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Pneumonia and infections

Any delay in adequate antibiotic treatment may compromise the outcome of ventilator-associated pneumonia (VAP). However, the diagnosis and optimal treatment of VAP remain a challenge for intensivists. Jung et al. [1] assessed the potential impact of using results of once-a-week routine quantitative endotracheal aspirate (EA) cultures to guide initial antibiotic treatment in a study of 113 episodes of bronchoalveolar lavage-confirmed VAP. When guided by EA, the initial antibiotic regimen was adequate in 85% of situations, a proportion significantly superior to that resulting from application of the ATS guidelines (73%). When clinicians did not have a pre-VAP EA to guide their treatment (EA not performed group), only 61% of treatments were adequate, confirming that routine surveillance cultures may help to improve the adequacy of empiric antibiotic therapy for VAP.

Respiratory physiotherapy and early mobilisation have been suggested to both prevent and treat VAP. Patman et al. [2] performed a prospective, randomised controlled trial in 144 patients with acquired brain injury (ABI) on the effect of physiotherapy. This study found that a regular respiratory physiotherapy regimen including positioning, manual hyperinflation and suctioning repeated six times per day, when provided in addition to routine medical/nursing care, did not significantly reduce the incidence of VAP, length of MV or ICU/hospital stay for adults with ABI. Due to the small number of patients diagnosed with VAP, it was not possible to draw any conclusions as to whether respiratory physiotherapy hastens the recovery from VAP in terms of duration of MV, length of ICU/hospital stay or clinical variables such as the daily CPIS score.

Previous studies have established that acquisition of *P. aeruginosa* is associated with the administration of antimicrobial agents devoid of antipseudomonal activity. In this regard, however, the role of antipseudomonal agents is less clear. During an intervention study aimed to compare a mixing versus a cycling strategy of antibiotics use in the critical care setting, Martinez et al. [3] were able to gather detailed longitudinal data about exposure to antibiotics and colonisation by *P. aeruginosa*. Their data suggest that quinolones and antipseudomonal cephalosporins may actually prevent the acquisition of *P. aeruginosa*, whereas piperacillin-tazobactam and amikacin may enhance it. With respect to the acquisition of resistance, they found that quinolones and cephalosporins were rather neutral, whereas all the other agents were associated with the acquisition of resistance also to other antibiotics. Interestingly, emergence of resistance never arose to detectable levels before 3 days of continuous therapy and combination treatment was not useful for prevention.

It remains uncertain why immunocompetent patients with bacterial community-acquired pneumonia (CAP) die, in spite of adequate antibiotics. In a secondary analysis of 212 patients admitted to 33 ICUs in Spain for CAP, ICU mortality was 20.7 and 28% [OR 1.49 (0.74–2.98)] among immunocompetent patients with *S. pneumoniae* ($n = 122$) and non-pneumococci ($n = 90$), in spite of initial adequate antibiotic treatment [4]. Multivariable regression analysis identified the following variables as independently associated with mortality: shock (HR 13.03), acute renal failure (HR 4.79) and APACHE II score higher than 24 (HR 2.22).

To investigate the effect of enteral Synbiotic 2000 FORTE (a mixture of lactic acid bacteria and fibres) on the incidence of ventilator-associated pneumonia (VAP) in critically ill patients, 259 enterally fed patients requiring mechanical ventilation for 48 h or more were enrolled in a prospective, randomised, double-blind, placebo-controlled trial [5]. No statistical difference was demonstrated between groups receiving synbiotic or placebo in the incidence of VAP (9 and 13%), VAP rate per 1,000 ventilator days (13 and 14.6) or hospital mortality (27 and 33%). These results are in agreement with two recent meta-analyses of small heterogeneous populations of critically ill patients, which also failed to show a reduction in infectious complications with symbiotic therapy.

A threshold of $\geq 10^4$ colony forming unit (CFU) ml^{-1} is currently used to define a positive quantitative culture result for BAL, and thus to diagnose VAP. Variation of dilution under a dilution factor of 10 or higher than a dilution factor of 100 could alter this cutoff, resulting in an inappropriate interpretation of the microbiological data and then in overtreating some patients or missing some episodes of pneumonia. In a study of 127 consecutive patients who were clinically suspected of having developed VAP and underwent BAL, Baldesi et al. [6] found that a misclassification of the BAL related to the dilution, as determined by the urea method, was observed in only 2.1% of the 241 BALs performed for a suspicion of VAP. Furthermore, this misinterpretation could have led to underdiagnosing a VAP in only two of the five cases.

Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) has proven to be a good biomarker for sepsis. For the diagnosis of ventilator-associated pneumonia (VAP), however, there have only been a few, relatively small studies on the role of this receptor. In a study of 240 BAL fluids obtained from patients with a clinical suspicion of VAP, the mean concentration of sTREM-1 was significantly higher in the BALF of patients with confirmed VAP than in that of patients without confirmed VAP. However, the area under the receiver-operating characteristic curve was 0.58 (95% confidence interval 0.50–0.65, $P = 0.04$), implying that the sTREM-1 assay used in this study may not be discriminative for VAP [7].

Jiyong et al. [8] presented a meta-analysis evaluating the clinical feasibility of using TREM-1 in bacterial

infections. After selection of 13 studies fulfilling the predefined criteria of the literature search, they found that TREM-1 has quite a high sensitivity and specificity of bacterial infections, but it is probably not a sufficient marker in the subgroup of urinary tract infections. Whether TREM-1 may be used to guide antibiotic therapy cannot be concluded by present data. Interestingly, similar to procalcitonin (PCT), TREM-1 seems to be able to identify negative patients in a very reliable manner, much better than its ability to predict the positive diagnosis "infection".

