Oral Presentations
Experimental features in sepsis and inflammation
0345-0350

0345

POLYMICROBIAL SEPSIS INDUCES LONG-TERM SUSCEPTIBILITY TO PSEUDOMONAS AERUGINOSA SECONDARY PNEUMONIA

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INTRODUCTION. Sepsis has been shown to impair the lung defense mechanisms in mice and to increase susceptibility to P.aeruginosa pneumonia immediately after the primary infection. Whether increased susceptibility persists in mice that survive to polymicrobial sepsis is unknown. In order to investigate the mechanisms of host pulmonary defense following infection, we developped a murine model of secondary P.aeruginosa pneumonia in survivors of polymicrobial sepsis.

METHODS. We used a murine model of polymicrobial sepsis through cecal ligature and puncture (CLP) followed by a short course of antibiotics and volume resuscitation. This model allows long-term survival of 60% of mice. Eight days after CLP, we performed intratracheal instillation of P.aeruginosa (PAO1) to induce secondary pneumonia. The lung response was assessed through quantification of inflammatory cells, myeloperoxydase (MPO) activity and cytokines levels in the bronchoalveolar lavage (BAL) fluid 4 and 24 hours after instillation. Bacterial lung clearance was evaluated through culture of BAL and lung homogenates. Bacteremic dissemination was assessed through culture of spleen homogenates.

RESULTS. All sham mice survived after instillation of 5.106 bacteria. In contrast, the mortality rate was 78% in post-CLP mice. Four hours after P.aeruginosa instillation, analysis of BAL fluid revealed increased lung recruitment of neutrophils in post-septic mice that correlated with higher MPO activity. Twenty four hours after P.aeruginosa instillation, IL-10 BAL levels tended to be higher in post-septic mice as compared to sham mice, whereas IL-12p70, TNF-alpha and IFN-gamma were similar in both groups. Pulmonary bacterial clearance was preserved, as shown by similar bacterial counts in BAL and lung homogenates 24h after P.aeruginosa challenge. In contrast, post-septic mice displayed a high rate of bacteremic dissemination (93%) as compared to sham mice (21%).

CONCLUSION. Mice that survive to polymicrobial sepsis display a high susceptibility to a secondary P.aeruginosa pneumonia. In this setting, lung response is caracterized by early cell recruitment and sustained MPO activity that did not prevent bacteremic dissemination.

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0346

ORGAN-SPECIFIC DNA PROTECTION OF SUPEROXIDE DISMUTASE OVEREXPRESSION IN MURINE SEPTIC SHOCK

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INTRODUCTION. Septic shock results in oxidative and nitrosative stress, which in turn may cause DNA damage. In vitro, increased superoxide dismutase (SOD) and catalase activity reduce NO-induced DNA damage (1). Therefore we investigated the effect of SOD overexpression on DNA damage during hyperdynamic murine septic shock.

METHODS. 15 h after cecal ligation and puncture (CLP) heterozygous (HE) and homozygous (HO) SOD-overexpressing mice or wildtype (WT) mice were anesthetized, mechanically ventilated and instrumented. Using the single cell gel electrophoresis (tailmoment in the comet assay) (2), we measured DNA strand breaks in liver and kidney tissue specimen collected immediately post mortem. Liver and kidney SOD and catalase activities were estimated using commercial kits. Data are shown as median and range. Intergroup differences were tested using an unpaired rank sum test.

RESULTS. While catalase activity did not show any intergroup difference, SOD activity was significantly higher in both organs in the HE and HO mice. Nevertheless, SOD overexpression attenuated CLP-induced oxidative DNA damage in the liver of HO mice only (see table).

#p<0.05 vs. WT	Liver WT	HE	HO	Kidney WT	HE	HO
Tailmoment [Units]	1.2 (0.0-3.8)	0.6 (0.2-3.0)	0.3 (0,1-0,5)#	0.3 (0.0-2.0)	0.2 (0.1-2.5)	0.2 (0.1-1.8)
SOD [U/mg protein]	32 (12-54)	46 (27-99)#	67 (61-87)#	9 (4-24)	27 (15-60)#	35 (18-58)#
Catalase [U/mg protein]	24 (13-27	18 (13-45)	23 (15-33)	25 (15-42)	32 (23-64)	20 (16-35)

CONCLUSION. Since even a 4-fold increase of SOD activity failed to decrease DNA strand breaks in the kidney, we propose that absolute amount of SOD activity plays crucial role in protection against oxidative DNA damage.

REFERENCE(S). 1). Doulias et al.: Free Radic Biol Med 2001; 30: 679-85; 2). Speit G, Hartmann A Methods Mol Biol 2006, 314:275-86

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0347

ENDOTOXEMIA INDUCES MICROCIRCULATORY HYPOXIC AREAS IN THE RENAL CORTEX IN THE RAT

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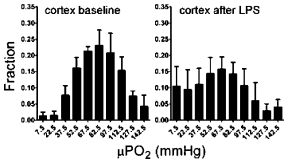
INTRODUCTION. Microcirculatory dysfunction is a cornerstone in the pathophysiology of sepsis. In several animal models septic renal failure was not accompanied by profound tissue hypoxia or decrease in microcirculatory PO_2 (μPO_2). We hypothesised that heterogeneity in μPO_2 in the kidney obscures microcirculatory dysfunction in average measurements. We studied the effect of endotoxemia on the heterogeneity of renal μPO_2 in rats.

METHODS. In 8 anesthetized and ventilated male Wistar rats arterial blood pressure and renal blood flow were recorded. Renal μPO_2 was measured by phosphorescence quenching allowing simultaneous measurement of cortical and outer medullary μPO_2-distributions. Renal venous PO_2 was also measured by phosphorescence quenching. Five animals received a 60-min infusion of LPS (10 mg/kg/hr), 3 animals were time-control.

RESULTS. TC = time-control; LPS = endotoxemia. T_0 = baseline, t_1 = after LPS-infusion (60 min); MAP = mean arterial pressure; RBF = renal blood flow; CL_{crea} = creatinine clearance; VO_{2ren} = renal oxygen consumption; $c\mu PO_2$ = cortical μPO_2; $m\mu PO_2$ = outer medullary μPO_2; * = anuria. No significant change in PO_2 histograms in outer medulla and TC.

TABLE 1.

	MAP mmHg	RBF ml/min	CLcrea µl/min/g	VO2ren ml/min/g	cµPO2 mmHg	mµPO2 mmHg
TC t_0	112 ± 2	6.3 ± 0.3	990 ± 87	0.13 ± 0.03	68 ± 3	51 ± 2
t_1	120 ± 2	6.0 ± 0.4	1084 ±253	0.19 ± 0.04	66 ± 4	50 ± 3
LPS t_0	116 ±7	5.8 ± 0.8	891 ± 119	0.10 ± 0.02	68 ± 4	55 ± 3
t_1	97±17	2.1 ± 0.2	*	0.07 ± 0.05	52 ± 6	45 ± 2



CONCLUSION. LPS infusion decreased renal blood flow and induced hypoxic microcirculatory areas in the renal cortex despite a relative mild reduction in average μPO_2. This indicates that hypoxia might contribute to the pathogenesis of septic renal failure and that manoeuvres to improve microcirculatory function might improve the outcome in ICU patients.

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0348

EFFECT OF SUPEROXIDE DISMUTASE OVEREXPRESSION ON MYOCARDIAL FUNCTION AND CATECHOLAMINE REACTIVITY IN MURINE SEPTIC SHOCK

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INTRODUCTION. Superoxide radical is referred to play a crucial role in sepsis-related myocardial dysfunction: Mimetics of superoxide dismutase (SOD), which detoxifies the superoxide radical, prevents oxidative catecholamine deactivation (1), and polyethylene glycol-SOD prevented endotoxin-induced cardiac dysfunction (2). Therefore, we examined the effect of genetic CuZn-SOD overexpression on myocardial function and catecholamine reactivity during murine septic shock (3).

METHODS. 15 h after cecal ligation and puncture (CLP) heterozygous (HE), homozygous (HO) SOD-overexpressing and wildtype (WT) mice were anesthetized, mechanically ventilated and instrumented (left ventricular pressure-conductance catheter) (3). Measurements were recorded 18, 21 and 24 hrs post-CLP. Hydroxyethylstarch and noradrenaline (NA) were infused to achieve normotensive and hyperdynamic hemodynamics. Heart SOD and catalase activities were estimated using commercial kits. Data are median (range), within group effects over time were tested with a Friedman ANOVA on ranks, intergroup differences were tested using an unpaired rank sum test.

RESULTS. While heart SOD activity was 9 (7-10), 40 (29-44), and 61 (56-65) U/mg protein in WT, HE and HO mice, respectively, there was no intergroup difference in tissue catalase activity (9 (8-10), 7(6-9) and 7(6-11) U/mg protein, respectively). Neither the NA infusion rate needed to achieve hemodynamic targets nor any parameter of myocardial function showed any intergroup difference (see table).

	NA µg/kgxmin	CO[µl/min] 18 hrs	24 hrs	EF [%] 18 hrs	24 hrs	EDV [µl] 18 hrs	24 hrs
WT	0.4 (0.2-7)	9 (7-17)	17 (9-33)	42 (29-64)	42 (18-48)	65 (31-83)	107 (57-13)
HE	0.5 (0.2-5)	11 (9-16)	15 (9-29)	47 (31-57)	29 (21-43)	54 (34-83)	95 (67-119)
HO	0.4 (0.2-1)	10 (10-12)	21 (13-24)	45 (35-67)	38 (33-57)	53 (23-71)	89 (69-106)

CONCLUSION. Transgenic CuZn-SOD overexpression did not improve myocardial function and catecholamine reactivity in murine septic shock, possibly due to the lacking effect on tissue catalase activity.

REFERENCE(S). 1. Macarthur H et al:. PNAS 2000;97:9753-8
2. Supinski GS, Callahan LA: Am J Respir Crit Care Med 2006; 173:1240-7
3. Barth E et al: Crit Care Med 2006;34:307-13

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0349

YERSINIA PESTIS V-ANTIGEN INHIBITS LIPOPOLYSACCHARIDE-INDUCED RESPONSES

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INTRODUCTION. Yersinia pestis, the etiological agent of plague, and the enteropathogenic species of Yersinia pseudotuberculosis and Yersinia enterocolitica all possess a 70 kb-conserved virulence plasmid named pYV. Yersinia enteropathogenic species largely rely on the virulence antigen (V-antigen, LcrV) for pathogenicity. The virulence antigen LcrV has been shown to "silence" the innate immune responses against stimulation with TLR2 agonists.

METHODS. In this study we investigated whether LcrV is only able to "interfere" TLR2-dependent inflammatory responses, or whether it is able to inhibit other pattern recognition receptors.

RESULTS. Our experiments demonstrate that LcrV is able to "silence" innate immune responses not only against TLR2, but also against TLR4 agonists in vitro. When tested in an in vivo sepsis model caused by Gram-negative bacterial products such as lipopolysaccharide (LPS), it was shown that pre-treatment with LcrV was able to inhibit LPS-induced inflammatory responses and improve the survival of the LPS-treated mice.

CONCLUSION. This study shows the ability of LcrV to inhibit TLR2 and TLR4 agonists and further demonstrates its potential use as a therapeutic intervention for sepsis and septic shock.

0350

THE ROLE OF PAR1-DEPENDENT PROTECTIVE EFFECTS OF VASCULAR BARRIER INTEGRITY BY ACTIVATED PROTEIN C

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INTRODUCTION. The clotting factor recombinant human activated Protein C (APC) has been shown to reduce mortality in septic patients, even though the mechanism is still under discussion and cannot only be explained by its anticoagulant activity. The prototypical thrombin receptor protease activated receptor-1 (PAR1) mediates protective effects of APC in cultured endothelial cells, including enhancement of endothelial barrier integrity, but it is controversially discussed whether APC-PAR1 signalling in sepsis is likely because systemic inflammation leads to thrombin generation and thrombin cleaves and activates PAR1 more efficiently than APC.

METHODS. Effects of APC on endothelial barrier integrity in the presence of thrombin were tested in-vitro in a dual chamber system. For in-vivo-experiments, murine APC or control was infused over several hours via a central venous catheter in male wildtype (wt) and PAR1-deficient C57BL/6 mice. Vascular endothelial growth factor (VEGF)-mediated hyperpermeability was analyzed in the skin detecting Evans blue extravasation in a modified Miles assay. Survival and pulmonary fluid accumulation were measured in a model of endotoxemia after intraperitoneal injection of 10-20 mg/kg lipopolysaccharide (LPS).

