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P1

Thrombin-activatable fibrinolysis inhibitor and organ dysfunction in disseminated intravascular coagulation associated with sepsis

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Introduction Fibrinolytic shutdown plays a pivotalrole in the pathogenesis of multiple organ dysfunction syndrome (MODS) in disseminated intravascular coagulation (DIC). We tested the hypothesis that the levels of thrombin activatable fibrinolysis inhibitor (TAFI) are not sufficient to overcome fibrinolytic shutdown, thus contributing to MODS and the poor prognosis in sepsis-induced DIC.
Methods Fifty patients with sepsis, severe sepsis, or septic shock were enrolled in the study. The DIC was diagnosed based on the Japanese Association for Acute Medicine (JAAM) DIC criteria. The overt DIC scores based on the International Society on Thrombosis and Haemostasis (ISTH) were also calculated. On the day of sepsis diagnosis (day 1), and days 3 and 5, we measured TAFI, soluble fibrin, and global coagulation and fibrinolysis markers.
Results The JAAM DIC scores on day 1 and maximum JAAM DIC scores were independent predictors of patient death and MODS, respectively. The JAAM DIC patients, especially those who simultaneously met the ISTH overt DIC criteria, showed lower TAFI antigen levels and activity, and higher levels of soluble fibrin in comparison with non-DIC patients. There were differences in the levels of soluble fibrin and TAFI activity between the patients with and without MODS. The findings of stepwise logistic regression and multiple regression analyses suggested that low TAFI activity is an independent predictor of patient death and MODS. A multiple regression analysis also indicated that soluble fibrin negatively correlated with the TAFI activity in DIC patients.
Conclusion Thrombin activation results in the consumption of TAFI. Low TAFI activity is involved in the pathogenesis of DIC-induced MODS and poor prognosis.

P2

Anti-endotoxin immunity in abdominal sepsis patients

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Introduction Anti-endotoxin immunity (AEI) has many biological effects but the problem of conjugation and elimination of lipopolysaccharides (LPS) in peritonitis patients is not discussed. We investigated the role of IgA, IgM and IgG in peritonitis and their association with humoral immunity (HI).
Methods We investigated 33 patients (male:female = 25:8) with abdominal sepsis (total peritonitis in appendicitis, perforated duodenal ulcer, pancreonecrosis). Anti-endotoxin (AE) antibodies (anti-LPS-IgA, anti-LPS-IgM, anti-LPS-IgG) were determined by original modification of hard-phase immunoenzyme analysis. *Escherichia coli K30* LPS was used as antigen for AE antibody detection. The level of general immunoglobulin was determined by the microturbidimetric method with human monospecific sera to IgG, IgA and IgM. All data were compared with healthy donors (99 patients).
Results A high level of AEI and HI was determined in 24% of patients who recovered rapidly without complication after surgery, discharged in 9 to 10 days. This was confirmed by clinical data (normalization of body temperature, peristalsis, spontaneous stool) by 4 to 5 days. A low level of AEI and HI was found in 42% of patients who recovered slowly; in a favorable course of peritonitis, the increase of parameters was marked by 8 to 10 days; in several with suppuration of wounds, discharge was in 14 to 16 days. A few patients with a low level of immunity against the background of abdominal sepsis required therapy with sandoglobulin H that was accompanied with a sharp positive change of a postoperative course of peritonitis and an increase of immunity indices. See Table 1. An evident decrease of AE antibodies may be a background for translocation of endotoxin from the intestine to the portal and systemic circulation. Disorder of AE mechanisms of endotoxin conjugation may activate other mechanisms of neutralization (endotoxin-conjugating protein) that stimulate CD14-receptor structures and mechanisms of active production of proinflammatory cytokines and starting systemic inflammatory response syndrome.
Conclusion Abdominal sepsis patients are determined dysfunction of AEI (decrease of AE IgM and IgG). Successful treatment of peritonitis is accompanied with normalization of the IgM and IgG concentration and an increase of IgA above standard. Dynamics of AE antibodies may be a marker of the clinical course and forecast of abdominal sepsis. Comparative analysis of HI and AEI demonstrates parallelism of the dynamic concentration of immunoglobulins during treatment.

Table 1 (abstract P2)

	AEI						HI					
	IgA		IgG		IgM		IgA		IgG		IgM	
	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
Peritonitis patients	0.28 ± 0.01, *P* <0.05	0.45 ± 0.02	0.12 ± 0.01, *P* <0/01	0.13 ± 0.02	0.21 ± 0.03, *P* <0/05	0.29 ± 0.04	2.26 ± 0.16, *P* >0.5	2.77 ± 0.18	10.1 ± 0.47, *P* >0.5	10.98 ± 0.5	1.39 ± 0.11, *P* <0.05	1.56 ± 0.12
Donors	0.35 ± 0.05		0.16 ± 0.01		0.33 ± 0.05		2.21 ± 0.08		10.54 ± 0.242		1.66 ± 0.06	

P3

Presepsin (sCD14-ST) as a new diagnostic biomarker of sepsis: development of diagnostic tools using the whole blood

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Introduction CD14 is present in macrophage, monocyte, and granulocyte cells and their cell membranes, and its soluble fraction is present in blood and is thought to be produced in association with infections. It is called the soluble CD14 subtype, and its generic name is presepsin. Presepsin is a novel marker for the diagnosis of sepsis, and the results of previous study in which an ELISA kit was used showed a specific increase in sepsis in the early stage that also correlated well with severity. In the present study we developed a new rapid measurement method for whole blood that use a chemiluminescence enzyme immunoassay. We assessed the usefulness of presepsin values in sepsis.
Methods The period of the study was the 10 months from August 2009 to June 2010. The subjects were 41 in-patients, age 62 ± 19 years old, who had been brought to the Critical Care and Emergency Center of Iwate Medical University and who fulfilled at least two of the diagnostic criteria for systemic inflammatory response syndrome (SIRS) on arrival. Blood specimens were collected a total of six times; that is, on admission, and 12 and 24 hours and 3, 5, and 7 days later. Presepsin values were measured by immunoassay analyzer (PATHFAST; Mitsubishi Chemical Medience Corporation, Japan). The sepsis marker PCT, IL-6, and CRP were also measured for comparison. In addition, 128 healthy subjects were assessed as controls.
Results The mean presepsin level in the 128 healthy subjects in the control group was 190 pg/ml. The corresponding presepsin levels were normal (non-infection), 294.2 ± 121.4 pg/ml; local infection, 721.0 ± 611.3 pg/ml; SIRS, 333.5 ± 130.6 pg/ml; sepsis, 817.9 ± 572.7 pg/ml; and severe sepsis, 1,992.9 ± 1,509.2 pg/ml; the patients with local infection or sepsis had significantly higher presepsin levels than the patients who did not have infection as a complication. In addition, the presepsin levels in SIRS that was not complicated by infection were significantly lower than in sepsis. When we divided the patients into an infection group and a no infection group and plotted the ROC curves of each of the markers to compare presepsin with other markers, the results showed that presepsin was the best.
Conclusion We were able to obtain results similar to those obtained with the conventional ELISA method, and it was possible to diagnose sepsis more rapidly and conveniently using the immunoassay analyzer.