Several evidence-based interventions are known to reduce the incidence of VAP. However, translating evidence-based findings into consistent delivered care at the bedside remains a challenge. Hawe et al. [9] evaluated the effects of introducing a bundle of six evidence-based interventions to reduce VAP (semirecumbent patient positioning, oral antisepsis with chlorhexidine, use of subglottic suction/drainage endotracheal tubes, daily sedation breaks, daily assessment of readiness to wean, and use of a heat and moisture exchange filter) via an integrated 'active implementation program' involving staff education, process and outcome measurement, feedback to staff and organisational change. Compliance with the VAP prevention bundle increased after active implementation. VAP incidence fell significantly from 19.2 to 7.5 per 1,000 ventilator days between passive and active periods and continued falling into the final quarter of the time period described (to 5.5 per 1,000 ventilation days).

Prophylactic antibiotic regimens, such as selective decontamination of the digestive tract (SDD) and selective oropharyngeal decontamination (SOD), reduce the incidence of respiratory tract infections (RTI) in ICU patients and improve survival. It is unknown how discontinuation of these interventions at ICU discharge changes the patients' microbial ecology and whether this influences their immediate risk of infections. To test the hypothesis that use of SDD or SOD may increase the incidence of hospital acquired infection (HAI) after ICU discharge, de Smet et al. [10] prospectively monitored the occurrence of HAI during the first 14 days after ICU discharge in all patients transferred to regular wards in two university hospitals, which were part of a large multicenter SDD-SOD trial. As compared to standard of care, the incidences of HAI in general wards tended to be higher in patients that had received either SDD or SOD during their ICU stay. The relative risks for developing HAI in the first 14 days after ICU discharge were 1.49 (CI_{95} 0.9–2.47) after SOD and 1.44 (CI_{95} 0.87–2.39) after SDD. Incidences of surgical site infections (per 100 surgical procedures) were 4 after standard treatment and 11.8 and 8 after SOD and SDD ($P = 0.04$). Whether discontinuation of the prophylactic regimens may have favoured the re-emergence of typical hospital pathogens in these patients remains to be determined.

Patients undergoing major heart surgery (MHS) are a particularly high-risk population for nosocomial infections during the postoperative period with a high incidence and related mortality. To assess the differential characteristics of patients who develop VAP and to identify risk factors amenable to intervention in such a setting, Hortal et al. [11] carried out a prospective study of VAP in 1,803 patients operated from 2003 to 2006 in their own institution. Overall, 106 patients developed one or more episodes of VAP (5.7%, 22.2 episodes per 1,000 days of mechanical ventilation). The independent risk factors for VAP were: age >70, perioperative transfusions, days of mechanical ventilation, re-intubation, previous cardiac surgery, emergent surgery and intraoperative inotropic support. Because VAP incidence was particularly high (46%) in patients requiring more than 48 h of MV, innovative preventive measures should be developed and applied in that "high-risk" population.

Controversies still remain in the management of hospital acquired pneumonia (HAP) [12] and ventilation-acquired pneumonia (VAP). Three European Societies, the European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Society of Intensive Care Medicine (ESICM), were interested in producing a document on HAP and VAP with a European perspective. The chairmen of this task force suggested names from each society to be a member of the panel. They also chose controversial topics of the field and others that were not covered by the last IDSA/ATS guidelines. Each topic was assigned to a pair of members to be reviewed and written. Finally, the panel defined 20 consensual points that were circulated several times among the members of the panel until total agreement was reached. A combination of evidence- and clinical-based medicine was used to reach these consensuses. This manuscript reviews in depth several controversial or new topics in HAP and VAP. This article may be useful for the development of future guidelines and to stimulate clinical research by lying out what is currently accepted and what is unknown or controversial. This article was followed by a letter to the Editor and its rebuttal [13, 14].

To assess the etiologies and outcome of acute respiratory failure (ARF) in HIV-infected patients over the first decade of antiretroviral therapy use, Barbier et al. [15] reviewed the medical charts of all HIV-infected patients admitted to their ICU for ARF between 1996 and 2006. ARF revealed the diagnosis of HIV infection in 43 (29.2%) patients. Causes of ARF were bacterial pneumonia ($n = 74$), Pneumocystis jirovecii pneumonia (PCP, $n = 52$), other opportunistic infections ($n = 19$) and noninfectious pulmonary disease ($n = 33$); the distribution of causes did not change over the 10-year study period. The 43 patients on antiretroviral therapy more frequently had bacterial pneumonia and less frequently had opportunistic infections. Factors independently associated with mortality were mechanical ventilation [odds ratio (OR) = 8.48], vasopressor use (OR, 4.48), time

from hospital admission to ICU admission (OR, 1.05 per day) and number of causes (OR, 3.19). HIV-related variables (CD4 count, viral load and ART) were not associated with mortality. These data confirm that hospital survival has improved in HIV-infected patients and depend on the extent of organ dysfunction rather than on HIV-related characteristics.

Current guidelines for both ventilator-associated pneumonia and *Candida* infections suggest that isolation of *Candida* spp. in BAL fluid from immunocompetent patients does not require treatment. However, these recommendations are contrasted by a survey showing that 24% of intensive care physicians would prescribe antifungal therapy for an immunocompetent, mechanically ventilated patient with *Candida* spp. isolated from a tracheal aspirate [16]. In a large retrospective study, in which all autopsies performed over a 2-year period in an adult medical ICU were examined at a very high 77% autopsy rate, no single case of *Candida* pneumonia was identified, even in the patients who had a positive respiratory sample for *Candida* spp. prior to death. In contrast, isolation of *Candida* spp. from respiratory specimens was very frequent in patients who died with pneumonia, occurring in 57% [17]. This study indicates that *Candida* pneumonia is an extremely rare occurrence in ICU patients and provides further evidence against the common use of antifungal therapy triggered by a microbiology report of *Candida* isolation from the respiratory tract.

