the disease required to restart ERT after 4–6 months. Future alternative treatments should be considered in order to maintain clinical-serological improvements previously obtained with imiglucerase therapy and prevent irreversible complications.

At day 3 after admission, 3 patients had died and 2 had been transferred to another ward; in the remaining ones, MEWS was reduced in 56%, stable in 34%, increased in 9%; ICNI was reduced in 13%, stable in 73%, increased in 14%, thus suggesting a trend towards improvement in clinical status, while the nursing care needs had remained substantially unchanged. Since 29 parameters (5 for MEWS + 14 for CIRS + 10 for ICNI) are too many to be routinely collected at admission to grade the intensity of care in each individual patient, a statistical analysis of their relationships will be performed to verify if a very limited set of them is suitable for a practical bedside use. To preserve the power of statistics planned at the beginning of the multicentric study, such an analysis will be performed only on the cumulative series of patients, after having completed the recruitment by all the partecipating centers.



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Healthcare resource use and costs among chronic and episodic migraine in Italy

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Background: Migraine is a common, disabling neurological disorder that imposes a significant burden on patients and healthcare systems.
Objective: The purpose of this study was to evaluate resource use (RU) and associated costs in chronic migraine (CM) and episodic migraine (EM) patients in Italy.
Methods: Cross-sectional data were collected via a web-based survey from February to April 2009. Respondents were classified as CM ($\geq$15 headache days/month) or EM ($\leq$14 headache days/month). Data collection included baseline demographic and clinical characteristics and medical RU for headache treatment (clinician visits and hospitalizations over the last 3 months and medications used over the last 4 weeks). Unit cost data were collected separately from the web-based survey using publicly available sources and applied to RU profiles. Cost estimates were annualized and presented in 2010 €. Cost calculations included imputation of missing RU data using mean values of the non-missing participants. Group comparisons of medical RU were made using Fisher's exact test.
Results: Of the 7,692 Italian panellists contacted, the final study sample comprised 976 respondents who met migraine criteria; 6% CM ($n = 55$), 94% EM ($n = 921$). The sample was predominately female (82%) and middle-aged (mean age 37). CM reported more severe headache pain (100 vs. 78%) and more comorbid health conditions than EM. Compared to EM, participants with CM were more likely to have a primary care provider (52.7 vs. 25.8%, $P < 0.001$) or neurologist/headache specialist visit (40.0 vs. 14.7%, $P < 0.001$). Similar proportions of CM and EM participants were treated in a hospital for headache (3.6 and 2.4%, $P = 0.64$). A greater proportion of CM participants reported having used headache-related medication over the last 4 weeks compared to EM (83.6 vs. 64.0%, $P = 0.002$). Mean annualized total per-patient costs were €1,801 higher for CM than EM (CM €2,631 vs. EM €830, $P < 0.001$).

Conclusions: CM was associated with higher medical RU and total costs compared to EM.
Study supported by: Allergan Inc.

Table 1 Healthcare resource use for headache treatment and associated costs

Study measure	CM ($n = 55$)	EM ($n = 921$)	P value
Primary care provider visits, *n*, % (95% CI)	29, 52.7% (39.5–65.9)	238, 25.8% (23.0–28.7)	<0.001
Neurologist/headache specialist visit, *n*, % (95% CI)	22, 40.0% (27.1–52.9)	135, 14.7% (12.4–16.9)	<0.001
Hospital admission, *n*, % (95% CI)	2, 3.6% (0.0–8.6)	22, 2.4% (1.4–3.4)	0.64
Use of medication for headache, *n*, % (95% CI)	46, 83.6% (73.9–93.4)	589, 64.0% (60.9–67.1)	0.002
Total annual costs per patient[a], mean (95% CI)	2,631 (1,621–4,271)	830 (739–936)	<0.001

CI confidence interval

[a] Missing RU data imputed using mean values of non-missing participants

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Allergology and Clinical Immunology

Secondary renal amyloidosis

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Introduction: Amyloidosis refers to a group of diseases due to the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. *Primary systemic amyloidosis* (AL amyloidosis) is composed of immunoglobulin (Ig) light chains (LCs) and arises from a clonal B cell disorder, whereas *secondary amyloidosis*, known as AA amyloidosis, is composed of the acute phase reactant serum amyloid A protein (SAA). Several other types of amyloidosis exist and are classified according to their precursor. AA amyloidosis mainly occurs as a complication of chronic inflammatory states (systemic autoimmune diseases, Chron's disease) or chronic infections such as tuberculosis or subacute bacterial endocarditis. However AA amyloidosis represent less than 1% of all cases of amyloidosis in USA and Europe. Moreover in Turkey and Middle East it has been described in association with Familial Mediterranean Fever. AA amyloidosis has only rarely been reported in association to Systemic Lupus Erythematosus (SLE). In these cases amyloidosis was diagnosed after a well established history of SLE. It is well known, indeed, that several years of inflammatory disease, causing chronic elevation of SAA, usually precede fibrils formation and deposition. We report the case of a woman in which renal AA amyloidosis represented an onset symptom of an undiagnosed SLE.
Case report: In February 2009 a 60-year-old woman came to our Outclinic Department with a history of asthenia, general uneasiness, polyarthritis, weight loss and a slight increase in blood pressure levels (BP 140/85 mmHg). In her past clinical history recurrent miscarriages, a thyroid nodule surgery and a previous renal tuberculosis were documented. She was affected by recurrent urinary infections. Laboratory tests showed a progressive increase of creatinine levels from 1.8 to 2.4 mg/dl and persistent microhaematuria with high values of C-reactive protein (CRP 61.5 mg/dl) and erythrocyte sedimentation rate (ESR 89 mm/h). Moreover positive anti-nuclear antibodies (ANA 1:160 homogeneous) and lupus anticoagulant (LAC) were documented. In the suspicion of a SLE a renal biopsy was performed which was consistent with the diagnosis of amyloidosis. The periumbilical fat biopsy confirmed the diagnosis. To further clarify the origin of the amyloid deposition the patient underwent serum and urine immunofixation. Serum κ and λ chains and 24 h proteinuria measurements were within normal range, whereas SAA was remarkably increased (42.1 mg/L, n.v. <6.4 mg/L). Thus, ultrastructural immunohistochemistry of periumbilical fat was performed which confirmed "amyloid deposition immunoreactive against a monoclonal anti-SSA antibody". Both cardiological and hepatic involvement were ruled out by laboratory and instrumental tests, thus the final diagnosis was "secondary AA amyloidosis with prevalent kidney involvement". Considering photosensitivity, polyarthritis, recurrent aftosis and positive ANA and LAC a diagnosis of AA amyloidosis secondary to SLE was made. The patient underwent corticosteroid and cholchicine treatment with a progressive reduction of the values of SAA (4.3 mg/L), ESR (11 mm/h) and CRP (<0.5 mg/dl). Creatinine levels stabilized at a value of about 2.8 mg/dl. After a follow-up period of 2 year there was no evidence of progression of the disease.
Conclusions: Renal AA amyloidosis represents a rare complication of the SLE that usually, develops after a long period of disease activity. In our case, interestingly, the detection of AA amyloidosis led to the diagnosis of a previously unknown SLE. Moreover, renal tuberculosis may have contribute to worsen the amyloidosis framework. We therefore would confirm the importance of the renal biopsy in patients with impairment of the renal function even in presence of other risk factors such as age or hypertension with the aim to perform the right diagnosis.

Clinical symptoms in a geriatric population sensitized to anisakis

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Anisakis simplex is responsible for allergic sensitization and gastrointestinal symptoms related to acute parasitism, known as gastroallergic anisakiasis. The most frequent allergic symptoms which arise after ingestion or contact with parasitized fish are: urticaria, broncospasm, angioedema, anaphylaxis. Gastrointestinal symptoms include cramps and abdominal pain, nausea, vomiting, diarrhea leading to acute abdomen. Anisakiasis has been most frequently reported in Japan, United States, the Scandinavian countries, the Netherlands and more recently in Spain but it has been rarely found in Italy. Thus far, nine Anisakis simplex antigens (allergens) have been characterized and particularly ES and Ani s 1, Ani s 4 and Ani s 5 have demonstrated their utility for diagnosis of Anisakis sensitization. In fact, allergenic reactions identified with Ani s 1 protein have been correlated to cross-reactivity between several

allergens, such as the dust-mite species. At the Geriatric lmmunoallergology Unit of the University of Bari, 180 subjects with allergic gastrointestinal symptoms were examined over a period of 2 months (March to May 2009). In particular, 21/180 patients presented the onset of symptom after having eaten raw fish. Therefore, the skin prick test (SPT) was performed with commercial Anisakis allergenes. In addition, the following allergens were used: cod, mussel, lobster, sardine, shrimp, D. Pteronissinus, D. Farinae. All patients were SPT positive to Ani s 1 and two patients demonstrated cross-reactivity with the dust-mite species and with the fish tested (3 patients with mussels, 3 patients with shrimp, 1 patient with lobster and 1 patient with sardines). The most important clinical reactions included angio-oedema (42%), urticaria (42%), gastrointestinal symptoms (24%), itching (14%), erythema (5%), and glottis oedema (14%). The latter patients were sent to emergency due to the severity of symptoms. These results are of great importance due to the habit of eating raw fish in this region however, this phenomenon would appear to be underestimated.

Does lung and abdominal bedside-ultrasound improve early diagnosis and patient allocation in subjects admitted from emergency (ED) into internal medicine (IM) departments?

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Aim: To evaluate the effect of lung and abdominal bedside-ultrasound (laBUS) on improving early diagnosis and patient allocation in a high (A) or low (B) level of care areas into a Department of Internal Medicine (IM).
Methods: From January 18th to March 17th 2010, we evaluated 215 subjects admitted from emergency department into our IM Unit (36 beds, A: 14 beds; B: 22 beds) of a 3rd level general Hospital (800 beds). Patients with stroke symptoms were excluded because previously addressed from ED to the Hospital Stroke Unit. At the arrival the patient was allocated in the appropriate level of care area according to its MEWS (1) score (A: $\geq$3 or B: $\leq$2). The MEWS score consisted of the sum of 5 clinical items (systolic blood pressure, heart rate, respiratory rate, body temperature and level of consciousness) graded 0–3. Between patients allocated in B area, any case with score = 2 in a single item underwent laBUS immediately after clinical evaluation. LaBUS was defined as a rapid US (time max: 8 min) to identify signs suggestive of interstitial syndrome (IS), alveolar consolidation (AC), pleural effusion (PE) for cardiorespiratory diseases and of cholecistytis/pancreatitis (CH/P), intestinal occlusion (IO) and free peritoneal fluid (FPF) for abdominal diseases. According to the positivity of any of LaBUS signs, patients were reallocated in the A area. Contingency 2 × 2 tables were used to calculate sensitivity (Se), specificity (Sp), positive and negative predictive values (PPV and NPV) for the MEWS score and laBUS separately as for their combination.
Results: A total of 71/215 (33%) admitted patients were allocated in A area and 23/144 (16%) subjects allocated in B area underwent laBUS, according a single MEWS item scored = 2. We found pathological US signs in 13/23 (56%) cases and early diagnosis were: IS (6), AC (3), PE (2), CH/P (2). In the days following admission 3/10 (30%) laBUS negative patients left in B area were reallocated in A for the developing of high level of care conditions (pulmonary embolism, coronary acute syndrome, low output heart failure). The accuracy for patient allocation of MEWS (a), laBUS (b) and their combination (c) were, respectively: Se = 81% (a), 81% (b), 96% (c); Sp = 100% (either for a, b,c); PPV = 100% (either for a, b,c); NPV = 89% (a), 70% (b) and 97%.
Conclusions: In patients admitted from ED in IM, laBUS may improve early diagnosis for cardiorespiratory and abdominal diseases as well patient allocation in appropriate level of care areas integrating clinical scores.
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Treatment of acute coronary syndrome in a hospital without a haemodynamic unit. Collaboration protocol between units of general medicine and of haemodynamic cardiology. One-year experience

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Introduction: Acute coronary syndrome (not STEMI) often needs early coronarograhy (as fast as possible). Its realization time depends on the Cardiology Department's availability of beds for patients after this surgical procedure; particularly for those patients not belonging to the Unit. The Board of our Public Corporation is made up of only one Coronarographic Unit in the biggest Hospital, and of another six smaller hospitals, each equipped with a General Medicine Department; our Medical Unit is short distance from the larger Hospital, only 6 km, which is a 15–20 min journey by ambulance.
Method: In 2009 we wrote a patient transfer protocol to speed up the execution of the revascularization procedure. Patients accessing our Hospital (Emergency Department or Medical Unit) would be enrolled in a fast dedicated transfer line and would be re-hospitalized in our Medical Unit as soon as they have completed the Coronarographic procedure in the Cardiology Surgical Emergency Room, without admission to this Unit.
Clinically unstable patients would remain in the Cardiology Unit for more specialized medical care.

In our clinical protocol guidelines we considered:

- patient selection principles;
- pre-operative criteria;
- the roles of all staff (medical and cardiological);
- therapies (who, where, when, paper registration);
- collateral effect treatments;
- ambulance transfer modalities with an internal doctor onboard the vehicle.

Results: In a 1-year period of protocol application (from April 2009 to April 2010) we treated 45 patients with ages ranging from 47 to 91 years old (medium age: 63,78) The following list shows our clinical achievements (divided in with or without re-hospitalization in our Unit):

- Transfers from medicine to coronarographic surgery room;
- numbers of coronarographic revascularizations;
- three vessels syndrome (requiring open-heart surgery);
- Aortic stenosis syndrome;
- Dilated heart disease;
- no need for revascularization procedure;
- no coronarographic procedure due to clinical instability;
- Rescue unit transfers.

The oldest woman died before the procedure and the oldest man was moved to the Rescue Unit.

None of the patients transferred to our Unit had clinical complications.
Discharge from our Unit was in the 48 h following surgical procedures.
In such a way we reduced the length of the hospitalization.
Conclusion: This clinical protocol allowed us to reduce the waiting list for haemodynamic procedures, improved clinical results, and shortened hospitalization time. We did not encounter critical points during the transfers or the need for rescue procedures on board the ambulance.

Case report: Lemierre syndrome or simply left internal jugular vein complete thrombosis?

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A 57 year old woman was enrolled in our Unity for a pain in her left thorax and a swelling at the basis of her left side of the neck. In her clinical history she had had a childhood paralysis with plegia in her left harm. In the last years she complained about osteo-articular aches with muscular contractions and reduced movements. In her recent history she had not had fever, sore throat or a cough; she was fatigued without lymphadenopathy. On physical examination she was mildly obese, aching, with the known left paralysis; a swelling in her left neck of about 5 × 7 cm, really close to the thyroid site. In effect it looked like a thyroid node and the diagnosis of sub-acute or acute thyroiditis was considered at first glance. Thyroid ultrasound examination showed that shelling was external of it and was in the neck soft tissue; so was performed a Total body TAC. In the haematologic exams the PCR was elevated: 25.4 mg/dl (ranging from 0.1 to 0.5) the white count was 16.51 mm^{-3}; Haemoglobin 13.4; Platelet count 381 mm^{-3}; AST 60 e ALT 73 U/l; LDH 273 (125–243); light movement of Di-Dimer 19.7 μU/ml; normal kidney functionality so as coagulation; normal were also thyroid function and its antibodies as well auto antibodies and neoplasm markers.

The TAC identified:

- Internal left jugular vein complete thrombosis extending from bulbar tract to the anonimous trunk confluence,
- flogistic thickening of the vein walls,
- Brachio-cefalicus trunk complete thrombosis getting near the confluence with the superior cava vein

No pulmunar nodes neither cerebral ones. Abdominal TAC was considered normal. Small fluid was present in the pericardium. Since the first recovery day she was treated with henoxaparin and ciprofloxacine because of light fever; anticoagulation therapy with warfarin was started. She was withdrawn from our ward few days later with a fast volume reduction of the neck swelling not aching any more, not fever; in good general condition; warfarin has been given as home therapy. In medical literature we find thrombophlebitis of internal jugular vein associated with Lemierre syndrome; this is defined as an "oropharynx bacterial infection characterized by thrombophlebitis in the internal jugular vein, leading to metastatic septic embolization and bacteriemia" In 81% of the cases the Fusobacterium necrophorum is the aetiologic agent. Diagnosis of Lemierre syndrome is not always straightforward as clinical features are variable and blood cultures are often negative. Our patient showed a short light fever so we did not blood cultures and needed antibiotic therapy for a week; the swelling reduced quite totally in few days with contemporary well being. Surely the paralysis could have contributed day after day to the vein thrombosis which extension was very long, so it was persistent to the neck swelling which was painful and hot: symptoms of an infection and was very responsive to ciprofloxacine. The patient could have suffered of an initial form of Lemierre Syndrome in persistent vein thrombosis.

Efficacy of a program for limiting salt intake in hypertensive patients in Calabria

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Excessive salt intake is associated with onset and progression of hypertension and other pathological conditions. The reduction in salt intake decreases blood pressure and reduce impact on morbidity and mortality. Salt consumption is high in Calabria. We wanted to assess, in a sample of hypertensive subjects in Cosenza, the possibility of reducing consumption of dietary salt through verbal and written recommendations. Secondary objectives were to know any reduction in blood pressure and the ability to increase the consumption of vegetables. We recruited the first 100 consecutive patients referred to our antihypertensive ambulatory. All the patients never received before diet recommendations about salt and food intake and all of them were stable with their medications for at least 3 months. The evaluation of input saline was done by determining the concentration of sodium and potassium in the urine of 24 h. For all patients was administered a questionnaire to gather information about food consumption and sodium intake. All subjects were instructed how to reduce the sodium intake and how to implement the consumption of vegetables. Patients were asked to use low sodium salt. Of the 100 patients, sixty completed the study (mean of follow-up: 13 weeks). Only 45% of subjects showed a reduction in sodium excretion (mean 0.0 ± 70.34 mg/24 h); the mean change was -47.31 ± 78.04 mg/24 h for patients that showed reduction of salt intake at the questionnaire. Only 18% of patients had regularly used low sodium salt. Of these users, all have achieved a reduction of sodium excretion of 24 h. For all 60 subjects was not obtained significant change in average pressure. For those who have achieved a reduction of sodium excretion, the change in systolic blood pressure was of −2.69 ± 15.69 mmHg. 80% of subjects increased the amount of vegetables in the diet (K-urine +8.41 ± 20.83 mg/24 h). The low percentage of patients returned to control may have affected results. The impact of therapeutic strategy based on dietary recommendations and written reports given to our patients appears to have been only partially effective. The difficulties encountered in implementing this program to reduce salt in diet could be due to established habits in the consumption of dietary salt in Calabria, which includes the use of large amounts of NaCl. It can be effective to change the intervention strategy with low sodium salt and increasing the motivation of our

patients about lowering the salt intake in the food.

Eosinophilia and myalgia in a 30-year-old man

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A 30-year-old man had been suffering from myalgias of upper and lower limbs for 7 months. Symptoms came up after a straining effort and were associated to progressive reduction on physical ability. History was silent for health troubles, but for a mild hypereosinophilia, which had been found 2 months before: stool exams for parasitical microorganism, viral serology, blood smear and abdominal ultrasound resulted negative. At clinical examination there were scleroatrophic areas on the extensory surface of the forearms and the patient was unable of bending and extending the wrists. Cutaneous and subcutaneous stiff oedema was rescountered on ankles and calves. Sclerodactylia and Raynaud phenomenon were absent. Eosinophils were persistently around 1,500 μL^{-1}. Capillaroscopy was negative. MRI of the right wrist showed fascial oedema; a biopsy from cutaneous to muscolar layers of the right wrist was performed and phlogosis with a prevalence of lymphocytes and histiocyte was highlighted. These findings together with the clinical picture promote the diagnosis of eosinophilic fascitis. Therapy was started with prednison 1 mg/kg/day with a clinical improvement in 2 weeks. Eosinophilic fascitis is a simil-sclerodermic disorder. Symmetric involvement of upper and lower limbs, but not of cinguli, with phlogosis, pain, stiffing oedema are present. Etiology is unknown. This disease comes up most frequently among 30 to 60-year-old people and often follows strenuous physical efforts. The first signs are fever and myalgia, followed by progressive stiffing oedema and reduction of joints movements. Hypereosinophilia, elevated ESR and occasionally ipergammaglobulinemia are found. Biopsy shows cutaneous, fascial and muscular infiltration with histiocyte, plasma cells, lymphocytes and sometimes eosinophils. MRI can show fascial thickening. The most of cases go to spontaneous remission or are well treated with steroids.

From anaphylactic shock to biliary fistula: evolution of a hydatic cyst

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A 74 aged woman was hospitalized in 1997 to anaphylactic shock due to spontaneous rupture of an hepatic hydatid cyst. During this hospitalization, ultrasonography and CT of the liver showed the presence of a 12 cm hydatid cyst and, inside, other cysts. At that time, was proposed to remove the cysts by surgery. According to the will of the patient, the surgical indication was amended in single drug therapy with albendazol. Patient was referred to the clinic of infectious diseases for the follow-up. After several cycles of albendazole, the cysts showed a reduction in volume. Since 2008, the size of the cyst showed, at echo, a slight increase, reaching 9.3 cm. For this reason patient underwent a new cycle of albendazole. The patient was now hospitalized to our Unit for onset of fever and weakness. Blood test showed PCr of 22.6 mg/l and ESR 120 mm 1 h. Clinical examination showed positivity of Murphy sign. Blood tests showed raised of cholestasis and inflammation index. Ultrasound showed a unique hydatic cysts at the liver and dilatation of the bile ducts. CT confirmed the liver formation, with daughters cysts, and a diameter of 15 cm. The cyst produced a mild compression of the bile ducts. The patient underwent to endoscopic retrograde cholangiopancreatography. With this exam, sphinterectomy of Oddy was performed followed by leakage of thick and dark mucus. In the late phase it showed opacification of the cystic formation due to biliary fistula with the cyst. The inflammation of bile tract was successfully treated with antibiotic therapy. The growth of echinococcus cyst in the liver can be followed in the rupture in the biliary tract. This complication occurs in about 5% of cases and may lead to fistula formation. The passage of cysts in the biliary tract can produce mechanical obstruction and infection of the cyst. Another possible complication is anaphylactic shock. This report seems to be interesting for the complications showed and for therapeutic implications. Infact, probably, the surgical therapy, proposal since the onset of infection, would resolved the disease, preventing the subsequent complications. The only medical therapy of hepatic hydatic cyst can resolve the disease in less than 30%. So we must kept in mind the need of surgery.

An unusual case of angioedema

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We report the case of a 30-year-old woman referring recent occurrence of exercise-induced recurrent non-pruritic painless swelling of the head, neck and extremities; she denied dyspnoea and abdominal pain. Antihistamines were used during some attacks with moderate improvement. Family history was negative, no drug exposure as well as suspicious food ingestion or insect stings were reported. Skin prick tests with common inhalant allergens and food allergen extracts were performed to rule out an allergic cause, and all them resulted negative. Routine blood investigations showed no abnormalities. Normal level of C3 and reduced levels of C4, C1q, C1INH were observed. The clinical presentation was suggestive of exercise-induced angioedema, but generally this condition is not associated with complement abnormalities that are more common in acquired angioedema (AAE). The differential diagnosis of angioedema includes allergic reaction to medications or foods, hereditary angioedema, acquired C1-INH deficiency, drugs related angioedema (ACE-I, NSAIDs, salicylates), environmental factors such as pressure on the skin and exercise. Finally it may occur in various other immune system disorders. Acquired C1-inhibitor deficiency is a rare syndrome characterised by localized subcutaneous non-itching swellings; unlike hereditary angioedema (HAE) it shows no family history of angioedema, characteristic onset of symptoms in middle age or later, lack of response to antihistamines or corticosteroids and inconstant response to C1-INH replacement. AAE is frequently associated with lymphoproliferative disorders, autoimmune deseases, less commonly with vasculitis or infections. C1 INH deficiency occurs as a result of (a) increased consumption by paraprotein or immunocomplexes (AAE

type 1), (b) direct cleavage by C1-INH autoantibodies (AAE type 2). In our case investigations for lymphoproliferative disorders by serum protein electrophoresis, serum and urine immunofixation, and flow cytometric analysis for monoclonal B or T cells proliferations yielded negative results. Anti-HCV, -HBV and -HIV antibodies were absent. The presence of an autoimmune disorder was excluded on the basis of history and laboratory examinations. In conclusion our patient presented unusual clinical features because, in spite of laboratory findings consistent with AAE, she developed symptoms only after exercise. Moreover she had improvement with antihistamines, and in particular the prophylactic treatment taken 1 h before the exercise was able to reduce clinical symptoms. Exercise-induced angioedema with a partial response to antihistamines has been described in literature, but to our knowledge complement defects are uncommon.

Macrophage activation syndrome (MAS) as a presenting feature of systemic lupus erythematosus (SLE)

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A 49-year-old woman had a clinical history that began at age 35, characterized by the presence of anemia, increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), hypergammaglobulinemia, symmetric polyarthritis involving the small joints in the hands and wrists, treated which resulted with improvement of symptoms. She was hospitalized in March because of fever and dyspnea. The chest CT scanning revealed interstitial pneumonia and pleural effusion, she was treated with antibiotic therapy for about 10 days. A medical examination showed fever, chest pain and cardipalmo and she was again hospitalized. At the clinical examination, she appeared unwell, febrile at 39°C, with a widespread vasculitic rash was present and most prominent on the legs. At the physical exam of the chest: dullness to percussion at the right base, with increased tactile fremitus and bilateral basal crackles. No evidence of lymphadenopathy was observed and the rest of the examination was unremarkable. During the hospitalization she presented pancitopenica, serum C3 level was decreased and antinuclear antibody, anti-dsDNA antibody, anti-SS-A, anti-SS-B, anti-Sm and anti-RNP antibody were positive. Furthermore she showed hyperferritinemia, hypofibrinogenemia, liver dysfunction with hypertriglyceridemia and raised liver enzymes, splenomegaly and bone marrow aspirate showed hemophagocytosis. Repeated urine and blood cultures were negative. Sputum was negative for bacterial and fungal cultures. A thorough infection screen, including a viral panel for Herpes Simplex, Herpes Zoster, Epstein-Barr, Cytomegalovirus, Hepatitis B, Hepatitis C, HIV, Echo and Coxsackie viruses was negative. She was diagnosed having Systemic lupus erythematosus (SLE) associated with Macrophage activation syndrome (MAS). She was treated only with corticosteroids (metilprednisolone) with improvement of symptoms.

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Endocarditis and lymphoma: what is the therapy?

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A 68 year old man presented with fever, anemia (6.8 g%), pancytopenia and weight loss. The fever, of 2 months duration, was characterized by daily intermittent peaks, accompanied by chills which did not respond to antimicrobial treatment. Chest X-ray was normal. Viral and serological investigations (Vidal-Writh and Weil-Felix, tests for leishmania and malaria) were negative. Blood cultures were positive for *Staphylococcus epidermidis*. A transesophageal echocardiography revealed valvular vegetations. Abdominal ultrasonography and total body CT scan demonstrated splenomegaly and enlarged lymph nodes. A bone marrow biopsy was performed showing a non-Hodgkin large B cells lymphoma (HL) grade IV. Additionally the patient was HBV positive. The Immunologist was consulted and he prescribed combined treatment with Gentamicin, Rifampicin and Vancomicin for 6 weeks and once echocardiography resulted normal, to start antineoplastic treatment. Instead, the haematologist recommended only steroid treatment followed by one infusion of Vincristin and once healed endocarditis, to give four cycles of R-CHOP, combined with Lamuvidin. From a review of the literature, we decided to begin therapy with antibiotics, steroids, Vincristine and Rituximab in four doses and prophylaxis with Lamivudine [1, 2]. The patient continued chemotherapy with a complete response after 6 months.

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Thromboembolic risk stratification for patients with atrial fibrillation in an emergency department

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Introduction: Atrial fibrillation (AF), the most common sustained arrhythmia, is associated with a high risk of thromboembolic events, especially stroke. Several clinical classifications have been proposed, but none of them was exhaustive. A more recent consensus document recommend that physicians should distinguish a first-detected episode of AF, that can be whether symptomatic or asymptomatic, self-limited or cardioverted within 7 days, so it is designated paroxysmal. But this definition is also comprehensive of cases for which is not possible to date back to onset of the arrhythmia, whether it is asymptomatic or accompanied by some slight neglet symptoms. The term recent discovery AF (RDAF) may be used for these cases. RDAF is often a problem in clinical practice. But studies on this particular subset of

AF, and indications for management are limited. Aim of this study was to clinically characterize and to thromboembolism-risk stratify patients who came to our emergency department (ED) with RDAF, comparing with those who came with recent onset AF (ROAF) and those with persistent AF (PAF).

Methods: 192 consecutive patients (115 men, 77 women) come to our ED from January to April 2010 with AF were enrolled, in order to perform clinical-anamnestic evaluation, and to notice their risk factors for thromboembolism. Patients were divided into three groups: 61 ROAF (38 men, 23 women), 35 RDAF (17 men, 18 women) and 96 PAF (60 men, 36 women) patients. Risk factors have been weighed according to guidelines (age $\geq$ 75 years, hypertension, diabetes mellitus, heart failure: moderate risk factors, CHADS(2) score = 1; previous stroke, TIA or embolism, mitral stenosis or prosthetic heart valve: high-risk factors, CHADS(2) score = 2). To calculate statystical differences of the proportions of risk factors, Chi-square tests for contingency tables were performed.

Results: Ten patients with RDAF were asymptomatics, discovering the arrhythmia occasionally. A RDAF patient had ischemic stroke. Another RDAF patient had TIA symptoms. Every other AF patients had arrhythmia-related symptoms (tachycardia, dyspnoea, chest pain, dizziness). The proportion of patients at high risk [at least one high or two moderate risk factors, CHADS(2) score $\geq$ 2] was significantly higher in RDAF and in PAF than in ROAF, while there were not significant differences between RDAF and PAF. Diabetes mellitus, heart failure, age $\geq$ 75 years, previous TIA/stroke were greater in RDAF than in PAF; proportions of heart failure, age $\geq$ 75 years, previous TIA/stroke and prosthetic heart valve were greater in PAF than in ROAF. Hypertensive patients proportion did not evidence differences between groups. For none of these risk factors there were statistical differences between RDAF and PAF.

Conclusions: A small part (18.2%) of all patients come to our ED with AF had RDAF. Nevertheless this group had a particularly high risk profile for thromboembolic events, comparable with PAF patients. This risk results linked to the same factors we found in PAF patients, with similar pattern. This is a very hazardous condition if taking into account that they were not protected by adequate antithrombotic therapy and that period from onset of the arrhythmia to her first detection is unknown.

Cutaneous leukocytoclastic vasculitis localized on lower limbs in a patient with chronic hepatitis B and recently treated with ciprofloxacin

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The cutaneous leukocytoclastic vasculitis may be idiopathic or caused by: drugs, serum sickness, infections, cancer and rheumatic diseases or part of a primary systemic vasculitis. A 68 years old Albanian man came to observation because of the appearance, since 2 days, of purpuric lesions on lower limbs. History: recent febrile syndrome treated at home with ciprofloxacin; this drug had been suspended about 7–10 days before admission; not reported other major diseases; took no other therapy. Cardiac, thoracic, abdominal, neurological and fundus oculi examination: normal; presence of purpuric lesions, suspicious for cutaneous vasculitis, on lower limbs. Routine blood tests: WBC 13,100–12,600 mmc^{-1}, ESR 70, CRP 1.59–1.82 mg/dl, glucose 127–173 mg/dl, HbA1c 6%; normal: Hb, platelets, PT, aPTT, fibrinogen, creatinine, sodium, potassium, AST, ALT, gamma GT, alkaline phosphatase, bilirubin, total protein, FT4, TSH, C3 and C4; ANA: 1/160, speckled appearance; negative: anti native DNA, anti ENA, MPO-ANCA and PR3-ANCA; positive: HBs-Ag, HBc-total IG Ab and HBe-Ab; negative: HBs-Ab, HBc-IgM Ab and HBe-Ag; HBV-DNA quantity: 0.343×10^3 IU/ml; negative: anti-HCV and anti-HDV. Urinalysis: protein 10 mg/dl and hemoglobin 0.20 mg/dl. ECG, chest X-ray, echodoppler of lower limbs: normal. Abdominal echography: modest fatty hepatomegaly with regular margins, gallstones, normal: pancreas, spleen, kidneys, bladder and abdominal aorta. Purpuric skin lesion biopsy: leukocytoclastic vasculitis. During hospitalization he has been treated with oral methylprednisolone (from 16 mg bid until the suspension after discharge, according to dermatologic evaluation) with progressive improvement of vasculitic lesions; since it has been found out an increasing of glycemia, compatible with diabetes mellitus, he has been treated with metformin (at discharge 1,000 mg bid); since the serology compatible with chronic hepatitis B, he has been treated with prophylactic therapy with lamivudine 100 mg uid, after hepatology evaluation, to prevent acute viral reactivation, because of the combinated therapy with corticosteroids. Vasculitic lesions at discharge had been almost healed and patient did not show involvement of other organs. We think that cutaneous leukocytoclastic vasculitis, presented by patient, may have been caused by concomitant viral hepatitis and/or recent therapy with ciprofloxacin (described several cases in literature, associated with this antibiotic). This disease affects small vessels and skin mainly is involved. It is important to classify vasculitis and exclude that vital organs are affected, through diagnostic tests, to determine proper therapy which may vary according to etiology.

Endocrinology

A case of major depression of unexpected origin

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A 75 years old man, FG, in the last 2 years has developed a deep sadness with delusions of ruin and unworthiness, anorexia (consequent to a delusion of constipation) with a weight loss of 20 kg; a MNR and a F18-FDG PET of the brain revealed a mild atrophy but neurologic and psychiatric examinations excluded Alzheimer disease and pointed to a diagnosis of major depression; a prolonged therapy with citalopram, lorazepam, amisulpride, vitamins, followed by haloperidol, promazina and mirtazapine was uneffective, so FG is admitted to the local psychiatric department for a depression state resistant to therapy. FG is cachectic, refuses food and movement, has a marked psychomotor retardation and a severe constipation. A colonscopy is scheduled, but during the preparation with laxatives FG develops a profuse diarrhea with hypotension, followed by a fainting episode; a chest x-ray is performed because of thoracic pain, rales in the lower left lobe and leukocytosis (2,3400 WBC/ml), and a pneumonic process in the aching area is revealed (with urinary antigens positive for streptococcus pneumoniae), so the patient is transferred to our Medical Division. On admittance, FG is afebrile but severely dehydrated (creatinine 1.88 mg/dl, BUN 107 mg/dl), has hypotension (70/50 mmHg) and oliguria (400 ml/day), hypernatremia (154 mmol/l), hypokalemia (2.89 mmol/l), hypercalcemia (11,9 mmol/l), hypoalbuminemia (1,8 g/dl); the hepatic function is impaired (AST = 53, ALT = 70, total bilirubine 3,5 with indirect bilirubine 2,2 mg/dl; cholinesterase = 1521, vn 4,600–11,500 U/l; INR = 1,6 but fibrinogen is above the normal

range). The patient has a significant edema of the left leg: an echo-color-doppler shows a deep venous thrombosis of the left common femoral vein. FG is treated with fluids and potassium ev, dopamine (for 24 h, at a renal dosage), albumine, antibiotics ev (first piperacilline-tazobactam and levofloxacin without effect, then vancomycine and imipenem), enoxaparin (anticoagulant dosage) with a good clinical result on general state, on pressure values and diuresis, on thoracic abnormalities (regression of rales and reduction of the extension of pneumonia at the chest X-ray), and with a partial resolution of the deep venous thrombosis (at a following echo-color-doppler); laboratory tests show the progressive normalization of creatinine and electrolytes, hepatic function, white blood cell count, and the reduction of RCP (from 28 to 7.9, with vn < 0.5 mg/dl). The correction of the hydration state reveals a moderate anemia (Hb 8.2 g/dl, MCV 93 fl) with low reticulocytes (0.3%, vn = 0.5–2.5), iron deficiency (19 mg/dl, vn = 60–160) but low transferrin (59 mg/dl, vn = 200–400) and very high ferritin (5,029, vn = 15–300 ng/ml). FG receives blood transfusions and nutrition via nasogastric tube; a series of tests are performed: an abdominal ultrasound (revealing mild pleural bilateral effusion and ascites), genetic test for hemochromatosis (negative), cancer markers (CA19.9, CEA, alphaFP, PSA, NSE, fecal occult blood: negative). On repeated checks, blood calcium remains always elevated (up to 11.9 mg/dl, vn = 8.8–10.6, with a ionized value up to 1.69 mmol/l, vn = 1.13–1.32); urinary calcium is high, too (450 mg/day, vn = 50–300); the D vitamin is in the normal range (13 ng/ml, vn = 10–50), while PTH is markedly increased (519 pg/ml, vn = 15–68); the thyroid function is normal. An ultrasound of the neck shows a nodular lesion of 2 × 1.5 cm with a peripheral vascularity in the left thyroid lobe; a scintigraphy of the parathyroids is performed, revealing that the nodular lesion evidenced by the ultrasound is suspect for an adenoma of the superior left parathyroid. A therapy with pamidronate, methylprednisolone ev, fluids and furosemide ev is started with partial reduction of calcemia (ionized 1.5 mmol/l) and PTH (256 pg/ml). The neurological and psychiatric state recover only partially: FG tends to mild drowsiness; refuses food and nasogastric tube, and develops on three occasions acute respiratory failure due to ab ingestis pneumonia: the first two episodes resolve after ventilatory support (and antibiotic theraphy) during short stays in intensive care unit, while the third one is fatal. In this complex case, prolonged hypercalcemia (due to the parathyroid adenoma) could be the cause of psychosis, drowsiness, constipation and anorexia of FG, and an important co-factor of dehydration; cachexia (consequent to anorexia) can explain many of the altered lab tests of the patient, and his susceptibility to infectious diseases, while drowsiness and impaired cough reflex have favoured ab ingestis episodes. This case shows the importance of excluding that psychiatric and neurological abnormalitis have organic basis, that should always be searched and possibly treated.

Increased levels of serum apelin in italian adults with type 2 diabetes mellitus

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Background: Apelin is a recently identified adipokine that plays a role in metabolism regulation and in cardiovascular function. Adipocitary apelin expression is regulated by insulin and directly correlates with its serum levels. However, the relationship between apelin serum concentration and dysmetabolic conditions such as type 2 diabetes mellitus (T2D) and metabolic syndrome (MS) is still controversial. Aims of our study were to determine the circulating levels of apelin in subjects with T2D and/or MS and to identify possible determinants of modified levels of this adipokine.
Methods: For this study we selected 42 T2D patients and we compared them with 41 healthy subjects. Participants underwent collection of medical history, physical examination, upper abdomen ultrasonography (US) and routine biochemistry. The additional diagnosis of MS was reached according to modified ATP-III criteria. Apelin levels were determined by EIA (immunoenzyme assay) on sera stored at −25°C for few days.
Results: Serum apelin levels directly correlate with the diagnosis of T2D ($p < 0.001$). Neither the additional presence of MS and its individual components nor glycaemic control were determinants of altered serum apelin concentration. 3-ways ANOVA analysis showed higher apelin levels in T2D compared to both healthy controls ($p < 0.009$) and subjects affected by MS with normal glucose tolerance (NGT) ($p = 0.03$). The linear association between increased apelin levels and T2D was confirmed by multivariate linear analysis, regardless of sex, age and metabolic parameters ($p = 0.02$).
Conclusions: Our results show that T2D is associated with elevated circulating levels of apelin independently from the presence of other metabolic abnormalities. SM per se is not a determinant of modified serum apelin concentration in an Italian adult population.

High prevalence of capillary abnormalities in patients with diabetes and association with retinopathy

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Introduction: Impairment of the vascular system is common in patients with diabetes, which involves both large and small blood vessels. Diabetic microangiopathy is observed in retinic and glomerular capillaries and can lead to specific forms of retinopathy and nephropathy. Nailfold video capillaroscopy (NVC) is a highly sensitive and noninvasive technique often used in Rheumatology to identify microvascular alterations in patients with connective tissue diseases. Aims of this study were: (1) to investigate the presence of nailfold abnormalities in patients with diabetes mellitus (DM) compared with healthy subjects, and then (2) to correlate these findings with the typical DM microangiopathic lesions detectable in retinic blood vessels.
Methods: 41 consecutive patients with DM (19 type 1 and 22 type 2) and 30 healthy subjects were enrolled. All patients underwent collection of medical history, clinical examination and routine biochemistry. Ophthalmoscopy examination was performed to these patients and was followed by retinic fluorangiography, when indicated. Subjects underwent NVC to evaluate density, length, morphology and distribution of capillary loops; presence of ectasia, microbleedings and blood flow modifications. A score (0–3) was applied to quantify NVC features.
Results: DM subjects showed a significantly increased ($p < 0.000$) NVC score and alterations of capillary morphology, density and distribution compared with control subjects. In addition, patients with T1D had a significantly higher score and greater morphologic alterations compared with T2D subjects ($p < 0.02$, $p < 0.03$). NVC score directly correlated with retinopathy, detected by both ophthalmoscopy

($p < 0.03$) and fluorangiography ($p < 0.02$), independently from sex, age, type of diabetes and all potentially confounder factors. Moreover, NVC was capable to identify alterations in almost 50% of diabetic patients without retinopathy.
Conclusions: Capillary abnormalities are frequent in diabetic patients and tightly correlate with retinal damage. Further studies are advocated to better elucidate the clinical significance of this finding and to possibly consider NVC use for diagnostic and prognostic evaluation of patients with diabetes.

A strange pericardial effusion…: not really cardiac but very internistic

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A 59-year-old woman, presenting with a long history of fatigue and chest discomfort relieved by sitting and leaning forward and intensified by lying supine. Blood pressure and heart rate were normal. The heart sounds were muffled. The skin was very pale. BMI was normal. The patient was hypertensive and dyslipidemic treated with doxazosin 2 mg and pravastatin 40 mg and had a histological diagnosis of non-alcoholic steatohepatitis (NASH). A chest X-ray revealed an enlarged cardiac silhouette (water-bottle aspect), and the ECG revealed low voltages in the praecordial lead. An echocardiogram confirmed the suspect of a pericardial effusion of about 500 ml. Furosemide, acetyl-salicylic acid and ceftriaxone were given without results. In order to identify the cause, the following blood tests were performed. Immunologic: Rheumatoid factor, immunoglobulin complexes, auto-antibody test (ANA, ENA, ANCA, anti-LKM, ds-DNA, APCA, AMA): normal; ASMA: ++–.
Neoplastic: CEA, alpha fetoprotein, CA125, CA19.9, CA15.3, βHCG: all negative.
Infective: EBV IgM, Toxo IgM, rubella IgM, CMV IgM, Ricketsial antibodies, HIV, Coxsackievirus A and B, hepatitis viruses, PCR and culture for tubercolosis: all negative.
Ematocrit and white cell count were normal. Muscular enzymes were elevated: LDH (×3), CK (×11), CK-MB (×2), myoglobin (×4). An abdominal-thoracal ultrasound revealed: hepatic steatosis, bilateral kidney stones with mild hydronephrosis, no ascites, no pleural effusion. Mammography was normal and total-body CT showed uterine fibromatosis more clearly that the sonography. Only an ultrasound of the neck led to the etiological diagnosis of pericardial effusion. This ultrasound revealed a thyroid very small showing a very heterogeneous parenchyma, with a typical aspect of chronic autoimmune thyroiditis. In fact the hormonal tests confirmed the suspected diagnosis of severe hypothyroidism, probably inveterate by chronic autoimmune thyroiditis: TSH 134.3 mlU/mL (0.35–5.5), fT3 0.7 pg/mL (2.3–4.2), fT4 0.1 ng/mL (0.75–1.8), anti-TG 2,250 U/mL (<60), Anti-TPO 4,761 U/mL (<60). The patient was immediately treated with a daily dose of levothyroxine 100 mcg. Clinical, instrumental and laboratory controls were required to be carried out after 2 months of treatment. When the patient returned to the control reported complete wellness. Thyroid function appeared completely normal with a TSH of 1.1 mlU/mL while the pericardial effusion was no longer present to the echocardiogram The originality of this case report is that the severe hypothyroidism produces, as unique clinical manifestation, a pericardial effusion that can be explained only by assuming the chronic autoimmune thyroiditis as an event of longstanding (according to the US pattern). Moreover, the hypothyroidism development has been so slow to allow an almost perfect adaptation of the body, thus preventing the rising of classic symptoms. Only very few cases similar to this herein reported are present in the literature.

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Rhabdomyolysis due to undiagnosed hypothyroidism associated with cytomegalovirus infection reactivation

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Introduction: it is well known that hypothyroid myopathy is quite frequent and usually manifests as weakness, myalgia, muscle stiffness and cramps, sometimes with only slight elevation of muscle enzymes. On the other hand it is known that rhabdomyolysis may result also from viral infections. We describe the case of a patient in whom rhabdomyolysis was documented as a complication of reactivation of viral infection in the course of overt undiagnosed hypothyroidism.
Case report: A 30-years-old man from Sri-Lanka, living in Italy since 4 years, presented to the emergency room for muscle weakness, pain and stiffness especially of the lower limbs. The patient was previously healthy, and his history was unremarkable except for weight gain (8 kg) in the last 6 months not attributable to increased caloric intake. On admission, his blood pressure, pulse rate, respiratory rate and body temperature were normal. On physical examination lower limb were swollen with non-pitting edema. Neurological examination showed mild proximal muscle weakness of the bilateral extremities with normal deep tendon reflexes. Laboratory findings showed: hemoglobin 14.0 g/dL, total leukocyte count 7,800 μL^{-1} with neutrophil granulocytes 35.6%, lymphocytes 54.9%, monocytes 7.2%, eosinophil granulocytes 1.8%, basophil granulocytes 0.5%; K 3.9 mmol/L (3.4–4.5), Na 135 mmol/L (136–145), creatinine 1.5 mg/dL (0.7–1.2), glucose 76 mg/dL (60-110). Serum muscle enzymes were markedly elevated: CK 3,808 UI/L (39–308), LDH 825 mg/dL (240–480), ALT 95 UI/L (<41), AST 92 UI/L (<40). The patient was admitted in the ward and hydration with IV saline solution was started at 220 ml/h. His laboratory findings on the second day from admission were as follows: total cholesterol 302 mg/dL (120–200), C-LDL 214 mg/dL (100–130), C-HDL 37 mg/dL (35–55), triglycerides 255 mg/dL (<180), TSH 350.6 µUI/mL (0.27–4.20), fT4 0.6 pmol/L (12–22); fT3 1.0 pmol/L (3.1–6.8), anti-thyroperoxidase antibodies 447 UI/mL (<34). Among screening tests for viral infections, IgG anti-cytomegalovirus (CMV) antibodies resulted >250 IU/mL (<6) and IgM anti-CMV index was 4.94 (<0.85) with IgG anti-CMV antibodies avidity index of 0.904. Other laboratory tests were normal. The diagnosis was rhabdomyolysis secondary to the additive effect of hypothyroidism and reactivated CMV infection. L-thyroxin 50 mcg daily substitutive therapy was started. His symptoms progressively improved in a few days although CK values remained 1,821 UI/L and creatinine was 1.4 mg/dL on the 6th day after admission, when the patient was voluntarily discharged from the hospital to come back to his native country. However we

recommended a reasonable period of appropriate hydration and physical activity limitation, with further appropriate gradual increase of dosage of L-thyroxin.

Conclusions: The report underscores that:

1. hypothyroid myopathy can induce significative elevation of muscle enzymes and that rhabdomyolysis can be the first manifestation of hypothyroidism;
2. the reactivation of CMV infection could have had a role in rhabdomyolysis in the case presented;
3. the normalization of muscle enzymes and serum creatinine in the case of hypothyroid rhabdomyolysis can be slower if compared with other cases of rhabdomyolysis: it's likely that adequate thyroid hormone replacement therapy can not only reverse rhabdomyolysis but can also improve renal function, as recently reported by some Authors.

Anti-thyroid peroxidase antibody in patients with latent autoimmune diabetes in adults (LADA)

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About 5–10% of all patients diagnosed with type 2 diabetes mellitus (T2D) have markers of beta cells autoimmunity, such as GAD65 and IA-2 autoantibodies (Ab). The presence of the islet cell antibodies is considered to reflect the process of autoimmune-mediated beta cell destruction. This form of "autoimmune" diabetes, defined by Zimmet as "latent autoimmune diabetes of adults" (LADA) presents clinical features somewhat intermediate between classic early-onset T1D and T2D and is characterised by absence of ketoacidosis and insulin therapy for variable periods of time. Patients with autoimmune type 1 diabetes mellitus have an increased risk of developing other autoimmune diseases,. Among them, autoimmune thyroid disease, mainly Hashimoto's thyroiditis, are more frequently observed. The frequency of autoimmune thyroiditis in type 1 diabetic adults equals about 20–40%, and in more than 50% of these individuals was demonstrated decreased function of the thyroid gland. Although many studies have shown the association between autoimmune thyroiditis and type 1 diabetes, little is known of the risk for thyroid autoimmunity in subjects with LADA. The aim of the study was to assess the prevalence of autoimmune thyroiditis in adult patients with LADA. 251 LADA patients (M = 117, F = 134; age 35–75 years) of Sardinian origin previously screened for the presence of pancreatic islet autoantibodies (GAD65 Ab positive) gave their consent to participate in the study. Thyroid Stimulating Hormone (TSH) and anti thyroid peroxidase antibody (TPOAb) were measured in all LADA patients as well as in a random sample of 251 all GAD65Ab-negative T2D patients. TSH was measured by IRMA method (TSH-US IRMA CT, Radim S.p.A., Rome). Anti thyroid peroxidase antibody (TPOAb) were tested by radioimmunoassay using commercial kits (Medipan, Berlin, Germany). Statistical differences between groups were tested using non-parametric Mann–Whitney *U* test. 104 LADA patients (41%) resulted positive for TPOAb, whereas 27 T2 D patients(10,7%) resulted positive for TPOAb ($P < 0.01$). TSH values above the cut-off limit of 4.0 UI/ml were detected in 12.7% of all LADA patients and even 21.2% in those who experienced beta cell failure within 4 years, whereas this percentage was as low as 4.5% in the random sample of 251 GAD65Ab-negative T2D patients. As far as gender is concerned, the female/male ratio patients with high TSH levels was 1.6 in LADA and 2.6 among GAD65Ab-negative T2D patients. The percentage of LADA patients with high TSH levels among TPOAb-positive and TPOAb-negative group were, respectively, 23.0 and 4.7%. Our result indicate that patients with LADA have an increased prevalence of TPOAb and have an increased risk for the development of other organ-specific autoimmune disease. The presence of TPOAb might indicate more active autoimmune process, and together with other immune parameters might be a marker of a more extended underlying immune process in predicting deteriorating beta cell function in LADA patients.

Cushing syndrome or pseudo-Cushing: analysis of 37 adrenal incidentalomas

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Introduction: Cushing syndrome (CS) is rare. Subclinical Cushing syndrome is relatively frequent in adrenal incidentalomas (AI) and in some patient groups (obese, diabetic, hypertensive, psychiatric) where possible hypercortisolism subclinical and Intermittent.

Aim: We analyzed the clinical and metabolic characteristics of 37 patients (pts) with AI All pts, were sought clinical signs of hyperfunction and/or adrenal hypofunction. After drug washout, the hormone assays were carried out basic tests and a night of suppression with low doses of dexamethasone (1 mg). The pts with suspected hypercortisolism (Cortisol > 5 μg/dL) underwent CRH test, CRH suppression test, the DDAVP test, ACTH test for 17OH-P.

Results: From 01.01.2007 to 01.01.2010 were enrolled 37 pts with AI: 18 females (mean age 66 ± 8.1 years.) and 17 males (mean age 60 ± 13 years.): 30 pts have an incidentaloma < 3 cm, not secreting, whose dimensions were unchanged at follow-up. 7 pts (6 M, 1 M) undwent surgery: 6 pts laparoscopic adrenalectomy and 1 pt transsphenoidal adenomectomy. In non-operated pts, 15 females (mean age 61.3 +13.7 years) and 15 males (mean age 61.9 +14.4 years), the most incidentaloma 'frequently size <2 cm (78% of cases), located on the left in 43% of cases and only in 5 bilateral cases. Was evident in 3 pts SCIC; In 14 pts, however, a PSC.; Both groups were characterized by a BMI > 40 kg/m^2. The metabolic syndrome (MetS), defined sec. NCEP-AtpIII, was present in 60% (10F, 8M) in pts and 9 (2F, 7M), there is a polidistrettuale arteriosclerosis, thromboembolism in 1 pt (1 pt) 's hypertension was present in 18 pts, 7 pts had a severe cardiovascular disease with diabetes mellitus, old. Frequent malignancies (27% of females and 35% of males) and benign (lipoma, angiomielolipoma, single and multiple cysts, liver angioma), epatosteatosis, cholesterol, fungal infections, HBV and HCV positivity. The thyroid disease (goiter and one or multiple nodules), and with hypo or hyperthyroidism was found most 'frequently in females (52% of cases) and osteoporosis with vitamin D deficiency (40% of cases). Inpatient surgery, 1 pt with subclinical hypothyroidism, Mets, osteoporosis and imaging suspicion of double adenoma, had a pituitary ACTH secreting microadenoma, diagnosed in dynamic testing, 5 patients a SC Of these, one with classic Cushing, 2 and 1 with malignancy associated with severe osteoporosis, cardiovascular disease and Mets. In a patient with PSC., A voluminous myelolipoma, synchronous bilateral familiar with SC, Diabetes mellitus (MetS) had laid claim to adrenalectomy.

Discussion: The most 'frequent problem in IEA differentiate adenoma from malignant primary or secondary. The diagnosis of a true SC can 'be confused with the PSC., where there may be a hyperactivity of the hypothalamic–pituitary axis. Hormonal examinations base, allow to identify the suspect SC But confirmation of etiological diagnosis (ACTH dependence, not addiction, ectopic secretion) is

long and sometimes not exhaustive. In fact, 2 pts showed clinical signs, classic Cushing's (pituitary microadenoma and from adrenocortical adenoma), while in other cases, the comorbidity and/or 'imaging (CT, PET, MRI, scintigraphy) were not decisive. In this group of pts, clinical characteristics peculiar as diabetes mellitus compensation difficult, refractory hypertension, depression, osteoporosis, appeared specific symptoms. As for the adrenal myelolipoma with clinical picture of CSF is exceptionally synchronous bilateral familial forms are not described, nor by syndromes of predisposition to adrenal tumors. Its location is among the forms and the association with non-secreting Mets has been described in some cases. It can not 'be excluded a possible hormonal secretion. After adrenalectomy, we observed the resolution of diabetes, hypertension and regression ridusione weight in 2 cases. This confirms the need for early diagnosis of SC, being aggravated by the development of cardiovascular complications, osteoporosis and increased mortality. The SCIC was identified, uncertainty remains for comorbidity. For patients with SCIC doubt whether to operate and when, remains.

Conclusions: Between disease and Cushing's syndrome, there are forms paucisintomatice in which hypercortisolism is conceivable, sometimes not certified. The differential diagnosis of hypercortisolism organic, functional and subclinical remains difficult. Some cases of uncertain must be brought to a personalized follow-up, for how long? For patients with SCIC doubt if work remains.

Primary aldosteronism due to adrenocortical adenoma with concurrent ileum carcinoid tumor: a case report

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We report a case of primary aldosteronism with concomitant carcinoid syndrome. A 55-year-old man was referred to our Departmental Unit of Secondary Hypertension, by his medical practice with a 20-year history of poorly controlled hypertension with multiple antihypertensive medications (losartan, clonidine, amlodipine) and recently severe hypokaliemia (2.5 mEq/L), without diuretic therapy. Moreover, he developed diffuse abdominal pain associated with nausea and change in bowel habits with diarrhea, palpitation and he referred a recent weight loss of 5 kg, over 2 months, and wheezing, flushing and muscle weakness. This clinical case was determined by an adrenocortical neoplasm and tumor of small intestine. At initial assessment, his blood pressure was 160/100 mmHg despite treatment with a calcium antagonist (nifedipine) and an alfa-blocker (doxazosin). Upon physical exam, the patient had a tense, distended abdomen. Rectal examination revealed no masses. Laboratory examination was remarkable from hypokaliemia (2.42 mEq/L), hypocloridemia (98 mEq/L) and a metabolic alkalosis (with a base excess of 7 mmol/L). Blood urea nitrogen (20 mg/dl) and creatinine (1.01 mg/dl) levels were normal. Complete blood cell count was within normal limits. Computed tomography (CT) of the abdomen and thorax revealed a hypodens lesion in ileum (diameter 2 cm) with hypervascolarization and 20 lesions located within the liver, that were consistent with metastatic tumor. The largest liver lesion measure 4 cm in diameter. The right adrenal gland was occupied by a nodular lesion that measures 2.5 cm. No other lesions were presented in the abdomen, pelvis and thorax. A whole body scan using somatostatin receptor scintigraphy (octreoscan 474 MBq e.v.) showed areas of increased uptake throughout the liver but no other regions. During adrenalectomy, a tumor on the ileum was found and was removed simultaneously. The pathological diagnosis was adrenocortical adenoma (aldosteronoma) and carcinoid tumor of ileum. Genetic evaluation was performed. Peripheral blood sample (10 ml) from the patient was collected after written informed consent. Screening for germinal mutations in the gene of MEN-1 (exons 2, 3, 4, 5, 6, 7, 8, 9, 10) did not reveal any mutations. After the surgery intervention, short-acting octreotide analogue test showed good response, so long-acting octreotide (S-LAR) was applied in an increased dose. The case may be considered a variant form of MEN, since the patient presented with two endocrine tumors. In addition, our patient present a polymorphism in the codon 541 of exon 10 of the MEN-1 gene. In conclusion, the concurrence of an adrenal cortical-aldosteronoma with ileum carcinoid tumor is unique. We believe that this case probably represents another variant of the MEN syndrome.

Gastroenterology and Hepatology

Serotonin metabolism alterations correlate with abdominal pain in patients with irritable bowel syndrome

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Background and aims: Serotonin (5-hydroxytryptamine, 5-HT) metabolism is altered in some gut disorders including the irritable bowel syndrome (IBS). The aims of the present study were to assess in patients with IBS in comparison with healthy controls (HC): (1) the number of colonic 5-HT-positive EC cells; (2) the amount of 5-HT released from the colonic mucosa; (3) the correlation between 5-HT metabolism and symptoms; and (4) the effects of mucosal 5-HT spontaneously released on electrophysiological responses from rat mesenteric sensory nerve fibers supplying the gut in vitro.

Methods: 25 Rome II confirmed IBS patients (12 IBS-C; 13 IBS-D; 17F; mean age 36.1 $\pm$ 10.3 years) were enrolled in the study. 12 HC (8F; mean age 26.9 $\pm$ 3.6 years) were recruited by public advertisement and included in the study after exclusion of gastrointestinal complaints. IBS symptom severity and frequency were graded by means of a five-point Likert scale. Mucosal biopsies were obtained from the descending colon. 5-HT-positive EC cell were identified immunohistochemically and quantified with a computer assisted method. Mucosal 5-HT was collected from biopsies and quantification was assessed using reverse-phase, ion-pair, high-performance liquid chromatography coupled with electrochemical detection. The impact of mucosal 5-HT on electrophysiological activity of rat mesenteric afferent nerves was evaluated in vitro.

Results: Overall, IBS patients showed a significant increase in the area of crypt epithelium occupied by 5-HT-positive cells compared with HC. This feature was significantly greater in diarrhea-predominant IBS in comparison with constipation-predominant IBS ($P = 0.03$; one-way ANOVA). 5-HT release in IBS patients was significantly increased by tenfold over the release found in HC. This

spontaneous release was not different in diarrhea and constipation predominant subgroups. A significant correlation was found between either severity and frequency of abdominal pain and the spontaneous mucosal release of 5-HT ($r_s = 0.832$, $P < 0.001$ and $r_s = 0.724$, $P < 0.001$, respectively; Spearman correlation). Average peak responses obtained with IBS supernatants were significantly increased by fivefold over that obtained with HC samples. The 5-HT_3 antagonist granisetron did not affect neuronal peak responses obtained by IBS sample. However, the area under the curve obtained with granisetron-treatment was significantly reduced with respect to that obtained with IBS samples (3,636.15 ± 1,396.38 vs. 1,133.60 ± 1,634.91, $P = 0.031$ one-way ANOVA).

Conclusions: 5-HT spontaneous release was significantly increased by tenfold irrespective of bowel habit and correlated with either severity and frequency of abdominal pain in patients with IBS. Our results provide novel insight into the mechanism underlying visceral hypersensitivity in IBS and open new perspectives in the treatment of IBS patients.

Detection of *Mycobacterium avium* subsp. paratuberculosis (MAP)-specific IS900 DNA and antibodies against map peptides and antigens in the plasma of Crohn's disease patients

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Background and aims: Crohn's disease (CD) is an idiopathic chronic inflammatory bowel disorder characterized by a fluctuating course. Due to its resemblance to John's disease, a chronic granulomatous gastroenteritis of ruminants, CD has been thought to be associated with infection by *Mycobacterium avium* subspecies *paratuberculosis* (MAP). Although considerable evidence exists to support the specific association between MAP and CD, causality remains unproven. The aim of the present study was to detect and type MAP DNA, and quantify the MAP-specific antibody production in CD.

Methods: The plasma of 70 patients with CD (mean age 34.2, range 15−63), 59 patients with ulcerative colitis (UC) (mean age 48.4, range 23–68) and 71 healthy volunteers (mean age 42.7, range 19–68) was screened by PCR for MAP-specific DNA insertion sequence IS900. The IS1311 PCR/restriction endonuclease analysis was used to differentiate between cattle and sheep MAP strains. The MAP-specific antibody production to recombinant MAP MptD peptide, MAP heparin-binding hemagglutinin adhesin (HBHA) and MAP lysate was assessed by ELISA.

Results: The number of CD patients positive for IS900 (48/70, 68.6%) was significantly ($p < 0.0001$) higher in comparison to UC patients (12/59, 11.9%) and healthy volunteers (19/71, 26.8%), without any significant difference between UC and healthy volunteers. Restriction analysis of PCR products, performed in the 48 IS900-positive CD patients, identified 38 patients positive for the cattle MAP strain (79.2%) and 3 patients positive for the sheep MAP strain (6.2%). No significant difference was found in the IS900 PCR detection rate when considering disease duration, intestinal location or clinical phenotype of CD. Humoral responses to MAP in CD patients did not differ from those of UC patients and healthy volunteers.

Conclusions: A significantly higher number of IS900-positive patients was found in the group of CD patients in comparison to UC patients and controls. The lack of a humoral response to MAP in CD patients may be secondary to immunosuppressive drugs which had been administered to the vast majority of the enrolled patients. Further studies are needed to clarify whether MAP is implicated in CD.

Immunological and morphological changes in a jejunal loop transplanted in oropharynx: a human model of small bowel ischemia–reperfusion injury

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Background and aims: The success of intestinal transplantation is influenced by the high susceptibility of the small bowel to ischemia–reperfusion injury**.** We here investigated through a human model the morphological and immunological changes occurring in the small bowel mucosa following transplantation.

Methods: A free jejunal loop was transplanted in the oropharynx of a man undergoing circular pharyngolaryngectomy for pharyngolaryngeal cancer. Jejunal biopsies were collected during transplantation procedures (cold and warm ischemia, reperfusion), during the 7 post-operative days through an exteriorized jejunal segment for flap monitoring, and 45 days after transplantation through an upper gastrointestinal endoscopy. Jejunal sections were morphometrically analyzed for surface area to volume ratio (SV) and enterocyte height measurement, and processed for terminal deoxynucleotidyl transferase-mediated digoxigenin-deoxyuridine triphosphate nick end labelling (TUNEL), Ki67, CD3, CD8 and phloxine-tartrazine staining. Matrix metalloproteinase (MMP)-3 and MMP-12 were detected by immunoblotting on mucosal homogenates.

Results: MMP-3 and MMP-12 increase was accompanied by a parallel rise in $TUNEL^+$ and $Ki67^+$ enterocytes, and by a concomitant reduction of SV and enterocyte height. Goblet cell hyperplasia coupled with Paneth cell disappearance at crypt base, while numerous phloxine-tartrazine$^+$ intermediate cells appeared at mid-crypt region. $CD8^+$ intraepithelial lymphocytes initially decreased, then increased in concomitance with the peak of enterocyte apoptosis. These changes partially reverted 45 days after transplantation.

Conclusions: We identified alterations in mucosal architecture, extracellular matrix regulation, epithelial cell turnover and lymphocyte infiltration which may give a window onto acute and chronic ischemia–reperfusion injury consequent to small bowel transplantation in humans.

The area under the curve of esophageal peristalsis waves is increased in patients with non-cardiac chest pain

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Background and aim: Non-cardiac chest pain (NCCP) is a common symptom in patients affected by gastroesophageal reflux disease (GERD) (1). It is already known that nutcracker esophagus is associated with NCCP (2), but not all patients with NCCP present this motor pattern suggesting that an increased wave amplitude is not sufficient to induce this condition. Therefore, the aim of this study was to analyse wave morphology in GERD patients with and without NCCP to determine which abnormality characterizes NCCP.
Patients and methods: We enrolled a group of 14 patients (4 males and 10 females, mean age 62 ± 13) with NCCP and 10 patients (5 males and 5 females, mean age 63 ± 12) with typical GERD. During stationary esophageal manometry, esophageal peristalsis was studied by ten liquid swallows of 5 mL water. Wave amplitude and duration at lower, medium and upper esophageal tract (respectively, 3, 8, 13 cm from the esophageal junction) were measured and, by using a computerized algorithm, the area under the curve for each wave was calculated.
Results: Wave duration and amplitude at the three levels in patients with NCCP were not different than in patients with typical GERD. On the contrary, the area under the curve of the wave at middle and lower esophageal level was significantly higher in patients with NCCP than in typical GERD: AUC (25th-75th percentile) at middle level: 0–187 versus 38–102 mmHg × s, respectively; AUC (25th–75th percentile at lower level: 23–253 versus 37–185 mmHg × s, respectively.
Conclusion: In patients with NCCP, esophageal peristalsis is characterized by waves with an increased area under the curve. The pathophysiology of pain could therefore be multifactorial: to induce symptoms, modifications of wave amplitude and wave duration must interact.

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Recurrent urinary tract infections are a frequent comorbidity in patients with irritable bowel syndrome

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Background and aims: It was previously shown that an increased prevalence of urinary symptoms is present in irritable bowel syndrome (IBS) (Whorwell et al. Gut 1986), but we have few information on the prevalence of recurrent urinary tract infections (UTI) in this condition. Therefore, the aim of the study was to analyze the prevalence of recurrent UTI in a group of IBS patients and the bacteria responsible for this condition.
Patients and methods: A group of 74 consecutive patients (mean age 29 ± 9 years, range 18–47, 49 females) with IBS (Rome III criteria, 29 diarrhoea, 12 alternating bowel, 33 constipation) took part in the study. All patients were asked about the presence of recurrent UTI. A control group of 68 sex and age comparable patients with gastroesophageal reflux disease (GERD) was also enrolled.
Results: Among IBS patients, 8 reported recurrent UTI, giving a prevalence of 11%. In GERD patients, one reported recurrent UTI (1.5%; $p = 0.03$). In the IBS group, 5 patients had IBS-diarrhoea, two patients reported IBS-constipation and one IBS-alternating bowel. In Four cases recurrent infection with *E. coli* was present, in the other case *P. mirabilis* was the responsible bacterium. In the GERD patient, recurrent UTI was caused by *E. coli*.
Conclusions: Recurrent UTI is highly prevalent in IBS patients. The presence of diarrhoea seems to have an important pathophysiological role.

Irritable bowel syndrome (IBS) and subclinical intestinal inflammation and small intestinal bacterial overgrowth (SIBO). Any connection?

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Background: Irritable bowel syndrome (IBS) is a complex disease in which different conditions may develop in subsets of patients, i.e. inflammatory component, small intestinal bacterial overgrowth (SIBO). Assessing calprotectine in feces is considered a reliable test for subtle changes due to bowel inflammation.
Aim: In patients with IBS we studied fecal calprotectine expression as a marker of intestinal inflammation; results were correlated with the presence of SIBO.
Methods: 40 patients with IBS (28 females, 22 males, mean age 43 years ± SD 15 years) diagnosed according to Rome III criteria were investigated by fecal calprotectine with a semiquantitative commercially available test (SOFAR, Italy). A group of 20 patients with inflammatory bowel disease (IBD) served as control group (15 ulcerative colitis, 3 Crohn, 2 nonspecific IBD) (12 males, 8 females, 47 ± 13 years). IBS patients were tested for SIBO with the oral glucose (75 g) and lactulose (10 g) H2 breath test using portable devices (Bedfont Microlyzer®) and LactoFan® (Italchimici).
Results: Calprotectine test was positive in all 20 IBD patients (16/20, 80% with severe inflammation). In IBS, calprotectine was mildly positive in 14/40 (35%) patients ($p < 0.01$ vs. IBD). The prevalence of SIBO was significantly ($p < 0.001$) greater in IBS patients with intestinal inflammation (71%) than IBS patients without intestinal inflammation (8%), as assessed by calprotectine test.
Conclusions: Fecal calprotectine can differentiate between IBD and IBS patients. Small intestinal bacterial overgrowth appears to be associated with mild intestinal inflammation in IBS, as suggested by a positive calprotectine fecal test.

Non-cirrhotic portal hypertension (NCPH) with large regenerative nodules

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Clinical presentation: On July 2009, a 62 year old Italian man was admitted to our hospital for recurrent melena. He had been in good general conditions till November 2008, when a first episode of melena occurred, in the absence of haematemesis and abdominal pain. The patient had no history of associated diseases and was not taking any medication. He had been admitted to another hospital where he had undergone the following investigations: a pancolonscopy, negative; upper intestinal endoscopy, which showed esophageal varices (not better described), portal hypertensive gastropathy, and the presence of coagulated blood in the stomach; abdominal ultrasonography, which evidenced liver enlargement, a diffusely disomogenous hepatic echotexture due the presence of multiple nodules (the bigger one of 4 cm in diameter), and mild splenomegaly; a transjugular catheterism in order to measure the hepatic pressure venous gradient (23 mmHg, severe portal hypertension), and to obtain a transjugular liver biopsy (nonspecific mild hepatocyte regenerative activity). The patient had been discharged without a defined diagnosis, with indication to a strict follow-up. At the admission to our hospital, laboratory tests showed anemia and leucopenia, a good renal function, and normal liver function tests. Serum α-fetoprotein level was in the normal range. Blood tests performed in the last few years were reassessed and showed only impaired glucose tolerance and mild elevation of the gamma-GT levels. Viral serology was negative. Autoimmune hepatitis, primary biliary cirrhosis, alpha 1 antitrypsin deficiency, Wilson's disease and hemochromatosis were ruled out by the specific investigations. Upper intestinal endoscopy confirmed esophageal varices—F2 blue with red wale markings—and severe portal hypertensive gastropathy. CT scan and MRI of the abdomen confirmed the presence of multiple nodules suspected for metastases. A US-guided liver biopsy was performed on one of the lesions, showing nonspecific chronic hepatitis without neoplastic cells.

Diagnostic hypothesis: Non-cirrhotic portal hypertension (NCPH) with large regenerative nodules.

Diagnostic deepening: As recommended in cases suspected for NCPH, the reticulin silver impregnation staining was performed in both liver biopsies, showing vaguely nodular arrangement of the liver, in which areas with hyperplastic hepatocytes, arranged in plates more than one cell thick, were alternated with areas in which the trabeculae were compressed and atrophic. The interface between nodules was not defined by fibrous septa. As NCPH has been described in association with blood coagulation disorders, myeloproliferative diseases, immunological alterations, systemic or intra-abdominal infections and exposure to toxic substances or to drugs, all these conditions were evaluated and excluded.