P4

Investigation into problems associated with the endotoxin activity assay

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Introduction Endotoxin activity assay (EAA) levels were compared with endotoxin levels determined by the turbidimetric kinetic method.
Methods A specific method for the measurement of endotoxin, in the blood of patients under various conditions, and the influence of steroids on EAA levels and contamination of tubes used for the measurements were investigated.
Results EAA levels increased in patients with injuries and acute pancreatitis. EAA levels did not increase in patients infected with Gram-positive bacteria. Endotoxin levels determined by the turbidimetric kinetic method did not increase in patients with injuries and acute pancreatitis and Gram-positive bacteria. When patients with long-term steroid use developed shock due to infection with Gram-negative bacteria, EAA levels did not increase but endotoxin levels determined by the turbidimetric kinetic method increased. EAA levels, but not endotoxin levels determined by the turbidimetric kinetic method, were suppressed by giving steroids *in vitro*. Endotoxin was detected in the tubes used for the measurements. This was suppressed by the addition of polymyxin B and anti-factor C antibody. EAA levels tended to increase immediately after direct hemoperfusion using a polymyxin-B-immobilized fiber column (PMX-DHP).
Conclusion Our findings suggest that the EAA had limitations as a method to measure endotoxin.

P5

Yale insulin protocol infusion in sepsis patients

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Introduction Tight glycemic control is a major concern in critical care. The objective of this study in the ICU was to evaluate the effectiveness and safety of the Yale insulin infusion protocol in sepsis patients.
Methods A retrospective, before–after cohort study. Selected endpoints were mean blood glucose levels, time to reach the target range of 100 to 150 mg/dl, percentage of blood glucose in the target range, and hypoglycemia incidence.
Results Were studied 78 patients: 42 in the control group (CG) and 36 in the protocol group (PG). Bedside blood glucose was measured 3,755 times for a mean value of 134.1 ± 15.4 mg/dl in the PG versus 1,730 times for a mean value of 172.7 ± 33.6 mg/dl in the CG. Blood glucose values were in the target range 63% and 37% of the times, respectively, for the PG and the CG (P <0.001). The median time to reach the glucose target range was 8 hours (range 5 to 17 hours) for the PG and 53 hours (range 23 to 218 hours) for the CG (P <0.001). The incidence of severe hypoglycemia reached a statistically significant difference: one patient in the PG versus four patients in the CG (P <0.01). All patients reached the target in 72 hours of insulin infusion in the PG while only 29 patients in the CG reached this target.
Conclusion The Yale insulin infusion protocol was effective and safe in sepsis patients admitted to the ICU.

P6

Early vasopressin application in shock

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Introduction Vasopressin is frequently used to maintain blood pressure in refractory septic shock. We hypothesized that early infusion of vasopressin compared with norepinephrine would decrease the mortality rate and severity of septic status.
Methods In this randomized, double-blind study, we assigned patients who need vasopressors and randomized to receive norepinephrine (0.05 to 2.0 μg/kg/minute) or vasopressin (0.01 to 0.03 U/minute) with norepinephrine. Both groups had the vasoactive drug infusions titrated and tapered to maintain a mean blood pressure between 65 and 75 mmHg.
Results A total of 387 patients underwent randomization with 191 patients receiving vasopressin and 196 receiving norepinephrine. There was no significant heterogeneity between these two study groups. There was a significant difference between the vasopressin and norepinephrine groups in the mortality rate of 14 days (29.3% vs. 36.7%, respectively, P = 0.05) and 28 days (34% and 42.3%, respectively, P = 0.03); however, in 7-day mortality there were no significant differences in the overall rates (21.2% vs. 23.9%, respectively; P = 1.1). Also note a reduction in the incidence of single organ dysfunction (37.7% vs. 49.2%, respectively, P = 0.02) and multiple organ dysfunction using vasopressin and norepinephrine (17.8% vs. 26%, P = 0.05; P = 0.03). The length of stay in the ICU was 14 and 17 days (P = 0.29) and the time of hospitalization was 23 and 28 days (P = 0.11), respectively, in the vasopressin and norepinephrine groups.
Conclusion Early application of vasopressin reduced mortality rates in 14 and 28 days as compared with norepinephrine alone, and also a difference in incidence of organ dysfunction. This observed difference can be attributed to early restoration of tissue perfusion and vascular smooth muscle responsiveness that directly influenced patient survival.

P7

Endotoxin removal by hemoperfusion in septic shock

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Introduction Many symptoms of septic shock are due to the presence of endotoxin in the bloodstream. The biological activity of endotoxins is associated with lipopolysaccharide (LPS). LPS induces systemic inflammatory response and a high level of endotoxin in blood is associated with worse clinical outcome. Reduction of the level of circulating endotoxins with hemoperfusion through the filter with high affinity for LPS could potentially interrupt the biological cascade of sepsis. The aim of the study was to evaluate the efficiency of extracorporeal endotoxin elimination in patients with Gram-negative septic shock.
Methods The study was conducted at the Department of Anesthesiology and Intensive Therapy, Wroclaw Medical University, Poland. Patients with septic shock, documented or suspected Gram-negative infection, and with high endotoxin activity (EA >0.6 units) were eligible for the study. The endotoxin activity in blood was measured with chemiluminescent activity assay. Based on the enrolment criteria and EA level, patients were assigned to the conventional treatment group (Group 1) or the conventional plus hemoperfusion therapy with LPS adsorber (Alteco Medical AB, Lund, Sweden) group (Group 2). Hemoperfusion was performed for 2 hours with blood flow maintained at 150 ml/minute.
Results Seventeen patients with low EA (0.42 ± 0.14, Group 1) and 12 patients with high EA (0.76 ± 0.13, Group 2) (P <0.05) were included. There were no significant differences between Group 1 and 2 regarding age (63 ± 2 and 61 ± 21), APACHE II score (22.7 ± 8.6 and 24.5 ± 7.2), SOFA score (9.8 ± 3.0 and 11.3 ± 4.1), mean arterial pressure (MAP, 66.2 ± 8.1 mmHg and 71.5 ± 7.3 mmHg), and PaO_2/FiO_2 (255 ± 59 and 216 ± 105) at entry to the study. In the hemoperfusion group, nine patients had Gram-negative and three had Gram-positive infection; seven patients survived to the 28-day follow-up. High endotoxin activity at baseline decreased significantly 24 hours after hemoperfusion to 0.5 ± 0.1 (P <0.01) in those who survived, but remained high (0.7 ± 0.1) in nonsurvivors. At 24 hours after hemoperfusion, MAP significantly increased (78.8 ± 20.8 to 89.2 ± 19.8 mm Hg, P <0.05) and vasopressor requirements decreased in survivors but not in those who died (MAP, 64.2 ± 9.6 to 71.8 ± 15.3 mm Hg, P = nonsignificant).
Conclusion Hemoperfusion with LPS adsorber added to standard treatment improved the hemodynamic status of patients with septic shock. The chemiluminescence assay for measurement of LPS activity was a valuable diagnostic tool for rapid detection of endotoxemia.
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P8

Urinary hepcidin is potentially a marker of systemic infection rather than inflammation, in the setting of preserved renal function

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Introduction Urinary proteomics have recently identified hepcidin, a key regulator of iron homeostasis, as a potential marker of tubular stress [1]. It appears to be released in response to situations that predispose to acute kidney injury (AKI), and greater concentrations of hepcidin in the blood and in the urine have been associated with reduced risk of AKI [2]. Catalytic iron is a biologically plausible mechanism for the development of AKI as a consequence of tubular oxidative stress [3]. The relationship between serum creatinine, urinary hepcidin and CRP may help define whether urinary hepcidin is more likely to reflect systemic inflammation or renal events. The relationship in septic patients has not yet been described. Patients with SIRS, oliguria and a 25 µmol/l increase from baseline creatinine are known to be at an increased risk of AKI [4]. We sought to determine if hepcidin correlated more strongly with CRP or creatinine in these patients with a diagnosis of sepsis and those without.
Methods Patients meeting the inclusion criteria within 48 hours of admission had their CRP, urinary hepcidin, and serum and urinary creatinine measured. The strength of the relationship between serum creatinine or CRP and urinary hepcidin corrected for urinary creatinine was determined using Spearman's rank correlation coefficient.
Results We enrolled 103 patients between 31 August 2010 and 17 November 2010; 22 of whom had an APACHE III diagnosis of sepsis. Serum creatinine only correlated weakly with direct and inverse urinary hepcidin measurements in septic and nonseptic patients alike. However, there was a moderately strong correlation between CRP and urinary hepcidin in septic patients, a relationship not demonstrated in the nonseptic group (Table 1).