Interestingly, invasive candidiasis was the topic of a two-part review by Guery et al [18, 19]. The authors present the current state of the art of managing invasive candidiasis and candidemia in adult non-neutropenic intensive care patients. Epidemiology and diagnosis are commented on in *Part 1* [18]: With *Candida albicans* as the most frequent fungal species followed by *Candida glabrata*, the diagnosis of invasive candidiasis involves both clinical and laboratory parameters. One of the main features is the evaluation of risk factors, such as neutropenia, chemotherapy, broad-spectrum antibiotic use and many more, for infection which will identify patients in need for pre-emptive or empiric treatment. Unfortunately, most laboratory or microbiological tests have only a low sensitivity and specificity, and the authors conclude that there is an urgent need for the development of additional laboratory markers. *Part II* of that review [19] deals with the options for treating candidiasis. The most recent standard drugs are presented, and it is pointed out that the choice of empiric therapy is dependent on the hemodynamic status of the patient. Treatment will probably involve the use of drugs from the echinocandin family if the patient is unstable. On the other hand, the stable patient can be treated with azoles as long as there is no other specific result from microbiologic testing. Finally, the authors point to the need for a re-evaluation of current guidelines.

Infections

Antimicrobial resistance remains important in ICUs, but the focus of this problem seems to be shifting from the gram-positive bacteria [such as methicillin-resistant staphylococcus aureus (MRSA)] to the gram-negative bacteria and yeasts. A surveillance study in 35 European ICUs in 2005 demonstrated wide variations in antibiotic use and proportions of multiresistant bacteria (both gram-positive and gram-negative). Average proportions of *Escherichia coli* and *Klebsiella pneumoniae* with the extended-spectrum beta-lactamase (ESBL) phenotype were 3.9 and 14.3%, respectively [20]. In a before-after study in a single German ICU, restriction of the use of third generation cephalosporins (which were reduced from 178.9 to 68.7 DDD/patient day) was not associated with a reduction in the prevalence of these multiresistant bacteria [21]. Another emerging gram-negative pathogen is *Acinetobacter baumanii*. In a cohort of 330 trauma patients, the incidence of *A. baumanii* infection was 11%, and these infections were independently correlated with longer duration of ventilation and trans-skeletal traction, but not with mortality [22].

It is still difficult to predict the development of invasive candidiasis in ICU patients. Prediction models based upon either clinical risk factors or *Candida*-colonisation parameters performed poorly in a large cohort of Australian ICU patients. Integration of these prediction rules might offer better results, but external validation in different settings is needed first [23]**.** The addition of procalcitonin measurements might further enhance the predictive values of such prediction rules, as suggested by one study of 136 patients [24].

What should be done when a central vascular catheter (CVC) tip culture grows *Candida* species, but the patient has no signs of systemic infection and there is no evidence of candidemia? In a small retrospective study among 58 non-neutropenic ICU patients antifungal treatment of such patients was not associated with improved outcome [25].

Another patient population at risk for fungal infections is those suffering from recurrent gastrointestinal perforation, anastomotic leakage or acute necrotising pancreatitis. In such patients ($n = 19$) preventive caspofungin therapy, for a median of 16 days (range 4–46 days), prevented intraabdominal candidiasis in all but one patient without adverse events requiring discontinuation of therapy [26].

ICU-acquired bacteremia is one of the most important complications of treatment in the ICU, and is associated with increased morbidity and mortality, prolonged length of stay and higher health care costs. Among 343 patients, of which 63 had diabetes mellitus, in a Greek ICU, 118 developed ICU-acquired bacteremia, and diabetes patients appeared to have a 1.7-fold risk of this complication [27]. Among 206 patients with acute liver failure,

35% developed bacteremia after a median of 10 days. SIRS scores on admission and the severity of hepatic encephalopathy were predictive of bacteremia, but not of mortality, which was only independently predicted APACHE II score [28]. In contrast, single-stage percutaneous dilatational tracheostomy was associated with bacteremia in 6 of 113 patients (5%), which, according to the authors, justifies withholding of antibiotic prophylaxis for this procedure [29].

Surgical treatment is crucial in the management of necrotising soft tissue infections. In a retrospective study of 106 patients, of whom 40.6% died during hospitalisation, time from the first signs to diagnosis of less than 72 h and time between diagnosis to surgical treatment longer than 14 h in patients with septic shock were both associated with hospital mortality [30].

Hand hygiene is one of the cornerstones of infection prevention. The old-fashioned practice of washing hands with water and soap should by now be replaced by alcohol-based handrubs in all ICUs. In a multicenter study using self-report questionnaires, use of alcohol-based handrubs was considered easier and quicker, and was associated with less hand erythema and itching than washing hands with water and soap [31].

Sepsis

Biomarkers of inflammation and host factors

A number of interesting novel findings in the areas of biomarkers of inflammation, host factors, diagnostic tests and pharmacology were published in 2009 in Intensive Care Medicine.

The need for accurate and reliable biomarkers useable for the monitoring of patients with sepsis is highlighted by the high number of publications related to this area. Indeed, the "standard" C-reactive protein (CRP) can no longer be considered as a reliable predictor of outcome in septic patients. In a systematic study carried out over a 14-month period, Silvestre et al. [32] included 158 consecutive patients with sepsis, severe sepsis or septic shock. The ability of CRP (value on the day of diagnosis of sepsis) to predict survival was lower than the severity scores (APACHE II, SAPS II) and the Sequential Organ Failure Assessment (SOFA) score, and in the same range as white cell count and body temperature.