Diagnosis and decision-making: The diagnosis of nodular regenerative hyperplasia (NRH) with large regenerative nodules was performed. To date, no predisposing disease has been found in our patient. During hospitalization, the patient underwent to varices endoscopic ligation. A substantial clinical and radiological stability is observed after almost 1 year of follow-up. The present case highlights the peculiar clinical picture of NCPH, and the confounding results from imaging studies, which often render these cases a real diagnostic challenge. It also underscores the importance of a careful histological assessment with specific staining when NCPH is suspected. Finally, this case evidences the problems which can be faced once the diagnosis of NCPH is reached. On the background of NRH, nodules of several centimetres—much larger than the typical NRH ones (1–3 mm)—are frequently evidenced. These nodules can be located in perihilar region, as in partial nodular transformation, but also in the rest of the liver, and a specific nomenclature for this "mixed patterns" has not been proposed. However, just these cases suggest that NCPH consist in a spectrum of abnormal hepatic-regenerative responses to different injuries, frequently determining microcirculatory alterations, which manifests itself accordingly to personal anatomy and possible underlying diseases.

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Selection and surveillance of 19 Lynch syndrome families: experience of Southern Italy

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The Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is an inherited autosomal dominant cancer predisposition syndrome. Lynch patients develop cancer at an early age (mean age 45 years) mainly in the colorectum and endometrium. Other target organs are the urinary and biliary tract, stomach, pancreas, brain, and skin. This syndrome is caused by germ-line mutations in the mismatch repair genes; nearly 90% of causative mutations occurs in the hMSH2 and hMLH1 genes while MSH6 (10%) and PMS2 (5%) are less frequently involved. We selected 28 non-related index cases from the Apulia region (Southern Italy) who were diagnosed with colorectal cancer (CRC) before reaching 50 years of age. A total of 15/28 patients fulfilled the Amsterdam criteria II (ACII) while the remaining 14 patients not satisfying the criteria, were selected because of early tumour onset ($\leq$50 years). In all index cases, the presence of microsatellite instability (MSI) in tumours was assessed; nineteen (15 AC+ and 4 AC−) were classified as MSI-high. Mutation analysis in MLH1 and MSH2 was performed in these latter 19 patients and a pathogenic mutation was identified in all. Fifteen mutations were found in the MLH1 gene and four in MSH2. Four mutations in MLH1 and two mutations in MSH2 were previously unreported. For three previously reported mutations in HNPCC families, the possibility of a founder effect was investigated. Genetic counseling was offered to all index patients and after the results of the proband molecular analysis, the gene test was extended to 183 relatives, 85 of whom turned out to be mutation carriers (52%). A total of 80 mutation carriers accepted to follow an accurate clinical and instrumental surveillance protocol. The results of this study confirm that selection of patients with Lynch syndrome should not be based exclusively on family history. Moreover, the data reported indicates that genetic counseling, molecular screening and subsequent instrumental surveillance can lower the mortality of new cancers among the patients and family members and reduce the overall cancer incidence.

Serology and HLA haplotype in adult celiac disease: limited accuracy in patients with mild histological lesions

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Background and aim: Celiac disease (CD) is a chronic, immune-mediated, gluten-dependent enteropathy which affects genetically susceptible individuals characterized by partial or total duodenal villous atrophy. The broad clinical spectrum of CD includes cases with either "typical" and "atypical" presentation or silent forms occasionally discovered after a serological screening. Aim of our study was to define the impact of IgA anti-actin antibody (AAA), anti-transglutaminase antibody (TGA) and anti endomisyal antibody (AEA) in the diagnose of adult CD and to assess their relationship with clinical presentation and severity of intestinal mucosal damage.
Methods: We prospectively assessed patients admitted to our Unit from January 2004 to December 2008 with abdominal pain, diarrhoea, malabsorption, iron deficiency anemia and aminotransferases elevation. Diagnosis was based on NIH Consensus Conference Statements on CD. TGA were analysed by ELISA; AEA and AAA were assayed both by indirect immunofluorescence (IF) technique. Intestinal specimens (3 at least) were histologically assessed by Marsh's Classification as follows: Marsh I-IIIA partial villous atrophy (PVA); Marsh IIIB-C total villous atrophy (TVA). We also evaluated 20 healthy subjects, admitted to our Department for abdominal pain and/or previous listed features, who underwent to upper G.I. endoscopy and small bowel biopsy.
Results: Out of 88 patients, 68 had a new diagnosis of CD. Among them 15 (22.1%) were men and mean age was 36.5 (range 15–80 years). Serum TGA/AEA were positive in 49 (72.1%) patients and in none of 20 healthy controls. Typical disease was present in 33 (48.6%) patients, 26 (38.2%) showed an atypical presentation and 9 (13.2%) had silent CD. Serum AAA IgA were positive in 12 (17.6%) CD patients and 2 (10.0%) out of 20 healthy controls. Patients with typical pattern had abdominal pain, diarrhea and malabsorption; patient with atypical pattern showed high levels of aminotransferases, iron deficiency anemia or autoimmune disease (e.g. hypothryroidism, m. graves, diabetes type I, herpetiform dermatitis) and ovarian disorders. Positivity of AEA, TGA and AAA and intestinal mucosa damage were significantly associated ($p > 0.001$) in 16 (53.5%) subjects with PVA and in 35 (92.5%) with TVA. Twelve patients (17.6%) with AAA positivity presented with TVA ($p < 0.012$). Only haemoglobin ($p = 0.06$) and ferritin ($p = 0.008$) were statistically associated with severity of clinical presentation.
Conclusions: Pattern of clinical presentation of CD is very heterogeneous and the diagnosis needs a combination clinical symptoms, hystopathological, serological and genetic tests. Severity of mucosal damage is the main factor governing the detectability of serological markers of CD. Sensitivity of serological tests is questionable among patients with minimal lesions.

Autoimmune atrophic gastritis: clinical and pathological findings in 60 consecutive patients

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Background: Autoimmune atrophic gastritis (AAG) is an inflammatory process involving the fundic and body mucosa that results in the atrophy of the corpus-type glands, leading to achloridria, the lack of the intrinsic factor, vitamin B 12 deficiency and pernicious anaemia. Biochemical markers, such as anti-parietal cell antibodies (APCA) and high serum gastrin concentrations are typical for the disease.
Aim: The aim of this study was to highlight the epidemiological, clinical, laboratory and pathological features of outpatients who have been attending our gastroenterology unit and were diagnosed with autoimmune atrophic gastritis.
Patients and methods: Clinical and family history, biochemical parameters and symptoms which led to diagnosis were assessed. All the subjects underwent upper endoscopy and gastric biopsies were collected and evaluated according with updated Sydney system. Diagnosis was made in patients APCA positive with a mild to severe corpus-restricted atrophic gastritis. Data were reported as mean ± SD for parametric values and as prevalence for pathological events.
Results: During the last 3 years AAG was found in 60 outpatients (ratio M:F 17:43, mean age 56 ± 17 years, range 17–81 years). In 23 patients (38%) the main symptom was referred to upper gastrointestinal tract (epigastric pain, nausea, heartburn) and 16 of them experienced proton pump inhibitor (PPI) therapy failure. Sixteen patients (27%) were diagnosed because of anaemia, 10 (16%) because of asthenia or malnutrition and 3 (5%) for a family history of AAG. Twenty-one patients (35%) experienced also neurological symptoms (paresthesias, memory loss, ataxia). The most frequent laboratory alterations were anaemia in 38 patients (63%), macrocitosis in 26 (43%), anisocitosis in 30 (50%), vitamin B 12 deficiency in 40 (67%), iron deficiency in 12 (20%), hypergastrinemia in 52 (87%), elevated chromogranin A levels in 34 (57%), hyperhomocysteinemia in 17 (28%). Folic acid value was normal in all patients. Thirteen patients (21%) had a history of deep venous thrombosis, cerebrovascular ischemic attack or myocardial infarction. In 34 patients (57%) the typical endoscopic pattern was found (evidence of the submucosal reticular vessels and ipotrophic gastric folds) and in 43 patients (72%) severe atrophy was assessed by histology. Three patients (5%) developed epithelial dysplasia of the gastric body and one a microcarcinoid. Thirty-nine patients (65%) were affected by at least one concomitant autoimmune disease: Hashimoto's thyroiditis (33%), type 1 diabetes mellitus (13%), coeliac disease (10%), Graves' disease (5%) and Addison's disease (2%).
Conclusions: Autoimmune atrophic gastritis is often misdiagnosed due to its wide spread of manifestations. When diagnosis is achieved severe neurological or even neoplastic complications are already present. It is important to consider AAG in patients with autoimmune disease, 1st degree relatives of patients affected by AAG and in patients with persistent gastro-oesophageal symptoms despite of PPI therapy.

Gastroesophageal reflux disease is associated with NAFLD

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Background and aims: To assessed prospectively the prevalence of symptoms of gastroesophageal reflux in NAFLD through a validated questionnaire.
Methods: 185 NAFLD patients and a age and gender matched group of 97 healthy volunteers (without NAFLD) were enrolled. NAFLD cohort was divided in 2 groups (test and validating group, 1:1). Reflux symptoms in the year preceding the survey (heartburn, regurgitation, chest pain, dysphagia, epigastric pain, eructation, acid in mouth, nausea and vomiting, cough, hoarsness, asthma) together with selected individual characteristics and lifestyle habits were investigated through a structured questionnaire. A subject was deemed to be suffering from gastroesophageal symptoms (GERS) when he/she reported having the symptoms during the year preceding the survey. Only those subjects experiencing heartburn and/or regurgitation more than once a week were considered to have gastroesophageal reflux disease (GERD). In the multivariate analysis, odd ratio was adjusted for confounding factors (age, gender, BMI, visceral obesity, NSAIDs, physical activity, metabolic syndrome).
Results: The results were confirmed in a validation set of NAFLD patients. The prevalence of GERS and GERD was significantly higher among NAFLD in comparison with healthy volunteers, respectively 52.2 versus 18.6% ($p < 0.001$) and 26.1 versus 11.3% ($p < 0.001$) and they were independently associated with the presence of NAFLD with an adjusted OR of 3,373 (95% CI 1,639-6,938) and 2,605 (95% CI 1,189-5,706). Concerning symptoms, NAFLD patients reported a statistically significant higher prevalence of regurgitation, chest pain, acid reflux, and eructation, than the healthy group, with adjusted odd ratio of 2,252 (1,107–4,583), 5,985 (1,771–20,229), 4,451 (2,248–8,814) and 2,193 (1,186–4,053), respectively.
Conclusions: NAFLD patients reported a higher prevalence of reflux symptoms than the healthy volunteers. GERS could be considered a clinical manifestation of fatty liver disease.

Case report: effects of a long-term treatment with octreotide in intestinal bleeding by angiodysplastic lesions in an old age patient with myelodysplasia and type 2 diabetes mellitus

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An 80 years old man was admitted to our institute with of persistent melaena. His clinical history was characterised by BPCO, systemic hypertension, mitro aortic valvulopathy, type 2 diabetes mellitus treated by insulin therapy, severe carotid atherosclerosis and myelodysplasia. Physical examination was negative except for severe right carotid murmur. The electrocardiogram showed sinusal tachycardia. Duplex ultrasound showed a severe stenosis of right internal carotid artery (80%). At admission the laboratory findings showed anaemia compatible to acute bleeding (haemoglobin 6.6 g/dl). Gastroscopy and colonscopy were negative for bleeding lesions. Video capsule endoscopy shown angiodysplasia of small intestine. An evaluation of the patient excluded the opportunity of a surgical or invasive endoscopic therapeutic approach; therefore we decided to initiate a long term treatment by somatostatine (sms) analogue. He was treated with blood transfusion (3 units of concentrated erytrocities) and octreotide 0.1 mg/ml three times per day s.c. for 30 days and he 15th day started octreotide long acting 20 mg i.m. per month for 6 months. After transfusion and induction therapy haemoglobine level improved (Hb 9.7 g/dl). For 20 successive months, so far no other digestive bleeding occurred, haemoglobin level and glycemic profile remained stable without transfusions and new hospitalisations.
Discussion: Angiodysplasia, is an arteriovenous lesion, causing either acute or chronic bleeding. Vascular abnormalities of intestinal mucosa are responsible for 2–8% of gastrointestinal haemorrhages and up to 40% of new bleeding episodes. Somatostatin analogue octreotide is the first choice treatment of gastrointestinal bleeding, due to its well known properties of lowering splanchnic blood flow gastrointestinal motility and acid secretion. Octreotide can also used with success in bleeding caused by extensive mucosal vascular abnormalities of the small bowel, like angiodysplastic lesions. Experimental animal models infact showed that octreotide inhibits growth factors EGF e IGF-1, causing angiogenesis suppression. In our patient are both present a thrombotic risk (T2DM, severe carotid aterosclerosis) and an haemorragic risk (angiodysplasia and refractory anaemia). The presence of refractory anaemia determine a high risk in case of bleeding due to reduced capacity of bone marrow to regenerate the haematic cells, and acute cerebral hypoxia related to anaemia. In this clinical report new cases of digestive bleeding after stopping drug administration and the arrest of bleeding by continous octreotide administration, suggested the efficacy of this pharmacological treatment. Our patient is also affected by type 2 diabetes mellitus treated by insulin therapy. Even if somatostatin inhibits insulin secretion in our patient the glycemic profile was satisfactory. Thus considering other case report in literature, we can exclude that diabetes mellitus is an absolute not-recommended condition for the sms analogues treatment.
Conclusions: Octreotide is a life-saving drug in patients who are not candidates for surgery due to old age and/or concomitant diseases. In conclusion we suggest to consider long-term sms analogue treatment in patients with lower digestive bleeding due to angiodysplasia, especially as one of the most effective treatment when the other possible therapy (surgery) are unavailable.

Vipoma in elderly

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Case report: MG, a 79 year-old man affected by hypertension and diabetes, suffered from diarrhea since 2000, after colonscopic polypectomy (histologic result was unknown, and he never repeated colonscopy), and pollakuria with urinary incontinence, after prostatectomy 2 years before (benign hyper-plasia with multiple foci of adenocarcinoma G1, Gleason 2), in therapy with cyproterone. A diagnosis of hepatic and cephalo-pancreatic cancer was made in 2006 with US and CT-scan examination, not better defined (it was supposed to be an endocrine neoplasm, but the patient refused bioptic examination). In June 2009 a new CT-scan resulted unmodified. In autumn 2009 he went to Emergency Department for deep weakness, disabling tetraparesis, more severe at the lower limbs, acute confusion and postural disability in orthostatism. At first, paraneoplastic polyneuropathy and/or radiculopathy caused by vertebral collapse was assumed. A vertebral CT-scan showed osteoporotic changes with a L3

Schmorl hernia. Blood test underscored the following data: $K = 1.6$ mmol/L (normal values: 3.5–4.5); $Na = 145$ mmol/L (136–144); $Cl = 116$ mmol/L (98–107); $Ca = 8.3$ mg/dL (8.5–10.5); $HCO_3 = 11.8$ mmol/L (22–26); creatinine = 2.3 mg/dL (0.6–1.3); CPK = 462U/L (21–232); MCV = 96 fL; Hb = 9.8 g/dL; rbc = 2.59 10^6 μL^{-1}. Urinary electrolytes: Na = 92 mq/L (20–110); K = 4.9 mq/L (12–62); Cl = 112 mq/L (55–125). Stool cultures were negative. This presentation was consistent with WDHA syndrome and the blood results were considered consequent to a chronic large-volume diarrhea with dehydration. Most common symptoms of vipomas include diarrhea, dehydration, weight loss, hypokalemia and achlorhydria. All these data were present in our patient. However, some features were little different from the typical setting of WDHA syndrome: first, he experimented a dramatic clinical picture with tetraparesis and confusional state related to acute hypokaliemia, and a macrocitic anemia with B12 depletion—MCV = 129 fL; Hb = 8.3 g/dL; vit. B12 < 60 pg/ml (378–1,526); folate = 6.6 ng/ml (5.6–19.8)—requiring a suppletive treatment. Second, his stools were almost semi-liquid and creatorrhoic instead of water-like (i.e. secretive), so we supposed he should have a malabsorptive or a maldigestive disorder related to wide pancreatic involvement and secondary metastatic liver involvement (according to the previous demonstration of a massive gastrointestinal cancer), being fecal elastase lowered (<15 mcg/gr fec.). Colonscopy disclosed colon diverticulosis. Normal values of PSA excluded prostatic cancer relapse. As regards the first point—his long-standing history—most reported cases of vipomas show a slowly progressing constellation of associated symptoms and, above all, that mild hypokalemia and hypoglycemia are noted incidentally on laboratory tests. In contrast with our report, acute tetraparesis (without or with rhabdomyolisis) are rarely reported. According to this statement we were able to control diarrhea with symptomatic drugs. A mild increased level of VIP (64.8 pmol/L; normal values: 8.0–28.0) confirmed the hypothesis of a WDHA syndrome depending on a vipoma (previously not-recognized). Most authors report very high levels of VIP, and consider levels > 75 pg/mL as a cut-off. By our opinion the moderate elevation of plasmatic VIP was able to justify the clinical setting, even if we could not explain the limited synthesis: cancer-growth and VIP-secretion—we speculated—might be down-regulated. Because previous scans had shown a large neoplasm involving pancreas with multiple lymph-nodes and hepatic metastasis, we performed a somatostatin receptor scintigraphy with octreotide (Octreoscan), which recognized diffuse captation in the neoplastic areas. Data from literature suggest that, even if surgical option is the most effective therapy and an aggressive approach resolves benign PET, somatostatin analogues can be used for palliation, alternative to surgical debulking of the mass. Up to date, long-acting somatostatin analogues are considered the drugs of choice in metastatic tumors, while experiences with chemotherapeutic agents are limited. Aggressive surgical approach, instead, are reserved to rare cases, just as radiofrequency ablation, hepatic artery chemo-embolization and liver transplantation. Massive involvement—unfit for a surgical approach—and advanced age of our patient were compatible with a palliative treatment. Acute management of the patient was hard. Correction of acid-basic equilibrium and hypokaliemia with fluids slowly ameliorated his weakness and tetraparesis. He also received blood units and his renal balance improved. Results were enforced by physical therapy. Then we decided to start a palliative long-term treatment with long-acting octreotide. At this time, 6 months after diagnosis (4 year after the first diagnosis of cancer), the patient is still alive with adeguate autonomy.

Conclusions: Most vipomas are malignant and slow-growing, and most patients present with metastatic disease when the excessive production of VIP cause symptoms leading to diagnosis, which is confirmed by the serum value of VIP. Somatostatin receptor scintigraphy and/or endoscopic US with biopsy may be necessary to confirm the diagnosis in the first stages as in the late ones. In these patients chronicity and progression of symptoms over time deserve great attention. Our report illustrates a classic case of vipoma and recall the need to consider this condition in the differential diagnosis of secretory diarrhea, even if alternative diagnosis are possible or surgical resection are already performed. Palliative treatment may be an alternative and successful option for aged patients, not candidate to surgery. Somatostatin (and long-term octreotide) controls symptoms and normalizes VIP levels, without significant side effects.

Internal medicine Magna Grecia network for the management of hepatocellular carcinoma

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Introduction: The hepatocellular carcinoma (HCC) is a leading cause of hospital stay in internal medicine divisions. It is an extremely complex disease that needs a multispecialistic approach by the integration and the knowledges exchange among the different involved disciplines: internal medicine, surgery, oncology, interventional radiology, pathology. Systemic approach, that is the cornerstone methodology of internal medicine, is warranted in the management of HCC at the level of screening (identification of risk subjects—viral and alcoholic hepatitis, diabetes, metabolic syndrome), of diagnosis, staging and treatment (comprehensive clinical evaluation) and of follow up (monitoring the evolution of HCC and of the underlying disease, evaluation of side effects of therapy).

Methods: Based on the awareness of the deep historical roots and of the many socio-demographic elective affinities, we have therefore promoted the implementation of a clinical Network of Magna Grecia regions for the management of HCC whose main aims are: sharing educational activities in the field of HCC; adopting a common clinical protocol for the management of HCC; realizing clinical research activities; realizing a web site; identifying industries partner interested in the project and possible research financial supports; organizing the activities within the network in "hub" and "spoke" units; taking a census of the activities and of the competencies in each node of the network; creating a common database for HCC patients; activating an epidemiological register of Internal Medicine units for HCC; activating the "teleconsultation" for specific topics (e.g. US imaging); creating a bio-bank; defining the accreditation criteria of a hepatology unit within the Internal Medicine Units.

Results: The Internal Medicine Units at the moment involved in the project are listed in the authors section of this abs. We have: started the sharing of different educational resources, realized an interregional course on the ultrasonography approach to the diagnosis of neoplastic hepatic diseases (Puglia, 22–24 April 2010), realized a clinical card for the census of each single node of the network, realized a preliminary report on the clinical resources and the management of HCC in each unit, whose main features are reported in the enclosed table.

Data on units of the network	Data on HCC management
No. of divisions: 15	% units that perform:
No. of regions: 5 (Basilicata, Calabria, Campania, Puglia, Sicilia)	– 6 month US follow up: 90
	– 6 month AFP follow up: 70
Average division beds: 30.1 (2–60)	– Exams for diagnosis:
No. of discharges/bed: 28.5 (25–50)	– US: 100
% of outpatient hepatology units: 100	– CEUS: 60
% of US diagnostic units: 90	– Biopsy: 90
% of interventional US units: 60	– CT/MR: 100
	% Availability in each own hospital (each unit):
Hepatology outpatient units:	– US: 100 (90)
Average visits/month: 72 (18–100)	– CEUS: 80 (40)
% HCC visits: 1 (1–60)	– Biopsy: 90 (70)
% CVH visits: 41 (5–80)	– CT/MR: 100/90
% NASH visits: 24 (2–60)	– RF/MW/PEI: 70/40/70 (30/20/30)
	– TACE: 60
	– Sorafenib: 70 (70)
	– Surgery: 80
	– OLT: 30

CVH chronic viral hepatitis; NASH non-alcoholic steato-hepatitis; US: ultrasound; AFP: αfetoprotein; CEUS contrast enhanced ultrasound; RF radiofrequency ablation; MW microwave ablation; PEI percutaneous ethanol injection; TACE trans arterial chemoembolization; OLT orthotopic liver transplantation.

Conclusion: The network of internal medicine for HCC is a great opportunity for the professional growth of the involved regions in the management of this important disease, for the diffusion and the sharing of information and competences, for the implementation and the improvement of clinical shared pathways through the valorization of the specific competences and the rational use of local resources.

A preliminary analysis of the epidemiology of delivered care for hepatocellular carcinoma (HCC) in Puglia

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Introduction: The hepatocellular carcinoma (HCC) is a leading cause of hospital stay in internal medicine divisions, but data on the real impact of this disease upon the sanitary system are still lacking in Puglia as well as in other Italian regions. By the use of the so-called Epidemiology of Delivered Care (a new methodological research approach in which strategies of analysis and use of computer science technologies are finalized to the realization of medical studies based on population), we have therefore realized an epidemiological study on the impact and management of HCC in Puglia in the period 2002–2008.

Methods: Data came from the hospital discharge forms of all Puglia resident patients collected through 2002–2008. Day hospital discharges were excluded. Analysis was limited to the following ICD-9 codes found both among principal and secondary diagnosis: 155.0 (primitive malignant tumor of the liver); 155.1 (primitive malignant tumor of intrahepatic biliary system); 155.2 (malignant tumor of the liver not specified if primitive or secondary). HCC is enclosed in the first code group. All of the following data were collected: prevalence and incident cases of HCC; no. of discharge forms with not identified codes; associated diseases; diagnostic and therapeutic procedures; discharging and hospital (in- or outside of Puglia) divisions. For each of those macrovariables, many statistical measures have been derived, e.g. absolute and 2002–2008 period years relative discharge forms; length of stay; median age of patients; sex ratio.

Results: Main results may be summarized as follows:

- No. of forms with diagnosis of malignant tumor of the liver: 25.188 of which 24.384 with identified code and 8.965 (36%) incident cases).
- The trend and the distribution of the n. of diagnosis through the period of observation is quite costant bot for prevalent and incident cases.
- No. of forms with 155.0 code: 18.819 (constant trend by the years but a modest increase in the last 3 years); 155.1 code: 1.010 (almost completely represented by colangiocarcinomas); 155.2 code: 5.350.
- General variables: principal (58%) and secondary (42%) diagnosis distribution; M: 72%, F: 28% (ratio M/F 2,5); average length of stay: 8.5 days; mean age of patients 69.2 (25%: 63.9, 50%: 70.6; 75%: 76.3).
- Main associated diagnosis: cirrhosis (17%), diabetes (4.7%), other hepatic diseases (11%).
- The association with diabetes causes a slight increase both in length of stay (average 9.1 days) and in mean age of the patients (70.6 years).
- Divisions of discharge were (%): Internal Medicine (33.6); General Surgery (21.7); Gastroenterology (20.5); Infectious Diseases (10.8); Oncology (4.2); Geriatry (3.2); Longstay Divisions (1.5); Other (<1); the trend and the distribution of discharging divisions through the period of observation has been quite costant.
- The ratio M/F is below 2 only in geriatry (1,3) and long stay (1,2) divisions.
- The mean age of patients is among 68 and 70 years in internal medicine, surgery, gastroenterology and infectious diseases divisions; is around 66 years in oncology, while is among 74 and 76 years for geriatry and long stay divisions.
- The duration of hospital stay is slightly higher in internal medicine divisions (almost 9 days) in comparison to other divisions, with the obvious exception of geriatry and especially of Longstaying divisions.
- Almost 15% of patients is discharged from outside Puglia hospitals; most of Puglia stays come from Policlinico University of Bari (14.4%).

Conclusion: The methodology of epidemiology of delivered care is crucial for the collection of data to be used for management and planning of clinical pathways for most of diseases. The chance to make a linkare between different record database (e.g. prescriptions of general practitioners, pharmaceutical expense trend) gives the opportunity to analyse how hospitalization relates to the natural

history of the disease and to its pharmaceutical management. The only limit of the methodology relies upon the complete and correct compilation of discharging forms.

Rosuvastatin enhances the early (EVR) and substained (SVR) virological response in chronic hepatitis C treated with peginterferon and ribavirin.

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Background and aims: HCV is strongly associated with lipids during its lifecycle, exploiting lipid metabolism by accelerating cholesterol and fatty acid synthesis in the HCV-infected liver. Lipid modulators such as statins were shown to suppress HCV replication in vitro. These findings suggest that lipid modulators, which suppress lipid synthesis, could enhance the efficacy of current peg-interferon (IFN) plus ribavirina (RBV) treatment. We investigated the effect of the HMG-CoA-reductase inhibitor rosuvastatin on HCV replication in patients treated with peg-IFN plus ribavirin.
Methods: 140 patients with high viral loads (>5.0 IU log/ml based on Cobas TaqMan real-time PCR assay) have been treated with rosuvastatin (10 mg/day) in addition to standard therapy with peg-IFNa2a plus ribavirina (RBV) since 2008. We compared the early virological response (EVR), rapid virological response(RVR) and sustained virological response(SVR) between patients treated with rosuvastatin versus patients treated without them in 2007. HCVRNA-negative blood was defined as a viral load <1.7 IUlog/ml or negative results for the Cobas Amplicor test (<15 IU/ml).
Results: In patients with genotype 1b, rosuvastatin increases EVR from 50% (57/114) to 68% (54/79). The rosuvastatin increases the HCV RNA-negative rate at week 48 of treatment from 70% (78/114) to 85% (64/79). In patients with genotype 2a or 2b,rosuvastatin increases RVR and SVR from 54% (27/50) and 70–82% (41/50) and 88% (44/50), respectively.
Conclusions: These results indicate that HMG-CoA reductase inhibitor rosuvastatin could enhance the efficacy of peg-IFN and RBV therapy in patients with hepatitis C.

Cholesterol metabolism in gallstone disease. Preliminary evidence from the analysis of circulating markers of sterol homeostasis

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Cholesterol gallstone disease is characterized by a very high prevalence in developed countries and its impact in terms of complications and hospitalization is relevant. The pathophysiology is still incompletely unknown; in particular, it is still debated whether this condition associates with specific alterations of the different pathways regulating cholesterol homeostasis [1]. Previous data in humans has suggested that in particular conditions reduced conversion of cholesterol to bile acid or increased cholesterol synthesis [2, 3] might account for increased availability of intracellular free cholesterol for biliary secretion, but the finding has never been substantiated directly.

Aim: To analyze the main metabolic pathways of cholesterol balance (synthesis, absorption, degradation) by means of the determination of circulating levels of oxysterols, in a large population of gallstone patients.
Methods: Serum samples from 123 adult subjects (61 with and 62 without cholesterol gallstones) from the M.I. COL. (Multicentrica Italiana Colelitiasi) epidemiological study were analyzed. Plasma concentrations of hydroxylated sterols, widely considered as markers of cholesterol synthesis (lathosterol), absorption (campesterol and sitosterol) and degradation to bile acids (7alpha-hydroxy-4-cholesten-3-one, or C4) were assayed by gas-chromatography mass spectrometry (GC–MS). The difference between the two groups was investigated by Mann–Whitney's *U* test.
Results: Circulating markers of cholesterol absorption (expressed as the ratio between plasma sitosterol, or campesterol, and total cholesterol) were not different in the two groups of subject, and neither was the ratio plasma lathosterol to cholesterol (as an index of whole body cholesterol synthesis). On the other hand, plasma levels of C4, a marker of the main metabolic pathway of bile acid synthesis, were significantly higher in gallstone patients (median 0.82 μg/dl; 25–75% confidence limits: 0.48–1.42) when compared to gallstone-free subjects (median 0.44 μg/dl; 25–75% confidence limits: 0.31–0.95).
Conclusions: From this preliminary set of data, no evidence can be brought regarding a "specific" defect in cholesterol synthesis and/or absorption underlying gallstone formation. The data on plasma C4 are in contrast with previous evidence linking reduced bile acid formation with increased biliary cholesterol saturation [3] and might reflect some degree of bile acid malabsorption occurring in gallstone disease, as postulated by some Authors [4]. The implications of this finding on gallstone pathophysiology and management in general terms is questionable; however, the possibility to identify a subpopulation at high risk for gallstone development, to be targeted for prevention strategies, must be considered.

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Gerontology and Geriatric Medicine

Atrial damage and systolic hypertension in the elderly

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Left ventricular hypertrophy (LVH) is an indipendent risk for cardiovascular events in hypertensive subjects. The goal of this study is to evaluate whether the hypertensive subjects with LVH have atrial damage that could contribute to a more dangerous prognosis causing

arrhythmias and left ventricular failure. We have studied 30 elderly subjects, 10 normotensives and 20 with systolic hypertension; they were submitted to 24-h ambulatory blood pressure monitoring (ABPM) with A&D TM 2420, and to M-Mode echocardiography (Penn Convention) to evaluate left ventricular mass (LVM), left atrial diameter (LA) and aortic root (AR). According to the blood pressure values and left ventricular mass index (LVMI, cut-off 125 g/m^2), we selected three groups of patients, well matched for age, gender and body mass index (BMI): ten normotensive subjects with normal LVMI (N), ten hypertensive subjects with normal LVMI (H), and ten hypertensive subjects with left ventricular hypertrophy (LVH). Atrial damage is expressed as left atrial diameter (LA) and as the ratio of left atrial diameter/aortic root (LA/AR). All the patients were in wash-out and were submitted to a diet containing 110 mEq of Na for 20 days, Exclusion criteria: secondary hypertension, cardio-respiratory and endocrinological disease, obesity (BMI > 30), neoplasms. The statistical analysis was carried out with Student's test and Sperman's test. The results are shown in the table.

Table	AGE	LVMI	SBP 24 h	DBP 24 h	LA	LA/AR	BMI	
N	60 ± 17.4	89.2 ± 11.2	134 ± 6.6	76.5 ± 6.2	34.9 ± 2.8	1.03 ± 0.1	26.5 ± 4.9	**N**
p	ns	ns	<0.05	ns	ns	ns	Ns	p
H	64.5 ± 12.8	100.7 ± 17.9	144.6 ± 13.3	81.6 ± 10.5	35 ± 3.2	1.07 ± 0.2	24.7 ± 2.4	**H**
p	ns	<0.001	<0.05	ns	<0.001	< 0.05	ns	p
LVH	63.2 ± 8.3	171.2 ± 24.8	146 ± 17.6	78.8 ± 9.4	44.1 ± 4.55	1.28 ± 0.1	25.3 ± 3.4	**LVH**

Atrial damage (LA and LA/AR) is significantly higher in LVH than in N or H. Furthermore it is well correlated with LVMI both as absolute values (rs = 0.633; $p < 0.01$) and as ratio to AR (rs = 0.502; $p < 0.01$) and more closely correlated with PAS than PAD. Thus atrial damage could account for the worse prognosis of hypertensive subjects with LVH.

Correlation between arterial hypertension and associated risk factors

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Introduction: Arterial hypertension is a very widespread risk factor in the industrial world and it is in constant increase. It is present in 62% of patients suffering from stroke, 49% in IMA and 24% in IRC. The presence of associated risk factors contribute to an increase of global cardiovascular risk, caused by synergism of summation at the physio-pathological level.
Aim: Evaluate the correlation between arterial hypertension and cardiovascular risk factors in hypertensive patients under care in our geriatric DH in 2008.
Materials and methods: We randomized 624 hypertensive patients, over 65 years of age, to evaluate all the risk factors observed (lipidic arrangement, carbohydrate metabolism and obesity).
Results: 30.2% of the hypertensive patients were suffering from dislipidemia, 19.1% suffered from obesity, 24.6% suffered from diabetes mellitus type 2.
Discussion: The cardiovascular risk factors associated with arterial hypertension are most significant diagnostic indicators for global cardiovascular risk and for the onset of cerebral and cardiovascular events. Despite the efficacy of new anti-hypertensive drugs, only 27–30% of hypertensive patients are treated properly and this justified the high number of patients affected by stroke. Furthermore, failing to achieve the pressure target is associated with a high prevalence of associated risk factors. It is therefore necessary to activate more aggressive strategies not only from the pharmacological but also from dietetic and behavioural points of view.

Urticaria and angioedema in geriatric patients

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Urticaria is serious disorder characterized by appearance of welts of varying size and extension accompanied by itching and angioedema of lips and larynx. When cutaneous lesions persist for at least 6 weeks, the disease is defined as chronic. Most frequently, cases of urticaria are correlated to a hypersensitivity to drugs, food and insects. However, also infections of diverse origin (viral, bacterial, yeast, parasite), various autoimmune diseases, and some cancers can trigger off this disorder. The present study was carried out to evaluate the frequency and diagnostic approaches for urticaria in all elderly patients observed in the Geriatric Immunoallergology Unit of the University of Bari over a period of 2 months. A total of 128 geriatric patients (age > 65 years) referred to our clinic presenting different symptoms of possible allergic origin including 12.5% with dyspnea-cough, 5% with asthma, 26% with angioedema, 22% with urticaria, 26.5% with rhinitis, 19% with conjunctivitis, 26% with itching, 13% with dermatitis, and 5% with eczema. Our data demonstrated that 50% of patients referring to our Unit had an urticaria-angioedema syndrome. For diagnostic purposes, instrumental examinations and biohumoral tests were performed. In particular, the skin prick test for diagnosis of food allergens, insects, latex and, when possible, drugs, RAST, routine biohumoral tests, inflammation markers, thyroid function tests and autoantibodies, urine analysis and culture, stool parasitological examination, urea breath test for *H. pylori* (HP) screening, and dental radiography were performed. In addition, a gender-specific screening protocol for the most frequent tumors was also carried out: clinical breast/gynecological examination with mammographic screening and Pap testing in women, and clinical urological examination, pelvic ultrasound and PSA testing in men. Based on the above diagnostic procedures, drug allergies were found in 39% of patients, a positive Anisakis prick test in 14%, autoimmune diseases in 18%, cancer in 7%, hypergammaglobulinemia in 4%, and HP test was positive in 7%. Among angioedema patients 36% had an adverse drug reaction (ADR), 15% demonstrated angioedema and urticaria during a raw fish meal, 6% had a reaction to contrast medium injection upon instrumental examination, 9% had positive skin prick test (SPT) to food allergens, 6% had reactions during dental procedures correlated to latex, 3% had a reaction to hymenoptera venom and, in one case, dental radiography identified evidence of a dental granuloma. Our data indicate the significant incidence of urticaria-angioedema after adverse reactions to drugs in over 65-year-old patients, most likely due to polypharmacy, comorbidities and drug-drug interactions. The etiological diagnosis is also of crucial importance. In fact, urticaria onset can unmask both common IgE-

mediated forms and infrequent internal diseases of great clinical significance, such as autoimmune, neoplastic, diabetes and thyroid disorders.

Orthostatic tremor in an older man

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Case presentation: A 69-year-old man was referred for a moderate tremor of the head, arms and legs, gradually becoming worse within a month. The tremor was determined by standing and did not disappear while walking. However, the symptoms disappeared when he sat or laid down. He had no history of drug abuse or use of medication, but reported a 20-pack-year smoking history. Neurological examination revealed a disabling shaking of the arms, legs and head while attempting to stand or walk. When he lay down, the examination was completely normal. No other neurological symptoms were present. Routine laboratory tests (including thyroid functions, calcium and phosphate), EEG and brain MRI were normal. A SPECT with DaT-SCAN was also performed to exclude a diagnosis of Parkinson Disease and showed a normal striatal morphology. Six weeks after the beginning of symptoms, he developed progressively dyspnoea and lost weight. A chest X-ray showed a new onset-discrete opacity in the left upper region. So we performed a thoracic CT that highlighted the presence of a lobulated-endobronchial nodule. After a bronchoscopy, a small cell lung cancer of the left upper lobe with lymph node and liver metastases was diagnosed. Anti-Hu antibodies were present in serum (titre of 1:3,200). A few days after the initiation of chemotherapy, the shaking gradually disappeared, and within a week only a slight tremor of the hands remained. He was able to stand and walk again.

Discussion and conclusions: Paraneoplastic syndromes are rare disorders that are triggered by an altered immune system response to a neoplasm. Ectopic expression of neuronal antigens by the tumour provokes an immune reaction that subsequently cross-reacts with similar antigens in the nervous system. They are defined as clinical syndromes involving nonmetastatic systemic effects that accompany malignant disease. These syndromes are collections of symptoms that result from substances produced by the tumor, and they occur remotely from the tumor itself. The symptoms may be endocrine, neuromuscular or musculoskeletal, cardiovascular, cutaneous, hematologic, gastrointestinal, renal, or miscellaneous in nature. Although fever is the most common presentation, several clinical pictures may be observed, each of which specifically simulates more common benign conditions. A large number of cancer patients show CNS involvement. Paraneoplastic syndromes may be the first or most important manifestation. When a patient without a known cancer presents with one of the "typical" paraneoplastic syndromes, a diagnosis of cancer should be considered and investigated. We presented a patient with subacute onset, disabling OT, who was subsequently diagnosed with SCLC. According to the diagnostic guidelines for PNS, the aetiology of the OT in our patient is definitely paraneoplastic because of its close temporal relation to the diagnosis of cancer, the presence of anti-Hu antibodies and the regression of symptoms after chemotherapic treatment. Although paraneoplastic cerebellar degeneration and brainstem encephalitis are usually accompanied by signs of a multifocal encephalomyelitis, this tremor was the only paraneoplastic symptom. Surprisingly, the symptoms improved after chemotherapy. In our patient, early chemotherapy may have limited irreversible cerebellar damage.

Osteoporosis in men, a significant problem for public health: population admitted to the osteoporosis and metabolic bone disease clinic of Geriatric Institute Pio Albergo Trivulzio of Milan

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One out of three osteoporotic fractures (FRC) usually occurs in men, but only few men at high risk of FRC are detected and treated. Fragility FRC represents the first clinical expression of osteoporosis (OP) in men, the most frequent sites being hip, vertebrae, humerus and distal forearm. Factors that may contribute to this lower fractures rate in men include the higher bone mass with larger bone size achieved during growth, a better preservation of trabecular structure in adult life, lower risk of falls and a shorter life expectancy in men. Moreover the consequences of fractures in older men, both in terms of morbidity and mortality, appear to be more severe in men. The therapeutic decision should be based on absolute fracture risk as estimated from age, Bone Mineral density (BMD), fracture history, and additional clinical risk factors. In men, secondary osteoporosis deserves particular attention. Osteoporosis thus represents a significant threat for the health and wellbeing of the ageing male population and a significant problem for public health.

The aim of the present report has been to define clinical characteristics, instrumental and laboratory findings of male subjects in order to obtain a deeper insight into prevalence, associated findings and clinical and epidemiological characteristics of this subpopulation.

Methods: During the past year we observed 1,240 patients (pts) with metabolic bone disease. There were 1,160 women and 80 men. In all of the 80 men the following data were collected: clinical and anamnestic evaluation, including risk factors for FRC, previous clinical FRC, BMD (DXA/QUS), X-ray and laboratory evaluations and past or previous treatment for OP.

Results: Of the 80 pts studied (m $\pm$ SD age:69.9 $\pm$ 11.6 years, BMI: 25.1 $\pm$ 3.4 kg/cm^2): 15 had positive familial history for hip FRC (18%), 5 a history of alcohol abuse (6%), 13 were smokers (16%) and 29 smoked in the past (36%),12 drank 3 or more cups of coffee/day (15%), 28 did regular physical exercise to keep fit (35%); 4 were taking corticosteroids (CS) (5%) and 11 took CS in the past (14%), 34 showed previous fragility FRC (42%) (20 vertebral, 4 femoral, 5 humeral, 5 at wrist, 1 at ribs and 1 at tibia). The daily calcium intake was 632 mg/day, but 58 pts (72%) had a calcium intake less than 1,000 mg/day. In particular only 16 pts (20%) were taking calcium supplements. Of the 75 pts who underwent spinal or femoral or calcaneal QUS, 35 showed T score < -2.5 SD (44%). Only 27 pts taking drugs for OP (34%). Of the 60 pts studied with X-ray and morphometric examination, 37 showed silent vertebral FRC (62%). Calcemia was in the normal range in all of the subjects (9.45 $\pm$ 0.7 mg/dl), whereas concentration of 25OH-D3 was below the normal range (<30 ng/ml) in 43 of the 56 pts (77%) studied and very low (<15 ng/ml) in 20 pts (36%). All the pts with low levels of calcium and/or vitamin D were supplemented with oral calcium and colecalciferol; 22 of 56 pts (39%) had the hyperPTH (2 primary and 20 secondary to reduced vitamin D levels). 10 of 56 pts (18%) had hypercalciuria (>300 mg/24 h) and 12 pts (21%) had low calcium excretion (<100 mg/24 h). Considering the global amount of clinical, DXA, morphometric and laboratory data, we detected 60 pts with OP presenting fragility FRC, which was clinically evident (29), and silent (31): 51 had idiopathic OP, 4 OP secondary to CS therapy, 3 OP secondary to hepatic failure, 1 OP due to renal transplantation, 1 celiac disease, 1 hypogonadism (treated with alendronate, risedronate, teriparatide). 2 pts had primary hyperparathyroidism (treated by surgery), 2 pts had Paget disease (treated with neridronate). Only 14 subjects had not OP or Metabolic bone diseases.

Conclusion: even if male OP occurs in only 6.5% of a population of the last year patients admitted to our service (80 of 1,240 pts), 60of 80 pts (75%) presenting OP with fragility FRC, only 27 of 60 pts (45%) were taking drugs for OP. Osteoporosis is a serious threat to the health and wellbeing of affected men, but is largely under-diagnosed and under-treated.

Anaemia in elderly hospitalized patients: prevalence and clinical characteristics

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Introduction: Anaemia is a frequent condition in elderly subjects. Numerous studies have confirmed this fact both in general population, whereas data inherent to elderly hospitalized patients are more scarce. Often the cause of anaemia are not identifiable; epidemiological studies have shown that in about 1/3 of the cases it is not definable (idiopatic anaemia).
Aim of the study: Evaluate the prevalence of anaemia in elderly hospitalized patients and describe the clinical characteristics.
Materials and methods: Data inherent to patients hospitalized in the long staying ward of our O.U. from March 2009 to February 2010; the criteria of inclusion of the subjects was age >65. The mean age was 70 for female and 80 for male. Anaemia was defined based on OMS criteria, for Hb values lower than 13 g for males and 12 g for females. Malnutrition, IRC, chronic inflammatory conditions and others (haemorrhages, hematological diseases) were considered as causes of anaemia.
Results: The prevalence of anaemia was 10% for males and 12.2% for females. Anaemia prevalence increased with age for both sex.
27% represented dialyzed patients or affected by secondary IRC anaemia. 35% represented subjects suffering from cancer. 2% represented microcitemical anaemia while 2% represented those suffering from anaemia caused by bleeding. 1.2% represented those suffering from natural anaemia deficiency.
Discussion: Even in elderly hospitalized patients anaemia is very frequent. It is usually associated with many clinical complications, even further studies are necessary to better define characteristics and physiopathological mechanisms.

Geriatric multidimensional evaluation in elderly cardiopathie

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Introduction: Cardiac functional loss is a frequent pathology in elderly subjects and causes serious disabilities. It is the end result of the interaction between modifications of cardiovascular apparatus correlated to aging, chronic affections like diabetes and high blood pressure, and the contemporary presence of ischemic cardiopathy and valvular pathologies. Use of VMD in elderly patients suffering from cardiac functional loss has the goal to better the study of the disease, thus permitting adoption of adequate modality of treatment. Elderly patients are usually fragile and complex individuals in which multiple elements, besides the seriousness of the cardio-pathology, take part to condition the clinical picture and the prognosis.
Clinical case: M.E., age 84, male. Often hospitalised for cardiocirculatory efficiency loss (IVNYHA) with dilated post-ischemic miocardiopathy. He suffers from oliguria, dyspnea at rest and ortopnea. Also: R.S. with con sub-endocardiac antero-lateral ischemia with ECG, Hb 1 l.2 g/dl, subsequently brought to 8.6 g/dl, K > 6.2, azotemia 89, creatinine 1.55, VFG 40.6 ml/min. The echocardiogram highlights a serious ventricular dilatation with pump deficit, parietal ipocinesia, FE del 25%, restrictive type diastolic pattern and aortic e mitral valvular functional loss. The subject is treated with Furosemide 125 mg/day, ace-inhibitor, FANS. Il MMSE was 25.24/30, ADL 2/6, IADL 6/8. Index of Barthel 33/50, CIRS was 2 for co-morbidity e 22 index of severity. After discharge the patient continued the same therapy prescribed in hospital. After 2 months he is again hospitalized suffering from oliguria, dyspnea at rest and ortopnea. Also, declining edema and crepitant rattle at lung base. Chemical blood tests underline GR 2.800.000, Hb 9.2 g/dl, VES 90, azotemia 67, creatinine 1.67, VFG 37.72 ml/min., EGA respiratory alcolosi. The echocardiogram shows a more serious pump deficit with F.E. at 18%. Despite treatment with Furosrmide e.v. in high doses associated with ace-inhibitor, and cardio-selective beta blockers, the patient shows only a relative improvement, his weight goes from 86 to 83.300 kg. at that point he is transferred to UTIC, where he undergoes a cardioverter implant with pacemaker, with subsequent general improvement.
Conclusion: The complexity of the elderly patient suffering from Cardiac functional loss depends on the interaction among cardiopathy, aging co-morbidity, functional and psycho-cognitive state and social-environmental factors. The principal goal should be that of improving quality of life in relationship to a psycho-physical well-being and a functional independence. The great variety of elements condition the clinical picture and prognosis. For this reason the use of VMD allows the activation of the most functional pathways that lead to necessities of elderly subjects, thus reducing costs and repeated hospitalization.

Cardiovascular diseases

Use of statins and recurrence of atrial fibrillation after catheter ablation or electrical cardioversion: a systematic review and meta-analysis

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Background: Statins have important pleiotropic effects and have been shown to reduce vascular inflammation. Some evidence suggests that statins may have a role in the primary prevention of atrial fibrillation (AF), whereas little is know on the role of statins in patients with existing AF. We performed a meta-analysis of the literature to assess the effect of statins on the recurrence of AF after electrical cardioversion or ablation.
Methods: MEDLINE and EMBASE databases were searched up to January 2010. Relative risks (RR) and 95% confidence intervals (CIs) were then calculated and pooled using a random-effects model. Statistical heterogeneity was evaluated through the use of I^2 statistics.
Results: Sixteen studies were included in our systematic review. Statins did not reduce the risk of AF recurrence after ablation (4 studies including 750 patients; RR, 1.04; 95% CI 0.85–1.28, $p = 0.71$; $I^2 = 34\%$). Conversely, the use of statins was associated with a significantly reduced risk of AF recurrence after electrical cardioversion (12 studies including 1,790 patients; RR, 0.78; 95% CI

0.67–0.90, $p = 0.0003$; $I^2 = 34\%$). This reduction was not statistically significant when the analysis was restricted to randomized controlled trials (RCTs) only (5 studies, 458 patients, RR, 0.76; 95% CI 0.48–1.20).
Conclusion: Statins may lower the risk of AF recurrence after electrical cardioversion, but not ablation. However, this finding should be considered with caution, and larger RCTs are warranted to confirm our preliminary results.

Syncope and pulmonary embolism

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Introduction: Pulmonary embolism (PE) is a relatively common cardiovascular emergency. By occluding the pulmonary arterial bed it may lead to acute life-treating but potentially reversible right ventricular failure. PE is a difficult diagnosis that may be missed because of non-specific clinincal presentation. Early diagnosis is foundamental, since immediate treatment is higly effective.
Case report: A 84-year-old man was admitted to Emergency Department where he was brought for a syncopal episode occurred during the transition from sitting to orthostatic position. The specialist neurologist suspected a neuro-mediated syncope. The patient, 4 months before, had already been admitted to our department for candidiasis lesions-like, some of them in bullous others in crusted stage, localized at the mouth, head, trunk, scrotum and perineal region. In this circumstance pemphigus vulgaris, chronic renal failure, hypertensive heart disease and monoclonal gammopathy was diagnosed. The patient was treated with pantoprazole, metoprolol, furosemide, canrenoato potassium, prednisone, propafenone, calcium carbonate, cacitriolo, cyanocobalamin. On entering our ward, the patient appeared in general clinical condition expired, asymptomatic for angina and dyspnea, but tachypnoeic (30 breaths/min). Arrhythmic heart action, as the presence of extrasystoles, tones preserved, mitral regurgitation murmur. Vescicolar murmur sounded harsh widely, with rales bilaterally at baseline. Normal abdomen examination. Sluggish peristalsis. No peripheral edema, normal peripheral arterial pulses. The neurological examination was normal. The electrocardiogram showed "sinus tachycardia with ectopic ventricular beats". The chest X-rays showed signs of COPD, and severe arthrosis of the left shoulder. In suspicion of neurological disease on the basis, the patient underwent electroencephalogram, that was normal, and a brain CT scan, that was negative for acute focal lesions. Blood tests performed on the ward showed increased troponin I (0.13 ng/ml) of myoglobin (156 ng/ml), D-dimer (6,817 ng/ml). In suspected pulmonary embolism, a blood gas analysis was repeated showing a mixed alkalosis with hypoxemia (pH 7.5, pO_2 48 mmHg, pCO_2 32 mmHg, HCO_3 27.6 mmol/l). Therefore, a contrast-enhanced CT was performed, that showed "vascular filling defect on segmental and subsegmental branches of left upper lobe, right superior lobe, middle lobe, left inferior lobe and right inferior lobe. No evidence of pulmonary consolidation areas. Marked and diffuse bilateral centrilobular emphysema. Infrarenal abdominal aortic aneurysm free from perivascular adipose tissue calcification. Deep venous thrombosis on the right and left common femoral artery". On the basis of the clinical-instrumental evidences, a therapy with low molecular weight heparin, O2 therapy and removable vena cava filter placed in the aorta was established, with improvement of the clinical and laboratory tests. In secondary prevention, the patient underwent to oral anticoagulation therapy (ACT), INR 2–3.
Discussion: PE is a common disease in hospital wards, especially among elderly patients with entrapment syndrome or neoplastic ones. It is a disease often misunderstood because of the complexity of the clinical symptons which it may arise. In elderly patients, especially because often bedridden, acute pulmonary embolism may occur even with syncopal episodes, as in the case report we described. Early detection, provides a targeted therapy with better prognosis.
Furthermore, patients with a previous episode of PE have a risk almost four times higher to have a second thromboembolic event in the following year. Secondary prevention with ACT is therefore necessary, mostly in patients older than 75 years, according to international guidelines, considering the increased risk of bleeding and it is important always to consider the risk/benefit.

Clinical significance and prognostic value of N-terminal pro-B-type natriuretic peptide in infective endocarditis: a preliminary study

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Introduction: The B-type natriuretic peptide (BNP) is rapidly and transiently induced within ventricular cardiomyocytes and may be detected in the serum of patients early after acute myocardial mechanical stress. Thus, it is a useful diagnostic and prognostic marker in patients with heart failure (HF). BNP increases along with rising ventricular wall stress and inversely correlates with ejection fraction. The N-terminal fraction of the BNP prohormone (NT-pro-BNP) has a longer plasma half-life, reaches higher plasma concentrations and correlates most closely with clinical and echocardiographic parameters, making it the preferred subtype to measure. HF is a major complication of infective endocarditis (IE) and it is not always predicted by the degree of valve dysfunction alone. The prognosis of IE is closely related to the occurrence and severity of HF. In this study, we aimed at evaluating the clinical correlates and the prognostic significance of NT-pro-BNP levels in a large cohort of consecutive IE patients admitted to our centre.
Methods: We studied 73 patients with definite IE admitted to our centre in the last 3 years. NT-pro-BNP levels were measured in a serum sample obtained on admission by means of an automated immunochemical assay. We analysed the possible relation existing between NT-pro-BNP levels and the following variables: heart side involved, affected valve, type of valve involved (native vs. prosthetic), rate of surgical therapy and outcome of hospitalization.
Results: Median age of patients was 66 years and 71% were males. NT-pro-BNP levels were above the normal range in 92% of cases. NT-pro-BNP levels were not significantly different in left-sided compared with right sided IE cases (1,500 vs. 1,782 pg/ml; $p = 0.45$) or in aortic versus mitral valve IE cases (1,268 vs. 2,242 pg/ml; $p = 0.57$). Prosthetic valve IE was associated with a higher level of NT-pro-BNP (3,904 vs. 1,116 pg/ml in native valve IE; $p = 0.03$). Patients with IE on pacemaker or defibrillator wires had lower NT-pro-BNP levels, despite a higher rate of dilated cardiomyopathy (1,503 vs. 1,620 in non-PMK/AICD; $p = 0.02$). Interestingly, patients who subsequently underwent a cardiac surgical operation also showed higher levels of serum NT-pro-BNP (1,824 vs. 1,368 pg/ml in medically treated patients; $p =$ NS). The outcome of IE also appeared to be related to NT-pro-BNP levels as patients who died showed higher levels of this biomarker (11,535 vs. 3,044 pg/ml in those discharged home; $p = 0.03$).

Discussion: Our preliminary experience suggests that NT-pro-BNP levels might have a prognostic value in IE. In particular, NT-pro-BNP levels were associated with both surgical indication and mortality. Also, there was a clear association between higher NT-pro-BNP levels and prosthetic valve IE, that has a worse prognosis compared with native valve IE. However, left sided IE or aortic valve IE, that seem to be more often complicated by HF, were not characterized by greater levels of this biomarker. Further studies on a larger patients cohort are necessary to define the potential usefulness of NT-pro-BNP determination in the management of IE patients.

An unusual cause of recurrent pericardial effusion

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A 65-year-old man was admitted to Hospital on November 2009 for worsening dyspnea, easy fatigability and frequent profuse sweating in patient with recurrent pericardial effusion. He had a medical history of arterial hypertension, myocardial infarction (NSTEMI in 2004, treated with single coronary stenting) without impairment of cardiac output, radical prostatectomy for carcinoma with no residual disease at follow-up, monoclonal gammopathy IgA lambda (since 1984). In December 2008 the patient suffered from fatigue, cough and fever, with X-ray detection of pleurical effusion; he was treated with antibiotic therapy with resolution of fever but persistence of fatigue with minimal efforts. On March 2009 he was admitted to Hospital for fatigue and dyspnea: the echocardiography showed diffuse pericardial effusion with reduction of ejection fraction (44%) with a restrictive transmitralic pattern and severe ventricular hypertrophy; a complete infectious and immunological screening for pericarditis was negative; coronarography was negative. A short course of corticosteroid therapy was started, but on August 2009 he had a second admission for pericardial effusion and further worsening of the ejection fraction (38%); a new cycle of corticosteroid therapy was started in association with colchicine, with partial reduction of the pericardial effusion; the diagnosis at dismission was "recurrent pericardial effusion during myopericarditis". At admission on November 2009, the visit revealed postural hypotension (the patient also complained of numbness extremities and dizziness) and the ECG showed low voltage (especially in the limb leads), an extreme right-axis deviation (180°), delayed atrioventricular conduction (PR 220 ms), negative T-waves in V5-V6. The echocardiography confirmed severe thickness of the left ventricular wall and of the interatrial-interventricular septum, diffuse hypocinesia (EF 35%), diastolic dysfunction with a restrictive pattern on Doppler mitral inflow assessment, and stable moderate posterior pericardial effusion. Laboratory investigations showed a normocytic anemia (Hb 11 g/dl), an increase of hepatic enzyme (ALT 56 U/l, GGT 109 U/l, normal ALP), troponin-T (0.3 ng/ml) and N-terminal-proBNP (5,184 ng/l); normal renal function, proteinuria 0.24 g/day; no variation of the well-known monoclonal gammopathy IgA lamba, with negative Bence-Jones proteinuria. The marked progressive concentric left ventricular hypertrophy with moderate/severe biventricular disfunction in the absence of high ECG voltages ("low voltage, high mass") suggested the presence of an infiltrative cardiomyopathy. Due to the presence of nervous disturbances, the hypothesis of systemic amyloidosis with cardiac involvement was considered. To exclude sarcoidosis, angiotensin converting enzyme measurement was performed and resulted normal. Moreover, serum lambda free-light-chain levels were elevated (144 mg/l) with a decrease of kappa-to-lambda ratio (0.07), and cardiac magnetic resonance imaging showed subendocardial late gadolinium enhancement, a feature which is consistent with cardiac amyloidosis. Finally, abdominal subcutaneous fat aspirate stained with Congo red showed the typical apple green appearance under polarized light, confirming the presence of amyloid deposits. The patient was entrusted to a specialized Center for Systemic Amyloidosis, where investigations were completed: the amyloid fibril typing showed positive reaction to lambda antiserum (negative to kappa antiserum, to anti-transthyretin and anti-apolipoprotein A antibodies); DNA-analysis excluded genetic mutations of transthyretin gene. No other criteria for multiple myeloma were satisfied. In conclusion, the diagnosis of primary amyloidosis (amyloid light chain [AL]) with prevalent cardiac and peripheral nervous system involvement was confirmed. Given the important cardiac involvement, chemotherapy was started using oral melphalan, associated with corticosteroids and low-dose thalidomide (considering the presence of neuropathy).

Congestive heart failure and risk stratification for in-hospital mortality

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Heart failure (HF) is the most frequent cause of admission to internal medicine wards; it causes considerable morbidity and mortality and produces a great burden on health care systems worldwide. The ability to predict mortality risk could inform decision-making and guide the appropriate application of monitoring and treatment. In the present study, we have evaluated in our HF patients the reliability of the risk-stratification model for in-hospital mortality proposed by Fonarow et al. [1], which is based on three simple variables, evaluated at admission: blood urea nitrogen (BUN), systolic blood pressure (SBP), serum creatinine. We retrospectively analysed the clinical records of all patients with primary diagnosis of HF (*DRG code 127*), discharged alive or died between June 1, 2008 and April 30, 2010. Our series consisted of 364 subjects (8.8% of 4,118 discharged); 58% were female; the mean age was 83.2 ± 8.3 years (range 47-99). The in-hospital overall mortality was 7.9%, so distributed:

Risk stratification	Prognostic variables	Number of patients	In-hospital mortality (%)
Low risk	BUN level < 43 mg/dL, AND SBP ≥ 115 FmmHg, AND any serum creatinine level	203 (56%)	2.0
Intermediate risk	Any combination of BUN, SBP and serum creatinine levels, EXCEPT those of low- and high-risk groups	145 (40%)	13.0
High risk	BUN level ≥ 43 mg/dL, AND SBP < 115 mmHg, AND serum creatinine level ≥ 2.75 mg/dL	16 (4%)	37.5

These results differ, at least partially, from those by Fonarow et al., who reported an in-hospital overall mortality of 4.2%, with rates of 2.1, 6.9 and 21.9% in low, intermediate and high risk groups, respectively. However, the mortality rate we observed was similar to that reported by others, ranging from 6.7 to 13.4% [2–4]. A possible explanation for these differences comes from the age of patients: in our subjects the mean age was much older than in Fonarow's series (83.2 vs. 72.5 years). It is well known that the number of deaths due

to HF rises generally with the ageing of population [3]. The in-hospital mortality increases from 7% in subjects aged 65–74 to 20% in subjects older than 85 [4]; in octogenarians hospitalized for HF it was reported to be 10.6% [5]. Indeed, ageing influences outcome in many ways: the presence of comorbidities, the impairment of functional status, and psycocognitive defects are all features more common in the elderly. Furthermore, risk factors for HF (e.g., hypertension, diabetes mellitus and hyperlipidemia) are generally not treated aggressively in the elderly, yet elderly patients commonly take medications that can exacerbate the syndrome of HF (e.g., non steroidal anti-inflammatory drugs) [6]. A further explanation for the discrepancy between Fonarow's and our results comes from the sources of patients: in Fonarow's series, subjects where hospitalized in clinically diverse centers and different specialty departments, while our patients came only from a ward of internal medicine, a specialty where comorbidities are the rule and play a major role in conditioning outcomes, also independently of age. In this respect, it is noteworthy that the percentage of low risk patients was lower in our series than in Fonarow's one (56 vs. 65%); however, in this group, our in-hospital mortality rate was just the same as that reported by Fonarow. Even if the small number of our subjects can be a limiting factor, the results of our study suggest that, in HF patients hospitalized in internal medicine wards, the model proposed by Fonarow et al. seems to underestimate the risk for in-hospital mortality. It is easy to apply at the bedside and useful to urge physicians to pay attention to relevant pathophysiological variables, but it cannot be the only approach to guide the appropriate monitoring and treatment. Further risk factors can exist in the same patient, and it remains challenging to integrate these various parameters into a clinical impression regarding prognosis.

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Hypertonic saline solution (SSI) with high doses of furosemide in cardiorenal syndrome

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Background: Heart failure is frequently complicated by renal failure and this association is a negative prognostic factor more important than the ejection fraction and NYHA functional class [1]. Patients with this clinical picture sometimes present oligo-anuria and resistance to therapy with loop diuretics even at very high doses (500–1,000 mg of IV furosemide/day). The cardiorenal syndrome is classified into five types [2]:

Type 1: Acute cardiorenal syndrome	Acute worsening of heart function with acute renal failure
Type: 2 Chronic cardiorenal syndrome	Progressive alteration of cardiac function with progressive renal damage that can be permanent
Type 3: Acute renocardiac syndrome	Acute renal impairment with acute damage of myocardial function
Type 4: Chronic renocardiac syndrome:	Kidney disease producing permanent damage or increased cardiovascular risk
Type 5: Secondary cardiorenal syndrome	Systemic disease that causes dysfunction of both contemporary organs.

In internal medicine departments we are dealing more frequently with the first two types: acute or chronic reduction of left ventricular function results in a decrease in blood flow with reduction of renal perfusion and activation of several neurohormonal systems [3] which in turn determine resistance to diuretic therapy and hyponatremia.
Materials and methods: during the period November 2009–May 2010 we treated 20 patients with cardiorenal syndrome with hypertonic saline solution (HSS) and furosemide using the following regimen [4]:

Saline	150 ml
Sodium chloride vials 10 ml (2 mEq/ml)	Natremia $<$ 125 mEq/l: 4 vials
	Natremia 126–135 mEq/l: 2–3 vials
	Natremia $>$ 135 mEq/l: 1 vial
Potassium chloride vials 10 ml (2 mEq/ml)	Kaliemia $<$ 3.5 mEq/l: 1–2 vials
	Kaliemia 3.5–4.9 mEq/l: ½–1 vial
	Kaliemia $\geq$ 5 mEq/l: no vials
Furosemide	125–1,000 mg

Treatment was carried out twice a day for an average of 7 days.
Results: In 18 patients (90%) resumption of urine output from the first hours of treatment, improvement of renal function were obtained. Moreover an improvement of clinical picture was evident from the first day of therapy and no side effects or adverse events were reported. 2 patients (10%) responded only partially to the treatment: one of two (in very critical condition since the time of admission) died, while the other needed the regular sessions of ultrafiltration.

Conclusions: The hypertonic saline solution, combined with high doses of furosemide, is a valuable aid in the treatment of cardiorenal syndrome resistant to diuretic therapy, even in subjects with normal natremia without significant side effects and with a very low cost, avoiding a large number of patients ultrafiltration.

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Anemia: impact on hospitalization in patients with heart failure and preserved left ventricular systolic function

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Anemia is frequently present in patients with heart failure with a prevalence that can vary between 5 and 55% due to an increase of mortality and morbility and a worsening of the cardiac insufficiency.
Aim of the study: To verify the prevalence of anemia and its impact on hospitalization in outpatients with heart failure but preserved left ventricular systolic function.
Materials and methods: 231 patients were examined between 1st January 2008 and 31st December 2009. Anemia was defined according to the WHO criteria as a level of concentration of hemoglobin less than 13 g/dl for males and less than 12 g/dl for females. The group of patients affected by anemia represented 38.5% (89 patients, of which 38 were males and 51 females, with an average age of 70 ± 4 years). The group with a normal level of hemoglobin consisted of 142 patients (61.4%), of which 66 were males and 76 females, with an average age of 68 ± 4 years. The criteria of exclusion were a concentration of plasma creatinine greater than 2.5 mg/dl, or patients with other diseases known to be causes of anemia. In the group of patients affected by anemia there was found to be a greater prevalence, even if not significant, of ischemic cardiopathy, a presence of BBS and renal insufficiency.
Results: After 1 year, the patient group affected by anemia revealed a significantly higher rate of rehospitalization at 1 year compared to the group without anemia 20 versus 9% ($p = 0.007$) and the group with normal Hb revealed a reduced average confinement in hospital ($p < 0.001$). These data proved to be significant in both sexes but were particularly evident in male patients ($p = 0.006$).
Conclusions: Our results confirm that the presence of anemia is associated with an increased frequency of hospitalization, that does not depend on age, serum creatinine and natremia, producing a prognostic factor independent of events.

Clinical predictors at admission and prognostic significance of worsening renal function in patients hospitalized with acute heart failure

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Background: The development of worsening renal function (WRF) is frequently encountered during the hospitalization for acute heart failure (AHF). Recently, it has been reported that WRF is associated with significantly worse outcomes in these patients.
Objectives: The aim of this study was to assess the prevalence and risk factors for WRF among patients hospitalized for AHF and to determine the prognostic significance of WRF in these patients.
Methods: A total of 265 consecutively hospitalized patients with AHF were evaluated. The Modification of Diet in Renal Disease (MDRD) equation was used to estimate Glomerular Filtration Rate (eGFR). Two different definitions of WRF were adopted: (1) an increase in serum creatinine of $\geq$0.3 mg/dL from baseline to discharge (WRF-Abs) 2) A decrease in eGFR of $\geq$25% from baseline to discharge (WRF%). Potential clinical predictors of WRF at hospital admission were investigated using multivariable logistic regression analysis. A 1-month, 6-months and 1-year follow-up was carried out.
Results: Nearly 15% of patients (14.3%) developed WRF-Abs during the hospitalization. The mean hospital length of stay during the index hospitalization was 8.8 ± 4.2 days [median 8 days; Interquartile range (IQR) 6–10] for the whole group. Patients with WRF-Abs had similar mean and median length of stay to those without WRF-Abs: 8.66 ± 4.4 versus 8.83 ± 4.2 days (median 7 days IQR: 6–10 vs. 8 days IQR: 6–11), $p = 0.8$. Mortality and re-hospitalization risks at 1-month, 6-months and 1-year were not significantly increased in patient who developed WRF-Abs ($p > 0.05$). Similar findings were observed when the second definition of WRF (WRF%) was adopted. In univariable analysis, clinical predictors of WRF-Abs were history of chronic kidney disease (CKD), Age > 75 years, admission systolic blood pressure $\geq$ 160 mmHg, admission tachycardia (BPM $\geq$ 100), baseline eGFR, use of calcium channel blocker and digoxin. When multivariable logistic regression analysis is performed, only CKD (OR 3,4 95% CI 1.13–10.33, $p < 0.05$) and age > 75 years (OR 2.73 95% CI 1.1–7.01, $p < 0.05$) remained independently associated with heightened risk of WRF-Abs.
Conclusion: WRF is a common finding among patients hospitalized with AHF. Patients with WRF compared with those without WRF experienced no significant differences in hospital length of stay, mortality or re-hospitalization rates. Different clinical predictors at hospital admission can be used to identify patients at increased risk for developing WRF. Since the current trend in in-hospital management is to curtail diuresis and withdraw important life-prolonging medication in the face of WRF, further prospective studies are needed to better clarify the prognostic significance of WRF.

Oxidative stress-mediated arterial dysfunction in smokers: effect of dark chocolate

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Background: Arterial dysfunction is a hallmark of early atherosclerosis. Recent studies revealed that cocoa exerts beneficial cardiovascular effects, probably mediated by polyphenols.
Aim: The goal of the present study was to investigate whether the beneficial antioxidant effect of polyphenol-rich dark chocolate can induce an improvement of endothelial function in smokers and healthy volunteers.
Methods: Flow mediated dilation (FMD) and oxidative stress, as assessed by platelet reactive oxygen species (ROS), were studied in 10 smokers (mean age: 26 ± 4 years) and 10 healthy subjects (mean age: 26 ± 4 years) in a randomized, double-blind, crossover design. FMD and oxidative stress were assessed at baseline, after 24 h abstinence from food rich in polyphenols, and 2 h after ingestion of chocolate, either 40 g of dark chocolate (>85% cocoa) or 40 g of milk chocolate (35% cocoa). Smokers were studied after a fasting period of 8 h and a smoke-free interval of at least 2 h before each experiment.
Results: No change in oxidative stress levels and FMD was observed 2 h after milk chocolate ingestion in smokers (ROS from 20.5 ± 2.3 SI to 21.6 ± 2.4 SI, p = n.s., and FMD from 4.1 ± 1.8 to 5.2 ± 3.8%, p = n.s.) and healthy subjects (ROS from 12.3 ± 1.1 SI to 13.4 ± 1.8, p = n.s., and FMD from 6.9 ± 3.2 to 6.3 ± 3.5%, p = n.s.).
Conversely, a decrease of oxidative stress (Figure) and an increase of FMD was observed in smokers (ROS from 19.8 ± 1.4 SI to 10.5 ± 1.7 SI, $p < 0.001$, and FMD from 4.0 ± 1.6 to 8.3 ± 2.8%, $p < 0.001$) and healthy subjects (ROS from 13.4 ± 1.2 SI to 9.3 ± 1.0 SI, $p < 0.05$, and FMD from 6.9 ± 3.3 to 8.4 ± 2.9%, $p < 0.05$).
Conclusion: The present study shows that the beneficial effects of cocoa are most likely due to a decrease of oxidative stress. This may explain the improvement in endothelial function observed in smokers and healthy subjects.