Table 1 (abstract P8). Relationships between hepcidin, creatinine and CRP

	Correlation			
	Nonseptic (n = 81)		Septic (n = 22)	
Variable	Serum Cr	CRP	Serum Cr	CRP
Urinary hepcidin	–0.272 (P = 0.013)	0.204 (P = 0.064)	–0.225 (P = 0.314)	0.506 (P = 0.016)
1 / urinary hepcidin	0.287 (P = 0.009)	–0.19 (P = 0.087)	0.225 (P = 0.314)	–0.506 (P = 0.016)
Urinary hepcidin corrected for urinary creatinine	–0.146 (P = 0.191)	0.241 (P = 0.029)	–0.276 (P = 0.227)	0.418 (P = 0.06)
1 / urinary hepcidin corrected for urinary creatinine	0.158 (P = 0.159)	–0.228 (P = 0.041)	0.276 (P = 0.227)	–0.418 (P = 0.06)

Conclusion Hepcidin is only weakly inversely correlated with serum creatinine. A stronger relationship exists between hepcidin and CRP in septic patients, suggesting that hepcidin may primarily be a marker of infection that is filtered in the urine when the glomerular filtration rate (GFR) is preserved and filtered in lower amounts when the GFR is lost. That this relationship is not replicated in nonseptic patients with clinical evidence of SIRS suggests that the underlying pathophysiological processes are different. Further investigation of the natural history of AKI and biomarker release is warranted.

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P9

Neutrophil gelatinase-associated lipocalin has a stronger association with serum creatinine than C-reactive protein in patients without sepsis; this relationship is lost in septic patients

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Introduction Neutrophil gelatinase-associated lipocalin (NGAL) predicts the development of acute kidney injury (AKI) amongst critically ill

patients [1]. Serum and urinary NGAL have been shown to be elevated in patients with SIRS, sepsis and septic shock [2], and the predictive ability of NGAL in these patients is not so certain [3]. It is unclear, however, whether this predictive relationship is due to the fact that NGAL is produced by neutrophils and is, therefore, a biomarker of inflammation and infection, or whether NGAL in blood and/or urine mostly reflects tubular release. It is also unclear if the type of AKI that develops in SIRS is different from that developing in septic patients.

Methods To test these hypotheses, we studied ICU patients with SIRS and oliguria or a 25 μmol/l increase in serum creatinine. We sought to determine whether blood and urine NGAL correlated more closely with CRP or creatinine at the time of enrolment. The strength of the relationship between serum creatinine or CRP and urine and serum NGAL, as well as urinary NGAL corrected for urinary creatinine, was determined using Spearman's rank correlation coefficient.

Results We recruited 105 patients between 31 August 2010 and 17 November 2010; 22 of these had an APACHE III diagnosis of sepsis. In nonseptic patients NGAL in blood or urine correlated only weakly with CRP, but a stronger and statistically significant relationship was observed between serum and/or urine NGAL and serum creatinine. A similar strength of relationship was observed between creatinine and NGAL and CRP and NGAL in septic patients, although it failed to reach significance. See Table 1.

Table 1 (abstract P9). Relationships between NGAL, creatinine and CRP in patients with and without sepsis

	Correlation			
	Sepsis (n = 22)		No sepsis (n = 83)	
Variable	Serum Cr	CRP	Serum Cr	CRP
Urinary NGAL	0.345 (P = 0.116)	0.302 (P = 0.173)	0.391 (P <0.001)	0.057 (P = 0.61)
Urinary NGAL corrected for urinary creatinine	0.311 (P = 0.171)	0.235 (P = 0.305)	0.514 (P <0.001)	0.070 (P = 0.532)
Serum NGAL	0.244 (P = 0.274)	0.411 (P = 0.057)	0.661 (P <0.001)	–0.034 (P = 0.763)

Conclusion In patients without a diagnosis of sepsis, NGAL is only weakly correlated with CRP and a stronger relationship is observed between NGAL and serum creatinine. This suggests that NGAL is more likely a biomarker of tubular injury or stress than systemic inflammation in these patients. Similar relationships of moderate strength are observed between NGAL in blood/urine and both serum creatinine and CRP in patients with a diagnosis of sepsis. This suggests that different pathophysiological processes may exist in the genesis of septic AKI when compared with inflammatory AKI. Further investigation regarding the natural history of AKI and the clinical and biochemical association of renal biomarkers is warranted.

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P10

Neutrophil gelatinase-associated lipocalin as a marker of tubular damage appears to be unrelated to fractional excretion of sodium as a marker of tubular function in septic patients, with or without AKI

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Introduction The utility of urinary biochemistry has recently been challenged [1], while there is emerging evidence that renal biomarkers may accurately quantify the risk of development of acute kidney injury (AKI) [2]. Neutrophil gelatinase-associated lipocalin (NGAL) is a marker of renal tubular damage [3]. Fractional excretion of sodium (FENa) is a marker of renal tubular function, and is a significantly cheaper investigation [4]. Insults damaging the tubules and resulting in AKI should both stimulate NGAL production and prevent resorption of sodium. Given the different pathological mechanisms underlying septic and nonseptic AKI, it is plausible that the relationship between these variables could be different in these two groups of patients [5].

Methods To test this hypothesis, we studied ICU patients developing SIRS and oliguria or a 25 μmol/l increase in serum creatinine within 48 hours of ICU admission. We sought to determine if a relationship existed between FENa and NGAL in patients, with and without sepsis, developing AKI. We measured the serum and urinary NGAL, creatinine and sodium of patients with SIRS and either oliguria or an increase in creatinine within 48 hours of admission to a tertiary referral ICU. Point-of-care creatinine measurements were used to identify the maximum RIFLE category of AKI developed within the first 5 days of admission. The strength of the relationship between variables was determined using Spearman's rank correlation coefficient.

Results We enrolled 93 patients between 31 August 2010 and 17 November 2010; 17 had an APACHE III diagnosis of sepsis. Serum NGAL and urinary NGAL when corrected for urinary creatinine were found to correlate moderately well with FENa in patients without sepsis, a relationship that weakens with the progression of AKI in this group. No other correlation showed a significant relationship (Table 1).

Conclusion The lack of a strong correlation FENa and NGAL in patients developing RIFLE I and F AKI suggests that changes in NGAL and changes in sodium resorption occur as a consequence of different stimuli in the pathogenesis of the syndrome. The absence of any observed relationship between NGAL and FENa in septic patients suggests a pathological process different from that underlying nonseptic AKI. The small sample size may be a confounding factor.