Hopefully, new insights in the putative pathogenetic mechanisms of sepsis could help to provide more reliable biomarkers. For instance, the decreases of serum selenium concentrations and of glutathione peroxidase (GPx-3) activity during inflammation were studied by Manzanares et al. [33]. These researchers reported an association between low admission selenium, low GPx-3 activity and the occurrence of SIRS (systemic inflammatory response syndrome) in a cohort of 36 patients (without SIRS, with SIRS and with SIRS and multiple organ dysfunction syndrome) in comparison to a control group of 23 healthy volunteers. An association between low selenium and ICU mortality was also found.

Similarly, Guignant et al. [34] measured in 99 consecutive patients the circulating levels of pro-vasopressin and pro-adrenomedullin, two vasoactive pro-hormones, in samples drawn the first week after the onset of septic shock. Both pro-hormones were higher in non-survivors than in survivors, and the combination of both measurements provided an even higher predictive value. These findings are consistent with a predominant role of the cardiovascular alterations of septic shock as a key determinant of outcome. In bacterial meningitis, Berg et al. [35] assessed the plasma levels of putative vasoactive mediators, calcitonin-gene related peptide (CGRP), vasoactive intestinal peptide (VIP) and endothelin-1 (ET-1), and compared these concentrations with a control group of healthy volunteers. The net cerebral fluxes of these peptides were also measured in different conditions. The arterial levels of CGRP were found elevated in patients with meningitis and decreased in volunteers during hyperventilation and after endotoxin infusion. These findings shed some light on the peculiarities of the cerebro-vascular alterations associated with acute bacterial meningitis.

Another functional assessment of novel mediators of sepsis, angiopoietin-2, von Willebrand factor (VWF) and angiopoietin-1, was reported by van der Heijden et al. [36]. As these mediators are considered as surrogate indicators of vascular permeability, a relationship between their plasma concentrations with fluid balance and oxygenation parameters was investigated in 50 patients with septic shock. The main finding was the positive correlation among angiopoietin-2 and fluid balance, pulmonary dysfunction and mortality. Both VWF and angiopoietin-1 were correlated with the magnitude of pulmonary dysfunction, but not with mortality.

The role of lipoproteins and apolipoproteins was explored in a study by Barlage et al. [37] in 151 septic patients. Both lipoproteins and apolipoproteins can play a role in the altered vascular cell function during inflammation. Total cholesterol, high-density-lipoprotein (HDL) and low-density-lipoprotein (LDL) cholesterol, apolipoprotein (apo)-AI and apo-B were all lower in non-survivors than in survivors. Apo-AI and HDL cholesterol further decreased in non-survivors during the ICU stay. Logistic regression analysis revealed apo-AI to be an independent predictor of 30-day mortality. Moreover, a significant inverse correlation was found for apo-AI/HDL-cholesterol and platelet activation.

The complexity of sepsis is even further amplified when considering individual host factors, related to genetic predisposition, either genotypic or phenotypic.

Su et al. [38] reported from data sampled in a large cohort of critically ill patients a significantly increased risk of ARDS in patients bearing a single nucleotide polymorphism of the Angiopoietin-2 gene, a regulator of lung inflammation and vascular permeability. The association was even stronger when extrapulmonary injuries were the cause of ARDS.

The functional consequences of the expression of the heme oxygenase-1 enzyme by monocytes and the arterial concentration of carbon monoxide were explored by Takaki et al. [39] in septic and non-septic patients. In septic patients, indeed, the expression of the heme oxygenase enzyme and the arterial blood CO was higher than in non-septic patients. A positive correlation was found between the increase in heme oxygenase expression, the survival rate, the CO concentration and the intensity of oxidative stress. Such findings are likely to foster sophisticated mechanistic hypotheses able to link the numerous abnormalities reported during sepsis.

Liver dysfunction is another example of severe complication of sepsis, and its pathogenesis is complex. The risk factors for hypoxic hepatitis, a common cause of hepatocellular injury, were explored by Fuhrmann et al. [40]. Low cardiac output and septic shock were the predominant disorders, and the severity of liver injury was related to outcome. In the same area, Thomson et al. [41] evaluated the prevalence, patterns and significance of deranged liver function tests in a group of 263 patients without prior hepato-biliary disease. Mild liver test abnormalities were commonly found and were associated with a increased 30-day mortality, but were not independent predictors of mortality after adjustment for APACHE II score. The severities of ventilatory, renal and circulatory compromises at admission were associated with an increased risk of alterations in liver function tests.

Pharmacology and supportive therapies

The metabolism of commonly used drugs can be altered during critical illness, sometimes leading to unexpected effects. The kinetics of a commonly used lipid-lowering drug, atorvastatin, was compared by Kruger et al. [42] in critically ill patients and in healthy volunteers. A single standard oral dose of atorvastatin was given, and different pharmacokinetic indices were recorded over 24 h. As compared with the volunteers and with the non-septic patients, the critically ill patients with sepsis had a delayed metabolism, implying the persistence of supratherapeutic circulating concentrations of the drug up to 20 h after the single dose was given. These findings are of major importance for the daily practice, since statins reduce the plasma levels of cytokines. In an elegant double-blind controlled randomised trial, Novack et al. [43] randomised 83 patients with suspected or confirmed bacterial infection to oral simvastatin or to placebo. The TNF-alpha and interleukin (IL)-6 levels, analysed in a subset of 20 in each group, were significantly reduced in the simvastatin group. No difference was observed in other clinical variables recorded, including mortality. Clearly, the role of statins in the management of sepsis needs to be further clarified, including the pharmacokinetic aspects.