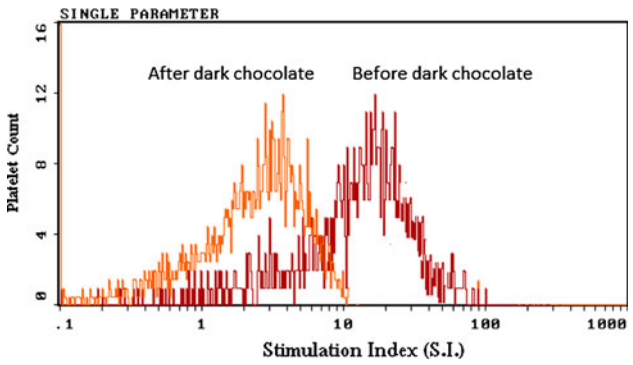

Figure Effect of dark chocolate on platelet ROS production

The morning peak of onset of Tako-Tsubo cardiomyopathy is independent of patients' clinical correlates

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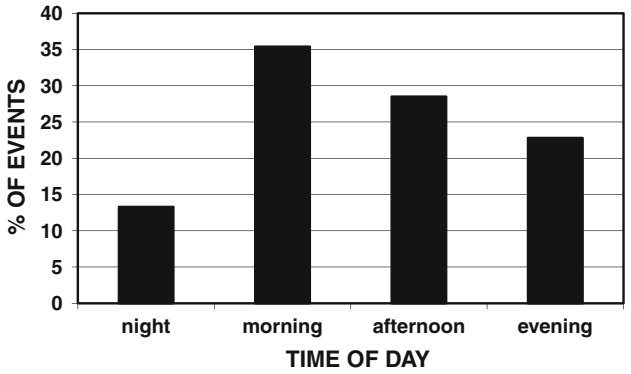
Background: Tako-Tsubo cardiomyopathy (TTC) is an acquired cardiomyopathy mimicking the clinical presentation of acute myocardial infarction (AMI) [1]. Recently, a temporal pattern of onset of TTC has been reported by our group in a multicenter cohort of patients in Italy [1], characterized by morning and summer preferred peaks of onset. Moreover, age (< or ≥65 years) did not affect the summer preference.[3] We aimed to investigate whether the temporal pattern of TTC onset may be dependent or not of underlying trigger events, major cardiovascular risk factors, or patients' clinical features.
Methods: We analyzed data from a cohort of 190 consecutive patients with TTC (January 2002–December 2009) admitted to seven Italian referral cardiac centers, and enrolled according to the Mayo Clinic diagnostic criteria for TTC [1]. Clinical variables included demographic (sex, age, date and time of onset), signs and symptoms at the event, medical history, trigger events, electrocardiographic ST-segment changes at admission, clinical observations during hospitalization (including major cardiovascular complications), T troponin level peak, and imaging studies (cardiac catheterization and echocardiography). The final set of data included subgroups by gender, age (< or ≥65 years), presence or not of prior stressor (physical or emotional), major cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking), ECG changes (ST-segment elevation), apical ballooning, evident symptoms (chest pain/dyspnea), reduced left ventricular ejection fraction (<35%), and possible in-hospital complications (a composite of cardiogenic shock, ventricular tachycardia/fibrillation, pulmonary edema). Time of symptom onset of each event was categorized into four 6-h intervals (night: 00:00–05:59 AM; morning: 06:00–11:59 AM; afternoon: 12:00–17:59 PM; evening: 18:00–23:59 PM). For statistical analysis, data grouped by 6-h intervals were tested for uniformity by the $\chi 2$ test for goodness of fit. The significance levels were set at $p < 0.05$.
Results: Data regarding diurnal distribution along the four 6-h periods were available in 158 cases (83.2%). TTC onset in total population was most frequent in morning ($n = 56$, 35.4%) and least so in night ($n = 21$, 13.3%) ($p < 0.001$) (Figure). This pattern was confirmed for most subgroups as well.
Discussion: The occurrence of acute cardiovascular events is not randomly distributed over time, but exhibits peculiar temporal patterns, i.e., circadian or seasonal. Morning hours represent critical periods for onset of AMI, sudden death, stroke, and rupture or dissection of aortic aneurysms. This study, conducted on the larger population available in literature, shows that the morning peak of TTC occurrence, quite similar to that of AMI[4], is independent of patients' clinical correlates. Stress and catecholamines, considering

also their temporal organization, might play a pivotal role, and a higher excretion of norepinephrine has been shown during the morning hours (09:00–15:00) [5]. The demonstration of temporal windows characterized by highest frequency of occurrence might help to ensure adequate protection during vulnerable periods.



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Day-of-week variability of acute cardiovascular events: does a gender difference exist?

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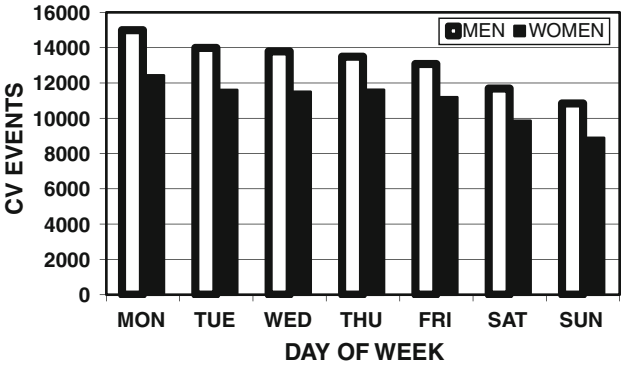
Background: Acute cardiovascular (CV) events are not randomly distributed over time, but exhibit temporal patterns, i.e., circadian or seasonal, in occurrence. Moreover, day-of-week variation has been also investigated, and a Monday preference was found for acute myocardial infarction (AMI) and stroke [1, 2]. We aimed to verify whether the weekly pattern of CV events may present differences by gender.
Methods: We analyzed cumulative data of previous studies from our group on day-of-week admission of AMI, stroke, transient ischemic attack (TIA), and aortic diseases [3–6], performed by using the region Emilia-Romagna (RER) database of hospital admissions (years 1998–2006 [3–5] and 2000–2006 [6]). This database, active since 1998, contains each patient's demographic data, date and department of hospital admission/discharge, and up to 8 discharge diagnoses, based on the International Classification of Diseases, 9th Rev, Clinical Modification (ICD-9-CM). Day of admission of CV events was categorized into seven 1-day intervals by day of week and subgroups by gender. For statistical analysis, data were tested for uniformity by the $\chi 2$ test for goodness of fit. The significance levels were set at $p < 0.05$.
Results: During this period, the RER database contained the records of 168.921 patients hospitalized for CV acute events (64.191 AMIs, 56.453 strokes, 43.642 TIAs, 4.615 aortic diseases; 54.4% males, 45.6% females). CV cumulative admissions showed a peak on Monday and a trough on Sunday (18.0 vs. 11.7%, $p < 0.0001$) (Figure), with no differences between men ($p < 0.0001$) and women ($p < 0.001$) (men vs. women: $p =$ NS). This pattern was confirmed for each subgroup by disease as well.
Discussion: Gender does not seem to influence the Monday preference in the occurrence of CV events. Working activity has been called as possible risk factor, but results are not univocal. Willich et al[7] found a Monday excess of AMI primarily present in the working population, but Spielberg et al. [8] observed the same pattern in both working and retired subjects. Several potential triggering factors, i.e., stress from commencing weekly activities, higher blood pressure levels. and unfavorable biochemical status, have been proposed [9, 10].



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Cystatin C as prognostic factor in acute cerebrovascular disease

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Aims and objectives: proper to the Acute Cerebrovascular Disease is a different functional outcome, from complete recovery to heavy handicap, and high comorbility. The literature defines many clinical elements (like hyperglicemia, hyperthermia, anemia) and biomarkers (like NSE, IL 6, v-cam, Cys C) as early prognostic factors (PF) of an unfavorable outcome. The purpouse of this study is to evaluate the prognostic function of cys C in relation to: mortality, recurrence of cardiovascular episodes (CV) and long term functional outcome in those patients that suffer from acute cerebrovascular Disease.
Materials and methods: 59 patients (average age of 74,81) hospitalized due to acute cerebrovascular disease, have been analized according to the presence of risk factors (RF) CV and AKI (Acute Kidney Injury), and have then been examinated after a year.
Results: Whithin a year, the patients that presented high Cys C values (>1.2 mg/l) at the moment of their admission had an higher mortality risk and an higher risk of suffer from a new CV episode, regardless of the presence of CV RF. Long term inpairments depend from age and former disability. AKI did not show any PF.
Conclusions: Whithin a year, Cys C represents an indipendent PF talking about mortality and new CV episodes, even in absence of AKI.

A rare case of heart failure

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Introduction: Isolated Noncompaction of the Ventricular Myocardium (IVNC) is a primary genetic cardiomyopathy. Before fifth week of intrauterine life, the myocardium forms a loose network of fibers and sinusoids which are in continuity with the ventricular cavity. Subsequently, the meshwork of fibers becomes 'compacted' and the sinusoids disappear. Pathological arrest of this compaction process leads to the persistence of ventricular hypertrabeculation, so called spongy myocardium or left ventricular (LV) non-compaction (NC).
Case: A 44 years old woman, was admitted to ER because of progressive dyspnoea. Some years before the patient underwent radical surgery for breast cancer and she was then treated with chemo- and radiotherapy. A previous, recent CT scan showed bilateral pleural effusion. A transthoracic echocardiogram was unremarkable. Stress test EKG was carried out three months before, at onset of dyspnoea, revealing no significant signs or symptoms. On admittance the patient was breathless with orthopnoea, rythmic cardiac activity, lower cardiac tones, 2/6 Levine systolic murmur. Chest physical exam revealed abolished lung murmur in middle-low lung fields bilaterally. Physical exam of abdomen was unremarkable. Lymphatic oedema of the left arm and peripheral oedema of the legs bilaterally were noticed. The EKG showed sinus tachycardia, normal A-V conduction, voltage features of LVH and mildly dilated left atrium. The BGA showed acute respiratory failure with hypoxia and hypocapnia (pH 7.4, pO_2 52 mmHg, pCO_2 30 mmHg, HCO_3 20.8 mmHg). Blood tests showed only an increase in D-dimer (2278 ng/dl). A urgent CT chest scan was performed ruling out pulmonary embolism, but apparently revealing a LV apex localised thrombotic lesion. This finding was confirmed by a further transthoracic echocardiogram that showed left ventricular non-compaction, dilated LV with severely reduced systolic function (EF 20%), extensive septal and lateral wall akinesis, apex dyskinesis and anterior and inferior wall hypokinesis. The patient was acutely treated with loop diuretics, aldosterone antagonists, β-Blocker and unfractionated heparin and warfarin on discharge, with complete remission of syndrome. A coronary angiography was performed to complete the diagnostic path revealing unremarkable coronary arteries. After 6 months from discharge the patient is still asymptomatic.
Discussion: Isolated noncompaction of ventricular Myocardium is a rare disease, often unknown also in specific setting. Although NC has generally been regarded as a familial cardiomyopathy, a family history of cardiomyopathy is not always present in adults or children with morphological characteristics of NC. At present, there is no consensus on the diagnostic criteria, and diagnosis is based on the morphologic features identified by cardiac imaging studies or at autopsy. Due to lack of standardization of the diagnostic criteria and little awareness of this condition among clinicians, the true prevalence of this disease is not clear. There is no specific therapy for this condition. The recognition of the disease is mandatory, because of its high mortality and morbidity due to the progressive heart failure, thromboembolic events and lethal arrhythmias.

Correlation between serum endothelin-1 levels and hemodynamic in chronic thromboembolic pulmonary hypertension

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Background: Endothelin-1 (ET-1) is considered to play a role in the pathophysiology of pulmonary arterial hypertension. Elevated ET-1 levels have been largely demonstrated in patients with non-thromboembolic pulmonary hypertension, correlating with the hemodynamic severity of the disease. We hereby report our findings in patients with chronic thromboembolic pulmonary hypertension (CTEPH) undergoing pulmonary endarterectomy (PEA).
Methods: From April 1994 to May 2010, 294 patients diagnosed with CTEPH underwent PEA at our Center. From October 2008 to March 2010, 75 consecutive patients were studied. Eighteen patients (24%) were excluded from the analysis as they were treated preoperatively with specific drugs for pulmonary hypertension. The ET-1 kit (Biomedica Gruppe) employs an enzyme immunoassay technique to quantitate endothelin in serum samples, and was performed according to the manufacturer's instructions and expressed as fmol/mL. The minimum detectable dose of endothelin is approximately 0.02 fmol/

ml. The mean value of endothelin concentrations in healthy adult controls usually is defined as 0.26 fmol/ml.

Results: ET-1 levels were increased in 49 patients (86%) diagnosed with CTEPH but a great dispersion was observed (table 1). Moreover, the correlations evaluated by the Spearman's correlation coefficient (r) between serum endothelin values and hemodynamic parameters (mPAP: mean pulmonary arterial pressure, CO: cardiac output, PVR: pulmonary vascular resistance) were not statistically significant: mPAP ($r = 0.095$, $p = 0.41$), CO ($r = 0.0141$, $p = 0.9035$) e PVR ($r = 0.0459$, $p = 0.6926$).

Table 1 Serum ET-1 levels (descriptive statistic)

Statistic variable	Value
Mean ± standard deviation	2.98 ± 3.98
Median	1.07
1st quartile	0.4
3rd quartile	4
Maximum	17.86
Minimum	0.07

Conclusions: Our data show a wide variability in the serum ET-1 levels of CTEPH patients. This could be due to the different length of the disease rather than the different hemodynamic impairment, since no correlation has been observed with the three hemodynamic parameters. An in-depth examination of our data is therefore needed, trying to find out some correlations with patient's medical hystory rather than the mere hemodynamic condition.

Extension of surgical criteria for pulmonary endarterectomy in distal chronic thromboembolic pulmonary hypertension

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Background: Pulmonary endarterectomy (PEA) is the treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH). For CTEPH with exclusively distal lesions, double-lung transplantation (DLTx) is, when indicated, the only available option. We hereby describe our recent series of successful PEA performed in patients with exclusively distal lesions.

Methods: At our Centre 294 PEAs were performed from April 1994 to May 2010. As our referral increased substantially during study period (Fig. 1), we became more confident to the procedure. Thus, the operability rate rose from 74% (year 2004) to 89% (year 2009). Up to date we found 13 pts amenable of PEA, previously judged inoperable.

Results: The outcome of these 13 pts was excellent. At discharge, pulmonary vascular resistance remarkably decreased (320 ± 124 vs. preoperative 1228 ± 424 dyne s cm^{-5}). Up to date they are all still alive in WHO class I (vs. preoperative III or IV). Only 2 complications occurred in 2 different pts: a reversible reperfusion edema after extensive PEA and a transient neurological event, both quickly resolved. Figure 2 shows a typical surgical specimen removed by distal PEA.

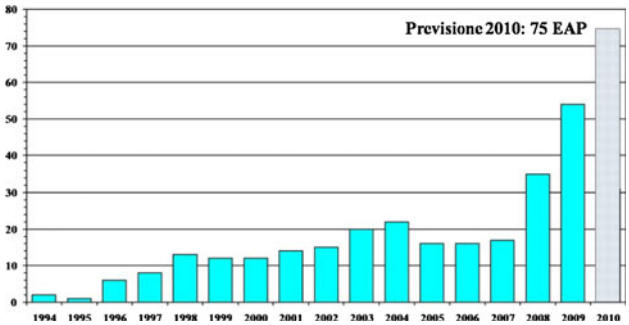

Fig. 1 Patients' referral by year (1994, predicted 2010)

Fig. 2 PEA of distal CTEPH

Conclusions: PEA is an elective surgery, non donor-dependent, and age is not a contraindication. PEA also is not burden with the typical complications described for DLTx. Outcome after PEA is excellent in terms of hemodynamic recovery, quality of life, functional improvement, and long-term survival (83% at 15 years, overall mortality 9%). Hence, CTEPH pts should be referred early to Centres experienced in both PEA and DLTx, to offer the best treatment and to achieve the best results. Moreover, this strategy maximizes the use of scarce donor organs by offering, when feasible, a non-transplant option.

Pulmonary endarterectomy in WHO II patients with chronic thromboembolic pulmonary hypertension

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Background: Patients with CTEPH may present with a variety of debilitating symptoms. Once diagnosed, pulmonary endarterectomy (PEA) is the most effective treatment. As referral is increasing, some pts are presenting with mild symptoms. However, indication for surgery in WHO functional class II pts is still controversial.

Methods: From April 1994 to May 2010, 294 PEAs were performed at our Centre. Patients presented pre-operatively with WHO II (6%), WHO III (46%) and WHO IV (48%) symptoms. Among WHO II pts (18) we observed a wide spectrum of clinical features: 5 patients were sportsmen (28%) with high exercise tolerance, and 10 patients had sedentary lifestyles (56%) and rarely competed with physical activity. Hence, into this group important differences come out in terms of hemodynamic and functional impairment, as shown in Fig. 1.
Results: Post-operative outcome after PEA in WHO II patients is shown in Table 1.

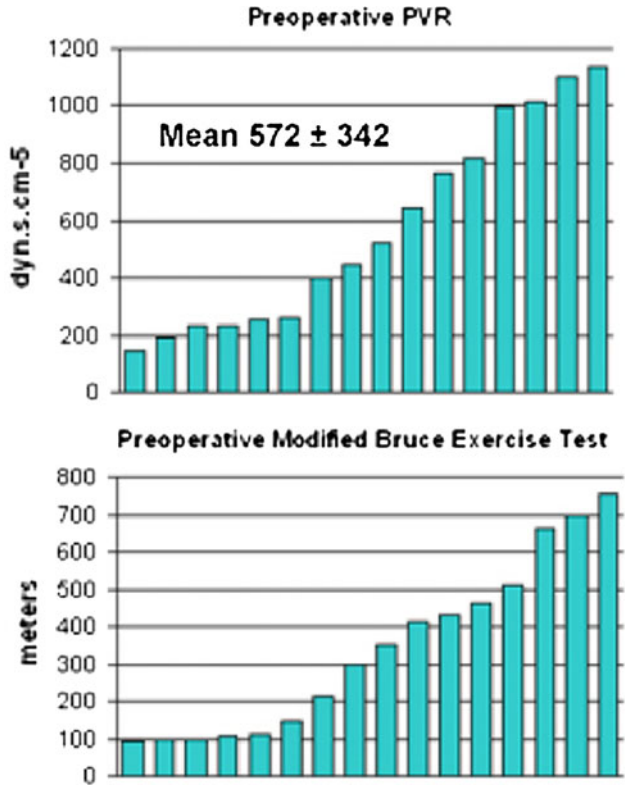

Fig. 1 Pre-operative WHO II patients differences in terms of hemodynamic and functional impairment.

Table 1 Results after PEA in WHO II patients

Preoperative PVR (dyn s cm^{-5})	566 ± 336
Postoperative PVR (dyn s cm^{-5})	187 ± 115
MV duration (days)	1 (3–1)
Postoperative hospital stay (days)	13 ± 7
Morbidity	5.6%
Mortality	0%

PVR pulmonary vascular resistance, *MV* mechanical ventilation

Conclusions: Once diagnosed, CTEPH patients must be referred to surgery immediately, before hypertensive vascular remodeling develops in the non-obstructed branches due to pressure and volume overload. Based on the excellent results in terms of hemodynamic improvement and low operative risk, our experience suggests that indication for PEA should be extended even to WHO II pts.

Single nucleotide polymorphisms (SNPs) of pro-inflammatory/anti-inflammatory and thrombotic/phibrinolytic genes in patients with acute ischemic stroke and relationship with TOAST subtype

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Background: The genetic basis of complex diseases like ischemic stroke probably consists of several predisposing risk factors, as genes involved in inflammation and thrombotic pathways. On this basis the aim of our study was to evaluate the role of SNPs (single nucleotide polymorphisms) of some pro-inflammatory/anti-inflammatory and coagulation/fibrinolytic genes in patients with acute ischemic stroke.
Methods: We enrolled consecutive patients with a diagnosis of acute ischemic stroke admitted to the Internal Medicine Department at the University of Palermo between November 2006 and January 2009, and control patients without a diagnosis of acute ischemic stroke.
Results: We observed a significant higher frequency of IL-10 1082 AA genotype in stroke patients ($p = 0.033$), with a significant risk trend at regression analysis (HR = 3.52; $p = 0.005$). We also reported a higher frequency with a significant hazard ratio at regression analysis, in stroke subjects in comparison to controls, of the TPA 7351-CT genotype ($p = 0.019$) (HR = 3.70; $p = 0.001$) and of IL-1 VNTR 86 bp 2/2 genotype ($p = 0.017$) (HR = 7.50, $p = 0.011$). In addition, we observed a significant relationship of lacunar TOAST subtype with a significant risk trend for CC-TPA (HR = 8.00; $p = 0.031$) and 1/1 IL -1 VNTR 86 bp (HR = 3.92; $p = 0.021$) genotypes.
Conclusions: Ischemic stroke is a common multifactorial disease, which is affected by a number of genetic mutations and environmental factors. Our findings showing a relationship between pro-inflammatory/anti-inflammatory and thrombotic/fibrinolytic genes SNPs and ischemic stroke may contribute to delineate a possible stroke risk profile in subjects with cerebrovascular risk factors.

Target organ damage in a population at intermediate cardiovascular risk with adjunctive major risk factors: cardiovascular prevention SACCO study (Capress)

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Background: Cardiovascular disease (CVD) is the leading cause of death in the world. More than 50% of patients with coronary heart disease had not been classified as at high risk. It is therefore important to correctly identify the patients most likely to benefit from primary prevention strategies.
Objective: To characterize a population at intermediate cardiovascular risk (10–20% 10 years CV risk) and one or more adjunctive major risk factors (AMRF), checking for the presence of target organ damage (TOD) with a safe, non-invasive procedure at carotid, cardiac, renal and peripheral vascular levels.

Methods: From March 2007 to July 2009, 11,618 people were screened by general practitioners for CVD risk assessment during an office visit; 10,639 were not eligible. Final population was composed by 979 subjects at intermediate cardiovascular risk, as indicated by the Italian algorithm "Progetto Cuore"; cases were aged 40-69 years, sensitized by one or more AMRF such as premature family history for cardiovascular disease (CVD), overweight/obesity and smoking habit (more than 10 cigarettes/day). We measured common carotid intima-media thickness (cc-IMT) and plaque at any level, left ventricular mass index (LVMI), urine albumin/creatinine ratio (UACR), and ankle-brachial index (ABI). TOD was considered present if: cc-IMT was >0.9 mm or a plaque (c-IMT > 1.3 mm) was detected at any level of the vascular tree; peripheral arterial disease (PAD) was considered present if ABI was <0.9 in at least one leg; left ventricular hypertrophy was defined as a LVMI exceeding 102 g/m^2 for men and 88 g/m^2 for women; low-grade albuminuria was considered present if the proportion of albumin to creatinine was >22 mg/g for men and >31 mg/g for women.
Results: The prevalence of at least one TOD was 63% (617 subjects), cc-IMT was high in 48.2% (472), UACR abnormal in 14.1% (138), LVMI high in 12.6% (117) and ABI pathological in 9.1% (89). In those with carotid damage 423 had a plaque, amounting to 43.2% of the total population. Among subjects with at least one TOD, 450 (73%) had 1 TOD, 136 (22%) had 2 TODs, 30 (4.99%) had 3 TODs and only 1 subjects had all 4 TODs; of notice carotid damage was present in all subjects with 3 TODs and in 92% of subjects with 2 TODs. A multivariate logistic regression model including conventional factors and AMRF indicated that age 50–69 years, systolic blood pressure, relevant smoking and CV risk score $\geq$15 were independently and significantly associated with at least one TOD and at least carotid damage. Among the AMRF, peripheral arterial disease was associated with relevant smoking, with an odds ratio (OR) of 3 (confidence interval, CI 1.80–4.97, $P < 0.0001$); overweight and obesity both had selective associations with cardiac damage with OR 2.75 (CI 1.2–6.3, $P < 0.01$) and OR 3.89 (CI 1.61–9.73, $P < 0.01$).
Conclusion: A substantial proportion of people at intermediate risk, with at least one AMRF have at least one TOD, a major predictor of cardiovascular outcomes. These findings support the idea that conventional scores underestimate risk in a significant proportion of people at intermediate risk.

Cardiovascular and metabolic alterations in patients with obstructive sleep apnea (OSAS)

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Background: Obstructive sleep apnea (OSA) a condition of repeated episodes of apnea and hypopnea during sleep, continue to be an important public health care issue.
Cardiovascular morbidities, such as stroke, coronary artery disease and heart failure are major health risks for OSAS patients.
Aim: The aim of the present study was to estimate in a consecutive series of hypertensive patients with sleep disorders some anthropometric, cardiovascular, inflammatory, and metabolic parameters and correlates these with those of apnea/hypopnea index (AHI).
Material and methods: We studied 307 consecutive newlydiagnsoed hypertensive patients who referred to Department Unit of Secondary Hypertension, Dpt. of Clinical Sciences, University of Rome "Sapienza", Italy. 254 hypertensive patients didn't presented sleep disorders (154 male, 100 female) (mean age 50.8 $\pm$ 7.5 years) and 53 patients (17%) (38 male, 20 female; mean age 50.5 $\pm$ 7.6 years) presented clinical signs of sleep disorders. The excessive daytime sleepiness was evaluated by the use of a specific questionnaire such as the Epworth Sleepiness Scale (ESS). If the results of the test was equal or major to 10, all patients were referred to Centre of Diagnosis and Cure of Roncopathy where they underwent to a polysomnography for the validation of OSA. Patients without diagnosis of OSA, were classified as habitual snorers. Body mass index (BMI), waist circumference, neck circumference (measured at the cricoid level) and Routine biochemical examination including C-reactive protein (CRP) and microalbuminuria were obtained in all the subjects. Ambulatory blood pressure monitoring (ABPM 24 h), echocardiographic study, polysomnography, were performed.
Results: All 53 hypertensive patients presented abdominal obesity patients with OSAS presented higher WC (108.2 $\pm$ 11.2 cm) respect to snorers patients (102.3 $\pm$ 11.6 cm) ($p < 0.05$).
As expect in patients with OSA the AHI (APNEA HYPOPNEA INDEX) was significant higher ($p < 0.001$) compared to snorers patient. None difference was found between age, clinical, blood pressure and heart rate in two groups. Echocardiographic study show that patients with OSA present higher values of aorta, interventricular septum, left ventricular posterior wall and left ventricular mass respect to those of snorers ($p < 0.01$).
Conclusions: Patients with OSA present an anthropometric, pro-inflammatory, and hemodynamic alterations with an high risk for cardiovascular disease.

Epicardial adipose tissue (EAT). New evidence of protective role of physical activity in metabolic syndrome

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Background: Epicardial adipose tissue (EAT) shows significant independent associations with cardiovascular risk predictors, such as hypertension, low HDL cholesterol, high LDL cholesterol, high triglycerides, insulin resistance. Recent evidence indicate that training, even without diet restriction, may be effective for decreasing EAT thickness.
Methods: According to this last suggestion we investigated the correlation between aerobic exercise and EAT in a population of 50 patients with metabolic syndrome underwent multi-detector computed tomography (MDCT) scan for coronary artery calcium (CAC). We divided all subjects in two groups on the basis of history of leisure time physical activity at the moment of MDCT.
The admission criteria in physical active group were almost 1 year moderate-intensive aerobic exercise training according the recommendation for Adults from the American College of Sports Medicine and the American Heart Association (ACSM/AHA).
Results: We investigated the patients for the presence of aerobic exercise and only 10% have ACSM/AHA criteria. The 45 sedentary patients show a EAT volume higher versus the 5 subjects with moderate intensive exercise training that have all extremely low EAT volume (Fig. 1). The statistical analysis, although the small sample size, found significant associations between physical activity level and EAT.
Conclusion: These results confirm the role of physical exercise in the EAT decrease and show improvement in obesity associated cardiovascular and metabolic abnormalities.

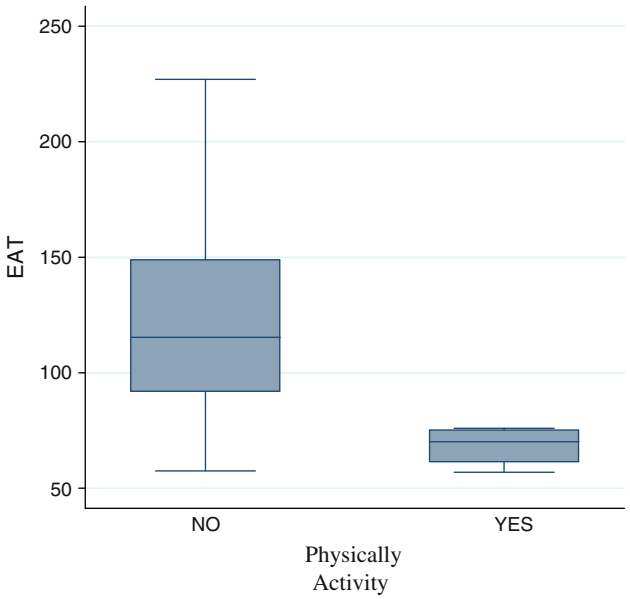

Fig. 1 EAT distribution and aerobic exercise training in metabolic syndrome

Infective Diseases

Mycobacterium chelonae and rheumatoid arthritis

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Report case: S.C., a 68-year-old man was admitted to the Internal Medicine "A. Murri" for fever and purple nodular cutaneous lesions on his left leg. The fever started 15 days before admission while skin lesions appeared 3 months before. At admission, he was on prednisone, methotrexate for his rheumatoid arthritis. He appeared suffering and asthenic. He referred swelling of the metacarpophalangeal joints and metatarsal phalangeal with functional impotence. His body temperature was about 39°C. Physical examination showed: a reduction an VM on both hemithorax. The lab test were all normal except an increase in circulated inflammatory parameters PCR: 212.9 mg/dl and leucocytosis (WB 15.650 μl^{-1}, N 86.0%). Blood cultures was found negatives. A chest RX scan on admission showed consolidations in bilateral lung fields.
Diagnostic hypothesis:

1. Bronchopneumonic process? Mycobacterium tubercolosis?
2. Infection in immunocompromised patient?

Mycobacterium chelonae infection was revealed through several skin biopsies with molecular sequence analysis. The therapeutic program consisted of a treatment with Clarithromycin and Doxycycline for 2 months. Methotrexate was immediately discontinued.
Discussion: Very few cases of cutaneous infection involving M. chelonae in association with an immunosuppressant treatment have been reported in the literature. It is important to perform skin biopsies following the appearance of skin lesions.

Retinitis, retinal vasculitis and papilledema of internistic interest: a case of ocular neurosyphilis

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The internal medicine physician is often sought by ophthalmologists to diagnose conditions presenting with uveitis, retinal vasculitis, papilledema. The diagnostic work-up and differential diagnosis are sometimes intricate, since specific causes of ocular conditions recognize numerous infectious, immunological and neoplastic etiopathogenesis. We describe a case of successfully diagnosed and treated ocular syphilis associated with neurosyphilis.
Case report: A 47-years-old patient with 46 XX male syndrome, who underwent in infancy removal of the gonads, penile reconstruction and testicular implants and who was taking testosterone replacement therapy since he was 14-years-old, was referred to us by ophthalmologists for further investigations. The patient complained a dramatic and progressive decrease of visual acuity and at the first ophthalmological examination the visual acuity in the right eye (OD) and in the left eye (OS) were 1/10 and 4/10, respectively. Fundus examination showed bilateral papilledema (OD > OS), with evidence of cystoid macular edema, papillary hyperfluorescence, sluggish retinal circulation and choroidal vessels hyperfluorescence at fluorescein angiography. The CT and MRI of the brain did not detect any abnormality. Then the patient was referred to our Internal Medicine Day Hospital. The results of routine biochemistry tests were unremarkable with C-reactive protein and eritrosedimentation velocity of 0.13 mg/dL (n.v. < 0.5) and 20 mm/h (n.v. < 15) respectively. Extensive viral and parasitological serology and auto-immune antibodies serology were negative, while the serodiagnosis for syphilis was indicative for recent or active disease: treponemal test CMIA 24.56 (n.v. < 10), rapid plasma reagin (RPR) 64 (n.v. 0), ELISA IgM anti-treponema pallidum 1.99 (n.v < 0.9) and immunoblotting for TpN47, TpN17, TpN15, TmpA resulted highly positive (+++). Testing for antibodies anti-HIV and for HIV antigen resulted negative. Results of other imaging techniques were unremarkable. Lumbar puncture was performed, with collection of clear cerebrospinal fluid (CSF). CSF Leukocytes count resulted 20 μL^{-1} (n.v. < 4), with normal glucose and protein levels: 56 mg/dL (n.v. 40–75) and 29 mg/dL (n.v. 15–45), respectively. CSF treponemal tests showed: anti-treponemal CMIA antibodies 11.21, anti-treponemal RPR negative, IgM anti-treponema pallidum 0.47 and immunoblotting positivity for TpN47 (+), TpN17 (+++), TpN15 (+), TmpA (±). Blood–brain barrier function indexes (albumin index and Link index) were normal, and the Reiber's graph, plotting albumin index and gamma-globulin index, was indicative of intrathecal synthesis of immunoglobulin. Then the patient was treated according to European and American current guidelines for managing syphilis in all forms, including eye disease and neurosyphilis. We started with ceftriaxone 2 g i.v. daily for 14 days (considering the current non-availability of acqueous penicillin G in Italy), followed by benzathine penicillin 2.4 million Units IM administered as 3 doses, given at weekly intervals. In the following months the patient recovered visual acuity gradually, with improvement of fundus examination and of fluorescein angiography.
Conclusions:

1. Although the annual incidence of primary and secondary syphilis has dropped to the lowest rate recorded, syphilis remains an important cause of ocular disease, and we should especially look for syphilis among men who have sex with men, independently of HIV infection status. Our patient eventually has reported

homosexual contact occurred approximately 3 months before the visual loss and was convinced to inform his casual partner to seek medical attention, given the successful treatment.
2. The CSF analysis confirms or excludes associated neurosyphilis, in order to start the appropriate treatment as in the case presented.

Pulmonary actinomadura in CVID: rare infection in rare disease

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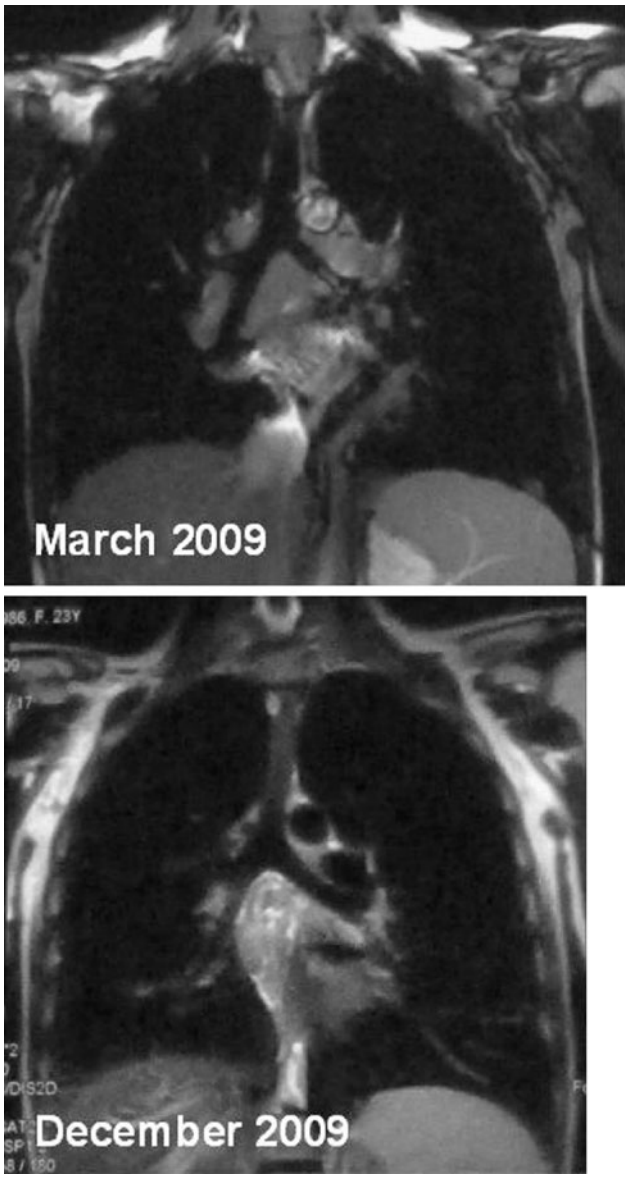
Common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by impaired B cell differentiation with defective immunoglobulin production and variable T cell abnormalities. Despite IgG replacement, recurrent respiratory infections and consequently bronchiectasis are the most frequent complications whilst reactive interstitial pneumonitis (lymphoid interstitial pneumonia and sarcoid-like granulomatosis) and pulmonary lymphoma involvement are rarer. We describe a case of pulmonary actinomycosis in CVID.

Case: In 2006 a 20-years-old CVID affected female started IgG replacement. In February 2008 because of dyspnea and fever she underwent a lung CT-scan that showed nodular infiltrates and mediastinal lymphadenopathy. Hilar lymphonode histopathology revealed T-cell lymphoid hyperplasia, no granulomata were seen. She became afebrile after antibiotics therapy. In March 2009 thoracic pain relapsed and NMR imaging showed inaltered parenchimal infiltrates but an increase of 20% in mediastinal lymphonodes enlargement. Pain recovered after antibiotic therapy. When in June 2009 thoracic pain and fever relapsed again, Actinomadura spp was diagnosed by PCR on 120-days sputum culture prepared for mycobacterium. Amoxycillin-clavulanate was started and after 3 months of therapy lungs nodular infiltrates drastically reduced and mediastinal lymphadenopaty decreased of about 20% on NMR.

Discussion: The pulmonary form of actinomycosis is observed as a secondary and localized infection, especially in residual cavities or bronchiectasis. Actinomadura spp. are Gram-positive, nonacid-fast, aerobic actinomycetes known as a major cause of cutaneous and subcutaneous mycetomas. Actinomycosis infection most commonly present as chronic, debilitating illnesses and is not often considered in the differential diagnosis of lung disease because of the spectrum of its clinical features, the similarity of its appearance to other granulomatous or neoplastic diseases, and coexistence of this infection with other pulmonary conditions. As recent studies suggest, it should also be considered as a causative agent for nonmycetomic infections as a consequence of impaired immunity. There is limited information on both computed tomography (CT) and magnetic resonance imaging (MRI) findings in pulmonary actinomycosis. Most of the published series are small retrospective studies. In pulmonary infections, the CT findings include patchy air-space consolidation, multifocal nodules, cavitation, pleural effusions or thickening and hilar and/or mediastinal lymphadenopathy. Diagnosis depends on a high degree of suspicion so as to alert the microbiology and pathology laboratories to employ special methods to identify the organisms. Early recognition and prompt treatment usually results in complete cure. Treatment of actinomycosis is usually simple, requiring long-term, high-dose intravenous penicillin. Early recognition and prompt treatment usually results in complete cure.



Prokaryomycetes in the pathogenesis of diseases correlated to Prokaryomycetes and to Prokaryolichenes

Della Porta Gi.P.

Primario in pensione, Milano, Italy

Prokaryomycetes (Pcm) and Prokaryolichenes (Pcl) and correlated diseases (c.Pcm) (c.Pcl) have been presented through posters at the 100°, 101°, 103°, 104°, 105°, 106°, 107°, 108°, 109° National Italian Congress of Internal Medicine, at the 38° National Congress of Italian Society of Microbiology and at the 49° National Congress of Italian Society of Cancerology. The following considerations, revised by further clinic and experimental confirmations, update the Pcm path-

ogenic mechanisms in neoplastic and not neoplastic diseases, correlated to Pcm.
Pcm cause c.Pcm diseases:

- Developing mycelium: pl1-plm1, pl2-plm2, more or less compact and vacuolized that realize the following lesions:
  - Inflammatory, even granulomatous stimulating the cellular proliferation and angiogenesis;
  - Degenerative, frequently inserting their produced subsances in pl1-pl2 vacuoles and in fibrillar tangles (see ahead);
  - Necrotic: colliquative and coagulative;
- Transforming themselves in plb-plmb that constitute the fibrillar tangles of degenerative lesions and the fibers of evolutive sclerosis of inflammatory and necrotic subacute or cronic lesions;
- Synthesizing chemical substances equivalent to those synthetized by the host or anomalous and complex, for realizing proteic, lipidic, glucidic deposits and pigments in vacuoles pl1, pl2 and in plb tangles of the degenerative lesions:
- Through not known mechanisms,
  - interferring in the metabolic and immunologic processes of the host,
  - stimulating cellular proliferations and angiogenesis,
  - Modifying and reactivating genes;
- Producing spores, extra and endocellular.

Pcm cause c.Pcl diseases:

- When they create, or when there is a biologic situation, in the host, favorable for generating Pcl, transforming themselves in *mycobiont* that, with a lichenization process, constitutes the *cytobiont*, generally monoclonal, rarely oligoclonal, deriving, from it, the progenitor cells from the host tissues and with angiogenic substances stimulates the development of a *vascular system* anatomized with those of the host.
  The numerous possibilities that mycobionts, deriving from Pcm with different constitutive characters (i.e. with different levels of aggrassiveness), associate with cytobionts derived by different progenitor cells, determine the morpho-structural and biological variety of Pcl that can cohabit or attack the host causing also death, rapidly developing and invading its tissues, secerning chemical substances (synthetized by micobiont and by cellular elements of cytobiont) and diffonding diaspors.
- With the possibility of realizing various diseases c.Pcm

Since Pcm do not contain DNA, they have also an important role in the evolution of organisms. To be published *The role of Prokaryomycetes and Prokaryolichenes in organism' evolution and pathology.*

An old woman with diarrhea: the usual suspects?

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A 79 years-old woman was hospitalized for diarrhea, abdominal pain and malar rash, on bad general conditions, afebrile. Reported a history of weight loss of about 14 kg in 3 months, diarrhea for about 2 years, in absence of therapy. Laboratory tests showed anemia (10.4 g/dL), ESR 80 mm/hr, CRP 20.5 mg/L, and increased amylase levels (556 mg/dL), for which began therapy with Total Parenteral Nutrition, Somatostatin and Gabexate Mesilate. We performed esophagogastroduodenoscopy and colonoscopy that were negative and a CT scan that showed multiple enlarged lymphnodes in the interaortocaval, para-aortic and retroperitoneal spaces with pleural and pericardial effusion. Urine cultures were positive for *Enterococcus spp*. and *Pseudomonas aeruginosa*. A stool sample showed no occult blood, in absence of *Shigella*, and *Clostridium difficile*. The 5-HIAA and chromogranin were negative. The serological tests showed negativity for hepatitis markers, treponema, toxoplasmosis and TB, while CMV-IgG were positive. An oral swab showed positivity for Candida albicans. On anamnestic deepening, we found that our patient had had numerous sexual partner despite age in the not too recent past. Thus, for complete diagnosis was made the search for anti-HIV that was positive with $CD4^+$ of 162 cells/μL (19%). Moreover, search for CMV disease showed gastric involvement (gastric aspirate positive). Thus, the patient had a diagnosis of AIDS (C3 category of CDC Classification System for HIV-infected patients), starting an anti-retroviral therapy with Emtricitabine (200 mg), Tenofovir (245 mg), Fosamprenavir (700 mg) and Ritonavir (100 mg). Our patient had diarrhea not otherwise explained since about 2 years, with a progressive deterioration of general conditions.

Excluding the main causes of diarrhea, it can be noted as well as in unsuspecting patients (in the elderly) the possibility of HIV infection should be considered, highlighting the importance of a medical history as complete as possible.

A cryptogenic *Klebsiella*

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A 54-year-old man was admitted to the Emergency Departement of L. Sacco Hospital of Milan complaining the onset history of fevers (39–40°C) associated with headache from 5 days. He did not report any other relevant symptoms. There was no history of recent travel, tick bites, or sick contacts. Three days before hospital admission he started therapy with Amoxicillina without benefit. The past medical history revealed pulmonary tubercolosis in 1981 treated with a 6 months multidrug regimen. On physical examination, the lungs were clear bilaterally, with no audible murmur on cardiac auscultation. The abdomen was soft and non-tender, with no hepatosplenomegaly; the skin was hot; there was no rush. The scleras were non-icteric. The neurologic examination was unremarkable. The chest X-ray was normal. The laboratory tests showed leukocytosis ($11{,}300\ mcl^{-1}$; 75% neutrophils), mild thrombocytopenia ($81{,}000\ mcl^{-1}$), creatinine increase (1.34 mg/dl), increased inflammatory indexes (D-dimer 4,434 ng/dl, fibrinogen 653 mg/dl, CRP 161 mg/l) and alterated liver function tests (AST 94 U/l, ALT 108 U/l, GGT 202 U/l) with normal bilirubin value. To exclude the suspicion of a reactivation of the tubercular illness, a chest-CT scan was performed that revealed only a fibrotic zone of the right upper lobe. Cerebral-CT scan and echocardiography were negative. The urine and blood colture and urine tests for mycobacterium species were negative. Viral markers were negative (HBV, HCV, EBV, CMV, HIV). The patient was empirically treated with intravenous ciprofloxacin and ceftriaxone. After 48 h, one of blood coltures was positive for *Klebsiella penumoniae* sensitive to the ongoing antibiotic therapy. Abdominal ultrasound and abdomen CT scan showed alitiasic gallbladder and an liver

lesion suggestive for abscess with local dilatation of biliary system involving the VII hepatic segment. Because of the risk of a polymicrobial etiology, it was started also therapy with Metronidazole. To exclude infectious sources, colonscopy was performed. It showed the presence of two sessile polyps with no-ulcerated mucosa that were endoscopically removed. Histological examination was negative for cancer. Neoplastic markers (CEA, CA 19.9 and alfa-fetoproteine) were normal. The patient clinically improved with complete regression of fever and laboratories returned to baseline after a 3-weeks of intravenous antibiotic therapy. Six weeks later, abdominal TC scan showed almost complete resolution of the abscess. The overall incidence of pyogenic liver abscess is still low (1–3:100,000), however the trend is increasing and *Klebsiella pneumoniae* is the major responsible. The aspecific symptoms coupled with the rarity of clinical cases bring to a delay in the correct diagnosis leading to an higher risk of early disseminated infection. This partially explains the unexpected low reduction in mortality despite improvements in diagnosis and treatment. Non-*Klebsiella* liver abscesses require the search of underlying deseases (especially intra-abdominal malignancies) and of specific therapies for polymicrobial abscesses. Conversely *Klebsiella* abscesses are unlikely of polymocrobial origin while often associated with diabetes mellitus. However it is important to highlight that about 60–70% of *Klebsiella* infections—as the case here described—are cryptogenic and characterised by the absence of underlying malignances, liver and biliary tract diseases or diabete mellitus. Indeed, in case of fever of unknown origin, weighting the individual risk factors, the hypothesis of pyogenic liver abscess should be investigated carefully towards an early diagnosis and the administration of appropriate treatments able to prevent organ failure, uncontrolled sepsis, DIC and metastatic infection (particularly of the eye and CNS typical of the infections from Klebsiella) correlated to an higher mortality.

Multiorgan failure in a cirrhotic patient with overimposed *Cryptococcus neoformans* infection

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We report a case of a 75-year-old woman with cirrhosis HCV related who developed high fever, chills and fatigue over the period of 1 month. She was treated at home with levofloxacin without benefits. On admission to the hospital, the patient was alert and oriented, even if a bit slackened. On physical examination, she had minimal ascitis and hepatomegaly and was anicteric. She had no signs of rigor. Cranial nerves examination was normal. There was edema of grade 2 in the lower extremity bilaterally. Blood laboratory tests revealed a sever iron deficiency anaemia (haemoglobin 7.6 g/dl) requiring several blood transfusions. She had elevated serum levels of all tumor markers, elevated liver enzymes and low synthesis liver index. Inflammation index parameters were all negative. She was initially treated with ceftriaxone without any effects on the thermic curve. Her blood culture grew yeasts compatible with *Cryptococcus neoformans*, so a therapy with fluconazole intravenously was initiated. A HIV serum antibody test resulted negative. The blood CD4 lymphocyte count and CD8+ T-lymphocyte count were within the normal range. She had full laboratory investigations including negative chest and brain CT. Cerebrospinal fluid was positive for Criptococcus Neoformans infection and revealed modestly elevated white cell counts (monocytes), elevated protein and low glucose. The patient had no exposure to risk factors. She remained febrile and after 13 days of antifungal therapy, she was managed in place of fluconazole with a lipid formulation of amphotericin B as a result of increase in blood creatinine. In the following days, the dosage was dramatically reduced because of the worsening of liver and kidney function. Despite 2 weeks of treatment and the absence of the fever, another brain CT revealed an abnormality in the left pulvinar suspected as a cryptococcosis-related lesion. The treatment with intravenous liposomial amphotericin B was followed for 23 days but it was interrupted for a week because of dramatic kidney damage. Because of the onset of leucocytosis with a mild increase of C reactive protein, the therapy was enforced by a broad spectrum antibiotic followed by Linezolid due to pluriresistant Enterococcus in the urine. After 19 days of therapy with amphotericin B, the patient fell into a deep coma. In the face of a possible acute deterioration of the situation, we recommended a CT of the brain, but this did not reveal any new lesions. According to hyperammoniemia (227 μmol/l) and an extended metabolic and liver panel demonstrating a general worsening, we feared a development of hepatic encephalopathy, explained by the effect of neurotoxic substances due to the long heavy antifungal therapy. Lactulose was administered as an enema and she was managed with branched-chain amino acids and albumin. Her intellectual impairment showed a slow but constant improvement but cryptococcal encephalitis was confirmed again by a second lumbar puncture with high positive cryptococcus antigen in the cerebrospinal fluid. In the following days, the patient developed multi-system organ failure. Because of her progressive clinical deterioration, she developed anasarca, jaundice, her abdomen was markedly distended consistent with ascites, even if she had not depressed level of consciousness. Laboratory tests were obtained and revealed a white blood cell count of 17×10^3 cells/mm^3, with 87% polymorphonucleated cells, sodium 127 mEq/l, potassium 5.4 mEq/l, calcium 11.6 mEq/l, BUN 162 mg/dl, undetectable creatinine for jaundice, total bilirubin 26.5 mg/dl, AST 105 U/l, ALT 82 U/l, and alkaline phosphatase 182 U/l. On day 34 the exitus occurred. Cryptococcus neoformans is an encapsulated yeast that causes serious infections in immunocompromised populations. We remark that liver dysfunction occasionally has been reported to be a risk factor for cryptococcosis; in fact cirrhosis may increase the risk because of its association with elevated levels of chemotactic inhibitors and reduced complement levels. Moreover, in this particular case, cirrhosis played an important role in causing the failure of the treatment and the multiorgan failure.

An association between EBV infection and hereditary hyperhomocysteinemia

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Hyperhomocysteinemia is an independent risk factor for venous thrombosis. Elevated plasma homocysteine levels have been associated with atherosclerosis, arterial thrombosis and venous thromboembolism. The increased levels are attributable to an altered homocysteine metabolism, which could be the result of both acquired causes, such as vitamin B6, B12 or folate deficiency, and hereditary enzymatic defects like Cystathionine-β-synthase deficiency or the expression of a thermolabile isoform of methylenetetrahydrofolate reductase (MTHFR). Since no threshold for hyperhomocysteinemia has yet been established, the possibility that both the acquired and the hereditary mechanisms, although unable alone to induce thrombosis, could constitute one of the

factors triggering thrombotic events, is particularly intriguing. In particular, a mild functional deficiency associated to a reduction by 50–70% of enzymatic activity in subjects with homozygosity for the MTHFR thermolabile variant has been reported. Here we describe the case of a 30-year-old male patient, referred from the emergency room with a diagnosis of fever associated to pancytopenia. The patient arrived with a sore throat, asthenia, abdominal pain and fever (maximum 38.5°C), all symptoms that had appeared about a week before. He had been taking Levofloxacin for 3 days. On arrival, laboratory tests revealed leukocyte and platelet depletion (WBC 3,400 μL^{-1} with normal differential WBC count, PLT 90,000 μL^{-1}), not present in a previous blood test brought by the patient. He had a family history of early cardiovascular disease (a 40-year-old uncle died of IMA and his father had been affected by ischemic cardiomyopathy since the age of about 50 years). Clinical examination revealed laterocervical lymphadenopathy and widespread abdominal pain. Further blood tests showed high amino transferase levels (ALT 4.5 XN, AST 3XN) and a high inflammatory index. Abdominal US showed splenomegaly with a bipolar diameter of 17 cm. Tests for immunological and hematological disorders were negative. Infection was a possibility because the patient was positive for EBV VCA-IgM. However, since the fever did not subside and the patient complained of breathlessness and abdominal pain, CT of the head–chest–abdomen was performed, for a suspected lymphoproliferative disorder. This revealed bilateral pulmonary thromboembolism and thrombosis partially obstructing the lumen of the inferior mesenteric artery. In subsequent tests the following thrombophilic defects were investigated: aPLs, lupus anticoagulant, homocysteinemia, protein C and protein S concentrations, activated protein C resistance, the presence of a mutated Factor V, prothrombin (G20210A) and MTHFR (C677T). The folate level was found to be lower than the normal range (2.1 ng/ml; n.v. 3–16). The final diagnosis was therefore pulmonary embolism and thrombosis of the inferior mesenteric artery associated to hereditary hyperhomocysteinemia and infectious mononucleosis. Warfarin therapy was started, in association with folate and vitamin B group supplements. The MTHFR mutation is present with a frequency of 5–15% in the European population and is mostly asymptomatic. Although an association between this genetic alteration and viral infection has been suggested only in HIV patients treated with antiretroviral therapy, the case we describe could indicate a possible association between the thrombosis and EBV, as an example of a gene-environment interaction. The EBV infection likely caused a decrease of folic acid, causing the genetic defect to manifest and inducing the described atypical signs of a common infectious disease.

Emergency Medicine

Pseudo-Bartter's syndrome with "metabolic madness" from multiple causes

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In clinical practice we often encounter cases where the diagnostic process is influenced by many confounding factors. However, though laborious, iterative work and careful history taking, come to diagnostic details with unexpected but exhaustive explanation of the entire clinical picture. A 42-years-old woman presented to the emergency room because of syncope and cranial contusion. She had history of prior episodes of syncope thought to be caused by orthostatic hypotension and she complained of cramps, paraesthesias in the arms and episodes of carpopedal spasms in the last 6 months. The patient reported using only amitriptiline 10 mg daily since 1 month. Blood pressure was 102/66 mmHg; heart rate, 95 min^{-1}; respiratory rate, 22 min^{-1}. Physical examination was unremarkable. Laboratory studies showed plasma levels of potassium 1.9 (3.4–4.5) mmol/L; calcium, 7.9 (8.6–10.2) mg/dL; ionized calcium, 0.98 mmol/L (1.14–1.29). The remainder of blood chemistry was normal. The electrocardiogram showed non-specific repolarization abnormalities and a corrected QT interval of 0.59″. After 16 h she spent in Cardiology ward where no life-threatening arrhythmias were observed, the patient was moved to our Internal Medicine ward. In spite of intravenous infusion of potassium chloride and calcium gluconate, on the 3rd day from admission, 24-h urine excretion of potassium, sodium, chloride, calcium, phosphate, magnesium and creatinine resulted: 8 mmol/24 h (25–125), <6 mmol/24 h (40–220), <6 mmol/24 h (110–250), 1.8 mmol/24 h (<7.5), 9 mmol/24 h (12.9–42), 4.5 mmol/24 h (3–5) and 609 mg/24 h (720–1,510), respectively, with a urine [potassium]/[creatinine] (K/C) ratio: (12 mmol/L/0.87 g/L) = 13.7 mmol/g. Determination of the urine K/C ratio should be the first step in the diagnostic algorithm based upon the causes and mechanisms of hypokalemia [1, 2]. A urine K/C ratio less than 15 mmol/g suggests: poor potassium intake, gastrointestinal loss, laxative use, hyperthyroidism, familial or sporadic periodic paralysis. A careful history taken discovered watery stools, daily intake of besacodyl 35–40 mg (7–8 pills) during the last months, use of herbal diuretic preparations and licorice, and assumption of desmopressin 60 mcg b.i.d. during the last 10 days prescribed by her general practitioner for polydipsia and hypotension. It is interesting to note, among other initial laboratory studies, direct renin and aldosterone plasma values of 209.5 μUI/mL (2.8–39.9) and 287 pg/mL (7.5–150) in clinostatism; 212.8 μUI/mL (4.4–46.1) and 359 pg/mL (35–300) in orthostatism, respectively. During hospitalization the patient complained mild transitory generalized oedema. Following laxative and—obviously—desmopressin withdrawal and the avoidance of herbal remedies and licorice, after 4 months we observed normalization of the entire clinical picture: the patient is well and laboratory findings have returned to normal values.

Conclusions:

1. The urine K/C ratio resulted very useful to approach the differential diagnosis of hypokalemia in the case presented.
2. We think that besacodyl abuse was the main pathogenetic cause. Stimulant laxative drugs, that often require increasing dosage to maintain their effect, enhance gut motility and water excretion, with electrolytes loss: hypokalemia, hypocalcemia, hypophosphatemia, hypomagnesemia are frequent findings.
3. Hypovolemia leading to hypotension induces hyper-reninemia and hyperaldosteronism, configuring the pseudo-Bartter's syndrome, well-documented in chronic laxative abusers.
4. In the case reported, insane habits and iatrogenic factors led to many confounding metabolic derangements, which has been already termed by some authors "metabolic madness".

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The Pearson test and P/F-PESI case study: correlative analysis of continuous variables in 20 patients with venous thromboembolism. Biennial experiences 2008–2009

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Introduction: The "P/F-PESI" study acronym resulting from "PaO_2/FiO_2-Pulmonary Embolism Severity Index", has analyzed 20 patients, aged between 48 and 82 years, with venous thromboembolism (central pulmonary embolism) hospitalized in "Degenza Breve" and "Sub-Intensive C" in Internal Emergency Medicine Department from January 2008 to December 2009. The case history showed in all patients with severe respiratory failure (value arterial $pO_2 < 60$ mmHg), may be associated with chest pain, confusion, hemodynamic instability (SBP < 90 mmHg) according to American College of Chest Physicians Evidence -Based Clinical Practice Guidelines (8th Edition). It was examined in all patients both PESI (Tables 1–2) and the P/F at the emergency department (Table 3) whose values are reported in Table 4. To determine the gas exchange the following formula is used PaO_2/FiO_2 (P/F). If this ratio is >400 gas exchange is normal, if <400 >300 is modified, if <300 >200 is deeply modified, if <200 is severely modified. Therefore, we created a database with Microsoft Access© called "P/F-PESI". The database contains the following fields: (1) patient number, (2) P/F score at the emergency department, (3) PESI score at the emergency department. Moreover a correlative analysis was performed for continuous variables with Pearson's parametric test to see if there is a significant relationship between the P/F values at the emergency department (a independent variable) and the PESI values at the emergency (variable and dependent), as shown in Table 4.

Purpose: The "P/F-PESI" case study has the following aims. To begin with, to verify any relationship between the P/F and the PEI values at the emergency department regarding 20 patients tested in "P/F-PESI" from January 2008 to December 2009. Secondly, to verify relevant statistics, by using the Pearson's parametric test, as a test of statistical correlation analysis for continuous variables to determine if the relationships of the variables considered happened by chance.

Methods: As far as the purposes of the test are concerned, a spreadsheet called Table 4 has been developed. The parametric Pearson correlation test associates the independent variable (at the emergency P/F) and the dependent variable (at the emergency PESI) in 20 patients identified by "P/F-PESI". To determine the test the Pearson correlation "*r*" coefficient formula is applied (indicating the strength of the association and the product compared with the average): $\Sigma\ (A - A)\ (E - E)/\sqrt{\Sigma\ (A - A)\ 2\Sigma\ (E - E)\ 2}$.

Results: The *r* value obtained with degrees of freedom (DF) = 19 is −0.96. Since the critical value (CV) of "*r*" is equal to 0.693 with DF = 19 $p = 0.001$, the "*r*" relative value (RV) of the Pearson test applied to 20 patients expressed a negative correlation between the absolute values of covariation of the two variables (A and E) found to be highly significant with $p < 0.001$.

Discussion: The obtained data suggest that the increase in P/F levels at the emergency department in the 20 patients examined in "P/F-PESI" study is associated with the increase in PESI values at the emergency observed in all patients, see Tables 2, 3 and 4. Consequently, the severity of the symptoms, as measured by P/F with $FiO_2 = 21\%$ at the emergency department, is correlated with the PESI score obtained with the tomographic test, according to the P/F and at PESI values in Tables 2, 3 and 4. By studying experiences in literature, the "P/F-PESI" study offers data that complete those provided by Qanadli, Nordenholz, Nural, Ghanima, Choi, Pech, Lewczuk, Hsu, Bova, Drodz, Matsuoka studies.

Conclusions: The "P/F-PESI" study carried out in 20 patients with venous thromboembolism (central pulmonary embolism) has shown that there is a correlation between the two variables considered: P/F and PESI. This reciprocity shows a negative correlation according to "*r*" coefficient of the Pearson correlation. This also means that it is not a random association, but a strong correlation between increased PESI values as well as increased reduction of the P/F value in 20 patients with central pulmonary embolism.

The Pearson test and PEI-PESI case study: correlative analysis of continuous variables in 20 patients with venous thromboembolism. Biennial experiences 2008–2009

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Introduction: The "PEI-PESI" study, acrostic resulting from Pulmonary Embolism Index and Pulmonary Embolism Severity Index, has analysed 20 patients, between 48 and 82 years, with venous thromboembolism (central pulmonary embolism) hospitalized in "Degenza Breve" and "Sub Intensive-C" in Internal Emergency Medicine Department from January 2008 to December 2009. The case history showed in all patients with severe respiratory failure (value arterial $pO_2 < 60$ mmHg) may be associated with chest pain, confusion, hemodynamic instability (SBP < 90 mmHg) according to the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). In all patients, both PEI (Table 1) and PESI (Table 2) have been calculated, whose values are given in Table 3. Consequently, a database was created with Microsoft Access called "PEI-PESI". This database contains the following fields: (1) patient number, (2) PESI score at the emergency department, (3) PESI class at the emergency department, (4) PEI score at the emergency department. Therefore, a correlation test was carried out concerning continuous variables with Pearson's parametric test. This is to see if there is a significant relationship between the PESI values at the emergency department (a independent variable) and the PEI values of at the emergency (E dependent variable), as shown in Table 4.

Purpose: The case study "PEI-PESI" has the following aims. First of all, to verify any relationship between the PESI values and those PEI values at the emergency department concerning 20 patients tested in "PEI-PESI" from January 2008 to December 2009. Secondly, to verify relevant statistics, by using the Pearson's parametric test, as a test of statistical correlation analysis for continuous variables to determine if the relationships of the variables considered happened by chance.

Methods: The 20 patients diagnosed with pulmonary embolism were examined according to the central database created with Microsoft Access called "PEI-PESI". Table 3 was created to compare the values of PEI (A independent variable) at the emergency department with the PESI values (E dependent variable) at the emergency department in the 20 patients examined. In order to try out the Pearson test it was created the spreadsheet called Table 4. The parametric Pearson correlation test associates the independent variable (at the emergency PESI) with the E dependent variable (at the emergency PEI) in 20 patients identified by "PEI-PESI". To determine the test the Pearson correlation "r" coefficient formula is applied (indicating the strength of the association and the product compared with the average): $\Sigma\ (A - A)\ (E - E)/\sqrt{\Sigma\ (A - a)\ 2\Sigma\ (E - E)\ 2}$.

Results: The r value obtained with degrees of freedom (DL) = 19 is 1.00. Since the critical value (CV) of r is equal to 0.693 with DL = 19 $p = 0.001$, the "r" relative value (RV) of the Pearson test applied to 20 patients expressed a positive correlation between the absolute values of the covariation of the two variables (A and E) found to be highly significant with $p < 0.001$.
Discussion: The obtained data suggest that the increase in PESI values at the emergency department in the 20 patients examined in the "PEI-PESI" study is associated with the increase in PEI levels at the emergency observed in all patients. Consequently, the severity of the symptoms, PESI measured, is correlated with the PEI score obtained by the tomographic test, according to the results of PESI and PEI values at the emergency department in Tables 3 and 4. By studying experiences in literature, the "PEI-PESI" study offers data that complete those provided by Qanadli, Nordenholz, Nural, Ghanima, Choi studies.
Conclusions: "PEI-PESI" study carried out in 20 patients with venous thromboembolism (central pulmonary embolism) has shown that there is a correlation between the two variables: PEI and PESI. This reciprocity shows a positive correlation according to r coefficient of the Pearson correlation. This also means that it is not a random association but a strong correlation between increased levels of PEI as well as increased value of PESI in 20 patients with central pulmonary embolism.

Prevalence of cardiac origin of chest pain in a rural area of Southeast Italy

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Background: Chest pain is one of the major causes of presentation of a patient to the Emergency Department (ED). Differentiation of chest pain causes is fundamental for a correct diagnosis and appropriate management of these patients. Thus, clinical assessment is still a very important factor in the appropriate management of this symptom.
Aim and objectives: This observational study was designed to assess the application of diagnostic guidelines to the management of chest pain, and it was carried out in a small town (Ragusa) located in a rural area of southeast Italy. It was expected to enable us to compare the Sicilian experience with other reports taken from the literature in Europe and the United States of America (USA).
Material and methods: In Ragusa, a town with 68,000 inhabitants, we examined all the patients referred for chest pain to the ED of "Civile-M. P. Arezzo" Hospital, that is the unique hospital in the city, during a period of 6 months (from January 1st 2008 to June 30th 2008). As much as 857 consecutive patients were studied. Clinical evaluation of chest pain and measurements of systolic blood pressure, diastolic blood pressure, heart rate and transcutaneous peripheral oxygen saturation were done. According to Guidelines, electrocardiography, measurements of cardiac markers (Troponin, Creatine Kinase MB, Myoglobin) and chest X-ray were also performed.
Results: The results of our study show that musculoskeletal chest pain is the most common final diagnosis (49%), followed by cardiac chest pain (26.3%), gastrointestinal chest pain (12.8%), pulmonary chest pain (7.1%), psychiatric chest pain (4.1%) and other causes (syncope, fainting, shock) (0.7%). The majority of patients (95%) never made contact with their primary care providers, and came straight to ED. As much as 58.5% were discharged, 22% were hospitalized and 0.5% died from sudden cardiac arrest. A total of 161 (19%) patients, although having normal diagnostic tests, were judged at high risk for cardiogenic chest pain. They were followed-up in the short-observation unit. In 37/161 patients who were followed-up in the ED, chest pain proved to be cardiogenic in origin later on before discharge.
Discussion: The pattern observed in our study regards the ED only, and indicates that most of the patients decided to bypass their own General Practitioner (GP), thereby shifting the evaluation of all incident new cases of chest pain to the ED. This pattern is similar to that seen in the ED of the USA (Kwan MA et al., J Emerg Med 29:383–390, 2005), but it differs from that observed by GPs in Great Britain (Erhardt L. et al. 23:1153–1176, 2002), where the percentage of noncardiac origin of chest pain is much lower than ours. Patients' fear and their feeling of needing a work-up would push them to bypass the primary care filter. Our data could also be explained by the growing knowledge regarding potential clinical evolution of chest pain, suggesting to patients to make shorter the interval between the onset of symptoms and a doctor's intervention.
Conclusions: Chest pain is one of the most common symptoms leading patients to ask for "help". Our results emphasize the need for reworking a strategy, perhaps making up a "Chest Pain Centre" outside of and near to the ED, as suggested by Storrow et al. (Ann Em Med.35(5):449–61, 2000), to avoid the situation in which all cases of non-emergency chest pain, such as musculoskeletal ones, come to the hospital for evaluation, thereby overwhelming the ED, particularly in rural areas where the management of any emergency is centralized in a single hospital.

A case of fever, confusion and skin rash in a young woman

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Clinical case report: A 26-year-old female patient was referred to our Emergency Room after developing of confusion, agitation and altered mental status. Clinical history was negative. In the last days, the patient had had fever, sore throat, headache and vomiting. On admission, a skin rash was present and a recent history of measles in the family (brother) was reported. The patient appeared confused, extremely agitated, with a slight rigor nucalis. The rash was judged by the dermatologist consistent with an infective origin. Blood exams showed en elevation in liver enzymes, cholestasis markers and CRP. A chest X-ray and a CT-scan of the brain resulted negative. A lumbar puncture was performed, showing a clear cerebrospinal fluid with a slight elevation in proteins (125 mg/dl) and white cells (180 mm^{-3}, predominantly lymphocytes), while glucose was 59 mg/dl. The bacterioscopic research was negative. Therapy with ceftriaxone, ampicillin and aciclovir was started and the patient was admitted to the Emergency Division. During hospital stay, clinical conditions progressively improved until normalization of the neurologic symptoms and disappearing of the fever and of the skin rash. Serological tests showed a positivity (both IgG and IgM) for measles infection. The patient was discharged after 8 days.
Meningoencephalitis: Meningitis is characterized by the classical triad headache-fever-rigor nucalis and by integrity of cerebral functions. On the other side, encephalitis is characterized by altered mental status; focal neurological signs are sometimes present. If both conditions coexist, the term used is "meningoencephalitis". CT-scan of the brain should be performed before lumbar puncture only in the suspicion of space-occupying lesions or endocranic hypertension, which can be excluded with an evaluation of the fundus oculi. The

EEG is often pathological in the acute phase of encephalitis, while a magnetic resonance of the brain can detect typical patterns in some specific cases. Therapy of meningoencephalitis includes a third-generation cephalosporin (ceftriaxone, cephotaxime), associated with ampicillin in patients over 50 years (for Listeria infections) and aciclovir (early antiviral therapy reduces mortality and morbidity from HSV-1). In geographical areas where a strong resistance to cephalosporins is reported, association with vancomycin is indicated. Moreover, empyrical therapy of meningitis includes desametazone, which should be continued for four days if a pneumococcal origin is confirmed.

Measles: It is a viral infection caused by an RNA virus of the Paramyxovirus group. Beyond the classical form, presentation of measles can include a variant form (in patients with anti-measles antibodies but an incomplete protection), an atypical form (in patients vaccined with attenuated or killed virus or in non-vaccined adults), a severe form in immunocompromised patients. Neurological complications include acute disseminated encephalomielytis (demyelinating disease caused by an autoimmune response, starting a few days after measles clinical resolution; mortality is 10-20% and neurological sequences in surviving subjects are very frequent) and subacute sclerosing panencephalitis (neurodegenerative and progressive disease, fatal, starting years after clinical recovery from measles). Atypical form of measles can be characterized by an atypical rash with unusual distribution and clinical characteristics. Lung involvement and hepatosplenomegaly can be present. Recovery is usually complete.

Climate influence on emergency department syncope attendances: the role of temperature variability

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Background*:* Human pathophysiology suggests that heat may promote syncope during standing. We tested the hypothesis that the increase of ambient temperatures from January to July would be accompanied by an increased rate of syncope resulting in a higher frequency of Emergency Department (ED) visits. We also evaluated the role of maximal temperature variability in affecting syncope ED admittances.

Methods*:* We included 770 of 2,775 consecutive subjects who were seen for suspected syncope at four ED between January and July 2004. This period was subdivided into three epochs: 23 January–31 March, 1 April–31 May and 1 June–31 July. In addition to tracking daily temperatures and heat indices, spectral techniques were used to analyze components of maximum temperature and syncope variability and to assess their relationship.