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Table 1 (abstract P10). Relationships between NGAL, FENa and AKI

			Urinary NGAL		Urinary NGAL corrected for urinary creatinine		Serum NGAL		Urine:serum NGAL ratio	
FENa		n	Spearman	P value	Spearman	P value	Spearman	P value	Spearman	P value
Nonseptic	No AKI	43	0.153	0.328	0.587	<0.0001	0.450	0.002	–0.009	0.953
	AKI	33	–0.039	0.830	0.438	0.011	0.258	0.148	–0.235	0.188
	RIFLE R–F	14	0.015	0.958	0.235	0.418	–0.077	0.793	–0.068	0.817
Septic	No AKI	12	–0.168	0.602	–0.007	0.983	0.232	0.467	–0.427	0.167
	RIFLE R–F	5	–0.300	0.624	0.500	0.391	0.112	0.858	–0.400	0.505

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P11

Renal biomarkers are less useful at predicting acute kidney injury in patients with sepsis than those without

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Introduction Multiple biomarkers have been proposed for identifying patients at risk of developing the syndrome of acute kidney injury (AKI) [1]. These biomarkers include urine and serum NGAL, and urinary hepcidin. The pathophysiology of AKI in sepsis appears to be primarily mediated by immunological, toxic and inflammatory factors as opposed to renal ischaemia [2]. Different aetiologies of AKI are likely to lead to differential release of serum and urinary biomarkers. We sought to determine if the predictive ability of several renal biomarkers for predicting AKI varied in the presence of sepsis in the context of routine ICU practice.
Methods We measured serum and urinary NGAL and urinary hepcidin in patients admitted to the ICU of a tertiary referral hospital with SIRS and either oliguria or a 25 µmol/l serum creatinine increase within 48 hours of admission. We used point-of-care creatinine measurements to identify the maximum RIFLE category of AKI within the first 5 days of enrolment. We corrected both urinary biomarkers for urinary creatinine. We calculated the reciprocal of hepcidin measurement and noted if serum NGAL was greater than the upper limit of normal (149 ng/ml). We derived the area under the curve (AUC) for the receiver operating characteristic curve (ROC) for all biomarkers.
Results Between 31 August 2010 and 17 November 2010, we enrolled 92 patients; 17 of these patients had APACHE II diagnoses of sepsis. In patients with a diagnosis of sepsis, the predictive ability of all of the biomarkers measured was worse than in those without (Table 1).
Conclusion Although the sample size is limited, there is a marked difference in the predictive ability of the measured biomarkers to predict AKI between septic and nonseptic patients. All patients admitted met the criteria for a diagnosis of SIRS, suggesting that inflammation and sepsis contribute to the development of AKI via different pathways. The ability of these biomarkers to predict AKI in patients with a diagnosis of sepsis in our cohort is limited. Further investigation is needed into whether the combination of specific biomarker patterns and clinical features can better identify patients at risk, particularly in the setting of sepsis. In addition, further work examining the relationship between the various biomarkers and the aetiology and natural history of AKI is required.

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P12

Cancer patients with sepsis admitted to a specialized onco-medical ICU: incidence, ICU course and outcome

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Introduction While cancer patients are known to be at higher risk for infection and subsequent complications, there is a scarcity of data regarding incidence and outcome of septic cancer patients admitted to ICUs. Hence, we aimed to assess the incidence of cancer patients admitted with sepsis to an onco-medical ICU and study their ICU course and outcome.
Methods Data were collected prospectively from all cancer patients admitted to a specialized onco-medical ICU of a tertiary care hospital, over a period of 6 months. Sepsis was defined as per the international guidelines. Cancer patients were divided into two groups on the basis of presence of sepsis on ICU admission and compared with regard to their need for organ support, length of ICU stay and mortality. Severity of illness was assessed by APACHE II score and organ failure by SOFA score. Qualitative data were analyzed using the chi-squared test or Fisher exact test as appropriate and quantitative data were analyzed using Student's *t* test. $P < 0.05$ was considered significant.
Results Out of 104 cancer patients admitted during the study period, 43 (41.3%) patients were admitted with sepsis. Even though there was no difference in age ($P = 0.13$), sex ($P = 0.382$) and presence of metastasis ($P = 0.314$) among the septic and nonseptic groups of patients, septic patients had comparatively higher admission APACHE II (21.4 ± 7 vs. 18.21 ± 6.9; $P = 0.023$) and SOFA (6.4 ± 3.8 vs. 4.56 ± 3; $P = 0.007$) scores, required invasive mechanical ventilation (65.1% vs. 19.7%; $P = 0.000$) and vasopressor support (74.4% vs. 19.7%; $P = 0.000$) more often, had a longer ICU stay (10.77 ± 8.4 vs. 7.44 ± 5.5; $P = 0.017$) and had a higher ICU mortality (62.8% vs. 18%; $P = 0.000$). The odds ratio and relative risk

Table 1 (abstract P11). AUC ROC for the prediction of AKI

	ROC AUC							
	RIFLE R, I or F				RIFLE I or F			
	Septic		Nonseptic		Septic		Nonseptic	
Test result variable	Area	SE	Area	SE	Area	SE	Area	SE
Urinary NGAL	0.367	0.136	0.561	0.068	0.367	0.136	0.633	0.090
Urinary NGAL corrected for urinary creatinine	0.417	0.136	0.578	0.066	0.417	0.136	0.670	0.082
Serum NGAL	0.375	0.162	0.639	0.065	0.375	0.162	0.685	0.087
Serum NGAL positivity	0.492	0.158	0.611	0.066	0.492	0.158	0.674	0.082
Urine:serum NGAL ratio	0.483	0.140	0.498	0.068	0.483	0.140	0.543	0.081
1 / urinary hepcidin	0.508	0.153	0.624	0.066	0.508	0.153	0.611	0.080
1 / urinary hepcidin corrected for urinary creatinine	0.483	0.156	0.598	0.067	0.483	0.156	0.578	0.083

SE, standard error.

of death for septic cancer patients were 7.67 (95% CI = 3.121 to 18.85) and 3.482 (95% CI = 1.945 to 6.234).
Conclusion A significant proportion of cancer patients are admitted with evidence of sepsis. These patients were generally sicker, required more intensive organ support, and had a longer ICU stay and a higher ICU mortality than those cancer patients admitted to ICU with other acute problems.

P13

Use of plasma protein fraction in patients with septic shock admitted to the ICU

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Introduction Certain colloids like albumin and plasma protein fraction (PPF) have been derived from human plasma and they are used as plasma expanders to treat patients with shock. PPF, which more closely resembles plasma in its constituents, contains albumin plus α and β globulins. We conducted this study to assess the effect of PPF on need for vasopressors, organ support and ICU mortality in patients with septic shock.
Methods A retrospective study was conducted and data were collected from the records of patients admitted to a 16-bed neuro and medical ICU over a 1.5-year period. All adult patients admitted with septic shock and requiring vasopressor support (for more than 6 hours) in spite of aggressive fluid resuscitation were enrolled. Patients who were transferred from some other ICU or ward and those who developed shock during their ICU course were excluded from the analysis. Patients were divided into two groups: patients in whom PPF was used along with resuscitative fluids comprised the study group, whereas others formed the control group. Patients in these groups were compared according to need for organ support, ICU mortality and time taken to stop vasopressor agents. PPF (Plasmanate®) was administered in a protocolized way at the dosage of 10 to 20 ml/hour for the first 48 hours. Development of any complication like allergy or hypotension associated with PPF was also noted.
Results There was no significant difference in the baseline characteristics of patients in both groups in terms of age ($P = 0.154$), sex ($P = 0.479$), severity of illness (APACHE II score, $P = 0.356$), and presence of organ failure (SOFA score, $P = 0.105$). Among the outcome parameters there was no significant difference in terms of need for renal support ($P = 0.814$), mechanical ventilation ($P = 0.776$), ICU stay ($P = 0.122$), hospital stay ($P = 0.054$) and ICU mortality ($P = 0.091$). However, there was a significant difference in time taken to stop the vasopressors ($P = 0.030$) (Table 1). There were no incidences of any complications or side effects in any group.
Conclusion PPF may be used safely and effectively for initial resuscitation of patients with septic shock requiring vasopressor support. It may lead to early termination of vasopressor support; however, it did not translate to lesser need for organ support or reduced ICU mortality in our patient cohort. To demonstrate such benefits, larger multicenter trials are warranted.