The exact role of protein C in the treatment of septic shock is eagerly debated. Two articles published in Intensive Care Medicine in 2009 added important contributions to this debate. The first report [44] described unexpected reversal of refractory septic shock with drotrecogin alpha (activated). The 23 patients included in this observational study had a 100% risk of death, according to a score based on the response to early continuous veno-venous hemodiafiltration. The actual 28-day mortality rate of the 23 patients who received drotrecogin alpha was only 39%, associated with a decrease in the magnitude of lactic acidosis and the dose of norepinephrine required.

In a double-blind randomised placebo-controlled trial, the safety and efficacy of extended drotrecogin alpha (activated) (DAA) was evaluated in 64 ICUs in nine countries. Patients ($n = 193$) received DAA for a maximum of 3 days. Yet, extended DAA treatment was not associated with reductions in day-28 all-cause mortality and in-hospital mortality, but also not with an increase in serious adverse events [45].

Heparin used concomitantly with drotrecogin alpha (activated) (DrotAA) was explored in the XPRESS study, and no heparin effect on mortality was observed [46]. In this article, the safety results were explored in more detail. The patients were randomised 1:1:2 to receive unfractionated heparin (UFH) (5,000 units twice daily; $n = 511$), low-molecular-weight heparin (LMWH) (enoxaparin, 40 mg per day; $n = 493$) or placebo ($n = 990$) every 12 h during the DrotAA infusion. The bleeding events during the DrotAA infusion period (days 0-6) were higher in the heparin than in the placebo groups (10.8 vs. 8.1%; $P = 0.049$), but serious bleeding events were similar (heparin 2.3% vs. placebo 2.5%; $P = 0.72$), and central nervous system (CNS) bleeds were rare in both groups (0.3 vs. 0.3%). Fewer heparin patients experienced an ischaemic stroke during infusion (0.3 vs. 1.3%; $P = 0.018$) and 28-day period (0.5 vs. 1.8%; $P = 0.009$). It was concluded that the coadministration of DrotAA with low-dose heparin in severe sepsis patients did not increase the incidence of serious bleeding. Fewer ischaemic strokes in the heparin group suggest heparin cessation should be avoided during DrotAA infusion.

Crivellari et al. [47] describe the outcome and the changes in coagulation and inflammation of nine consecutive patients with severe sepsis who received human protein C zymogen concentrate after cardiac surgery. The increase in protein C levels was accompanied by an early drop in interleukins and near-normalisation of prothrombin time, activated partial thromboplastin time, antithrombin and thrombin-antithrombin complex levels.

The 30-day mortality was unexpectedly low as compared to the prediction.

Diagnostic tests

The daily practice of intensive care medicine implies the use of routines and of some less frequent diagnostic tests. Some new insights into the usefulness and the relevance of some of these common practices were reported in the Journal last year.

Prat et al. [48] assessed the impact of the implementation of clinical practice guidelines by a multifaceted intervention, including a daily routine prescription help guide developed by a multidisciplinary group and displayed at patients' bedsides, educational sessions and feedbacks by information on volumes of prescriptions. The results essentially demonstrate a dramatic reduction of the number of laboratory tests and of chest radiographs, resulting in significant reductions of costs. Importantly, the mortality rate was unchanged after the implementation of the guidelines, when the severity of disease was similar.

Briegel et al. [49] evaluated the inter-laboratory and inter-assay measurements of total cortisol in patients with septic shock. Samples from the CORTICUS study [Sprung et al. N Engl J Med 2008] were assayed in duplicate, by the chemical laboratory of each participating site and by a central laboratory. In addition, cortisol levels measured by tandem mass spectrometry were used as a 'gold standard' reference method in a subset of samples. The concordance between tests was highly variable, and the rate of diagnosis of corticosteroid insufficiency was divergent due to inter-assay variations in up to 27% of cases.

The effects of another potential confounder of the diagnosis on adrenal responsiveness, etomidate, was assessed by Cuthbertson et al. [50] on another subset from the CORTICUS study. The proportion of non-responders to corticotropin was significantly higher in the 96 patients who received etomidate within the 72 h prior to inclusion than in the others. Importantly, etomidate therapy was associated with a higher 28-day mortality, even after correction for the severity of illness.

The timing of sample draw could also represent a potential confounder. In contrast to previous beliefs, Riutta et al. [51] reported that the diurnal variations of cortisol, as well as melatonin, are maintained in intensive care patients. A sample of 40 non-septic patients was studied. The urinary metabolites of melatonin and the serum cortisol concentrations differed between daytime and nights.

Risk factors and outcome

Risk and outcome of critically ill patients remain one of the most important topics in clinical research. In 2009, *Intensive Care Medicine* presented some papers on this issue: the first deals with the impact of obesity on outcomes after critical illness [52]. Hogue et al. performed a meta-analysis finally including 22 studies with more than 88,000 patients. The result was indeed more than surprising: pooled analysis demonstrated no difference in ICU mortality, but lower hospital mortality for obese and morbidly obese subjects. Moreover, obesity was not associated with the time of mechanical ventilation. The authors conclude that we still do not understand the altered physiology of obese subjects and that there is a need for more research activities on this topic. How difficult it is to apply complex statistical methods when estimating mortality in clinical trials was nicely shown by Wolkewitz et al. [53]. Although not easy to understand for the "statistical layman", the study demonstrated that some methods like logistic regression have their weaknesses, whereas cumulative hazards and probability plots add important information. This sound and most valuable piece of work should help to encourage researchers working in hospital epidemiology to apply adequate statistical models to complex medical questions that frequently rise in intensive care medicine. The third paper touches a really difficult field of outcome research: Buschmann et al. [54] investigated complications of resuscitation attempts requiring invasive iatrogenic manipulations on the patient, such as intubation or punctures. The authors differentiate between frequent and rare complications, and present several examples in different areas of the body. Most importantly, they point on the fact that these complications may happen even with adequate execution of the manipulations during resuscitation. Hence, it is of utmost importance that clinical practitioners should know about the relevance and frequency of these injuries to avoid these traumas if possible, but also to be able to distinguish them from injuries of other origin.