RESULTS. APC enhanced barrier integrity of cultured endothelial cells in the presence of up to low nM thrombin concentrations. A protective response also resulted when cells were co-incubated with thrombin and the zymogen protein C indicating that exogenous and endogenously generated APC can mediate barrier protective effects in the presence of thrombin. Infusion of APC in mice protected vascular barrier integrity from locally-induced VEGF-mediated hyperpermeability in the skin. APC had highly significant protective effects in wt, but not in PAR1 deficient mice. Finally, in a mouse model of systemic inflammation, APC led to a small survival benefit and did not alter interleukin-6 levels. However, intraperitoneal injection of LPS induced pulmonary edema formation after 5h and APC infusion reduced fluid accumulation by 61% (p=0.013) in wt animals whereas it lacked a significant protective effect in PAR1 deficient mice. The murine APC variant 5A-APC with diminished anticoagulant but retained cytoprotective activity was used to establish that protective APC effects are not mediated indirectly by downregulating thrombin generation.

CONCLUSION. Our results demonstrate that PAR1 plays a major role in mediating protective effects of APC on vascular permeability in-vitro and in-vivo. The findings strongly support the concept that PAR1-dependent enhancement of vascular barrier integrity contributes to protective effects of APC in sepsis.

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Oral Presentations
Advances to improve outcome 0351-0356

0351

LEVOSIMENDAN REDUCES MORTALITY WHEN COMPARED WITH DOBUTAMINE IN PATIENTS RECEIVING BETA BLOCKERS: THE SURVIVE STUDY

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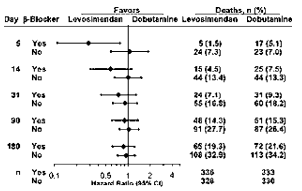
INTRODUCTION. Evidence-based guidelines recommend ß-blockers for the treatment of chronic heart failure (HF). Therapeutic effects of ß-agonists may be adversely impacted by ß-blockers; however, the hemodynamic effects of levosimendan appear to be enhanced by ß-blockade (LIDO). We compared the effect of levosimendan or dobutamine (DB) on all-cause mortality (ACM) in patients receiving ß-blockers at baseline in the SURVIVE study.

METHODS. SURVIVE was a multicenter, double-dummy, double-blind study of 1327 hospitalized patients with acute HF who had failed to respond to IV diuretics and/or vasodilators. The primary endpoint was 180-day ACM in patients who were randomized to levosimendan or DB. In patients treated with ß-blockers, pre-specified analyses of 31- and 180-day ACM and post-hoc analyses at 5, 14, and 90 days were conducted.

RESULTS. The 180-day ACM hazard ratio (HR; levosimendan:DB) was 0.91 (95% CI, 0.74–1.13; p=0.40). A total of 50.4% of the patients received ß-blockers at baseline. A significant interaction was noted at day 5: 5 of 336 patients (1.5%) treated with levosimendan died while 17 of 333 patients (5.1%) treated with DB died (HR=0.29; 95% CI, 0.11–0.78; p=0.014). After 14 days, 15 patients (4.5%) and 25 patients (7.5%), respectively, died (HR, 0.58; 95% CI, 0.31–1.10; p=0.096) and after 180 days, 65 patients (19.3%) and 72 patients (21.6%), respectively, died (HR, 0.87; 95% CI, 0.62–1.22; p=0.42).



CONCLUSION. SURVIVE did not meet its primary endpoint. However, the benefits of levosimendan in patients treated with ß-blockers were evident early, and were consistent with hemodynamic results reported in the LIDO study. Levosimendan may provide an effective alternative to DB particularly in patients receiving ß-blockers.

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0352

REDUCTION IN B-TYPE NATRIURETIC PEPTIDE FOLLOWING TREATMENT FOR ACUTE HEART FAILURE IS ASSOCIATED WITH IMPROVED SURVIVAL: SURVIVE

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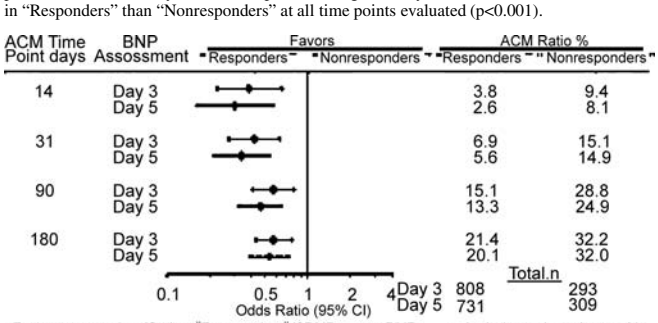
INTRODUCTION. B-type natriuretic peptide (BNP) level may be used to assist in the diagnosis of acute heart failure (AHF). The utility of BNP as a marker of therapeutic benefit or risk of all-cause mortality (ACM) in AHF remains uncharacterized. Association between the change in BNP level and ACM was assessed retrospectively in SURVIVE, an international randomized controlled trial comparing levosimendan, a vasodilator and enhancer of cardiac contractility, to dobutamine in 1327 patients with AHF.

METHODS. The primary endpoint was 180-day ACM [hazard ratio (levosimendan:dobutamine) = 0.91; 95% CI, 0.74–1.13; p = 0.40]. BNP level was determined at baseline, Day 3, and Day 5. Patients were classified as "Responders" if BNP(Day X) < BNP(Baseline); otherwise they were classified as "Nonresponders." Fisher's Exact test and logistic regression analyses of the effect of BNP responder status, independent of treatment, on ACM were performed as post hoc analyses.

RESULTS. When treatment groups were combined, 808 patients (73.1%) on Day 3 and 731 patients (70.3%) on Day 5 were "Responders." Significantly lower ACM rates were observed in "Responders" than "Nonresponders" at all time points evaluated (p<0.001).



Patients were classified as "Responders" if $BNP_{Day\ X} < BNP_{Baseline}$ includes only patients with BNP values on Day X and at baseline: ACM, all-cause mortality: BNP, B-type natriuretic peptide.

CONCLUSION. Patients whose BNP level declined following treatment for AHF appear to have a substantial reduction in ACM when compared to patients whose BNP level did not decline. These results suggest that short-term changes in BNP level during treatment of AHF may predict both short- and long-term mortality risk.

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0353

EFFICACY AND SAFETY OF COMBINATION GLYCOPROTEIN IIB/IIIA INHIBITORS AND REDUCED-DOSE THROMBOLYTIC THERAPY VERSUS THROMBOLYTIC THERAPY ALONE FOR ST-ELEVATION MYOCARDIAL INFARCTION (STEMI).

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INTRODUCTION. Pharmacologic combination reperfusion therapy (Combo) achieves faster, longer-lasting and more complete myocardial reperfusion than thrombolytic therapy alone (TL) and a reduction in recurrent myocardial infarction. Although Combo is an attractive option in the absence of primary percutaneous coronary intervention (primary PCI), the higher rate of bleeding, possibly associated with the high doses of unfractionated heparin (UFH) used in the large trials of Combo and a similar mortality rate have hindered the generalisation of its use. We assessed the efficacy and safety of Combo in association with the very low doses of UFH used in the TIMI 14 phase II trial, as compared with TL.

METHODS. We undertook a prospective study of patients admitted consecutively to our Intensive Cardiology Care Unit with STEMI from January 2002 to December 2006 (n=796), treated initially with drug-reperfusion therapy. The criteria for Combo (half dose of rt-PA + abciximab + very low-dose UFH, 4 IU/Kg/h): High-risk patients with STEMI (TIMI score $\geq$ 4, and/or ECG suggestive of proximal involvement of the affected vessel, primary VF, or new LBBB), age $\leq$ 75 years, and no high risk for haemorrhage (n=117). The others (n=679) received TL. The Combo group underwent coronary arteriography within the first 24 hours. We analysed the efficacy, rate of early reocclusion after initial efficacy, TIMI flow, need for rescue PCI and complications.

RESULTS. Clinical efficacy (cessation of pain, drop in ST and myoglobin ratio) Combo vs TL: Efficient, 76.1% vs 61.0%; doubtful, 12.6% vs 18.3%; failed, 11.1% vs 20.8% (p<0.01). Early reocclusion, 1.1% vs 22.7% (p<0.001). Rescue PCI, 11.1% vs 25.9% (p<0.002). Safety (including 17 cases not diagnosed with AMI on discharge)(Combo vs TL): Intracranial haemorrhagic, 0% vs 0.57% (ns). Ischaemic stroke, 0.8% vs 0.72% (ns). Thrombocytopoenia, 2.5% vs 0.14% (p<0.01). Major and minor bleeding: Combo (n=117) 2.5% and 5.9%, TL (n=518),1.7% and 1.7% (p<0.02 for minor bleeding), TL + rescue PCI with no anti IIb/IIIa (n=74) 1.3% and 0%, TL + rescue PCI + anti IIb/IIIa (n=102) 5.9% and 8.6%. Planned coronary arteriography during the first 24 hours in the Combo group in 95.3% of the patients, with pre-PCI TIMI flow: III, 73.2%; II, 10.7%; I, 3.6%; 0, 11.6%.

CONCLUSION. In our experience, Combo proved more effective than TL. It was associated with a significantly lower rate of early reocclusion, and provided a very high rate of TIMI II/III flow, with reduced requirement for rescue PCI. The rate of haemorrhage with Combo using half the dose of thrombolytic therapy, abciximab and very low doses of UFH was acceptable, with no significant increase in major bleeding, although we did see a significant increase in minor bleeding. There was a significantly greater incidence of major haemorrhagic complications in the patients who received anti IIb/IIIa during rescue PCI after failed TL alone.

0354

PALONOSETRON, A NOVEL 5HT3 ANTAGONIST, DOES NOT PROLONG QTC INTERVAL IN PATIENTS UNDERGOING SURGERY

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INTRODUCTION. In patients undergoing surgery, caution must be used due to potential risk of QTc prolongation which may lead to adverse effects such as life-threatening ventricular arrhythmias, especially in patients with potential cardiac risk. 5HT3 receptor antagonist (RA) agents frequently used for the prevention of nausea and vomiting associated with chemotherapy or surgery have been associated with QTc prolongation.(1) With palonosetron (PALO, Aloxi, Onicit), a differentiated 5HT3 RA with a long half-life and high binding affinity, an ECG evaluation of patients was performed.

METHODS. Patients enrolled in two large phase 3, multicenter, randomized, stratified, placebo controlled, dose-ranging trials evaluating the efficacy and safety of PALO vs placebo for the prevention of postoperative (PONV) and post-discharge (PDNV) nausea and vomiting were pooled to evaluate their QTc profile. Patients enrolled were: > 18 yrs, ASA 1-3 scheduled to undergo major breast, gynecological or laparoscopic surgery under general endotracheal anesthesia. PALO IV 0.025, 0.05, or 0.075 mg or placebo was given immediately prior to a standardized anesthesia technique (hypnotic, inhalation agent, opioid, muscle relaxant and reversal). For the first time in a pivotal study, triplicate standardized 12-lead ECGs were performed at baseline (screening) and as a single recording at 15 min and 3-6 hrs post-dose. An independent, blinded cardiologist read all ECGs with manual QT interval measurement using the lead of the most distinct T-wave. QT interval was corrected for heart rate from the preceding RR-interval using Bazetts formula.(2) Data are expressed as mean msec QTc interval change vs baseline. Data was evaluated by T-test for comparison of post-dose vs baseline and F-test from ANOVA for PALO doses vs placebo. Significance was p<0.05.

RESULTS. Out of 1216 patients enrolled, ECGs were obtained on 1045 and 1087 patients at 15 min and 3-6 hrs, respectively post-dose. Among groups no difference in patient demographics were shown. At 15 min post-dose, the mean QTc interval was significantly prolonged (18-21 msec) vs baseline; however, this prolongation was consistent across all treatment groups. At 3-6 hours post-dose, mean QTc intervals (11-13 msec) vs baseline were still increased in all groups; however, they tended to normalize vs baseline compared with the 15 min post-dose values.

CONCLUSION. PALO 0.025, 0.05, or 0.075 mg IV given immediately prior to anesthesia induction showed no dose related increase in QTc prolongation at 15 min and 3-6 hrs post-dose. Importantly, the prolongation of QTc at all 3 dose levels of PALO was consistent with that seen for placebo at both 15 min and 3-6 hrs post-dose. Consequently, the prolongation of QTc intervals cannot be attributed to PALO.

REFERENCE(S). Drug Safety 2003;26(4):227-59; Heart 1920;7:353-70

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0355

THE DIAGNOSIS OF RIGHT VENTRICULAR ENLARGEMENT IN ARDS PATIENTS: DIFFERENCES BETWEEN TRANSTHORACIC AND TRANSESOPHAGEAL ECHOCARDIOGRAPHY

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INTRODUCTION. Detecting a right ventricular (RV) enlargement by echocardiography is essential for diagnosing RV failure during acute respiratory distress syndrome (ARDS). RV enlargement is defined by an increased RV end-diastolic area (RVEDA) over left ventricular end diastolic area (LVEDA) ratio. Although initially described by using the transthoracic approach, RV enlargement is now often assessed via the transesophageal route. However, the echo beam crosses the ventricular cavities at different levels depending on the echocardiographic route. This may result in differences in ventricular end-diastolic dimensions. Our objective was to compare the transthoracic and transesophageal echocardiographic diagnosis of RV enlargement.