Table 1 (abstract P13). Comparison between patient characteristics and ICU course among patients in control and PPF groups

Parameter of interest	Control group ($n = 87$)	PPF group ($n = 99$)	*P* value
Age (years)	64.11 ± 15.4	67.28 ± 14.8	0.154
Sex, male	50 (57.5%)	63 (63.6%)	0.479
APACHE II score	20.69 ± 6.2	21.64 ± 7.6	0.356
PDR	39.51 ± 19.2	42.47 ± 22.5	0.341
SOFA score	9.53 ± 3.5	10.38 ± 3.7	0.105
RBC transfusions	32 (36.8%)	33 (33.3%)	0.735
Renal support	31 (35.6%)	38 (38.4%)	0.814
Mechanical ventilation	50 (57.5%)	60 (60.1%)	0.776
Time taken to stop vasopressors (hours)	**70.69 ± 55.2**	**51.29 ± 64.5**	**0.030***
ICU stay (days)	10.38 ± 11.4	13.42 ± 14.8	0.122
Hospital stay (days)	12.91 ± 11.8	16.83 ± 15.3	0.054
ICU mortality	34 (39.1%)	52 (52.5%)	0.091

*P <0.05. Bold text indicates statistically significant.

P14

ICU scoring systems: which one to use in patients with sepsis?

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Introduction Disease-severity scoring systems have been developed for stratification of ICU patients. These systems have been tested and validated in various general medical and surgical ICU patients. However, the validity and efficacy of these systems, especially the newer generation, has not been assessed in patients with sepsis, which is the commonest indication for admission to a medical ICU. Hence, we conducted this study to assess the performance of various ICU scoring systems – Acute Physiology and Chronic Health Evaluation (APACHE) II, III, IV; Simplified Acute Physiology Score (SAPS) II, III; Mortality Prediction Model (MPM) II_0, III_0; and Sequential Organ Failure Assessment (SOFA) scores – in septic patients admitted to a medical ICU.
Methods A prospective, observational study was conducted in a tertiary care medical ICU and consecutive patients fulfilling the diagnostic criteria for sepsis during the first 24 hours of ICU admission were included over a 2-year period. Data related to patient demographics and that required to compute various scores were recorded. Predicted mortality was calculated using original regression formulas. The standardized mortality ratio (SMR) was computed for mortality prediction. Calibration was assessed by calculating the Lemeshow–Hosmer goodness-of-fit C-statistic. Discrimination was assessed by calculating the area under the receiver operating characteristic (AUROC) curves. ICU mortality was the primary outcome measure.

Table 1 (abstract P14). Comparison of the actual and predicted mortality rates for the various scoring systems

Variable	Actual mortality	Predicted mortality	SMR
APACHE II	0.244	0.296	0.824
APACHE IV	0.244	0.206	1.18
SAPS II	0.244	0.297	0.822
SAPS III	0.244	0.249	0.98
MPM II_0	0.244	0.314	0.777
MPM III_0	0.244	0.216	1.13

Table 2 (abstract P14). Area under the curve for predicting ICU mortality for various scoring systems

Scoring system	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)
APACHE II	0.880	0.845 to 0.914	>18.5	86.9	75.8
APACHE III	0.880	0.847 to 0.914	>63.5	82.2	70.4
APACHE IV	0.882	0.848 to 0.916	>17.7	83.2	74
SAPS II	0.849	0.808 to 0.890	>41.5	82.2	70.4
SAPS III	0.873	0.838 to 0.907	>53.5	85	72.2
MPM II_0	0.849	0.807 to 0.891	>30.1	77.6	76.1
MPM III_0	0.872	0.835 to 0.909	>18.7	81.3	77.9
SOFA	0.889	0.857 to 0.922	>5.5	86.9	79.2

Results Data were analyzed for 438 septic patients. The mean age of patients was 64.5 ± 16.3 years and 301 (68.7%) were male. The mean ICU and hospital length of stay was 6.39 ± 9.7 and 9.99 ± 10.5 days, respectively. The observed ICU mortality was 107/438 (24.4%). Mortality predicted by SAPS III score was closest to that of actual mortality with a SMR of 0.98 followed by that of MPM III_0 (SMR – 1.13) and APACHE IV (SMR – 1.18) scores (Table 1). APACHE IV (χ^2 = 4.416; *P* = 0.818) had the best calibration followed by SAPS II (χ^2 = 6.073; *P* = 0.639) and SAPS III scores (χ^2 = 6.538; *P* = 0.587). There was no statistically significant difference between the AUROCs of these scores; SOFA (AUROC = 0. 0.889) performed the best followed closely by APACHE IV (AUROC = 0.882) and APACHE III (AUROC = 0.880) scores (Table 2).
Conclusion Overall, the newer generation of scoring systems performed better than their older counterparts and was more accurate. Older scoring systems had a tendency to overpredict mortality. However, all the scores tested had good efficacy and the difference in efficacy was not statistically significant.

P15

Comparison of the value of plasma and urine cystatin-C and neutrophil gelatinase-associated lipocalin levels in prediction of acute kidney injury in sepsis

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Introduction The aim was to study the impact of inflammation/sepsis on the concentrations of cystatin-C and neutrophil gelatinase-associated lipocalin (NGAL) in plasma and urine in adult ICU patients and to estimate the predictive properties of cystatin-C and NGAL in plasma and urine for early detection of acute kidney injury (AKI) in patients with sepsis.
Methods The RIFLE class for AKI was calculated daily, while plasma and urinary Cys-C and NGAL were determined on days 0 and alternate days until ICU discharge. Test characteristics were calculated to assess the diagnostic performance of urinary and plasma Cys-C and NGAL. The diagnostic and predictive performances of the markers were assessed from the area under the receiver operator characteristic curve (AUC).
Results One hundred and twenty-eight patients were studied, and three groups were defined: normal (*n* = 41); sepsis (*n* = 45); and sepsis and AKI (*n* = 42). AUCs for diagnosis of AKI using plasma and uCys-C were as follows: 0.89 (*P* <0.0001) and 0.91 (*P* <0.0001) Cut-off points for AKI for plasma and uCys-C were 1.7 mg/l (sensitivity: 83%, specificity: 77%)and 0.11 mg/l (sensitivity = 92%, specificity = 80%), respectively. Urinary NGAL showed fair discrimination for AKI diagnosis (AUC = 0.85). Although plasma NGAL performed less well (AUC = 0.58).
Conclusion Plasma and urinary Cys-C are useful markers in predicting AKI in sepsis. pNGAL is raised in patients with sepsis, and should be used with caution as a marker of AKI in ICU patients with sepsis. uNGAL is more useful in predicting AKI as the levels are not elevated in septic patients without AKI.