Results: There was no correlation between daily maximum temperatures and rates of syncope. Conversely, maximal temperature variability analysis showed a major fluctuation characterized by a 23-day period and two minor oscillations with 3- and 7-day periods. This latter oscillation was linearly related to a similar 7-day fluctuation in ED visits for syncope. ED visits for syncope were lower in June and July when maximal temperature variability declined, although the maximal temperatures themselves were higher.

Conclusions: A 7-day rhythm characterized both variability of daily maximal temperatures and ED visits for syncope, suggesting that climate variability may have a significant effect on the pattern of syncope occurrence. ED visits for syncope were not predicted by maximal daily temperature, but did correlate with increased temperature variability.

The management of acute respiratory failure in general medical wards: the development of a bedside trolley for non-invasive ventilation

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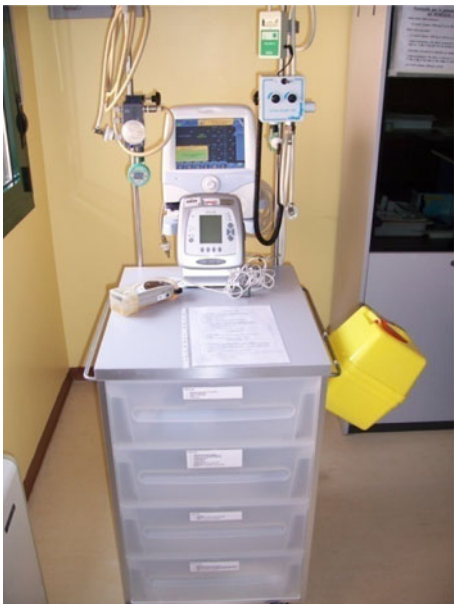
Background: In the last years non-invasive ventilation (NIV) have reached an important role in the treatment of acute respiratory failure (ARF) improving clinical features and arterial blood gases and in particular clinical conditions, such as acute cardiogenic pulmonary edema and acute exacerbation of chronic obstructive pulmonary disease, decreasing the need for intubation and in-hospital mortality compared to standard medical treatment. NIV's success seems to be determined by early application, staff training and a good organization of the setting. Although the first important data on NIV are from studies performed in Intensive Care Units (ICUs), subsequently these methodologies of ventilation have been successfully used in Emergency Departments and general medical wards as a result of an increasing number of elderly patients with various chronic diseases, complicated clinical conditions in which endo tracheal intubation (ETI) lead to poor outcomes (immunodeficiency, neoplasm…), a lack of bed places in ICUs.

Aim: In order to improve the organization of the ward, to optimize the treatment of patients with ARF we developed a trolley for NIV in which all the devices for ventilation, oxygenation, aerosol therapy, are easily and quickly available at the bedside of the patient.

Methods: In the rear panel we attached two IV drip poles used for IV therapy but also used to sustain two Venturi—like flow generator for CPAP (Continuous Positive Airway Pressure) with oxymeters. On the top are present two ventilators, a smaller one (domiciliary) and a bigger one (ICU ventilator): they are able to perform different kinds of ventilation such as controlled (pressure and volume, generally used for intubated patients), assisted/controlled, SIMV (synchronized intermittent mandatory ventilation), PSV + PEEP (Pressure Support). In the front panel there are 4 drawer. In the first one are present sets to draw venous or arterial blood sample, a pulse oxymeter and essential drugs (IV diuretics, IV steroids, short acting beta 2 agonists). In the second drawer we put simple oxygen therapy devices: nasal prongs, Venturi masks, reservoir masks, aerosol kits, 2-15 L/m flow meters. In the third drawer we find CPAP complements such as facial masks, PEEP valves, circuits. In addition a complete Boussignac CPAP system is present: 2-30 L/m flow meter, Boussignac devices, a manometer. In the last drawer are present complements for ventilators: circuit, nasal masks, facial masks, total face masks, helmets, aerosol kits. A check list is verified every day.

Results: The management of every kind of ARF results simpler, easier and safer with this trolley: every device needed is promptly disposable at the bedside of the patient and useless lacks of time are avoided.

Conclusion: This bedside NIV trolley, as far as the emergency trolley, could be useful in general medical ward lacking in critical care areas in order to improve interventions in patients with ARF.



A case report of Sneddon syndrome

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Introduction: Sneddon's syndrome also known as "Idiopathic livedo reticularis with cerebrovascular accidents") is a form of arteriopathy characterized by several symptoms, including: cerebrovascular disease, livedoid reticularis, hypertension. It is named for Ian Bruce Sneddon (a British dermatologist) who in 1965 reported 6 patients that had a distinct skin rash and cerebral vascular accidents (strokes). This association has since been reported many times, but the precise etiology still remains elusive. The skin rash, termed livedo reticularis, is not specific to this disease and can be seen in numerous conditions (systemic vasculitis, hepatitis C among others), but most of the time it is not associated with anything. It refers to a characteristic net-like, pink to red to blue discoloration of the skin. When this rash occurs with cerebrovascular disease it is considered Sneddon syndrome. This syndrome affects adult women. Usually the rash appears first followed by a stroke. Both systemic lupus erythematosus and antiphospholipid antibodies are associated with Sneddon syndrome. The condition may be inherited in an autosomal dominant fashion. It can also be associated with the presence of anti-cardiolipin antibodies (the Antiphospholipid syndrome).
Case report: A 36-year-old woman, smoker, was admitted for recurrent left-sided sensory-motor symptoms, vertigo, diplopia, and imbalance. Medical history included headaches, labile hypertension, left leg venous thrombosis treated on anticoagulants. On examination she had livedo reticularis, limited left eye abduction, and left hemiparesis. She appeared very suffering and asthenic, with impairment of left leg, pale, extremely anxious owing to the onset of asthenia and, over all, of left hemiparesis. Normal body temperature T 36.5°C; BMI 26. At cardiac evaluation BP 170/100 mmHg, HR 100 b/min, EKG pointed out left ventricular hypertrrophia signs. Laboratory data pointed out slight leukocytosis (WBC 12.100 mmc^{-1}, N 53,6%, L 32,6%), increase of ALT (70 U/L), triglycerides (253 mg/dl) and homocysteine (IMX Abbott, 19.6 μmol/l, nr 5.0–15.0); normal resulted glycaemia, urea, creatinine and electrolytes, normal dosage of Icc and FT3, FT4, TSH, TPO, ATA, Ab Antiendomisium and Ab-anti-trans-glutaminase. Normal resulted PT, APTT, fibrinogen, C3 and C4 dosage, and negative ANA, AMA, ASMA, anti-DNA, P-ANCA, C-ANCA, ENA, LA, as well as ATIII, C and S proteins but remarkable rise of anticardiolipin antibodies immunoglobulin G isotype only (IgG ACA) and decreased the levels of folic acid and B6 vitamin. On the grounds of particular clinical picture and for the presence of livedo racemosa, we suspected a case of Sneddon's disease and requested a dermatological evaluation which confirmed our suspect (the multiple skin biopsies performed showed distinct histopathological findings: the involved vessels were small to medium-sized arteries at the border between dermis and subcutis. Early inflammatory reactions were followed by subendothelial proliferation and a late fibrotic stage). Magnetic resonance imaging (MRI) showed right frontal, left parieto-occipital and pontine high intensity lesions consistent with ischemia. Transesophageal echocardiography and electroencephalogram were normal. She responded favorably to carbamazepine as treatment of presumptive focal seizures, and long-term anticoagulation. It was started a rehabilitative program with recovery. Anticoagulation, steroids and anti-platelet agents were empirically associated as long-life therapy. At follow-up 1 year later she presented in quite good clinical conditions.
Discussion: Sneddon's syndrome is a rare combination of generalised livedo reticularis and cerebrovascular accidents. Its clinical presentation varies widely and its aetiology is still not known. 60–80% of patients are female. First symptoms of the syndrome are mostly repetitive cerebral strokes, but reduced perfusion of the skin, seen as blue or red-brown mottling, precedes the strokes. The vascular disease is generalised and often accompanied by arteriosclerosis, systemic arterial hypertension, valvular heart disease and the presence of antiphospholipid antibodies. The diagnostic procedures are complicated and have to exclude other autoimmunological diseases. Therapeutic options are anticoagulatory therapy with warfarin, ASS or heparin, reduction of endothelial proliferation with ACE-inhibitors, and improvement of microvascular perfusion with prostaglandine.

Frontal head trauma worsened a case of Sunct syndrome

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Introduction: Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT) is a syndrome predominant in males, with a mean age of onset around 50 years. The attacks are strictly unilateral, generally with the pain persistently confined to the ocular/periocular area. Most attacks are moderate to severe in intensity and burning, stabbing or electrical

in character. The mean duration of paroxysms is 1 min, with a range of 10–120 s. Prominent, ipsilateral conjunctival injection and lacrimation regularly accompany the attacks. Nasal stuffiness and rhinorrhoea are frequently associated. Moreover, there is subclinical forehead sweating. During attacks, there is increased intraocular pressure on the symptomatic side and swelling of the eyelids but there is no changes in pupil diameter. Attacks can be triggered mostly from trigeminally innervated areas, but also from the extratrigeminal territory. There are also spontaneous attacks. An irregular temporal pattern is the rule, with symptomatic periods alternating with remissions in an unpredictable fashion. During active periods, the frequency of attacks may vary from <1 attack/day to >30 attacks/h. The attacks predominate during the daytime, nocturnal attacks being seldom reported.

Case report: A 42 year-old woman was admitted to our Department because of recurrent pain in the left peri and supraorbital regions. Her short-lasting pain episodes (<1 min), accompanied by conjunctival injection, tearing, rhinorrea, ptosis and periorbital sweating had started about 2 years earlier and currently occurred over 100 times per day. Left peri- or supraorbital pain attacks were precipitated by chewing, stress, and hot or cold food intake and touching or cold breeze on the frontal region. Pain episodes initially occurring 15–20 times a day, were described as blunt, pinpricking, burning-like or pressure-like in nature. Initially she had been treated on carbamazepine (CMZ) at another institute and pain was relieved somewhat for 3 months, but did not completely disappear. Since the frequency of pain attacks reduced from once a day to once a week, it was continued CMZ and then oxcarbamazepine (OCZ) was administered for about 2 months with moderate benefit on the frequency, but not on the severity of pain attacks. Unluckily, she experimented a sudden blunt head trauma at her left frontal region with no loss of consciousness and she started to complain more of 100 head pain attacks per day. Due to this she became unable to talk and work. For this reason, she was hospitalized and underwent haematological, serological, biochemical and radiological investigations; magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT) of the cranial structures did not reveal abnormal findings Due to the increase of frequency of pain attacks and irresponsiveness to OCZ, lamotrigine (LTG) treatment was given at 200 mg/day obtaining a remarkable reduction of pain attacks. After the patient had ceased LTG therapy due to she felty completely recovered, she was readmitted due to pain episodes recurring 2–4 times per hour. LTG was prescribed again but did not lead to complete recovery. She therefore, started therapy on prednisolone, gabapentin (GBP), LTG and transcutaneous electrical stimulation (TENS) combination with no benefit. Trigeminal block resulted in partial improvement while she was taking topiramate (75 mg/day) and LTG (250 mg/day. Indomethacine was also given, but it was quickly discontinued because of severe gastrointestinal side effects. Many drugs as methylprednisolone, LTG, indomethacin, OCZ, amitriptyline, topiramate were used in our patient but all with only partial recovery.

Discussion: In the vast majority of patients with a SUNCT-like picture, aetiology and pathogenesis are unknown. In SUNCT syndrome, there is a lack of persistent, convincingly beneficial effect of drugs or anaesthetic blockades that are generally effective in cluster headache, chronic paroxysmal hemicrania, trigeminal neuralgia, idiopathic stabbing headache ("jabs and jolts syndrome"), and other headaches more faintly resembling SUNCT syndrome. Single reports have claimed that carbamazepine, lamotrigine, gabapentin, corticosteroids or surgical procedures may be of help. A recent case study demonstrated the release of both trigeminal and parasympathetic neuropeptides during a bout of pain in the same pattern previously described in cluster headache. The SUNCT syndrome is a distinctive rare condition characterised by less severe pain but marked autonomic activation during attacks. Interestingly, in our case, after head frontal trauma, the severity of the attacks worsened and the frequency increased (from 10–20 to over 100 times/day), despite our efforts to treat the unlucky patient!

Lou Gehrig's disease: an increasing reality in emergency medicine

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Background: Amyotrophic lateral sclerosis (ALS, also referred to as Lou Gehrig's disease) is a form of motor neuron disease. Als is a progressive fatal, neurodegenerative disease caused by the degeneration of motor neurons, the nerve cells in the central nervous system that control voluntary muscle movement. The condition is often called Lou Gehrig's disease, after the famous New York Yankees baseball player who was diagnosed with the disease in 1939. Today, renowned physicist Stephen Hawking is the best-known living ALS patient. The disorder causes muscle weakness and atrophy throughout the body as both the upper and lower motor neurons degenerate, ceasing to send messages to muscles. Unable to function, the muscles gradually weaken, develop fasciculations (twitches) because of denervation, and eventually atrophy because of that denervation. The patient may ultimately lose the ability to initiate and control all voluntary movement; bladder and bowel sphincters and the muscles responsible for eye movement are usually (but not always) spared.

Case report: We here report the case of 42-year-old male, layer, who suddenly began to have trouble moving his feet and legs. Initially he went to a chiropractor, but he referred him to a neurologist. Though there is no definitive test for ALS, he had an electromyogram, spinal tap, and muscle biopsy that indicated a probable case of ALS. The diagnosis was, of course, devastating. The patient was constrained to use a cane by June, and in August he was in a wheelchair suffering with fasciculations in his thighs. By November, he was afflicted by complete quadriplegia and was admitted to our Dept in respiratory failure. Noninvasive ventilation was attempted, but failed. A tracheostomy was performed and invasive mechanical ventilation was initiated. At this time, his face was animated and he was able to speak using a Passy-Muir valve attached to his tracheostomy tube. He was re-admitted in the hospital for 1 month secondary to right pneumonitis, while Medicaid and home care arrangements were established. He was sent home with 16 h of nursing care a day. One month after his left leg became swollen, red, and painful. He was readmitted to the hospital and diagnosed with a deep vein thrombosis (DVT). Following a 4-week hospitalization and adequate therapy, he was discharged home on warfarin for blood clot prophylaxis, baclofen for fasciculations, and triamcinolone cream at the tracheal stoma and sertraline for depression. He was a partner in his care this time, and one of the first decisions he made was to discontinue his canned tube feedings. A registered dietician provided aid with nutrient calculations, and the team began experimenting with different menus of whole food to puree, strain, and use in place of canned feedings. By May, his voice deteriorated rapidly, and by August he was virtually unintelligible. A hand-held letter board helped supplement speech, with upward eye movement indicating "yes." A switch activated by head movement allowed our patient to be able to use a letter board scanning system. During this time, Medicaid requested a psychiatric consultation to determine his competence in making resuscitation

decisions. Initially, he was determined competent, and chose resuscitation should his heart stop. Later, our patient was still determined to live, but chose not to be resuscitated (DNR) should his heart stop. His comments, however, spelled out letter-by-letter on the letter board remained colorful and prolific. An assistive technology group was consulted, and augmentative communication software and hardware were purchased for his laptop computer. But he was no longer able to turn his head enough to activate the switch, and his eye movements were not reliable, so the team tried a biofeedback electromyography (EMG) device that responded to muscle movement so subtle it was only observable by the needle of the EMG monitor. He was able to use this device with a letter board, and eventually just for "yes–no" responses until the fall of the following year. On December his heart stopped and he ended to live.

Discussion: Over time, Lou Gehrig's disease involve the motor neurons in the brain and spinal cord which shrink and disappear, so that the muscles no longer receive signals to move. As a result, the muscles become smaller and weaker. Gradually the body becomes paralyzed, since the muscles no longer work. However, someone with ALS, even at an advanced stage, can still see, hear, smell, and feel touch. The nerves that carry feelings of hot, cold, pain, pressure, or even being tickled, are not affected by Lou Gehrig's disease. The parts of the brain that allow us to think, remember, and learn are also not affected by the disease. ALS represents an increasing reality in the Emergency Medicine Departments. This report represents our tribute to these unlucky patients who conscious see their slow and ineluctable decadence and death.

Ups and downs of a patient with acute pulmonary embolism and renal insufficiency

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A 59-years old man was taken to Emergency Room because of dyspnoea and chest pain. He reported a history of arterial hypertension and chronic kidney failure as a result of pyelonephritis; moreover, 2 weeks ago he underwent a neurosurgical operation for frontal meningioma. At his arrival clinical parameters are the following: systemic arterial pressure (SAP) 119/70 mmHg, cardiac frequency (CF) 120 bpm rythmic, SpO2 79% with FiO2 21%; EKG shows sinusal rhythm, S1Q3T3 pattern; creatinin = 1.8 mg/dl, haemoglobin = 10.9 g/dl, D-dimer 20.6 nicg/ml. Agio-CT of the chest shows perfusional defects of pulmonary arteries in both lungs as a bilateral thormboembolism: anticoagulation is started with i.v. unfractioned heparin with regard of his to renal insufficiency. Two hours later SAP falls to 80/60 mmHg, CF rises to 125 bpm, with a corresponding shock index (CF/SAP) of 1.56. Clinical status is turning on shock, so echocardiography is performed urgently and shows right cardiac chambers dilatation and right ventricular hypocinesia, suggesting an evolution to haemodinamically unstable pulmonary embolism, which requires thrombolysis. Since the recent surgical intervention absolutely controindicates a systemic thrombolysis, locoregional mechanical and pharmacologycal thrombolysis are performed by the interventional radiologiststhe with good results (improvement of pulmonary perfusion and clinical conditions, shock index fell to 0.9). During the radiological procedure a caval filter was set. After 5 days the platelets count begins to go down until 35,000 μL. Suspecting a heparin induced thrombocytopenia, clinicians replace UFH with lepirudin with dosage adjusted for kidney failure and aPTT maintened among 1.5 and 2× normal value; anti-Platelet Factor 4 antibodies result positive, confirming HIT. During the following days platelets count progressively increases: on 12th day platelets count is 220,000 μL and warfarin is started. After 12 months anticoagulation was stopped, but 2 months later limbs become edematous with a prevalence of the right side and a thrombosis of the caval filter was shown by echocolordoppler. Considering the previous HIT, anticoagulant therapy was started with fondaparinux embricated with long-term warfarin. Nowadays, 2 years later the previous facts, no new thromboembolic events have been recorded and patient feel good.

Controindications to systemic thrombolysis (ESC2008)

Absolute	
	Haemorrhagic stroke or stroke of unknown origin at any time; Ischaemic stroke <6 months; CNS damage or neoplasms;Major trauma/surgery/head injury <3 weeks; GI bleeding <1 months; known bleeding
Relative	
	TIA <6 months; Oral anticoagulant; pregnancy or post partum <1 week; non-compressible punctures; traumatic resuscitation; refractory hypertension; advanced liver disease; Infective endocarditis; active peptic ulcer

Clinical clues for HIT (Circulation 2004)

Clues/score	2	1	0
Thrombocytopenia	>50% PLTS fall	30–50% PLTS fall	<30% PLTS fall
Timing of onset	Days 5–10, or <1 day 1 if heparin in the past 30 days	<Day 10 or timing unclear; <day 1 if heparin in the past 31–100 days	<Day 4 (no recent heparin)
Thrombosis/other sequelae	Proven new thrombosis; skin necrosis; acute systemic reaction after i.v. UFH bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis	None
Other cause(s) of platelet fall	None evident	Possible	Definite
HIT probability	6–8 indicates high; 4–5, intermediate; 0–3, low		

Oncology

Atypical onset intrahepatic cholangiocarcinoma

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Introduction: Intrahepatic cholangiocarcinoma (ICC) is a fatal cancer arising from the epithelial cells of intrahepatic bile ducts. Globally ICC is the second most common primary hepatic malignancy after hepatocellular carcinoma. The peak age is the seventh decade, with a high incidence in man. Risk factors are primary sclerosing cholangitis, inflammatory bowel disease, biliary tract stone disease, cronic liver disease, HCV infection and, lately, obesity, diabetes and smoking seem to be involved. However many tumours arise in the absence of any known predisposition. ICC can spread along biliary ducts, invade perineural and vascular tissues, infiltrate adjacent structures, invade lymph nodes or develop distant metastasis. The only effective treatment is radical surgery, but it is not frequently applicable because late diagnosis and moreover local recurrence are very common. Consequently, the 5-year survival rate after attempt curative resection is only 20–40% and unresectable patients have 12–24 month median survival.
Case: Last December a 66 years old man came to our attention for uncontrolled glycemia lasting about 1 month and frequently hypoglicemia. He was affected by insulin-treated type 2 diabetes, ipertension, hiatus hernia, tumour of the left vocal cord removed years ago and IV cranial nerve paralysis right with temporo-occipital headache associated for 2 months. The patient had suffered for coxartrosis since few months. Entering the patient was in good general condition, no pathological findings was detected but only the presence of bilateral carotid vascular murmurs and the absence of left leg peripheral pulses. Moreover, we observed diplopia in the central and lateral right gaze without any other neurological signs. Blood tests showed only hyperglycemia and Hb glycated and PCR increased. The chest X-ray excluded parenchymal lesions and the electrocardiogram showed sinus bradycardia, normal A-V conduction and ectopic prematuric beats. Patient reported neurological and visual visits resulting negative, but because of continuous headache and to investigate the diplopia, we performed a brain MRI which highlighted a change signal intensity with post-contrast enhancement covered the right half of the clivus, the apex of the petrous, the walls of the carotid canal and Meckel's cavus, as phenomena bone marrow replacement. So integration with CT focused on the study of skull base confirmed the disomogeneus appearance of the right half of the clivus without cortical interruption either bone lysis. To exclude hematologic diseases was performed a bone marrow needle biopsy, but it showed a normal plasma cell count. We therefore planned a total body CT scan with contrast that disclosed the presence of solid nodular subcentimetric lesions localized on both lungs and another bigger (58 × 58 cm) localized on IV hepatic segment, such as metastatic lesions. Lymph nodes were present along small gastric curvature, in the subdiaphragmatic area and hepatic hilum. Moreover, osteolytic area with cortex erosion was detected in the subtrochanteric zone of left femur. In order to find the primary tumour the patient was subjected to esophagogastroduodenoscopy and colonoscopy which were negative. The serum determination for tumor markers, such as CA 19.9, NSE, TPA, Cyfra 21.1, 5-hydroxy-3-indoleacetic acid and cromogranina, was high. Eventually diagnosis was obtained through echo-guided liver biopsy and the histologic exam showed a intrahepatic cholangiocarcinoma with lung and bone metastasis.
Discussion: ICC is a rare malignant tumour usually appears as a mass-forming lesion within the liver, which is mostly confused with metastatic tumour. These tumours usually progress insidiously, are difficult to diagnose and have poor prognosis. Nerve paralysis, due to a bone metastasis localized along its course, was the first neoplasia manifestation in our case. Since the neuronophaty is common complication around diabetic patients, the true diagnosis was not suspected by the beginning. So this case emphasizes the importance of thoroughly investigating also cases deceptively simple.

Following a thrombus: a dangerous game

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In January 2010, a 53-year-old man was seen in Internal Medicine Dep. because of painful erythema and swelling on his right leg. He was affected by arterial hypertension, treated with a CCB, and by intestinal polyposis in regular follow-up. He had smoked about 30 cygarettes/day until 4 years ago and used a couple of wine glasses each day. He was slightly over weighted (BMI 27). He reported also a beta-thalassemic trait. Laboratory data indicated raised WBC ($13{,}600/mm^3$) and slight anaemia (Hb 12.7 g/dL, MCV 57 f), hyperfibrinolysis (FDP 15 μg/L, D-dimer 6,941 μg/mL). Protein C, protein S and antitrombina III levels were normal and both LAC and anti-cardiolipin-β2-glycoprotein I complex antibody were negative. Plasma homocysteine level was elevated (30.4 μmol/L). We found the presence of a MTHFR homozygotic mutation A1298C. All the remaining study was normal. Physical examination revealed right leg erythema, tumefaction and pressure pain. US showed deep vein thrombosis of saphena. Anticoagulant therapy was performed: LMWH (0.8 mL two times/day, days 1–7) and warfarin sodium (5 mg/day). Warfarin dose was augmented to achieve therapeutic INR range (2.5–3.5). The patient was given also folic acid supplementation. His clinical condition improved and he was discharged with oral therapy. Three weeks later, the patient was hospitalised again for fever (TC 39°C), dyspnea and neck pain and tumefaction. US study showed a thrombosis in the right jugular vein for a length of 8 cm (occurred during anticoagulant therapy with INR in therapeutic range!). CT scan excluded pulmonary thromboembolism. He started unfractionated heparin (25,000 U/day iv, monitoring aPTT) and piperacillin-tazobactam ($4.5\ mg^3$/day). In order to exclude paraneoplastic syndrome, CT-TB scan was performed and showed only a small right kidney. Two weeks after treatment, ultrasound revealed partial recirculation of the jugular vein and the patient was free of symptoms, so he was dismissed with indication to maintain therapeutic INR between between 3 and 3.5. Although INR was optimal (3.12), deep vein thrombosis recurred in the left leg in May 2010. We decided to perform an abdominal RMN- to exclude abdominal cancer- without significative results. Even if we achieved target INR, we decided to test polymorphisms of the vitamin K epoxide reductase-oxidase complex gene (VKORC1), often associated with warfarin resistance, but mutated allele were not found. During hospitalization, the man had worsening dyspnoea: further CT was performed and now showed an upper right lobe pulmonary nodule, investigated with FNAB, showing SCLC at limited stage according to VALCSG system. The patient began chemo- (cisplatin and etoposide) and

radiotherapy. Venous thromboembolism is a common complication in patients with malignant disease. However, the presence of MTHFR polymorphism and first radiological studies negative put us on the wrong track. The recurrence in spite of appropriate therapy roused suspicion. An occult cancer has to be always suspected in deep vein thrombosis, especially when the thrombosis is recurrent and resistant to anticoagulant therapy.

Atypical presentation of lung adenocarcinoma

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Introduction: This report describes the case of a young woman diagnosed with lung cancer which presented exclusively with esophagal, gastric and depressive symptoms following the sudden death of two relatives and a 2 months long vacation in Brazil, thus highlighting the significant symptom variability of lung cancer which often results in a diagnostic challenge.
Case report: A 36-year-old woman, former smoker, with a family history of bowel and prostate cancer, psoriasis and sclerodermy consulted her doctor because of 5 months of nausea, episodic vomiting, dysphagia and dysphonia. The initial endoscopic esophagus examination resulted negative and the patient received psychiatric care as somatic symptoms were attributed to the co-occurring depressive symptomatology which was present as well. Two months later she presented to the hospital because of deteriorating vomiting and dysphagia. The physical examination revealed cachexia, bilaterally decreased lung murmur at the inferior lung fields, increased heart beat rate (100 bpm) and sovraclavear lymphnodes of about 15 mm. The gastroscopy was repeated and revealed a concentric stenosis at 28 cm of the superior dental arch with normal appearing of the mucosa. Further exams were perfomed (such as barium swallow X-rays, mediastinal and pulmonary CT, bronchoscopy) which confirmed a 6 cm esophagus middle third stenosis and revealed extended and irregular accentuation of the right pulmonary design, solid tissue occupying the mediastinal space and extrinsic compression of the right main bronchus' posterior wall. At the throat visit a left vocal cord paralysis was showed and echographic neck's scan demonstrated metastasis-involved lymphnodes of about 11×16 mm and 36×11 mm. Lymphnode biopsy was held and proved bronchiole-alveolar adenocarcinoma'cells. After 14 months (and five cycles of cisplatin and gemcitabine chemotherapy) the patient died from cachexia, without respiratory symptoms, with only gastrointestinal signs and after losing completely her voice control.
Discussion: This case illustrates the atypical way of lung cancer's presentation; initially the gastro-intestinal symptoms and the psychological symptoms along with the unremarkable endoscopic examination led the differential diagnosis towards a depressive disorder with somatic symptoms. Due to her recent vacation to an endemic area, the hypothesis of Chagas disease (Trypanosomiasis) was also considered; laboratory tests had been requested but lymphnode biopsy firmly established the diagnosis of lung adenocarcinoma with mediastinal metastasis. It should be noted that although no pulmonary symptoms were present, the lung tumor positively resulted in esophageal compression thus leading to prevalent esophageal and gastric symptoms and possible contributed to the development of depressive symptoms. Thus clinicians should be reminded of the great variability of lung cancer in its presenting symptoms.

Acute hemiparesis and dysarthria, brain metastasis in patient with atrial fibrillation

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Introduction: Brain metastasis is the most common intracranial tumor in adults and it affects 20–40% of cancer patients. Intracranial metastasis develop in approximately one third of patients with lung carcinoma; 50% of brain metastasis result from this type of cancer.
Case report: A 82-year-old man, with persistent atrial flutter under antiplatelet therapy, blood hypertension, type 2 diabetes mellitus treated with insulin and diffused arteriopathies, presented to the "S. Andrea" Hospital for a sudden appearance of right hemiparesis and dysarthria. Noncontrast computed tomography (CT) of the brain showed "large hypodense subcortical area localized in left temporal and parietal lobe; cortical calcification in left frontal lobe; median line in axis" and chest radiography revealed "non infiltrative parenchymal lesions". The atrial flutter was confirmed at the ECG and laboratory investigations showed a moderate hypochromic microcytic anemia and an increased concentration of D-Dimer (667 ng/ml) and RCP (3.34 mg/dl). Physical examination showed arytmic cardiac activity, free pauses. Vesicular murmur was diffusely reduced with right basal crepitations. The neurologic exam showed a deficit of muscular strength interesting the right side of the body. The patient was prescribed mannitolo in addiction to antiplatelet drug and progressive improvement of the motor function was obtained. In consideration of clinical picture, the most likely diagnostic hypothesis was ischaemic stroke due to cardiogenic thromboembolism or carotid atherosclerotic obstruction. To exclude these hypothesis we requested transthoracic echocardiography and epiaortic vessels echocolordoppler. The first one excluded the presence of intracavitary thrombi, and the second one resulted negative for hemodynamically significant stenosis of carotid arteries. During the patient stayed in Hospital, he presented a further short episode of dysarthria and right emiplegia. So, a non-contrast brain CT was done because he, having an artificial crystalline lens, was not suitable to magnetic resonance imaging (MRI). The new images appeared exactly alike to the previous but, in this case, the neuroradiologist, in consideration of the brain vasogenic edema, suggested a further diagnostic study through contrast-enhancing CT or MRI, in order to exclude a secondary expansive pathology. Immediately the patient was subjected to total body contrast-enhancing CT. The investigation revealed the presence of a left frontal cortical solid lesion (approximately 26 mm of diameter) with a central area of necrosis, periferic enhancement and white matter perilesional edema. Chest images showed many nodular lesions localized in the right superior and inferior lobes, whose the largest measured approximately 21 mm of diameter and it had spiculated margins. There were also a solid pleuric lesion and many conglomerated nodes with a maximal extension of 7 cm in right paratracheal position. In consideration of the patient age and comorbidities, the toxicity of a brain radiation therapy and the disease extension, he was referred to a palliative care.
Discussion: Approximately 60% of patients with brain metastasis have subacute symptoms. Headache and seizure are the two most common presenting symptoms. In addition patients presents cognitive and behavioural disfunctions. Motor and sensitive deficits can occur but, generally, they presents with slow and progressive onset in absence of acute brain bleeding. In this case, symptoms presented suddenly and the clinic features mimed an acute ischaemic stroke. After having excluded brain hemorrhage through CT, the most

probable diagnostic hypothesis was cardioembolic ischaemic stroke, especially in consideration of the cardiac arytmia without anticoagulant prophylaxis. Moreover, normal chest radiography and the absence of pulmonary or systemic neoplastic symptoms and signs, sent the diagnosis. Therefore, this case would like to be a cue to reflect about how the clinical reasoning can be conditioned by confusening factors such as comorbidities or atypical disease onset, delaying the diagnosis. A further reflection concern the different interpretation of two similar CT images by two differents physicians. In this case, the attentive evalutation of the imaging has permitted to undertake the following diagnostic iter and to obtain the diagnosis.

Troublesome pain in a crusty man

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On March 2009 a 63-year-old man came to our observation with intense low back pain with functional limitation. He took different medication (NSAIDs- steroids- tramadol-acupuncture and ozone) and he underwent several rounds of physical therapy rehabilitation without getting any benefit. The patient had a family history of cardiovascular and liver disease, previous bilateral extracorporeal shock wave lithotripsy for uretral stones for 15 years, L4–L5 disc herniation known for several years. No smoking history. For about 2 years he also reported mild dyspeptic symptoms investigated by endoscopy (cardial incontinence and non-HP related hyperemic gastritis), for which the patient assumed pump inhibitors. On admission, the patient appeared suffering, unfriendly and bad temperate: he needs help to walk, he had bedsores obliged on his left side and deflected mood. The patient reported a weight loss of about 10 kg over the last 6 months. Clinical examination wasn't significative. Laboratory tests showed mild neutrophilia (probably caused by steroid therapy), hypokalemia and hypomagnesemia, severe hypercalcemia (15 mg/dl), known- according to the patient- for many years. This finding was never subjected to further investigation. The ECG showed a short QT interval, so he began hydration therapy (normal saline solution 0.9% 1,500 cc/day) and forced diuresis (furosemide 80 mg/day). Bone loss in right iliac wing and in right femoral head appeared at MRI; CT TB scan was performed and showed increased right lobe of the thyroid and wall thickening of the gastric antral region, multiple osteolytic lesions of iliac wings, alteration osteodystrophy of the right femoral head. PTH serum concentration was 1,385 pg/ml (nv 6–65 pg/ml). We analysed PTH-mediated causes of hypercalcemia: the negative history of drug-taking mood stabilizers excluded iatrogenic lithium-associated hypercalcemia. We also ruled out the presence of familial hypocalciuric hypercalcemia (FHH) because of negative family history. A parathyroid gland scintigraphy showed hyperfunctioning parathyroid tissue at the lodge parathyroid right, so we performed a diagnosis of primary hyperparathyroidism. Anyway, we had a strong suspicion of gastric cancer because of persistent nausea, abdominal pain and clinical conditions. EGDS evidenced many erosed and crumbly elevations in the subcardial region and in antrum, with hystological findings of gastric poorly differentiated adenocarcinoma. Parathyroidectomy and total gastrectomy were performed so we confirmed two different diagnosis: primary hyperparathyroidism from parathyroid adenoma and gastric adenocarcinoma. Surgery elective treatment of symptomatic parathyroid adenoma is decisive in 80–90% of cases. The patient is followed by our clinic: there isn't recovery of gastric disease and the patient is well balanced with calcium supplements and vitamin D3. This case report shows marked hypercalcemia dues to parathyroid adenoma associated with stomach cancer. In literature is well known association between neuroendocrine tumors of the stomach and parathyroid adenoma, while there are few records between it and gastric cancer. Moreover, sporadic cases are known as gastric cancer associated with paraneoplastic hypercalcemia, therefore, we have also debated whether the hypercalcemia may have played a role in the development of gastric ulcer and its subsequent cancerous.

Rheumathology

Dercum's disease in the course of SLE

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Pathological lipomatosis represent well identified syndromes, the best known of which are multiple symmetric lipomatosis, symmetric lipomatosis with cervical predominance (Launois–Bensaude syndrome) and painful Dercum lipomatosis. The cause of these lipomatosis is unknown, even though genetic predisposition seems to play an important role, on which contributing factors would act (obesity, endocrine disorders, metabolic disorders). We describe the case of a woman suffering from SLE, in chronic steroid treatment, who developed a painful and widespread lipomatosis in the course of just a few years.

Clinical case: SF woman of 54 years. Obesity at a young age. Suffering from SLE since the age of 35, in chronic steroid treatment. Since the age of 44, hypercholesterolemia. From the age of 46, asymmetric subcutaneous swellings of various sizes begin to appear in the arms, torso, abdomen and thighs; a soft and changeable consistency, some highly painful with a slow and progressive growth. The presence of normal adipose tissue, compatible with the diagnosis of lipoma, was identified after the surgical removal of the most painful swellings at the histological examination. After a hysterectomy for fibromatosis, numerous other lipomatosis configurations developed in the surgical scar, these also being painful. With menopause, the patient was up against a progressive worsening of the disease.

Discussion: Multiple symmetric lipomatosis is characterized by lipomas with a characteristic of symmetrical disposition, predominantly in the upper limbs and are rarely painful. Symmetrical lipomatosis with cervical predominance is characterized by masses predominantly localized in the cervical region, with a deformation feature called "Madelung's neck". Dercum's disease is characterized by multiple painful lipomas in obese women, often close to menopause. They are often accompanied by autonomic symptoms such as fatigue and depression, and sometimes even major psychiatric symptoms. The tenderness of the lipomas is due to the compression of peripheral nerves and often has stabbing and tormenting traits. Our patient was within the criteria of classification for the latter type of lipomatosis. The association between SLE and Dercum's disease has never been described. In our case, chronic systemic inflammation may have been the initial cause, which has acted on the genetic predisposition. Speaking of which, case studies have identified an increase of inflammatory cytokines in these patients [1] and success in therapies with Infliximab and Methotrexate [2].

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Vascular involvement in systemic sclerosis

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Background: Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by vascular damage and varying degrees of fibrosis of the skin and visceral organs. Endothelial injury, immune activation and collagen deposition by activated fibroblasts are involved in the pathogenesis of the disease. It is agreed that the microvasculature is primarily affected. Large vessel disease, possibly due to accelerated atherosclerosis, may also occur.
Objective: The aims of this study were to evaluate cardiovascular risk and signs of early atherosclerosis in SSc patients by measuring lipid profile and carotid eco-Doppler.
Methods: 55 SSc patients (M/F 7/48, median age 61, range 31–76 years) and 26 healthy subjects matched for age and sex were recruited. Lipid profile, serum sVCAM (soluble vascular cell adhesion molecule) and common carotid IMT (intima-media thickness) were evaluated and cardiovascular risk was estimated.
Results: In our study SSc patients exhibited lower serum level of HDL-colesterol (HDL-C) and higher levels of triglycerides (TG) compared to controls ($p = 0.05$ and $p = 0.03$, respectively). Serum sVCAM, an established marker of vascular damage, was higher in patients than in controls ($p = 0.06$). Estimated 10-year absolute cardiovascular risk was similar in SSc patients and controls. We did not find differences in BMI (body mass index), systolic and diastolic arterial pressure between the two groups. IMT was markedly higher in patients ($p < 0.001$), as the prevalence and number of carotid plaques ($p < 0.01$ and $p = 0.01$, respectively). HDL-C levels correlated with BMI ($R = -0.28$, $p = 0.02$) while TG levels correlated with age and BMI ($R = 0.31$, $p < 0.01$ and $R = 0.32$, $p < 0.01$ respectively). HDL-C was lower in diffuse than limited SSc ($p = 0.03$) and higher in patients treated with glucocorticoids ($p = 0.05$). The presence of carotid plaque was not related to lipid profile. IMT correlated strongly with age ($R = 0.52$, $p < 0.001$), BMI ($R = 0.28$, $p = 0.01$), systolic an diastolic arterial pressure ($R = 0.40$, $p < 0.001$ and $R = 0.36$, $p < 0.01$, respectively), while no correlation were found with lipid profile and sVCAM. In SSc patients, IMT correlated positively with echocardiographic evaluations such as trantricuspid velocity, systolic pulmonary arterial pressure and myocardial mass ($R = 0.53$, $p = 0.001$ and $R = 0.34$, $p = 0.02$ and $R = 0.34$, $p = 0.03$, respectively), while showed a negative correlation with creatinine clearance ($R = -0.54$, $p < 0.01$). No differences in IMT were noted in relation to autoantibodies, cutaneous involvement (limited vs. diffuse form) and drug treatment.
Discussion: Evidences show that immune system is involved in the atherosclerotic process, being crucial in plaque growth and rupture. Moreover, in many autoimmune rheumatic diseases, an accelerated atherosclerotic process, not entirely explainable by traditional risk factors, has been demonstrated. SSc may be an exception to this scheme but data are still controversial. In SSc patients, our findings confirm an increased prevalence of macrovascular/atherosclerotic disease. The pathogenetic mechanisms involved in the changes of the macrovascular vessel wall in SSc are still unknown. However, both endothelial injury and the migration of smooth muscle cells in the intima might be considered two candidate events contributing to the IMT. Further and larger studies are required to clarify the mechanisms involved in the acceleration of macrovascular disease in SSc.

Capillaroscopy in dermatomyositis and Sjogren's syndrome

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Objective: Capillaroscopy is a substantial value method for diagnosis and differentiation of primary and secondary Raynaud's phenomenon in rheumatic diseases. We analysed the capillaroscopic changes in patients with dermatomyositis (DM) and Sjögren's syndrome (SS).
Methods: Capillaroscopy was performed by the means of nailfold stereomicroscopy (100× magnification) (Intralux 6000, Volpe). Among our series of 272 consecutive patients seen in 2009, we analysed the capillaroscopic pattern of patients with DM, diagnosed according to the Bohan and Peter's criteria, and with SS, diagnosed according to the American-European criteria.
Results: Eighteen patients with DM (F/M 13/5; mean age 51) and 25 with SS (F/M 24/1; mean age 51.5) were studied. All of them had Raynaud's phenomenon. Abnormalities that show microvascular involvement, as irregularly enlarged loops, giant loops, isolated microhaemorrhages have been detected in all of the patients with DM and in ten patients with SS (40%). The scleroderma-like pattern, characterised by the presence of dilated capillaries, haemorrhages, avascular areas, and neoangiogenesis was documented in ten (55%) patients with DM and four (16%) with SS, respectively. An isolated pattern of reduction in capillary density was seen in other five (20%) patients with SS. The correlation with disease duration and severity was analysed.
Conclusion: Capillaroscopy confirms its valuable importance in the detection of early and late abnormalities of the microvascular damage in subjects with DM and SS.

Efficacy and safety of biological drugs: a study performed in south-western Piedmont

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Background: The introduction of the anti-TNFalfa drugs strikingly modified the outcome and prognosis of rheumatoid arthritis and other autoinflammatory diseases; indeed, the long-term efficacy and safety of those drugs are not still fully clarified.

Purpose of the study: To draw up a register of patients treated with biologic drugs in our area and to look after their outcomes and drugs safety.

Materials and methods: By taking LORHEN and MonitorNet registers as a starting point, all the patients treated with Infliximab, Etanercept or Adalimumab and followed up in the Internal Divisions of Cuneo, Mondovì and Alba Hospitals were included in a database. Age at the starting of biological drugs, haemoglobin, ERS, CRP at baseline and at the last control, DAS28, Visual analogue scales (VAS) for general health (GH) and use of steroids and NSAIDs at baseline and at the last control in RA, calprotectin at baseline and at the last control for IBD were considered as clinical outcomes; infusion-related reactions, infections and immunological reactions were considered as adverse effects.

Results: Rheumatoid Arthritis, Seronegative Spondyloarthropathies, Inflammatory Bowel Diseases, Beçet Disease and TNFReceptor-Associated Periodic Syndrome (TRAPS) were the treated diseases; the prevalence of each one is shown in Table 1. Fifty patients were collected and each one has been affected by no more than one of these diseases. Prevalence of diseases is reported on Table 1. The mean length of disease before starting biological drugs was 7.3 years. The mean length of follow-up was 25.4 months. Table 2 lists clinical which showed a statistical difference between the baseline and the last control after a period of treatment with biological drugs. There was no statistical difference between the three biological drugs as regards to clinical outcomes. Thirteen patients headed adverse effects: 3 infusion-related reactions (2 severe) with Infliximab, 1 with Adalimumab; 1 community-acquired pneumonia for each drug; 1 Lupus-like syndrome with Infliximab; 1 optical neuritis with Etanercept; 5 mild topic reactions with Adalimumab and Etanercept. No case of TBC or neoplasm has been registered. Thirty-seven patients are still treated with the drugs used at the beginning, while 13 ga.

Table 1 Prevalence of autoinflammatory diseases in our register

Autoinflammatory disease	Nr.	Prevalence (%)
Rheumatoid arthritis	35	70
Psoriasic arthritis	6	12
Ankylosing spondylitis	2	4
Crohn disease	3	6
Ulcerative colitis	2	4
Behçet disease	1	2
TRAPS	1	2
Total	50	100

Table 2 Clinical outcomes

Outcome	Baseline	Last control	*P*
VES (mm/h)	43.18	21.86	<0.001
PCR (mg)	15.1	4.85	<0.001
Hb (g/dL)	12.49	13.45	<0.001
Rheumatoid arthritis			
DAS28	6.24	3.53	<0.001
GH	79.36	29.31	<0.001
Prednisone (mg/day)	8.21	4.7	0.0004
NSAIDs (cp/mo)	33.5	12	<0.001
Inflammatory bowel diseases			
Calprotectin (μg/mL)	124.66	31.43	0.0445

Endothelial microparticles and progenitor cells in patients with inflammatory rheumatic diseases: the effect of anti-inflammatory therapy

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Background and objectives: Rheumatoid arthritis (RA) is a multisystem disease with high rates of cardiovascular morbidity and mortality. Also, Polymyalgia rheumatica (PMR) has been associated with increased risk of atherosclerosis development. Chronic inflammation has been suggested as the possible explanation for the association between AR, PMR and premature atherosclerosis. Indeed, chronic activation of the inflammatory cascade might be responsible of endothelial injury, that is accepted to promote atherosclerosis-related diseases. Since a dysregulation of the balance between endothelial injury and repair by stem cell progenitors is believed as a novel mechanism in the pathophysiology of atherosclerosis, we investigated in patients with AR and PMR the degree of endothelial injury by measuring the number of circulating endothelial microparticles and their repair potential by endothelial progenitor cells measurement. Moreover, the effect of anti-inflammatory treatment on the balance between endothelial injury and repair was evaluated.

Methods and results: Twenty patients with never-treated RA, 20 with untreated PMR and 30 healthy controls were recruited for the case–control study. A subgroup of 14 RA and 16 PMR patients participated in the prospective anti-inflammatory intervention open label study. The number of circulating endothelial microparticles (CD31+/CD42−) and endothelial progenitors (CD34+/KDR+) was quantified by FACS analysis. The number of endothelial microparticles was higher in patients with either RA (676 ± 96 n/μL) or PMR (692 ± 49 n/μL) than in control subjects (420 ± 39 n/μL; $p < 0.05$ for both comparisons). Also, patients with RA and PMR had lower numbers of circulating progenitors than controls (162 ± 41 and 180 ± 62 n/mL vs. 453 ± 91 n/mL, $p < 0.05$ for both comparisons). No difference in the number of endothelial microparticles and progenitors was found between AR and PMR patients. Anti-inflammatory treatment was associated with a consistent attenuation of the inflammation status, as demonstrated by C-reactive protein level reduction, in RA (from 3.2 ± 1.0 to 0.9 ± 0.3 mg/dL) and in PMR patients (from 3.5 ± 0.7 to 0.6 ± 0.2 mg/dL). Also a significant 29% decrease in the number of endothelial microparticles and 160% increase in the number of endothelial progenitors was observed in PMR patients, and a 60% increase in the number of endothelial progenitors in AR patients. A significant correlation between C-reactive protein and endothelial microparticles reduction was found ($r = 0.37$, $p = 0.04$).

Conclusions: AR and PMR are associated with a significant imbalance between endothelial injury and repair, an increased number of endothelial microparticles and a reduced count of endothelial

progenitors being found in both the inflammatory diseases. Attenuation of systemic chronic activation of the inflammation cascade contributes to limit endothelial fragmentation in PMR and promote endothelial repair in both PMR and AR patients.

Aortic stiffness is increased in polymyalgia rheumatica, and improves after steroid treatment

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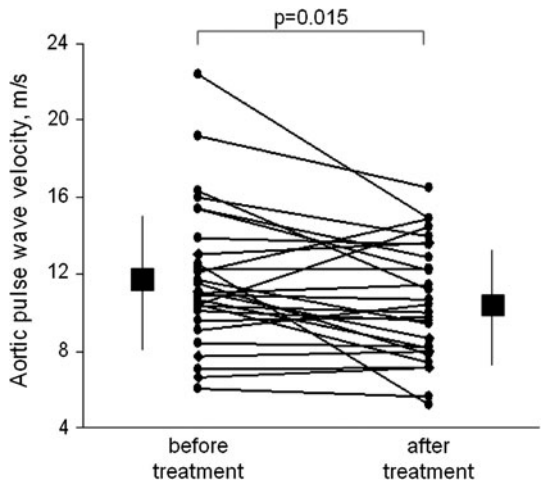
Background: Increased arterial stiffness and cardiovascular risk have been observed in diseases inflammatory diseases. Polymyalgia rheumatica (PMR) is a disease which affects primarily the elderly and exhibits evidence of a systemic inflammatory response, but little is known about aortic involvement in PMR. We investigated whether aortic stiffness, an early marker of arteriosclerosis, is increased in PMR, and whether it improves after steroid treatment.
Methods: Thirty-nine patients with PMR (age 72 ± 8 years, men 45%, blood pressure 134/75 ± 16/9 mmHg) and 39 age-, sex- and blood pressure-matched control subjects underwent aortic pulse wave velocity (PWV) determination with an applanation tonometry device (Sphygmocor). Aortic augmentation as a measure of the impact of the reflection wave on central hemodynamics was also measured, and corrected for heart rate. Twenty-nine of the PMR patients were reexamined after 4-week treatment with prednisone (starting dose 12.5–50 mg/day).
Results: Aortic PWV was significantly higher in PMR patients than in control subjects (12.4 ± 4 vs. 12.2 ± 2 m/s, $p < 0.01$). Treatment was followed by a reduction in heart rate (from 78 ± 12 to 70 ± 10 bpm, $p < 0.001$), and no significant change in BP (from 134/75 ± 16/8 to 134/75 ± 15/9 mmHg, both p = n.s.). As shown in the Figure, aortic PWV decreased significantly after steroid treatment (from 11.8 ± 4 to 10.5 ± 3 m/s, $p = 0.015$), and the difference was independent from changes in blood pressure and heart rate. Treatment was also associated with a significant reduction in aortic augmentation. Augmentation index corrected for a heart rate of 75 bpm decreased from 0.34 ± 0.07 to 0.29 ± 0.08, $p < 0.01$.
Conclusions: Polymyalgia rheumatica is associated with increased aortic stiffness, which may improve upon reduction of systemic inflammation determined by treatment with corticosteroids.



Moyamoya syndrome associated with LES and antiphospholipid syndrome

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Moyamoya disease is a rare cerebrovascular disorder characterized by occlusion or stenosis of bilateral internal carotid arteries and development of collateral vessels. Ischemic strokes or other vascular accidents can occur. We report an 22-year-old female patient with systemic lupus erythematosus and positivity to antiphospholipid tests who presented with the sudden onset of dysarthria. Brain magnetic resonance imaging showed infarctions in the subcortical white matter of bilateral frontal lobes. Cerebral angiography showed occlusion of the bilateral internal carotid arteries with rich basal collateral vessels. EchoDoppler of carotid artery did not showed atherosclerosis. Echo of the heart did not showed abnormalities. Glucocorticoid therapy was used to control the systemic lupus erythematosus. This report seems to be interesting for the complications of moyamoya vessels in a patient with systemic lupus erythematosus and with antiphospholipid positivity.

Miscellanea

Analysis of difficult discharges in a large hospital in Northern Italy and effect of a cooperation protocol between the hospital and the community care services. Prospective 6-year study

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Background: Clinics are pressurized to discharge patients as soon as possible. When clinics have to deal with very complex, multi-disease patients, often with socio-economical problems, a difficult discharge situation arises.
Aim: The aim of this study was to gauge the extent to which this phenomenon exists and the results obtainable through the application of an integrated hospital-community protocol.
Methods: The study was conducted at Parma University Hospital, Italy, involving all the departments admitting adult patients. After agreeing upon the definition of a "difficult discharge", all patients were admitted to a tailored clinical/organizational scheme for the purpose of being discharged as soon as possible in safe conditions and in accordance with community social/health care services.
Results: During 6 years, 5004 difficult discharge cases were identified, showing a progressive increase that reached the 3.5% of all hospitalized adults. The majority of these patients were very old, suffering from serious diseases and with high consumption of social and economic resources. In the 6 years marked improvements in the management of these patients were observed, with an average

reduction in length of stay to 11 days. Also the rate of readmission dropped over time, both in short- and long-term (30 and 365 days).
Conclusions: There is a substantial fraction of patients who are difficult to discharge thereby running the risk of either becoming bed blockers, or being discharged in unsafe conditions. These patients must be identified at an early stage and treated with tailored clinical/organizational protocols featuring a strong element of hospital-community integration.

Assessment of cognitive functions in hereditary hemorrhagic telangiectasia patients

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Background: Visceral arteriovenous malformations (MAV) may determine brain damage by means of several mechanism including bleeding. There is no data in the literature which assesses the cognition in HHT patients without a history of CNS disorders.
Objective: To evaluate the influence of hereditary hemorrhagic telangiectasia on cognitive functions in patients without a history of CNS (Central Nervous System) disorders.
Methods: Subjects were enrolled from the patients referring to the University Interdepartmental Center for HHT at the Department of Internal Medicine and Public Health, University of Bari. All patients were compared with a control group matched for age and educational status. The following standardized neuropsychological tests were utilized: Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Raven Coloured Progressive Matrices, Rey Auditory Verbal Learning Test, Digit Span (forward and backward), Rey–Osterrieth Complex Figure, Digit Cancellation Test, Trail Making Test A and B, Verbal Associative Fluency Test and Stroop Test.
Results: Fifty patients (44% males; age 47.1 $\pm$ 16.13 years; education 11.1 $\pm$ 4 years) and fifty control subjects (50% males; age 49.4 $\pm$ 14.35 years; education 11.9 $\pm$ 5.2) were enrolled in the study. Neuropsychological investigations demonstrated decreased performances in various domains in the HHT patients. Global cognition and general intellectual functioning evaluated with MMSE (27.5 vs. 28.7; $p = 0.001$) and CPM (26.8 vs. 28.1; $p = 0.044$) were significantly worse in the HHT group even in tests assessing executive functions, such as Digit Backward Test (3.5 vs. 4.1; $p < 0.00001$), Trail Making Test (Part B) (108.14 vs. 86.42; $p = 0.023$) and Stroop Test (26 vs. 19.75; $p = 0.016$). Conversely, there were no significant differences between two groups in verbal memory (4.55 vs. 4.82; $p > 0.05$), attention (47.67 vs. 49.1; $p > 0.05$) and verbal fluency (27.67 vs. 29; $p > 0.05$).
Conclusion: This study offers the first evidence that MAV are significantly associated with executive functional impairments in HHT patients in absence of clinically relevant neurological events. These results should be cautiously considered. Further larger studies are required to confirm this hypothesis.

Evidence for preferences of patients for specialist physician attire

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Background: Relationship between patient and physician is complex and includes multiple factors most not having to do with the quality of medicine practised which is not directly discernable to the physician. One fact is the perception of how a doctor should interact with the patient including their attire. A number of studies have demonstrated that the appearance of physicians plays an important role in the trust and confidence of patients.
Aim: The objective of this study was to explore Italian patients' preferences regarding physician attire and appearance.
Methods: A questionnaire was developed and used to survey outpatients in the waiting room of different medical specialties. Each subject was asked to choose one picture for either a male o female physician from a selection of different attires including professional, casual, classic, and trendy. Patients were also interviewed about issues such as presence of a name tag, hair length, trousers on women, amount of make up, presence of tattoos and body piercing. Statistical analysis was performed using Chi-square test.
Results: A total of 765 questionnaires (534 completed from patients waiting for a Internist visit and 231 for other subspecialties) were collected for analysis. The majority (45%) of patients preferred Internists to wear the uniform with a white coat. For the other clinicians patients agreed for both, uniform or formal dress under the with coat ($P = <0.05$), with a name-tag. A trendy attire was preferred only by 9 patients (1.1%). Both group judged inappropriate for clinicians to have long hair, trouser, excessive make up, visible tattoos or body piercing.
Conclusion: This is the first study conducted in Italy about physician attire. As previously demonstrated in other Western countries, Italy patients favour physicians in a professional attire with a white coat. Wearing professional dress is part of "etiquette based-medicine" and may favourably influence clinician-patient relationship and in the end patient's compliance.

Adult Still's disease in an elderly patient

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Adult Still's Disease (ASD) mainly affects adults between the second and the fifth decade. Owing to the rarity in the elderly, the diagnosis in advanced age may be difficult, even when the clinical picture is suggestive. We describe here a case of ASD in a 77-year-old male who came to our observation in September 2009. The diagnosis was not made immediately, but only after about

4 months from the beginning of symptoms. A 77 year old man was admitted in July 2009 to the Division of Infective Diseases for a 2 weeks history of fever, sore throat and arthralgia. Leukocytosis, elevation of Reactive C Protein (RCP) and mild abnormalities in liver function tests were detected. No other abnormality was found, with the exception of urine culture, with isolation of *E. coli*. Antibiotic treatment with imipenem was prescribed, fever gradually subsided and the patient was discharged. After 3 weeks fever reappeared, with a continuous-intermittent pattern and the patient was admitted to our department. On physical examination a frank arthritis of the right knee was noted. High RCP (180 mg/L), leukocytosis (22.700/mmc, neutrophils 89%), mild anaemia of chronic disorder, thrombocytosis and elevations of AST and ALT 4–10 times the normal value were found on laboratory examination. Serum procalcitonin was in the normal range, and ferritine was 1,340 ng/ml. Blood and urine culture were negative. The patient was submitted to an extensive evaluation, comprehensive of PET, CT of chest and abdomen, but no abnormality was found. A transesofageal echocardiography (TEE) showed a thin filiform excrescence on the ventricular side of the aortic valve, and the patient was treated with ampicillin- sulbactam and gentamicin for suspected endocarditis. An arthrocentesis of the right knee was performed, with extraction of a sterile exudative fluid. In the suspicion of reactive arthritis (secondary to endocarditis), methylprednisolone was administered at the dose of 30–40 mg ev (the patient was allergic to nonsteroidal antiinflammatory drugs). Fever rapidly disappeared, AST and ALT normalized, and RCP decreased near the normal value. The patient was discharged after a complete course of antibiotic therapy with the diagnosis of possible endocarditis (in according to Dukes criteria) with reactive arthritis. A TEE performed at the end of antibiotic treatment showed a small reduction in length of the aortic excrescence. A gradual tapering of oral prednisone was prescribed. After about 2 months, during steroid withdrawal, the patient complained again of high fever, sore throat and arthritis of the right elbow, with marked elevation of RCP and moderate elevation of AST and ALT. A transthoracic echocardiogram was performed, with a normal picture. At this point the patient was readmitted to our unit with the suspicion of ASD. No sign of infection or autoimmunity was detected. Six of the Yamaguchi criteria for the diagnosis of ASD (three major and three minor) were present: 1-fever of at least 39°C lasting at least 1 week, 2-arthralgias or arthritis lasting 2 weeks or longer, 3-leukocytosis (10,000/μL or greater), with at least 80% granulocytes, 4-sore throat, 5-abnormal liver function studies, 6-negative tests for antinuclear antibody and rheumatoid factor. Prednisone was administered at the dose of 50 mg/day, with rapid normalization of the clinical picture and laboratory tests. After 4 months, at the dose of about 25 mg/day of oral prednisone an arthritis of the right elbow reappeared, and methotrexate was added. Although a disease primarily of young age, ASD should be considered in the evaluation of fever of unknown origin also in the elderly patient. Yamaguchi criteria may help in the differential diagnosis, after exclusion of infections, malignancy and other more frequent autoimmune diseases. The difficulty in a prompt diagnosis in our patient was favoured by advanced age but also by misinterpretation of the TEE detection of a thin filiform valvular excrescence: an echocardiographic finding, not infrequent in healthy subjects as it has been described in medical literature, which was interpreted as a vegetation. Since now, to our knowledge, in medical literature, ASD has been reported rarely in the elderly.

Patients affected by hereditary hemorrhagic telangiectasia (a rare disease) wait for the correct diagnosis more than 30 years

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Background: Hereditary Hemorrhagic Teleangiectasia (HHT) is a rare dominant-inherited disorder characterized by the presence of epistaxis mucocutaneous teleangectasies and visceral arteriovenous malformations (AVMs) in liver, lung, brain and gastrointestinal tract. Because of the variable HHT phenotype expression and the lack of knowledge on the part of most physicians, the time required for a correct diagnosis is usually quite lengthy. In fact, the aim of this study was to determine the time period between onset of symptoms and first correct HHT diagnosis in a patient population.
Patients and methods: Over a period of 4 months, a questionnaire based on a telephonic interview was carried out with all patients and their relatives who refer to our university interdepartmental HHT Centre. The interviews investigated patient demographics and details regarding the first visit for HHT manifestations including date, place and physician's specialty and whether the diagnosis proved to be either right or wrong.
Results: A total of 234 consecutive patients were involved in the study, 115 first probands and 119 relatives. In the proband group, the timelag for correct diagnosis was of 31.5 years (0.73) and 22 (−4.68) in the group of relatives. In both groups, female gender was associated with a shorter time-lag when compared to males ($p = 0.5$, $p < 0.05$). Having a high school or university degree was associated with a shorter time-lag for diagnosis ($p < 0.05$, $p < 0.001$). When comparing the two genes responsible for HHT, subjects with an ALK1 gene mutation required a shorter time period for diagnosis than those with the ENG mutation in both patient groups ($p < 0.001$, $p < 0.001$).
Conclusions: HHT is a rare disease and, similar to other rare diseases, is characterized by a lengthy time interval for correct diagnosis. Female gender, ALK1 gene mutation and high grade of scholarization are associated with a shorter time interval for a correct diagnosis.

Does chronic *Helicobacter pylori* gastric infection influence clinical features of migraine attacks?

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Introduction: In recent years *Helicobacter pylori* (*H. pylori*) infection has been supposed to play a role even in many extra-gastrointestinal illnesses [1], migraine among these [2]. Several mechanisms could link chronic *H. pylori* infection and vascular diseases including a low-grade acute phase response, free radical formation and immune-mediated mechanisms. However, the precise mechanism by which chronic *H. pylori* infection mediates these

vascular effects remains unclear. Previous studies on seropositivity for *H. pylori* in migraine patients showed contradictory results.
Aim of the study: The purpose of this study was to investigate whether chronic gastric infection by *H. pylori* is in some way linked to the presence of gastrointestinal symptoms during migraine attacks.
Materials and methods: A group of 104 patients (78 women and 26 men, age range 21–59 years, mean age ± SD 39.70 ± 12.41 years) attending the Headache Centre of the University of Turin, suffering from migraine without aura according to the International Headache Society criteria (ICHD-II), were studied. *H. pylori* gastric infection was diagnosed by means of both the ^{13}C-urea breath test and the presence of antibodies against *H. pylori* in serum. In accordance with previous published research guidelines, only patients with positive results for both tests were defined as infected by *H. pylori*. The patients were divided into three groups, according to the presence of nausea (group A: 37 patients), both nausea and vomiting (group B: 54 patients) or the absence of both (group C: 13 patients) during the attacks.
Results: In group A, 13 patients (35.1%) were positive and 24 (64.9%) negative to the infection; in group B, 20 (37%) were positive and 34 (63%) were negative to the infection; finally, in group C 2 (15.4%) were positive and 11 (84.6%) were negative to the infection ($p = ns$).
Discussion and conclusions: On the basis of these data the presence of chronic gastric *H. pylori* infection does not seem to be related to gastrointestinal features during attacks, even though patients with gastrointestinal symptoms have a higher percentage infection than those without (36.3 vs. 15.4%). This observation could suggest the opportunity to ascertain the presence of the infection particularly in this group of patients.

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Bioethics and biolaw. The difference between moral law and civil law. The interest of medicine

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The author intends to analyze the problem of the distinction between bioethics and biolaw, because it is crucial to confirm the importance of the normative potentiality of the bioethics. Now, since it is the law to create the norm, we must be been careful not to confuse the moral norm with the juridical norm. Bioethics and biolaw, in fact, are not the same thing. Difference founds it on the distinction and on the relationships among moral law and reads civil. The biolaw, that is born within the bioethics, risks today to create an overlap and an improper predominance that it could cancel the bioethics or to purely estrange it from its connected finality to its epistemological identity of philosophical discipline straight. The bioethics cannot take the risk to be confused. And then the philosophical debate on the relationship among reads civil and reads moral constitutes the substantial element to affirm this distinction today. Not only. To stop on the natural law is never today essential, since it designates in the one insignia fiercely fought by wide sectors of the contemporary culture. But its refusal is largely based on an incomprehension. Necessary it is then an afterthought of this moral law, that should be intended with great flexibility. The natural law is not one some law of the nature, immanent to the physical and biological world but the same truth of the man as law of its self-realization; a truth that is universal and particular together, individualized in every single person, but founded upon elements common to every man. The all in a game of universality and particularity that play him in the historicity of the time and the space of the existence of every human being and the whole humanity. Between mutability and immutability. What is unchangeable however they are not the different ones "formulations" of the natural law but the natural law as reality "inside to the man", constitutive of its truth. I am not even there difficulty to lately admit the character of mystery and never exhaustively analyzable of the truth of the man, that we find incarnate in the characters of the real or fictitious histories of the concrete world and the literary, poetic and narrative world. Finally, the natural moral law cannot be a positive law or as a positive law, on the contrary a critical appeal and a moral protest towards what of not enough correct it stays inside every human law. So, the doctors must know the difference between bioethics and moral law for the interest of medicine. Because the difference between moral law and civil law is fundamental. In fact, not always what it is right it is also good.

Exercise as prescription: a proposal program

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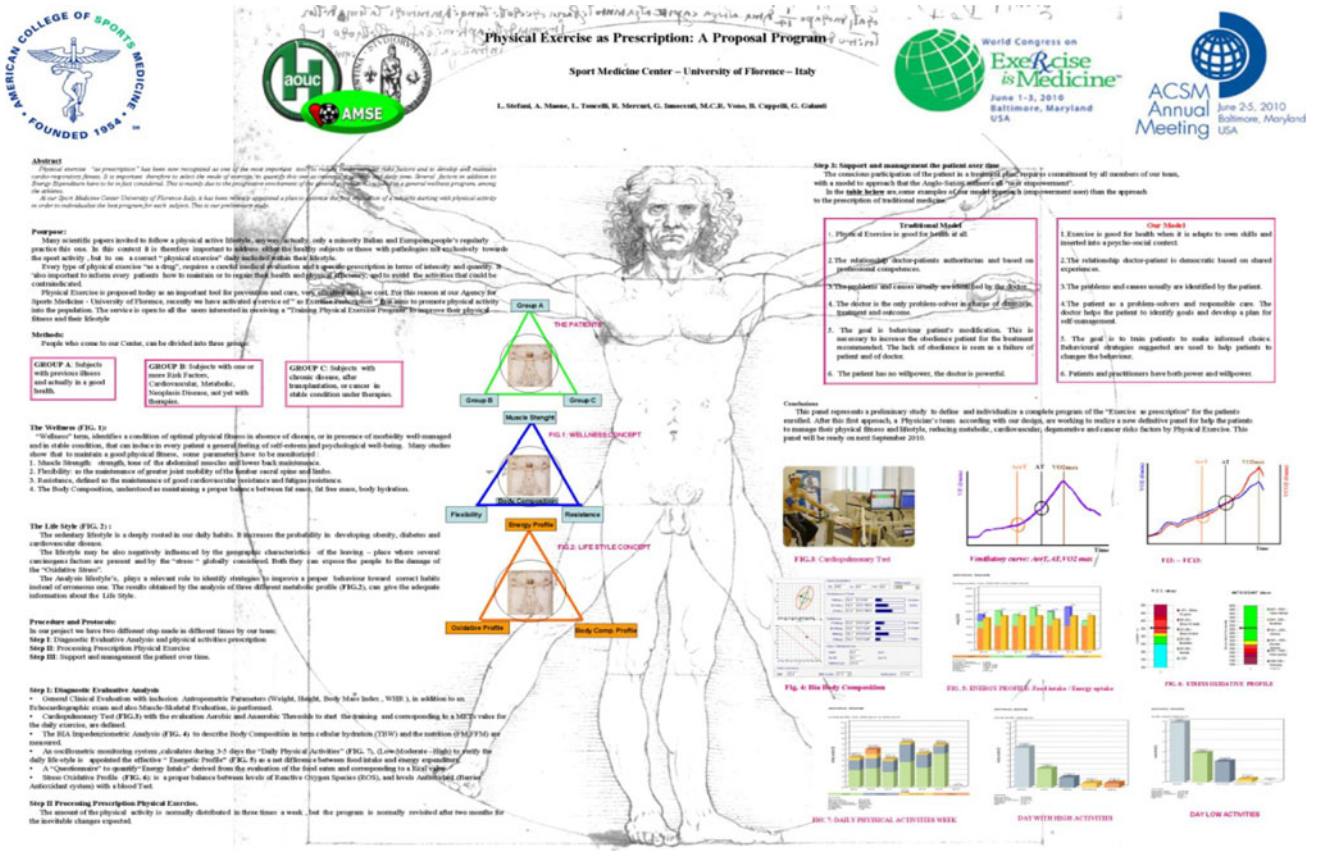
Background: It is not that physical activity can improve the general performance and the quality of life in people practising this one. Epidemiological clinical and laboratory studies have in fact provided many evidences on capacities of Physical Exercise to reduce morbidity and mortality in several diseases. Although only few Italian and European people regularly follow this program and therefore it remains the main issue on behalf of the health institutions. The physical exercise "as prescription", requires a careful medical evaluation and a specific recommendation in terms of intensity and quantity. At the same time it is also important to inform every patients how to maintain or to regain their health and physical efficiency, and to avoid the activities that could be contraindicated. This matter is a peculiar competence on behalf of Sport Medicine discipline.
Material and methods: At our Sport Medicine Center University of Florence-Italy, it has been recently appointed a plan to optimize the first evaluation of a subjects starting with physical activity in order to individualize and personalize the best program for every one. The population enrolled is normally over 40 years, affected by several pathologies like diabetes, hypertension, coronary artery disease and obesity, but in stable condition. The complex evaluation protocol of "Physical Exercise as Prescription", and the methods currently adopted on behalf of our specialist's team, to elaborate an effective wellness program and to reduce the negative impact of the risks factors strongly related with them, are showed in the picture below.
Conclusions: The pilot protocol adopted at our sport medicine center since last year, has demonstrated a relative easy use and application, improving the management and the quality of life of the patients enrolled. It is reasonable to think to extend the program to several else Sport Medicine Center.



The health of irregular and illegal immigrants: analysis of day-hospital hospitalizations in a service of medicine of migrations

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Aim: The attempt to scientifically evaluate the health of immigrants is fraught with a number of technological and methodological difficulties. On the public health assistance front, for some years now we have been recording data on non-Italian patients related to hospital admissions, whether ordinary or day-hospital. Though generally limited to a single hospitalization, this information is of specific interest, in particular if it is analyzed diachronically. On the contrary, little is known about the complete track of assistance of the irregular and/or illegal immigrants through the network of the diverse services and structures. Knowledge of this track is important, as by analyzing and studying risk factors and social determinants it is possible to identify their health needs.

Methods: The population was divided into: regular immigrants, people with citizenship in countries with strong migratory pressure (CSMP) regularly present in Italy with a valid residence permit; illegal/irregular immigrants with citizenship in countries CSMP and residence abroad (STP); Italians and foreigners from more developed countries (MDC). Our study includes the analysis of day-hospital admissions during the period between 2003 and 2009. The medical records used for managing the Day-Hospital activity was validated in 2002 with the "OSI project".