METHODS. Nineteen ARDS patients with respiratory support were studied. Transthoracic echography could not be performed in 3 patients because of poor echogenicity. In the 16 remaining patients (SAPSII=48±8, PaO2:FiO2 ratio=130±80mmHg, tidal volume=6.9±0.9mL/kg, PEEP=7±4mmHg), we measured the RVEDA/LVEDA ratio through simultaneous transthoracic and transesophageal long axis 4-chambers views. Caution was paid to obtain the view providing the largest value of ventricles long axis in both routes. RV enlargement was defined as a RVEDA/LVEDA ratio greater than 0.6.

RESULTS. The LVEDA was 12% lower with transesophageal than with transthoracic echography (24±6 vs. 28±9cm^2, respectively, p<0.05) while the RVEDA value was similar. As a result, the RVEDA/LVEDA ratio was significantly higher at transesophageal than at transthoracic echography (0.67±0.15 and 0.59±0.18, respectively, p<0.02). The difference in the RVEDA/LVEDA ratio provided by the two techniques was greater than 25% in 4/16 patients. Furthermore, a RV enlargement was diagnosed in 7 patients by transthoracic echography and in 3 additional patients by transesophageal echography, i.e. the two techniques provided a divergent diagnosis in 3 patients.

CONCLUSION. Transthoracic and transesophageal echographic views may provide different values of the RVEDA/LVEDA ratio, leading to divergent diagnoses of RV enlargement during ARDS. The cut-off value of the RVEDA/LVEDA ratio considered for defining a RV enlargement could be different depending on the chosen echographic approach.

0356

PATIENT-ASSESSED IMPROVEMENTS IN DYSPNEA AND GLOBAL STATUS ARE ASSOCIATED WITH REDUCED RISK OF MORTALITY: REVIVE I & II

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INTRODUCTION. One goal when treating patients with acute decompensated heart failure (ADHF) is to improve symptoms, but it is not known whether short-term symptomatic improvement is associated with reduced all-cause mortality. We evaluated the relationship between symptomatic improvement and mortality in the REVIVE I & II studies (REVIVE). The studies enrolled 700 patients with NYHA class IV ADHF who were randomized to either levosimendan, a vasodilator and enhancer of cardiac contractility, or placebo, each in addition to standard-of-care.

METHODS. Patients assessed their change in global status related to ADHF (PGA) and dyspnea, relative to baseline, on separate 7-point categorical scales at 6, 24, and 48 hours, and Days 3 and 5. A post-hoc analysis combining both treatment groups compared the 31- and 90-day mortality of patients who were "Improved" (defined as moderately or markedly improved at $\geq$3 of the first 4 time points, and on Day 5) to that of patients who were "Unimproved;" 6 patients were excluded from this analysis because of missing PGA or dyspnea assessments.

RESULTS. A total of 231 patients (33.3%) for PGA and 236 patients (34.0%) for dyspnea were classified as "Improved." Patients who were "Improved" on either assessment had a significant reduction in mortality rates at both 31 and 90 days, compared to patients who were "Unimproved" (Table). Results from logistic regression analyses also demonstrated that ratings of moderately or markedly improved on PGA and dyspnea assessments, at individual time points, were associated with lower probability of 31- and 90-day mortality.

31- and 90-Day All-Cause Mortality Rates

Mortality Time Point, days	Patient Self-Assessment	"Improved"	"Unimproved"	P-Value, Fisher's Exact
31	PGA	1.7%	6.9%	0.003
31	Dyspnea	2.1%	6.8%	0.010
90	PGA	9.1%	14.5%	0.052
90	Dyspnea	8.9%	14.6%	0.040

CONCLUSION. In this study, symptomatic improvement over 5 days was associated with reduced mortality.

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Oral Presentations
Emergency department medicine 0357-0362

0357

PLASMA DNA IS OUTCOME PREDICTOR IN EMERGENCY DEPARTMENT PATIENTS WITH SEPSIS.

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INTRODUCTION. The prognostic value of circulating markers,including NF kappa B (1),cytokines, PCT (2) and, recently, plasma DNA (3) has been demonstrated in patients in the ICU. However, outcome studies of sepsis in the emergency department (ED) are limited. We hypothesized that plasma DNA may be used to predict disease severity or prognosis in sepsis patients in the ED.

METHODS. Blood samples from 86 consecutive patients with bacteriologically documented infections who met the sepsis criteria were taken at the time of diagnosis in the ED. Routine laboratory tests, plasma DNA measurements by real-time quantitative PCR assay for the human b-globin gene, APACHE II and the Mortality in Emergency Department Sepsis (MEDS) score were noted. Samples from 60 age- and sex-matched healthy controls were analysed. Hospital mortality rate and length of stay (LOS) of surviving patients were the outcome measures.

RESULTS. 21 of the 86 sepsis patients developed severe sepsis within 12 hrs of ED arrival and were admitted to the ICU, whereas the remaining patients (74.7 %) were admitted to the medical ward. 9 patients were transferred within 3 days from the medical ward to the ICU because of severe sepsis, and 16 patients died within 1 month. The median (IQR) plasma DNA concentrations in the control, sepsis, and early severe sepsis groups were 21 (12-30), 76 (40-155), and 184 (160-348) ng/ml, respectively. Patients who developed late severe sepsis or died had 2.6- and 4.3-fold higher plasma DNA concentrations than those who did not. Plasma DNA correlated with the MEDS score ($r=0.57$; $p<0.01$) but not with the APACHE II score. Plasma DNA was unrelated to hospital LOS. ROC analysis indicated a better performance in mortality prediction by the admission plasma DNA (AUC 0.77; 95% CI: 0.70-0.84) compared with the MEDS score (AUC 0.71; 95% CI: 0.62-0.70). Multiple logistic regression analysis showed that plasma DNA on admission to the ED is an independent predictor of death (odds ratio 1.26) together with MEDS score (OR 1.18).

CONCLUSION. Our results indcate that plasma DNA can be used at the bedside in the stratification of high risk patients with sepsis in the ED.

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0359

LIVER PERFUSION AND OXYGENATION DURING INDUCED HYPOTHERMIA

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INTRODUCTION. Induced therapeutic hypothermia is accepted to improve outcome in patients with postanoxic coma following cardiac arrest and patients with severe traumatic brain injury(1). It is well known, that hypothermia can provoke various complications concerning different organ systems, in particular dysfunction of coagulation and hypoperfusion of organs(2). Hypoperfusion of splanchnic organs, e.g. the liver, is a possible cause of SIRS, sepsis and multiorgan failure. Therefore we investigated the effects of induced hypothermia on perfusion and oxygenation of the liver.

METHODS. After ethical approval 25 anaesthetized (ketamine, flunitrazepam, fentanyl, rocuronium) and ventilated pigs were studied. For induction of hypothermia an intravascular system (COOL-GARDâ) was inserted into the femoral vein. An ultrasonic flow probe was placed around the hepatic artery and the portal vein. Catheters were inserted into the femoral artery, portal vein and pulmonary artery. Tissue surface pO2 was measured by a multiwire surface electrode as described by Kessler(3). Animals were randomly assigned to two groups: group 1= t (pH-stat) and group 2 = b (alpha-stat). All animals were continuously cooled down from 36 ˚ C (Baseline) to 30 ˚ C. Measurements were made at 36 ˚ C, 33 ˚ C, 30 ˚ C and following warming up at 36 ˚ C. Group 1 was ventilated with baseline ventilation parameters. In group 2 the ventilation parameters were reduced according to alpha-stat management. Statistics: Median with 25 – 75 % interquartile range, non parametric tests were used for comparison within each group and between groups (# = $p < 0.5$ vs. baseline in the same group; § = $p < 0.5$ vs. t at corresponding levels).

RESULTS. The cardiac index decreases in both groups until 27 ˚ C and turns back to baseline values following rewarming; the systemic oxygen delivery is constant, while the systemic oxygen uptake decreases in both groups; in group 1 pH at 37 ˚ C is constant, in group 2 temperature corrected pH is constant. The portal vein blood flow decreases in both groups with 27 ˚ C. In group 1 the fraction of total hepatic blood flow from cardiac output is constant during the whole experiment. In group 2 the fraction of total hepatic blood flow from cardiac output increases at 30 ˚ c and 27 ˚ C, the hepatic arterial blood buffer response is maintained under hypothermia. Oxygenation of hepatic tissue is unaffected in group 1 and decreases in group 2.

CONCLUSION. In induced hypothermia the „hepatic arterial buffer response“ is sustained in both groups and tissue oxygenation of the liver is not severe disturbed. Although a redistribution of cardiac output under alpha-stat for the benefit of the liver exists, there is no influence on liver tissue oxygenation.

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0360

EFFICACY AND SAFETY OF EPTACOG ALPHA (ACTIVATED) IN INTRACTABLE BLEEDS IN THE CRITICALLY ILL

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INTRODUCTION. Intractable hemorrhage due to disease or surgical procedures is a serious problem frequently encountered in the operating theatre and the intensive care unit. When surgical and interventional therapies, prohemostatics and transfusion of blood products, fail to control the bleeding, eptacog alpha (activated) can be administered to promote coagulation. In the absence of pre-existing congenital or acquired hemophilia, this administration concerns off-label use of eptacog alpha (activated). We investigated the efficacy and safety of this intervention in the critically ill.

METHODS. Retrospective cohort study of prospectively gathered data by means of an intensive care information system (MetaVision®, iMDsoft, Israel). Eptacog alpha (activated) (recombinant factor VIIa, NovoSeven®, Novo Nordisk, Denmark) was administered as a bolus of 90 μg/kg bodyweight (1 mg = 120 U) to be repeated every 2 hours until control of the hemorrhage was achieved. Efficacy was defined as the achievement of control of bleeding within 4 hours of administration of eptacog alpha (activated). Development of new thrombo-embolic complications after administration of eptacog alpha (activated) was used as safety parameter.

RESULTS. Between January 2004 and February 2007, 21 patients (11 males/10 females, 12 surgical/9 non-surgical bleeds, age 58.4 ± 20.3 years (mean ± standard deviation), APACHE II score 21.2 ± 7.9 points, received eptacog alpha (activated) (535 ± 229 U) following administration of red blood cells (17.5 ± 10.8 U), plasma (7.1 ± 5.8 U) and platelet concentrates (2.1 ± 1.7 U). In 15 patients (71.4%) successful control of hemorrhage was achieved. In the other 6 patients, 3 had hysterectomy performed, 1 had an intra-uterine balloon inserted and 2 died due to intractable bleeding. Transfusion needs strongly reduced following administration of eptacog alpha (activated): red blood cells (5.2 ± 6.6 U; p=0.000), plasma (3.7 ± 3.0 U; p=0.04) and platelet concentrates (1.6 ± 1.9 U; p=0.35). New thrombo-embolic complications occurred in 2 patients (9.5%); 1 patient suffered fatal intestinal ischemia and 1 patient suffered multiple cerebellar infarctions. ICU mortality was high (38.1%).

CONCLUSION. Eptacog alpha (activated) appears to be effective in the treatment of intractable hemorrhage in the critically ill with an acceptable risk of thrombo-embolic complications.

0361

PROGNOSTIC FACTORS OF ACUTE INTOXICATIONS WITH CALCIUM CHANNEL BLOCKERS

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INTRODUCTION. Incidence of acute calcium-channel blocker (CCB) poisonings is increasing, representing to date the first cause of toxic death in the US. Our objectives were to describe the CCB-poisoned patients admitted in intensive care units (ICU) and to determine the prognostic factors and the interest of plasma concentration measurement on admission.

METHODS. Retrospective collection of clinical data of CCB-poisoned patients admitted in 3 ICU in 2000-2006; determination of plasma concentration using HPLC (REMEDI); description (median, [25-75% percentiles]); comparisons using Mann-Whitney and Chi-2 tests; multivariate analysis using a step-by-step logistic regression model.

RESULTS. Eighty-four patients (47M/36F, 44 years [31-56], SAPS II: 15 [8-25]) were included. Verapamil (39/83), diltiazem (13/83), nifedipine (11/83), nicardipin (9/83), and amlopdipine (8/83) were involved. On admission, systolic blood pressure was 105 mmHg [86-118], heart rate 76 /min [67-91], QRS duration 85 ms [80-110], and plasma lactate concentration 2.86 mmol/l [1.79-5.98]. Poisoning features included shock (42/83), atrioventricular block (34/83), asystole (8/83), and/or ventricular arrhythmia (4/83). All patients received fluid replacement, 50/83 epinephrine infusion (maximal rate: 3.0 mg/h [1.4-8.0]), and 27/83 norepinephrine (5.0 mg/h [2.9-15.0]). 33/83 were mechanically ventilated. Treatments included: calcium salts (22/83), glucagon (18/83), dobutamine (18./33), 8.4% sodium bicarbonate (16/83), isoprenaline (14/83), insulin + glucose (13/83), terlipressin (4/83), electrosystolic stimulation (2/83), and extracorporeal life support (ECLS, 5/83). Eleven patients (13%) died in ICU. Plasma verapamil concentration was significantly different on admission regarding survival (800 versus 2,522 mg/l, $p<0.05$). If excluding SPAS II from the model, multivariate analysis showed that QRS duration (>100 ms; Odds ratio, 5.3; 95%-confidence interval [1.1-27.0]) and maximal epinephrine rate (>5 mg/h; OR, 27.6; IC, [5.3-144.7]) were the only 2 predictive factors of death ($p=0.007$). If not, SAPS II was the only predictive factor of death (>60, OR, 97.5; IC, [14.2-665.2], $p=0.0009$). Shock was refractory if epinephrine + norepinephrine was >8 mg/h with renal (creatinine >150 μmol/l) or respiratory failure (PaO2/FiO2 >150 mmHg) (sensitivity, 100%; specificity, 89%).