Acute necrotising pancreatitis is associated with high morbidity and mortality. Little is known about the long-term outcome and quality of life in these patients. A prospective investigation of 31 patients showed a 68% survival to hospital discharge [55]. One year later patients showed improvement in their physical function and the physical component of their QOL, but overall both functions remained significantly reduced compared to the general population. For example, even walking distance was significantly lower that expected after 12 months, i.e., 424 versus 503 m ($P = 0.014$).

Independent of diagnosis leading to ICU admission, health-related quality of life (HRQoL) prior to admission appears to be a major determinant of ICU survival and long-term outcome. A prospective cohort study in 377 patients admitted to the ICU [56] clearly demonstrated that diminished quality of life assessed by a HRQol score of >8 is associated with a nearly two-fold risk for morality 12 months after ICU admission. Reduced life

quality is also reflected by the two other variables found to be associated with increased mortality, namely pre-ICU admission hospital length of stay >2 days (OR 2.6) and high work load assessed by Nine Equivalents of Nursing Manpower score >30 (OR 3.6).

The SAPS 3 score was introduced as a further refinement of the widely applied SAPS II score [57] and was established by including data from 303 ICUs from 52 countries. Application of this score in specific countries may show different performances as this is already know from other severity scores like SAPS II and APACHE II. A prospective observational study including 28,000 patients from 147 Italian ICUs included in the national database of the Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva (GiViTI) [58] found good discrimination, but poor calibration leading to overestimation of hospital mortality in this large sample of Italian ICU patients. Though investigations in other countries did not find similar deficits in calibration [59], further adaptation of SAPS 3 to specific national or regional situations may be necessary.

The Austrian validation and customisation of the SAPS 3 Admission Score group [60] evaluated the prognostic performance of the SAPS 3 Admission Score in a regional cohort and empirically tested the need and feasibility of regional customisation. Data on a total of 2,060 patients consecutively admitted to 22 intensive care units in Austria from October 2006 to February 2007 were collected. The original SAPS 3 Admission score overestimated hospital mortality in Austrian intensive care patients through all strata of the severity of illness. This was true for both available equations, the general and the Central and Western Europe equation. For this reason a customised country-specific model was developed, using cross-validation techniques. This model showed excellent calibration and discrimination in the whole cohort (Hosmer-Lemeshow goodness of fit: $H = 4.50$, $P = 0.922$; $C = 5.61$, $P = 0.847$, aROC, 0.82) as well as in the various tested subgroups. Authors concluded that the SAPS 3 Admission score's general equation can be seen as a framework for addressing the issue of outcome prediction in a general ICU adult population. However, for benchmarking purposes, more differentiated levels of comparison are needed, and region-specific or country-specific equations seem to be necessary in order to compare ICUs on a similar level.

Azoulay et al. [61] report on the incidence and characteristics of decisions to forgo life-sustaining therapies (DFLSTs) in the 282 ICUs that contributed to the SAPS3 database. Data were reviewed in 14,488 patients, and DFLSTs occurred in 1,239 (8.6%) patients: 677 (54.6%) had withholding and 562 (45.4%) had withdrawal decisions. Overall hospital mortality was 21% (3,050/14,488), and 1,105 deaths occurred after DFLSTs. Hospital mortality in patients with DFLSTs ranged from 80.3 to 95.4%. Independent predictors of DFLSTs included 13 variables associated with increased incidence of DFLSTs and 7 variables associated with decreased incidence of DFLSTs. Among hospital and ICU-related variables, a higher number of nurses per bed was associated with increased incidence of DFLSTs (OR 1.03), while availability of an emergency department in the same hospital (OR 0.65), presence of a full time ICU specialist (OR 0.96) and presence of doctors during nights and weekends (OR 0.72) were associated with a decreased incidence of DFLSTs. The authors concluded that the finding that organisational factors may have significant impact on the incidence of DFLSTs raises crucial questions about the determinants and definition of optimal DFLSTs. They also acknowledged that certain types of cultural variations are permissible and should not be perceived as incorrect practices.

Therapeutic advances have improved survival in patients with myeloma (MM) over the past decade [62]. The authors investigated whether survival has also improved in critically ill myeloma patients. Consecutive myeloma patients admitted to a teaching hospital ICU between 1990 and 2006 were analysed in a retrospective manner. Three year-of-admission groups (1990–1995, 1996–2001, and 2002–2006) were compared that matched changes in myeloma treatment (chemotherapy only, stem cell transplantation and new molecules, respectively). A total of 196 patients were included. Reasons for ICU admission and patient characteristics were similar across groups; however, less use of conventional chemotherapy and radiotherapy and greater use of steroids were noted in the more recent periods. Over time, vasopressors and invasive mechanical ventilation were used decreasingly, and non-invasive ventilation increasingly, to treat acute respiratory failure. Hospital mortality decreased from 75% in 1990–1995 to 49% in 1996–2001 and 40% in 2002–2006 ($P = 0.0007$). Mortality was associated with poor performance status (OR 2.27, 95% CI 1.04–4.99), need for mechanical ventilation (OR 4.33, 95% CI 1.86–10.10), need for vasopressors (OR 2.57, 95% CI: 1.12-5.86) and admission for an event related to myeloma progression (OR 2.77, 95% CI 1.13-6.79). ICU admission within 48 h after hospital admission was associated with lower mortality (OR 0.28, 95% CI: 0.19-0.89). It was concluded that hospital mortality has decreased significantly over the last 15 years in myeloma patients admitted to the ICU. Risk factors for death were organ failure and poor chronic health status. Early ICU admission was associated with lower mortality, suggesting opportunities for further improving survival.