Results: The sample consists of 1,758 patients hospitalized in Day-Hospital from 2003 to 2009. Calculating a presumed presence (missing irregular) of 23.812 immigrants in Palermo in January 2009, the sample is representative of 7.4% of potential users. It should be noted that slowly but gradually increase the patients "extreme": children, often born in Italy, and the elderly. More than half (58.03%) of our patients come from Africa, 21.01% from Asia, 18.96% from Europe and only 1.99% from South America. The countries represented are a total of 70, with a wide prevalence of African countries. Over the years the more represented nationalities were those of Ghana and Bangladesh. Males are 1034 (58.8%) and females 724 (41.2%). Married people are few and especially prevalent among women. Among those who have children, women are 59.5% against 40.5% of males. Patients that we follow-up come in our island for economic reasons. Indeed the majority (78%) is in Palermo for work. The asylum seekers make up 9.6%. The most frequent employment both among men and women is the domestic help. Then follows the trade, catering, construction, study, agriculture and assistance to the elderly among males, while among women prevail: elderly care, study and housewives. The most important observation is the large percentage of unemployed (34.1% calculated on 1087 cards examined) especially among males (23.73 vs. 10.39% among women). They have a quite good level of education. Illiterates are only 4.3%. Those who have a high school degree or who are graduates represent 31.7% of the sample while 45% are those held by middle school. Most of our patients come to the service at least 2 years after arriving in Italy and many arrive after 4 years. Only 10% of the sample comes after less than a year. Regarding the legal status, 73.2% of our patients is irregular/illegal. Regarding the diseases data confirm a marked persistence of the phenomenon known as the "healthy immigrant effect" in these types of patients, as well as the prominent role played by "social determinants" in conditioning the health of immigrants, as in

the case of some infectious diseases in particular. However, this fact should not justify the existence of policies paying little attention to the defense of health of this population, also because we are beginning to see signs here of an increase in some chronic-degenerative pathologies typical of western countries. On the contrary, it suggests a need for policies fostering protection and social integration.

The reactivation of biochemical memories as a nutraceutical prevention mechanism

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The EU recommendation of April 28th 2010 related to a joint programming initiative of research in the field of a healthy diet for a healthy life. Recent developments in the nutraceutical field have found out new ways to correct some dangerous "deviations" of the human nutritional process. A series of repetitive biochemical memories seems to be implied: they play a role in leading Krebs cycles of fats and the urea. If only one of these memories loses its function, some damages may occur. Recent studies of computational biology are focusing their attention on the kind of biochemical memories and their role (memory "switch" in chemical reaction space). Recently, a new biodynamic supplement has been tested (Equì®) and seems to enhance the reactivation of these memories with the aim of correcting the anomalies affecting any of the homeostatic cycle. A study on ethyl alcohol metabolism shows that some dietary supplements have achieved encouraging results in leading effectively the enzymatic activities, as in the case of ethyl alcohol pushed towards the Krebs cycle and the aerobic metabolism. Interesting preliminary results have shown how this biodynamic supplement can reduce effectively the blood alcohol content and improve cenestesis—that is to say, the sensory perception of feeling well or bad—and your own performance status. It has been specifically observed how the tested dietary supplement (containing vitamin B6, retinol, folic acid, sugars and coenzymes extracted from corn) can help recover cenestesis and psycho-physical efficiency, besides reducing the blood alcohol level (blood alcohol content was measured and proved through precision instruments). This important outcome is simply linked to the ability of the dietary supplement to activate alcohol dehydrogenase and aldehyde dehydrogenases enzymes which might convey easily the ethyl alcohol towards the aerobic metabolism with the production of ATP, water and carbon dioxide. These enzymatic systems avoiding also the accumulation of detoxifying acetaldehyde. Folic Acid also promotes the transport of methyl group in the liver destroyed by the effect of ethanol. The mechanisms with which the elements of the dietary supplement (Equì®) would enable this enzymatic activation need to be analyzed in a deeper way, but the reduction of the blood alcohol content and the recovery of the psycho-physical efficiency encourage to carry on the research both on the clinical and the cellular side in order to verify these results. Further studies seems to be needed to analyze the enzymatic involvements in the food metabolism and the restorative power of this line of biodynamic supplement. This is because of the precautionary goals set out in the above mentioned EU recommendation on prevention through a healthy diet and the reactivation of the normal biochemical memories. This appears to be a new goal of prevention and a nutraceutical supplement in the treatment of many current diseases.

Monday, October 18th 2010

Clinical Cases for the Gymnasium Session

A woman with mental status change and severe metabolic alkalosis

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A 52-year-old woman was admitted to the emergency department because of mental status change with sensory clouding and slurring of speech. The patient had been well until 3 days earlier. She is an alcoholist, but she denied alcohol consumption in the last 8 weeks. She suffers from alcoholic cirrhosis, hypothyroidism and hypoparathyroidism after thyroidectomy for goiter. Her medications included potassium canrenoate 200 mg, furosemide 75 mg, calcitriol 0.75 mcg, calcium carbonate-gluconate 1000 mg, levothyroxine 175 mg.

On examination: GCS 11, temperature 36.5°C, BP 110/70 mmHg, HR 70/min, RR 10 breaths per minute. The skin and mucous were dehydrated, no ascites or oedema, neither flapping tremor. A rapid screening test for alcohol, ammonia, benzodiazepines and other illicit drugs was negative. The emogasanalysis showed severe metabolic alkalosis, pH 7.64, and respiratory hypercapnic failure, pO_2 48, pCO_2 60, due to the pulmonary attempt to balance the metabolic state. Laboratory tests showed hypochloremic metabolic alkalosis, $HCO_3 > 60$ mEq/l, with hypercalcemia, Ca 3.4 mmol/l, and severe electrolytes reduction (Na 121; K 2.2; P 0.74; Mg 0.4 mmol/l). PTH < 0.5 ng/l, VitD3 1,25(OH) 120 pg/ml, TSH 0.51 mU/l, GFR > 60 ml/min. Other routine laboratory tests were in line with the alcoholic cirrhosis. Urine pH 5.9 even if bicarbonate concentration was above the kidney threshold (26–28 mEq/l). This is a case of paradoxical aciduria.

Differential diagnosis: 1,25(OH)2-D3 is above the normal range. Patient medications included calcium salts and a large amount of calcitriol, that she took from several years. Calcium salts could be, together with the hypochloremia, the cause of paradoxical aciduria and perpetuation of alkalosis. Chloride lack increases the electrical difference created by the sodium reabsorption and stimulates protons elimination. Idrogenion is the only cation that can be exchanged, in case of reduced distal tubular intracellular K. Furthermore, augmented distal delivery of non-reabsorbable anions, such as calcium salts, stimulates urine acidification, by making lumen more negative. Hypercalcemia increases renal bicarbonate absorption and, at the same time, metabolic alkalosis decreases calcium excretion. These effects create a vicious cycle, similar to what happens in the milk-alkali syndrome. However renal failure did not develop, probably because medications had been stopped in time. Calcitriol, calcium salts and furosemide are overdosed and interfere each other in the development and perpetuation of this complicated acid–base and electrolyte disorders. Furthermore the furosemide/canrenoate ratio is higher than it would have been in case of compensated phase cirrhosis.

Clinical diagnosis: Severe hypochloremic metabolic alkalosis associated to severe hypercalcemia and electrolyte reduction due to vitamin D3 and calcium salts intoxication associated to abuse of furosemide.

Pathological discussion: The patient has been an alcoholist for a long time and she stopped consumption 8 weeks earlier. Alcohol has a direct effect on vitamin D metabolism. It inhibits 1 alfa hydroxilase

and stimulates 24 hydroxilase, consequently reducing 1,25(OH)2-D3 and enhancing 24,25(OH)2-D3, the inactive form of the hormone. Alcohol withdrawal could have decreased the journal calcitriol requirement of the patient.

Discussion of management: Calcitriol has a short half-life, so the only suspension could probably have restored normal calcemia. However, because of the extremely severe situation we decided to treat the patient. After suspension of calcitriol and calcium salts, replacement of chloride is the most important feature of the management. First of all NaCl replaces the volemia, reducing the proximal sodium and bicarbonate reabsorption. Secondly chloride takes place of non-reabsorbable anions in distal tubule lumen, blocking the bicarbonate reabsorption by the Cl/HCO_3 exchanger and increasing bicarbonate secretion. Finally KCl restores intracellular potassium, interfering with the K/H exchange and restoring intracellular pH in the tubular cells as well. $MgSO_4$ corrects hypomagnesemia related hypokalemia due to the effect of low magnesium concentration on Na/K ATPase.

The patient showed a progressive improvement of the mental status and hydro-electrolyte equilibrium.

Pleural and pericardial effusions of uncertain origin

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We report a case of a 67-year old woman who developed shortness of breath, malaise and fatigue during the last month. Her medical history was positive for type 2 diabetes mellitus, idiopathic arterial hypertension, chronic renal failure and psoriatic arthritis. After admission to medical ward, chest x-ray revealed cardiomegaly and bilateral pleural effusions. Patient's blood tests showed a macrocytic normochromic hyporegenerative anaemia (Hb 9.8 g/l, MCV 95 fl, MCH 32 pg, Reticulocitary index 0.7) and a moderate renal failure (creatinine 2.6 mg/dl, BUN 45 mg/dl). She resulted negative for pANCA, cANCA, ENA and weakly positive for ANA. Interferon-gamma-release-assay (TB-gold) was negative, such as serological tests for EBV and CMV. Pleural effusion analysis was compatible with a transudate. An echocardiographic examination showed an hypertrophic left ventricular wall with normal parietal kynesis, a mild mitralic insufficiency, a moderate amount of pericardial effusion and an ejection fraction of 55%. Patient's pharmacological history resulted positive for the use of methotrexate (MTX) to control psoriatic arthritis. MTX had been started 7 years earlier and she had ingested a cumulative dose of 5 g (5040 mg). Significant improvement of pleural and pericardial effusions was achieved after discontinuation of MTX. There was also a significant improvement of anaemia (Hb 11 g/l, MCV 85 fl) and kidney function tests (creatinine 1.2 mg/dl, BUN 20 mg/dl) after 1 month from MTX withdrawal. MTX, a synthetic folic acid antagonist, is among the most effective disease modifying anti-rheumatic drugs (DMARDS), widely used in acute leukemia, rheumatoid arthritis, psoriatic arthritis but also in selected cases of inflammatory bowel diseases. Even though several side effects are well known, such as bone marrow aplasia, teratogenicity, renal and hepatic toxicity, very few cases are reported in literature regarding the relation between MTX use and the development of pleural and pericardial effusions.

Infliximab in inflammatory bowel disease

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Introduction: Infliximab, a chimaeric IgG1 monoclonal antibody to TNFα, represents a significant advance in the treatment of Inflammatory Bowel Disease (IBD). However side effects associated with this drug are still important points of inquiry. A 57 years old man with a history of indeterminate colitis since the age of 19 years old was admitted to the Department of surgery in 2003 for a relapse of bloody diarrhoea, abdominal pain, anemia, subocclusion, anorexia (weight loss of 20 kg) and increase in acute phase reactants. Was performed a diagnostic laparoscopy that showed a stenosis of the distal ileal loop; for that reason he underwent resection of that segment. He was treated at home with Mesalazine 500 mg. The patient was healthy until October 2005 when he relapsed and was introduced the following therapy: mesalazine 500 mg, metronidazole 1 g, budesonide 9 mg, pantoprazolo 40 mg. In 2007 the patient was first admitted in our Clinic and he was treated with prednisone 20 mg, metronidazole 2 g, mesalazine 2.4 g and ciprofloxacine due to a clinical relapse with diarrhoea (more than seven bowel movements per day), abdominal pain and weight loss. The abdominal TC revealed two ileal stenosis, for which he was subjected to a second ileocolic resection in October 2008. Since the Crohn's disease was complicated by multiple stenoses, and was refractory to the above mentioned medications, infliximab at dose of 5 mg/kg was given 2 weeks after the ileocolic resection and every 8 weeks. In January 2010 the patient developed a new onset knee arthritis and arthralgia affecting the small joints. Laboratory investigation revealed that anti-neutrophil cytoplasmic antibodies (ANCA) titer, anti-ds DNA antigen tested by enzyme-linked Immunosorbent Assay (ELISA), Anti-double-stranded-DNA Antibodies (anti-ds DNA) and Anti-Nuclear Antibodies (ANA) tested by Immuno Fluorescence Assay (IFA), were positive. Anti-extracted Nuclear Antigen (ENA), Anti-Endomysial Antibodies (EMA), Anti Reticulin Antibodies (ARA), Antiparietal Cell Antibodies (APCA), Antimicrosomal Antibodies Renal Epatic (LKM type), tested by Immuno Fluorescence Assay (IFA), Antibodies Against Cyclic Citrullina (CCP), Anti-Beta 2 Glycoprotein 1 Antibodies (IgG, IgM) (beta2GPI), Anti-nucleosome Antibodies tested by Enzyme Linked Immuno Sorbent Assay (EIA), Antihistone Antibodies tested by ELISA, Lupus Anticoagulant (LAC) and Anti-Cardiolipin Antibodies (ACL) were negative. Because specific criteria for the diagnosis of drug-induced lupus erythematosus (DILE) have not been established, we considered these criteria proposed in a Mayo Clinic study in 2009: a temporal relationship between clinical manifestations and anti-TNF-α therapy; at least 1 serologic American Congress of Rheumatology (ACR) criteria of systemic lupus erytematosus (SLE) (e.g., Anti-Nuclear Antibodies (ANAs), anti–double-stranded-DNA (anti-dsDNA) antibodies); and at least 1 nonserologic ACR criteria (e.g., arthritis, serositis, hematologic disorder, malar rash). According to Mayo Clinic criteria, the patient was shown to have a diagnosis of lupus-like syndrome induced by anti-TNFα-therapy. Due to investigate for internal organ involvement was carried out an echographic investigation of abdominal organs, an abdominal TC and an echocardiography that didn't show any significant alteration. The patient's symptoms improved after discontinuation of infliximab and treatment with prednisone (5 mg/day).

Conclusion: Recognition of DILE in patients receiving anti-TNFα-therapy can be difficult due to the symptoms of their underlying disease and due to the wide range of clinical manifestation. A temporal association of the drug with characteristic or suggestive symptoms, and resolution of symptoms on withdrawal of the drug is the best evidence for this diagnosis. It is important a careful clinical and immunologic evaluation upon starting anti-TNF- therapy.

Basilar type-migraine

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We describe the case of a 56-year-old woman with alteration of consciousness followed by headache, admitted in our department in May. Patient's medical history reported headache from 18 years, characterized by pulsing pain in the right hemisphere, associated with nausea, vomiting, photophobia, lasting 3 days and preceded at times by visual aura lasting 15 min. The headache, according to the IHS criteria, was diagnosed as migraine with and without aura and treated with antiepileptic and sumatriptan the need. In our case the patient, at the start of visual aura, took one tablet of sumatriptan 50 mg, without resolution of symptoms but instead with loss of consciousness which lasted about 3 min. When she resumed consciousness, the patient described a violent headache, classifiable as migraine without aura. She was subjected to cranial CT scan and neurological examination, which were negative. When she arrived in our department, she reported again, an intense headache, so we decided to administer oxygen, with improvement of symptoms. The patient was subjected to angio-RM, transcranial and epiaortic ecodoppler, study of persistent foramen ovale, Holter ECG, blood pressure monitoring, thrombophilia screening, personality test which were all negatives and we diagnosed basilar-type migraine [1, 2]. Basilar-type migraine is a rare form of migraine in which aura arise from brainstem region and/or reflect simultaneous involvement of both hemispheres. It is more similar to hemiplegic migraine than to classical migraine with aura. Migraine with aura and basilar-type migraine can coexist in the same patient, but the diagnosis should be preceded by a thorough search of secondary causes, especially if patient is more than 50 y.o. Triptans must be avoided for this type of headache, but how could our patient know in advance what would be happened?

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Unusual evolution of persistent weakness

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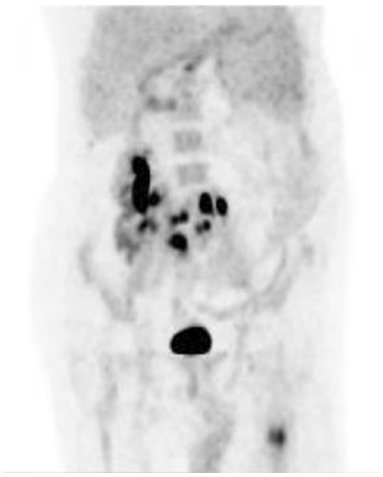
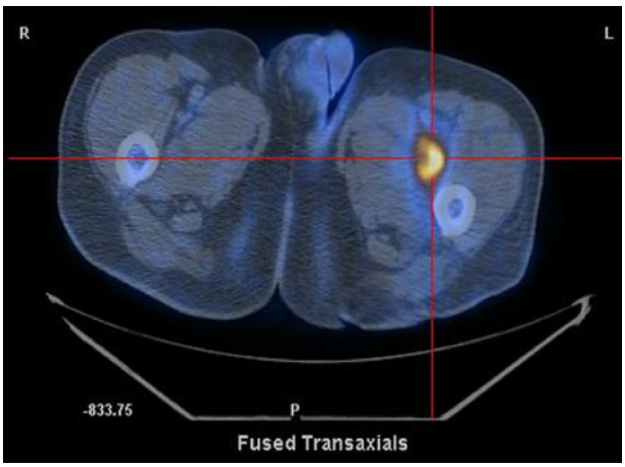
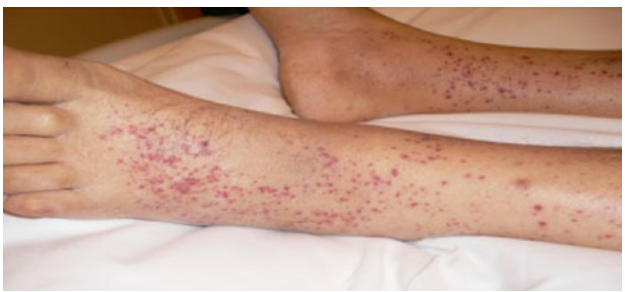
F.G., Caucasian male aged 69, came to our attention for the evaluation of a worsening weakness, which had begun 2 months earlier, associated to a weight loss of 4 kg in spite of regular caloric intake, without fever or other systemic symptoms. Blood tests performed before the admission to our center had shown increased values of ESR (52 mm/h), CRP (77 mg/dL) and ferritine (1,686 ng/mL). His clinical history was negative apart from elevated arterial blood pressure, treated with ACE-inhibitors. On admission to our hospital, the physical examination revealed splenomegaly and a cardiac diastolic murmur 3/6 L that the patient reported since childhood. Laboratory exams confirmed the increase of the inflammation parameters and showed a moderate sideropenic anemia. Neoplastic serological markers, antibodies against main hepatotropic viruses, HIV, transglutaminase, non-organ-specific antibodies and the Mantoux intradermic-reaction resulted negative. To rule out the hypothesis of a malignancy and bleeding sources, endoscopic examinations of the upper and lower GI tract were carried out. The upper GI endoscopy showed chronic gastritis and the colonoscopy demonstrated sigmoid diverticulosis. Chest X-ray revealed findings compatible with chronic obstructive pulmonary disease. The ECG showed sinusal rhythm, right bundle branch block and aspecific alterations of ventricular repolarization. The patient also underwent abdomen ultrasound scan that confirmed the presence of marked spleen enlargement (section area 120 cm^2) with homogeneous ultrasound pattern, but the subsequent CT scan (thorax + abdomen) with contrast medium showed hypodense areas in the splenic parenchyma, suggesting infarctual lesions. The haematologist, suspecting a lymphoma, performed a bone marrow biopsy, that showed normal findings, and suggested a FDG-PET that demonstrated hypermetabolic areas in the spleen and at the root of the left thigh (Pictures 1, 2). These findings corroborated the hypothesis of septic embolism, thus a trans-thoracic echocardiography was carried out. The exam showed the presence of endocarditic vegetations adherent to the aortic valve, causing moderate-to-severe valvular insufficiency. Seriate haemocultures were then performed, even if the patient didn't have fever, revealing positivity for *Streptococcus gallolyticus* sepsis. Appropriate antibiotic therapy with piperacilline/tazobactam and gentamicine i.v. was then initiated. During the following days, the patient developed fever and a painful swelling at the left thigh. A petechial cutaneous rash also appeared at 4 limbs (Pictures 3, 4). We decided to study the arterial vessels of the legs with an ultrasound Doppler examination, that demonstrated an ectasis at the origin of the left femoral artery, with echogenous matter inside the lumen and collateral bloodstreams, compatible with the diagnosis of mycotic pseudo-aneurism measuring 6 × 5 cm. Thus, the patient was addressed to the Vascular Surgery Unit to undergo an operation to treat the lesion. Despite systemic antibiotic therapy, seriate echocardiographic controls showed an increase of the dimension of the aortic valve vegetations, which were widely floating in the left ventricle outflow tract. At this point, we transferred the patient to the Cardiosurgery Unit, where he underwent substitution of aortic valve with a biologic prosthesis. Post-operatory course was regular, and after recovery the patient was discharged on anticoagulant therapy to be continued for 30 days. Sub-acute bacterial endocarditis is a treacherous pathology which often begins insidiously and presents with various clinical manifestations mimicking other systemic diseases. This case confirms the difficulties encountered during the diagnostic process in paucisymptomatic patients. Septic embolism occurs in 20–50% cases and may involve different organs and systems; it often precedes aetiological diagnosis and can affect patient's clinical course and prognosis. Mycotic pseudo-aneurism is a rare complication and often requires surgical intervention. Hypermetabolic area at detail of the hypermetabolic left femoral artery level. Area described before.



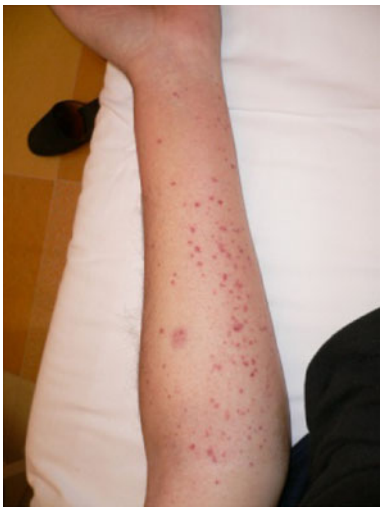
Picture 1 FDG-PET scan



Picture 2 FDG-PET scan



Picture 3 Petechial rash of the limbs



Picture 4 Petechial rash of the limbs

An unusual cause of iron deficiency anemia

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A 78-year-old man presented with a six-month history of asthenia and hypochromic microcytic anemia, with a hemoglobin level of 8.5 g per deciliter, a mean corpuscular volume of 74 μm^3 and a serum ferritin of 5 ng/ml. His medical history was unremarkable, except for osteopenia. Currently He was taking no medications. Repeated endoscopy of both upper and lower gastrointestinal tract was unremarkable. Despite tests for fecal occult blood on three samples were negative, a small-bowel follow-through barium examination was perfomed. The exam revealed a short patchy stricture in the upper jejunum with mild, fluctuating proximal dilatation. Push and pull enteroscopy showed an ulcerated polypoid mass occupying one-thirds of the lumen of the proximal jejunum and an endoscopic tattoo was performed. Biopsy was not performed because the small bowel could not be distended sufficiently. At laparoscopy, a proximal jejuno-jejunal intussusception with evidence of regional ischemia was found and thus an jejunal resection with primary end-to-end anastomosis was performed. On macroscopy the lesion appeared as an ulcerated and pedunculated polyp measuring 6.5 by 4 cm. Pathological examination revealed a well-differentiated adenocarcinoma of the jejunum arising within a tubulo-villous adenoma. The patient's post-operative course was uneventful.

Atrial fibrillation and anemia: to anticoagulate or not? This is the dilemma

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An 81-year-old man presented to Sacco Hospital for worsening of anemia (hemoglobin level 7 g/dl, while 10 g/dl four months earlier) and congestive heart failure. The medical history was significant for permanent atrial fibrillation, high blood pressure, ischemic stroke, peptic ulcer and moderate chronic renal failure. The patient was under treatment with warfarin among other medications. Considering anemia on one hand and atrial fibrillation and comorbid conditions on the other, the clinical dilemma was to continue or withdraw warfarin. Therefore, we decided to quantify the net clinical benefit of using anticoagulant therapy in patients with atrial fibrillation. We performed a systematic research on MEDLINE to find risk prediction rules both for ischemic stroke and bleedings related to antithrombotic therapy. Moreover, the estimates of the ischemic risk reduction and the bleeding risk increase in patients taking oral anticoagulants were assessed as the rates of mortality and disability in ischemic and hemorrhagic events, respectively. The following previously validated CHADS2 score (1 point for Congestive heart failure, Hypertension, Age, Diabetes, 2 points for previous Stroke or transient ischemic attack) and HAEMORR2HAGES (1 point for Hepatic or renal disease, Age, Ethanol use, Malignancy, Older age, Reduced platelet count or function, 2 points for Re-bleeding, 1 for uncontrolled Hypertension, Anemia, Genetic factors, Elevated risk of falling, Stroke) were used to predict the ischemic stroke and bleeding risk, respectively. The mortality and disability rates were 50 and 26%, respectively for intracranial hemorrhages, 2 and 1% for extracranial hemorrhages, 15 and 40% for ischemic events. The following formula has been used to obtain the net clinical benefit of warfarin therapy: reduction in ischemic risk—0.75 $\times$ increase in hemorrhagic risk. The weighting factor of 0.75 has been chosen to normalize the hemorrhagic and ischemic risk on the basis of the insight of the consequences of the adverse events. The annual ischemic risk of our patient without or with anticoagulants was 12.5 and 7.85%, respectively; on the other hand, the hemorrhagic risk with or without anticoagulants was 10.4 and 5.2%, respectively. So, the net clinical benefit has been calculated: $(12.5–7.85\%) - 0.75 \times (10.4–5.2\%) = 0.75\%$ annual absolute reduction of major clinical complications with antithrombotic therapy. Thus, because of the absolute reduction of 0.75%, we decided to treat our patient with anticoagulants. The formula could be arranged depending on the variables considered and the patient insights of the gravity of the event and can not be considered as a rule to apply strictly. However, the quantitative assessments of the net clinical benefit for each patient proposed for anticoagulation therapy could help physicians to improve the decision making regarding antithrombotic therapy for stroke prevention in atrial fibrillation.

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The management of an unusual case of constrictive pericarditis

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We describe the case of a 72-year-old man who was hospitalized for persistent fever at 39°C preceded by chills, chest pain and dyspnea. A history of diabetes mellitus type II on diet therapy and obesity (BMI 40) were present. At home, he had taken unspecified antibiotic therapy without benefit. At a chest X-ray examination, signs of ileoparenchymal congestion, with small bilateral pleural effusion and enlarged cardiac shadow, were documented. At admission to our unit, the patient appeared frankly dyspnoeic with hypotension and fever (37.4°C). At ECG: regular sinusal rhythm, low precordial R wave, nonspecific repolarization changes. At the physical examination the patient was conscious, well oriented and cooperative; at chest auscultation the vesicular murmur was ubiquitously reduced with hypophonetic bases at percussion. At cardiac auscultation the heart tones were reduced but in rhythmic succession, with apparently no abnormal sounds or murmurs. The abdomen appeared to be enlarged due to fat, not painful at superficial and deep palpation; it was also appreciated painless hepatomegaly with normal spleen area. The chest pain was reported by the patient as a continuous, stabbing type, without irradiations or relief positions. Biochemical tests showed only neutrophilic leukocytosis and increased CRP; markers for myocardial lesions were repeatedly negative and arterial blood gas analysis was consistent with a hypoxic hypercapnic respiratory failure. Therefore, a O_2-therapy mask with O_2 delivery at 4 L/min was applied to the patient, and medical treatment initiated with antibiotic combination (piperacillin/tazobactam and azithromycin), paracetamol, enoxaparin (bedridden patient), low-dose oral furosemide, NSAIDs and s.c. insulin. On day 2 the patient was still febrile (38°C) and dyspnoeic; he complained of profuse sweating and intense headache; in the suspicion of acute pericarditis a echocardiography was performed that documented an ubiquitous moderate pericardial effusion with anterior diastolic diameter of maximum 2.6 cm in the absence of constrictive physiology. At the same time a wide search for etiologic causes was started, including serological, microbiological, autoimmune and biochemical assays: all turned out to be negative. We concluded for an idiopathic pericarditis and then, according to the European guidelines, the patient was put on anti-inflammatory therapy with full doses Ibuprofen. However, the patient had no benefit and on day 8, due to the worsening clinical status, and inspite of underlying diabetes, a full-dose steroid therapy was started. This led to progressive improvement of the patient's general condition. However, hypotension and dyspnea persisted whereas CRP progressively rose. A control echocardiography was performed: severe thickening of the pericardial layers with minimal pericardial fluid and the presence of constrictive physiology were documented. The patient was first evaluated by chest and abdominal CT-scan to exclude a paraneoplastic syndrome and then sent for cardiosurgical evaluation with the specific indication for pericardiectomy. The manoeuvre was carried out in our Reference heart surgery Center, 1 month from the onset of symptoms. Histology documented "fibrous tissue with acute and chronic inflammation, bleeding and extravasation ectasia of the vessels, partly covered with

reactive mesothelium". At 1 month after surgery the patient has fully recovered, and has not shown any sign of relapse. The diagnosis of acute pericarditis is relatively simple and is based on the presence of two of four criteria- typical chest pain, pericardial friction rub, widespread ST-segment elevation and pericardial effusion (new or worsening)-while the management should be targeted towards the specific etiology, if known. Most cases of acute pericarditis are idiopathic (80–85%) or viral; major non-idiopathic etiologies includes tuberculosis, neoplasia and systemic (generally autoimmune) diseases. For cases that are idiopathic or suspected viral, the first-line approach and mainstay of treatment, according to European guidelines, are aspirin or NSAIDs, but in our case the use of full-dose Ibuprofen failed while, the use of high-dose corticosteroids (Prednisone 1–1.5 mg/kg/day) led to a clear improvement of patient's clinical status, although did not avoid the cardiosurgical procedure. Usually, there is a long delay between the initial pericardial inflammation and the onset of constrictive physiology; but in our patient, the clinical course was rapid and standard-of-care approach failed. Most likely hepatomegaly, pleural effusions, haemodynamic impairment and the presence of comorbidities (diabetes) were early signs of poor-prognosis and indicated a high-risk patient that, in spite of current guideline indications, would have likely benefited of an early treatment with steroids.

A case of small intestine angiodysplasia

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A 69-year-old-man was admitted to our hospital for dyspnea and deep asthenia. Laboratory tests revealed of microcytic anaemia. The patient was suffering of hypertension, chronic renal failure, and previous placement of abdominal aorta prosthesis, 10 years before; he reported several hospital admission in recent years because of the finding of microcytic hypochromic anemia with low levels of serum iron and ferritin. One year ago he received a diagnosis of polyposis of colon with histological signs of "tubular adenoma with moderate dysplasia". On admission, general physical examination showed diffuse pallor of the skin and mucous membranes with tachycardia and normal blood pressure. Laboratory tests showed microcytic anemia (Hb 6.9 g/dl, MCV 72 fl, RBC 2,950,000/mmc; MHC 23.2 pg, HCT 21.2%), serum iron of 26 mcg/dl, ferritin of 4.4 ng/ml, transferrin of 315 mg/dl, BUN of 56 mg/dl, creatinine 3.3 mg/dl with a creatinine clearance (Cockcroft-Gault) amounted to 29.3 ml/h.

The following diagnostic hypotheses were considered

- Hyporigenerative anaemia, due to kidney failure
- Bleeding from gastrointestinal tracts
- Dissecting aneurysm of abdominal aorta

The patient was treated with erythropoietin, iron therapy and vitamins without a substantial improvement of hemoglobin levels. During the hospitalization several episodes of acute anaemia occurred, that required blood transfusions. Therefore, the patient underwent the following investigations: CT of abdominal aorta that was negative for dissecting aneurysm; Technetium-labelled red blood cells scintigraphy, which showed the presence of abnormal red cells labeled in the region of the left side of abdomen; a gastroscopy and a colonoscopy that were normal although the fecal occult blood was positive. The patient underwent exploration of the digestive tract trough videocapsula that showed the presence of *angiodysplasia in duodenum and ileum*. Endoscopic treatment with electrocautery was attempted, but it failed because of the small bowel location and extension of the lesions. We proposed angiography with embolization to the patient before considering surgery, that is the treatment of choice for patients large transfusion requirements or life-threatening hemorrhage. The patient took the decision to wait for a follow up period.

An atypical presentation of Bechet's disease

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A 54 years old university professor went to Emergency in Milan for unremitting temperature over 38°C associated to pharyngodynia, oral aphthous, cutaneous migrans and erythema nodosum-like subintrant lesions.In the past he was a moderate smoker, abstemious, affected by arterious hypertension, that was pharmacologically controlled with sartan, and without signs or symptoms of systemic organ damage. There were no other signs or symptoms, a part from deep exhaustion. He reported his symptoms began 15 days before, while he was staying in a rural area, rich in farms with live stock (horses). He also referred that during his stay he was bitten by an hematophagus insect. He was treated with antibiotics therapy (amoxicillin and clavulanic acid), which was ultimately unsuccessful, showing no improvement of temperature and symptoms. Therefore the patient was admitted to the Internal Medicine Department. The medical diagnosis was: no cause-associated persistent elevated temperature. Antibiotic therapy was suspended, followed by further diagnostic and culture tests during the antibiotic wash-out period. At the beginning of his hospitalization, the patient's objective examination found sinus tachycardia related to elevated temperature, erythema nodosum, aphthous stomatitis, lingual and oral multiple aphthous ulcerations. Differential diagnosis included many feverish diseases, associated to cutaneous and mucous lesions due to infective or immunological trigger events. Erythema nodosum is observed in many infective circumstances/conditions (such as tuberculosis, leprosy, sarcoidosis, streptococcal pharyngitis, pertussis, measles, primary atypical pneumonia, lymphogranuloma venereum, syphilis and mycotic infections, HIV) and it is also reported as an extra-intestinal ulcerative colitis sign, appearing as a reaction to drugs. Furthermore mouth injuries and aphthous ulcerations are frequently observed as a primary manifestation of Syphilis, Herpes simplex, Rickhettsial diseases and other viral infections. Inflammatory bowel disease and Behcet's syndrome are associated with aphthous stomatitis and blood dyscrasias too. On the one hand biochemical examinations demonstrated undetermined/aspecific active inflammation (C reactive protein—CRP 9.6 mg/dl, ESR 63, WC 13.9 10^3/mmc with a normal differential leukcocyte cell count). Microbiological tests for Typhus, Paratyphus, Brucella, Rickettsiae and antibodies against Borrelia bugdoferi came out as negative. Immunological HIV, CMV, EBV e parvovirus were also negative. Blood culture, urine culture, pharyngeal, nasal, auricular swabs and coproculture turned out to be negative for pathogens. On the other hand instrumental examinations allowed the exclusion of infective focuses, lymphoadenopathies or solid masses. From these negative results for infectious diseases, we were directed towards systemic immunological diseases, such as vasculitis or granulomatosis, despite the antibodies, the autoimmunity profile and the complement assay were within the normal range. Further symptoms developed during hospitalization, and helped to clarify the diagnosis. The patient complained about a headache and a left OCULODINIA, that was compatible with anterior uveitis. There are many diseases, involving ocular structure/system and they are considered in

differential diagnosis: Reiter's syndrome, sarcoidosis, Stevens-Johnson's syndrome, familiar mediterranean fever, multiple sclerosis, Systemic Erythematous Lupus, and connectivities. But the patient did not present with the classical triad of the Reiter's syndrome (arthritis, uveitis, uretritis), or the typical Stevens-Johnson's pulmonary involvement, or sarcoidosis associated lymphoadenopathy. Further, painful neat borders ulceration on the skin of the genitals suggested a form of systemic vasculitis, in particular Behcet's syndrome. Pathergy test was performed with a negative outcome. However it is reported in the literature that this test is negative in about 80% of Behcet's syndrome cases in Europe. Behcet's syndrome is not reported in literature as having fever as a first clinical symptom. Therefore this patient's diagnosis had to go through a long path of exclusion, because the major diagnosis criteria (oral recurrent aphthous ulcerations, ocular, genital and cutaneous lesions) presented later. After the diagnosis of Behcet's syndrome the patient was sent to the Dermatological Department for vasculitis histological confirmation. Colchicine treatment for aphthous ulcerations was started, dapson and corticosteroids were administered for iridocyclitis and mucocutaneous lesions. The patient recovered in 1 month, without permanent scars from mucocutaneous manifestations and fever disappeared on third day of therapy.

Incidental finding of cavitary pulmonary lesions in a young woman

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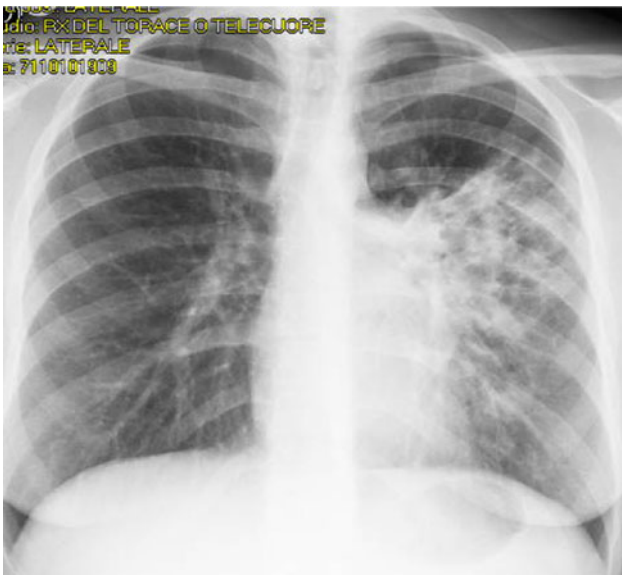

Cavitary pulmonary lesions represent a diagnostic challenge since they may be due to several causes, including congenital malformations, infections, autoimmune disorders or malignancies. Here, we report a 21-year old female patient who presented in Emergency Room after a car accident. She did not report any trauma. She had no fever, cough, dyspnoea or any other symptoms. The blood tests revealed no signs of infection or inflammation. Chest X-ray showed a big cavitary nodule in the left lung. She was hospitalized and she underwent transbronchial pulmonary biopsy showing necrotizing granulomatosis with vasculitis, suggesting the diagnosis of Wegener's disease. Then she was referred to the pediatric clinic of our hospital. CT scan showed multiple cavitary lesions in the left lung. PPD was negative. Multiple blood and BAL cultures were negative for bacteria, mycobacteria and fungus. Fungal and viral serologies were negative. C-ANCA p-ANCA and other autoimmune tests were negative. Genotyping for cystic fibrosis was negative. Left thoracoscopy with wedge biopsy was performed. Histology was characterized by vasculitis, granulomatous inflammation with multinuclear giant cells and necrosis, confirming the diagnosis of Wegener's granulomatosis. During hospitalization she developed transient left hemiparesis and seizures. Neuro-imaging tests showed a small ischemic lesion in the right frontal lobe. Furthermore a small cutaneous maculo-papular lesion of the left leg was biopsied and showed perivascular infiltration of mononuclear cells and neutrophils. These data were consistent with systemic vasculitis, supporting the diagnosis of Wegener's granulomatosis. Treatment with steroids and methotrexate was started. During the following weeks she progressively developed cough, hemoptysis, fever, neutrophilic leukocytosis and elevated C-reactive protein. She was treated empirically with broad spectrum antimicrobial coverage without any improvement. The follow-up CT scan showed multiple bilateral cavitary lung nodules increased in number and size. Therefore, she was treated with prednisone and cyclophosphamide. Subsequently, the patient was referred to our department. Since no clinical neither radiological response to previous therapies was obtained, sequential treatments with high dose intravenous immunoglobulins, anti-TNFalpha agents, rituximab and mycophenolate mofetil were attempted, still without any success. After a transient improvement her clinical conditions worsened. CT scan showed further increase in number and size of lung lesions. PET/CT revealed elevated fludeoxyglucose activity involving the multiple cavitary lung nodules and lymphadenopathy with a reactive pattern. The biopsy of a small lymph node, found later in cervical region, allowed the final diagnosis of classic Hodgkin lymphoma, nodular sclerosis type. A second review of the lung wedge biopsy done during the initial hospitalization revealed markers consistent with Hodgkin lymphoma (CD30+ cells). Given the diffuse lung disease and presence of "B" symptoms, her disease was classified as stage IV-B and treated with multi-agent chemotherapy (adriamycin, bleomycin, vinblastine, dacarbazine [ABVD]). The B symptoms and the neutrophilic leukocytosis resolved after the first course of chemotherapy. This case illustrates an unusual presentation of Hodgkin lymphoma mimicking Wegener's granulomatosis. Thus, pulmonary lymphoma, even in presence of confounding factors, should be considered in the differential diagnosis of cavitary lung lesions.

Osteonecrosis of the jaw by Ibandronate: causal or casual association?

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Case presentation: A 65-year-old caucasian woman presented oral pain and swelling in the posterior left side of the jaw. At the time of the consultation, the medical history revealed that 10 years earlier, rheumatoid arthritis had been diagnosed and treated with corticosteroid (metilprednisolon 4 mg daily) and immunosuppressive therapy (azathioprine 50 mg three times a week). In order to avoid loss of bone induced by chronic treatment with corticosteroid, the patient, who presented a condition of osteopenia (T score -1.44), received ibandronate for 2 years (Bonviva 150 mg, oral doses monthly). She

had not a history of radiation therapy to the head or neck and reported also teeth extraction on the left superior dental arch.
Clinical oral examination showed a fenestration in the area of the left mandibular alveolar ridge that exposed a necrotic bone fragment. An osteonecrosis of the jaw (ONJ) was suspected. Several instrumental exams were performed. Panoramic radiographs (OPT) showed an empty socket with associated periosteal reaction and loss of corticomedullary differentiation. Jaw scan revealed periosteal interruption (8 mm) and thickening of masseter muscle. ^{99m}Tc-Sn-MDP Scintigraphy demonstrated an increased uptake on the left jaw, subsequently confirmed as suppurative material at cytologic examination. MRI showed high signal intensity related to osteonecrosis, lymphadenopathy and soft tissue enhancement surrounding the left mandible. A dentascan jaw CT showed sclerosis of the left mandible with areas of cortical erosion both internal and external, in particular close to the angle of the mandible; it revealed also an dishomogeneous lesion in close contact with masseter muscle. According to the clinical presentation and radiographic pictures, diagnosis of bisphosphonate-associated osteonecrosis complicated by osteomyelitis was made. The protocol followed by the patient consisted of metronidazol 250 mg 2 times daily, chlorexidine mouthwashes 3 times daily and chewing exercises. Ibandronate was stopped and it was changed with strontium ranelate. Symptoms improved and the patient, after 6 months, shows a complete recovery of the pre-existing lesions.
Discussion: Osteonecrosis of the jaw (ONJ) is a rare side effect described during bisphosphonate use. The prevalence of ONJ associated with osteoporosis, which is treated with less powerful and low doses oral biphosphonates (alendronate, risedronate and ibandronate), has been estimated between 0.0004 and 0.04%. The growing numbers of spontaneous reports about ONJ, in patients who are taking oral bisphosphonate, suggests that this adverse event may be multifactorial and that the type, the dose, the duration of treatment and the route of administration of bisphosphonate are not enough to determine this rare condition. In the case described was not possible to determine with certainty whether the ONJ was determined exclusively by use of ibandronate or has been favored by the coexistence of risk factors: advanced age (65 years), rheumatoid arthritis, poor oral hygiene and edentulous regions and the use of glucocorticoids and immunosuppressive agents. The presence of a dysregulation of the host inflammatory response could improve the risk to develop ONJ: recent studies have demonstrated the frequent association between periodontal disease and chronic inflammatory diseases, such as rheumatoid disease. Probably the underlying common pathway involves the releasing of cytokines such as interleukin (IL)-1beta, tumor necrosis factor (TNF)-alpha, and IL-6 which causes tissue destruction through the production of collagenolytic enzymes. Common dental comorbidities such as poor oral hygiene, periodontitis, presence of edentulous regions impose a dental examination to identify and correct predisposing conditions before and during treatment for the prevention and delaying of the ONJ. The use of glucocorticoids and immunosuppressive agents could interfere with wound healing and epithelialization through two mechanism: on one hand they could cause a mucosal damage that exposed bone to oral infections, on the other hand they have angiogenetic properties that reducing possibility to meet an increased demand for repair and remodeling owing leading to an avascular necrosis. All patients are potentially at risk to develop ONJ and the identification of predisposing factors in patients who are undergoing bisphonate therapy is mandatory. The evaluation of benefit and risk assessment in all patients who are undergoing antiresorptive therapy could allow to detect the eligibility to the treatment and to choose other alternative medications.

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Lower limb ischemia due to long-term abuse of cocaine

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Chronic use of cocaine is known to cause endothelium dysfunction and atherosclerosis and consequently, as reported in the literature, injuries to cardiac, pulmonary, intestinal, placental, and musculoskeletal vessels; however, injury of the pedal vessels is rare. This case report describes a 45-year-old man with severe arterial ischemia leading to ulceration and amputation of one foot fingers, presumably due to long-term abuse of cocaine. Known causes for peripheral occlusive disease, such as atherosclerosis, vasculitis or collagene vascular disease were excluded. Differential diagnosis with diabetes' arteriopathy and Buerger's disease, considered at a first time as diagnostic hypothesis, was conducted on the basis of conventional angiography findings, which showed occlusions of plantar artery on the right side, badly recovered with angioplasty. Even if cocaine has been reported to be associated with necrotizing vasculitis mainly of cerebral, cardiac and renal arteries, there are some case describing vasculitis-like arteriopathy attributed to the abuse of cocaine. The abuse of cocaine also appears to play a role, as described in this case report, in the development of peripheral arterial occlusions and seems to have broad similarities with Buerger's disease.

Never undervalue a dry cough

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A 62-year-old-woman, came to our observation complaining persistent dry cough and fever in the last 4 months. Other symptoms or clinical signs were irrelevant. She visited the family doctor for the development of stabbing chest pain at the left baseline in association to the cough. For that reason a chest X-ray was performed. The study of the chest revealed an area of parenchymal lung consolidation in the anterior basal left with moderate pleural effusion. A diagnosis of pneumonia infection was suspected and she was treated with quinolones and beta-lactam antibiotics, without resolution of symptoms. More importantly, a second chest X-ray performed 3 weeks later for control showed a worsening characterized by the presence of lesions termed "striae disventilatorie" in the right middle field, with widespread interstitial and fissural thickening. A protocol treatment with penicillin in association with beta-lactam plus aminoglycoside for 20 days was recommended by the lung specialist. Clinical and radiological improvement did not followed treatment. Bilateral

pleural effusion associated to widespread frosted glass-like lung hyperdensity with the presence of small para-aortic lymph nodes, without the involvement of the mediastinum were detected by contrast-enhanced chest CT. The patient was admitted to our hospital for further investigations. The physical examination was notably only for objective signs of bilateral pleural effusion. Routine blood tests were normal; thoracentesis showed erythrocytes, lymphocytes, granulocytes and rare mesothelium cells in the pleural effusion sediment. In order to exclude an infectious etiology the sputum was cultured and resulted negative. BAL (broncoalveolar liquid) showed mucus, lymphocytes, histiocytes and rare well-differentiated bronchial cells. Mycobacteria was not detected. Bronchoscopy resulted negative for tumors. Infective etiology was excluded. Given a previous autoimmune-likely pleuro-pericarditis on the history a possible autoimmune disease was considered. This hypothesis was not confirmed by the laboratory tests, although the patient took advantage from high dose of steroids associated with a broad-spectrum antibiotic therapy. The chance of a lung cancer and interstitial disease was excluded by imaging examinations. On the base of history of previous gastric ulcer *Helicobacter pylori* related, that have been successfully treated, a gastroscopy was performed. A small erosions of the mucosa, slightly bleeding was observed in the gastric angulus and biopsies collected. Unfortunately, morphological examination of the gastric mucosa displayed signet-ring cells infiltrating the mucosa with a final diagnosis of poor differentiated gastric adenocarcinoma. In the antrum, focal areas of metaplasia were observed. Total body CT scan showed no distant metastasis (T3 N3a M0 for TNM staging). Our final diagnosis was malignant pleural lymphangitis from gastric adenocarcinoma. The patient underwent a total gastrectomy that revealed an exophytic malignant, poorly differentiated gastric mass infiltrating the entire wall thickness and perivisceral adipose tissue with perineural infiltration and several perigastric lymph nodes. Interestingly in the past the patient underwent several times to the gastroscopic examination and biopsies were repeatedly collected but the exophytic dissemination of the tumor masked the truth to the operators for long time.

A case of fever and refractory hyponatremia

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A 79-year-old man was admitted after a 5 days history of malaise, fever, chills, anorexia, and dysuria for which he was taking norfloxacin. Over the last 2 days progressive confusion and dizziness had developed. The patient suffered from hypertension for which he was taking hydrochlorothiazide/amiloride. He did not refer recent exposure to sick persons, exposure to tuberculosis, or travels outside Europe. At clinical examination, blood pressure was 160/70 mmHg, heart rate 72 bpm, temperature 38.5°C. Thoracic, cardiac, abdominal examination was normal. No focal neurological signs were found. Serum creatinine was 1.1 mg/dL, urea 36 mg/dL, Na^+ 116 mEq/L, K^+ 3.2 mEq/L, CRP 1.1 mg/dL, WBCs 10,640/mm^3 (68% PMN), Hb 13.3 g/dL, PLT 193,000/mm^3. ECG showed a first-degree AV block. Chest X-ray showed no infiltrates. The patient was admitted with a presumptive diagnosis of urinary tract infection and iatrogenic hyponatremia. Therefore, diuretics were discontinued, i.v. ceftriaxone and electrolyte repletion were started. Despite continued antibiotic and rehydration therapy, a >38°C fever persisted. WBCs decreased to 8,270/mm^3 (70% PMN), CRP to 0.7 mg/dL and Na^+ ranged between 120–130 mEq/L. Other routine blood chemistries were normal. The urinalysis was negative as were serial blood and urine cultures. In the setting of a fever >38.3°C on several occasions, lasting more than 2 weeks, with an uncertain diagnosis, we decided to perform a broad assessment of infections, connective tissue diseases or malignancies assuming we were facing a fever of unknown origin. Serologic tests for HAV, HBV, HCV, CMV, EBV, HSV, VZV, HIV, together with those for Bartonella, Brucella and Rickettsia species, Toxoplasma, *Mycoplasma pneumoniae*, Chlamydiae (PLT group), Borrelia burgdorferi and Weil-Felix, Widal, TPHA/VDRL tests were all negative. A TT echocardiography revealed no vegetations. Tests for ANCA, ENA antibodies, reumathoid factor were also negative, while ANA tests were positive with a titer of 1:160. Oncomarkers were not altered. Abdominal US and upper endoscopy were negative. CT scan of the abdomen, head and neck was normal, while chest CT scan revealed apical bilateral infiltrates. Therefore, BAL fluid cultures and QuantiFERON-TB tests were performed and were negative. Total body PET-scan was also normal. Since all laboratory and imaging tests were negative and the patient's condition worsened, additional history was elicited. He referred to own canaries and make frequent visits to animal fairs. This suggested an exposure to a zoonotic infection, so we decided to extend our research looking for antibody titers to Chlamydia psittaci and Coxiella burnetii and to replace ceftriaxone with doxicicline. Unfortunately, our referential laboratory was not able to measure out antibody titers for these bacteria and we found an equipped laboratory only 1 week later, when antibiotic therapy was already begun by 1 week. Meanwhile, in spite of fluid and electrolyte repletion, symptomatic hyponatremia persisted. Since hypo and hypervolemic hyponatremia was excluded, we focused on causes of euvolemic hyponatremia. We excluded current use of thiazides, hormonal changes and decreased intake of solutes, while we couldn't rule out a syndrome of inappropriate secretion of ADH (SIADH). Urine Na^+ excretion was 300 mEq/24 h. Plasma osmolality was 262 mOsm and urine osmolality 495 mOsm. These data confirmed the suspicion of SIADH. Major causes of SIADH were investigated: laboratory and imaging studies didn't reveal malignancies; the patient wasn't taking any drug potentially inducing SIADH; CNS disorders were ruled out with brain MRI; viral and bacterial infections were previously investigated, with the exception of *C. psittaci* and *C. burnetii*. This last pathogen was found to be occasionally associated with SIADH. Three weeks after the hospital admission, we received positive test for *C. burnetii* (IgG phase 1, 1:128; IgG phase 2, 1:512; IgM phase 1 and phase 2, <1:16) which suggested an acute Q fever with IgM titers negative due to ongoing antibiotic therapy with doxicicline. In support of this hypothesis, the patient clinical status improved and fever disappeared after 7 days of therapy. We continued doxicicline administration for 14 days. While flu-like syndrome progressively resolved, hyponatremia persists, despite standard repletion therapy with fluid restriction, salt administration and hypertonic solution in association with **a loop diuretic**. Vaptans have been developed for treating conditions characterized by euvolemic hyponatraemia and could be a valuable therapeutic option in this patient.

Sliding PET (Positron Emission Tomography)

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A 62 years-old woman came to our attention complaining cough, chest pain and worsening dyspnea in the last 2 months. She was a

smoker and her past medical history was negative. A chest X-ray revealed a pleural effusion in the lower half of the left lung field. Bloodworks were normal (in particular no increase in white cell count and CRP); arterial blood gas, tested in ambient air, showed pH 7.45, pCO_2 35, pO_2 65, HCO_3 24. ECG and echocardiogram were normal. We decided to perform a thoracentesis: the biochemical analysis showed an exudative pleural fluid. Since the patient asked us which were the possible causes of her effusion and which exams she would undergo, we made a bibliografic research in order to find the diagnostic yield of the single tests we should perform. We found that the most frequent causes of exudative pleural effusions are malignancy (50% of cases), tuberculosis (27%) and parapneumonic effusion (17%). These frequencies represented the pre-test probabilities, that is to say the probabilities that our patient, with an exudative pleural effusion, had one of the previous diseases [1]. Likelihood ratios (LRs) are measures of diagnostic test performance. A positive LR is calculated by dividing sensitivity by 1 minus specificity [sensitivity/(1-specificity)]. Similarly, a negative LR is calculated by dividing 1 minus sensitivity by specificity [(1-sensitivity)/specificity]. Positive and negative LRs allow to calculate how much the result of a test changes the pre-test probability [2]. Both cytology and microscopic analysis for *Mycobacterium tuberculosis* of our patient were negative. We found that the negative LR of cytology is 0.37, so the post-test probability that the patient had a neoplasm decreased from 50 to 22%. The negative LR of microscopic analysis for M. tuberculosis is 0.76, which did not change significantly pre-test probability of tuberculosis [3, 4]. These results were not enough to rule out or rule in the diagnosis, therefore we decided to perform a CT scan, that showed a posterior parietal pleural thickening suggestive of malignancy. Searching in Medline, we found that parietal pleural thickening has a positive LR of 4.66 for cancer diagnosis [3]. The post-test probability of malignancy increased from 22 to 53%. Therefore, we asked ourselves if we should perform a PET (Positron Emission Tomography) scan. We found that PET scan has a negative LR of 0.03–0.1 and a positive LR of 7.5–8 [5]. If PET was negative, post-test probability would be 5–10%, certainly quite low, but not enough to let us tell the patient she had no cancer. If PET was positive, post-test probability would be 90%, which means that the patient almost certainly had cancer. However, which cancer? And how should we treat her? Cochrane said that if the results of a diagnostic test will not change your clinical practice, you shouldn't perform it. Regardless of the result of the PET scan, we would have submitted our patient to a thoracoscopy. In fact, if performed after the CT scan, a positive exam would increase post-test probability of malignancy from 53 to 100% (positive LR+∞), while a negative result would bring the likelihood of cancer from 53 to 7% (negative LR 0.08) [6]. Only in this case we could reassure our patient and ourselves performing a PET scan, which, if negative, would have further reduced the probability of a malignancy to 1%. This case allowed us, using bibliographic research to find diagnostic tests performance, to reflect upon the role of PET scan in the diagnostic workup of pleural effusions suspected for malignancy. We suggest its use only in cases in which thoracoscopy is not diagnostic.

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The unusual case of MRS Q

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An 80-year-old female, in good general conditions, with a history of diabetes mellitus type II and chronic HCV infection, came to our observation in March 2010 for the onset from about 3 months of a deep oval ulcer, 6–7 cm diameter, with sharp and infiltrated margins, painless, deep almost to the level of bone, localized on the anterior surface of the right leg. In the early months of 2008, the patient had presented an important systemic symptomatology characterized by initial onset of peripheral edema, about malleolus bilateral erythematous lesions with small abrasion on the right side, diffuse xerosis, easy crusting blood in the left nasal cavity, left hypoacusia and subsequent onset of serotine fever, dyspnea and fatigue, with the RX-chest finding of a parenchymal consolidation in the right apex, and some opacity with hazy margins bilaterally. Chest CT confirmed the presence of parenchymal consolidation areas and nodular lesions compatible with neoplastic or inflammatory diseases. However, subsequent investigations (CT-total body, bronchoscopy with biopsy and bronchial aspirate) had excluded the presence of cancer and bacterial or fungal infections. Even the search for Mycobacterium tuberculosis in urine and sputum (microscopic examination and culture) was found to be negative, with positive intradermal Mantoux. The lung biopsy had shown the presence of fibrosis and an isolated giant cells granuloma histo-epithelioid marginally. The suspected diagnosis of Wegener's granulomatosis was excluded by the absence of histological confirmation and the negativity of ANCA profile, while it appeared more likely the diagnosis of sarcoidosis, based on histology, despite dose ACE negative. During these investigations, the patient took an antibiotic therapy (imipenem/cilastatin, teicoplanin, levofloxacin) and steroids (methylprednisolone, 32 mg/day) with gradual resolution of clinical signs and reduction of pulmonary consolidation areas, with persistence of some fibrosis areas in the radiological imaging. Considering the positive development of the clinical conditions and without a definitive diagnosis, it was considered appropriate to continue in the following period the treatment with steroids to reduce gradually. Subsequently, even the Quantiferon assay was found positive (recently the patient had had a positivization of the intradermal Mantoux, while it was negative 3 years earlier). Later, the ulcerated lesion appeared on her right leg, without other associated symptoms. The skin biopsy on the lesion showed rare acid alcohol resistant elements at the Ziehel Nielsen histochemical staining. Cultural examination isolated acid-alcohol resistant bacilli in slow growth, compatible with Mycobacteria. The microscopic examination and PCR for Mycobacterium tuberculosis on the lesion were negative, and the search for systemic infection by Mycobacterium tuberculosis too (in urine and gastric aspirates). It was confirmed the Quantiferon positivity. Based on these results, the diagnosis was "atypical Mycobacterial skin ulcer", which still has to be typed. An histological revaluation of the previous lung biopsy was made to evaluate the possible correlation between current symptoms and systemic manifestations previously presented, but it did not reveal acid-alcohol resistant elements, despite the difficulties of the examination linked to the lack of material. At the same time, the autoimmune profile study was repeated to exclude other granulomatous diseases and it showed a slight but not significant positivity for antiphospholipid antibodies (anticardiolipin IgM Ab and antibeta2glycoprotein IgM Ab), and a positivity for cryoglobulins; the ACE

dosage was repeated and it resulted slightly higher than the normal range (91.5 U/L). Moreover, the dosage of anti-Leishmania antibodies and the search for Treponema pallidum were performed and they resulted negative. Waiting for the typing of Mycobacteria isolated, the steroid therapy, that the patient followed with low dosage, has been discontuined, and topical therapy with Sulfadiazine silver was undertaken with initial improvement of the ulcer, which appeared progressively less deep, with the formation of granulation tissue inside and infiltrated and erythematous margins. Moreover, a systemic antibiotic therapy was started with clarithromycin. In the following period, the patient felt healty and the skin ulcer is improving.

Multicentric Castleman disease as cause of fever of unknown origin in HIV infected patient

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A 41-year-old man was admitted to our Department because of fever with chills, sweats, and mild diffuse abdominal pain beginning about 20 days earlier; during the two previous months he lost about 5 kg of weight and fatigue also developed. On examination, the patient appeared to be fatigued, the blood pressure was 140/80 mm Hg, the pulse 100 beats per minute, the respiration was 20 breaths per minute and the temperature was 38.5°C. The oxygen saturation was 88% while he was breathing ambient air. The skin was hot and sweaty, the conjunctivae were pale and oral cavity and pharynx were normal. Non-tender lymph nodes of 1–2 cm in diameter where palpable in laterocervical, axillary and inguinal chains. The remainder of the examination was normal. Laboratory tests showed hemoglobin 10.2 g/dl, RBC 3,790,000, MCV 81.3 fl, reticulocytes 1.3% WBC 14,000 (neutrophils 46%, eosinophils 2%, basophils 0.1%, lymphocytes 36%, monocytes 14%), platelets 204,000, hematocrit 34.5%, erytrocyte sedimentation rate 50 mm/h. Serum protein electrophoresis showed mild hypoalbuminemia (albumin 3.2 g/dl) and polycolal hypergammaglobulinaemia. Chest radiograph and a echocardiogram were negative. Abdominal ultrasound was performed and showed a slight increase in liver volume with a gallstone of about 1 cm in diameter in the gallbladder lumen. The patient had never used intravenous drugs or tobacco, he was not taking medication and there was no exposure to animals, tick bites, recent travel, or contacts with people with tuberculosis. He had homosexual contacts and he did not use condoms regularly; he also worked as porter in a Hotel and so he was exposed to contacts with people from other geographical areas. The patient had syphilis when he was 35 years old and, shortly after, testing for human immunodeficiency virus (HIV) was positive. At 39 years of age, the patient was diagnosed with cholelithiasis and treated with acid ursodeoxycholic. At 40 years of age, the patient reported traumatic rupture of the spleen and underwent splenectomy with normal findings on histological examination. The same year, for the reduction in CD4+ T cells count, the patient was started on antiretroviral therapy that was suspended 1 month before admission to our Department for a urticarial skin reaction. During hospitalization, the patient had persistent fever and microbiological tests such as cultures of blood, stool and urine were negative. The differential diagnosis of a HIV positive patient presenting with fever, lymphadenopathy and splenectomy is very broad. FUO in HIV-positive patients, in contrast to that of HIV-negative patients, is caused more frequently by infectious disease and less frequently by neoplastic and autoimmune diseases. More than half of infectious diseases are caused by tuberculosis, equally represented by *M. tuberculosis* and atypical mycobacteria. The remainder of infections is supported by opportunistic pathogens such as CMV, EBV, Leishmania, Toxoplasma and Pneumocystis Jiroveci. Tuberculin skin test, serologic testing for CMV, EBV and Toxoplasma were consistent with past infection. For the presence of gallstones and abdominal pain, in order to rule out cholecystitis, biliary juice specimens were collected and testing of them was normal. Because of splenectomy and immunosuppression, to prevent possible early sepsis by bacteria capsulate such as *S. pneumoniae*, *H. influenzae*, *N. meningitidis*, to which splenectomized patients are particularly vulnerable, the patient was treated with ceftriaxone and vancomycin, without obtaining changes in the temperature curve. Following, the more frequent non–infectious causes of FUO in HIV were considered, namely non-Hodgkin's lymphoma, Castleman disease and Kaposi's Sarcoma. The early implementation of CT chest-abdomen is useful to detect two of the most common causes of FUO, tuberculous infection and lymphoproliferative disorders. Cranial CT may be useful to identify the presence of Toxoplasma or cerebral lymphoma. Therefore, a total body CT scan was performed which showed several enlarged lymph nodes in laterocervical, axillary, paraaortic, mesenteric and inguinal region. The lymph node biopsy has a role in identifying some of the most commonly represented causes of FUO in HIV infections, including tuberculosis, toxoplasmosis, or Castleman's disease. Therefore, a biopsy of the laterocervical lymph node was performed which showed histological features consistent with Multicentric Castleman disease associated with human Herpes virus 8 (also known as Kaposi's Sarcoma), Plasma cell variant. There are not currently specific treatment recommendations even though some drugs have proved useful, such as rituximab (Gerald L et al. Clin Oncol, 2007), etoposide, interferon alpha, and CHOP chemotherapy. Poor results are reported with ganciclovir (Casper C et al. Blood, 2004) or cidofovir. Neutralizing antibodyes against IL-6, which plays an important role in the pathogenesis of the disease, have shown encouraging results (Beck JT NEJM, 1994). The patient was therefore treated with highly active antiretroviral therapy and monoclonal antibobies directed against IL-6 with substantial clinical improvement in the first 2 months of treatment. Subsequent clinical evolution is unknown.

Abdominal pain and purple: the role of hepatitis HCV-related

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Case report: A 65-year-old patient was admitted for severe abdominal pain, with a history of fever (T_{max} 38.5°C) for a week and abdominal pain. He referred the same symptoms in the past, and a previous diagnosis of cryoglobulinemia and hepatitis HCV-related (cryoglobulinemia 14%). Last colonscopy showed hyperemia, edema, ecchymosis and histology demonstrated a flogistic lymphoplasmacellular infiltration. Since that diagnosi, the patient started therapy with mesalazyne (800 mg^2/day). On the admission in our unit laboratory examinations showed cryoglobulinemia: 10%, ESR 22 (v.n. 1–20), C_4 2.6 (v.n. 10–40), C_3 80.5 (v.n. 90–180), FR: 92.1 (v.n. 0–20). HCV RNA, urine culture, stool culture and blood culture were negative. Abdominal ultrasonography underlined splenomegaly, and a new colonscopy showed aspecific sygmoiditis. During the hospitalization the patient had a burden of abdominal pain, fever, diarrhea and purpuric manifestations at both legs. A corticosteroid therapy was started (Metilprednisolone 40 mg/day) with a subsequently improvement of the symptomatology and disappearance of the diarrhea. He was discharged with diagnosis of: Mixed cryoglobulinemia,

cryoglobulinemic enteritis, hepatitis HCV-related and therapy with Prednisone 10 mg, tapered to 5 mg after a week.

Discussion: We suppose that clinical features characterized by purpura, diarrhea and abdominal pain were related to a cutaneous and gastrointestinal cryoglobulinemic vasculitis, even if in the literature we could not find a clear evidence of enteritis cryoglobulinemia-related.

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Bone marrow findings in systemic lupus erythematosus

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A 43-year-old male patient, affected by no treated psoriasis, was admitted to our Department for symptoms started about 6 month before, characterized by a diffuse lymphadenopathy, slight evening fever, macrocytic anemia (Hb 11 g/dl, MCV 111,4 fl), leukopenia (WBC 2500/mmc; N 967/mmc; L 1007/mmc, M 428/mmc), platelet count at the lower limit of normal and ESR increased levels. There was no history of alcohol abuse, smoke and recent abroad travels. The physical exam was remarkable for bilateral lymphadenopathy in the cervical, supraclavicular, axillary and inguinal regions and for mild psoriasiform injuries on the back, both elbows and legs; the abdominal palpation showed a moderate hepato-splenomegaly. The rest of the examination was unremarkable. Laboratory exams on admission confirmed the haematological disorders and showed increased ESR and ferritin levels; iron, vitamin B12 and folate serum levels were normal. The protein electrophoresis revealed hyper-gammaglobulinemia, while urinalysis pointed out proteinuria. Thus, we investigated the most common causes of this clinical feature, considering infective, haematological and immunological etiology. A total body CT, effectuated to assess a systemic involvement, showed multiple gross nodal swelling in the neck, mastoid, mediastinic, axillary, all abdominal and pelvic regions; CT was negative for abnormalities of liver and biliary tract, pancreas, spleen, kidneys, urinary tract and pelvic organs. The axillary node biopsy revealed a reactive mixed-type lymphadenitis, characterized by follicular hyperplasia, with aspect of thrombotic microangiopathy, vascular hyalinosis, fibrinoid necrosis in the wall of some medium caliber vessels. An infection screen, including a panel for EBV, CMV, HBV, HCV, HIV and toxoplasma, was negative. A peripheral blood film showed a marked increase of mature monocytis with polymorphic pattern, rare mature intermediate stages of myeloid series, erythrocyte macrocytosis. Therefore a bone marrow biopsy was carried out and showed a gelatinous feature and hypercellularity, with a selective expansion of myeloid precursors, particularly myelocytes and promielocytes, blasts (1%), interstitial small lymphocytes CD3+ and CD8+ (5–10%) and monocytis (15–20%); dysgranulopoiesis and dyserythropoiesis; increase in megakariocytes; absence of iron store, not fibrosis. A FISH test, performed to detect chromosomal abnormalities, was negative. All these haematological disorders led to the diagnosis of a myelodisplastic syndrome (MDS), according to the Vienna Working Conference criteria. An autoimmune profile revealed ANA title >1/160 with homogeneous pattern, positivity for LAC and anti-platelet antibodies; ANCA, ENA, anti-DNAds, anti-cyclic citrullinated peptide, anti-cardiolipin, anti-phospholipid antibodies and rheumatoid factor were negative. The immunoglobulin dosage showed mild increased level of total IgG and IgA. C3 and C4 serum levels were normal and proteinuria was 393 mg/24 h. During hospitalization, patient developed a rash; a skin biopsy revealed epidermitis with acanthosis and hyperkeratosis, lymphocytic dermal infiltrate with plasma cells and apoptotic bodies with lichenoid pattern; there were signs of exocytosis and liquefying necrosis of some basal cells. Overall, finding accounting to a lichenoid subacute inflammatory reaction, compatible with autoimmune form. We conclude that our patient had an immunological disorder, strongly suggestive for Systemic Lupus Erytematosus(SLE)-like disease; infact skin and node biopsy findings, associated to bone marrow abnormalities, as well as dyserythropoiesis and dysgranulopoiesis, lymphocyte infiltrate, megakaryocytes increase and the gelatinous transformation are present in SLE; in our case we also found an unusual selective medullar expansion of myelocytes and promielocytes, with an increase of peripheral monocytes. MDS have been associated with Sjogren's symdrome, polymyalgia rheumatic, SLE and rheumatoid arthritis, but frequently in the advanced immunological disease. This is a rare case of immunological disease with an hematological onset associated to limphoadenopathy. The therapy with hydroxychloroquine (200 mg) improved clinical and laboratory findings.

A patient with diverticulitis and severe idiopathic dilated cardiomyopathy: a difficult therapeutic decision

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A 58-year-old man with idiopathic dilated cardiomyopathy was admitted to the Department of Internal Medicine because of lower abdominal pain, fever and diarrhea. The patient had a previous history of pituitary microadenoma, liver hemangiomas, an L2/L3 disc herniation with lumbosacral arthrosis, benign prostatic hyperplasia, erectile disfunction and an episode of acute prostatitis. Idiopathic dilated cardiomyopathy was diagnosed 8 years earlier and conditioned several episodes of acute heart failure requiring hospitalization. Six years after presentation of dilated cardiomyopathy, a biventricular ICD was implanted because of worsening heart failure (NYHA III); 1 year later he was included in the waiting list for cardiac transplantation. One year before presentation, a colonoscopic examination, performed because of lower abdominal pain, showed evidence of diverticulitis with stenosis of the sigmoid colon, in its middle third. Monthly cycles of treatment with rifaximin did not improve pain control. On admission the patient complained of pain in the lower abdominal quadrants that was exacerbated by right quadrant palpation. Symptoms of bladder irritation (stranguria and pollakiuria) with negative urine culture were present. A transabdominal bowel sonography showed a severe stenosing sigmoiditis with perivisceritis, which was suggestive of inflammation associated with diverticulosis; in the pelvis inflamed, aggregated ileal loops, with adjacent mesenteritis and contiguous abscesses, were observed. A rectosigmoidocolonoscopy showed diverticulitis and perivisceritis, whereas a CT scan confirmed the presence of pelvic abscesses. A broad-spectrum antibiotic therapy, including ceftriaxone, metronidazole and ciprofloxacin, was instituted and lead to improvement of the patient's symptoms. Although the NYHA III heart failure significantly increased the surgical risk, the patient underwent left hemicolectomy with latero-terminal colorectal anastomosis and

segmental resection of the abscess surrounding last ileal loop (which was stenotic and characterized by ileo-ileal adhesions). Peritonitis secondary to perforation of a colonic diverticulum was present. The postoperative course was regular despite persistence of low blood pressure (SBP 80–90 mmHg). Thus, surgery confirmed the ileal involvement that had been detected by ultrasonography, but missed by the endoscopic and abdominal CT examinations.