CONCLUSION. Despite optimal management in ICU, CBB poisoning mortality remains high (13%). In case of shock, increasing cathecholamine dosage may be life-saving. In case of bad prognostic factors and especially of refractory cardiac shock, ECLS should be proposed. However, the place of possible new antidotes (2,3-diaminiopyridine) remains to be determined.

0362

ACUTE INSULIN SELF-INTOXICATION: PROGNOSTIC FACTORS AND INTEREST OF TOXICOKINETIC / TOXICODYNAMIC RELATIONSHIPS

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INTRODUCTION. Insulin self-overdoses are rarely described in the literature. The prognostic factors and the optimal conditions of glucose infusion are not established. The interest of the plasma insulin concentration is unknown. We aimed to investigate the prognostic factors and the toxicokinetic / toxicodynamic (TK/TD)-relationships.

METHODS. Prospective chart review of patients admitted in an intensive care unit; TK/TD modeling between glucose infusion rate and plasma insulin concentration (MEIA technology, Axsym system, Abbott; limit of quantification: 1.0 mU/l); multivariate analysis using step-by step logistic regression to explore prognostic factors; determination of correlations (Pearson tests); presentation of the results as median [25%-75%-percentiles].

RESULTS. Twenty-five patients (14F/11M; 46 years [36-58], 52% diabetic, and 20% nurses) were studied. On presentation, Glasgow Coma Score was 9 [4-14] and capillary glucose 1.4 mmol/l [1.1-2.3]. Seven patients were intubated and 5 received catecholamine. Plasma insulin concentration was 197 mIU/l [161-1,566] and total glucose infusion 301 g [184-1,056]. Outcome was favorable except 2 non-survivors and 2 patients with significant neurological sequellae. There was no significant correlation between the injected insulin dose and the administered glucose quantity (R2=0.12; p=0.1) or the plasma insulin concentration (R2=0.07; p=0.9). There was a weak correlation between the duration of glucose infusion and the injected insulin dose (R2=0.25; p=0.02). Delay-to-therapy >6h (Odds-ratio (OR), 60.0; 95%-confidence interval (CI), [2.9-1,236.7]) and ventilation >48h (OR, 28.5; 95%-CI, [1.9-420.6]) were independent prognostic factors. Insulin elimination was of first-order (half-life, 4.3 h [3.7-8.2]; N=4). During the poisoning course, TK/TD-relationships between glucose infusion rates and insulin concentrations well-fitted the Emax-model (Emax, 29.5 g/h [17.5-41.1]; EC50, 46 mIU/l [35-161]; N=6).

CONCLUSION. TK/TD-relationships are useful to quantify the need of glucose during insulin acute self-poisonings. However, the existence of important inter-individual variable responses to insulin necessitate careful monitoring of glucose level and infusion rate in order to improve the prognosis.

0364

TRACKING SURVIVAL AFTER CRITICAL ILLNESS: HOW SHORT IS TOO SHORT AND HOW LONG IS LONG ENOUGH?

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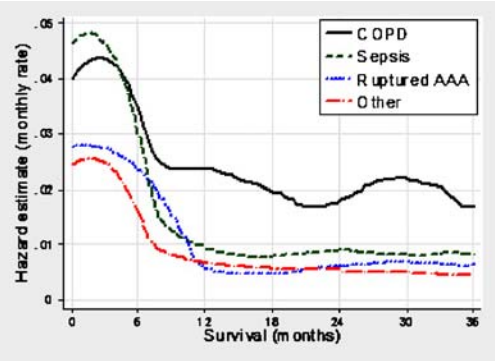
INTRODUCTION. Survival 28-days after admission and hospital survival are typical endpoints in critical care outcome studies. Hospital survival is prone to bias and 28-day survival may not capture the increased mortality imposed by critical illness. The time after critical illness when death rates become constant (baseline hazard rate) may be a more relevant end point. The purpose of this work was to examine death rates after critical illness in 3 diagnostic groups.

METHODS. Admissions during 2001-2006 due to acute on chronic obstructive pulmonary disease (COPD), ruptured abdominal aortic aneurysm (AAA) and sepsis were identified by their ICD-10 codes in the Swedish Intensive Care Registry. The unique personal number was used to exclude readmissions and to capture vital status through the national population registry.

RESULTS. There were 99648 first admissions during the study period (COPD 1079, AAA 964, Sepsis 3362 and Other 94243). Death rates differed between the diagnostic groups and became constant at different times (about 9 – 15 months) after admission.



CONCLUSION. Acute and baseline death rates vary with diagnosis, and the increased acute rates decline towards a baseline rate at different times after critical illness. Tracking survival 3 and 6 months may be too short, while 12 months may be long enough.

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Oral Presentations
Long-term outcome 0363-0368

0363

SEXUAL LIFE IN TRAUMA PATIENTS MORE THAN 3 YEARS AFTER DISCHARGE FROM THE ICU

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INTRODUCTION. Quality of life (QoL) constitute essential outcome measures after intensive care. Sexual function is important for well-being, and should be part of a full QoL assessment. The aim of this study has been to investigate changes in trauma patients' evaluation of their sex life from prior to trauma and up to 3-9 years after ICU discharge. A further aim was to investigate possible determinants of deteriorated sex life.

METHODS. Cohort study of adult ICU trauma patients admitted to a university hospital during 1998-2003. A postal questionnaire survey was conducted in 2006, using a self-report instrument to investigate changes in sex life, and the Hospital Anxiety and Depression Scale to detect psychological symptoms. Patients were asked to score their sex life prior to trauma and at present, and to specify if possible changes were caused by the trauma.

RESULTS. Of the 210 eligible patients, 156 (74%) entered the study. Mean age was 46 years (range 22-88), and 80% were males. Median ICU stay was 3 days, mean SAPS II 31, median ISS 25, and mean total maximum SOFA score 7. The questionnaires were successfully completed by 145 patients. There was a significant reduction in the patients' rating of their present sex life (p<0.001), table 1. At follow-up 55% reported that the trauma still influenced their sex life: 3% had a better sex life, 18% had an altered sex life, but neither to the worse nor to the better, and 34% experienced deterioration due to the trauma. In an ordinal logistic regression analysis adjusted for scores prior to trauma, poorer sex life at follow-up was associated with increasing age (p<0.001), not being in a regular relationship (p=0.02), and depression (p<0.01). There was no association between reported sex life and gender (p=0.42), time since trauma (p=0.31), total maximum SOFA score (p=0.90), or anxiety (p=0.65). After the trauma 36 patients got divorced. In 46% of these cases the trauma was reported to be a significant contributor to the breakdown of the relationship.

ICU trauma patients' evaluation of their sex life prior to and 3-9 years post injury

n (%)	Poor	Not very good	Quite good	Good	Very good
Prior to trauma	9 (6)	13 (9)	33 (23)	60 (41)	30 (21)
At follow-up	19 (13)	29 (20)	36 (25)	43 (30)	18 (12)

p<0.001, marginal homogeneity test; (n=145)

CONCLUSION. More than 3 years after discharge from the ICU, one third of trauma patients experienced impaired quality of sexual life, and related this to the trauma. Poor sex life was significantly associated with increasing age, being single, and symptoms indicating mental depression. Total maximum SOFA score, as a measure of severity of injury, was not related to patients' rating of their sex life.

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GRANT ACKNOWLEDGEMENT. Helse-Vest, Norway

0365

QUALITY OF LIFE AFTER INTENSIVE CARE: A BAYESIAN APPROACH

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INTRODUCTION. Bayesian networks are a formal representation of uncertain knowledge, combining a qualitative model of relations among variables, with a quantitative model consisting of a set of conditional probabilities. This approach has been interesting more and more researchers as possibilities of application emerge in different areas, such as health care. Health Related Quality of Life is a subjective concept which basically reflects the patient's individual attitude, evaluating the patient's health state, physically and mentally, and their own well-being. In this work, the instrument used was the EQ-5D questionnaire. The main goal of this work is to apply Bayesian techniques to the problem of prognosis of quality of life, 6 weeks and 6 months after intensive care unit (ICU) stay.

METHODS. At 6 weeks and 6 months after ICU discharge, survivors went to a follow-up consultation and EQ-5D was applied. Data collection included background variables i.e. age, gender, main activity, previous health state; ICU variables i.e. admission diagnostic categories, APACHE II and length of ICU stay (ICU LOS); and EQ-5D variables i.e. mobility, self-care, usual activities, pain and anxiety/depression, EQ-VAS and EQ-Index. Five models were created representing the five dimensions, for each of the corresponding periods. Construction of the model also includes permanent contact with an expert, who analyses, evaluates and modifies the learned structure.

RESULTS. Experimental results show that quality of life increases from 6 weeks to 6 months, with the probability of not having problems varying from 31% in the mobility dimension at 6 weeks, to 72% in the self care dimension at 6 months. For a 6 weeks prognosis, the main results show that women, elders, or people with longer ICU LOS have higher probability of having more problems. For the 6 months prognosis, and excluding anxiety/depression dimension, women, elders, people with longer ICU stay or with higher APACHE II have a higher probability of having problems. For anxiety/depression the youngest and the retired have a higher probability of having problems.

CONCLUSION. When used as a classification model on goal variables (of quality of life), Bayesian networks present competitive performance with other less descriptive learning strategies, presenting also some of the relations gathered by previous works. The main advantage of this technique is its ability to incorporate domain knowledge, and aggregate the competitive performance with a better interpretability of the generated model, as thus, may promise a better performance than previous prognostic models.

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0366

THE EFFECT OF BLOOD TRANSFUSION IN THE ICU ON LONG TERM SURVIVAL

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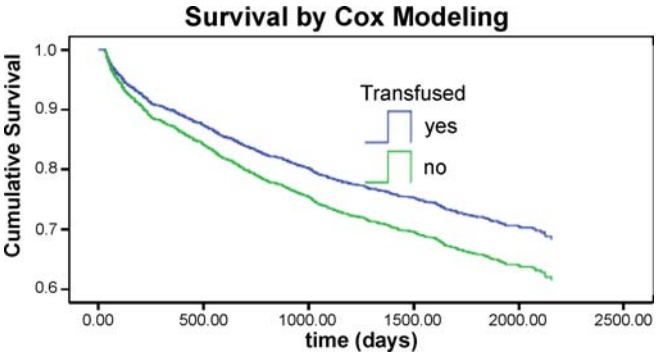
INTRODUCTION. While transfusions are common in the ICU, there is little evidence of its long term effects on survival. The purpose of this study is to evaluate the effects of transfusion on long term survival.

METHODS. The ICU database was reviewed for all patients admitted to five ICUs between January 27, 2001 and April 30, 2002. Cox modeling was used to find the predictors of mortality. Because, Cox modeling assumes that the risk of death is constant across the time interval, inspection of a Kaplan-Meier curve of all patients was used to show where changes in risk of death occur. Then each time interval, with constant risk of death, was analyzed separately.

RESULTS. 404 of the 2223 patients (18%) received transfusions. 1042(47%) were dead at followup. Patients who died were more likely to have received blood transfusions. They were also sicker- being more likely to be tracheally intubated on arrival in the ICU; to receive central venous lines, pulmonary artery catheters, hemodialysis, continuous veno-venous hemofiltration (CVVH), and mechanical ventilation. They were also more likely to suffer arrests in the ICU or be reintubated. They were older, had lower Glasgow coma scores, and had higher BUN, creatinine and APACHE II scores but lower hemoglobin levels. Transfusion had no effect on 30 day mortality. However, after correction for severity of illness, transfusion was associated with a 22% (95% confidence interval: 3.3 – 36.7%) reduction in relative risk of mortality in those patients who survived at least 30 days.



CONCLUSION. Transfusion in the ICU was associated with a 22% decrease in relative risk of dying, but had no effect on 30 day mortality.

0367

LONG-TERM SURVIVAL FOLLOWING TRACHEOSTOMY IN THE ICU

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INTRODUCTION. Tracheostomy is common in the ICU, but the appropriate timing is controversial. Our objective was to determine whether earlier timing is associated with greater survival.

METHODS. We included all mechanically-ventilated ICU adult patients who received tracheostomy in Ontario, Canada during April 1, 1992 to March 31, 2004, excluding extreme outliers (<2 or >=28 days). Tracheostomy timing was classified as early (<=10 days) versus late (>10 days) and mortality was measured at multiple follow-up intervals. We used stratification, propensity-score, and instrumental variable analyses to adjust for patient differences. Cox-proportional hazards survival analyses considered tracheostomy as a time-dependent variable to adjust for measurable confounders and to account for possible survivor treatment bias.