Pre-existing organ impairment may be a significant risk factor for intoxication by usually quite harmless fruits and vegetables. This could be drastically demonstrated in a study including six cases with chronic renal insufficiencies, who were admitted to the ICU for severe star fruit intoxication. Two patients did not survive. This report emphasises the fact that star fruits may not be

consumed by people with impaired renal function under any circumstances [63].

Acute renal failure

Defining acute renal failure or acute kidney injury (AKI) is an important issue in critical care since it was already demonstrated in the past that the patients' prognosis is dependent on that grade of alteration of renal function.

Two large groups consented in the definition of AKI criteria: the first is the Acute Dialysis Quality Initiative (ADQI), which developed the RIFLE criteria (RIFLE is the eponym for the extent of AKI, coming from *Risk,* followed by *Injury, Failure, Loss of function* (for patients being more than 4 weeks on RRT) and *End-stage kidney disease* (ESKD) [64]. The second is the Acute Kidney Injury Network (AKIN), which developed the AKIN criteria [65]. Joannidis et al. published a very interesting post hoc analysis using more than 14,000 patient files from the SAPS III trial to compare RIFLE and AKIN criteria in critically ill patients [66]. Both strategies to stratify the risk of patients with AKI were comparable regarding the overall survival, showing a stepwise increase of the 30-day mortality, beginning with the lowest in patients without AKI, followed by worse outcome in those with AKI (increasing from risk, injury, to failure and from stage 1, 2 to 3, using RIFLE versus AKIN criteria, respectively). With regard to a possible misclassification, the RIFLE criteria were more robust than the AKIN criteria. Hence, this important study will hopefully lead to more acceptance and a higher rate of clinical use of well-established criteria such as RIFLE in critically ill patients.

It is well known that AKI is a frequent complication in severe sepsis and septic shock [67]. A large retrospective cohort study using data of 4,532 patients from 22 units in three countries found a remarkably high incidence of AKI in patients with septic shock [68]. Roughly 64% of these patients developed early AKI as determined by the RIFLE criteria. It also became obvious that delayed administration not only increases mortality as shown previously [69], but also enhances the incidence of AKI. Patients with AKI had a higher probability of having experienced delayed administration of antibiotic therapy (6.0 vs. 4.3 h in non-AKI).

In contrast to several studies trying to validate the severity stages, the outcome stages have not been widely evaluated. A retrospective analysis including 11,644 ICU patients is the first one that takes a deeper look into these categories [70]. As reported by other studies, about 50% of patients developed AKI, and 19% of those (i.e., 1,065 patients) required RRT. Seven hundred eighty-four patients survived to hospital discharge, 97 (4.9%) patients progressed to Loss and 282 patients remained in ESKD. The main risk factors for developing ESKD were reported to be elevated baseline creatinine and treatment with intermittent haemodialysis.

Long-term outcome of AKI is still a field of controversy. A prospective multicentre study in France including 205 patients with AKI treated with RRT showed that 6 months after inclusion, only 62% of the patients were still alive. Their SF-36 items were significantly decreased compared to the reference population, especially with respect to physical items [71]. Two-thirds of the survivors lived an autonomous life in their homes, and 12% of the survivors still required RRT. Interestingly, nearly all survivors (94%) would agree to undergo intensive care management again.

Mannitol is an osmotic diuretic often administered for treatment of acute cerebral oedema and is also recommended as prevention against AKI in crush injury. Despite this, little is known about its effects on renal metabolism. By determining renal extraction of (51) Cr-EDTA, it could be demonstrated [72] that in addition the expected urine flow, also the glomerular filtration rate (GFR) and filtration fraction were increased by 20%. Unfortunately, due to increased sodium load and concomitant tubular enhanced sodium reabsorption, renal oxygen consumption is also increased. Combination of mannitol with furosemide normalised oxygen consumption of the kidney. Mannitol thus appears to be a good example of the assumption that increasing GFR needs not necessarily be a desired effect, because it may be associated with increased oxygen consumption, putting the kidney at risk of a demand supply imbalance.

Renal hemodynamics and hence function may be significantly influenced by intra-abdominal pressure. This was demonstrated by the finding that paracentesis combined with albumin substitution in patients with tense ascites resulted in decreased renal resistive indexes associated with a drop in intra-abdominal pressure from 20 to 12 mmHg [73]. This change was associated with a nearly twofold increase in GFR from 5 to 9 ml/min accompanied by increased urinary output.

Mild hypoxemia also appears to be a relevant factor influencing renal hemodynamics. As shown in patients with acute lung injury (ALI) requiring mechanical ventilation, an arbitrary reduction of FiO_2 resulted in increased renal resistive indices associated with increased GFR [74]. Urinary output and sodium excretion appeared unaltered. The underlying mechanism as well clinical relevance of these findings still needs to be further elucidated.