P16

Clinical and biological effects of high-dose sodium selenite, continuously administered in septic shock

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Introduction Sodium selenite (Na_2SeO_3) has been proposed as an early treatment of septic shock with discrepant results [1-3]. Beneficial action is mainly believed through improvement of major antioxidant selenoenzymes, but could on the contrary be related to a therapeutic oxidant action reducing activity of hyperactivated circulating phagocytic cells [4]. It has been suggested that the absence of beneficial effect of high-dose Na_2SeO_3 continuously administered [2] might be related to toxicity, especially on the lung, of too much selenium (Se) as mentioned in recent parenteral nutrition guidelines in intensive care [5]. On additional clinical and biological data, our purpose was to assess if there was argument for Na_2SeO_3 toxicity, especially on the lung, under continuous administration of high-dose Na_2SeO_3 in the SERENITE study.
Methods In a randomized, double-blind multicenter study performed in 60 septic shock patients [2], the efficacy and tolerance of Na_2SeO_3 (4 mg Se on day 1 (D1), then 1 mg/day during 9 days or placebo) were evaluated on all components of the SOFA score measured daily, infection rate, and plasma Se, selenoprotein-P (Sel-P), glutathione peroxidase (GPx), lipid peroxidation, cytokines, and procalcitonin measured at D0, D4, D7, D10 and D14.
Results No deleterious effect of Na_2SeO_3 especially on the lung was observed for any clinical or biological variables. PaO_2/FiO_2 was strictly identical between groups (Table 1). As compared with placebo, mean time occurrences of infections were delayed in the treated group (18 ± 24 days vs. 34 ± 28 days, respectively; *P* <0.0001). Plasma Se, Sel-P and GPx concentrations were increased at D4 in the treated group, achieving the high reference value for the plasma Se concentration (Figure 1).
Conclusion Continuous administration of high doses of Na_2SeO_3 (4 mg Se D1) did not induce any deleterious effect in septic shock patients. We did not observe a beneficial effect, contrasting with a comparable study administering Na_2SeO_3 in bolus, potentially more toxic [1]. In agreement with results obtained on a peritonitis sheep model [6], our data support a therapeutic oxidant action of Na_2SeO_3, opening a new field in septic shock treatment based on oxidant selenocompounds.

Table 1 (abstract P16). PaO_2/FiO_2 according to group and time

	Baseline (D0)	D2	D3	D4	D7	D10	D14
Na_2SeO_3	20 ± 15	23 ± 12	24 ± 10	25 ± 14	26 ± 11	30 ± 13	28 ± 15
Placebo	22 ± 13	21 ± 11	25 ± 13	26 ± 11	28 ± 14	33 ± 17	36 ± 17
P value	0.60	0.37	0.92	0.81	0.65	0.52	0.13

Data presented as mean ± SD (KPa).

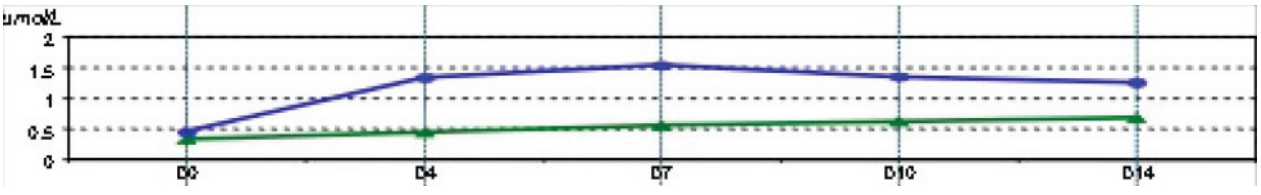

Figure 1 (abstract P16). Plasma Se concentration according to groups and time. Data presented as mean ± SD (µmol/l). Reference value for plasma Se concentration: 1 ± 0.15 µmol/l. Treated group indicated in blue and nontreated in green.

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P17

Temperature management of patients with sepsis and inflammation in Australian and New Zealand ICUs: a point prevalence study

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Introduction The use of pharmacological and physical antipyretic therapies to reduce fever in febrile patients is common in hospital settings. Actual evidence on the frequency of antipyretic use is limited, however, both in general hospital populations and, more specifically, in adult intensive care [1-3]. We undertook a prospective point prevalence study with the aim of identifying the prevalence of physical and pharmacological antipyretic therapies in intensive care patients with sepsis and inflammation. We also recorded the indication for antipyretic therapies, temperature measurement site, and mean temperatures on the study day.

Methods We conducted a single-day observational point prevalence study in 38 ICUs in Australia and New Zealand. All patients in participating ICUs at a 10:00 am census point were studied. Data were collected for the 24-hour study day that included the 10:00 am time point.

Results We studied 506 patients, with a mean age 59 years (SD = 17 years); 65% male; APACHE II score 17 (SD = 7), 28-day mortality 14%. Eighty percent of the ICU admissions were unplanned. Of the 506 patients, 311 patients had sepsis and inflammation with mean peak temperature of 37.3°C (SD = 0.8°C). Of these, 35% (n = 100/311) had a mean peak temperature above 38°C. In the 24-hour period, paracetamol was used 50% (n = 152/311) of the time, nonsteroidal anti-inflammatory drugs (NSAIDs) 0.6% (n = 2/311) and physical cooling 1% (n = 3/311) (Figure 1). Of patients that had an indication for paracetamol recorded, 64% was for pain (n = 92/152), 18% for both pain and fever (n = 26/152); and 10% for fever alone (n = 14/152) (Figure 2). Sixty-four percent (n = 92/152) of the patients who had paracetamol were prescribed regular paracetamol and 36% (n = 51/143) had a PRN order. Of the 40 patients who received paracetamol for an indication of fever, the mean peak temperature was 38.3°C (SD = 0.8°C; range 36.1 to 40.2°C). Of the three patients who received physical cooling, the mean peak temperature was 39.2°C (SD = 0.9°C; range 38.5 to 40.2°C). Temperature measurement sites were mainly noncore (n = 251/311) with axillary (37%; n = 116/311) and tympanic (35%; n = 110/311) most common (Figure 3).

Conclusion This point prevalence study of intensive care patients with sepsis and inflammation identified pharmacological antipyretics are used regularly for pain management rather than fever management, with paracetamol the most common therapy. The use of physical cooling was rare, and noncore temperature measurements were common. These results are important in understanding current temperature management practice in intensive care and will aid in designing future clinical trials on the subject.

Acknowledgements This study was undertaken as part of the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG) Point Prevalence Program. The authors would like to thank all participating sites.

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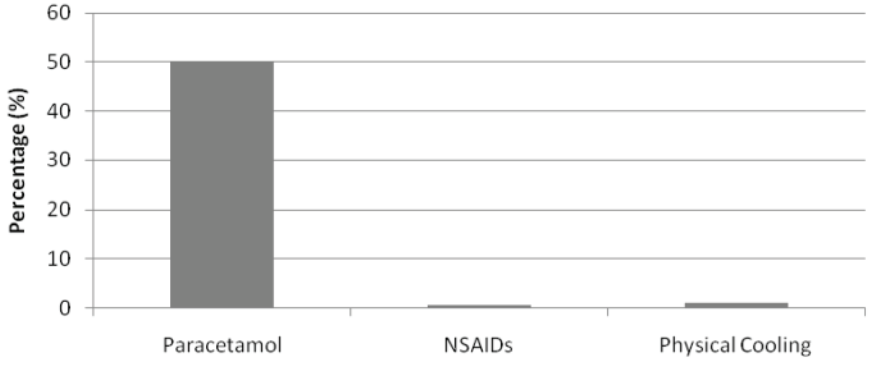

Figure 1 (abstract P17). Type of antipyretic and physical cooling used on the study day (n = 311).

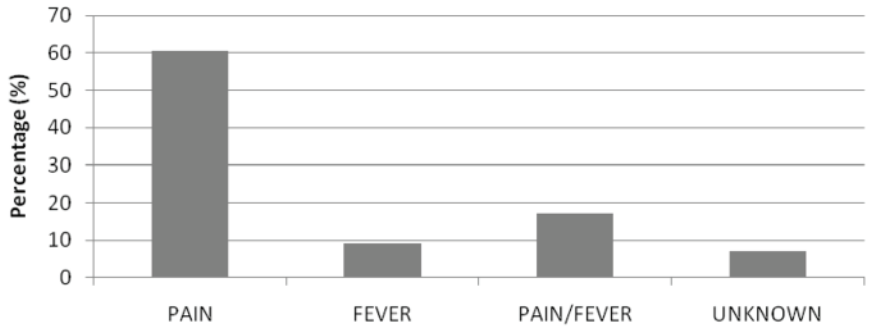

Figure 2 (abstract P17). Indication for paracetamol administration (n = 152).