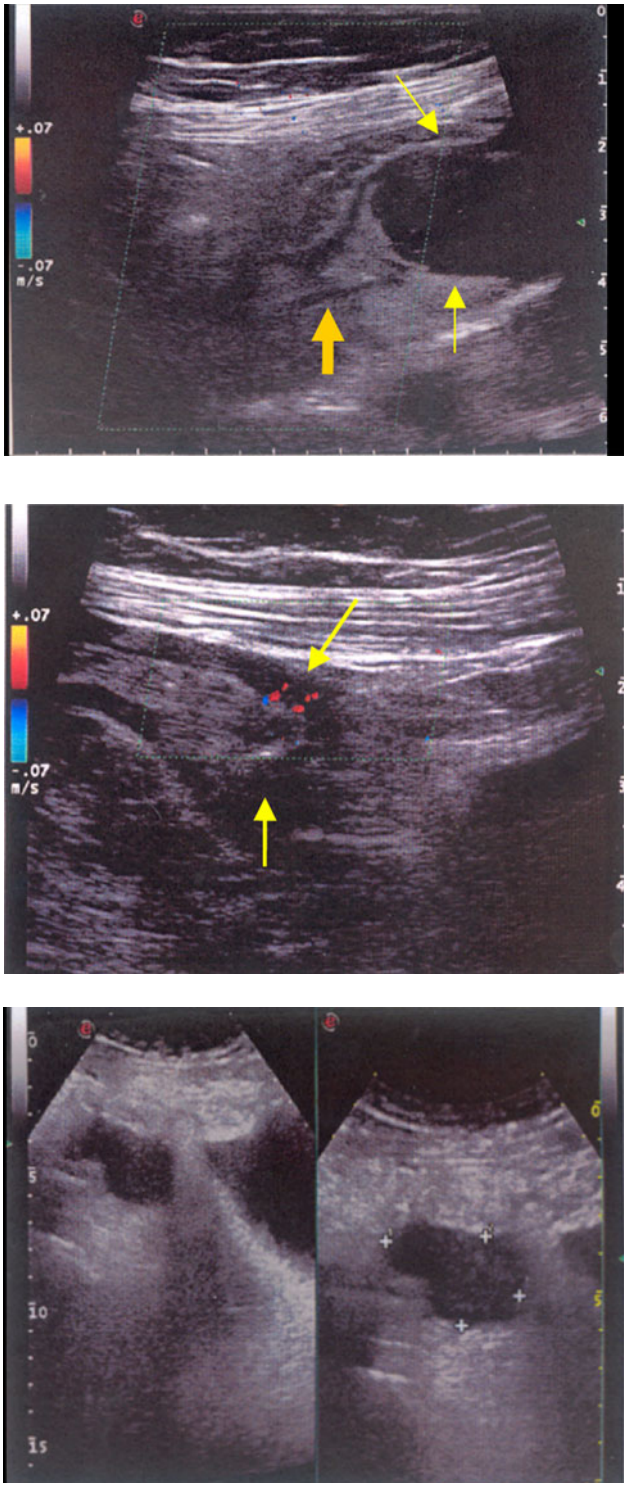

Figure a Large abscess (*thin arrow*) near inflamed ileum (*thick arrow*), **b** increased vascularization in sigmoid colon, **c** two abscesses in pelvis

The present case report shows how a high-risk patient with a diagnosis of large bowel diverticulosis was followed for approximately 1 year, because of fever and pain, without being investigated for the possibility of an extraluminal extension of the disease. The patient was correctly diagnosed following an accurate physical examination and non-invasive abdominal sonography. In this patient surgery was a high-risk procedure, due to the severe cardiac comorbidity. In our opinion, however, it was the only means that, through the complete resolution of the infectious foci in the patient's pelvis, could preserve the possibility of cardiac transplantation in the near future.

A case of botulism

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A 55 years old male patient, affected by metabolic syndrome (diabetes mellitus type II, arterial hypertension, hyperlipidemia, overweight) came to our attention for a worsening dysphagia since a few days. This symptom did not allow him having usual statins and oral hypoglycemic drugs. He was a former pipe smoker and he was also intolerant to aspirin and non-steroidal anti-inflammatory drugs (NSAD). Discussing with the patient we learned he had acute gastroenteritis 9 days before the recovery, complicated with temperature, diarrhea and vomit. These symptoms spontaneously remitted within 3 or 4 days. When he restarted feeding some symptoms appeared: dyplopia, bilateral palpebral ptosis, dysphagia for liquid and solid foods and xerostomy. At objective evaluation performed in Emergency Department patient was well oriented, eupneic but slowed down. Blood pressure was 120/70, cardiac rate was 60 bpm, respiratory rate was 22 min^{-1}, O_2 saturation was 93%, body temperature was 36°C and glycemia was 138 mg/dl. Physical examination showed mucocutaneous dehydration, whereas cardiac and abdominal inspection were normal. Pulmonary examination highlighted a harsh vesicular murmur with bilateral crepitations. Neurologic objectivity also revealed bulbar eye involvement with bilateral palpebral ptosis, diplopia in side vision, heavy dysphagia for liquid and solid foods. Laboratory findings showed an increase in Reactive C Protein-RCP value, hyperglycemia (240 mg/dl) and increased lactate. Hemogas analysis showed a picture of hypoxic-hypercapnic respiratory failure (pH 7.29, pCO2 40 mmHg, pO_2 60 mmHg, HCO_3 lower limits). The chest radiograph showed a modest framework of emphysema while the ECG and ultrasonography of the abdomen were within the limits (marked hepatic steatosis). The CT findings were negative for hemorrhagic lesions or ischemic in place. Radiography of the digestive system showed an incomplete coordination of oropharyngeal muscles. The patient was treated with glucose solutions buffered with intravenous insulin and potassium, low-flow oxygen therapy with restoration of metabolic control and improvement of respiratory exchanges. It is known that a clinical picture characterized by the presence of neurological involvement of peripheral bulbar or cranial nerves (oropharyngeal dysphagia, ophthalmoplegia, hypoxemia) in diabetic patients, with recent episode of infection, required to take into account several diseases for the differential diagnosis: ischemic brain lesions, central nervous system infections, intracranial tumors, myasthenia gravis, Guillain Barré syndrome, diabetic polyneuropathy or other etiologies. Cranial tomography allowed to exclude vascular damage or expansive intracranial lesions. The acute onset of a bulbar paralysis in the patient suggested to exclude diabetic polyneuropathy and myasthenia, since these diseases are known to have a slower onset and a progressive evolution. Also acute diabetic mononeuritis, which

typically produces diplopia in oculomotor paralysis, could be excluded because a sequential involvement of different cranial nerves was documented in this case. The set of clinical data pointed to an infective or post infective etiology of polyneuropathy. The anamnestic data of the recent gastroenteritis could suggest the Guillain–Barrè syndrome but had also led us to investigate the history of food intake: between the resolution of gastroenteritis and the occurrence of neurological signs, the patient had indeed taken a fortunately very small amount of food probably contaminated (preserved artichokes). Under suspicion of botulism intoxication the patient was moved to Neurology Department of Niguarda Hospital, where he underwent targeted examination such as lumbar puncture (Cerebral Spinal Fluid, CSF, negative for infection) and brain MRI, which excluded encephalitis. The Electromyography, EMG, showed a presynaptic neuromuscular plaque disease, compatible with botulism. The guinea pig inoculation of contaminated material confirmed the clinical suspicion of botulism. In the one hand the patient received artificial enteral nutrition via nasal gastric tube, in the other hand he got immediate treatment with botulinum antitoxin which resulted in a prompt improvement of clinical neurological and respiratory condition. Complete regression of neurological disorders was achieved in the 19th day of hospitalization.

Conclusions: Botulism is characterized by symmetric, descending, flaccid paralysis of motor and autonomic nerves, usually beginning with the cranial nerves involvement. Blurred vision, dysphagia and dysartria are common initial aspects. The diagnosis of botulism is based on compatible clinical history of exposure to suspected foods and supportive ancillary testing to rule out other causes of neurologic dysfunction. Disorders that mimic botulism include stroke, the Guillain–Barré syndrome and Myastenia gravis. Treatment consists of supportive care in addition to trivalent equine antitoxin, which greatly reduce mortality if administered early.

A difficult haematological condition

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We present the case of a woman, Mrs. SA, 74 years old, sent to our ward by the colleagues from the Department of Hematology, to investigate about thrombocytopenia, anemia and bleeding disorders, seen in blood tests performed for fatigue. In the Hematology ward a peripheral blood smear was immediately performed and it showed anisopoichilocitosi, schistocytes, metamyelocytes and myelocytes in the periphery; a bone marrow aspirate displayed an almost complete infiltration of bone by an atypical cell population. At the admission the patient was in good general condition and at the physical examination only some bruising at the medial thigh struck our attention. The blood tests showed microcytic hypochromic anemia (Hb 9 g/dl), thrombocytopenia (plt 47,000 μL^{-1}), elevated D-dimer (19.76 mg/L), decreased fibrinogen (Clauss 107 mg/dL, with VN 170-410), reduced PT% (59%, INR 1.33) and decreased protein C (60%, nv 70–120). Considered a such important hematological situation, which constituted a credible intravascular coagulation, we promptly put considerable problems both about therapy and in the research of a cause, since the only really useful therapy would have been causal therapy. The hypothesis that we considered were invasion of bone by non-hematologic tumoral cells or hemophagocytic syndrome developed after an infection or malignancy (the cells seen at the bone marrow aspirate could be compatible with macrophages that had invaded the bone, as it happens in this syndrome). In suspicion of hemophagocytic syndrome, we investigate viral infections, rickettsiosis and leishmaniosis. To search for possible malignancy, total body CT was performed in the first instance, given the severity of situation, especially bone marrow aspirate and blood tests and because of the absence of clinical signs that could lead to a diagnosis: this instrumental exam highlighted a possible lesion in the colonic and injuries of unclear nature in the liver. It was also performed a marrow biopsy in order to better characterize the cells. Meanwhile, the patient began to get progressively worse in terms of hematological features and coagulation (progressive reduction of fibrinogen and elevated prothrombin time) and proceeded to treatment with fresh frozen plasma and red blood cell transfusions. Numerous and widespread spontaneous bruising started to appear. We also investigated congenital defects of coagulation, given the extensive haemorrhagic component of the framework. After some days of hospitalization we received test results performed for infections, among which anti-rickettsial IgM were positive. Although rickettsiosis was not the most probable hypothesis, also for the possible false positive result, we decided to start treating with doxycycline and to send a new test at another center (Istituto Zooprofilattico) because in some cases rickettsia can cause a haemorrhagic picture and considering that the conditions of the patient were progressively worsening and we wanted to do all it was possible. After some days a negative result arrived. A few days later the patient underwent colonoscopy, which revealed a tumor in the right colon of about 10 cm in size, that caused a stenosis of the lumen. It was also performed abdominal ultrasound, which confirmed the presence of metastatic lesions in the liver. In the meantime we received the results of biopsies of bone marrow and colon, who confirmed that it was a little differentiated adenocarcinoma of the colon that had given the bone metastases. The patient had since gradually worsened with anemia up to 5.6 g/dL, despite the almost daily transfusions, thrombocytopenia until 2,000 μL^{-1}, subject to replacement therapy, and deficiency of coagulation; furthermore, from the standpoint of clinical onset, she started to present melena, hematuria and petechiae of the oral cavity. The hematological situation has been attributed both to the intravascular coagulation induced by tumor and to the infiltration of the bone and resulting gradual loss of function of it. It has been not possible to make any causal therapy, because of the hematological situation that prevented the implementation of any kind surgery (which was not indicated, given the advanced disease) and any type of chemotherapy. About 1 month after admission the patient died. We present this case because of the atypical presentation of the disease, that in the beginning put us several diagnostic doubts, as well as non-frequent bone metastasis of colon cancer, because of the therapeutic difficulties we encountered, especially related to having an inability to perform a causal therapy, and of the rapid progression of the disease, that had almost exclusively manifestation in hematological problems.

Hypereosinophilia and hepatitis C: two diseases? One therapy?

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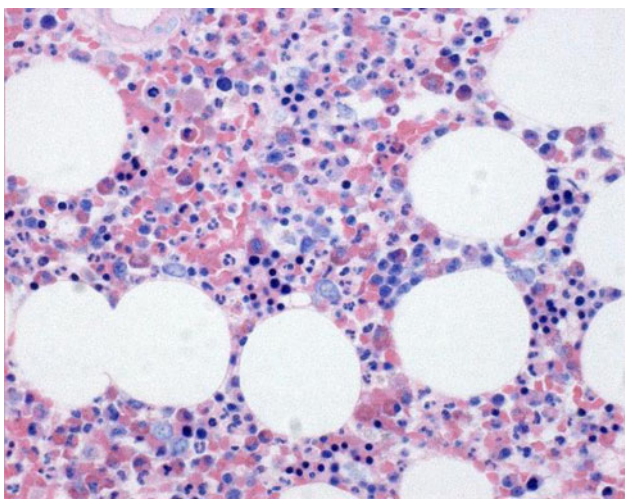
We report a case of a 59-year Italian man with a history of diabetes, sinusitis, hypertension, alcoholic abuse and sustained peripheral blood eosinophilia since 2 years. He presented to our hospital with progressive oedema and palpitations: heart failure and atrial fibrillation were observed and two-dimensional echocardiogram revealed a severe hypocinetic dilated left ventriculum (EF 25%). During hospital stay a progressive increase of liver enzymes and LDH was observed: hepatomegaly and ecstasy of superior caval vein were detected at ultrasound. After high-dose diuretic therapy, his body weight decreased by 17 kg and

liver enzymes normalized. Coronarography showed critical stenoses in two vessels but revascularization was postponed. Since a positive serology for HCV was reported, HCV RNA was quantified (>8 million units/ml), HCV genotype was typed (2 CV7875927) and liver Fibroscan was performed (15.8 kPa stiffness; F4). During hospital stay, peripheral blood eosinophils were 9.6 × 10(9)/l (60%) without itching, therefore different causes of persistent eosinophilia were searched: serial stool studies for ova and parasites and serology for Toxocara canis were negative, as were HIV serology and autoimmune workup; PCR analysis for FIP1L1-PDGFR apha rearrangement were also negative, as well for p210 and p190 BCR-ABL transcript. A bone marrow biopsy and molecular investigations were performed to rule out primary hematologic disorder: cellularity was 60% with marked increase in mature eosinophils (Figure) but no increased myeloblasts; mild fibrosis (grade 1) and rare interstitial CD20+ lymphocytes. The patient was dismissed and received wafarin, digoxin, enalapril, loop diuretics and insulin. In order to exclude organ involvement, 2 months later the patient underwent an endomyocardial biopsy, which did not reveal any eosinophil infiltrate, and, subsequently, coronary revascularization with drug-eluting stents was performed. No abnormality was detected at pulmonary function tests. In the meanwhile, bone marrow investigations showed and abnormal karyotype (47 XY + m in 3/12 mitoses); TEL-PDGFR beta and BCR-FGFR1 transcripts were not detected at nested PCR in marrow and peripheral blood; WT1 copies in marro blood were 35/10(4) ABL; no clonal T-lymphocyte population was detected in peripheral blood by polymerase reaction of TCR. Sonogram of the abdomen did not show splenomegaly. Due to the presence of a clonal marker, but absence of hystologically proved organ involvement, we could diagnose a chronic eosinophilic leukemia (CEL-NOS) according to 2008 WHO classification of hematologic malignancies. In order to limit the progressive increase of eosinophil count, the patient received a test course of oral prednisone at the dose of 1 mg/kg body weight, which resulted in a rapid increase, rather than the expected decrease, of the eosinophil count. Due to the severe hepatopathy and the mild HCV genotype, along with the therapeutic effect of IFN in chronic myeloid disorders, the patient was treated with peg-interferon alpha-2a 180 mcg weekly and ribavirin 1,000 mg daily. One month later the patients showed a 50% decrease of eosinophil count, mild thrombocythopenia [114 × 10(9)/l] and normalization of liver enzymes. An eosinophilic infiltrate of liver tissue was observed in 31% of patients with hepatitis C (Tarantino, 2008) mainly in patients assuming drugs. Moreover, HCV-RNA was reported in 40% of circulating eosinophils (Toro, 1999), but the role of hepatitis C virus in inducing clonal proliferation of eosinophils is still unclear. To our knowledge, only one prior case of concurrent hepatitis C and CEL-NOS was reported (Kamineni, 2006).



Renal failure, peripheral neuropathy, skin bullae and iron overload: how many rare diseases can occur in the same patient?

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We report the case of a 77-year woman, with hypertension, hypotiroidism, diabetes and coronaropathy, who had been diagnosed AL amyloidosis 6 years ago, when she showed peripheral neuropathy and renal failure: bone marrow was severily infiltrated by plasma cells, therefore melphalan and prednisone had been prescribed. Due to lack of response to melphalan, the patient received cyclophosphamide obtaining a complete marrow remission with persistence of increased serum IgA (6 g/l) and two mild IgG k and lambda monoclonal components along with a mildly hyperthrophic interventricular septum (13 mm). In the subsequent years the patient underwent three life-threatening infective episodes, but kept a good performance status. In October 2008 mildly elevated GPT and GGT were occasionally reported, therefore, the possible causes of hypertransaminasemia were investigated. Serology for hepatitis viruses was negative and the lipidic profile was normal, as well as ceruloplasmin. At sonography, the liver was enlarged and with an hyperechogenic texture. However, a markedly elevated serum ferritin was reported (3,602 ng/ml) along with an increased transferrin saturation (92%). Iron overload was not iatrogenic and could not be caused by amyloidosis nor by hemotransfusions, since the patient had received only 2 units of blood in her whole life. HFE mutations were, therefore, searched and liver was investigated by Fibroscan. HFE C282Y heterozygote mutation was detected (H63D, H63H V53 M, S65C, Q127H, Q283P, E168Q, E168X, W169X HFE and Y250X mutation of the transferrin receptor 2 gene were not detected) and a severe increase of liver stiffness was reported (17.3 kPa = F4 Metavir). An idiopathic hemochromatosis was therefore diagnosed and magnetic biosuscettometry (SQUID) was planned in order to quantify total body iron. In August 2009, however, skin bullae erupted onto the arms of the patient. Skin biopsy showed intradermic bullae. Urinary uroporphirin was increased (987 mcg/l) and fecal protopofirin were also increased (162 mcg/g dw). Porphyria cutanea tarda was therefore diagnosed. SQUID showed a markedly increased iron body content (178 mg/kg body weight) and a severe liver iron overload (2,885 mcg/g wet weight). Due to the severe organ iron overload, despite the old age of the patient, a therapy was planned in order to reduce body iron. Deferoxamine, which should be administered during overnight subcutaneous route, was not practical and prescription was limited by severe renal failure (creatinine clearance 25 ml/min). Deferiprone, an oral iron chelator, could not be prescribed due to the prior bone marrow disease and chemotherapy that predisposed the patient to agranulocytosis; moreover, there are no data available on the use of deferiprone in patients with renal failure. Deferasirox, a novel effective oral iron chelator, is contraindicated in patients with renal failure. The patient hemogram showed hemoglobin 12 g/dl, therefore, we decided to start the patient on bimonthly blood lets, which were expected to drive about 200 mg iron each. Porphyria cutanea tarda is a rare disease occurring in 1 out of 25,000 individuals, more probably in those with severe iron overload, often sustained by HFE mutations. AL amyloidosis is also a very rare disease. The forecasted probability that a second rare disease occur in a patient with AL amyloidosis is quite low but not null. The present, to our knowledge, is the only reported case of concurrent porphyria cutanea tarda, C282Y HFE mutation and AL amyloidosis. New oral iron chelators are quite effective but their use can be limited in old patients with comorbidities: blood lettings are still a therapeutic means to limit iron overload in non-anemic patients.

Hypokalemia: what else?

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A 17 year-old male presented to our Department of Internal Medicine at the San Salvatore Hospital of L'Aquila due to the acute onset of bilateral paralysis involving both the proximal and the distal muscles of the lower limbs. No respiratory or swallowing difficulties were evident. Patient was able to move his neck, the upper limbs and all of the facial muscles. No pain or paresthesia were present. On physical examination patient vital signs were stable, blood pressure was 110/70 mmHg, heart rate was 75 bpm. Neurologic examination revealed patient had a Glasgow Coma Scale = 15/15, flaccid paralysis of all extremities (involving both proximal and distal muscles). Deep tendon reflexes were very-slightly diminished. Cranial nerve function was grossly intact. Motor neurography revealed muscle membrane block induced by long exercise test, responsible for a reduction of composite muscle action potential amplitude. Routine haematochemical tests were all normal but serum potassium level was markedly reduced (2.9 mmol/L). In this latter regard, patient reported no recent episodes of vomit, diarrhea, diet or weight changes. Further, he did not take any medication, including diuretics, and was not a licorice abuser. Finally, he also denied the assumption of either alcohol or drugs. In contrast, patient reported a recent (3 months ago), transient episode of lower limb weakness. In our patient, we firstly corrected hypokalemia by intravenous potassium administration and observed the rapid disappearance of any neurological abnormality. After the exclusion of the most common causes of hypokalemia [serum thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), cortisol and aldosterone levels were all normal. Haemogasanalysis was also normal], we hypothesized an hypokalemic periodic paralysis and performed appropriate genetic testing. An autosomal dominant mutation p.Arg1132Gln of the SCN4A gene was found and the diagnosis of hypokalemic periodic paralysis type 2 was then made. This mutation accounts for approximately 8–10% of affected individuals, and results in an altered function of sodium channels with enhancement of both fast and slow inactivation as well as depolarizing shift of the activation curve, leading to membrane hypoexcitability, muscle weakness and hypokalemia. Thus, after patient discharge we prescribed acetazolamide (500 mg/day), spironolactone (50 mg/day), a low sodium diet rich in fruits and vegetables and daily potassium supplementation. We carefully recommended to the patient to increase potassium supplementation in the case of physical activity, increased sweating, fever, vomiting or diarrhea. By means of this approach, after more than 1 year no other episodes have been observed and serum potassium levels were always in the normal range. Our case report indicates that appropriate lifestyle changes and pharmacologic therapy can prevent both hypokalemia and paralysis due to the above autosomal dominant mutation. Of note, undiagnosed or untreated patients can manifest with an increased susceptibility to fatal ventricular arrhythmias. Thus, although it is a rare condition, hypokalemic periodic paralysis must be always suspected in unexplained hypokalemic episodes accompanied by even mild symptoms.

The past… sometimes returns

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A 61 years old male patient suffering from isolated and severe systolic hypertension came to our out-patients' department for a visit. He referred his disorder began 1 year ago and it has been treated with a progressive step up therapy. Although an antihypertensive multi-drug approach (ACE inhibitor-linisopril, diuretic-hydroclorothiazides, calcium-antagonist amlodipina and nitroglycerin on demand if systolic blood pressure >185 mmHg), patient reported an incomplete effectiveness of this treatment and the persistence of high systolic pressure values. The patient also was suffering from diabetes mellitus type II diagnosed from the age of 58 years under hypoglycemic therapy with methformine and glimepiride, hypercholesterolemia statin-treated, retinal thrombosis cured with ticlopidine and previous duodenal ulcer. In 1969 following an inquiry for the detection of juvenile arterial hypertension, he was diagnosed coarctation, corrected with successful cardiac surgery. For the subsequent 40 years the patient reported good health and controlled pressure values. We therefore decided to shelter him for rehabilitation and for investigation on diagnostic hypotheses: essential arterial hypertension in patient with aortic coarctation versus hypertension from recurrent aortic coarctation. After the recovery in Internal Medicine Department the patient appeared lucid, oriented, eupneic with a good hemodynamic compensation at clinical examination. The body structure was slightly discordant due to predominance of the upper limbs compared to pelvic girdle. Muscles trophism and cutaneous appendages were normal. Anterior chest auscultation revealed systolic diamond-shaped murmur 2/6 on all heart focuses, while on the back an important systolic murmur 3/6 could be heard in the interscapular region, with decreasing intensity downwards. The patient also presented a visible subscapular scar on the left side. The blood pressure values measured on both upper limbs were high (Blood Pressure, BP, 175/60 in clinostatism in both upper limbs, 175/70 in orthostatism), whereas systolic BP measured at the lower peripheral pulse was 80 mmHg. Laboratory findings were not defined as meaningful, including proteinuria, renal function appears within limits (MDRD Calculated GFR: 50 ml/min) while plasmatic renin activity and aldosterone were rather high. In order to assess staging of organ damage and to exclude secondary causes of arterial hypertension, the patient underwent Echocolordoppler of supra-aortic trunks, renal arteries and lower limbs that documented the widespread presence of angio-sclerosis without hemodynamically significant stenosis. The angiographic magnetic resonance imaging of the brain excluded circle of Willis aneurysms. The echocardiogram, apart from the already known hypertensive heart disease with preserved ventricular function, showed aortic root dilatation (40 mm) with normal-sized tubular ascending aorta tract (3.4 cm) and also descending aortic coarctation at the isthmus with maximum speed sampled up to 1.5 m/s. The most important examination was the angioTAC because it allowed for the recognition of anatomical regularity and size of the ascending aorta and its arch. In this case, the transition between aortic arch and descending aorta showed a change in size which stretched for more than 3 cm with a diameter of at least 9.7 mm. This anatomic deformity could be related to the outcome of known previous aortic coarctation surgery. After the stenotic tract the size of the descending

aorta was increased in a post-stenotic aneurysmal dilatation of 3 cm. The angioTAC also revealed mammary arteries ectasia, especially in the left one.

Discussion: The history of previous surgery of aortic coarctation, the presence of isolated systolic hypertension resistant to therapy, the objective proof of an interscapular murmur and a pressure differential between upper and lower limbs (excluding lower limb peripheral arterial stenosis), led us to consider recurrent coarctation. The angioTAC confirmed our hypotesis, already evident through other instrumental examinations such as echocardiography. The patient was suffering from Secondary Arterial Hypertension in recurrent isthmic coarctation likely due to a previous surgery scar, which could be treated either with cardiac surgery or radiological therapy. Considering the age of the patient and his previous cardiac risk the specialist suggested to go for radiological intervention.

Complications of HCV infection in HIV patient

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A 45-year-old man was admitted to our ward for the onset of asthenia and dyspnea which had begun about 7 days previous. For the last 25 years the patient has been treated with antiretroviral therapy for an infection of HIV. For the last year he has been affected by chronic renal failure. About 9 months ago he was diagnosed with a chronic HCV-related liver disease; therapy was begun with Interferon and Ribavirine, which was interrupted because of the onset of anemia. Upon admission to our ward clinical examination showed tachypnea and tachycardia with blood pressure of 160/95 mmHg, hepatomegaly and mild hepatojugular reflux. Laboratory tests revealed anaemia with Hb 11 g/dl and MCV 107 fl; serum creatinine was 1.62 mg/dl, BUN 21.5 mg/dl; albumine was 3.3 mg/dl. D-dimer was normal. EGA showed hypoxemia (pO_2 69 mmHg) and metabolic acidosis with a mild respiratory alkalosis (pH 7.37; pCO_2 24 mmHg; HCO_3^- 13.9 mmol/l). Electrocardiogram showed first degree AV block, incomplete RBBB and negative T waves in all precordial derivations; cardiac enzymes were normal. Urine analysis showed the presence of proteins (+++), while microscopic sediment revealed presence of red cells (10 pcm), white cells (2–5 pcm), white cell casts and granular casts. The 24 h urine protein content was of 4 g/24 h. The patient did not have pneumonia; the normal levels of cardiac enzymes excluded coronary diseases and a normal cycloergometry stress test ruled out coronary diseases. Due to the presence of coinfection by HIV and HCV and focusing on the long-term complications of HIV and the possible role of HCV as booster, we considered the hypothesis of hydiopatic pulmonary hypertension, pericarditis, myocarditis, pulmonary embolism or valves disease as cause of his symptoms. A transthoracic echocardiogram showed dilation of right atrium and ventricle, dilation of pulmonary artery and PAPS 90 mmHg and a cardiac catheterization confirmed PAPS 90 mmHg, in absence of modification after nitric oxide test. The ventriculography showed multiple aneurysms in the inferior part of left ventricle; the myocardial biopsies in proximity of these lesions gave histological response of "focal active miocarditis" with PCR positivity for HCV. The HCV-RNA showed the presence of an active viral replication with 2,000,000 gen/ml, while the dosage of cryoglobulinemia was negative. We started therapy with Sitaxentan, a new drug for the treatment of pulmonary hypertension; therapy with interferon and ribavirine was also begun. Regarding the chronic renal disease: a renal biopsy will be soon performed to assess the etiology of this disease, to evaluate if is secondary to HIV or HCV infection. Both myocarditis and pulmonary hypertension are complications of HIV infection (Sudano et al., American Heart Journal, June 2006; Lederman et al., AIDS, 2008), however the risk of contracting it is higher when HCV coinfects these patients (Freiberg et al., AIDS, January 2007; Tedaldi et al., HIV/AIDS, February 2003). The higher risk of myocarditis in coinfected patients is probably due to some mechanisms mediated by HCV: some of them could raise ROS concentration in the myocardial cell, others could act indirectly through involvement of B and T cells (Sanchez et al., Medical Science Monitor, May 2008). No data are available about the mechanism of HCV in developing pulmonary hypertension in HIV patients, but it is possible that HCV could raise concentration of growth factors and proinflammatory cytokines which are the cause of pulmonary hypertension in HIV patients (Lederman et al., AIDS, 2008).

A sudden tumor of the forearm during antibiotic therapy for infective endocarditis

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A 59 year old patient came to our observation after 4 months of persistent fever, associated with arthalgia, myalgia, and asthenia. Before being hospitalized, the patient was treated empirically with antibiotic therapy, but fever persisted. The patient's medical history was unremarkable, except for chronic prostatitis. Physical examination was negative save for a systolic murmur present on the cardiac apex. Body temperature ranged during the day between 37.5 and 38.7°C, heart rate was 90 bpm, respiration rate 20 min^{-1}, blood pressure 130/80 mmHg. The laboratory findings showed leucocytosis (neutrophils 10,440 mm^3), 1 h erytrosedimentation rate was 20, CPR 6.3 mg/dl, LDH 488 U/L, fibrinogen 693 mg/dl, sideremia 24 mcg/dl, ferritin 324 mg/dl. All the other blood parameters were normal. Chest X-ray was normal. Abdomen echography showed many liver angiomas and prostatic hyperplasia. Three initial blood cultures, taken 1 day apart, were positive for *Streptococcus bovis* and transthoracic echocardiography showed a vegetation on the anterior flap of mitralic valve, associated with a medium regurgitation. Bacterial endocarditis diagnosis was confirmed by transesophageal echocardiography. Antibiotic treatment for infective endocarditis was started with ceftriaxone (2 gm IV once daily), which had been shown to be active on the *S. bovis* isolated from the blood cultures. After a week of treatment, new blood cultures were negative, mitralic vegetation volume appeared to be reduced, and normalization of body temperature and inflammation markers were observed. Because of the well known association of S. Bovis infection with digestive tract disease, in particular with colon carcinoma, we carried out a screening colonoscopy: four masses were discovered with histopathologic proof of adenomatosis. Unexpectedly, 2 weeks after the beginning of ceftriaxone therapy, the patient developed a red painful palpable tumor on the anterior side of the left forearm, body temperature rose again. Quickly a forearm echography was performed: a $\sim$8 cm cyst with fluid content, in conjunction with the radial artery, was described. A second antibiotic was added (Gentamicin, shown previously to be active on the germ isolated from the blood culture: 1 mg/kg b.w. every 8 h). Laboratory data showed an increase of inflammation markers, with blood cultures negative for germs. After surgical advice, under echographic monitoring, a compression for 20 min of the forearm was applied twice, 12 h apart, to try to block vascular supply of the saccule. The result was unsatisfactory. The patient was then moved to a

surgical division, where diagnostic and therapeutic surgery was performed. During the surgery, a big clot came out after the incision of the brachial fascia; it was sterile at microbiological examination. The reason of blood extravasion was attributed to several lacerations present on different sides of radial artery. Then, the vessel integrity was reconstructed. During the following days, fever disappeared and all the laboratory markers returned to normal. After 4 weeks from the beginning of ceftriaxone administration and the 2 weeks of combined gentamicin treatment, antibiotic therapy was stopped. After waiting another week, without the appearance of any new pathologic finding, the patient was dismissed from the hospital. Since then, more than a year ago, he has been healthy. Since no trauma of the forearm was recorded during the treatment and no clinical or laboratory signs of autoimmune diseases were present, we think that the more likely explanation for the damage of the radial artery might be bacterial colonization of the vessel. We believe that, once the therapy was started, the vessel was sterilized, but the damage to the vascular wall had been already established. *Streptococcus bovi*'s infection is responsible for 27% of all bacterial endocarditis. A variety of complications, involving cardiac and extracardiac structures may occur: metastatic abscesses, mycotic aneurysm, osteomylitis, septic arthritis, etc. Lacerations of the radial artery have never been reported. Our case illustrates the need of an early diagnosis and treatment of *S. bovis* endocarditis in order to avoid chronic vascular inflammation and the onset of dangerous complications; moreover a careful clinical observation is suggested even when the clinical course seems to be devoid of adverse events.

Not only pneumocystis

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We describe the case of a 69-year-old woman with history of hypertension, diabetes mellitus type 2 and hypercholesterolemia, who came to our observation for the onset of fever and dyspnea; about a month before, this patient was admitted to our department, transferred from the intensive care unit for further details on a Pneumocystis carinii pneumonia and a contemporary episode of pulmonary embolism. Her medical history was started about 2 weeks before the admission to the intensive care, with the appearance of fatigue, poor appetite, evening fever (TA 37.5° C) with persistent non-productive cough. Because of the persistence of symptoms, the patient was first admitted to a medical ward, where blood samples were performed and evidenced the increase in VES (108 mm/1°h, PCR (14.2 mg/dL), mild iron deficiency anemia (9.8 g/dL), and neutrophilic leukocytosis. Therefore, the patient performed first chest X-ray and then chest CT with contrast which showed extensive parenchymal consolidation bilaterally, both in basal and in apical areas. As they suspected infectious lesions, they tried different antibiotic therapies (cefotaxime, clarithromycin, teicoplanin, imipenem, piperacillin + tazobactam, primbactam and fluconazole) without any benefit. The clinical conditions of the patient deteriorated rapidly for the onset of a severe respiratory insufficiency, so that she was transferred to the intensive care, where they found pulmonary embolism (CT pulmonary arteries) and identified the probable causative agent of pulmonary inflammatory infiltrates: Pneumocystis carinii, isolated in BAL after fiber-optic bronchoscopy. Once stabilized, the patient was transferred to our department for investigation and to pursue targeted therapy with sulphametoxazole and trimetropin, methylprednisolone and oral anticoagulants. Since Pneumocystis carinii pneumonia occurs almost exclusively in immunosuppression states, in the presence of cancer and in the HIV infection, we looked for all these risks factors with negative results. The clinical conditions and the radiographic outcomes improved completely with sulphametoxazole and trimetropin and corticosteroids. The patient was discharged in good general conditions, without fever and with an almost complete cleansing of areas of the inflammatory parenchymal consolidations and with the same entrance diagnosis of Pneumocystis Carinii pneumonia and pulmonary embolism made in the intensive care unit. We recommended to the patient to gradually reduce the corticosteroid dose until full suspension. A month after the discharge, the patient came back to our department for the reappearance of fever and dyspnea. Iin order to evaluate the acute exacerbation, we performed blood test that showed an elevation of inflammation biomarkers and a moderate leukocytosis (12,220 white blood cells). New chest Rx and chest CT with contrast were executed and pointed out bilateral diffuse areas of consolidation affecting the majority of lung segments without images related to pathological lymphnodes swelling. Since the worsening of the respiratory and objective conditions, assuming the recurrence of Pneumocystis carinii pneumonia, we practiced Bactrim therapy without any benefit for about 5 days waiting the opportunity to effectuate bronchoscopy with bronchoalveolar lavage to make etiological diagnosis. Just after the introduction of corticosteroids (60 mg methylprednisolone), there was a net, and suddenly striking improvement of the clinical and radiological manifestations. The BAL examination obtained with bronchoscopy did not isolate any pathogen, neither after cultural examination. Because of the impressive clinical and radiological improvement after the introduction of corticosteroid, we assumed that we were in front of Bronchiolitis obliterans Organising Pneumonia (BOOP) consequent to a Pneumocystis Carinii infection. Currently the patient is followed periodically in our Institute and she is now healthy.

Conclusions: This case is very interesting for two reasons: the first is that it is very unusual the occurence of Pneumocystis carinii infection in the immunocompetent patient and the second reason is the consequent onset of a clinical condition, BOOP, which was confused with a relapse of the infective disease, causing a delay in the diagnosis and in the treatment: it has endangered our patient's life. The clinical syndrome "Bronchiolitis obliterans Organising Pneumonia" (BOOP) has to be considered in patients with a flu-like illness since some weeks, fine crackles, and chest X-ray on bilateral patchy infiltrated not responsive to antibiotics.

Hypocupremia: an under recognized cause of peripheral neuropathy

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A 47 year-old woman was admitted to our Division of Internal Medicine because of 1 year history of severe weakness, cramping pain to the lower limbs and right upper limb, bradykinesia, and strong restriction of normal daily activities. These symptoms were associated to xerophthalmia, xerostomia and dysphagia (solid foods). Apart from the above, both personal and familial medical histories were not significant. On examination patient blood pressure was 110/70 mmHg, heart rate was 76 bpm. Neurologic

examination revealed a Glasgow Coma Scale = 15/15, positive Romberg's test, fasciculations to the upper limbs, muscular hypotrophy, power reduction (particularly at the lower limbs) and limitation in deambulatory ability. The remaining examination was unremarkable. On admission, laboratory tests showed thrombocytosis and low uric acid serum levels. Fasting glycemia, electrolyte, creatine phosphate kinase, lactic dehydrogenase, inflammation indexes, and myoglobin levels were all normal. Firstly, we investigated the most common causes of similar clinical conditions, considering neurologic, infective, immunological and metabolic etiologies. Briefly, brain and cervical spine magnetic resonance and lower limb muscles electromyography with edrophonium test were all negative. Muscular biopsy showed minimal signs of neurological chronic injury. Laboratory tests excluded EBV, CMV, Borrelia burgdorferi and other infections. Immunological screening was also negative for any autoimmune condition. Serum levels of thyroid hormones, ACTH, cortisol, vitamin B12 and folates were also within the normal range. Based on these clinical and laboratory findings, we searched for the rare causes of such syndrome and found low serum levels of both copper and ceruloplasmin. As is known, copper is a component of numerous metalloenzymes and proteins that have a key role in maintaining the structure and function of the nervous system. Because of its wide distribution in foods and low daily requirement, a copper deficiency due to an inadequate diet is rare. However, an acquired copper deficiency can occur in premature and malnourished infants, in parenteral nutrition without copper supplementation, in patients with malabsorption and kidney diseases and as a complication of zinc, penicillamine and/or alkali administration. The most frequent copper deficiency manifestations are the haematological disorders, particularly anemia and neutropenia. These disorders are rarely associated to thrombocytosis. In the past few years the neurological manifestations have been also recognized, the most common of which is myelopathy with sensory ataxia. Our patient did not show signs of malnutrition, malabsorption and other possible causes of copper deficiency. She had not taken medications that might interfere with the copper metabolism. Although it was not possible for us to evaluate serum zinc levels, this metal is known to be contained in food supplements, toothpaste and fixatives, soaps, body and hair creams. A more accurate investigation found in our patient the long-lasting daily abuse of personal care products (as skin cosmetics). In particular, the body cream largely and daily used by the patient contained significant amount of zinc. Thus, although we had no definitive proofs about possible zinc intoxication, the patient was advised to reduce the use of these cosmetics to normality. Further, oral copper supplementation was started. Within 3 months all symptoms completely disappeared. All laboratory tests returned to normal levels and, after 1 year, patient is completely healthy. Thus, we concluded for a syndrome of copper deficiency of uncertain origin (according to different reports describing no apparent causes for the observed copper deficiency). In particular, in our patient the copper deficiency was responsible for no overt neurological disease with unusual hematologic manifestations and rapid response to replacement therapy. Although we have not the possibility to evaluate serum zinc levels, neither in our lab nor in other labs that we contacted by phone or e-mail, we strongly suspected the cause of transient copper deficiency was zinc accumulation, in turn due to long lasting abuse of zinc-containing cosmetics.

Fever associated with psychomotor retardation in a middle-age man

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A 53 year-old Egyptian man was admitted to our department for fever started 1 week before, associated with psychomotor retardation and mutacism. The patient past medical history was negative, except for a previous depressive episode. Medical examination revealed the presence of resting tremor, together with myoclonic seizures characterized by contractions of limb and face muscle groups, and a single diffuse erythematous skin lesion on the back. Laboratory tests showed normal white blood cell count with relative lymphocytosis and normal levels of inflammatory markers. Plasma electrolyte levels were also normal. We started empirically piperacilline/tazobactam and performed a computed tomography (CT) scan of the head that revealed a hyperintense lesion in the left subcortical occipital area and a limited hypodensity of the left parietal white matter. Conventional T2-weighted magnetic resonance imaging (MRI) technique showed increased signal of white matter in the parietal lobes. EEG was abnormal because recordings from the parietal electrodes demonstrated slow lateralized activity. Since the clinical features and the EEG pattern suggested the diagnosis of encephalitis, acyclovir 10 mg/kg three times daily intravenously was started without improvement. Immediately after, the examination of the cerebrospinal fluid (CSF) confirmed the presence of an inflammatory disease of the CNS, with elevated leucocytes, elevated protein and glucose concentration. Serum Western Blot examination showed the presence of IgM antibodies to Borrelia burgdorferi. Thus, we started antibiotic therapy with doxicycline obtaining rapid defervescence and resolution of psychiatric/neurologic signs. *B. burgdoferi* encephalitis is a very unusual clinical condition. Lyme disease affects the nervous system in about 10% to 15% of infected individuals. Neurologic features of early disseminated Lyme disease may include acute neurologic abnormalities, such as meningitis, cranial neuropathy, and motor or sensory radiculoneuropathy. CNS involvement is rare, but patients may present with myelitis or encephalitis. Clinical manifestations like confusion, cerebellar ataxia, opsoclonus–myoclonus, ocular flutter, apraxia, hemiparesis or Parkinson-like symptoms have been associated with B. burgdorferi infection. Poliomyelitis-like syndromes and acute stroke-like symptoms caused by cerebral vasculitis have been documented only in single case reports.

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Weber–Christian disease accompanied by hepatic steatosis: a case report

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A 67 year old woman was admitted to the hospital because of episodes of elevated fever (38°–38.5°), occurring almost every week for a year. In the previous week a vescicolar-pustule-erythematosus-type skin damage occurred. It was located on the back, abdominal region and lower limbs. The case history highlighted mastectomy and radiotherapy for breast cancer, arterial hypertension, type 2 diabetes. Moreover, 3 years before, she underwent draining of fluids from the left kidney area. Besides, one year ago she was diagnosed with cryptogenic liver cirrhosis. A CT scan of the abdomen, demonstrated blurred areoles with concentrated subcutaneous fat deposits located on the right side of the belly button and in the sacral region. The patient was being treated with betablockers, furosemide, spironolactone and insulin analogues. Upon admission she had fever (38.4°), her blood pressure was 120/80 mmHg and her heart rate was 80 min^{-1}. Physical examination showed vescicolus-pustule type skin damage localized on her back abdominal region and thighs and other reddish lesions with apparent infiltration on the lower limbs. Laboratory results showed normal liver and renal function, increased inflammatory proteins (ESR: 67, PCR: 26.5 mg/L). AFP and ferritin levels were normal, neoplastic markers and cryoglobulinemia were negative. A dermatological evaluation made the diagnosis of "nettle rash on the back and suspicion of panniculitis of the lower limbs". Therefore, a skin biopsy of the thigh was performed. Meanwhile, the patient was further investigated in order to detect the origin of the fever: culture examination for bacteria were negative, dosage of procalcitonin was within the normal range, intradermal reaction with PPD was negative, dosage of AMA, ASMA e anti-LKM antibodies were negative, dosage of complement, of immunoglobulins, ENA, ANA, ANCA and LAC were negative. Infectious diseases were excluded and haematological evaluation excluded haematological problems. Echocardiographic examination, thorax CT scan, abdominal ultrasound and PET, bone scintiscan excluded infections or neoplastic lesions. Abdomen ultrasound however demonstrated the presence of hypertrophic cirrhosis with splenomegaly and an liver biopsy showed an evolved NASH. Cutaneous biopsy demonstrated the presence of a "mixed cellular infiltration represented by small lymphocytes in the perivascular areas, both in the dermal surface as well as in the deep strata". The subcutaneous adipose tissue showed the presence of "steatonecrosis with wide lymphocytes, mostly centrolobular; a lymphoid population infiltrates vessels' wall without clear vasculitic features. The morphological pattern may be ascribed to lobular panniculitis. There are not elements that could be referred to as erythema nodosum". Subsequently, we tried to define the type of panniculitis. Clinical classification of panniculitis include: rheumatologic disorders, dermatologic disease, infections, malignancies and the idiopathic panniculitis or Weber–Christian disease (inflammatory disease of adipose tissue, characterized by cutaneous nodules associated with other symptoms such as fever, arthralgia and myalgia). A further clinical evaluation excluded al the previously mentioned causes of panniculitis except for idiopathic panniculitis (Weber–Christian disease). The syndrome presents with a high level of ESR, anemia, leucocytosis or leucopoenia and, occasionally, thrombocytopenia. Some patients can also show hypocomplementemia with low level of IgM. Patients have subcutaneous nodules located on the extremities; other frequent areas are the back, abdominal area, buttocks, breasts and face. These nodules could also be located in the abdomen (as abscessual lesions) or could involve mesentery of the small or large bowel with possible obstruction. An hepatic involvement under the form of a steatonecrosis can also be present. Panniculitis is typically lobular, even if it can also be septal. Other histological characteristics include mononuclear or pleomorphic cellular infiltrate with fat laden macrophages and varying degrees of small vessels vasculitis. Our patient presented all the previous characteristics and it's highly probable possible that the pararenal abscess could be regarded as the first manifestation of the disease. She was treated with prednisone 10 mg/day associated with hydroxychloroquine 200–400 mg with a rapid disappearance of the fever, improvement of symptoms and disappearance of the skin nodules. The patient has been followed long term, with persistence of well-being.

What does dyspnea hide?

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In December 2009, a previously healthy 48 year old man was admitted to the emergency department complaining of worsening dyspnea. He had a history of alcohol and tobacco abuse (more than 20 cigarettes/day). He denied use of any medications. Mild dyspnea and fever (TA 39°C) acutely began 3 weeks before. Fever solved without any therapy in few days and the mild dyspnea persisted. Ten days prior admission, dyspnea was still ongoing and an isolated hemoptysis occurred. At Emergency Room, the patient presented overweight, afebrile, diaphoretic but not cyanotic. His blood pressure (BP) was 220/120, heart rate 120 bpm, respiratory rate 35 breaths/min. On chest examination normal lungs breath sounds and a 3/6 heart systolic murmur were heard. ECG showed sinusal tachycardia, RBBB and S1-Q3 pattern. Room air ABG analysis showed pH 7.47, pO_2 57 mmHg, pCO_2 33 mmHg, HCO_3 25.4 mmol/L, SaO_2 93.4%. Laboratory tests were normal excepted for WBC count 10.200 mmc^{-1} ($N = 80\%$), C-RP 1.31 mg/dL ($nr < 0.5$), creatinine 1.4 mg/dL, K 3.0 mEq/L, LDH 493 U/L ($nr < 480$), D-dimer 438 ug/mL ($nr < 250$). Under suspicion of pulmonary embolism he underwent a CT chest scan. Bilareral diffuse ground glass shadows and bilateral pleural effusion were seen. No emboli were observed and an interstitial pneumonia was hypothesized. He was started with oxygen therapy and empirical wide spectrum antibiotics. Because of his severe hypertension, he was promptly started with nitroglicerine ev. After 48 h his BP was still 180/100 and secondary hypertension was ruled out by normal findings of renal artery doppler US, plasmatic catecholamine and renin aldosterone dosage. Echocardiogram showed left ventricle severe hypertrophy, mild pulmonary hypertension, severe mitralic and moderate tricuspidalic failure. Slight pericardial effusion was described. Molecular test for H1N1 and HIV Ag/Ab detection were negative. Urinary Ag-detection and blood tests for common atypical pneumonia pathogens were negative. Serological tests for *Aspergillus* spp., CMV, EBV, ECHO virus, Coxsackie, Adenovirus, Parvovirus were negative for acute infection. At the end, patient was again asked for illicit agents use and he finally declared to be an habitual daily cocaine "sniffer" since he was 40-years old. Hence, acute crack lung syndrome was recognized out of the most common presentation signs and symptoms: cough with sputum production (61% of cases), dyspnea (44%), hemoptysis (6–26%), interstitial pneumonitis or fibrosis (38%). The latest findings

indicate frequent aspiration of adulterants in the smoked mixture. Fever and hypoxiemia are also reported. Although 25–60% of crack users presents respiratory symptoms after using the drug, few of them seek emergency treatment. As in our case, the most common CT findings are interstitial opacities with a diffuse micronodular pattern, ground-glass attenuation, with or without pleural fluid. Diagnosing drug-induced diseases still remains a challenge for clinicians and radiologists: it should be noted that many users initially deny using illicit drugs. The cocaine vasoconstrictive effect on the pulmonary vasculature can mimic a pulmonary embolism; its potent sympathomimetic action activates endothelium, inducing damage to capillary endothelium, determining either pulmonary hypertension or severe systolic hypertension. Myocardial ischemia and infarction could be found also in absence of chest pain. Indeed, pain could be hidden by adulterants (lidocaine, benzocaine) commonly used to cut cocaine. In order to prevent myocardial ischemia, coronary evaluation and administration of appropriated medications are advised. Our patient presented common complains such as severe systolic and pulmonary hypertension. Coronarography showed no coronaric stenosis, but BP levels normalised only after he was treated with association of diuretics, sartanics, beta-blockers, Ca-antagonists and alpha-litics. Systemic corticosteroid therapy for interstitial pneumonitis is still debated, even if the lung injury may respond when it a prominent inflammatory cell infiltration is present. Follow-up of these patients demonstrate that despite discontinuation of drug abuse, interstitial fibrosis progresses, with development of respiratory insufficiency and significant mortality. Establishing a diagnosis of crack lung has important diagnostic and therapeutic implications: it must be kept in clinicians' mind, especially for acute dyspnea differential diagnosis in the emergency setting.

Spondylodiscitis and infectious endocarditis: a round-trip to be considered

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A 57 year-old man affected by type 2 diabetes mellitus was admitted to our Division of Internal Medicine because of a recent history characterized by transient acute increments of body temperature (even up to 38–39°C) and sub-continuous low back-pain. Patient reported also a septic arthritis of the knee in his recent past, due to acute septic arthritis. Physical examination showed severe low back-pain. In addition, rubor, tumor, calor and functio laesa were present at the anterior third of the left foot. Erythrocyte sedimentation rate and C-reactive protein levels were markedly increased. Blood culture was positive for Enterococcus faecalis on repeated occasions. The throat swab culture was positive for *Streptococcus pyogenes* without significant increment of the antistriptolysine title. Magnetic resonance (MR) imaging showed a D9-D10 spondylodiscitis. Transthoracic echocardiogram was performed and showed left atrial dilation, mitral valve sclerosis with thickening valve leaflets, a moderate mitral valve regurgitation and a vegetation of 0,4 cm^2 on the anterior mitral valve. Global systolic function of the left ventricle was normal. As a consequence, patient was treated with imipenem/cilastatin 500/500 mg 4 times per day and teicoplanin 400 mg once daily. Lysine acetylsalicylate and tramadol hydrochloride were also given. A marked improvement of the general patient condition and laboratory abnormalities was observed within 2 weeks, including the disappearance of inflammation at the left foot level. Repeated transthoracic and transesophageal echocardiograms revealed the progressive regression of the vegetation to 0.2 cm^2. MR was repeated after 1 month and excluded the evolution of spondylodiscitis. The last MR and laboratory controls (at 6 months) showed an almost complete resolution of all abnormalities. Patient is currently in good general condition. Infective endocarditis in association with spondylodiscitis is not frequently observed: in retrospective studies only from 0.6 to 2.2% of patients with established spondylodiscitis had infectious endocarditis, while from 10 to 15% of patients with established endocarditis diagnosis had a screening for suspected spondylodiscitis. Infectious discitis caused by enterococci are also uncommon and few cases have been already reported in the literature. Enterococci are implicated in 5–20% of infective endocarditis and commonly occur in patients with intravascular, intra-abdominal and/or urinary devices and/or (as in our patient) after septic arthritis and wound infections. The other common predisposing factors are male gender, diabetes mellitus, age > 50 years, immunosuppressive drugs, surgical/invasive procedures, hospitalization for more than 3 weeks and use of broad-spectrum antibiotics. Usually, patients manifest with moderate to severe low-back pain, exacerbated by movements, with radiological evidence of septic discitis and/or vertebral osteomyelitis. The most common localization is the lumbar region (prevalence of about 70%). Early diagnosis is done by MR. Quoad vitam prognosis mainly depends on heart localization and correct antibiotic therapy. We conclude that the association of spondylodiscitis with infectious endocarditis should always be suspected in predisposed individuals with low back pain and fever of uncertain origin.

Brodifacoum intoxication: a case report

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Case presentation*:* A 66-year-old man was admitted to hospital because of syncope and anaemia. On physical examination he presented bilateral knee haematic effusion, swelling and an extensive haematoma of his left forearm and hand and some widespread ecchymosis. At the admission laboratory, tests showed normocitic anaemia and elevated INR and pro-thrombin time values. In the following days the patient was treated with fresh-frozen plasma transfusion and vitamin K, with consequent normalization of PT and INR values. During a previous admission to another hospital a deficiency of vitamin K-dependent coagulation factors was found. Consequently, a treatment with vitamin K by oral administration was started. When he was admitted to our hospital he had just stopped vitamin K assumption.

Differential diagnosis*:* The patient did not have a history of genetic coagulopathy and was not taking any anti-coagulant therapy. Moreover, he had normal liver function and diet which, in particular, did not show a deficient vitamin K assumption. Hence, we hypothesized an intestinal malabsorption or an accidental assumption of warfarin or related compounds. Digestive endoscopy, anti-transglutaminase and anti-endomisium IgA dosage allowed us to exclude a malabsorption form. On the other hand the patient was positive for brodifacoum exposition, a superwarfarin pesticide.

Conclusions: Brodifacoum has a longer half-life and a greater potency compared to warfarin: it can cause a more intense inhibition of epoxide reductase with a subsequent greater deficiency in the regeneration of active vitamin K, thus resulting in a prolonged deficiency of vitamin K-dependent coagulation factors.

An unusual presentation of sarcoidosis

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We herein report the case of a generally healthy 40-year-old woman came to our attention complaining a 2 months history of low-grade fever, arthralgia and pretibial red and painful nodules. Prior NSAID treatment did not affect the symptoms. At the presentation, the patient had prominent erythema nodosum, consisting of bilateral tender nodules on the anterior surface of the legs, affecting the lower anterior shins. Complete blood count, measurement of kidney and liver function tests, rheumatoid factor and angiotensin converting enzyme were within the normal range. Erythrocyte sedimentation rate was elevated at 40 mm/h. C-reactive protein level was 1.85 mg/dl. Chest radiography and computed tomography showed bilateral hylar adenopathy and nodular shadows. Pulmonary function study indicated normal respiratory functions. Bronchoscopy revealed a submucosal network formation of capillary vessels in the bronchi. Bronchoalveolar lavage fluid showed a slightly lymphocytosis, mostly CD103− (CD103+/CD4+: 0.12) and a high CD4+/CD8+ cell ratio (5.3, normal range 1–2.3). Sarcoidosis is a granulomatosis multi-system disorder of unknown causes with a variable presentation and clinical course. Any systems can be affected, most commonly lungs (90% of cases) and skins (30% of cases). In the present case, based on symptoms as well as laboratory and imaging tests, we diagnosed a variant of sarcoidosis known as Lofgren's syndrome, an acute form of the disease characterized by a combination of low-grade fever, arthritis/arthralgia, erythema nodosum lesions and abnormal chest imaging showing hilar lymphadenopathy. Erythema nodosum is common but not specific symptom and is usually predictive of a milder, transient form of the disease. The conditions tends to be transient usually remitting within 3–4 months with or without anti-inflammatory therapy. The patients received a course of prednisone and her symptoms progressively resolved within 6 months.

Vanishing acoustic shadows

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A 80 years old man sought medical care after 2 days of lower abdominal pain and vomiting. Physical examination revealed diffuse abdominal tenderness to all quadrants, with no signs of peritonitis or constipation and a normal peristalsis, and conjunctival jaundice. He denied fever in the past days. Laboratory findings showed leukocytosis with neutrophilia (14.810 WBC per microliter, N 90%), hyperglicemia (331 mg of glucose per deciliter), slight increase of serum creatinine levels (1.40 mg per deciliter), hyperkalemia (5.4 mmol per liter) and marked increase of C-reactive protein (144.3 mg per liter). All other exams were unremarkable. Ultrasonography showed the presence of air in the bile ducts with biliary sand and small calculi in the gallbladder. He had a medical history of diabetes mellitus type 2, hypertension and benign prostatic hypertrophy. He was discharged 10 days before from the General Surgery Unit, after he was diagnosed acute pancreatitis associated with biliary lithiasis and treated with endoscopic retrograde cholangiopancreatography sphincterotomy. A CT scan performed before being discharged from the surgical ward showed large gallbladder calculi. The patient was waiting to undergo a routine cholecystectomy. The differential diagnosis taken into consideration at this time was acute cholecystitis, biliary colic, a second episode of pancreatitis (maybe related to the ERCP). On this basis we decided to investigate further with a magnetic resonance cholangiography, that could not be performed because of an episode of supraventricular tachycardia (SVT; 180 bpm) and hypotension (80/40 mmHg) which was successfully treated with intravenous adenosine. On the next day the clinical conditions of the patient were quickly worsening, with laboratory studies showing renal failure and a electrolyte imbalance, despite proper intravenous supplementation. The patient suffered of recurrent episodes of symptomatic SVT that would spontaneously settle. The physical examination remained unchanged, except for an absent peristalsis. An abdomen X-ray that showed a few fluid levels in upper quadrants. A nasogastric tube was put in place with the immediate evacuation of a large amount of gastric content. A new abdominal CT scan showed the presence of a cholecysto-duodenal fistula through which two large calculi (>2.0 cm diameter) migrated into the ileum, and the smallest one got stuck in the ileocecal valve, causing a biliary ileus. The patient was then transferred to the Surgery Unit to sustain an urgent operation. The two calculi were removed and the small intestine was decompressed; the fistula was sutured and cholecystectomy was performed. The patient recovered well, with no post-surgery complications. He had no more episodes of tachyarrhythmia, that may have been stimulated by the intense pain and vagus nerve activation due to gastric dilation. Should we have suspected a bowel obstruction sooner, on the first day? A literature reviews show that biliary ileus is a rare complication (1%) of gallbladder lithiasis, but it's more likely to happen if there are stones bigger than 2 cm diameter like in our patient: guidelines recommend to perform cholecistectomy immediately in cases as such. The duodenum is usually the most common site of fistulization, counting up to 80% of all complications, followed by cholecysto-colic fistula. The most common radiological signs of gallstone ileus are fluid levels and aerobilia (due to fistulization). We think that anamnestical history of large biliary calculi left in place for a long period of time and the presence of acute abdominal pain and vomiting should bring into consideration biliary ileus, especially if we can find air in the bile ducts with an echo scan. Such diagnosis should be considered because even if this condition is rare, mortality and morbidity are high. Early diagnosis and treatment usually improve the outcome.

A 69-year-old man with multiple basal-cell carcinomas and massive hydrocephalus

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In March 2007, a 69-year-old retired bank clerk was admitted into hospital for left calf deep vein thrombosis; he had been bedridden for over a year after a fall causing a lumbar vertebral fracture. Over the same period of time, he had developed increasing lower limb rigidity, apathy and worsening cognitive

performance: his wife reported that he was no longer able to baby-sit the grandchildren as he used to. His previous medical history included cisternoventriculostomy for benign aqueduct stenosis (aged 7), neurosurgery for right parietal meningioma (aged 48), multiple basal cell carcinomas of the scalp requiring repeat skin grafting, fibrosarcoma of the left shoulder, mycosis fungoides. On examination, his left calf was oedematous and painful. He was orientated and cooperative but slightly slowed; he had some degree of frontal bossing and macrocephaly, lower limb rigidity with adductor muscle spasticity ('scissor legs'); he was unable to recognise objects with his left hand in the eyes-closed condition (left hand tactile agnosia). He had three skin lesions compatible with basal-cell carcinoma on his scalp and forehead. Heart/lung/abdominal examination were unremarkable. He was treated with low-molecular weight subcutaneous heparin. Given the medical history and the clinical features, nevoid basal-cell carcinoma, or Gorlin's syndrome (1), was suspected and confirmed by the presence of hydrocefalus and extensive calcification of the falx cerebri on CT (Fig. 1). Cerebral MRI (Fig. 2) revealed the presence of aqueductal stenosis and the patient was referred to neurosurgery for potential third-ventriculostomy. The patient declined neurosurgery and plastic surgery for the newly diagnosed basaliomas but accepted testing for germline mutations associated with Gorlin's syndrome (genes PTCH1, SUFU), which were negative on sequencing; PTCH1 was negative also on multiple ligations probe analysis. His neuropsychiatric and neurological condition continued to worsen; he developed incapacitating rigidity and dysphagia and eventually died in July 2009. Gorlin's syndrome is a rare autosomal dominant genetic disorder with high penetrance and variable phenotype; in consequence, up to 30–50% of patients are not aware of the presence of the disease within the family. The syndrome is caused by mutation of PTCH1 gene in the majority of cases; more recently, SUFU germline mutations have been described in one family [2]. The diagnosis is based on the presence of two major or one major plus two minor clinical criteria [3]; the demonstration of known mutations is not required. A number of congenital malformations, skeletal abnormalities and neoplasms have been associated with the syndrome but are not formally recognised for purposes of diagnosis [4]. In our patient, the diagnosis was based on two major (multiple basal cell carcinomas and calcifications of the cerebral falx) and one minor (macrocephaly) criteria. The case is of particular interest for two reasons: (a) despite considerable hydrocephalus and cerebral atrophy, most likely of long standing, the patient had lead a substantially normal life, managing to complete high school, to have a family and to keep his job up to retirement; (b) the diagnosis was made, as in a similar case reported recently [5], in old age. Internists and radiologists should be alert to the possibility that Gorlin's syndrome, once a paediatric interest, can become apparent later in life, with an extremely diverse phenotype. Even at this stage, diagnosis is crucial both in terms of management (i.e. basal cell carcinoma monitoring and treatment) and genetic counselling of the offspring.

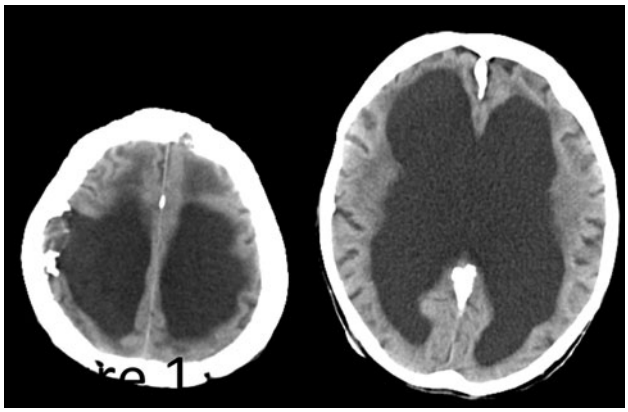

Fig. 1 Axial CT image without contrast showing a parietal scull breach due to previous meningioma removal, with parietal calcifications, and extensive calcifications of the tentorium, one of the major criteria for diagnosis of Gorlin's syndrome

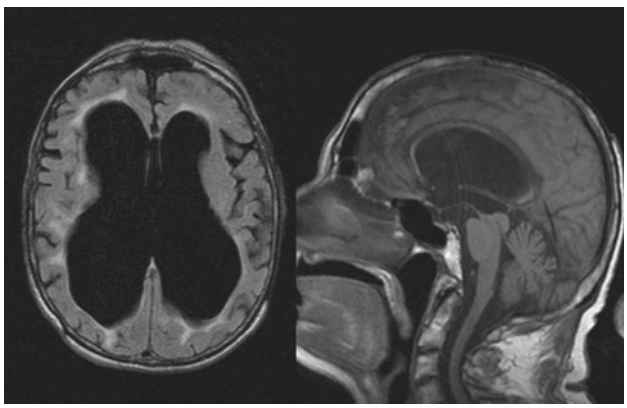

Fig. 2 Axial T2 (Flair) weighted MRI image showing considerable triventricular hydrocephalus in benign aqueductal stenosis. Sagittal T1 weighted MRI image showing remarkable dilation of Monroe hole and secondary corpus callosum atrophy

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Clinical Pharmacology

Pharmacological approach to a correct choice of antibiotics in nosocomial infection

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Several clinical trials about the severe nosocomial infections prove a significant correlation between an adequate or inadequate empiric therapy and mortality. They show that the wrong antibiotic is associated to a higher mortality, but they show that the mortality is high in case of adequate choice too (mortality between 30 and 50%). Similar data are noticed in less serious infections, such as the Ventilation Assisted Pneumonia (VAP). For this reason it is important to extend the meaning of "adequate therapy", in fact the therapy doesn't depend only on the sensibility of the germ, but it depends on a correct dosage and on the ability of the drug to reach the infected site preserving the MIC (Minimum Inhibitory Concentration) too. The doctors usually need to start the therapy before the result of the antibiogram (empiric therapy) so that the clinical characterization of the infection and the fast evaluation of the more presumable germ are fundamental. The next step is remember the importance of the pick-concentration and of the conservation of the MIC between the administrations to avoid the risk of worsening and the increase of resistance. For example the aminoglycosides are characterized by the first exposure effect so it's necessary to administrate the daily dose in a single solution. The β-Lactam antibiotics have an efficacy time-dependent, that is the effectiveness increases when the time of exposition of the patient to the antibiotics becomes higher. Other antibiotics have an efficacy Area Under Curve(AUC)-dependent, the AUC depends on the exposure of a particular tissue or of all organism to the medicine. The AUC can be increased using a higher concentration pro dose or more doses pro day. The evaluation of all the variables can be difficult so the recent literature suggests 2 main criterions:

1. The precocious beginning of the empiric therapy, because the trials prove a less risk of mortality and morbility with a reasonable therapy than the start and correction of therapy after the result of antibiogram.
2. The evaluation of the real ability of the drug to preserve the MIC in the infected site.

We can show the example of the linezolid's and vancomicin's use in the therapy of the nosocomial pneumonia. Even if in vitro the linezolid is not more effective than vancomicin, a lot of studies show that the linezolid is better than vancomicin against Gram+ and *S. aureus* pneumonias, above all against the MRSA pneumonias. This superiority is caused by the high concentration of linezolid in the alveolar fluid (ELF); in fact the concentration of linezolid in this site is higher (450% of blood concentration) than the vancomicin concentration (only 11–17% of blood concentration). In conclusion the doctors have to know the clinical criterions to identify the more probable germs and the pharmacokinetics and pharmacodynamics of the antibiotics to prescribe a rational empiric therapy and to reduce the risk of morbility and mortality of the nosocomial infections.

Drug-induced liver injury: the need for a reappraisal of pre-existing chronic liver disease

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Background and aim: Drug-induced liver injury (DILI) may range from mild aminotransferase elevation to severe acute liver damage. We describe the clinical course of patients presenting with DILI, according to the presence of pre-existing chronic liver disease (CLD).
Patients and methods: All records of patients discharged with a diagnosis of DILI from our tertiary referral Unit between 1996 and March 2010 were reviewed retrospectively, constructing a database with data on socio-demographic and disease features at onset, drug history and follow-up. A diagnosis of DILI was made when at least three of the International Consensus Criteria (J Hepatol 1990) were present. Liver damage was defined as hepatocellular, cholestatic or mixed. All patients had regular follow-up visits every 3 months for at least 1 year, and were recontacted to update outcomes.
Results: Out of 9,000 patients, 104 (47 men, 45.2%) were diagnosed as DILI. Mean age was 52.6 years (range 11–88), with 70% of subjects older than 40 years. Twenty four patients (23.1%) had pre-existing compensated CLD (10 chronic viral hepatitis, 6 cirrhosis and 8 autoimmune liver disease). DILI was classified as cytolitic in 51 patients (49.1%, 32 non-CLD, 19 CLD), cholestatic in 30 (28.8%, 26 non-CLD, 4 CLD) and mixed in 23 (22.1%, 22 non-CLD, 1 CLD). In 9% of cases, two or more drugs were involved. NSAIDs or paracetamol (NSAIDS = 29; paracetamol = 1), immunosuppressants ($n = 16$) antimicrobials ($n = 17$) and anti-platelet agents ($n = 11$) were the drugs most commonly involved, followed by psychotropic drugs, statins and oral anti-diabetics. NSAIDs were involved in all cases of hepatic failure presenting with encephalopathy (one, without CLD, was listed for OLT but died). The overall clinical pattern of DILI in CLD was no more severe than in non-CLD cases and none decompensated. Three months after discharge full recovery was obtained in 30/51 (58.8%) with cytolitic liver injury (20 non-CLD and 10 CLD), 16/30 (53.3%) with cholestatic liver disease (15 non-CLD and 1 CLD) and 13/23 (56.5%) with mixed liver injury (12 non-CLD and 1 CLD). During the first year of follow-up the remaining 32 non-CLD patients normalized liver tests, whereas 12 subjects with CLD reverted to their pre-DILI status.
Conclusions: Patient admitted for DILI at a referral unit are frequently over 40 years and have been exposed to NSAIDs, antibiotics or immunosuppressants. Recovery is very common, albeit sometimes slow, with low mortality risk even in patients with-pre-existing liver disease.

Gastroenterology and Hepatology

Evaluation of liver function by dynamic tests, Indocyanin Green (ICG) and Hippurate Ratio in patients with hepatocellular carcinoma (HCC) candidate to surgery: preliminary note

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Aim: The object of this study was to analyze the effectiveness of ICG and P-aminobenzoic acid (PABA) tests in evaluating the parenchyma function in patients affected by HCC in underlying liver chronic disease candidate to surgical resection. The quantitative methods, based on elimination of ICG reflected by plasma disappearance (by ICG-pulsion, Limon medical system) and on the measuring plasma concentration of PABA metabolite, are used to accurate judgement about remnant liver function.
Materials and methods: Patients aged 65 years and more affected by HCC and chronic liver disease candidate to surgical resection were studied. Diagnosis was based by imaging (US, TC or RM) and the volume of the remnant liver parenchyma was determined based on planned resection by means of CT scanning. Liver function was evaluated by means of Child-Pugh score and dynamic tests. A score greater than 8 was considered an absolute contraindication for surgery. Patients with plasma disappearance rate of ICG less than 12 and Hippurate Ratio less than 18 were excluded from large liver resections.
Results: Eight patients, aged 65–89 years were unrolled in this study. Two minor resection and 6 major resections were performed. Plasma disappearence of ICG and Hippurate level ranged 15–35% ratio and 30–40% before surgery, >20 and 40% 6 months from surgery were, respectively, measured.
Conclusions: Even if no statistical significance was reached because of the small number of our sample, dynamic tests of IGG and Hippurate Ratio in this preliminary study may provide a direct evaluation of liver function. These are safe and can be used to predict the risk of postoperative liver failure.