Acid base

Acid-base analysis

There has been a steady inflow of technical and physiological reports during 2009. A highlight has been two

reports on Stewart's acid-base approach. Daniel Doberer et al. [75] have pointed at limitations of this approach and confusion in the interpretation of results. Gattinoni et al. [76] have found Stewart's approach useful also in the clinical situation. An editorial by Andrew Davenport and a number of letters to the editor have clearly demonstrated the interest that has been stirred up by these papers [77–79]. Not too far from this subject is a study by Zanella et al. [80]. They showed in animal experiments how blood acidification at the inlet of membrane lung for extracorporeal CO_2 removal (and oxygenation) improves the extraction of CO_2 from the passing blood. The rationale for this test is that only a limited blood flow is possible through the membrane lung, 0.5 l/min, compared to the much higher ventilation, 10 l/min. Means to improve CO_2 elimination will thus be the only means of compensating for the flow limitation. Further testing may be needed in clinical conditions.

Acid-base analysis has experienced considerable advances since the introduction of the Steward approach [81]. One study investigating the frequency of acid-base disturbance in 175 critically ill patients demonstrated that, by applying Stewart's approach, additional diagnosis of metabolic disorders was made possible in 33.7% of patients with normal standard base excess [82], indicating enhanced sensitivity by applying Stewart's approach over conventional analysis.

An investigation performed in patients after successful CPR treated with therapeutic hypothermia showed that an increased strong ion gap (SID) 12 h after ROSC may be associated with unfavourable outcome [83].

Nutrition

In a large point prevalence study over nutrition practise in 107 ICUs across 37 countries around the world, Alberda et al. [84] report an average caloric intake of 1,034 kcal/day. When using the collected data as an observational cohort study related to BMI, the authors demonstrated that an increase of 1,000 kcal/day in energy intake would be associated with a decrease in mortality when BMI <25 or when BMI >35. It was also reported that the caloric intake was independent of BMI and that the the actual caloric intake corresponded to approximately 60% of the prescribed calories.

Several articles have addressed techniques to facilitate administration of enteral nutrition. Using a capsule monitored by a video camera, Rauch et al. [85] evaluated small bowel transit time. No difference was found when critically ill neurosurgical patients ($n = 16$) were compared to healthy ambulatory subjects ($n = 16$), although a larger variability in transit time was observed among the critically ill patients. Holzinger et al. [86] report about a self-advancing jejunal tube. Randomised ICU patients on mechanical ventilation ($n = 21 + 21$) had a lower success rate of correct placement as compared to the conventional endoscope-guided technique. Eventually also all initially non-successful cases with the self-advancing tube had correct placement by conventional endoscopic guidance. No differences in outcome parameters were seen, and no predictor of success for the initial use of the self-advancing jejunal tube was detected. To determine if a simple aspiration test would be sufficient to detect the accuracy of oesophageal placement of a fine-bore feeding tube, Ward et al. [87] randomly inserted tubes in the trachea and oesophagus in patients ($n = 20$) undergoing elective surgery. A blinded investigator insufflated and aspirated 10 ml of air and monitored the effect on capnography. In the small series, the test accurately differentiated between the two placements. Still the authors emphasise the possibility of false-positive results.

The current literature demonstrates the provision of early enteral nutrition (EN) having clinically important benefits in non-critically ill patients. Doig et al. [88] present a systematic review on early EN in critically ill patients using a meta-analysis of randomised controlled trials. One criterion was the early application within 24 h of "injury" or intensive care unit admission. The authors were able to select six RCTs with a total of 234 patients. Early EN was associated with a significant reduction in mortality by roughly 65%, and secondary pneumonia by nearly 70%! Although these findings are robust and were confirmed by sensitivity analysis and a simulation study, a major limitation of the presented analysis is the overall low quality of the trials, as well as the low number of included patients. Unfortunately, in current clinical practice only 40 to 60% of patients who are eligible for early EN still fail to receive early EN within 48 h of ICU admission. Altogether, it must be concluded that this impressive benefit should be confirmed by conducting large multicentre trials enrolling critically ill patients.

Glycaemic control

The interest in tight glucose control and glucose monitoring har resulted in several articles. In a retrospective analysis, Kreutziger et al. [89] demonstrated that admission blood glucose is an independent predictor of mortality in polytraumatised patients, also when regression analysis controlled for age, gender and injury severity. This is an original observation that needs to be confirmed. It may motivate consideration in the handling of trauma cases. Cordingley et al. [90] investigated the possible advantage with a computerised algorithm for the insulin infusion in order to obtain blood glucose control. In a feasibility study the comparison between two university hospital ICUs demonstrated similar time-weighted glucose averages when applying the algorithm advising

insulin infusion rates. When standard care was used a significant difference in the time-weighted glucose averages occurred. Furthermore, the glucose sampling interval decreased when the computerised algorithm was used. Holzinger et al. [91] report the effect of noradrenaline when a subcutaneous glucose monitoring system was used. A multiple regression analysis was performed demonstrating that noradrenaline dose, BMI, glucose level and severity score had no influence on the accuracy of the continuous glucose monitoring system in ICU patients.

The multiple studies on the practical use of tight glycaemic control (TGC) were in some ways more confusing than helpful, since they used varying patient populations and different protocols. In this context, several studies tried to implement new technologies called computerised decision-support systems (CDSS) to establish supporting process management when using TGC. Hence, the systematic review by Eslami et al. [92] came at the right time. Using a predefined algorithm, 11 systematic trials were selected. Although most studies reported a positive effect on at least one quality indicator, the protocols revealed a considerable diversity. The authors conclude that, at present, it is impossible to define the exact success factors. Although this may be disappointing at the first view, it is important to realise that "calling for technical support" using TGC is rather a view into the future than a solution for the next years. Hence, the physician is still dependent on sound protocols and clinical assessment of the critically ill patient.

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