RESULTS. A total of 10 927 patients received tracheostomy during the study, of which one-third (n=3758) received early and two thirds late (n=7169). Patients receiving early tracheostomy had lower unadjusted 90-day (34.8% vs. 36.9%; p=0.03), one year (46.5% vs. 49.8%; p=0.001), and study mortality (63.9% vs. 67.2%; p<0.001) than patients receiving late tracheostomy. This observation was consistent across multiple subgroups. Time-dependent multivariable Cox-proportional hazards models used to account for possible survivor treatment bias and adjust for measurable confounders showed that each additional delay of one day was associated with increased mortality risk (hazard ratio 1.008, 95% confidence interval 1.004 to 1.012), equivalent to an increase in predicted baseline mortality from 36.2% to 37.6% per week of delay.

CONCLUSION. Physicians should consider performing tracheostomy earlier only to achieve the established benefits of the procedure and not in anticipation of a large potential survival benefit. Future research should concentrate on identifying which patients will receive the most benefit from the procedure.

0368

SHORT AND LONG-TERM OUTCOMES IN A VERY ELDERLY COHORT OF PATIENTS SUBMITTED TO MECHANICAL VENTILATION

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INTRODUCTION. Few and conflicting results have been reported addressing the prognosis in the elderly population submitted to mechanical ventilation in intensive care (ICU), partly because of differences in study design that compromise the comparability among them. The objective of this study was to measure short and long-term outcomes of the patients more than 80 years old submitted to mechanical ventilation compared to those younger.

METHODS. Primary endpoints were six-month (6m) survival, ICU mortality, length of stay under mechanical ventilation (MVLOS), in the ICU (ICULOS) and in hospital (HLOS). Secondary endpoints were the incidences of ventilation associated pneumonia (VAP), shock and hemodyalisis-dependent acute renal failure (hdARF). We followed a concurrent cohort of 233 patients (group E of 80 or more years old, n=116 and group Y of the younger, n=117) under mechanical ventilation for more than 48 hours. The short-term follow up extended until 48 hours after extubation, death or 60 days of ventilation, while the long-term until 6 months (Kaplan-Meier method). Patient severity was accessed with APACHE II and initial SOFA scores. Categorical variables were compared by the chi square test and continuous data by the Wilcoxon test. Potential biases were controlled by multiple linear and logistic regression models.

RESULTS. In the groups E and Y, the results were respectively: APACHE II median 18 (interquartile range - IR=13-22) versus 15 (IR=12-20, p=0.01), SOFA median 5 (IR=3-7) versus 5 (IR=3-8, p=0.4), female sex 66% (IC=57-74) versus 57% (IC=48-66, p=0.2), clinical diagnosis 80% (IC=70-90) versus 63% (IC=55-72, p=0.0003), neurological reason for ventilation 34% (IC=26-43) versus 25% (IC=17-33, p=0.02), 6m survival 28% versus 47% (OR=1.69, IC=1.28-2.24, p<0.0001), ICU mortality 44% (IC=35-53) versus 40% (IC=31-49, p=0.56), MVLOS median 13 days (IR=7-25) versus 10 (IR=6-20, p=0.13), ICULOS median 17 days (IR=11-28) versus 15 (IR=9-24, p=0.08), HLOS median 34 days (IR=17-55) versus 31 (IR=11-55, p=0.09). In multivariate analysis, age (OR=1.03, IC=1.01-1.05), shock (OR=3.88, IC=1.94-7.76) and hdARF (OR=2.87, IC=1.39-5.89) were independently associated with long-term survival, while for ICU mortality shock (OR=4.38, IC=1.94-9.84), male sex (OR=0.36, IC=0.18-0.71), hdARF (OR=4.03, IC=2.11-7.71) and VAP (OR=3.04, IC=1.37-6.75) remained independent predictors of events. In linear regression only VAP and shock were directly related to MV LOS.

CONCLUSION. The present study revealed no difference in length of stay under mechanical ventilation, ICU or in hospital attributable to advanced age, nor could we demonstrate significant difference in ICU mortality. On the other hand, six-month survival is poor in the very elderly compared to patients younger than 80 years old.

GRANT ACKNOWLEDGEMENT. ESHO

Oral Presentations
Outcome in respiratory failure 0369-0374

0369

AN EARLY PEEP/FIO2 TRIAL IDENTIFIES DIFFERENT DEGREES OF LUNG INJURY IN ARDS PATIENTS

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INTRODUCTION. Current American-European Consensus Conference (AECC) definitions for ALI and ARDS are inadequate for inclusion into clinical trials due to the lack of standardization for measuring the oxygenation defect. We questioned whether an early assessment of oxygenation on specific ventilator settings would identify patients with established ARDS (persisting over 24h).

METHODS. At the time of meeting ARDS criteria (Day 0) and 24 hours later (Day 1), arterial blood gases were obtained on standard ventilator settings, VT 7 mL/kg PBW plus the following PEEP and FiO2 settings in sequence: (1) PEEP>=5 cmH2O and FiO2>=0.5, (2) PEEP>=5 cmH2O and FiO2 1.0, (3) PEEP>=10 cmH2O and FiO2>=0.5, and (4) PEEP>=10 cmH2O and FiO2 1.0.

RESULTS. 170 patients meeting ARDS criteria (PaO2/FiO2 128+33 mmHg) were enrolled. Overall hospital mortality was 34.1%. The standard ventilator settings that best identified established ARDS patients and predicted differences in ICU mortality were PEEP>=10 cmH2O and FiO2>=0.5 at Day 1 (p=0.0001). Only 99 (58.2%) patients continued to meet ARDS criteria (PaO2/FiO2 155.8 + 29.8 mmHg, ICU mortality 45.5%) while 55 patients were reclassified as ALI (PaO2/FiO2 246.5 + 25.6 mmHg, ICU mortality 20%) and 16 patients as acute respiratory failure (ARF) (PaO2/FiO2 370 + 54 mmHg, ICU mortality 6.3%) (p=0.0001) on these settings.

CONCLUSION. Patients meeting current AECC ARDS criteria may have highly variable levels of lung injury and outcomes. A systematic method of assessing severity of lung injury is required for enrollment of ARDS patients into randomized controlled trials.

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0370

DO NIGHT AND DAY SHIFTS INFLUENCE THE INTUBATION RATE OF PATIENT FAILING NIV?

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INTRODUCTION. Reduction of personnel during the night shifts may jeopardize the success of NIV. The aim of this study was to analyze if the time of NIV failure in critical ill patients requiring ventilatory support for acute respiratory failure might be influenced by diurnal or nocturnal shifts.

METHODS. Three months observational study, with prospective inclusion of all patients requiring ventilatory support. Epidemiological and physiological characteristics were gathered for all patients. For patients failing NIV the moment of intubation was carefully recorded.

RESULTS. 183 patients were admitted to the ICU over the study period, of the 107 patients who received NIV, 48 (45%) had NIV as first line intervention for their acute respiratory failure (group A), and in 59 (55%) NIV was administered after extubation failure (group B). In group A (tab 1), 23 (48%) patients failed, 6 (26%) during night shift and 17 (73%) during day shift (p=0.0013). In group B (tab 2), of the 59 patient treated, 34 (57%) failed, 9 (26%) were intubated during night shift and 25 (74%) during day shift (p<0.001). In both groups, the baseline characteristics of patients intubated during day and night were similar. Mortality rate between those intubated during the day and night was not different in the two groups.

TABLE 1.

NIV failure (n=23)	Hypoxiemia (n)(%)	Hypercapnia (n)(%)	SAPS II (mean±SD)	Helmet/ mask(n)	Live/ Dead (n)
ETI during day shift	14(60)*	3(14)	32±8	9/8	10/7
ETI during nightshift	5(22)	1(4)	32±15	4/2	3/3

Group A. NIV applied as first line intervention

TABLE 2.

NIV failure (n=34)	Hypoxiemia (n)(%)	Hypercapnia (n)(%)	SAPS II (mean±SD)	Helmet/ Mask(n)	Live/ Dead (n)
ETI during day shift	19(56)*	6(18)	43±15	11/14	18/7
ETI during nightshift	8(23)	1(3)	42±12	3/6	7/2

Group B. NIV applied after extubation failure

CONCLUSION. 1) Differently from expectations, patients who failed NIV were more frequently intubated during day shifts. 2) The moment of intubation did not influence the mortality rate. 3) The high failure rate recorded in our population was basically due to the severe hypoxemia and high severity scores. 4) The interface used to deliver NIV had no influence on failures during both nocturnal and diurnal shifts.

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Legend:Hypoxemia=PaO2/FiO2<=200mmHg; Hypercapnia=PaCO2>=45mmHg with pH<7.35; ETI=endotracheal intubation. *p<0.01.

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0371

THE ROLE OF NONINVASIVE POSITIVE PRESSURE (NIPPV) VENTILATION IN POST-EXTUBATION RESPIRATORY FAILURE: AN EVALUATION USING META-ANALYTIC TECHNIQUES.

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INTRODUCTION. Re-intubation, which occurs in about 6 to 23% of cases after planned extubation, is an independent risk factor for mortality and increased hospital stay. NIPPV has been considered as a promising therapy to prevent extubation failure and re-intubation. Recent studies however have shown conflicting outcomes. The aim of this review is to assess the role of NIPPV in extubation failure by meta-analytic techniques.

METHODS. MEDLINE, EMBASE and Cochrane databases were electronically searched between the years 1950 to January 2007 for all Randomized Controlled Trials (RCT's) where NIPPV was used after post-extubation respiratory failure. Trials where NIPPV was used as a means of chest physiotherapy, and nonrandomised trials were excluded. Identified RCT's were classified as either prophylactic or therapeutic. Outcomes of interest were episodes of reintubation, ICU and hospital length of stay and mortality. Treatment effects were assessed as risk ratio (RR, random effects estimator) for binary events and weighted mean difference (WMD) for continuous measures. Covariate influence was determined by metaregression.

RESULTS. Twelve RCT's of which eight were prophylactic studies with 659 total subjects in the control and 655 in the NIPPV group were evaluated. There was variable reporting of outcomes, and the pooled estimates showed statistical heterogeneity in all outcomes except hospital mortality. Reintubations and hospital deaths were decreased with NIPPV (Table 1-RR<1 indicates NIPPV beneficial) and the number needed to treat (NNT) for 1 favourable outcome for the above two outcomes were 11 and 20 respectively. Only these two outcomes were appropriately powered (87% and 79%) with adequate patient numbers. All other outcomes had null effects(Table 1). Meta-regression did not show any significant influence of COPD, heart failure and time to initiation of NIPPV as covariates on the rate of reintubation or hospital deaths. There was no single influential study.

Outcome, heterogeneity I^2=(%) N=RCTs, n=subjects	RCT's: NIPPV as prophylaxis RR /WMD (95%CI)	RCT's:NIPPV as treatment RR /WMD (95%CI)	Overall RR /WMD , (95%CI)
Reintubation, I^2=66% N=10, *n* =1235	0.48(0.22-1.06) $p = 0.07$	0.78(0.49-1.25), $p = 0.31$	0.63(0.41-0.97), $p = 0.03$
Hospital mortality, I^2=0% N=7, *n* =717	0.65(0.39-1.08), $p = 0.10$	0.54(0.19-1.52), $p = 0.25$	0.68(0.47-0.99), $p = 0.049$
ICU mortality, I^2=73% N=6, *n* =765	0.53(0.09-3.02), $p = 0.47$	0.13(.43-2.99), $p = 0.79$	0.73(0.26-2.01), $p = 0.55$
Hospital stay(days), I^2=97% N=9, *n* =1000	-3.18(-9.8- 3.47), $p = 0.3$	-0.7(-4.09 - 2.60), $p = 0.6$	-1.8(-7.2 - 3.5), $p = 0.49$
ICU stay(days), I^2=91% N=9, *n* =979	-1.6(-3.7- 0.47), $p = 0.13$	-1.2(-2.0 to -0.35), $p = 0.006$	-1.5(-3.5 -0.09), $p = 0.07$

CONCLUSION. NIPPV decreases reintubation and hospital mortality but larger studies are needed to explain the divergence in various patient outcomes.

0372

CLINICAL OUTCOMES OF TRACHEOSTOMIZED PATIENTS SUBMITTED TO MECHANICAL VENTILATION

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INTRODUCTION. It has been a common practice to perform tracheostomy in patients that cannot be weaned easily. Nevertheless, few studies have been conducted to detect unequivocal advantages to weaning or shorten stay in hospital (HLOS) and in the intensive care unit (ICU LOS). The aim of this study was to evaluate the influence of tracheostomy on the clinical course of mechanical ventilation (MV) and to determine the factors involved in its indication.

METHODS. We followed a concurrent cohort of 233 patients under MV for more than 48 hours. We compared the tracheostomy group (n=103) with the control (endotracheal tube) group (n=130). Primary endpoints were ventilation duration (MVLOS), ICU LOS and HLOS. Secondary endpoints were ICU mortality and the incidence of ventilation associated pneumonia (VAP). Categorical variables were compared by the chi square test and the continuous variables by the Wilcoxon test. Prognostic factors were identified with logistic regression and markers of tracheostomy indication with linear regression.