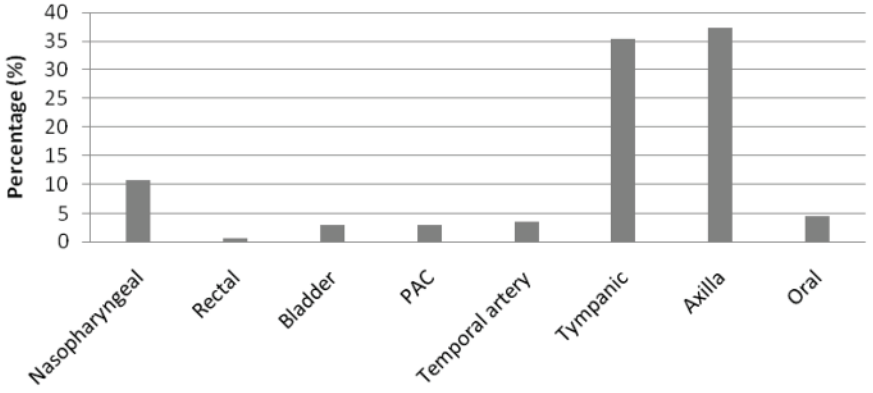

Figure 3 (abstract P17). Temperature measurement site for patients with sepsis and inflammation (n = 311). PAC, pulmonary artery catheter.

P18

A survey of fever management in febrile intensive care patients without neurological injury

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Introduction Fever is a common observation during critical illness [1,2] and may be due to many possible causes such as infection, sterile inflammation and neurological injury. Clinical trials of fever management lack sufficient methodological quality to answer the question of whether attempts at reduction in temperature improves patient-centred outcomes in patients with sepsis, inflammation or neurological injury [3-7]. We undertook a survey to describe the attitudes of critical care clinicians in Australia and New Zealand towards fever management in critically ill patients without neurological injury or hyperthermic syndromes.

Methods An online scenario-based questionnaire survey was distributed to medical and nursing members of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) and their intensive care colleagues. Main outcome measures: the choice of drug and preferred threshold temperature for intervention with antipyretics in clinical practice and in a clinical trial.

Results There were 588 email invitations distributed through the ANZICS-CTG and Research Coordinator mailing list. Four hundred and forty-seven responses were received from 308 nurses (69%), 137 doctors (31%), and two others (0.5%). The majority of respondents having more than 8 years of experience (62%) worked in mixed medical and surgical units (84%) in a metropolitan or tertiary hospital setting (77%). The primary findings of our survey suggest that fever management is highly variable. Most clinicians administer an intervention to reduce temperature at or below 39°C (Figure 1); and initially use a combination of both pharmacological and physical interventions, with an increase in intensity of physical interventions for persistent fever (Figure 2). There were differences between the professions, with doctors choosing higher temperature thresholds for intervention and nurses generally using more physical cooling (Figure 1 and Table 1); fourthly, temperature thresholds for a clinical trial were 39.0°C (SD = 0.7°C) for a permissive strategy and 38.0°C (SD = 0.75°C) for an intensive strategy; finally, there was broad support for a clinical trial of fever management.

Conclusion This survey suggests there is considerable clinical variability in fever management in patients with sepsis and without neurological injury or hyperthermic syndromes. At present, no particular management strategy is known to be superior to any other and it remains possible that current practice may be harming substantial numbers of patients. A temperature threshold of up to 40°C may be acceptable to clinicians for the design of a future randomized controlled trial. Further observational data may be informative for the design of such clinical trials.

Table 1 (abstract P18). Preference of first-line and second-line interventional category of antipyretic by profession

	First line (n = 418)			Second line (n = 409)		
	Nurse (%)	Doctor (%)	P value	Nurse (%)	Doctor (%)	P value
Pharmacological only	23	40	0.0002	5	5	0.87
Physical only	13	5	0.0087	58	62	0.36
Pharmacological and physical	64	55	0.077	38	33	0.39

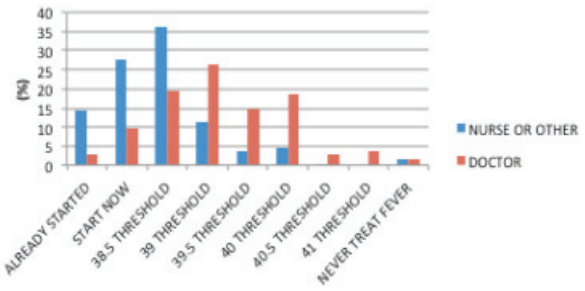

Figure 1 (abstract P18). Thresholds for initiation of antipyretic interventions between professions. Nurse/other (n = 289); doctor (n = 134) (P <0.0001).

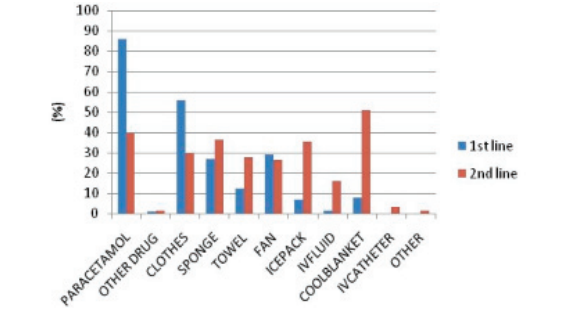

Figure 2 (abstract P18). First-line and second-line treatment preferences for fever management (n = 458).

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P19

Assessment of the usefulness of presepsin (soluble CD14 subtype) in septic patients

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Introduction Sepsis is a life-threatening condition characterized by a whole-body inflammatory state. The early diagnosis and treatments of sepsis will improve the outcome of patients. The aim of this study was to compare blood levels of presepsin (renamed from soluble CD14 subtype), procalcitonin (PCT), IL-6 and C-reactive protein (CRP) and to investigate the most useful biomarker for early diagnosis of sepsis.
Methods A single-center, prospective, observational study. Patients who had one or more systemic inflammatory response syndrome criteria were included in this study. The blood samples for measuring the biomarkers were collected and the severity of sepsis was evaluated at the time of admission and every other day for a week. Forty-two patients were enrolled for the prospective study from June 2010 to December 2010.
Results Twenty-three patients were diagnosed with sepsis and 19 patients were without sepsis. In the receiver operating characteristics (ROC) curve analysis, the area under the curve (AUC) to distinguish sepsis was the largest for presepsin (0.930) followed by IL-6 (0.896), PCT (0.854) and CRP (0.840). Presepsin may be able to discriminate between patient groups with or without sepsis. From the ROC curve analysis, a cut-off value of presepsin was 929 pg/ml with sensitivity and specificity of 76% and 81%, respectively, with odds ratios and 95% CIs of 0.996 (0.992 to 0.998) and 3.376 (1.497 to 6.094). And the presepsin values were significantly higher in the patients with the more severe septic condition (for example, sepsis, severe sepsis, septic shock). In addition, a significant correlation was found between the Sepsis-related Organ Failure Assessment scores and the presepsin values (r^2 = 0.320; P = 0.0003). But there was a no significant correlation between APACHE II scores and the presepsin values.
Conclusion In this study, presepsin is the most valuable predictor about sepsis compared with PCT, IL-6 and CRP. Moreover, the results suggest that presepsin values can serve as a parameter that closely reflects the pathology. So we strongly suggest that the presepsin will be not only a very useful new biomarker of the diagnosis of sepsis, but also useful for monitoring the severity of the disease in the near future.