Hematopoietic stem cells and intestinal stem cells involvement in intestinal regeneration following gluten-free diet in celiac patients

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An increased traffic of haematopoietic stem cells (HSC) has been reported in peripheral blood (PB) of patients affected by celiac disease (CD). This has led to speculation about the role of HSC as a supplementary bone-marrow derived stem cell supply, for the replacement of enterocyte cell loss. Aims of the present work were: (1) to investigate the longitudinal modifications of PB-HSC trafficking, and (2) to correlate them with the mucosal inflammation and regenerative response in CD patients before and after gluten-free diet (GFD). Thirty patients were enrolled, after receiving CD diagnosis. Circulating CD133+/CD34+ HSC were measured by flow-cytometry, at the enrolment and after 3, 5, 7 days and 1, 3, 6, 12, and 24 months of GFD. Ten healthy subjects were used as controls. Histological severity of duodenal damage was evaluated by Marsh score, while immunohistochemistry was employed to assess the lymphoid infiltrate and the local regenerative response. Endoscopy was performed at the time of diagnosis and then repeated at 3, 6, 12, and 24 months following GFD. Prior to GFD, PB-HSC were increased in CD patients versus healthy subjects. During the first month of GFD, a further increase of the HSC traffic was observed. Afterward, the levels of PB-HSC cells progressively decreased. At the enrolment, all patients presented with villous atrophy, abundant CD3+/CD8+ intraepithelial lymphocytes (IEL) and rare CD133+ intestinal stem cells. IEL started to decrease at 3 months following GFD, together with an increase of CD133+ cell density. These early modifications were followed by progressive villous regeneration and clinical improvement, that were observed from about 6 months of GFD. After 24 months of GFD, all patients were asymptomatic and the integrity of the duodenal mucosa was restored. Our preliminary results indicate that HSC might participate to the enteric repair process mainly in the first weeks of GFD. GFD induces a reduction of the immune-mediated intestinal damage and an increase in PB-HSC. This is followed by expansion of the CD133+ intestinal stem cell compartment, which leads to villous regeneration. This study sheds light on the dynamics underlying intestinal regeneration following GFD in celiac patients and might offer new insights for the development of HSC-based treatments against CD.

HCC personalized treatment in the multimodal management era: the hepatocat group experience

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Background: The management of hepatocellular carcinoma (HCC) has been progressively improved through the past years, evolving in a multimodal and personalized therapeutic approach, often requiring repeated treatments, in order to avoid tumor recurrence and improve the overall survival.
Objectives: We describe retrospectively the experience of the multidisciplinary hepatocellular carcinoma group of the Catholic University of Rome (HEPATOCAT) in the management of liver primary cancer.
Methods: Between September 2008 and May 2010, 330 patients referred to our Center with the diagnosis of hepatocellular carcinoma. Among them, 135 subjects (109 males, 26 females; mean age 65.4 years) with at least 1 year of follow-up after the first therapeutic decision were included in the retrospective analysis. Hepatocellular carcinoma was diagnosed following AASLD guidelines and all patients received different treatments, either alone or combined, basing on a personalized approach to BCLC guidelines. Tumor response was assessed according to the mRECIST criteria and a combined treatment was performed in patients with no response or partial response to the first-line treatment. Time to recurrence and overall survival were calculated in selected patients. The impact of age, sex, etiology of liver disease, levels of α-fetoprotein, inclusion in Milan criteria, presence of portal vein thrombosis and single versus

multimodal treatment on recurrence rate and 1-year overall survival was evaluated. Frequency distributions were compared using the $\chi 2$ or Fisher's exact test as appropriate and the analysis of survival was performed using Kaplan–Meier curves.
Results: The initial tumor was completely treated in 63% (85/135) of patients, whereas a multimodal approach was performed in 37% (50/135) of them. Thirty-four out of 135 patients (25.2%) experienced a tumor recurrence, with a mean time to recurrence of 13.7 ± 14.4 months. Tumor dimension within the Milan criteria and the use of a multimodal treatment were associated with a longer time to recurrence ($p = 0.048$, OR 0.32 and $p = 0.003$, OR 0.17, respectively). The cumulative overall survival rate was at 1 year of 82% (111/135). The presence of portal vein thrombosis was the only factor significantly associated with a reduced survival ($p < 0.001$; OR 12.1).
Conclusion: The management of HCC with a multimodal approach seems to be associated with a good 1-year survival and a delayed recurrence. Our experience shows that, in the multimodal management era, HCC could be treated with the best results using an iterative treatment, based on the improvement of patients' selection criteria and on the use of a personalized approach.

Fibromax® for noninvasive assessment of hepatic steatosis in patients with chronic liver disease

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Background: A major problem in hepatology is to estimate noninvasively the extent of liver steatosis, inflammation, fibrosis in patients with chronic liver disease. A better identification of the subset of patients at risk of progression of liver disease will improve the selection of those requiring liver biopsy and histology for ultimate stage definition of liver damage. The ideal tool should be both informative and noninvasive, and easily appliable to a large number of subjects, due to the high prevalence of chronic liver disease due to metabolic-viral hits. Fibromax® (Biopredictive, France; Istituto Biochimico Italiano, Aprilia, Italy) is an algorhythm which includes ten simple serum parameters plus age, sex and body mass index (BMI), and therefore extrapolates information on the grade of liver inflammation (NASHtest), steatosis (Steatotest) and fibrosis (Fibrotest) in extremely frequent chronic liver diseases (e.g. metabolic, viral, alcoholic).
Aim: To test the accuracy of Fibromax in a cohort of outpatients with chronic liver disease.
Methods: Forty-one patients (age range 21–74 years, M:F = 28:13) with chronic (6> months) elevation of serum transaminases levels and ultrasonographic patterns of chronic liver disease were recruited. Anthropometric data were recorded and a blood sample for Fibromax® was obtained from overnight fasting patients. Metabolic syndrome (ATPIII criteria), HCV infection and alcohol hepatitis were present in 24, 8 and 9 subjects, respectively.
Results: A significant relationship was observed between Steatotest values and BMI suggesting that overweight, and obesity in particular, are risk factor for hepatic steatosis. Higher values of Steatotest were observed in both metabolic syndrome patients and alcoholics compared to HCV infected patients. Overall, Steatotest was significantly related with serum glucose levels ($r = 0.662$, $p < 0.001$), serum triglycerides ($r = 0.550$, $p < 0.001$), while no relation was observed with serum total cholesterol. In alcoholics, Steatotest was significantly related with serum triglycerides ($r = 0.719$, $p < 0.02$). NASHtest was not significantly related with ALT values.
Conclusions: Fibromax® is a promising noninvasive tool able to provide information on the grade of liver steatosis in different types of chronic liver disease conditions. The final outcome of this approach for better patients' selection needs to be assessed with respect to liver biopsy, natural history of the disease, and effect of therapy.

Amiodarone induces liver toxicity by impairing liver mitochondria bioenergetics and redox balance

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Background and aims: Amiodarone is the most prescribed antiarrhytmic drugs. Despite its beneficial properties, it causes liver damage by inducing micro- and macrovesicular steatosis which may progress to steatohepatitis in chronically treated patients. The pathogenesis of liver damage caused by amiodarone is not completely understood, even though alterations in mitochondrial function such as uncoupling of oxidative phosphorylation and electron transport chain impairment have been described. Furthermore, amiodarone interacts with phospholipids, suggesting that this compound may modify the composition of mitochondrial membranes. However, all these findings have been demonstrated only in "in vitro" studies or after short term high dose. Moreover, the role of free radicals in amiodarone hepatotoxicity is still debated. We aimed to study the mechanisms of mitochondrial hepatotoxicity induced by amiodarone mimicking a human therapy protocol on an animal model.
Materials and methods: Rats were randomly divided in 2 groups: (1) controls (CTRL) and (2) rats treated with amiodarone (AMIO). All the compounds were administered by intragastric gavage using equivalent human dose. Liver mitochondria were isolated to explore bioenergetics parameters (oxygen uptake, proton leak, ATP homeostasis), and phospholipid composition of membranes. Moreover, the rate of mitochondrial hydrogen peroxide production, peroxidised lipid and cardiolipin, as well as hydroxynonenal (HNE)-protein adducts were also measured.
Results: Liver mitochondria bioenergetics was impaired in AMIO group, since amiodarone uncoupled oxidative phosphorylation from ATP synthesis, reducing hepatic ATP content. Moreover, we found a decreased Complex I respiratory and enzymatic activity in AMIO rats as compared with CTRL. We also observed a modification of the membrane lipid composition, together with increased hydrogen peroxide production rate and HNE-protein adducts, as weel as lipid and cardiolipin peroxidation in liver mitochondria from AMIO rats rather than controls.
Discussion: Daily administration of amiodarone causes a slow hepatic accumulation of the drug and its metabolites which results in a progressive liver damage, dependent on mitochondrial bioenergetics adaptation. The tertiary amine moiety of amiodarone exhibits a pK_a in the physiological pH range. This, along with the lipophilic feature of the drug, accounts for its protonophoric uncoupling property. This study shows that amiodarone induces dissipation of the proton motive force in liver mitochondria and, very interestingly, impairment of Complex I activity, which in turn impair hepatic ATP homeostasis. The amiodarone-dependent inhibition of Complex I causes enhanced production of free radicals and consequent cardiolipin peroxidation. Cardiolipin is a mitochondria inner membrane located phospholipid which plays a pivotal role in the regulation of mitochondrial bioenergetics by optimizing the activities of key mitochondrial inner membrane proteins involved in oxidative phosphorylation. We

suggest that oxidative modifications of cardiolipin induced by amiodarone may explain, almost in part, impaired activity of Complex I. Thus, both free radicals and peroxidized cardiolipin further inhibit Complex I. This conclusion strongly suggests that an antioxidant treatment may prevent liver mitochondria toxicity induced by amiodarone.

Extended treatment with human leukocyte IFN-alfa plus ribavirin of chronic hepatitis C: a retrospective analysis

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Background and aims: Treatment of chronic hepatitis C is often ineffective because of relapse, especially in advanced stages of disease. Human Leukocyte interferon-α can be a well-tolerated and effective alternative to pegylated interferon, particularly when longer treatment is considered.
Methods: We identified 55 consecutive patients with treatment-naive hepatitis C from our historical database and divided them into two groups according to the stage of fibrosis (Ishak-Knodel score, stage 1–2: 22 patients, stage 3–4: 28 patients). Each group was further divided into patients receiving a combination therapy with human leukocyte interferon-α (3 MU tiw) and ribavirin (800–1,000 mg/day) for 12 months and those treated with the same regimen for 24 months. 80% of patients were infected with HCV-genotype 1. Endpoints were virological response and ALT normalization. Haematologic and thyroid adverse events were also considered. Finally, we evaluated the end-of-treatment reduction of fibrosis score.
Results: At the end of treatment, the partial (reduction of more than 2 log HCV RNA) and complete (HCV RNA undetectable) responses were 58 and 44% for stage 1–2 and 3–4, respectively, when treated for 12 months versus 54 and 60% for stage 1–2 and 3–4, respectively, for the 24-month therapy. The biochemical response rate was significantly higher in patients treated for 24 versus 12 months, regardless of the stage of disease ($P = 0.001$). Fibrosis stabilized or improved in 60% of all patients with extended treatment versus 40% for 12-month therapy. As regards platelet and/or neutrophil reduction and thyroid disfunction, these events were mild and and not influenced by treatment duration ($P = 0.0132$, $P = 0.0253$, $P = 0.1032$, respectively). None of them led to discontinuation of treatment.
Conclusion: This study demonstrates a significant improvement in positive virological and biochemical responses when treatment is extended to 24 months, especially for more advanced stages of disease. This result has important consequences for the improvement of histological severity of fibrosis, which shows a significant reduction in patients who are given longer treatment. Finally, the choice of leukocyte interferon-α, due to its positive tolerability profile, could allow longer therapeutic courses even in more severe stages of disease.

A right atrial mass, an atypical early sign of hepatocellular carcinoma

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A 76-year-old man was admitted to the hospital for evaluation of a right atrial mass. During the week before admission dyspnea occurred and the patient went to emergency room. Chest X-ray was normal; a transthoracic echocardiogram revealed a right atrial mass, 4.3 cm by 2.5 cm. He had history of hypertension, hyperlipidemia, atrial fibrillation, aortic stenosis and hepatitis B virus (HBV) infection. He had had a stroke 10 years earlier with no residual defect and a coronary-artery bypass graft was performed within the past year because of angina. His medications were aspirin, warfarin, furosemide, bisoprolol and atorvastatin. The results of examination revealed no abnormalities except for a systolic murmur grade 3 of 6 at the right upper sternal border radiating to the neck and hepatomegaly. Laboratory investigations showed a macrocytic anemia and hepatocellular liver disfunction; serum albumin was low and serologic tests for hepatitis B surface antigen and hepatitis C virus (HCV) antibody were positive. Alpha-1 fetoprotein (AFP) was not elevated and other cancer markers were not either. Three main entities in the differential diagnosis at the time of this patient's initial presentation include both haematogenous and tumor thrombosis, atrial mixoma and endocarditic vegetation. Some malignancies such as kidney cancer and caval leyomiosarcomas may invade the inferior vena cava (IVC) giving thrombosis, instead vena caval thrombosis occurs rarely in other tumours; in this case the heterogeneous hypoechoic hepatic nodule and intrahepatic venous thrombosis revealed on abdominal ultrasonography ruled out these disorders. Causes of hepatic mass included both benign lesions and malignancies such as hepatocellular carcinoma (HCC), cholangiocarcinoma and metastatic tumours. Abdominal CT scanning and MRI of the liver, performed after administration of oral and intravenous contrast material, confirmed the presence of a mass, greater than 5 cm, protruding from the hepatic surface with satellite nodules around. Lesion appeared hypervascular with wash-out in the portal vein phase, intrahepatic venous thrombus had diffuse enhancement too: it was indicative of tumor thrombosis. Arterial hypervascularity with wash-out in the portal venous phase was suggestive and the lesion was diagnosed as HCC. Because of vascular invasion and comorbid conditions patient didn't undergo invasive treatment and he died two months later. Few tumours may be associated with IVC invasion or atrial tumor thrombosis. Venous tumor thrombosis is characteristic of kidney cancer and caval leyomiosarcomas, it rarely occurs in other malignancies. HCC with an extension to IVC or righ atrium is uncommon, it occurs in a terminal stage and its prognosis is poor. HCC is frequently diagnosed late in its course because of the absence of pathognomonic symptoms and the liver's large functional reserve; as a result many patients have an untreatable disease when first diagnosed. AFP had been used as a serum marker for HCC for many years, however it is not elevated in all patients with HCC, not all tumours secrete AFP and serum concentrations are normal in up to 40% of small HCC and in well-differentiated tumours; AFP isn't therefore a sensitive marker to detect the presence of HCC. Detection of nodules with arterial hypervascularization in two imaging modalities is considered diagnostic of HCC; neither AFP nor biopsy are necessary for diagnosis of HCC. Persistent infection by HCV or HBV is a background factor in almost all cases of HCC; chronic HBV infection is the major cause of end-stage liver disease and hepatocellular carcinoma. HBV-related HCC is often accompanied by portal vein tumor thrombus. Due to ability of HBV genome to be mantained in the nuclei of hepatocytes, infected patients are at life-long risk of disease reactivation and should be regularly monitored to detect active disease. In hepatitis B carriers prevention of HBV-realted HCC should include clinical, haematologic and ultrasonographic monitoring every 6 months. Surveillance program using ultrasonography may detect both small HCC and venous tumor thrombosis, as a result many patients may received early and aggressive treatment in order to improve mortality.

Recurrent hepatitis C (genotype 1) after orthotopic liver transplantation: role of therapy with peginterferon alfa-2A/ribavirin in maintenance

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30 consecutive prospectively followed patients (pts) diagnosed with recurrent HCV (GENOTYPE 1) were considered candidates for antiviral therapy with PEG-IFN alfa-2A and Ribavirin. Qualitative and quantitative detection of HCV-RNA was performed with the Cobas Amplicor Hepatitis C Virus Test, version 2.0 and the Cobas Amplicor HCV Monitor, version 2.0 (Roche Diagnostics, Branchburg, NJ, USA). PEG-IFN alfa-2A was given at 90 μg weekly for 4 weeks, then at 180 μg weekly; Ribavirin at 400–600 mg daily for 4 weeks, than at 800–1,000 mg. Response to therapy: sustained virological response (SVR), sustained biochemical response (SBR) and non-response (NR). Histological evaluation has been effected in some subjects at the end of treatment and in NR and SBR pts after a period of 12 months of maintenance therapy (PEG-IFN alfa 2A at 90 μg/week and Ribavirin 400–600 mg/day). 8 pts stopped therapy for side effects, a SVR was observed in 7 cases, a SBR in 6 and NR in 9 cases. Improved fibrosis score was observed in all pts with SVR, improved score in 2 pts with SBR and stable score in 4 pts with SBR, worse score in 3 NR pts and stable score in 6 NR pts. 8 pts (5 NR and 3 SBR) with stable score undergone to maintenance therapy: improved score in 1 and stable score in 8 patients. In conclusion it emerges how side effects are an important limiting factor, the therapy independently to the type of response slowly fibrosis and maintenance therapy may slow the progression of chronic HCV.

Conclusion: No response to antiviral therapy in patients with genotype 1 infection represents an important percentage (40%). It emerges how in patients without a response an eventual maintenance therapy may slow the progression of chronic recurrent hepatitis C. Our results strengthen the concept that an eventual maintenance therapy in those cases without a positive response may alter the progression of chronic recurrent hepatopathy HCV by either reducing hepatic inflammation and/or by acting as a direct antifibrotic agent. In accordance to others authors (1) failure to antiviral treatment should not necessarily lead to treatment discontinuation as a subgroup of patients may benefit from maintenance treatment.

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Correlation between hepatic arterio-venous malformations (HAVMS) and gastro-intestinal bleeding in Italian patients

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Hereditary Hemorrhagic Telangiectasia (HHT) (or Osler-Weber-Rendu syndrome) is an autosomal and age-dependent vascular disorder diagnosed according to clinical criteria: epistaxis, telangiectases in specific skin sites, and visceral involvement including arteriovenous malformations (AVMs) in lung, brain and liver or telangiectases in the gastrointestinal tract. Two main loci have been identified as the genes responsible for about 85% of cases in HHT: endoglin (*ENG*; 9q34) in HHT type 1 and the activin receptor-like kinase-1 (*ALK1* or *ACVRL1*; 12q13) in HHT type 2. Recently, a third and a fourth loci for HHT have been mapped to chromosomes 5 and 7, respectively, but the specific genes have not yet been identified. In addition, related diseases demonstrating symptoms of HHT include juvenile polyposis/hereditary haemorrhagic telangiectasia (JPHT) caused by MADH4 mutations, and primary pulmonary hypertension caused by BMPRII or ALK1 mutations. Gastrointestinal telangiectases have been reported in about 50% of HHT patients but become symptomatic with GI bleeding resulting severe anemia and extensive blood transfusions in only 25% of these subjects. Telangiectases can be multiple and distributed throughout the GI tract, thus determining great difficulty for treatment. Despite the significant morbidity associated with GI bleeding in HHT patients, there is limited published data in large patient cohorts. In our HHT population, hepatic malformations are present both in HHT1 and HHT2, whereas GI bleeding has been more frequently identified in HHT2. Therefore, we hypothesize that the more severe hepatic involvement in HHT2 might be the cause of the GI bleeding in this patient subgroup. A total of 105 HHT patients were enrolled and subjected to hepatic echo-color Doppler (ECD) and gastro-duodenal endoscopy, resulting in 21 patients with GI teleangiectases and bleeding, 44 with GI teleangiectases without bleeding, and 38 patients without GI teleangiectases. In the first patient subgroup (21/105), 13/21 had a causative mutation in ALK1 (HHT2), 2/21 had a causative mutation in ENG (HHT1), while molecular testing has yet to be completed in the remaining 6/21 patients. The hepatic artery flow (measured with ECD) in the first HHT subgroup (21/105) was found to greater compared to the other two groups (44/105 and 38/105). This result can be likely explained by the fact that the more serious liver involvement in HHT2 generates an hyperdynamic state determining an attack to the endothelial wall of the GI teleangiectases, thereby causing GI bleeding.

Metabolic resistance of liver cancer cells and putative cancer stem cells to the multikinase inhibitor sorafenib

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'Smart', molecularly targeted drugs have recently raised the hope of overcoming the pitfalls of conventional chemotherapy in terms of low effectiveness, heavy side effects and induction of chemoresistance. Among these new compounds, Sorafenib (Nexavar®), an orally bioavailable multikinase (B-Raf, VEGFR-2) inhibitor endowed of elevated growth inhibitory and anti-angiogenic potential, is being successfully translated to clinics for the treatment of advanced stage malignancies. Thus, a better understanding of its mechanism of action is critically needed to help developing more effective compounds and avoiding the emergence of selective chemoresistance. Anticancer therapy's success depends on its capacity to eradicate Cancer Stem Cells (CSC), a tumor cell subset endowed of self-renewal capacity and supposed to spawn all the other cell populations and seed the disease at metastatic sites. We have recently described the derivation, from chemically induced rat Hepatocolangiocarcinomas, of cell lines

(LCSCs) with morphologic features and molecular markers of Oval Cells (liver stem cells); these lines induce hepatocolangiocarcinomas in immunocompromised hosts, and therefore represent putative cancer stem cells. One of these lines (LCSC-2) was only moderately sensitive to SFB, and exposure to the drug marginally inhibited the ERK cascade. Instead, SFB increased the intracellular content of reactive oxygen species (ROS), reduced intracellular ATP and altered the mitochondrial transmembrane potential, indicating that mitochondrial function likely represent a major target for the drug in this cell model. Interestingly, LCSC-2, as recently observed in breast cancer stem cells, were found to be heterogeneous with respect to intracellular ROS content, assessed by flow cytometry of cells loaded with the redox sensitive dye DCF-DA. Cells with low ROS, presumably reflecting low mitochondrial activity, were selectively spared by SFB, and after DCFDA-based sorting, appeared, significantly resistant to the drug, compared to cells with high ROS. Additionally, gene profiling of LCSC2 cells exposed to SFB clearly indicated metabolic cell reprogramming towards aerobic glycolysis. Taken together these findings indicate in mitochondrial damage a major mechanism of action for SFB, and warn on the possibility that CSC metabolism based on low mitochondrial activity and elevated glycolysis may provide ground for selective stem cell resistance to the drug.

Diabetes mellitus as a risk factor for arterial hypertension development in patients treated with Sorafenib for hepatocellular carcinoma

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Introduction: Sorafenib, a multi-kinase inhibitor with antiangiogenetic and antiproliferative properties, represents the first systemic therapy able to prolong survival in advanced Hepatocellular Carcinoma (HCC) with preserved liver function and has been recently approved for the medical treatment of HCC. As with others angiogenesis inhibitors, a common side-effects of this drug is arterial hypertension development, although the molecular mechanism is not yet well understood. The aim of this study is to identify major risk factors related to arterial hypertension development in patients receiving Sorafenib for HCC, in order to optimize the clinical management of treated subjects.
Materials and methods: We retrospectively reviewed 59 subjects with HCC arisen on hepatic cirrhosis treated with Sorafenib 400 mg twice daily (50 males, 9 females, mean age ± SD 70.6 ± 10.8 years). According to current guidelines, arterial hypertension was defined as the threefold presence of arterial blood pressure >140 or 90 mmHg or antihypertensive drug treatment. Diabetes mellitus was defined according to American Diabetes Association indications.
Results: Eighteen of 59 patients (30.5%) developed arterial hypertension during Sorafenib treatment (13 males, 5 females, mean age ± SD 73.5 ± 9.61 years). Out of 59 treated patients, 24 were diabetics and among these, 13 developed arterial hypertension ($p = 0.0001$ at exact Fischer test). Patient's gender and age were not significantly related to arterial hypertension development ($p > 0.05$).
Discussion: Arterial hypertension development is a frequent side-effect during Sorafenib treatment for HCC. Thus, patients taking Sorafenib need to be closely monitored for the detection of hypertension development. In addition, our preliminary data suggest that we must pay a special attention in diabetics subjects given Sorafenib since the statistically higher risk of arterial hypertension development, in order to obtain an early diagnosis and an effective clinical management.

The cholecystokinin (CCK) knockout mice lack endogenous CCK: a condition promoting cholelithogenesis which is relevant to celiac disease

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Celiac disease is becoming an increasingly recognized autoimmune enteropathy caused by a permanent intolerance to gluten. In cliac patients, CCK release from the small intestine and gallbladder emptying in response to a fatty meal are greatly decreased before starting the gluten-free diet, and this puts the patients at risk of increased gallstone incidence rates.
Aims: To better provide a pathophysiologically relevant basis in celiac disease, and by using a novel mouse model (the CCK KO (−/−)), we investigated the effect of the absence of endogenous CCK on cholecysto-intestinal motility and underlying mechanisms of gallstone formation.
Methods: The CCK KO (−/−) mice were generated by using a gene targeting strategy in which lacZ reporter gene was inserted into the mouse *Cck* gene, resulting in a null mutation. After cholecystectomy, fresh gallbladder bile was examined for the presence or absence of mucin, solid and liquid cholesterol crystals, and cholesterol gallstones by polarizing light microscopy in male CCK (−/−) and (+/+) matched mice ($n = 4$ per group) before and at frequent intervals following a lithogenic diet (containing 1% cholesterol, 0.5% cholic acid, and 15% butter fat) from day 1 to 28. Gallbladder size and emptying function were measured by gravity after an overnight fast or a high-fat meal, respectively. Biliary lipid secretion was determined enzymatically. Small intestinal cholesterol absorption was measured by fecal dual-isotope ratio methods, as previously described by our group.
Results: Fasting gallbladder volumes (50–65 μL) were significantly ($P < 0.05$) increased in (−/−) mice compared with (+/+) mice (20–30 μL). Gallbladder emptying response sto the high-fat diet was impaired in (−/−) mice. During 28 days of feeding the lithogenic diet, there was earlier onset and severity of cholesterol gallstone formation in (−/−) mice compared with (+/+) mice. Due to the absence of CCK, small intestinal transit time was prolonged so that intestinal cholesterol absorption was significantly increased (31 vs. 39%). These observations could explain, in part, why hepatic secretion of biliary cholesterol was higher in (−/−) mice than (+/+) mice. The combination of increased bile cholesterol levels and gallbladder stasis due to the absence of CCK-induced contraction, enhanced crystallization and growth of classic plate-like cholesterol monohydrate crystals, and promoted gallstone formation in (−/−) mice. In contrast, daily CCK intraperitoneal administration (0.1 μg/kg, twice per day) could reduce gallstone formation in (−/−) mice challenged to the lithogenic diet.
Conclusions: The lack of CCK impairs gallbladder motility function, inducing enlarged gallbladder size and prolonged the residence time of excess cholesterol in the gallbladder lumen to promote cholesterol crystallization, as well as retards small intestinal transit times, resulting in increased intestinal cholesterol absorption and biliary cholesterol secretion rates. All these changes enhance cholelithogenesis. These results could partly explain why gallstone formation is increased in patients with celiac disease.

Comparison of contrast enhanced ultrasonography and contrast-enhanced CT in monitoring HCC patients treated with antiangiogenic drugs: which is the better?

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Background: Identification of signaling pathways responsible for HCC growth and progression has determined crucial molecular targets and led to development of novel promising targeted therapies acting on tumor angiogenesis. Since sorafenib received approval as a standard of care treatment for patients with advanced HCC, many clinical trials are now undergoing to evaluate the efficacy of other antiangiogenic agents in HCC treatment. These drugs act by inducing alterations in tumor vascularity that cannot be evaluated by traditional morphological criteria to assess tumor response. For this reason, the classical CT response criteria based on tumor shrinkage were replaced by the recently developed mRECIST that take into account the presence of viable tumor tissue. At the same time the recently developed dynamic contrast-enhanced ultrasound (D-CEUS) with the new quantitative approach has shown great promise in revealing effective tumour response to antiangiogenic drugs before tumour changes occur.
Aim*:* To compare the feasibility of dynamic CEUS and contrast enhanced CT in the assessment of early vascular effect of antiangiogenic drugs in patients with advanced HCC.
Patients and methods*:* Patients with advanced stage HCC treated with antigiogenic drugs, were enrolled in this study. CEUS was performed at baseline, after 15 days of treatment and than every month during the follow up. Tumor vasculature was assessed qualitatively and in a specific harmonic mode associated with a perfusion and quantification software (Q-Lab, Philips) and two parameters extracted from the time-intensity curves of contrast uptake were evaluated: the peak intensity (PI) and the time to PI (T_{PI}). For each kinetic parameter the impact of antiangiogenic treatment was analyzed based on the difference between the pre and post-treatment evaluation. Response to therapy was assessed according to mRECIST criteria, using CT scans performed before treatment and every 2 months during the follow up.
Results: A total of 15 patients were evaluated in this study. Among them, 10 patients were classified as nonresponders (5 with progressive disease and 5 with stable disease) and 5 as responders (partial response in 3 cases and complete response in two cases) according to mRECIST at 2 months. When patterns of enhancement on sonography were compared with those on CT, we found a total agreement in 13 out of 15 patients. However an arterial phase discordance occurred in two cases. In the first patient the target lesion was seen as hypervascular in the arterial phase of CEUS and hypovascular on contrast-enhanced CT. The quantitative measurement of echo level in relation to time showed a reduction in PI (about 23% at 1 month) without significant changes in T_{PI}.. In the second patient with stable disease according to CT, D-CEUS showed a significant increase in tumor vascularization, expressed as an augmented PI at any time points during the follow up (more than 30% at 1 month). Later on during the follow up, this patient presented an increase in tumor size and in number of lesions.
Conclusion: A high level of agreement in type and pattern of enhancement is seen between CEUS and CT. Nonetheless occasional instances of discordance occur in the arterial phase of dynamic study and can be explained on the basis of different mechanisms and speeds of image acquisition with the two techniques. CEUS is a real time dynamic study in which differences in enhancement are recorded continuously regardless of the the rate at which they occurr, whereas in contrast-enhanced CT the arterial phase is evaluated by a single slice sometimes registered when the peak of HCC enhancement had already passed.

Cardiovascular Diseases

Osteoprotegerin and the metabolic syndrome

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Introduction: Metabolic syndrome (MS) is commonly defined as the cluster of glucose metabolism abnormalities, central adipose tissue accumulation, dyslipidemia, and abnormal blood pressure regulation and is combined to an increased cardiovascular risk. However, MS also includes the presence of a low-grade inflammatory state that, in turn, is known to up-regulate the receptor activator of nuclear factor-kB (RANK) ligand (RANKL) and thereby can lead firstly to increased bone reabsorption and finally to osteoporosis in MS patients. Concordantly, osteoporosis has been described in MS patients, particularly in female ones. In this context, the binding of RANKL to RANK is inhibited by osteoprotegerin (OPG), i.e. the natural decoy receptor for RANKL. An alteration in the balance between RANKL and OPG is therefore crucial in the pathogenesis of several bone diseases with increased RANKL levels and is associated with augmented bone reabsorption as demonstrated by the increased serum OPG levels that have been described in women with overt osteoporosis. However, due to the OPG biological properties, it is also reasonable to speculate that it might also primarily contribute to the onset of low-grade inflammation in women with MS, regardless to the presence of osteoporosis.
Aim of the study: To evaluate serum OPG levels in MS women without osteoporosis.
Methods: After evaluation of anthropometric parameters, blood pressure, serum lipid and glucose levels we identified 17 premenopausal, untreated MS women (43.76 ± 8.58 years) according to the Adult Treatment Panel III (ATP-III) criteria. To exclude patients with abnormal bone metabolism, bone mass density and microarchitectural properties of bone was performed by quantitative ultrasound (GE Achilles Lunar Express). Bone metabolism was evaluated by well-recognized parameters, serum OPG levels were evaluated by a commercial Elisa Kit. All of the above variables were also measured in 17 healthy premenopausal, untreated women who were matched for age.
Results: MS women had higher levels of OPG than control women (235.29 ± 83.3 vs. 152.35 ± 60.88 pg/ml, respectively, $p = 0.002$) but similar levels of serum calcium (9.3 ± 0.42 vs. 9.20 ± 0.35 mg/dl), alkaline phosphatase (157 ± 55.84 vs. 139.23 ± 38.16 UI/l) and the carboxy-terminal cross-linking telopeptide of type I collagen (β-CTX 176.93 ± 141.09 vs. 207.33 ± 147.14 pg/ml). We found a significant positive correlation between OPG and serum LDL cholesterol levels in MS but not in healthy women ($r = 0.73$, $p = 0.0005$). The mean T-score and Z-score of both patients and controls were in the normal range.

Discussion: The current study clearly demonstrates that MS premenopausal, untreated women selected for having no bone metabolism abnormalities had higher serum OPG levels than healthy control women. No correlation was found between circulating OPG and β-CTX levels in both groups. In contrast, only MS patients manifested with a direct correlation between serum LDL and OPG levels. As a possible explanation of our findings, the increased serum OPG levels and the lack of any correlation between OPG and β-CTX in MS women might indicate that MS per se promotes OPG release into the bloodstream. Concordantly, the direct correlation between serum OPG and LDL-cholesterol serum levels was found only in MS but not in healthy women. In conclusion, our results show for the first time that high serum levels of OPG are present in women with MS selected for having no osteoporosis. Thus, it is reasonable to hypothesize that the increased OPG level contributes to generate low-grade inflammation (or is a consequence of the same inflammation) in women with MS.

Brachial systolic and diastolic blood pressure at different arm heights: a novel index of arterial function

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Background: The dynamic behaviour of systolic and diastolic blood pressure (BP) over different mean pressure levels has been used to generate the ambulatory arterial stiffness index, and may reflect functional arterial properties. According to Stevin's law, hydrostatic pressure depends linearly on the height of the liquid column. Thus, mean pressure changes obtained by changing arm position may theoretically represent a tool to investigate arterial function at the bedside.
Methods: In 46 healthy subjects (37% men, age 46 $\pm$ 18 years, BP 125/71 $\pm$ 18/10 mmHg), we measured brachial BP and carotid-radial pulse wave velocity (PWV). Twelve BP measurements were obtained with the arm in 4 different positions (at the heart level, and at +25, +15 and -10 cm, respectively), 3 measurements per position. Subjects remained sitting with arm supported during the procedure. The SBP-on-DBP slope, estimated by the ratio of their standard deviations (SBP-SD/DBP-SD), was defined as BPVR (BP variability ratio). Recent model expresses BPVR as the systolic-to-diastolic stiffness ratio. According to the Bramwell-Hill formula, diastolic stiffness was expressed by PWV^2 .
Results: In comparison with the values obtained at the heart level, mean arterial pressure changed as predicted on the basis of the arm-heart vertical distance (-14 mmHg, -8 mmHg, and +7 mmHg, respectively, at +25, +15 and -10 cm). The BP variability generated by the arm height changes showed high SBP-DBP correlation ($r = 0.90 \pm 0.07$). As expected, diastolic PWV^2 had a linear relationship with DBP ($r = 0.43$, $p = 0.05$). Also, calculated systolic stiffness (BPVR $\times$ diastolic PWV^2) correlated with SBP ($r = 0.51$, $p < 0.05$). No relation was found between BPVR and PWV^2 ($r = -0.18$, $p =$ n.s.). BPVR had a significant direct relation with age ($r = 0.35$, $p < 0.01$) and a strong one with the Framingham-based 10-year coronary risk ($r = 0.57$, $p < 0.001$).
Conclusions: The dynamic changes of SBP and DBP at different arm heights may provide a novel and simple measure of arterial function. The resulting SBP-on-DBP slope (BPVR) had no correlation with diastolic arterial stiffness, and increased with increasing SBP, age and estimated coronary risk. Results support the theoretical expression of the SBP-on-DBP slope as the ratio between systolic and diastolic stiffnesses.

Combined effects of office and 24-h blood pressure on aortic stiffness in human hypertension

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Aortic stiffness, a prognostically adverse marker of arteriosclerosis, is critically dependent on blood pressure (BP). However, BP values measured in the office may not always reflect BP behaviour away from the medical environment, and it is uncertain whether office or out-of-office BP values are stronger determinants of arterial stiffness. In 539 untreated patients with uncomplicated essential hypertension and 71 normotensive subjects, we measured 24-h BP and carotid-to-femoral pulse wave velocity (PWV), a direct measure of aortic stiffness.Aortic PWV was lower in normotensives than in white-coat hypertension (8.4 ± 2 vs. 9.3 ± 2 m $\times$ s^{-1}, $p = 0.019$) and in sustained hypertension (9.8 ± 2 m $\times$ s^{-1}, $p < 0.001$). To examine the independent effect of office BP on aortic PWV beyond the influence of 24 h BP, subjects were classified according to the difference between observed and predicted office systolic BP (the latter determined by regressing 24-h BP on office BP). Despite having comparable 24-h BP values (131/82 vs. 131/84 mmHg), the subjects with higher-than-predicted office BP had higher aortic PWV than the subjects with lower-than-predicted office BP (10.1 ± 2 vs. 9.2 ± 2 m $\times$ s^{-1}, $p < 0.001$). Similarly, after regressing office BP on 24-h BP, we obtained 2 groups with identical office BP (152/95 vs. 152/96 mmHg) but different 24-h BP. The group with higher-than-predicted 24-h BP had significantly higher aortic PWV (9.9 ± 2 vs. 9.5 ± 2 m $\times$ s^{-1}, $p < 0.05$). In a multiple regression model, both 24-h and office mean BP were independent predictors of aortic PWV. In conclusion, both office and out-of-office blood pressures are independent predictors of aortic stiffness in hypertension.

Th1/Th2 balance in vulnerable atherosclerotic lesions after acute plaque disruption

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Background: The adaptive immunity regulates the inflammatory response. In this light, it is remarcable that atherosclerosis is now well recognized as an inflammatory disease. T cells are involved not only in atherosclerosis initiation but may also influence the stability of the atherosclerotic plaques and thus the clinical outcome. There are 2 types of CD4+ T cells, the so-called Th1 and Th2 that can be distinguished by their cytokine expression profiles. Th1 cells, which are reliant on IFN-γ and IL-12, drive cell-mediated immunity and contribute to the progression of atherosclerotic lesions toward a vulnerable profile by mediating inflammatory cells recruitment and matrix degradation by up-regulation of matrix metalloproteinases (MMP) expression and activity. Instead Th2 subset, which depends on IL-4, IL-5 and IL-10, drives humoral immunity and may induce plaque stability via up-regulation of matrix collagen synthesis and down-regulation of its degradation. Several studies have demonstrated that Th1-cytokines dominate in acute syndromes due to plaque rupture; however, it is still unknown if a Th1/Th2 balance

disequilibrium is associated to acute plaque rupture. Thus, the aim of this study was to investigate the Th1/Th2 balance in the setting of atherosclerotic plaques instability.

Methods and results: We obtained atherosclerotic plaques from 28 patients undergoing carotid endarterectomy due to severe (>70%) stenosis of the extracranial tract of the internal carotid artery. Atherosclerotic plaques were divided in asymptomatic (14) and symptomatic (14) according the clinical evidence of ischemic events. This clinical evidence was provided by assessment of recent symptoms attributable to the atherosclerotic lesion and by the evidence of ipsilateral cerebral lesion determined by brain computed tomography. We performed ELISA assays on plaques homogenates to assess the level of IL-4 and IL-12 (which reflect Th2 subset), and IL-12 and INF-gamma (which reflect the Th1 subset). Results did not show significant differences between asymptomatic and symptomatic plaques in the expression of IL-4 (5.28 vs. 5.07 pg/mL) and IL-10 (1.00 vs. 0.93 pg/mL); IFN-gamma levels were more elevated in asymptomatic plaques (1.71 vs. 0.79 pg/mL) whereas IL-12 levels were more elevated in symptomatic plaques (3.14 vs. 2.07 pg/mL), however in the presence of high inter-individual bioavaibility (see Table).

	IL-4 (pg/mL)	IL-10 (pg/mL)	IFN-gamma (pg/mL)	IL-12 (pg/mL)
Asymptomatic	5.28	1	1.71	2.07
Symptomatic	5.07	0.93	0.79	3.14

Conclusions: This study shows for the first time that after an acute ischemic event there is not a persistent disequilibrium in the Th1/Th2 balance. These results seem to suggest that the Th1/Th2 balance is quickly restored after acute plaque rupture.

1-h post load plasma glucose levels and left ventricular mass

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Left ventricular hypertrophy (LVH) represents an independent risk factor for cardiovascular (CV) morbidity and mortality both in essential hypertension and in the general population. The increase of left ventricular mass (LVM) recognizes a complex and multifactorial pathogenesis, including hemodynamic factors, salt retention, genetic, hormonal and metabolic factors. Recent studies have shown that a cutoff point of 155 mg/dl for the 1-h post-load plasma glucose during an oral glucose tolerance test (OGTT) is able to identify subjects with normal glucose tolerance (NGT) at high-risk for future DM2. We designed this study to address the question if glucose tolerance status, and in particular 1-h post-load plasma glucose levels, may affect LVM and cardiac geometry in a group of never treated hypertensive subjects. The study group consisted of 767 patients with essential hypertension, 393 females and 374 males with a mean age of 49.6 ± 8.5 years. All participants had never been treated with antihypertensive drugs. All patients underwent OGTT for the evaluation of the glucose tolerance and standard echocardiography. The LVM was calculated using the formula of Devereux and normalized (LVMI) by body surface area. The insulin sensitivity was assessed by Matsuda index. Among the patients enrolled 514 had normal glucose tolerance (NGT), 168 had impaired glucose tolerance (IGT) and 85 were diabetic (DM2). A 1-h post load plasma glucose cut-off point of 155 mg/dl during OGTT was used to divide subjects with NGT into two groups: 356 subjects with plasma glucose <155 mg/dl, and 158 subjects with plasma glucose ≥155 mg/dl. NGT patients with glucose ≥155 had a worse insulin sensitivity in comparison with those with glucose <155 (Matsuda index 63.9 vs. 88.8, $P < 0.0001$). Analysis of echocardiographic parameters and LVM in the four groups was performed according to sex. In male group, NGT subjects with glucose ≥155 had a significantly higher LVMI than those with NGT < 155 (126.6 vs. 114.3 g/m^2; $P = 0.002$). In the male population, we also observed a significant difference in LVH prevalence between NGT subjects with glucose ≥155 (41.1%) and <155 (25.8%) ($p < 0.0001$). From the stepwise multiple regression analysis, the plasma glucose at 1-h resulted the main determinant of LVMI, in whole population, explaining 9.2% of its variation ($P < 0.0001$). In NGT subjects ≥ 155 ($P < 0.0001$), IGT ($P < 0.0001$) and diabetics ($P < 0.0001$), it explained respectively 23.1, 19.2 and 22.7% of the variation of the LVMI. These data show that subjects NGT but with 1-h post load plasma glucose ≥155 mg/dl have higher LVMI values and greater prevalence of LVH compared with subjects NGT with 1-h post load plasma glucose <155 mg/dl; this observation has an important clinical implication, considering the impact that LVH may have on the development of CV events. In CV risk stratification of hypertensive patients is not only important to assess the status of glucose tolerance but also consider the value of 1-h post load plasma glucose.

Hemoglobin level and endothelial function in hypertensive patients

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Hemoglobin (Hb) is an important nitric oxide (NO) buffer and modulator of NO bioavailability. Furthermore, Hb is a major determinant of blood viscosity and vascular shear stress, which impairs endothelial-dependent vasodilation through stimulation of endothelial NO synthase. We examined the relationship between Hb and endothelial function in 174 non-smoking uncomplicated, never treated hypertensive patients to assess the potential role of Hb in endothelial dysfunction. Endothelium-dependent and -independent vasodilatation was assessed by measurement of forearm blood flow response during intra-arterial infusion of increasing doses of acetylcholine (ACh) and sodium nitroprusside (SNP) using strain-gauge plethysmography. Correlation with known risk factors of endothelial dysfunction was performed. The vasodilatory response to ACh was inversely ($P < 0.001$) related to Hb and this relationship was dose-dependent ($P < 0.001$), being minimal at the lowest dose and maximal at the highest dose. No association was found between Hb and the vasodilatory response to SNP. In a multiple linear regression model, adjusted for Framingham risk factors (age, sex, blood pressure, cholesterol, body mass index, glucose) and emerging risk factors (homeostasis model assessment index, C-reactive protein and the estimated glomerular filtration rate), Hb maintained a strong and independent link with the vasodilatory response to ACh ($P < 0.001$). In conclusion, in a large group of non-smoking untreated hypertensive subjects, the Hb level is inversely related to forearm endothelium-dependent vasodilatation. Hb levels should be taken into account,

especially in conditions associated with a low Hb, when performing vascular function studies.

1-h post load plasma glucose levels and vascular stiffness

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Recent studies have shown that a cutoff point of 155 mg/dl at 1-h post-load plasma glucose is able to identify subjects with normal glucose tolerance (NGT) at high-risk for future type 2 diabetes mellitus (DM2). Moreover, 1-h post-load plasma glucose value show a stronger correlation with carotid intima-media thickness, that is a well-established index of early atherosclerosis and an independent predictor for cardiovascular (CV) events. The vascular stiffness (VS) is recognized as an important risk factor for CV disease, being able to increase the afterload and to influence arterial compliance by modulating the bioavailability of nitric oxide, probably as a consequence of a reduction of shear stress. The aim of this study was to evaluate the influence of glucose tolerance state on VS, in particular the 1-h post load plasma glucose. The study included 175 never-treated essential hypertensive patients, aged 51 ± 10 years, that underwent to oral glucose tolerance test (OGTT). In particular we considered 157 NGT and 18 diabetic subjects. A 1-h post load plasma glucose cut-off point of 155 mg/dl was used to divide NGT subjects into two groups: 91 subjects with glucose <155 mg/dl, and 66 subjects with glucose ≥155 mg/dl. VS was studied by pulse wave velocity (PWV), that measures with a tonometric applanation method the velocity of pulse wave from a proximal artery (carotid) to a distal artery (femoral). PWV mean values were 6.9 ± 2 m/s in NGT < 155, 7.1 ± 1.8 m/s in NGT > 155, 8 ± 1.7 m/s in diabetic patients. From the linear regression analysis, the plasma glucose at 1-h resulted the strongest predictor of PWV, explaining 2.5, 6 and 9.9% of PWV variation, in NGT < 155, NGT > 155 mg/dl and diabetics, respectively. In conclusion, these data show that NGT subjects with glucose ≥155 mg/dl have higher stiffness values compared with those with glucose <155 mg/dl; moreover a worsening of glycemic state (DM2) is associated with a further increase of VS. The clinical relevance of these findings consists in the fact that NGT status by itself does not allow to stratify the CV risk of patient, because those with 1-h post-load glucose ≥155 mg/dl have an increased VS when compared with those with glucose <155 mg/dl. Obviously, present data should also alert the physicians to early detect metabolic abnormalities that are able to promote the appearance and progression of vascular damage.

Aerobic and anaerobic threshold in athletes: a comparison with healthy population

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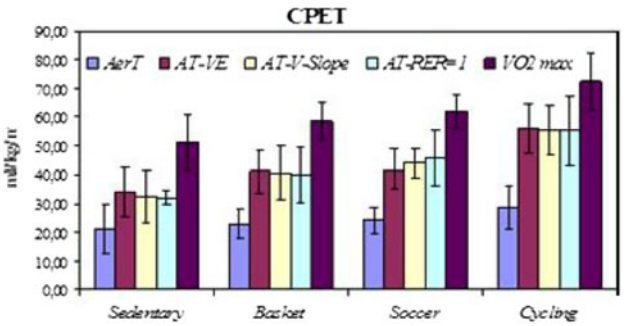
Backgroung: The Anaerobic Threshold (AT) and VO_2 max are currently used to evaluate the athlete's performance while the Aerobic Threshold (AerT), (for blood lactate of 2 mmol/l), has been recently used. The aim of this study it is to compare VO_2 max, AT and AerT of different sports.

Methods: A group of 41 athletes (16 soccer, 10 basket and 15cyclists) and 10 healthy subjects were submitted to a Cardio Pulmonary Test (CPT). The AerT, AT (in three different methods: V-slope, Ventilatory Equivalents, Respiratory Exchange Ratio) and VO_2 max were evaluated. The statistical analysys was performed with *T* Student test ($P < 0.05$ significant).

Results: The AT values, were in athletes statistically different versus controls. On the contrary the AerT values were higher only in the cyclist group.

Conclusions: The results confirm the consistency of the methods to calculate AT. Only in cyclists the AerT measure seems to give an additional information in evaluating the cardiovascular performance. The VO_2 max and AT remain the main parameters in defining the athletes performance. Therefore we cannot exclude any further utility of the AerT in normal subjects but regularly trained.

	Sedentary	Basket	Soccer	Cycling	*P* value
AerT	21.03	22.76	24.00	28.47	0.041
AT-VE	34.03	41.24	41.90	56.15	0.000001
AT-V-Slope	32.25	40.46	43.98	55.43	0.0000016
AT-RER = 1	3195	39.93	45.63	55.07	0.0006
VO_2 max	51.17	58.64	61.96	72.40	0.000017



Prevalence of congenital heart disease in athletes by echocardiographic evaluation

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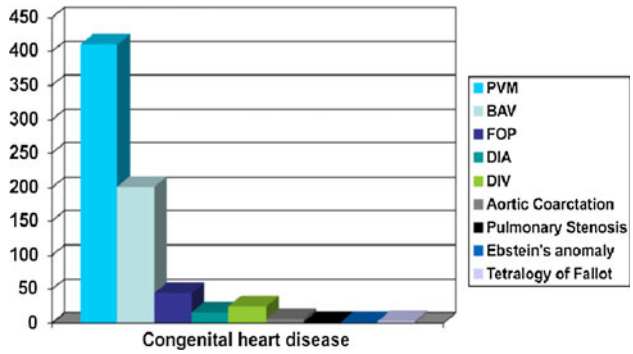
Background: Congenital Heart Disease (CHD) are more frequently diagnosed at the birth or in young age. The new pharmacologic and surgery treatment has gradually improved the childhood survival allowing a normal life and also sport activity either agonistic or not agonistic. In asymptomatic subjects with possible clinical effects, the echocardiographic exam represent the first evaluation. The aim of the study is to analyzed at our Sport Medicine Center in Florence the prevalence of CHD, including Mitral Valve Prolapse (MVP) and also to clarify when the eligibility is permitted.

Methods: From 1999 to 2008 at our Sport Medicine Centre of University of Florence 10018 echocardiographic exams have been performed in athletes usually as the second level check up Among them it was possible to determine the prevalence of the most common

minor CHD present in adult population including the aortic bicuspid valve (BAV) and also the prevalence of mitral valve prolapse (MVP).
Results: Among the athletes analyzed 410 MVP (4.10%), 201 BAV (2.05%), 45 Foramen Ovale Pervium (PFO) (0.45%), 16 Atrial Septal Defects ASD (0.16%), 25 Ventricular Septal Defects VSD (0.25%), 7 Coarctation of the Aorta C/O (0.06%), 3 Tetralogy of Fallot T/F (0.03%), 2 Pulmonary Valve Stenosis PS (0.02%), 2 Ebstein's anomaly (0.02%) were found. None of the athletes diagnosed for CHD, resulted in first line to be eligible for competitive sports. They were all submitted to a physical echo-stress in order to decide to practise agonistic sport activity or not. The 97% of the athletes affected by MVP were eligible for competitive sports as well as the 96.5% of athletes with BAV, the 89% of athletes with PFO, the 50% of athletes with ASD and the 28% of athletes with VSD.
Conclusion: These results are in agreement with the data of the current literature: the same prevalence of CHD has been described in fact in general population. This investigation suggests, therefore, that the athletes generally show the same prevalence of CHD like normal population, anyway only BAV and MVP are often compatible with sport activity.



Congenital Heart disease from1998 to December 2008 (10035 casi)

Left ventricle twist in aortic valve insufficiency: a study in athletes with bicuspid aortic valve

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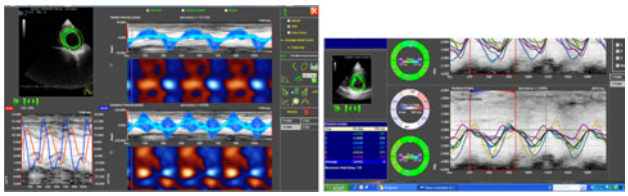
Backgound: Deformation parameters are recently used to predict subclinical LV dysfunction in minimally symptomatic patients affected by aortic valve dysfunction. More recently the role of rotation and torsion has been evaluated in aortic stenosis while no data are available on aortic valve insufficiency. Bicuspid Aortic Valve is one of the most common cause of insufficiency in young and in athletes were it remains asymptomatic for along time despite a progressive enlargement of the Left Ventricle chamber (LV). The aim of this study is to evaluate the role of Endo/Epi rotation and torsion to define the LV performance in two groups of asymptomatic athletes: one with Bicuspid Aortic Valve (BAV) and mild insufficiency compared to athletes with normal Tricuspid Aortic Valve (TAV).
Methods: 30 BAV athletes matched with 30 TAV athletes, were submitted to an echocardiographic exam. The 2D-standard and deformation echo parameters (LV basal and apical Endo/Epi rotation, torsion, circumferential strain) were calculated by the speckle tracking multi-layer approach (X-Strain -ESAOTE-Italy). Statistical analysis includes T-Student pair and unpaired test.
Results: The 2D standard echo parameters show significant differences between the two groups: the Ao-Root value ($31.11 \pm 1.8^{BAV} > 26.22 \pm 2.3^{TAV}$, $p < 0.05$);the IVRT($80.55 \pm 9.09^{BAV} > 69.44 \pm 7.26^{TAV}$, $p < 0.01$) and LVSD ($33.9 \pm 2.6^{BAV} > 30.44 \pm 1.5^{TAV}$, $p < 0.05$). The EF is normal in both (66.29 ± 5.2 vs. 64.6 ± 4.7, p NS) In BAV only the Epi/Endo apical rotation are significantly higher than TAV (BAV Endo 8.64 ± 4.0 vs. TAV 5.89 ± 1.8 with $p < 0.05$; BAV Epi 5.74 ± 1.4 vs. TAV Epi 3.40 ± 1.6, $p < 0.01$) but not at basal level (Endo BAV -4.46 ± 2.4 vs. Endo TAV -5.95 ± 2.7, p NS; Epi BAV -4.00 ± 1.2 vs. Epi TAV -3.93 ± 2.5 with p NS). Circumferential strain results to be in BAV (Apex Endo -22.20 ± 7.26; Epi -13.96 ± 4.30; Base Endo -19.5 ± 4.08; Epi -13.11 ± 4.20) similar to TAV (Apex Endo -26.10 ± 6.96; Epi -14.05 ± 4.25; Base Endo -21.60 ± 5.89; Epi -13.67 ± 3.59) with p NS for all. In consequence of the low values at basal segments the endo/epi torsion result to be therefore normal in both (Endo Twist BAV 13.51 ± 5.0; Epi Twist BAV 9.45 ± 2.5; Endo Twist TAV 11.80 ± 2.4; Epi Twist TAV 7.31 ± 3.4).
Conclusions: The multi-layer approach by 2D speckle tracking imaging provides relevant information on assessment of LV myocardial function in aortic valve insufficiency. Augmented apical endocardial rotation does not anyway contribute to increase the LV twist in BAV. The normal value of the twist in this particular group of athletes could be suggestive for a possible protective role of the sport activity in them. In view of the mild alteration of the diastolic parameters found in BAV group respect of TAV one, the evaluation of the untwisting phase of the LV chamber could be considered for further investigations.



Complication of anticoagulant therapy in patient with non valvular atrial fibrillation

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Introduction: Atrial fibrillation (AF) is considered an important risk factor for stroke. Non valvular AF, the most common form of this arrhythmia, increases the risk of stroke approximately fivefold. Valvular AF increases the risk up to 17-fold. One of the primary therapeutic endpoint in AF is the reduction of stroke risk through prevention of thromboembolism. Anticoagulation therapy with warfarin, leading to therapeutic INR range values (2–3), reduces stroke risk by 65% in patients with AF; whereas antiplatelet agents reduce stroke by 20%. However, the benefits of warfarin use in routine practice are offset by the possibility of increased bleeding, including intracerebral hemorrhage.
Case report: A 65-year-old man with hypertension, aortic insufficiency and persistent non valvular atrial fibrillation on anticoagulation therapy with warfarin, was admitted to "S. Andrea Hospital" Emergency Department complaining sudden onset of approximately 5–6 h long lasting headache in frontal and occipital areas, loss of balance and spatial orientation. Physical examination showed BP 180/80 mmHg, HR 78 bpm, arrhythmic cardiac activity, systolic murmur on aortic area, right sided lung basal crackles. Neurological examination was unremarkable.

AF was confirmed by ECG. Laboratory tests were overall normal except for INR values (1.38) to be considered out of therapeutic range. Chest X-ray showed "thickened interlobular septa, increased prominence of hilar vasculature and left heart contour". Noncontrast cerebral computed tomography (CT) showed "large hypodense right temporal-parietal-occipital area, with ipsilateral cortex flattening likely compatible with subacute ischemic damage. Chronic ischemic outcomes in the left basal ganglia". Twenty-four hour control CT head scan showed "hemorrhage infarction of stroke". Considering the whole clinical condition, persistent AF and new onset of cerebral hemorrhagic stroke, the oral anticoagulant therapy was replaced with low molecular weight heparin 6,000 IU s.c. bid upon review of neurological consultation. In order to complete the diagnostic path a ColourDoppler US of neck vessels was performed showing "mild unilateral non-stenosing (45%) parietal carotid plaque" and a head MRI confirmed the cerebral lesions described on the CT. During hospitalization the patient was asymptomatic and showed no new onset of neurological signs or symptoms. He was then discharged with low molecular weight heparin treatment. He was also recommended to repeat a cerebral CT scan in 10 days but on the eighth day after discharge the patient came back to the Hospital for relapsing headache on frontal, occipital and periorbital areas of the head. The cerebral CT scan performed at Emergency Department showed "markedly increased hemorrage infarction area upon ischemic region in right cerebral parietal-occipital hemisphere compressing lateral ventricle with evidence of mild ipsilateral subarachnoid hemorrhage". The neurosurgeon ruled out the need for surgical treatment and the patient was transferred to our Department appropriate medical treatment. On admission he was fully alert and oriented, BP 160/90 mmHg, HR 66 bpm. The neurological examination showed mild disartria and left sided muscular motor weakness. Based on clinical and radiological findings anticoagulation therapy was stopped, and mannitol 18% was administered. The antihypertensive therapy was optimally titrated as well and progressive improvement of whole neurological condition was noticed. Based upon neurological consultation and evidence of partial reabsorption of haemorrhage suffusion on head control CT scan, it was then decided to introduce antiplatelet therapy and discharge the patient. Finally, 8 months after discharge, the patient is on warfarin and he is still asymptomatic.

Conclusion: Patients with non valvular AF are exposed to high risk for thromboembolic strokes. Treatment based on anticoagulants, within correct therapeutical INR range, substantially reduces this risk, but the common hemorrhagic adverse effects with currently available anticoagulation therapy may sometimes outweigh the benefits. Anticoagulation therapy it's highly recommended in primary prevention of stroke in patients with AF with further risk factors for stroke. One of the most accurate risk score tool reaching a greater predictive value for stroke among patients with AF is the CHADS2 VASc based on the presence of heart failure, hypertension, age, diabetes, prior stroke, vascular disease, sex category. Anticoagulation therapy should only be prescribed to those patients with moderate to high risk of stroke whom the benefits clearly outweigh the risks.

Effects of metabolic syndrome and altered glucose tolerance on arterial stiffness, diastolic cardiac function and intima media thickness

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Background and aims: Metabolic syndrome (MS) and type 2 diabetes are both associated with high risk for cardiovascular diseases. However the respective role of MS and altered glucose tolerance on vascular damage is under debate. We investigated whether MS, with or without altered glucose tolerance, affects early markers of vascular injuries.

Materials and methods: 132 subjects, divided in two groups by the presence of MS according to ATP III criteria, underwent to an OGTT. Intima-media thickness (IMT) was assessed by carotid ultrasound. Augmentation and augmentation index (Aug and Aug I), surrogate markers of arterial stiffness, and subendocardial viability ratio (SEVR), index of diastolic cardiac function, were assessed by applanation tonometry.

Results: Gender, age, BMI, waist circumference, total and LDL cholesterol were not significantly different among subjects with ($n = 64$) or without MS ($n = 68$). Subjects with MS had significantly higher levels of triglycerides, fasting glucose and blood pressure and lower levels of HDL-cholesterol. Maximal IMT was significantly higher in MS than in non MS groups [1.35 mm (CI 1.21–1.51) vs. 1.05 mm (CI 0.96–1.16), $p = 0.001$]. Aug and Aug I were higher, but not significantly, in MS subjects (13.4 ± 17.5 vs. 8.4 ± 5.5 mmHg, $p =$ ns and 25 ± 14.4 vs. 24 ± 13.3 mmHg, $p =$ ns, respectively). SEVR was significantly reduced in MS compared to non MS (149 ± 26.9 vs. 159.9 ± 31.7 mmHg, $p = 0.03$). After OGTT, the subjects were divided in normotolerants (NT) and with altered glucose tolerance (AGT, blood glucose at 120′ >140 mg/dl). IMT was similar in AGT subjects with MS [1.37 mm (CI 1.21–1.55)] and without MS [1.38 mm (CI 1.11–1.70)], $p =$ ns. In contrast, IMT was significantly higher in NT subjects with MS [1.32 mm (CI 1.05–1.55)] as compared with NT without MS [0.91 mm (CI 0.8–0.98), $p < 0.001$]. SEVR was significantly reduced in AGT patients with MS (148 ± 28 mmHg) compared to AGT without MS (163 ± 30 mmHg, $p = 0.05$) and in NT with MS (148 ± 23 mmHg) compared to NT without MS (159 ± 32 mmHg, $p < 0.05$). Logistic regression analysis showed that both altered glucose tolerance and MS were independently associated with high risk of increased IMT (OR = 2.326, $p = 0.03$ and OR = 2.771, $p = 0.03$ respectively).

Conclusion: Diastolic cardiac function is impaired in MS independently of the presence of altered glucose tolerance. In contrast, IMT was increased both in altered glucose tolerance and MS.

Early post-discharge ambulatory follow-up aimed to monitor congestion and tailor diuretics and fluid intake in cardiac failure: a pilot study

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Introduction: Congestive heart failure (HF) is a leading cause of hospitalization and readmission in many hospitals worldwide today. Fluid accumulation plays a key role in the pathophysiology of the recurrent events of acute decompensation in HF. To date, successful treatment has been limited because no agent has been shown to reduce post-discharge readmission rate, and patients frequently remain symptomatic after treatment.

Aim: We evaluated the effectiveness of a post-discharge early ambulatory follow-up program (on clinical outcome and quality of life.

Methods: 43 consecutive recently re-stabilized congestive HF patients (age 69 ± 7 years; NYHA class II–III) were recruited. All patients were discharged on a daily fluid restriction of 1 liter and were on treatment with the higher tolerable oral doses of furosemide able to maintain clinical stability during the last three consecutive days of

hospitalization. Group A (22 patients) was randomised to an ambulatory post-discharge follow-up model consisting in an early clinic visit within 1–2 weeks; then, a second visit 1–2 weeks later the first; finally another visit 1 month after hospital discharge. Group B (21 patients) was randomised to a conventional ambulatory clinic follow-up at 1 month after discharge and during this visit the treatment was subsequently optimised. The ambulatory approach in both groups was finalised to monitor congestion (clinical monitoring of signs/symptoms of congestion and body weight, on the evaluation of body hydration state by using bioelectrical impedance analysis) and laboratory data and tailor diuretic treatment and daily fluid intake accordingly. All the patients were clinically re-assessed without change in treatment at 3 and 6 months. Bioelectrical parameters and B-type natriuretic peptide (BNP) plasma levels were collected in both groups at baseline, 1, 3 and 6 months after hospital discharge.

Results: The post-discharge early ambulatory follow-up program, in comparison to the other, resulted in a more significant maintenance of compensation and freedom from congestion demonstrated by NYHA functional class, abdomen ultrasound, HF congestion score (HCFS) and bioelectrical parameters. A significant worsening of the clinical systemic congestion was, instead, observed in the same period in B group. Moreover, the early ambulatory strategy was significantly associated during the 6 months after discharge to a decreased hospital readmission rate ($p < 0.03$) and to improved NYHA class, HCFS and quality of life at Minnesota living with heart failure questionnaire. During the follow-up period BNP plasma levels showed a significant decrease in A group in comparison with B group where they increased.

Conclusions: We concluded that the investigated ambulatory strategy is helpful and may be recommended in the early post-discharge phase to optimize the clinical (congestion) and pharmacological (particularly diuretics and daily fluid intake) management and to maintain effectively cardiac compensation in HF.

Atypical clinical presentation of acute myocardial infarction in a diabetic woman: a case report

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A 76 woman with insulin-treated type 2 diabetes mellitus and obesity (BMI 32.4 kg/m^2) who presented to our Emergency Department (ED) in mars of current year with unexplained anxiety state, initially underwent basal electrocardiogram, that was normal. Then she underwent psychiatric counsel and took a sedative drug. Her anxiety did not seem to be due to any well known cause and it emerged she had never suffered from anxiety states, depression states or another psychiatric disorders. So we decided to keep her under clinical observation and to do later a psychiatric revaluation. Serum levels of myocardial enzymes troponin I (cTNI) and myoglobin were normal at arrive on ED. Our patient went on complaining anxiety and did not feel chest pain, palpitation, fatigue, or dyspnea. But another basal electrocardiogram we performed after an hour her arrive on ED surprisingly showed significant and persistent ST-segment elevation in inferior derivations (DII, DIII, aVF). The patient underwent primary percutaneous intervention (PCI) for inferior wall STE myocardial infarction (STEMI). That woman came back to our ED 10 days later complaining once again the same anxiety state. We performed immediately an electrocardiogram, which did not show any significance ST abnormality. Nevertheless we decided to keep her under clinical observation to ECG and myocardial enzymes monitoring at admission, 6 and 12 h. All serial electrocardiograms were normal. Instead serum levels of cTNI were normal at arrive, but became high at subsequent determination. So the patient underwent PCI for anterior wall non STE myocardial infarction (NSTEMI). Post-infractual course was favourable and without complications. A considerable percentage of patients with acute myocardial infarction are still inappropriately discharged from the emergency departments. Atypical presentation is the leading cause of this poor outcome (1). Moreover diabetic women with acute myocardial infarction are more frequently accompanied by atypical symptoms (2). Nevertheless official guidelines are not exhaustive about this question. Acute myocardial infarction in obese diabetic and elderly women is not rare. But atypical presentations can be a true challenge for emergency physicians. Our patient had a high cardiovascular risk for her clinical features, but she did not complain symptoms referable to cardiovascular illness. During second heart attack the woman described the same sintomatology that she experienced during previous myocardial infarction, a thing that aided physicians. But in first heart attack absence of chest pain and atypicity of symptoms could have lead to under-recognition of the disease and under-treatment. Official guidelines do not clearly indicate what clinical management is correct or opportune for similar cases. No protocol exist for patients with atypical complaints (3). Perhaps more detailed indications will need for some subcategories of high cardiovascular risk patients with very atypical symptoms.

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Metabolic syndrome and homocysteinemia

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Introduction: Moderate hyperhomocysteinemia is a risk factor for atherosclerotic vascular disease and for recurrent venous thromboembolism. Studies investigating the association between total homocysteine (tHcy) levels and insulin resistance have shown conflicting results.

Objectives: We analyzed the association of tHcy levels with metabolic syndrome and its components in a group of obese or overweight subjects.

Methods: In the period 2006–2009 plasma tHcy levels were measured in 695 subjects (210 males, mean age 43.7, SD 10.9; 485 females, mean age 45.5; SD 11.6 years). Diagnosis of metabolic syndrome (MS) was made when the subject satisfied any three of five traits (ATP III criteria 2005). We compared mean values of tHcy between subjects with and without MS using Mann–Whitney test. Comparison among subgroups categorized by the numbers of the metabolic components was analyze by Kruskal–Wallis test. Correlations between tHcy and other clinical variables were performed with Spearman rank order correlation analysis.

Results: The overall mean value for serum tHcy concentrations was 11.4 (SD 4.7) μmol/L. It was significantly correlated with fasting

glucose and urate levels. Subjects with MS (No. 342) showed serum tHcy slightly higher than the non-MS individuals (11.8, SD 5.5 vs. 11.1, SD 4.1; $p = 0.04$). Subjects with higher fasting glucose, lower HDL-C, and higher blood pressure showed significantly higher tHcy levels ($p < 0.05$). There was no difference in MS frequency dividing the cohort into two groups by a tHcy cut off of 10 μmol/L. Moreover, no significant difference in the serum tHcy levels was detected according to the number of satisfied criteria to diagnose MS.

Conclusions: Our preliminary analyses confirm the relationship between metabolic syndrome and tHcy levels. We found no link between tHcy levels and the prevalence of MS or the MS diagnostic criteria. Future analyses will use multiple regression models to take into account several factors simultaneously.

Oxidative index: a new tool to evaluate oxidative stress in obesity

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Obesity, a fast growing problem reaching epidemic proportions worldwide, increases the risk of cardiovascular disease and premature death. Elevated cardiovascular morbidity and mortality in obese subjects are only partially explained by classical cardiovascular risk factors. Recently other less conventional risk factors have been postulated as different and/or additive mechanisms linking obesity to cardiovascular disease. Aim of the present study was to evaluate the involvement of oxidative stress, defined as an excess of pro-oxidants not counterbalanced by adequate antioxidant system. With this purpose, reactive oxygen species (ROS) concentrations and Total Antioxidant Capacity (TAC) were measured by the relevant commercial kits (dROMs test and OXY-Adsorbent test, respectively, Diacron International, Italy) in 137 overweight-obese subjects (44 M/93 F; age 46.7 ± 9.8 years; BMI 34.4 ± 5.5 kg/m^2) and in 183 normal-weight subjects (50 M/133 F; age 43.9 ± 13.9 years; BMI 25.5 ± 4.6 kg/m^2). For each subject an oxidative index (Oxy-I), reflecting both the pro-oxidative and anti-oxidant counterparts, was calculated subtracting the TAC standardized variable from the ROS standardized variable [1]. Our results showed that Oxy-I was significantly higher in obese than in control group (0.65 ± 1.15 vs. 0.15 ± 1.44 AU; $p < 0.001$). Considering the whole study population, females showed Oxy-I significantly higher than males (0.64 ± 1.31 vs. −0.31 ± 1.20; $p < 0.0001$). Moreover, a significant positive correlation was found between Oxy-I and BMI ($r = 0.213$; $p = 0.002$), Oxy-I and age ($r = 0.137$; $p = 0.0139$), Oxy-I and fibrinogen ($r = 0.379$; $p < 0.0001$) and Oxy-I and C Reactive Protein ($r = 0.283$; $p = 0.0016$). After adjustment of significant determinants for elevated oxidative stress (Oxy-I > 75th percentile corresponding to 1.115 AU), the multivariate logistic regression analysis indicated obesity as an independent factor for oxidative stress (odds ratio = 1.75, confidence intervals = 1.03–2.96, $p < 0.05$). The prooxidant/antioxidant balance is altered in obese subjects and closely related to inflammatory processes. Interventions focused on weight loss may decrease the inflammatory and oxidative burden, and attenuate or delay the onset of complication in such high-risk population.