RESULTS. The baseline characteristics of the control and tracheostomy groups were respectively: age median 78 years (interquartile range - IR=64-84) versus 81 (IR=70-87, p=0.14), APACHE II median 17 (IR=13-22) versus 16 (IR=12-21, p=0.94), admission SOFA median 5 (IC=3-8) versus 5 (IC=3-7, p=0.5), female sex 56% (IC=50-63) versus 68 % (IC=61-75, p=0.08), clinical diagnosis 71% (IC=63-79) versus 79% (IC=71-87, p=0.17), neurological reason for MV 23% (IC=16-30) versus 38% (IC=28-47, p=0.05). The clinical outcomes of the control and tracheostomy groups were respectively: MVLOS median 7 days (IR=4-10) versus 23 (IR=15-38, p<0.0001), ICU LOS median 10 days (IR=7-15) versus 27 (IR=19-42, p<0.0001), HLOS median 19 days (IR=10-41) versus 48 days (IR=29-73, p<0.0001), ICU mortality 52% (IC=44-61) versus 30% (IC=21-39, p<0.0006), VAP incidence 16.02 cases/1000 ventilator days versus 17.08/1000 (p<0.0001). In multivariate analysis tracheostomy, VAP and shock were independent predictors of MVLOS and ICULOS. Shock (OR=4.38, IC=1.94-9.84, p=0.0004), acute renal failure (OR=4.03 IC=2.11-7.71, p<0.0001), VAP (OR=3.04, IC=1.37-6.75, p=0.006), tracheostomy (OR=0.17, IC=0.08-0.37, p<0.0001) and male sex (OR=0.36, IC=0.18-0.7, p=0.003) were independently related to ICU mortality. In logistic regression, MV LOS (OR=1.31, IC=1.22-1.41, p=<0.0001), neurological reason for MV (OR=2.37, IC=1.10-5.08, p=0.02) and shock (OR=0.31, IC=0.12-0.77, p=0.01) were independently associated with indication of tracheostomy.

CONCLUSION. This study demonstrates that the performance of tracheostomy does not reduce the duration of MV, ICULOS or HLOS, as well as it relates to a decrease in ICU mortality, results which are sustained in multivariate analysis.

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0373

A RANDOMISED, CONTROLLED TRIAL OF CONVENTIONAL WEANING VERSUS AN AUTOMATED SYSTEM (SMARTCARETM/PS) IN MECHANICALLY VENTILATED CRITICALLY-ILL PATIENTS

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INTRODUCTION. Automated weaning systems using continuous monitoring and real-time interventions may improve adaptation of ventilatory support to patient needs.

METHODS. A randomised, controlled study was conducted in 102 Australian ICU patients to determine the efficacy of an automated weaning system (SmartcareTM/PS) compared to usual weaning management performed collaboratively by medical and nursing staff in the absence of formal weaning protocols. Study patients had received mechanical ventilation with a non-spontaneous mode for > 24 hours and subsequently passed a 30-minute trial of pressure support ventilation. The primary study outcome was the Kaplan-Meier estimated median time to "separation potential," defined as the interval between study inclusion and the declaration of "separation readiness" by SmartCare/PS or the equivalent clinical state in the usual care group.

RESULTS. The median time to declaration of separation using automated weaning (20 h, IQR 2-40, n = 51 subjects) was similar to that of the usual care group (8 h, IQR 2-43, n = 51 subjects; log-rank p=0.3). Also, there was no evidence of large differences between groups in the median total duration of successful weaning (43 h vs 40 h, p=0.6) ventilation (119 h vs 129 h, p=0.9), or ICU stay (146 h vs 196 h, p=0.7). After SmartCare/PS had identified separation readiness, delays in completed extubation exceeding 1 h occurred due to: altered conscious state (n=12), respiratory failure (n=8), awaiting medical confirmation of extubation decision (n=4), unavailability of staff to re-intubate (n=3), patient's inability to protect airway (n=3), and excess secretions (n=1). Rates of reintubation, non-invasive ventilation post-extubation, tracheostomy, and use of sedation or neuromuscular blockade were comparable between study groups. The median number of changes to pressure support levels during weaning were 7 with usual care and 34 with SmartCare/PS (p=<0.001). Episodes of non-compliance with the study protocol occurred in 20% of the SmartCare/PS group and 39% in the usual weaning group (p=0.03).

CONCLUSION. This study found SmartCare/PS was comparable to weaning management provided by trained specialists working with qualified and experienced registered nurses. No significant difference was noted between the two methods of weaning management in the time required for weaning, ventilation, and ICU stay, or the rate of complications associated with mechanical ventilation. We conclude that SmartCare/PS shows clinical promise as an alternative to conventional weaning from mechanical ventilation.

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0374

THE IMPACT OF THE TRACHEOTOMY IN THE OUTCOME OF PATIENTS REQUIRING PROLONGED MECHANICAL VENTILATION.

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INTRODUCTION. Mechanical ventilation (MV) is one of the most usual procedures performed in the ICU. A lot of patients receiving prolonged MV underwent tracheotomy. Despite tracheotomy has many potential advantages over translaryngeal endotracheal intubation, it is not exempted from complications and there are several questions unanswered concerning the procedure yet. The aim of our study was to describe the clinical characteristics and outcome of patients requiring prolonged MV, to assess the differences between tracheostomized and not tracheostomized patients and the impact of the timing of the tracheotomy in their clinical outcome.

METHODS. Prospective observational study involving all patients (n= 205) admitted in a surgical-medical ICU requiring MV for more than 7 days from October 2001 to October 2003. Patients were divided into 3 groups: Group 1: with no tracheotomy. Group 2: tracheotomy performed before the 14th day. Group 3: tracheotomy performed from the 14th day. Characteristics of patients, underlying disease, duration of MV, length of stay (LOS), need of sedation and antibiotics, respiratory infections, complications related to endotracheal intubation (CREI), mortality, APACHE III and predicted mortality (PM) were studied.

RESULTS. The mean age was 55(18,85). Fifty nine patients(29%) had neurological disease(N), sixty eight(33,17%) had respiratory disease(R) and seventy eight(38%) formed an heterogeneous group(HG). Tracheotomy was performed in 138 patients (67,3%). The results were as follows:

N=205	Group 1(N=67)	Group 2(N=92)	Group 3(N=46)
N/R/HG1 (%)	15/21/31	24/36/32	20/11/15
Age	52	57	56
APACHE III	82	68	62
Mortality (%)*	37,3	28,3	47,8
CREI (%)	8,9	21	24
VAP/LRTI*(%)	18/10	22/36	19,6/18
VM (days)*	13	27,5	38
LOS (days)*	17	36	41,5
Sedation/Antibiotic (days)*	11/18	14/28,5	21/33

*VAP:Ventilator-associated pneumoniae. LRTI: Lower respiratory tract infection.*p<0,05.*

CONCLUSION. 1) Most of the patients requiring prolonged MV underwent tracheotomy. 2) Neurological disease was the most frequent into the group of patients with early tracheotomy. 3) Patients without tracheotomy had the less duration of MV, LOS in ICU, need of antibiotics and sedation. 4) Comparing tracheotomized patients, with similar gravity, in those with early tracheotomy, LOS in ICU, duration of MV, need of sedation and antibiotics were shorter. 5) CREI were more frequent and serious in patients with delayed tracheotomy. 6) Patients with delayed tracheotomy had the lowest gravity and the highest mortality.

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Oral Presentations
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0375

ACUTE KIDNEY INJURY IN LIVER TRANSPLANT PATIENTS

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INTRODUCTION. The incidence of acute kidney injury (AKI) after liver transplantation ranges between 12% and 64%, depending on the definition used and the cohort studied. The lack of a consensus definition for AKI has resulted in a wide variation in the reported incidence and associated mortality. The aim of the study was therefore to apply the RIFLE classification to determine the epidemiology, including long term renal outcomes of AKI in this specific cohort.

METHODS. All consecutive liver transplant patients between January 2003 and January 2007 were included in this retrospective study. AKI was defined using the RIFLE criteria, i.e. RIFLE-Risk when creatinine increases 1.5 times above baseline, RIFLE-Injury when creatinine doubles, and RIFLE-Failure when creatinine trebles or increases with more than 0.5mg/dL to a level greater than 4 mg/dl. In case of re-transplantation, only the first transplantation episode was considered. We excluded patients under 18 years old, patients receiving haemodialysis before or during operation and patients having both kidney and liver transplantation.

RESULTS. A total of 170 patients was included. Median age was 56 yrs (interquartile range [IQR] 48-62), 72.4% were male. 7 % of patients received a graft for acute liver failure. Split grafts were transplanted in 22.9% of patients. AKI developed in 28.2 % of patients with maximum RIFLE-Risk in 43.8%, RIFLE-Injury in 25.0%, and RIFLE-Failure in 31.3 % of AKI patients. Demographic characteristics of patients with and without AKI were comparable. Aetiology of liver insufficiency was not predictive for AKI, however, AKI patients had more severe liver insufficiency, as expressed by a higher MELD score (16, IQR: 14-21 vs. 14, IQR: 11-18; p=0.023), a higher INR (1.55, IQR: 1.30-1.95 vs. 1.39 IQR: 1.15- 1.66; p=0.014) and a lower albumin level (3.0 g/dL, IQR: 2.44-3.6 vs. 3.2 g/dL, IQR: 2.8-3.9; p=0.022). Renal function at baseline, other co-morbidities, or receiving a split graft were not predictive for AKI. Seven patients with AKI (14.6%) required renal replacement therapy. AKI patients had a longer length of hospital stay (30, IQR: 20-48 vs. 24 d, IQR:16-37; p=0.042), and a higher in-hospital mortality (18.8% vs. 6.6%; p=0.017). Creatinine levels were higher in AKI patients at 3 months (n=132, 1.15, IQR: 0.99-1.37 vs. 0.97 mg/dL, IQR: 0.81-1.19 ; p=0.005) and 1 year after liver transplantation (n=84, 1.30 IQR: 1.12-1.63 vs. 1.12, IQR: 0.94-1.39; p=0.017).

CONCLUSION. AKI defined by the sensitive RIFLE classification occurred in almost one third of adult liver transplant patients during ICU stay. Severity of liver insufficiency before transplantation was associated with AKI. AKI after liver transplantation was associated with higher hospital mortality, and decreased kidney function at 3 months and 1-year follow up.

0376

COMPARISON OF RIFLE VERSUS AKIN FOR CLASSIFICATION OF ACUTE KIDNEY INJURY

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INTRODUCTION. Acute kidney injury (AKI) is associated with significantly increased morbidity and mortality. Comparison of studies investigating AKI, however, is hampered by lack of a uniformely accepted definition. RIFLE classification was introduced by the Acute Dialysis Quality Initiative (ADQI), recently the Acute Kidney Injury Network (AKIN) suggested staging AKI by a similar system but based on dynamic changes within a maximum period of 48 hours [1]. This study was aimed at comparimg these two classification systems with regard to predicting hospital mortality.

METHODS. SAPS III database containing data from 15789 was used for analysis. 989 patients with chronic renal failure had to be excluded as well as 9 patients having undergone renal transplantation. Furthermore data of 389 patients for incomplete data sets. Analysis included the first three days of admission. Classification was performed according to RIFLE (risk, injury, failure) or according to AKIN (stage I, II, III). Baseline serum creatinines were calculated by the MDRD formula assuming a normal GFR of 70 ml/min/m^2 for all patients for RIFLE. Changes of serum creatinine as well as urinary output within a 48 hours observation period were compared to admission values for AKIN. Primary endpoint was hospital mortality. Ratios of observed versus expected mortality were calculated based on SAPS III scores without creatinines for all stages of AKI.

RESULTS. Hospital mortality was significantly increased for patients classifying for AKI with either system. Average mortality of AKI classified by AKIN criteria was 28,9% compared to 34,6% classified by RIFLE.

TABLE 1. AKI by RIFLE classification

RIFLE	Hospital Mortality	SAPS III score	O/E Ratio	Patients (number)
Normal	13,87 %	44	0,81	9395
Risk	29,58 %	55	0,92	994
Injury	32,41%	54	1,05	1552
Failure	42,19 %	56	1,24	2415

TABLE 2. AKI by AKIN classification

AKI	Hospital Mortality	SAPS III Score	O/E Ratio	Patients (number)
Normal	15,85%	45	0,81	10219
Stage I	34,71%	53	1,17	1063
Stage II	29,21%	50	1,17	1027
Stage III	40,55 %	54	1,30	2047

CONCLUSION. AKI classified by either RIFLE or AKI is associated with increased hospital mortality. However, only RIFLE classification exhibit a clear correlatoin between observed versus expected mortality ratios and severity of AKI.

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0377

VALIDATION OF SHORT DURATION CREATININE CLEARANCE, CYSTATIN C AND BETA-2 MICROGLOBULIN ANALYSIS FOR ASSESSMENT OF RENAL FUNCTION IN CRITICALLY ILL PATIENTS

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INTRODUCTION. Various tests have been shown to be reasonably accurate markers of chronic renal impairment. However, there is lack of data regarding bias, precision and accuracy in critically ill patients with acute renal failure (ARF). The aim of this prospective observational study was to evaluate short duration creatinine clearance, cystatin C (CysC) and beta-2-microglobulin (B2m) as surrogate markers for 24-hour creatinine clearance in intensive care patients with various degrees of ARF.

METHODS. The study group consisted of 101 patients (65 males, median age 62y, APACHE II 21, SAPS II 40, length of stay in ICU 8d, ICU mortality 9.9%) who were admitted to our mixed 20-bed ICU between April 2005 and June 2006. Urine was collected in three consecutive blocks of 4, 8 and 12 hours. Urine output, urine creatinine concentration and serum creatinine level, during each time interval, were used to calculate the creatinine clearance over 4, 8, 12 and 24h (CrCl4, CrCl8, CrCl12 and CrCl24 resp). Additionally, blood levels of CysC and B2m were measured. Agreement of short duration creatinine clearance with CrCl24 was expressed by bias (mean of differences) and limits of agreement (mean ± 2SD). ROC plots were obtained for all investigated renal markers at cut-off levels of 30, 60 and 90 ml/min of CrCl24.

RESULTS. Mean serum creatinine (sCr) and mean CrCl24 were 108 ±69 µmol/L and 102 ± 68 ml/min, respectively. The bias (95% CI) of CrCl4, CrCl8 and CrCl12 were 7.3 ±6.1, 1.7 ±3.6 and 1.0 ±2.7 ml/min respectively. The limits of agreement were bias ± 72.2, 42.8 and 32.0 ml/min (95% CI: ±10.5, 6.3 and 4.7 ml/min resp). The ROC plots suggested a higher accuracy of B2m than CysC (z-score 0.9 to 1.8) and sCr (z-score 1.4 for CrCl24 <90 ml/min). The AUC of CysC was similar to sCr (z-score 0.3 to 1.0). Short duration creatinine clearance showed a higher AUC than serum markers which was statistically significant for patients with CrCl24 <90 ml/min.

TABLE 1.

ROC: AUC ±SE CrCl24 cut-off	CysC	B2m	sCr	CrCl4	CrCl8	CrCl12
< 30 ml/min	0.90 ±0.06	0.95 ±0.04	0.94 ±0.05	0.99 ±0.01	0.99 ±0.01	0.99 ±0.01
< 60 ml/min	0.90 ±0.04	0.94 ±0.03	0.94 ±0.31	0.97 ±0.02	0.98 ±0.01	0.99 ±0.01
< 90 ml/min	0.85 ±0.04	0.91 ±0.03	0.86 ±0.04	0.95 ±0.02	0.99 ±0.01	0.99 ±0.01

CONCLUSION. Our study shows that a creatinine clearance with collection intervals of 4, 8 or 12 hours has overall poor agreement with CrCl24 in critically ill patients. However, ROC-plots confirm that short duration creatinine clearance with a collection interval as short as 4 hours identifies patients in various degrees of renal impairment with excellent accuracy. ROC-plots indicate that CysC, B2m and sCr are accurate surrogate markers of reduced CrCl24 without statistical significant differences compared to each other.

0378

RENAL EFFECTS OF DIFFERENT TARGETS FOR ARTERIAL OXYGENATION DURING ARDS

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INTRODUCTION. Recommendations for arterial oxygenation during ARDS vary from 88% to 95 or 98% of SaO2. However, short term hypoxemia of moderate intensity has an impact on diuresis, natriuresis and renal resistive index of healthy subjects [1]. We evaluated the renal effects of three levels of SaO2 during mechanical ventilation.

METHODS. Prospective, physiological, study performed on patients requiring mechanical ventilation for ALI/ARDS, without severe shock or acute renal failure. Sedation was achieved by continuous infusion (Ramsay score > 4). Patients were successively ventilated at baseline, SaO2 88% and SaO2 98%. Diuresis, natriuresis, creatinine clearance and Doppler-based renal arterial resistive index [(peak systolic velocity-minimum diastolic velocity)/peak systolic velocity; normal 0.5-0.7] were measured. Results are reported as median [IQR].

RESULTS. 12 patients of 62 [42-72] years were included. At inclusion PaO2/FiO2 was 167 [131-177] mmHg, respiratory rate 20 [18-24] c/min, tidal volume 6.2 [5.6-6.9] ml/kg of ideal body weight and PEEP level 9 [5-11] cmH2O. During the three steps, the SaO2 was of 96% [94-98], 89% [89-90], and 99% [98-99] with FiO2 of respectively 0.5 [0.5-0.6], 0.25 [0.23-0.32] and 0.7 [0.6-0.8]. The intra-abdominal pressure measured via the bladder was of 10 mmHg [8.5-12]. Main results are reported in the table 1.

TABLE 1.

	Baseline	SaO2 88-90%	SaO2 98-100%	P
Heart rate (bpm)	80 [68-93]	83 [71-97]	78 [67-97]	0.09
Mean arterialpressure (mmHg)	78.5 [74-87]	80.5 [74-86]	79 [74-92]	0.26
Lactate (mmol/l)	1.1 [0.8-1.3]	1.0 [0.7-1.2]	0.8 [0.7-1.1]	0.09
CaO2 (ml)	13.9 [10.6-14.8]	12.8 [10.2-14]	14.4 [11.7-16.1]	0.02
sPAP (mmHg) [n=9]	34 [15-44]	35 [21-43]	32 [21-36]	0.11
Cardiac output (l/min) [n=9]	5.2 [4.3-5.8]	6.2 [4.8-6.5]	5.7 [4.7-6.6]	0.15
Diuresis (ml/2h)	95 [65-128]	135 [110-210]	100 [90-120]	0.0003
Creatinine clearance (ml/min)	44 [28-86]	63 [45-101]	35 [30-89]	0.002
FeNa (%)	0.42 [0.19-1.98]	0.64 [0.48-2.32]	0.67 [0.38-1.88]	0.002
Renal resistive index	0.73 [0.59-0.8]	0.78 [0.66-0.85]	0.72 [0.60-0.78]	0.0001

sPAP: systolic pulmonary arterial pressure; FeNa: Fractional excretion of sodium

CONCLUSION. In patients with ARDS/ALI, a moderate level of hypoxemia is associated with an increased diuresis and fractional excretion of sodium, but also a better creatinine clearance. The increase in renal resistive index suggests intra-renal mechanisms which need to be investigated.

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0379

FUROSEMIDE IN THE RECOVERY PHASE OF ACUTE KIDNEY FAILURE: A DOUBLE BLIND RANDOMISED CONTROLLED TRIAL

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INTRODUCTION. Furosemide promotes diuresis and lowers tubular oxygen consumption. However, this can not prevent acute kidney failure (AKF) and there is no evidence that its use improves outcome. Forced diuresis by furosemide with titrated fluid substitution in the recovery phase of AKF can theoretically improve creatinin clearance. We studied the effect of furosemide in patients recovering from AKF on creatinin clearance, duration of AKF, long term dialysis dependency and mortality.

METHODS. Patients with AKF who were treated with hemofitration were included at the end of their first hemofiltration session after written informed consent was obtained. Patients with chronic kidney failure were excluded. In a double blind randomised design, patients were treated with either furosemide (0.5 mg/kg/hr by continuous infusion) or placebo. I.v. fluid infusion rate in both groups was adjusted hourly and was set as the volume of diuresis of the previous hour to prevent dehydration. Creatinin clearance was calculated from a 4 hour urine sample before start of the medication and daily. End points were creatinin clearance above 30 ml/min or declining serum creatinin level. When a new hemofiltration session was needed based on pre-defined criteria, the same treatment was re-instituted at the end of that hemofiltration session. Non-parametric tests or Chi-square test was used.

RESULTS. 69 patients were included, one patient however did not meet the inclusion criteria, and was excluded from further analysis. Thirty-four patients were treated with furosemide (F), 34 with placebo (P). There was no loss of follow-up. Data are presented as median (interquartile range IQR), F vs. P. APACHE II score was 22 (9.5) vs. 24 (9.5). Median creatinin clearance at the start of treatment was 13 (30) ml/min vs. 16 (21). Fluid balance during hemofiltration was similar in both groups. Length of stay in the ICU was 23 (18) vs. 19 (23) days (p=0.4). Duration of mechanical ventilation was 19 (15) vs. 15 (15) days (p=0.2). ICU mortality was 4/34 vs. 6/34, p=0.7. Hospital mortality was 12/34 vs. 11/34, p=1.0. Duration of hemofiltration was median 8.5 (12) vs. 7.0 (10) days (p=0.74). Dialysis dependency at ICU discharge was 26% vs. 14%, p=0.3. Long term recovery of renal function in hospital survivors was 79% in the furosemide group versus 82% in the placebo group.

CONCLUSION. The use of furosemide in the recovery phase of AKF is not associated with beneficial effects in outcome of renal function, length of stay or mortality compared to placebo.

0380

RENAL INJURY SUSTAINED DURING OFF PUMP CABG IS SIMILAR TO CABG WITH CPB WHEN MEASURED WITH URINARY NGAL

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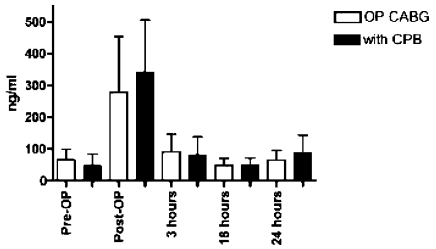
INTRODUCTION. The evidence with regard to renal outcome between off-pump CABG (OP CABG) and CABG with cardiopulmonary bypass (CPB) is conflicting (1). The commonly used endpoint serum creatinine is insensitive to detect renal injury. Urinary NGAL is a novel, sensitive & early marker for renal injury (2,3) and may be able to better detect differences between OP CABG and CABG with CPB.

METHODS. 34 patients undergoing OP CABG were matched to 34 patients undergoing CABG with CPB by age, sex, Parsonnet score, BMI, EF, preOP creatinine and number of grafts. Urinary NGAL was measured pre-, immediately post surgery and 3, 18 & 24 hours later and compared using t-test. The study design was powered to detect a difference of 150 ng/ml NGAL (mean, common SD = 200 ng/ml).

RESULTS. Baseline demographics were not different between the 2 groups. In both groups urinary NGAL increased significantly after surgery and remained elevated 3, 18 and 24 hours later. There was no difference of urinary NGAL between the OP-CABG and the CABG with CPB groups at any time-point after surgery. (see Fig. 1).

Fig 1: Urinary NGAL after CABG: OP vs CPB



CONCLUSION. This study further adds evidence using a highly sensitive marker that there is no difference between OP and on pump CABG with regard to renal injury. Using NGAL as a marker for renal injury allows detection of minor differences in renal injury that would otherwise remain unnoticed.

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0381

BACTERAEMIA IN ICU PATIENTS: IMPACT ON MORTALITY & LENGTH OF STAY (LOS)

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INTRODUCTION. Bacteraemia is a well recognised complication of critical illness with patients suffering an excess mortality and stay in ICU and hospital. This study quantifies this excess highlighting the need to target strategies at this high-risk ICU population group.

METHODS. A retrospective analysis of clinical and microbiological records for patients admitted to the ICU in 2006. Bacteraemia was defined as one or more positive blood cultures from any site. Data was arranged into pathogen-patient episodes as well as into pathogenic groups. This data was then compared against non-bacteraemic patients admitted during the same period. Student's t-test was used to compare LOS whilst Chi-squared was used for mortality data.

RESULTS. Of 351 admissions in 2006, 67 (19.1%) were associated with bacteraemia. This represented 62 patients with a mean age of 59.6 years, 41 (66.1%) of whom were male. 33 (53.2%) were admitted from medicine, 27 (43.6%) from surgery and 2 (3.2%) from obstetrics. Of note, 15 (24.2%) were from hepatobiliary surgery, 11 (17.7%) from cardiothoracic surgery, 10 (16.1%) from nephrology and 9 (14.2%) from haematology. The remainder representing less than 10% included patients from oncology, cardiology, gastroenterology, care of the elderly, infectious diseases and general surgery. This reflects our hospital's speciality mix. Twenty (32.3%) patients grew multiple organisms. When organised into pathogen-patient episodes, the data analysed is as follows:

Pathogen	Nr.	Unit LOS Days	Hospital LOS Days	Unit Mortality %	Hospital Mortality %
Controls	276	5.4	28.3	18.4	24.3
Bacteraemic	62	20.2**	54.3**	38.7**	54.8**
Candida spp.	4	14.5*	23.0	75.0*	100.0**
Non-VRE	11	22.2*	78.9*	18.2	36.4
VRE	7	24.1*	62.1*	57.1*	85.7**
Gram Negs.	24	21.7**	62.8*	33.3	52.2*
MSSA & MRSA	5	22.5	32.8	40.0	40.0
Coag. Neg. Staph	33	22.2**	59.0*	36.4	59.4**
Other Gram Pos.	6	12.0	23.6	33.3	33.3

*LOS Average Nr. of Days * p<0.05 **p<0.001*

CONCLUSION. Bacteraemia is associated with significantly higher patient mortality, 54.8% versus 24.3% (p=0.000002) as well as longer LOS. More specifically, certain pathogens such as Candida, Vancomycin Resistant Enterococci (VRE) and Coagulase Negative Staphylococci (CNS) inferred a particularly high mortality risk. These pathogens should prompt early and aggressive treatment.