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Metabolism, diabetes and clinical nutrition

Hyperamylasemia in patients suffered from diabetes mellitus type 2 in therapy with vildagliptin

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Vildagliptin belongs to the inhibitor of DPP-4, a new class of oral hypoglycaemic drugs which use a glucose-dependent mechanism. It stimulates the insulin and it reduces the glucagon secretion from pancreas, so it promotes the surfeit sense too. The collateral effects signaled in literature are: rhinitis, migraine, hypertransaminasemia (0.3–0.8%), skin manifestation; the hypoglycaemia is rare. We describe two patients in therapy with this drug. F.A. is a 69-year-old man, diabetic for 6 years with hypertension in therapy with amlodipin for 3 years. The therapy with maximal dose of metformin was failed two times so on June 2009 we started a therapy with vildagliptin 50 mg b.i.d. in association with metformin 1,000 mg^3/day. After 3 months we made the first follow-up and we found the reduction of the glycate haemoglobin (from 8 to 7.2%) and of the fast glycaemia (from 173 to 158 mg/dl), the vanishing of glycosuria, normal hepatic and renal indexes and normal pancreatic amylasemia. During the second follow-up (after 6 months) we found a further reduction of glycaemic indexes (glycate Hb 6.8%, fast glycaemia 131 mg/dl) but an increase of pancreatic amylase (8 times higher than the normal value, 575 U/l instead of 70 U/l) without any symptom. The hyperamylasemia was confirmed by two blood exams, made 15 days after the second follow up. We excluded other pancreatic, hepatic or bile ducts diseases making an abdominal ultrasound. After 1 month since the suspension of vildagliptin the amylase value become normal. M.A. is a 58-year-old man, diabetic for 3 years with negative anamnesis for other diseases. The therapy with maximal dose of metformin was failed two times, so on October 2009 we started a therapy with vildagliptin 50 mg b.i.d. in association with metformin 1,000 mg^3/day. After 3 months we made the first follow-up and we found a reduction of glycaemic indexes (glycate Hb from 7.6 to 6.7%, fast glycaemia from 173–150 mg/dl) but we found an increase of pancreatic amylasemia too (346 U/l instead of 70 U/l). After few days we remade the analysis and these exams confirmed the hyperamylasemia (4–5 times higher than the normal value) and the ultrasound confirmed the lack of other diseases. After 1 month since the suspension of vildagliptin the amylasemia was become normal. In conclusion, in our clinical experience with about thirty patients, vildagliptin proves itself efficacious to reduce the glycaemic indexes in diabetic patients in association with other oral hypoglycaemic drugs, but it's necessary to check the pancreatic amylasemia during the follow-up to avert the risk of acute pancreatitis.

Visual alterations in a patient affected by type 2 diabetes under treatment with pioglitazone

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Pioglitazon is an oral antidiabetic, it belongs to thiazolidinediones. These drugs reduce the insulin-resistance in peripheral tissue (adipose tissue, muscle) and they inhibit the gluconeogenesis in the liver. This

medicine proves itself to be useful in secondary failure of metformin and diet in literature and in our clinical experience. The known collateral effects are: water retention (edema), increase of weight, migraine, superior breathing apparatus diseases, heart failure. D.G.S. is a 64-year-old man, he came in our diabetic centre with high glycaemic index (165 mg/dl) and glycate Hb (7.2%). During the anamnesis the patient retailed hypertension in therapy with lisinopril 20 mg/day and diabetes in therapy with metformin 2,000 mg/day. We made the physical examination in which we found rhythmical heart sounds, normal heart rate (80 bpm), BP = 135/80 mmHg, normal abdominal palpation, absence of edemas, bilateral murmur vesicular without pathological sounds in the thorax, weight = 75 kg (BMI = 29). The echocardiography showed a normal ejection rate. We prescribed a therapy with pioglitazon 30 mg/day in addition to metformin 2,000 mg/day. In the course of the first follow-up, after 3 months, we found a reduction of fast glycaemic index (137 mg/dl) and of the glycate Hb (6.8%), absence of glycosuria and absence of edemas, normal cholesterol, triglycerides, transaminases, azotemia and serum creatinine. The weight was 76.5 kg and BMI = 29.5. During the second follow up, after 6 months, we observed a furthermore reduction of glycaemic index (115 mg/dl) and of glycate Hb (6.2%) but the patient retailed an obfuscated sight "like a veil in front of the eyes". The ophthalmologist found a bilateral macular edema more marked in the right side. We suspended the pioglitazon and we started a therapy with sitagliptin 100 mg/day in addition to metformin 2,000 mg/day. During the next follow up, after 2 months, the patient related a considerable improvement of sight and the ophthalmologist noted an important reduction of macular edema. In literature the prevalence of macular edemas in therapy with pioglitazon is 6–9%; therefore it's important to investigate about alteration of sight during the follow-up of the patients in therapy with thiazolidinediones.

Adipocytokines in obesity

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Background: Obesity is a chronic pathological condition with high cardiovascular morbidity and mortality rates, frequently associated with various metabolic disorders defined as metabolic syndrome. The syndrome is associated with insulin resistance and systemic low-grade inflammatory state. Adipose tissue is now widely accepted to be an endocrine organ secreting various adipokines, which regulate wide spectrum of metabolic and immune processes. It releases a large number of bioactive mediators that influence not only body weight homeostasis but also insulin resistance as well as alterations in lipids, blood pressure, coagulation, fibrinolysis and inflammation, leading to endothelial dysfunction and atherosclerosis. These immunological mediators, proinflammatory cytokines, chemokines, growth factors and complement proteins (adipocytokines) contribute to the cardiovascular outcome in overweight and obese people.
Aim: To evaluate the "adipocytokines profile" in obesity.
Material and methods: We enrolled 141 obese subjects (47 M; age 46.6 ± 9.8 years; BMI 34.5 ± 5.4 kg/m^2) without any previous cardiovascular disease. Serum soluble cytokines and adhesion molecules were measured by Flow Cytometry method (FACScan, Beckton Dickinson) using the relevant commercial kit (Human Obesity 9plex Kit; Bender MedSystems, Austria). The following analytes were measured: Soluble CD 40 Ligand (sCD40L); Soluble Intercellular Adhesion Molecule-1 (sICAM-1); h IL-6; Leptina; Monocyte chemoattractant protein-1 (*MCP-1*); Myeloperoxidase (*MPO*); *Osteoprotegerin* (OPG, also known as Osteoclastogenesis inhibitory factor); Resistina; sTNF-R. We also measured serum C Reactive Protein (CRP) and lipid panel by routine method. Results about soluble cytokines and adhesion molecule were compared with a reference control population matched for age and sex. Statistical analysis was performed by GraphPad Prism 5 and data were considered to be significant at $p < 0.05$.
Results: Obese subjects showed leptin and sICAM-1 concentrations (94 ± 89, 506 ± 237 ng/mL) significantly higher than controls (25.2 ± 23, 339.2 ± 120 ng/mL; $p = 0.006$ and $p = 0.01$, respectively). Also sCD40L and resistin levels were higher in obese subjects than controls, even if the difference was not significant. A strong correlation was found between BMI and CRP ($r = 0.4$, $p < 0.0001$).
Conclusions: significantly elevated serum leptin levels were found in 51% of our obese subjects, implying resistance to endogenous leptin in obesity. Moreover, in our obese subjects the high levels of sICAM-1 and the correlation between BMI and CRP confirmed the presence of low-grade inflammatory condition, associated with obesity.

Effects of a 6 days a week low protein diet regimen on depressive symptoms

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Objectives: Late-life depression is one of the main health problems among elderly diabetic subjects. In addition, depression is a common psychopathological condition among renal failure patients and most of these patients follow a low protein diet regimen (LPD). However, the effects of LPD on depressive symptoms are unclear.
Design: In the present study, the effects of LPD regimen on depressive symptoms in elderly type 2 diabetic subjects with renal failure were investigated.
Participants: Fifty-two young-old type 2 diabetic patients with renal failure were enrolled in the study. All participants after normal protein diet regimen (NPD) providing 1.2 g kg^{-1} day^{-1}, were instructed to consume either a LPD providing 0.8 g kg^{-1} day^{-1}, 7 days a week (LPD 7/7) or 6 days a week (LPD 6/7) randomly.
Results: Mean GDS-15 (2.0 ± 0.6) and BDI (4.1 ± 1.0), during NPD, significantly increased to (6.7 ± 1.6) and (12.2 ± 0.1.4) respectively, after LPD 7/7 ($p < 0.05$ vs. NPD). However, after LPD 6/7, mean GDS-15 and BDI significantly decreased to (4.4 ± 1.5) and (6.7 ± 1.6), respectively ($p < 0.05$ vs. LPD 7/7).
Conclusion: LPD 6/7 regimen significantly decrease depressive symptoms in young-old type 2 diabetic patients.

Role of type 2 diabetes in atherosclerotic disease

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Over 100 million people worldwide suffer from diabetes. 5–10% of this population suffer from type 1 diabetes while the remaining 90–95% suffer from type 2 diabetes, also known as adult-onset diabetes mellitus. Due to the increasing obesity and unhealthy lifestyles, it is expected that the incidence of type 2 diabetes will increase to hit 35–40% of the population over the next decade. Diabetes is a powerful and independent risk factor for accelerated development of atherosclerotic coronary artery disease which leads to an increase in morbidity and cardiovascular complications. Angioscopic studies show a higher incidence of coronary thrombosis in diabetic patients. Ultrafast CT studies showed an increased extent of calcification. IVUS studies have suggested a reduction of adaptive remodeling in diabetic patients than non-diabetics. Histological samples obtained from biopsies performed during coronary atherectomy or carotid endarterectomy have shown that in diabetics there is an increase in inflammatory infiltration compared with nondiabetic. Prolonged exposure to hyperglycemia is now recognized as a major factor in the pathogenesis of diabetic complications, including atherosclerosis. Hyperglycemia induces a large number of alterations at the cellular level of vascular tissue that potentially accelerates the atherosclerotic process. These include: glycosylation of proteins and lipids, which can interfere with their normal function; activation of protein kinase C with subsequent alteration in growth factor expression; promotion of inflammation through the induction of cytokine secretion and hyperglycemia-induced oxidative stress. It is widely accepted that hyperglycemia-induced reactive oxygen species contribute to cell and tissue dysfunction in diabetes. These biochemical changes are reflected on the endothelium: vasoconstriction, activation of adhesion molecules, inflammation and thrombosis caused by hypercoagulation and platelet activation are the major changes at this level. Therefore, it seems clear that proinflammatory and prothrombotic state associated with diabetes play an important role in inducing the morphological change of the atherosclerotic plaque, although the mechanisms by which hyperglycemia, insulin resistance and oxidative stress causing these changes have not yet been clarified completely. In summary, diabetes is associated with a more abundant inflammatory infiltrate (macrophages and activated T lymphocytes), increased size of the necrotic core of atherosclerotic plaque and diffuse coronary atherosclerosis. Further studies are needed to better understand the relationship between hyperglycemia, insulin resistance and greater induction of inflammation seen in atherosclerotic arteries of diabetic patients. However, it has been proven that the control of hyperglycemia alone is not sufficient to reduce macrovascular complications of diabetes. Appears necessary to simultaneously reduce the systemic inflammation that does not seem to be closely linked to high blood glucose. Remains controversial the mechanism by which hyperglycemia might directly promote vascular inflammation, an early event in the genesis of atherosclerotic plaque.

A new bioimpedenziometric technology for the prediction of visceral fat tissue and bio-humoral parameters of the metabolic syndrome

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Introduction: The visceral fat is considered the most important predictor of metabolic abnormalities in obesity. The measurement of this fat requires CT, MRI or ultrasound, which is not easy to use in clinical practice. The aim of our study was to test various anthropometric measures and a new method based on BIA technology (VISCAN, Tanita) for the prediction of visceral fat tissue and bio-humoral parameters of the metabolic syndrome.
Materials and Methods: We analyzed 62 subjects (29 M, 33 F) with mean BMI 29.2 ± 5.3 kg/m^2. In all patients were determined: Col-tot, HDL, LDL, triglycerides, blood glucose, insulin, waist circumference and sagittal diameter of the abdomen (SAD), abdominal fat by Vi-scan and ultrasound measurement of peritoneal fat (distance between M. rectum-aorta).
Results: We made a simple regression analysis of the relationship between anthropometric measures, Viscan and ultrasound measurement (considered as gold standard), and found for all methods a high degree of correlation between waist circumference (r = 0626, $P < 0.000$), SAD ($r = 0774$, $P < 0.000$), ViScan ($r = 0634$, $P < 0.000$). Then, we prepared a multiple regression model using the ultrasound measurement as dependent variable and BMI, waist circumference, SAD and Vi-scan as independent. In this model, SAD correlates significantly with the ultrasound ($P < 0.000$). When we considered the correlations with metabolic variables, Ultrasound confirmed a good correlation with HDL ($r = -0584$, $P < 0.000$), triglycerides ($r = 0.375$, $P < 0.01$), blood glucose ($r = 0.576$; $P < 0.000$) and insulin ($r = 0345$, $P < 0.01$). SAD and Vi-Scan also have similar correlations.
Conclusion: Both SAD and ViScan of the visceral fat correlate significantly with ultrasound measurement and with metabolic alterations. However, SAD was a better predictor of visceral fats accumulation.

Insulin resistance is linked with kidney damage

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Insulin resistance is present in many diseases: diabetes mellitus, abdominal obesity, hepatic steatosis, atherosclerosis, polycystic ovary syndrome, hyperandrogenism. Kidney dysfunction can be present in these conditions and gives an additional risk of cardiovascular and cerebrovascular disease. Aim of our study was to evaluate the correlation between levels of insulin resistance and serum creatinine.
Materials and methods: We evaluated the presence of insulin resistance (HOMA index) in 395 patients, aged between 17 and 93 years, consecutively referred to our Unit of Internal Medicine. All patients underwent a medical examination, anthropometric measurements and blood test including serum creatinine levels.
Results: The average age was 54 years. Patients were divided into two groups. Group A patients with HOMA index $\leq$2.5. Group B: HOMA index >2.5. Group A consists of 190 subjects (95 males and 95 females) showed average values of creatinine of 0.9 mg/dl. In group B, consisting of 190 subjects (97 males and 93 females), mean creatinine was 1.4 mg/dl. Within group A, there were no significant differences in creatinine levels between male (0.90 mg/dl) and female (0.86 mg/dl). In group B, consisting of 190 subjects (97 males and 93 females), mean creatinine was 1.4 mg/dl. Within group A there were no significant differences in creatinine between the average male (0.90 mg/dl) and female (0.86 mg/dl). In group B there was a slight increase in woman than in man (0.7 vs. 0.83 mg/dl).

Conclusions: Our study shows that the highest values of insulin resistance, expressed as HOMA index, are associated with higher serum creatinine values, and this is a index of organ damage. This association is stronger in female sex.

Insulin resistance and HDL cholesterol levels in a south Italian outpatients group

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Low HDL levels and high insulin resistance are risk factors for cardiovascular diseases. The aim of our study was to evaluate the possible correlation between HDL levels and insulin resistance. Were evaluated 395 consecutive outpatients, mean age 54 years referred at our Unit of Internal Medicine. All patients underwent a medical examination, anthropometric measurements and blood tests. Of 395 patients, average blood glucose was 101 mg/dl, total cholesterol 188 mg/dl, triglycerides 127 mg/dl and HDL 50 mg/dl. Patients were divided into two groups. Group A: patients with HOMA index $\leq$2.5. group B: patients with HOMA index >2.5. Group A consisted of 190 patients (95 males and 95 females) and showed a mean of HDL 52 mg/dl, while group B consisted of 190 patients (97 males and 93 females) and showed values of HDL 51.7 mg/dl. Between the two groups there were not substantial differences in HDL concentrations. In group B the results showed a lower, but not significant, value of HDL concentrations in females. In our study there were not significant differences in HDL cholesterol concentration in relation to HOMA index values.

Different effects of lean and fat mass on urinary stone risk factors and on bone mineral density in healthy women

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Background: The role of body weight, BMI and body composition in determining lithogenic risk and the effects on bone mineral density are still debated. In particular it is not clear the distinctive contribution of lean and fat mass.
Aim: To verify: (1) whether the urinary excretion of stone risk factors is influenced by weight entirely or by its composition in lean and fat mass, (2) the relationship with bone mineral density, (3) in which body areas bone density is influenced more by lean or fat mass.
Materials and methods: 78 healthy volunteers women (age 46 $\pm$ 6 years, range 31–59) were studied, undergoing 24-h urine collection, evaluation of bone density and body composition by dual-energy X-ray absorptiometry (DEXA) and compiling a 3-day food diary. Two mathematical indexes to highlight separately lean mass (index of lean mass, ILM) and fat mass (index of fat mass, IFM) were defined. Urinary, food and densitometric data analysis was made after the division of women on the basis of median of ILM and IFM indexes.
Results: Women with higher ILM did not differ in body weight and BMI but show lean mass and height significantly greater (40 $\pm$ 4 vs. 45 $\pm$ 5 kg and 159 $\pm$ 6 vs. 163 $\pm$ 5 cm, $p < 0.0001$), bone mineral density significantly better in both upper and lower limbs and at the ribs and higher excretions of creatinine, potassium, phosphorus, magnesium, citrate and oxalate in the absence of differences in food intake. Women with higher IFM did not differ in height but show significantly higher BMI (23 $\pm$ 2 vs. 28 $\pm$ 3, <0.0001), total mass of the trunk (28 $\pm$ 4 vs. 35 $\pm$ 6 kg, $p < 0.0001$) and legs (21 $\pm$ 3 vs. 25 $\pm$ 3 kg, <0.0001) and total body fat (17 $\pm$ 3 vs. 27 $\pm$ 5 kg, $p < 0.0001$). Pelvic, lumbar and femoral bone mineral density was significantly better. No differences in urinary and food intake values.
Conclusions: In healthy women, with similar food intake, fat mass seems not to influence the urinary stone risk factors excretion, more dependent on lean body mass. Bone mineral density seems influenced by fat mass while lean mass appears to exert a positive role particularly on extra-axial skeleton.

Relationship between obesity indices and cardiovascular risk factors in type 2 diabetic patients

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Background and aims: Risk factors of cardiovascular diseases have been investigated by different studies. There were few studies which evaluate the relationship between obesity index and cardiovascular disease in type 2 diabetes mellitus (T2DM) patients. The aim of the study was to investigate which index of obesity is the best discriminator of cardiovascular risk in T2DM patients.
Methods: The study involved 475 T2DM patients from Second University of Naples. We measured body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) in all patients. Systolic and diastolic blood pressure, hsCRP, homocysteine, fibrinogen, total cholesterol (TC), triglyceride (TG), HDL and LDL cholesterols, Apo B, ApoA1 and microalbuminuria were regarded as CV risk factors. BMI was positively correlated to SPG, TG, LDL and Apo B. WC was significantly correlated to hsCRP, homocysteine, TG, HDL, LDL and ApoB.WHR was positively correlated to hsCRP, homocysteine, TG and HDL. WHtR was significantly correlated to SPB, TG, HDL, LDL and ApoB. WC but not BMI and WHR, showed significant differences.
Conclusions: WC and WHtR are more significant related to CV risk factors than BMI or WHR. Our study support the superiority of measuring of WC and WHtR over BMI and WHR, for assessing CV risk in T2DM patients.

Ambulatory blood pressure monitoring in clinical practice: an experience of more than a decade

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Introduction: Ambulatory blood pressure monitoring (ABPM) was first reported more than four decades ago. Several studies have demonstrated that ABPM is the best method of estimating cardiovascular risk in untreated and treated patients with hypertension, and a better predictor of cardiovascular events than the office BP monitoring. Moreover the 2007 European guidelines for management and treatment of hypertension state that 24-ambulatory BP monitoring should be considered, in particular, when: (1) considerable variability of office BP is found, over the same or different visits; (2) high office

BP is measured in subjects otherwise at low total cardiovascular risk; (3) there is a marked discrepancy between BP values measured in the office and at home; (4) resistance to drug treatment is suspected; (5) hypotensive episodes are suspected, particularly in elderly and diabetic patients; (6) office BP is elevated in pregnant women and pre-eclampsia is suspected. In respects of these recommendations most physicians still base treatment decisions on traditional office measurements, using a mercury sphygmomanometer or other similar devices. But although it is now accepted that office-based BP readings provide a little amount of information and have poor reproducibility, despite the availability of numerous and effective nondrug lifestyle modifications, as well as pharmacological therapy, BP control remains suboptimal and only one-third of hypertensive patients reaches the target. This could be in large part explained considering that conventional office-based BP readings provide limited and sporadic informations in order to establish an adequate pressor control. On the other hand it must consider the white-coat effect and the masked hypertension, in addition to low adherence to therapy by patients. At last labile hypertension and poor BP measuring technique complicate the office BP evaluation.

Objective: Our aim is to strengthen the opinion that the ABPM has growing indications.

Methods: On the basis of our experience matured for more than a decade on more than three thousand consecutive patients, we have observed that most of the hypertensive patients were treated in primary care offices and the use of ABPM could improve the management of some of them. Besides the ABPM can reveal pseudo-resistant or resistant hypertension and helps to distinguish, mainly in elderly patients with history of dizziness and syncope, related to postural hypotension or autonomic dysfunction by impaired noradrenergic transmission, and consequent reduced vasoconstriction and intravascular volume, between these two entities allowing furthermore to establish the best therapy to obtain BP target and decrease side effects. The ABPM must be considered in patients with masked hypertension that have an increased cardiovascular risk and are difficult to identify. ABPM also aids to monitoring the response to therapy and provides information useful for suitable therapeutic choices. The phenomenon of "morning surge", the BP abruptly rise upon arising from sleep, seen as part of normal circadian rhythm and, as amply described, accompanied by an increased prevalence of all cardiovascular events (i.e. stroke, cardiac arrest, rupture of the abdominal aorta, etc.), can be evaluated by ambulatory blood pressure monitoring and advise an other possible area of intervention in patients at high risk. The use of ambulatory BP monitoring is also increasing in clinical trials aimed to assess the effects of antihypertensive therapies.

Conclusions: Hardware and software for ABPM are expensive and this technique in routine use is not recommended by Scientific Societies. But the utility of ambulatory BP monitoring in the diagnosis, treatment and monitoring of hypertensive patients has been proved in large clinical trials. It is superior to common office-based BP readings and particularly provides a better picture of the fluctuations in BP levels associated with daily activities, sleep included, and allows physicians to improve BP control in their patients with a positive impact in their cardiovascular risk status. In conclusion a steadily growing literature has attested to the value of this technique and we share the enthusiasm of O'Brien when he states in a recent paper that "every patient suspected of having hypertension should have ABPM to confirm or refute the diagnosis, and every patient with uncontrolled hypertension should have ABPM repeated as necessary until 24-h control of BP is achieved". Finally in order to quantify realistically the high cost of routine ABPM application, it is necessary to bring trials to their own conclusions so that it can be possible to establish whether a strategy based on ABPM is in effects more expensive than a strategy based on multiple OBP and home BP readings considering the effective benefit-cost ratio.

Possible use of the ambulatory blood pressure monitoring in assessment of cardiac dysautonomy in patients with diabetes mellitus type 1

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Introduction: The diabetes mellitus can produce a trouble of the neurovegetative system (SNV). In this context cardiac autonomic neuropathy (CAN) most commonly results in resting tachycardia and postural hypotension. Although electrophysiologic and other functional testing can detect abnormalities in a relatively large fraction of the diabetic population, screening for subclinical disease is generally not warranted. Moreover, the methods of detecting subclinical disease are not widely available. However the demonstration of CAN will provide added benefit. The diagnosis of the trouble of SNV is possible thanks to Ewing's test and the analysis of the heart rate variability (HRV). The SNV is physiologically responsible, by means of biological clocks, of the regulation of circadian rhythms (CR) at heart of the majority of biological function.

Objective: the aim of this study is to investigate initially the CR of the heart rate (HR) and blood pressure (BP), in patients with diabetes type 1, hypothesizing that diagnosis of subclinical cardiac dysautonomy (SCD) is possible through the observation of troubles of CR including the worst one: the disappearance of CR.

Material and methods: we have investigated 60 subjects of both sexes, 40 men and 20 women, mean age 23.4 years, range 11–38 years (most frequently about 15 and 25 years), with history of diabetes type 1 for at least 10 years. Everyone has been submitted to ambulatory blood pressure monitoring (ABPM) by means of an oscillometric automatic device (Pressurometer P6 Del Mar Avinocs) that registered BP every 15 min by day and every 30 min by night, during normal daily activities. All of them was asked to fill out a diary and to press the key day-night in order to start the convenient algorithm asleep-awake (sleep-waking??). Only the texts with a minimum of 90% of useful values were considered. The values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR have been analyzed by means of conventional statistical analysis of their circadian variability.

Results: The analysis of ours data has not allowed us to confirm definitively the presence for both HR and BP of a circadian variability statistically significant, whereas other Authors have demonstrated with the same statistical methods the presence of this rhythm; they have also demonstrated, thanks to methods of chronobiologic analysis (Cosinor method or analysis of periodic regression that defines rhythmicity of a single series of data), that HR has not a significant CR in diabetic patients type 1. This apparent partial discordance could be due to the ages of patients (our patients are frequently very young and their biologic rhythms could not be entirely mature).

Discussion and conclusion: The possible disappearance of the CR of the HR would allow us to presume that the involvement of biologic neurovegetative clock expresses itself with a desynchronization especially between CR and HR. Our data are preliminary and must be confirmed by further studies that comprise normal subject and eventually older patients with diabetes type 2. Moreover the choice and the correct use of the suitable methods of statistical analysis could define better our data. If the disappearance of both the CR of HR and BP was proved definitively by a suitable statistical analysis, the ABPM could be a practical and repeatable technique, at low cost and without particular risks for assessment of SCD at least in diabetes mellitus type 1.

Correlation between glycemic trends assessed by 24 h continuous monitoring and autonomic activity in patients with type 2 diabetes of recent onset

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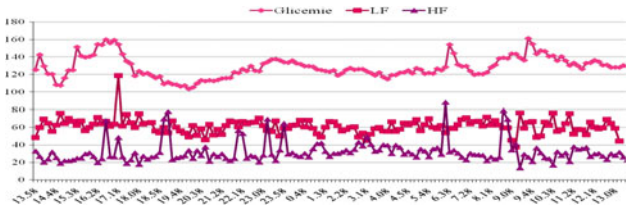
Introduction: Autonomic neuropathy is one of the most common and serious complications of diabetes, with a significant negative impact on survival and life quality of patients, although this is one of the lesser known complications of this disease. The clinical symptoms of autonomic neuropathy generally occur long after the onset of diabetes, while the sub-clinical autonomic dysfunction may be present at the time of diagnosis of type 2 diabetes. One of the least studied among the complications of diabetes mellitus is the cardiovascular autonomic neuropathy (CAN), that is associated with major cardiovascular events. The recognition of subclinical diabetic autonomic dysfunction is important for risk stratification and the management of type 2 diabetes. In addition to the direct role of hyperglycemia, in subjects with insulin resistance the heart rate variability (HRV) show the sympathetic-vagal balance shifted to sympathetic hyperactivity. From these observations we can deduce that the alterations of autonomic nervous system (ANS) appear early, and is possible to consider that the sympathetic hyperactivity has a role in the genesis of the alterations of glucose metabolism.
Object of the study: Our study aims to observe, in patients with type 2 diabetes of recent onset, the cardiac autonomic response to changes in blood glucose within 24 h; this activity was evaluated by monitoring continuous glucose (CGMS), with simultaneous recording of heart activity by HRV within 24 h. Our goal is to confirm the presence of significant alterations in cardiac autonomic activity in patients with type 2 diabetes of recent onset; also plan to evaluate the possible rule of autonomic nervous system within 24 h using the CGMS.
Materials and methods: Were enrolled ten patients (6 men and 4 women) suffering from type 2 diabetes. Were excluded from the study: patients suffering from diseases of autonomic activity; taking drugs that act on autonomic nervous system or on glucose metabolism; who have a diagnosis of type 2 diabetes more than 2 years; smokers; who developed macro- and micro-vascular complications. For each of the subjects enrolled was performed a 24 h electrocardiographic dynamic monitoring with analysis of HRV; simultaneously on each subject was performed a continuous glucose monitoring by Gluco-Day system.
Results: The analysis of the sympathetic (LF) and parasympathetic (HF) components documented a constant sympathetic hyperactivity in patients, especially during the night, as demonstrated by the increase in LF and the increase of LF/HF ratio. The measurement of blood glucose during 24 h, used for the first time, demonstrated that the autonomic nervous system maintained a slight physiological response in correspondence of hyperglycemia.
Discussion: We evidenced in our study the correlation between glycemia and ANS response to instantaneous changes of glucose; this correlation was studied for the first time through the continuous glucose monitoring (CGMS). Although it is already shown in the literature the role of hyperglycemia in HRV changes, in these patients (with optimal glycemic control, as shown dall'A1C) our data have shown that the instantaneous changes in blood glucose was accompanied by minimal changes in the ANS, while the circadian rhythm of sympathetic-vagal balance is early altered, shifted to sympathetic hyperactivity. In future it will be crucial to understand whether these alterations could be affected by a very early change of lifestyle and pharmacologic intervention, both in patients with insulin resistance, both in subjects with normoglycemia but with a family history of type 2 diabetes, in which has already been demonstrated alteration of ANS.



Circulating levels of visfatin and adiponectin in patients with pheochromocytoma

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Background: Pheochromocytoma (pheo) and paraganglioma are rare tumours of neuroectodermal origin. Adipose tissue is considered an endocrine organ able to produce adipokines and other products that plays a very important role in homeostasis of the tissue itself and regulation of several metabolic pathways and inflammatory status. In particular visfatin and adiponectin have been studied to have effects in regulating lipidic and glidic metabolism, their circulating levels are influenced by body fat composition and distribution.
Aim: To evaluate in a series of patients with pheo, anthropometric parameters and circulating levels of adipokines (visfatin and adiponectin) comparing these with those of a group of 25 subjects with essential hypertension (EH) and 20 healthy subjects (HS) matched for age and sex.
Material and methods: 11 patients with pheo (5 M–6 F mean age 55.6 ± 14 years), 25 EH (12 M–13 F, 53 ± 6 years), 20 HS (8 M–12 F, 55.7 ± 6 years). Anthropometrics data, fasting venous blood samples for medical routine and lipids profile, 12-lead resting electrocardiogram (ECG), 2-D transthoracic echocardiography, ABPM 24 h (ambulatory blood pressure monitoring) were obtained from overall subjects. In all patients were obtained blood samples to determine plasmatic levels of adiponectin and visfatin. Diagnosis of pheo was made determining catecholamine production [vanillylmandelic acid (VAM) and metanephrines] and then the location of lesion was obtained performing imaging techniques (abdomen CT scan, MR, MIBG scintigraphy and PET). All pheo patients underwent surgical treatment to remove the lesion.
Results: EH have higher ($p < 0.001$) WC and BMI values respect to pheo and HS. Pheo and EH present higher blood pressure levels with statistical significative differences ($p < 0.001$) respect to HS. Adiponectin levels (12.6 ± 5.4 μg/ml) result lower in EH ($p < 0.001$) compared to those in pheo and HS (24.2 ± 16 and 22.4 ± 8, respectively) while visfatin levels were higher ($p < 0.002$) in EH (27 ± 16 μg/ml) respect to those in pheo and HS (14 ± 10 and 12.2 ± 4.2 μg/ml, respectively). The study of correlations shows a negative correlation between adiponectin and glycemia (r −0.607; $p < 0.0047$), visfatin and LDL cholesterol (r −0.652; $p < 0.0028$) in pheo patients, furthermore in this group we found a positive correlation between VMA and adiponectin (r 0.6; $p < 0.0048$). The echocardiographic study shows that both pheo patients and EH have cardiac remodeling due to hypertensive status. In particular study of

correlations shows negative correlation between circulating levels adiponectin and left atrium diameter in pheo patients (r −0.827; $p < 0.0016$).
Conclusions: Activation of sympathetic nervous system via β 3 adrenoreceptors due to catecholamine overproduction in patients with pheo could explain modification in adipokines concentration, although further studies are requested to demonstrate this hypothesis.

Metabolic syndrome: echographic measurements and lipid profile

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Background: Metabolic syndrome (MS) is a widespread disease in the Western World and obesity, especially visceral fat, plays a key role in its pathogenesis.
Aim of the study: Evaluation of sonographic technique for the measurement of the abdominal fat and analysis of the correlation between the amount of abdominal fat and standard anthropometric and biochemical parameters of MS.
Subjects and methods: 62 Caucasian volunteers, 34 affected with SM and 28 not affected, selected on the basis of diagnostic criteria for MS according to ATP-III (Adult Treatment Panel III), all subjects underwent the following measurements:

- Anthropometric parameters: blood pressure, heart rate, weight, height, body mass index, waist and hip circumference, sagittal abdominal diameter.
- Biochemical serum parameter: total, HDL and LDL cholesterol, triglycerides, LDL density (density gradient ultra-centrifugation), Lp(a), blood glucose, insulin, HOMA-IR (HomeOstasis Model Assessment of Insulin Resistance), homocysteine, hs-PCR, Tumor Necrosi Factor-α, Tumor growth factor-β, IL-6, adiponectin, leptin.
- Ultrasound parameters: liver size, presence and degree of steatosis, intra-abdominal fat thickness divided into subcutaneous, visceral, pararenal, perirenal and perihepatic.

Exclusion criteria were serious liver or kidney failure, thyroid hormone imbalance, acute coronary syndrome within 3 months, diabetes mellitus treatment with insulin sensitizers (metformin and glitazones), lipid-lowering drugs, rimonabant, sibutramine and orlistat.
Results: Sonographic measurements of peritoneal, perirenal, pararenal and perihepatic fat show a close association with the presence of MS, while the thickness of preperitoneal fat does not correlate with MS and its metabolic characteristics. Sonographic measurements of fat thickness (except preperitoneal fat) also correlate significantly with the values of HDL-cholesterol, triglycerides and blood glucose parameters. There were no relations between the presence of inflammatory cytokines and the presence MS. We found a significant relation between LDL fraction and peritoneal AND perihepatic fat thickness; even more significant was the difference in concentration of lipoproteins present in subjects with metabolic syndrome that have higher concentration of VLDL, IDL and "small dense" LDL and lower concentrations of HDL cholesterol and "large buoyant" LDL than non-affected.
Conclusions: Ultrasonographic parameters were significantly different in patients affected with MS compared with normal subjects; likewise the ultrasonographic parameters correlated significantly with lipid parameters of the same syndrome as hypertriglyceridemia, low HDL and abnormalities of glucose metabolism. Measurements based on the use of ultrasound offer a promising method for the evaluation of abdominal visceral fat, being quick, repeatable and free of side effects, complemented by other traditional methods in the evaluation of patients with metabolic syndrome.

Artificial nutrition support and survival in patients with amyotrophic lateral sclerosis

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Background: Amyotrophic lateral sclerosis is a progressive neurodegenerative disease characterized by progressive muscle atrophy leading to respiratory failure and dysphagia. Five-year survival ranges 18–40%. Home enteral nutrition (HEN) through percutaneous endoscopic gastrostomy (PEG) is then indicated to prevent the risk of aspiration pneumonia, dehydration and protein-energy malnutrition. PEM is an independent negative prognostic factor in ALS.
Aim of the study: To gain possible insights into the implementation of HEN protocols for the prevention and treatment of malnutrition in patients with ALS.
Materials and methods: We retrospectively analysed the clinical records of 129 ALS patients (61 M, 68 F) referred to our Clinical Nutrition Unit from 2002 to 2010 to initiate HEN.
Results: Out of the 129 patients, 79 (35 M, 44 F) died and 50 (27 M, 23 F) are currently on HEN. Mean time between ALS diagnosis and PEG placement was 624 ± 541 days, median 540 days. In the group of the 79 patients who died, mean HEN duration was 220 ± 214 days. Moreover, time interval between ALS diagnosis and PEG placement was apparently related to survival. In fact, patients who had a PEG placed within 1 year of diagnosis ($n = 27$) survived 593 ± 259 days, median 534 days, while those having PEG placed more than 1 year after diagnosis ($n = 52$) survived 1,059 ± 586 days, median 897 days, respectively ($p < 0.001$) The proportion of bulbar onset ALS was higher in the first group. Nutritional status was maintained in both groups.
Conclusions: Patients with rapidly progressive disease (i.e. bulbar onset ALS) develop indication for PEG placement earlier and die earlier despite appropriate nutritional intervention. Novel nutritional and metabolic strategies are needed to modify the rate of disease progression, which may influence some of the prognostic factors of ALS.

Taking care of diabetic patients in a multiethnic and multicultural society: troubles and possible solutions

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Introduction: The number of foreigners in Italy has been increasing in last few years; job and family needs have brought more than 3 million immigrants to Italy. Delivering towards health care to this demographic group can be especially difficult.

Objective: To evaluate compliance of foreign diabetic patients, analyze difficulties and hurdles noticed during treatment, and test empirical approaches to handle them.
Study design: Retrospective and prospective cohort study of 42 diabetic foreign patients recruited from database of a university-based doctor's office in Rome from 1996 to 2008.
Methods: For evaluating compliance we used following rates: T_a (number of drop out/total patients), T_c (months of adherence to therapy/total months of therapy), V_u (number of patients who were visited only once). In order to analyze hurdles we used direct or telephone interviews and intervened with the following methods: telephone re-calling of dropped-out patients, exploiting of interpreters during clinical visits, involving religious representatives and using illustrated and translated dietary schedules.
Results: From 1996 to 2008 we saw 62 foreign patients, of whom we selected 42 affected by diabetes mellitus. Mean age was 46.5 years old (SD 13.2 years); 61.9% was male and 38.1% was female; most of the patients were from Europe (28.5%), the Indian subcontinent (21.4%), or the Middle East (19%). T_a was 59.5% in general population; in Romanian and Philippine population it was 100%, while in Bangladeshi group it was the lower (37.5%). T_c was 61.1% (SD 23.5%) in the general population, with the highest value in Peruvian population (100%) and the lower in Philippine population (27%). V_u were in total 13 (30.9%); the worst rate was in the Romanian population where 57.1% were seen only once. In order to understand the reason of drop out, we contacted telephonically drop-out patients. We discovered that four people dropped out because of relocation, two because of misunderstanding, two because of health problem, two because of job needs, and one because of carelessness. We used an interpreter with one of these patients, obtaining an improvement of HbA1c never seen before. Through telephone re-calling we could see about a third of lost patients again. Moreover the problem of the glycemic control during Ramadan of those patients who were contacted by religious representative get better after this event.
Conclusion: The number of foreigners is rising in Europe and in Italy; the need for health care for these patients is raising as well. Diabetic foreign patients are very fragile: they often drop out therapy treatments. This is due to organizational difficulties like relocations, administrative troubles, demands of jobs, the language barrier or other cultural difficulties, such as religious impositions or dietary habits. For these reasons, in order to improve adhesion to therapy treatments, it's necessary to reinforce health care systems with professional figures like interpreters and cultural mediators. To optimize adhesion it is also useful to call drop-outs again and involve religious representatives in the care process.

Pneumology

Case report: *Pseudomonas aeruginosa* community-acquired pneumonia in an adult woman

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A 42 year old, nursing assistant, woman was admitted to our hospital complying fever during the last 2 days, with dry cough and pleuritic chest pain. She had been healthy previously, and she was no smoker. Physical examination indicated a temperature of 37.2°C, blood pressure 110/60 mmHg, SpO_2 98% with FiO_2 0.21, and reduced breath sounds. Laboratory findings revealed leukocytosis (WBC count 13.700/microliter, absolute neutrophil count of 11.000/μl), anaemia (Hb 11.7 g/dl, MCV 78 μm^3), and elevated VES (103 mm). The electrocardiogram was normal. Examination of chest radiograph and computerized tomography revealed bilateral opacities, consolidation shadow with multiple cavities and bronchiectasis in the left upper lobe, pleural effusion and consolidation shadow with cavity in the right lower lobe. The patient underwent to several laboratory tests as Mantoux test and blood sample for anti-HCV, HbsAg, anti-HIV, IgM and IgG Cytomegalovirus, IgM and IgG Epstein–Barr, cancer markers. She also underwent to abdomen echography. All these results were negative. The following empirical antimicrobial agents were given to the patient: piperacillin-tazobactam plus ciprofloxacin. The results of the cultures of sputum specimen and bronchoalveolar lavage yielded *Pseudomonas aeruginosa*, susceptibility only to colistina. Accordingly, the treatment switched to this agent. The last chest TC examination, after 30 days in hospital, indicated bilateral fibrotic areas and a bronchiectasis in left upper lobe. Later, the patient was discharged asymptomatic, without fever and with normal WBC.
Discussion: Community-acquired pneumonia (CAP) due to Pseudomonas aeruginosa is an uncommon pathology, but it may be associated with a adverse outcome. The incidence of this disease is quite variable, ranging from 1 to 5%. However, in severe CAP, the incidence is higher, reaching 12% of cases. The majority of patients with *P. aeruginosa* CAP have an underlying medical condition, including malignancy, bronchiectasis, cystic fibrosis, aplastic anemia, severe immunosuppression. In general population risk factors includes the presence of pulmonary comorbidity (as chronic obstructive pulmonary disease), previous hospitalization, previous antimicrobial treatment and probable aspiration to the lower airways. Previous studies have been shown that these are independent risk factors for *P. aeruginosa* CAP, and they might have an additive role. The risk for this aetiology increases with the increasing numbers of risk factors on the hospital admission. The mortality associated to CAP due to *P. aeruginosa* is about 28%, and it can be higher in patients with pulmonary disease. The patient of this case report had not common risk factors. *P. aeruginosa* CAP in previously healthy patients is rare, and it is more frequent in smokers. *P. aeruginosa* pneumonia has been associated also with exposure to contaminated aerosolized water, and with occupational exposure (nursing assistant). The patient of this case report may have been colonized by microorganisms after occupational exposure and than she developed a *P. aeruginosa* infection. Patients with severe CAP should receive a broader combined therapy with agents as an antipseudomonas penicillin, carbapenem, cefepime plus macrolide, or fluoroquinolone or aminoglycoside. The use of monotherapy with antipseudomonas penicillins or cephalosporins can lead to the emergence of resistant stains.
Conclusion: *P. aeruginosa* CAP should be considered in the differential diagnosis of severe pneumonia, especially in patients with common risk factors, but also in previously healthy patients. Occupational exposure should be assessed in each patient. An initial empirical antimicrobial coverage of these pathogens should consist in a combination of anti-Pseudomonas agents, rather then a single agent therapy, to prevent the emergence of resistance.

Effect of smoking cessation on circulating endothelial coagulative biomarkers

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Background: Smoking is associated with cardiovascular morbidity and mortality. Exposure to cigarette smoke can cause endothelial dysfunction and this may contribute to changes in haemostasis and predispose smokers to atherothrombosis. Here we look at the effects of smoking cessation on circulating levels of biomarkers that have been implicated in the pathogenesis of artherothrombosis.
Method: This 12-month prospective study of 174 smokers with no commonly acquired atherothrombotic risk factor undergoing an intensive cessation program, investigated the effect of quitting on circulating levels of vWF and sTM, D-D and F1+2, and PF4 and βTG. Blood samples and study measures were collected at baseline and at 2, 6, and 12 months after cessation. Data from quitters were compared with those from relapsers.
Results: No statistically significant differences in demographic or laboratory parameters measured at baseline were observed between groups. Significant reductions in several surrogate markers of endothelial cell activation/injury, hypercoagulability state, and platelet activation after stopping smoking were observed in the quitters. The most substantial changes were observed as early as 2 months after cessation for vWF:Ag activity and 12 months after cessation for F1+2. We have also shown some positive association between baseline levels of these biomarkers and number of pack/yrs.
Conclusions: Chronic exposure to smoke sustains the activation of the endothelial-coagulative system and abstinence may result in the reversal of several endothelial-coagulative abnormalities in smokers. This may translate into an overall decline in cardiovascular risk. Identification of a panel of endothelial-coagulative biomarkers reflecting cardiovascular health may be used as an additional motivational tool for those trying to quit smoking.

Comparison of health care associated pneumonia (HCAP) and community acquired pneumonia (CAP) in Italian patients

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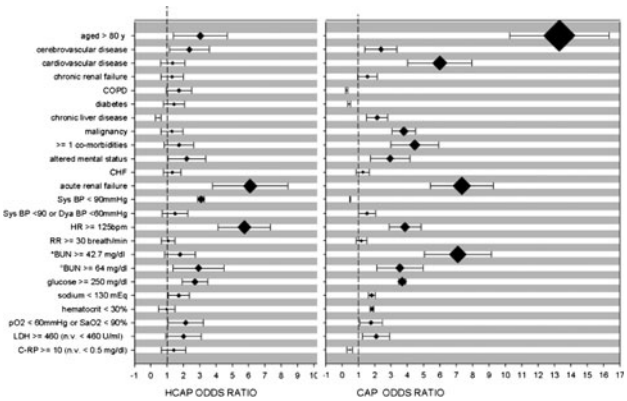
HCAP patients tend to be at higher risk for unfavourable outcomes than patients with CAP. Prior studies show that HCAP patients are older and have more comorbidities, and therefore have higher PSI scores. If mortality in HCAP patients is predicted by standard CAP severity indexes, is there any rationale for categorizing them separately?
Aim and methods: To compare baseline characteristics, outcome and aetiology of HCAP ($n = 238$) and CAP ($n = 255$) patients in a prospective 6-years observational study of 493 consecutive inpatients (269 men, mean age 73 $\pm$ 15.5).
Results: The mean age was 72 years ($\pm$14) for HCAP and 74 years ($\pm$17) for CAP patients, 33.2% of HCAP and 47.1% of CAP patients were older than 80 years of age. Overall 30-day mortality rate was 24.8% in HCAP and 8.6% in CAP. HCAP patients were different from CAP patients for prevalence of cerebrovascular disease (21.8 vs. 31.4%; $p = 0.019$), COPD (13.4 vs. 25.1%; $p = 0.001$) and malignancy (68.9 vs. 3.1%; $p < 0.0001$). At admission, 48.5% of HCAP and 29.1% of CAP got antibiotics in the days prior to presentation. According to Pneumonia Severity Index prediction variables, HCAP patients had lower blood pressure (27.7 vs. 16.9%; $p = 0.005$), lower sodium levels (8.6 vs. 2.7%; $p = 0.005$), lower haematocrit values (29.7 vs. 3.7%; $p < 0.0001$), and were less hypoxic than CAP (23.9 vs. 32.9%; $p = 0.032$). Staphylococcus aureus was isolated in 14.8% (9/61) of HCAP (5/9 MRSA) versus 6.7% (3/45) of CAP (2/3 MRSA); Pseudomonas aeruginosa in 13.1% of HCAP (8/61) versus 8.9% of CAP (4/45); *Streptococcus pneumoniae* in 11.5% of HCAP (7/61) versus 33.3% of CAP (15/45). HCAP itself was found to be an independent risk factor for mortality OR 3.9 (95% CI 2.06–5.91).
Conclusion: Data in Italian patients confirm that HCAP should be regarded as a separate category of respiratory infection with etiologic differences requiring different therapies.



Odds ratios for 30-day mortality in HCAP and CAP affected patients.

Severity assessment in health care associated pneumonia (HCAP)

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HCAP develops in patients who have ongoing interaction with the health care system and drug-resistant pathogens. Hence, their treatment choices may differ dramatically from CAP as the ATS/IDSA recommend in the 2005 guidelines. Despite high mortality rate has been reported, none of the prediction scores usually adopted for CAP has been validated in patients with HCAP for mortality risk evaluation and resources allocation.
Aim: The aim of this study is to compare the ability of three prediction rules validated for CAP to predict mortality in HCAP patients: Pneumonia Severity Index (PSI), CURB and CURB65 scale.
Patients and methods: A prospective observational study of 238 consecutive inpatients with HCAP (140 men, mean age 72, SD 14 years) was performed in a tertiary care teaching hospital during 2003–2008. The patients were stratified into three risk groups (low, intermediate and high) according to each rule. The ability of the three rules to predict 30-day mortality was compared.
Results: The overall 30-day mortality rate was 24.8%. PSI, CURB65 and CURB performed similarly. The areas under the receiver operating characteristic (ROC) curve for PSI was 0.66 (95% CI 0.59–0.73;

$p < 0.0001$), for CURB65 0.62 (95% CI 0.55–0.70; $p = 0.0008$) and for CURB 0.62 (95% CI 0.54–0.70; $p = 0.0013$). Larger proportions of patients were identified as low risk by CURB65 (31.9%) and CURB (59.2%) than by PSI (13.9%). At every given threshold, the PSI had higher sensitivity and lower specificity than both CURB scores (Figure).

Conclusion: At admission, the PSI correctly identified mortality risk and could be adequate for decision making. CURB and CURB-65 are not advisable in the emergency department because of their low-risk classes high aggregate 30-day mortality rate.

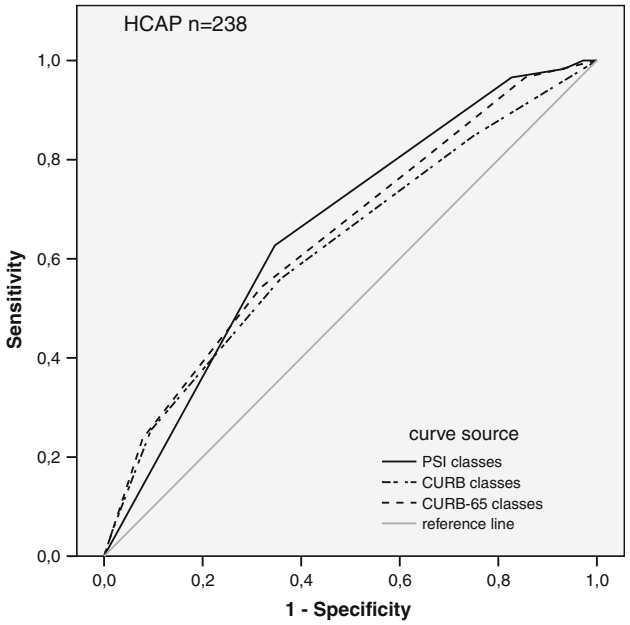

Figure ROC curves

E-cigarettes: successful smoking cessation in recurring relapsers

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Case series: Here we described the case of three smokers, with an established history of chronic relapsing disease despite intensive management at specialized smoking cessation clinics, who eventually quit tobacco smoking by experimenting with an e-cigarette. The e-cigarette was well tolerated with no reported adverse effects in all three cases.

Patient 1 A 47-year-old man smoking 30 cigarettes/day (44 pack/years) with a diagnosis of severe nicotine dependence (FTND = 9) was subjected to intensive treatment for nicotine dependence (nicotine patches + bupropion + motivational counseling) four times, in February 2007, September 2007, July 2008 and May 2009. Last relapse was noted on June 2009. During a routine telephone follow-up in December 2009, he reported having quitted smoking on its own after taking up an e-cigarette. He was invited to call at our clinic in January 2010 to collect more details and for further investigations. Experimentation with an e-cigarette (loaded with 7.2 mg nicotine/cartridge) started in August 2009 and, a few weeks later, he was able to discontinue tobacco smoking completely. He kept using his e-cigarette for another couple of months before stopping the e-cigarette as well. Abstinence from tobacco smoking was objectively confirmed by exhaled breath carbon monoxide concentration (eCO = 4 ppm). He has been quitting tobacco smoking for approximately 5 months.

Patient 2 A 38-year-old woman smoking 20 cigarettes/day (25 pack/years) with a significant level of nicotine dependence (FTND = 8) and mild depression was subjected to intensive treatment for nicotine dependence (nicotine patches + bupropion + motivational counseling) three times, in June 2007, October 2007, and January 2009. Last relapse was noted on February 2009. During a routine telephone follow-up in December 2009, she reported having quitted smoking on its own after taking up an e-cigarette. She was then invited to attend for a follow-up visit at our clinic in January 2010. Experimentation with an e-cigarette (loaded with 7.2 mg nicotine/cartridge) started in April 2009 and, 3 months later, she was able to discontinued tobacco smoking completely. She kept using the e-cigarette with high nicotine concentration for another month before switching to mentholated cartridges. Abstinence from tobacco smoking was confirmed objectively (eCO = 2 ppm). She has been quitting tobacco smoking for approximately 6 months.

Patient 3 A 65-year-old male heavy smoker (88 pack/years) with an associated longstanding history of alcohol abuse and COPD was assisted to quit on two occasions in January 2004 and September 2007 (nicotine patches + group counselling sessions). Last relapse was noted on October 2007. During a routine follow up in our COPD clinic in November 2009, he announced having quitted tobacco smoking on its own after taking up an e-cigarette (loaded with 7.2 mg nicotine/cartridge) in March 2009. Two months later, he was able to discontinue tobacco smoking completely. He is still using his e-cigarette but on a lower nicotine dose (4.8 mg nicotine/cartridge). Abstinence from tobacco smoking was confirmed objectively (eCO = 5 ppm).

Discussion: Here we report for the first time that e-cigarettes can be a powerful smoking cessation aids. Larger controlled studies are needed to confirm the importance of integrating e-cigarettes into standard smoking cessation programs.

Project for creating a multicenter care outline to treat skin ulcers in autoimmune diseases

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Background: Many patients suffering from autoimmune diseases develop one or more slow-resolving skin ulcers, which remarkably worsen one's quality of life. Despite their low absolute prevalence, their complexity and severity of prognosis make autoimmune ulcers serious, very hard to treat conditions. Medical literature contain very few and low-quality information, resulting in highly variable prognoses and therapies which will likely have a negative impact on management, finance, and clinical outcomes.

Objectives: Improve clinical conducts and their pertinence. Creation of dedicated health care practices aimed at improving patients' management. Recording of clinical data through clinical audit and benchmarking, in order to constantly meet international health care standards. File and analyze clinical data to develop new research processes.

Methods: Evidence-based therapy profile for patients suffering from autoimmune ulcers. Presently, the following operating units are involved in this process: SOD Clinica Medica Umberto I, Ancona; Azienda USL Bologna (dermatology clinic); Azienda Ospedaliera Macchi, *Varese (department clinic);* S.I.T.R.A. service Ospedale Civile, *Legnano;* and Distretto Sanitario 1 ASS 1, Trieste. A shared document, containing decision algorithms and clinical recommendations, has been issued. Moreover, an online multimedia database has been created. The data will be analyzed in order to obtain information on autoimmune ulcers' prevalence and clinical features (cross-sectional study), and information on prognosis, healing time, risk factors and complications (prospective cohort study). This project has been developed thanks to the Italian Nurse Association for the Study of Skin Lesions (AISLeC). Clinical activity will begin on 1 July 2010. Quality checks and quarterly reports will be issued.
Results: The outline has been defined, detailed, and shared between health centers. It has also been internally and externally revised. The database has already been developed and it is being implemented. The first data will be analyzed after 6 months from implementation.

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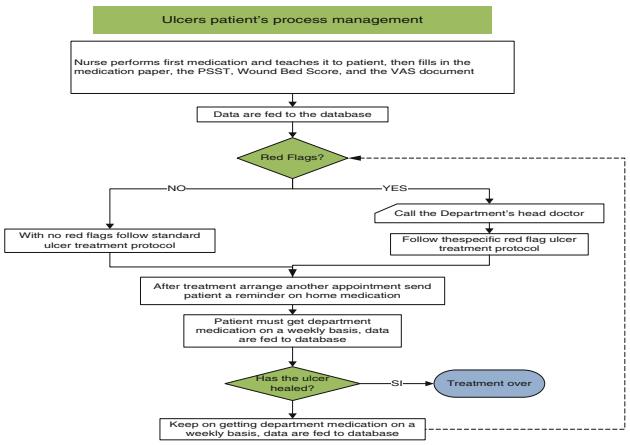

Lung tuberculosis with "booster effect" in a 18-year-old women

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Introduction: We describe the case of an 18-year-old woman of Indian origin, who was referred to us because of suspected tuberculosis.
Clinical picture: In the last month the patient complained of persistent low grade evening fever (on average 37.5°C) and non productive cough, which hadn't responded to the administration of antibiotics (quinolones) and mucolytic drugs. To persist this symptomatology she went to an Emergency Department and admitted, after the chest x-ray result, with diagnosis of suspected tuberculosis. The familiar pathologic history was negative for neoplasms, COPD, autoimmune and hematologic diseases. Her physiological history was negative for alcohol, smoke allergy to pollens, foods or drugs.
Clinical examination and laboratory results: Abdominal, cardiac, neurological, superficial lymphatic examination and the chest auscultation were normal. ESR 52 mm h^{-1} (n.v. 2–37), CRP 32.8 mg/L (n.v. 0.0–5.0), fibrinogen 447 mg/dL (n.v. 200–400), iron 33 µg/dL (n.v. 50–150), ferritin 165 µg/L (n.v. 10–160), hematocrit 39.4% (n.v. 41–53), MCV 76.2 fL (n.v. 80–99), PLTS 445.000/mm^3 (n.v. 140.000–440.000), ALP 160 U/L (n.v. 35–104). Haemoglobin, erythrocyte and white cell count, total protein, albumin, protein electrophoresis, coagulation tests and urinalysis were normal, hepatitis markers, HIV and antibodies of treponema were negative. The Mantoux test, evaluated at 48 and 72 h, resulted negative. The Mantoux test, repeated 14 days later, resulted intensely positive at 48 and 72 h with development of a skin ulceration.
Instrumental, microbiological and histological examinations: The chest radiography on admission showed consolidation in the paramediastinic portion of the upper right lobe with the mediastinum enlarged. A first bronchoscopy showed a purulent tracheo-bronchitis and microscopic examination of bronchoaspirate was negative for acid-fast bacilli. The PCR for Mycobacterium Tuberculosis Complex on bronchoaspirate resulted negative. The second culture of bronchoaspirate Mycobacterium become positive on the 21st day. A chest CT-scan showed a large non homogeneous consolidation at the right apex, with mediastinal extension. Abdomen ultrasound was negative. After 14 days a second bronchoscopy was performed with lymphonodal TNBA and TBLB which showed granulomatosis with caseous necrosis, pathognomonic for tuberculosis.
Clinical course: On the grounds of such a diagnosis treatment with isoniazid (200 + 100 mg/pd), ethambutol (400 + 200 mg/pd) and rifampicin (600 mg/pd) was started. A chest CT-scan after 30 days of treatment showed a significant reduction of the bulky consolidation previously detected. An abdominal CT-scan, performed short before discharge, was negative except for an oval little hypodense mass adnexal (still under study).
Discussion: In this case lung tuberculosis appeared to be the most probable diagnosis in regard of the clinical presentation also if the first Mantoux test and the first direct bronchoaspirate microscopic examination were negative. For this case there is the possibility a differential diagnosis vs. other pathologies, lymphomas in particular. The positivization of the second Mantoux test was due to a "booster effect". The booster phenomenon is thought to represent remote tuberculous infection where tuberculin reactivity has waned [1]. A negative Mantoux test at 48 and 72 h, in patients with a strong suspicion for tuberculosis, should always be repeated [2]. The false negative tuberculin can be caused also by booster effect but also by others conditions like: alcohol abuse, malnutrition, gastrectomy or enteric by-pass states, sarcoidosis, etc. [3]. The booster effect can also be responsible of false positive responses to the skin tuberculin test; it's therefore recommended to repeat the test 1–3 weeks later to rule out false positivity [4].
Conclusions: Presently the QuantiFeron-TB Gold test can be used to rule out false positive and false negative results in all cases in which skin tuberculin test is indicated. This new test can differentiate non tuberculous reactions, obviating the necessity of repeating in two steps the tuberculin test and, so, the booster effect [5].

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Beneficial role of nicotine free inhalator for smoking cessation

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Introduction: Cigarette smoke harms nearly every system of the human body, thus causing a broad range of disease, many of which are fatal. The risk of serious diminishes rapidly after quitting and lifelong abstinence is known to reduce the risk of lung cancer, heart disease, strokes, chronic lung disease and other cancer (1). However, given that too many smoking respond poorly to smoking cessation efforts with rather disappointing overall success rate of long-term abstinence, the need for more effective smoking cessation interventions is firmly established.
Nicotine free inhalers may be a efficient tool used in the context of smoking cessation interventions. Anecdotal evidence about its beneficial role is available, but there is no formal demonstration supporting the efficacy of these device in smoking cessation studies. This is the first clinical trial designed to assess the effect of using a nicotine free inhalator ("PAIPO"; Echos Srl, Milan—ITALY) as a part of a smoking cessation program for smokers willing to quit.
Methods, study population, study design and procedures: Regular smokers ($\geq$20 cigarettes/day for at least 10 years), consecutive attendees who booked for the first time with the call center of our clinic for smoking cessation were all invited to participate in the study at the time of their first consultation. Smokers with an exhaled breath carbon monoxide (CO) concentration of $\geq$10 ppm were recruited. Subjects with a history of alcohol and illicit drug use, major depression, or other psychiatric conditions were excluded. The study protocol was approved by the local institutional ethics and review board. This prospective study was designed as a two-group randomized clinical trial to compare the effect of a nicotine free inhalator ("PAIPO") on quit rates at 4 and 24 weeks in smokers undergoing a standard smoking cessation program; participants were randomly assigned in block of four either to a nicotine free inhalator ("PAIPO") or to a reference group. At the baseline, a detailed smoking history was taken and individual pack-years calculated together with scoring of their level of nicotine dependence by means of a standard questionnaire the Fagerstrom test of nicotine dependence (FTND). A measure of the behavioural aspects of smoking addiction was obtained by means of the Glover–Nilsson Smoking Behaviour Questionnaire (GN-SBQ). Subjective ratings of depression were assessed with the Beck depression inventory (BAI). Level of motivation was assessed by Mondor test. Additionally, exhaled CO was measured (Micro CO, Micro Medical, Rochester, UK). Participants were prescribed with medications for nicotine dependence and craving tailored to their individual needs. Participants were then assigned to either "PAIPO" group or to reference group. Subjects assigned to the "active" group were given a free supply of "PAIPO" inhalators. Participants were invited to review at week 4 and week 24 their abstinence was by measuring the concentration of exhaled CO.
Study efficacy measures and statistical analyses: The primary efficacy measure was the 24-week success rate (24WSR). The co-primary efficacy measure was the 4-week success rate (4WSR). One way analysis of variance (ANOVA) was used to test difference between means and χ^2 statistics was used to calculate the significance of observed differences in distribution of 4 and 24 week quit rates.
Results: 120 smokers were enrolled. At 24 weeks, subject who were lost to follow up accounted for 16/60 (26.7%) in PAIPO group and 19/60 (31.7%) in reference group ($p = 0.547$, χ^2). In the whole sample, no significant differences was found in quit rate between PAIPO and reference group. However, when study participants were separately on the basis of their GN-SBQ value at baseline, a striking difference was found in frequency distribution of quit rates: in fact among subjects with hight GN-SBQ the quit rate in PAIPO group was significantly higher than in reference group.
Conclusion: This is the first study to demonstrated that supplementing a smoking cessation programm with the use a nicotine free inhalator may be beneficial, particularly for those smokers for whom handling and manipulation of their cigarettes play an important part of the ritual of smoking.

New-onset asthma in allergic subjects who smoke is of greater severity

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Background: Active smoking and second hand smoke exposure are major triggers of asthma symptoms and increase asthma prevalence, but little is known about the association between smoking and asthma severity. We calculated asthma severity and control to determine the importance of smoking as a determinant of disease severity and control in a cohort of clinic-referred allergic subjects who developed new onset asthma.
Method: Allergic rhinitis subjects with no asthma were followed-up for 10 years and routinely examined for asthma diagnosis. In those who developed asthma, clinical severity class was calculated by GINA 2002 severity class. Levels of asthma control were determined by NAEPP EPR3 criteria.
Results: When comparing current or past smokers to never smokers they had a higher risk of severe asthma in the univariate analysis, which became non-significant in the multivariate. On the other hand, the categories of pack-years were significantly related to severe asthma in a dose response relationship in both the univariate and multivariate: compared to 0 pack years, those who smoked 1–10 pack-years had an OR (95% CI) of 1.47 (0.46–4.68), those who smoked 11–20 pack-years had an OR of 2.85 (1.09–7.46) and those who smoked more than 20 pack-years had an OR of 5.59 (1.44–21.67). Smokers with asthma were also more likely to have uncontrolled disease. A significant dose–response relationship was observed for pack-years and uncontrolled asthma. Compared to 0 pack-years, those who smoked 1–10 pack-years had an OR of 5.51 (1.73–17.54) and those who smoked more than 10 pack-years had an OR of 13.38 (4.57–39.19).
Conclusion: The current findings support the hypothesis that smoking is an important predictor of asthma severity and poor asthma control. Physicians have the responsibility to alert their patients about the additional risk of developing severe asthma symptoms if they smoked and to direct the they to smoking cessation.

Effects of continuous positive airway pressure (CPAP) on plasminogen activator (PA) system in OSAS

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Objective: Patients with OSAS are at increased risk of cardiovascular events that may affect mortality. Intermittent hypoxia has been demonstrated as the initiator inflammatory process mediated by cytokines release. Recently it has been also been hypothesized a prothrombotic state resulting from elevated procoagulant molecules. Aim of the present study was to investigate the PA system (uPA, PAI-1) and TGFβ in a group of OSAS patients, before and after CPAP treatment.
Methods: Twenty-five patients (58 + 10 SD years; BMI 38 ± 8) with moderate to severe OSAS (AHI >37 + 26; ODI 43 ± 23) were studied. uPA, PAI-1 and TGFβ (ELISA) were measured, before and after 1 month of CPAP treatment; 10 age matched healthy subjects served as controls.
Results: At baseline, PAI-1 and uPA levels were significantly higher in OSAS patients compared to controls: PAI-1 111 ± 8 versus 85 ± 7 ng/ml ($p < 0.001$); uPA 0.10 ± 0.01 versus 0.06 ± 0.01 ng/ml ($p < 0.05$). After CPAP treatment, a mild decrease in PAI-1 and a significant increase in uPA 0.10 ± 0.01 versus 0.158 ± 0.01 ng/ml ($p < 0.01$) was observed. No significant changes were observed in the levels of TGFβ were observed neither at baseline nor after CPAP.
Conclusion: Parameter reflecting a procoagulative state are increased in OSAS; importantly CPAP treatment, by increasing uPA values, is capable to ameliorate the coagulative state.

Cardiovascular autonomic regulation during pneumonia and its correlation with clinical outcome

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Background: In patients affected by community acute pneumonia (CAP), clinical failure has been observed between 6 and 24% of cases and in 80% of these patients the cause of unfavorable outcome is related to pulmonary infection and systemic response to the infection. Previous studies described that infectious conditions, e.g. severe sepsis, are characterized by an impaired autonomic cardiovascular control and altered heart rate variability (HRV) parameters, such as a reduction of parasympathetic and an increase of sympathetic cardiovascular modulation. However, no data are available on the possible role of cardiovascular autonomic regulation during pneumonia and the correlation of these parameters with clinical outcome. The aim of the study was to assess whether, in CAP patients, HRV parameters could identify patients with poor prognosis during the first stages of the disease.
Methods: We enrolled consecutive patients affected by CAP ($n = 42$, M/F = 20/22, mean age 75 ± 14 years) diagnosed in the emergency room on the basis of clinical, laboratory and radiological examinations. At the time of the enrolment in the study, we recorded two signals: a one-lead ECG (lead II) and respiratory rate via a pneumothoracic belt using a telemetric device (BT 16 Plus, Francesco Marazza Elettronica, Monza), with a sampling frequency of 256 Hz. The patients were evaluated during the clinical course and divided into two groups: patients with a clinical and radiologic response to therapies (good outcome, group A) and patients who developed respiratory complications (acute pulmonary deterioration with the need of either non-invasive or invasive mechanical ventilation) or death (poor outcome, group B). Autonomic cardiac modulation was assessed by spectral analysis of HRV. Briefly, spectral analysis is a technique capable of characterizing the main oscillatory components of the RR interval time series: two main components are identified, a low frequency component (LF), marker of sympathetic modulation, and a high frequency component (HF), marker of vagal modulation. After detecting the QRS complex and locating the R apex, the heart period was calculated on a beat-to-beat basis as the time interval between two consecutive R peaks (RR interval). On short time series of 300 beats for each recording (T0 and T1), spectral analysis was applied in order to identify LF and HF components of HRV of the RR signals. Respiratory rate was also recorded. A t-test for unpaired data was applied to assess differences among the groups and a $p < 0.05$ was considered statistically significant.
Results: Seven out of the 42 patients enrolled presented a respiratory complication during the clinical course. Comparing the two groups, we found that group A was characterized by a significant lower heart rate compared to group B (81 vs. 98 bpm). As to spectral parameters, HF expressed in normalized units (nu), marker of vagal modulation, was significantly higher in group A with respect to group B (44 vs. 15 nu). Respiratory rate was similar in the two groups. These results were independent from age, sex and cardiovascular and respiratory comoribidities.
Conclusions: In conclusion, these preliminary data seem to indicate that CAP patients characterized, at baseline, by an increased heart rate and a reduced parasympathetic modulation; have a worse respiratory outcome. Therefore, cardiac and autonomic cardiac parameters seem to be able of identifying CAP subjects at higher risk of poor prognosis for respiratory complications.

Detection of radio-occult pneumonia by lung ultrasound in an Internal Medicine Unit

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Background and aims: Lung ultrasound (US) has recently shown to be useful in the diagnosis of pulmonary disease. We aimed to evaluate the diagnostic accuracy of lung US as compared to chest X-ray (C-XR) and chest computed tomography (CT) used as gold standard in detecting lung consolidation in patients with a clinical suspicious of pneumonia.
Patients and methods: Twenty-four patients (14 ♂, 10 ♀, mean age $\pm$ SD = 73.8 ± 14 years) with clinical signs suggestive of pneumonia (including cough, dyspnea, pleuritic chest pain and/or fever of unknown origin) underwent lung US, C-XR and chest CT. 3.5–5 MHz convex probe and high-resolution 7.5–10 MHz linear probe were employed. Detection of peripheral alveolar consolidation defined by hypoechoic subpleural images, the presence of air bronchogram and the pleural disruption with thickening and irregularity of the line were evaluated.
Results: Lung US was positive for the diagnosis of pneumonia in 20 of 24 patients, whereas C-XR was positive in 10, dubious in 4 subjects and in 5 showed pleural effusion only. In 22 of 24 cases, lung US and CT findings were comparable. In two patients with negative US and

respectively positive and dubious C-XR, the CT findings was negative. In one subject with both negative US and C-XR, CT did not detected a parenchymal consolidation but demonstrated diffuse ground-glass opacity. In one patients with a C-XR diagnosis of right basal pneumonia, lung US and CT also showed a left basal consolidation. In comparison to chest CT, the specificity of lung US in pneumonia detection was 100%, the sensibility 91%, the positive predictive value 100% and the negative predictive value 50%. In 9 of 24 cases (37.5%) lung US detected C-RX radio-occult pneumonia.

Conclusions: Our preliminary data suggest that lung US is a simple, reliable diagnostic tool that can be used bedside by the clinician in the clinical suspicious of pneumonia. Additionally, lung US provide more information than conventional C-XR without the risk of irradiation and it can lead to decrease the need for CT examination.