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0382

DAILY SEDATION INTERRUPTION IN CRITICALLY ILL SEPTIC PATIENTS: MORPHINE OR REMIFENTANIL?

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INTRODUCTION. To assess hemodynamic and respiratory impact in critical ill ventilated septic patients during recommended (1), Daily Sedation Interruption (DSI), we compared Morphine (Mo) based sedation and a multimodal short acting regimen using Remifentanil (R), Ketamine (K) and Magnesium (Mg). DSI was performed two times a day to reach a Ramsay Score of 3 (Rs) until the day of possible extubation.

METHODS. 164 septic intubated patients (requirement of Noradrenalin infusion (Na) despite optimal fluid preloading) were prospectively randomised in 2 groups; both sedated by midazolam (Mi: 0.01-0.5 mcg/kg/min). The first group (G1: n=80) was sedated with Mo (60-160 μ/kg/h) and the second (G2:n=84) with R (0.02-0.35 μ/kg/min) + K (0.5-3 μ/kg/min) + Mg (0.04-0.09 g/kg/d). Mean Arterial Pressure (MAP) and Hypoxic Index (HI) were assessed during DSI period with adaptation of NA and FiO2 requirements; boluses (B) of Mi (0.4mg/kg) were administered whenever the patient became agitated (Rs>5). The weaning time (Wt: time to achieve a calm, comfortable and cooperative patient, was assessed after DSI every day), the extubation time (Et: time necessary to perform spontaneous breathing without endo-tracheal tube) and the global hospitalisation time (GHt) were compared. For statistical analyses a Shapiro-Wilk test, Wilcox and a Student T-test were used.

RESULTS. Demographic data were comparable in G1 and G2 (mean Severity Acute Physiologic Score: 30+/-2 SD; mean age: 67+/-5 SD; gender: 32+/-2% female SD). Patients were ventilated and sedated during a similar period of time in G1 and G2 (5+/-1d SD). In G2 DSI was not necessary, 100% of patients were hourly in Rs3 versus 20% in G1 ($p<0.03$). In G1 the Wt was 15+/-10 min following DSI at day 1 and 2; 22+/-10 min at day 3; 30+/-14 min at day 4; 39+/-15 min at day 5 and 45+/-10min at day 6. In G2 no B were needed, no MAP or HI changes were noted. In G1 after each DSI, B were needed; Na showed a 11% fluctuation in daily dose requirement and HI showed a 15% swing . The Et was in G1 8+/-0.4 hours and in G2 6+/-3min ($p=0.01$). The GHt in G1 was 7+/-2.4d and in G2 5+/-0.1 d ($p<0.05$).

CONCLUSION. The multimodal short -acting regimen with remifentanil allows us to keep the patient in a Ramsay score of 3 avoiding the necessity of daily sedation interruption for clinical evaluation thus avoiding the necessity of additional hypnotic boluses and a subsequent risk of accumulation. Daily sedation interruption promotes the need for hypnotic boluses thus enhancing hemodynamic and respiratory impairments. The multimodal analgo-sedation with remifentanil diminished time of extubation and time of hospitalisation.

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0383

ASSESSMENT OF GLOBAL COAGULATION BY THROMBOELASTOGRAM TEST IN CRITICALLY ILL PATIENTS

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INTRODUCTION. Disseminated intravascular coagulation (DIC) is associated with development of multiple organ failure and worse outcome. Thromboelastography (TEG) is a whole blood assay allowing to evaluate the viscoelastic properties during blood clot formation and lysis. TEG has not been tested in critically ill septic patients. The aim of this study was to compare the TEG measurements in septic and non-septic patients.

METHODS. We investigated 15 septic patients and 20 non-septic patients (neurological post surgery, cerebral hemorrhage) on the first day of ICU admission. We performed TEG measurements (Intem and Extem) and measured PT, APTT, fibrinogen, D-dimers and platelet count. We calculated the DIC score validated by the International Society on Thrombosis and Haemostasis (ISTH). TEG parameters includes coagulation time (CT), the kinetics of clot formation (CFT), the kinetics of clot firmness (angle α), maximum clot firmness (MCF) and maximum clot lysis (ML). All parameters were analyzed with SSPS statistical program and compared by a Student's T-test. A p value < 0.05 was considered as significant.

RESULTS. All laboratory tests count were more altered in patients with than without sepsis: PT (58.7 [35.7-81.7] vs 93.6 [78.3-108.9], $p<0.001$), APTT (45.9 [25.9-65.9] vs 28.9 [26.9-31.9], $p<0.001$), fibrinogen (662 [375-949] vs 414 [204-624], $p=0.007$), platelet count (195.10^3 [40.10^3-350.10^3] vs 280.10^3 [135.10^3-425.10^3], $p=0.11$). Accordingly, the DIC score was significantly higher in septic compared to non-septic patients (3[2.3-3.8] vs 2[1.5-2.0], $p < 0.001$). In contrast, all TEG parameters were identical except for the extrinsic clot time (117,9[111,7-124,1] vs 82,2[41,2-123,2], $p=0.048$).

CONCLUSION. TEG may not reliably track DIC in critically ill septic patients.

0384

FIRST-LINE MANAGEMENT AND OUTCOMES OF BACTERAEMIA IN THE CRITICALLY ILL: RESULTS FROM BASIC (BACTERAEMIA STUDY IN INTENSIVE CARE)

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INTRODUCTION. The lacking in PRCT informing practice has resulted in wide variability in clinical practice in treating bacteraemia in the critically ill and has likely contributed to the highly variable resistance patterns seen within ICUs worldwide. We therefore conducted a multinational multi-centre prospective observational study to investigate the type and duration of antibiotic(s) used to treat bacteraemia, and any relationship with (i) the incidence of fungaemia and multi-drug resistance, breakthrough and relapse rates; (ii) patient clinical response and outcome.

METHODS. All participating ICUs were asked to collect data on at least 20 consecutive, microbiologically confirmed, bacteraemic or fungaemic patients, over a period no shorter than 4 months and no longer than 8 months commencing January 2002. We collected prospectively on a standard electronic access type proforma: demographic data (age, gender, medical/surgical), SAPS II or APACHE II score (first 24 hours); risk factors (i.e. diabetes, immunosuppression, MRSA carriage) and comorbidities (e.g. chronic renal and liver failure); microorganism characteristics: Gram stain, identification & antibiotic sensitivity patterns of isolates, and likely source of bacteraemia/fungaemia; antibiotic therapy (type, duration); ACCP/SCCM sepsis criteria.

RESULTS. We recruited 132 ICUs from 26 countries [European (78.5%) , Australasian (10.5%) , South American (7.5%) and Asian (3.5%)] and 1703 patients that developed 1937 bacteraemic episodes over the study period. A Multivariate Logistic Regression Model found age >75 yrs (OR: 2.1, 95% CI=1.6-3.6, $p<0.0001$), SAPS II death prediction (OR: 1.1, 95% CI=1-1.1, $p<0.0001$), immunosuppression (OR:1.7, 95% CI=1.1-2.7), unscheduled surgery (OR:2.3 95% CI=1.3-4.1), severe chronic liver failure (OR: 4.5, 95% CI=1.6-12.8, $p=0.0322$), septic shock (OR:7, 95% CI=4.6-10.7, $p<0.0001$) and mechanical ventilation >7 days (OR: 1.8, 95% CI=1.2-3, $p=0.0121$) were independent predictive factors of death. No antibiotic policy-associated variable was a statistically significant predictor of death, however appropriately-targeted antibiotic therapy was protective (OR: 0.8, 95% CI=0.6-1.3, $p=0.512$).

CONCLUSION. Antibiotic therapy practices are highly variable worldwide. Randomised, multicentre trials are urgently needed to establish the optimal duration, timing and combinations of treatment.

0385

ROLE OF OMEGA-3 FATTY ACID INFUSION IN SURGICAL OUTCOME OF PERFORATION PERITONITIS PATIENTS

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INTRODUCTION. Peritonitis is a common surgical emergency worldwide. Despite advances in surgical techniques, anti-microbial therapy and intensive care support, management of peritonitis is associated with high rate of morbidity and mortality. Omega-3 fatty acid (a poly-unsaturated fatty acid) is an immune enhancing essential fatty acid that has been found to have anti-inflammatory properties.

METHODS. 70 consecutive patients in the age group of 18-70 years that were operated for perforation peritonitis were included in this study after taking informed written consent. Patients with hepatic dysfunction, renal dysfunction, congestive cardiac failure, electrolyte imbalance, unconscious patients, and patients with known hypersensitivity to ingredients of parental 10% fish oil emulsion were excluded from this study. Patients in the test group received 10% omega-3 fatty acid emulsion at the rate of 2-ml/kilogram-body weight/day for 5 (five) postoperative days. Patients in the control group received placebo (normal saline) in place of fish oil emulsion. C-reactive protein level and CD-4 count estimation was done before the start of the drug/placebo and after 5 days of infusion of drug/placebo. Clinical parameters recorded included: 1. Duration of hospital stay, resumption of oral feeding. 2. Post-operative pyrexia, chest infection. 3. Frank pus discharge, gaping of wound, burst abdomen. 4. Weight loss/gain by the patient.

RESULTS. In the control group 82.84 % of patients developed postoperative pyrexia while in the test group only 22.85% the patient developed fever. In the control group 31.42% patients developed chest infection in comparison to 5.71% in the test group. In the control group about 74.28% patients had pus discharge from wound while it was only 17.14% in test group. The duration of naso-gastric feeding, return of bowel sound, passage of flatus and duration of hospital stay was found to be significantly low in test group. There was a significant weight gain in the test group patients but nil in the control group. In the control group about 48.57% patients developed gaping of wound in comparison to 17.14% in test group. The test group had 11.42% burst abdomen rate & in the control group it was 31.42%. There were 4 deaths in the control group but none in the test group.

CONCLUSION. Post-operative perforation peritonitis patients receiving omega-3 fatty acid are at a lesser risk of developing post-operative complications like pyrexia, chest infection, pus discharge, gaping of wound, burst abdomen. Patients on omega-3 fatty acid had shorter duration of hospital stay. Omega 3 fatty acid infusions reduce mortality significantly.

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0386

IMPACT OF AN ANTIBIOTIC RESTRICTION PROGRAM ON PRESCRIBING HABITS OF ICU PHYSICIANS

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INTRODUCTION. Antimicrobial resistance of microorganisms to broad spectrum antibiotics is an important problem which is partly due to inappropriate use of antimicrobial agents. To combat this phenomenon, an antibiotic restriction policy was applied for an 18 months period in our ICU. A significant reduction in the consumption of restricted antimicrobials as well as overall antibiotic consumption was noticed. Our aim was to determine if the antibiotic consumption after the end of the restriction period was affected.

METHODS. This retrospective study included data concerning antibiotic use in patients hospitalized in the 10 - bed multivalent ICU of a tertiary 700 – bed general hospital. The antibiotic restriction program started on 1st July 2003 and lasted until 30th June 2005. Change of antibiotic consumption between three semesters was calculated. First semester was between 1st January 2003 to 30 June 2003 (before the restriction period). Second semester included the last 6 months of the application of the restriction (1st January 2005 to 30 June 2005). Third semester was between 1st July 2006 and 31 December 2006 that is 18 month after the end of the restriction. Antibiotic consumption was recorded in DDDs /100 patient – days.

RESULTS. During these three semesters, patients hospitalized were similar in gender, age, number, mean ICU length of stay and Apache II severity score. In the following table, consumption of usually consumed antibiotics is presented during the three periods.

antibiotics (DDDs)	**1st semester**	**2nd semester**	**third semster**
colistin	0	19.6	23.5
carbapenems	71.3	53.1	97
ceftazidime	71.3	0.4	0
ciprofloxacin	11.2	4.4	8.3
cefepime	29.9	7.4	3.8
piperacillin/tazobactam	30	23.4	4.2
total	139.6	108.3	136.8

CONCLUSION. Physicians continued not to use formerly restricted antibiotics though the restriction policy was officially stopped. Overall antibiotic consumption remained lower than in the period preceding the application of the restriction, but carbapenem consumption showed an unexpected increase. The 23 percent increase which was observed in total antimicrobial consumption between periods 2 and 3 shows that care must be taken so that avoiding antibiotic overusage must be continually ensured. Certainly other factors such as patients' origin, local flora and corresponding resistance as well as outbreaks of several microorganisms must be taken into account when evaluating the kind and quantity of antibiotics consumed.