P20

An audit of awareness about maternal sepsis in a UK district general hospital

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Introduction The UK national body, which reviews maternal mortality (Centre for Maternal and Child Enquiries (CMACE)), has recently published their 2006 to 2008 report. This highlighted an increase in maternal sepsis, making it the leading cause of direct death amongst peripartum women in the UK (26 out of a total 107 direct deaths) [1]. The Surviving Sepsis Campaign (SSC) published updated sepsis resuscitation and management bundles in 2008 [2]. We decided to audit awareness about sepsis amongst staff caring for perpartum women.
Methods A questionnaire was devised and distributed to midwives, obstetricians and anaesthetists. This asked the criteria for the systemic inflammatory response syndrome (SIRS), common sites of maternal sepsis, the initial duties of care ('sepsis six' resuscitation bundle: delivery of oxygen, intravenous fluids, intravenous antibiotics, taking of blood cultures, measurement of plasma haemoglobin, lactate and urine output) and recognition and management of severe sepsis.
Results There was a 98% response rate with 41 completed questionnaires returned, 15 from midwives, 13 from obstetricians and 13 from anaesthetists. We found that awareness was suboptimal within all groups. Of the six criteria for SIRS, suggested by the SSC, two criteria (altered consciousness and hyperglycaemia) were poorly identified and few responders were aware that two or more criteria indicated SIRS (Figure 1). Most healthcare professionals correctly identified genital tract infection as the leading source of maternal sepsis. The majority of responders had not heard of the 'sepsis six' (Figure 2). Out of the initial duties of care, delivery of oxygen and monitoring urine output were poorly identified. Respondents were not confident in identifying features of severe sepsis and with the exception of hypotension despite fluids, other markers of end organ dysfunction were underreported.
Conclusion It is all of our responsibilities to focus efforts on the emerging threat of maternal sepsis as highlighted by CMACE. Historically, we have seen a significant improvement in maternal mortality rates when specific interventions have targeted those issues raised in previous

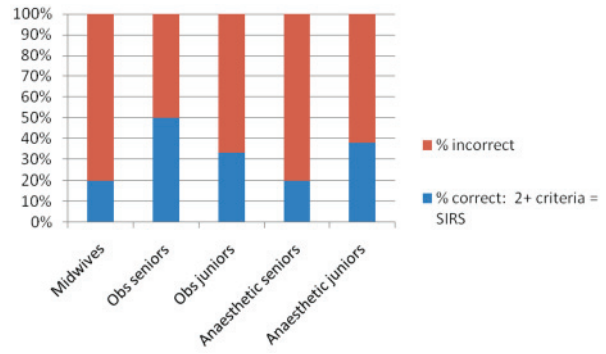

Figure 1 (abstract P20).

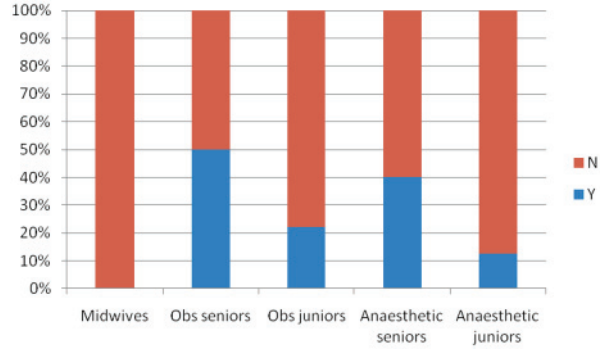

Figure 2 (abstract P20).

CMACE reports (for example, venous thromboembolism). We therefore propose to develop local clinical guidelines, posters and factsheets with formal teaching sessions and multidisciplinary simulator workshops to raise awareness, optimise care and minimise preventable deaths from maternal sepsis. We will re-audit awareness in 6 months time to complete the audit cycle.

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P21

Septic shock and vasopressor requirement is associated with lower vitamin D levels in critically ill children

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Introduction Vitamin D plays an important role in immune and cardiovascular function. There is evidence that low 25-hydroxyvitamin D (25(OH)D) levels are associated with an increased risk of life-threatening infections [1,2]. Our objective was to determine the prevalence of 25(OH)D deficiency (<20 ng/ml) in critically ill children and to identify any association with illness severity and infection.

Methods From November 2009 to November 2010, we collected blood samples and clinical data on children (<21 years old) near the time of admission to the pediatric ICU, excluding those admitted for short-term monitoring. We measured plasma 25(OH)D concentrations in plasma using Diasorin radioimmunoassay on all subjects. Vasopressor requirement was measured using the cardiovascular component of the Sequential Organ Failure Assessment (CV-SOFA) score.

Results Among 511/818 (62.5%) eligible children, 40.1% were 25(OH)D deficient (median level 22.5 ng/ml (IQR = 16.4, 31.3)). Children with a confirmed (n = 144, 28.2%) or suspected (n = 94, 18.1%) diagnosis of infection on admission did not have lower 25(OH)D levels overall, except for those presenting in severe septic shock (n = 51, median = 19.2 ng/ml, IQR = 12.6, 24.8; P = 0.0008). In the multivariate analysis, older age and nonwhite race were associated with vitamin D deficiency while summer season, vitamin D supplementation and formula intake were strongly protective. Patients with higher pediatric ICU admission day illness severity by PRISM-III score quartiles had lower vitamin D levels (OR = 1.19 per 5 ng/ml decrease in 25(OH)D, 95% CI = 1.10, 1.28, P <0.0001) after adjusting for risk factors. When septic shock was added to this model, there was no effect on the association between 25(OH)D level and PRISM-III quartile (OR = 1.18 (95% CI = 1.09, 1.27, P <0.0001)). There was also an inverse association between 25(OH)D level and maximal vasopressor use as measured by the CV-SOFA score in a multinomial regression model (OR = 1.13, 95% CI = 1.01, 1.27, P = 0.03). Including septic shock in the multivariable model did not affect the effect of vitamin D level (OR = 1.16, 95% CI = 1.02, 1.31, P = 0.02)) on CV-SOFA score.

Conclusion The overall prevalence of vitamin D deficiency in critically ill children is high, and patients with severe septic shock had significantly lower vitamin D levels than the general population. This association between vitamin D and septic shock may be due to the cardiovascular effects of vitamin D or to increased severity of infection with diminished 25(OH)D levels. These results suggest a role for the vitamin D axis in sepsis and hemodynamic instability that deserves further investigation.

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P22

The endothelial glycocalyx degenerates with increasing sepsis severity

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Introduction The endothelial glycocalyx is a recently discovered structure at the luminal side of blood vessels consisting of proteoglycans and glycosaminoglycans, which play an important role in vascular barrier function and cell adhesion. Due to its vulnerability, the endothelial glycocalyx may easily be altered by hypoxia [1], TNFα [2], oxidized lipoproteins [3] and other nonphysiological conditions. We raised the question of whether the glycocalyx may be shed from the endothelium in dependence of severity of sepsis.

Methods This clinical prospective study – approved by the local ethics committee – was performed to assess plasma levels of the glycocalyx components (hyaluronane, syndecan, heparan sulfate) by ELISA technique and polymorphonuclear leukocyte (PMN) function by flow cytometry in eight healthy volunteers (HV) and 37 patients who were prospectively enrolled within 24 hours of onset of signs of infection, if they met the criteria for sepsis (n = 10), severe sepsis (n = 9) and septic shock (n = 18) as defined by the members of the ACCP/SCCM Consensus Conference Committee (Table 1). Blood was drawn within

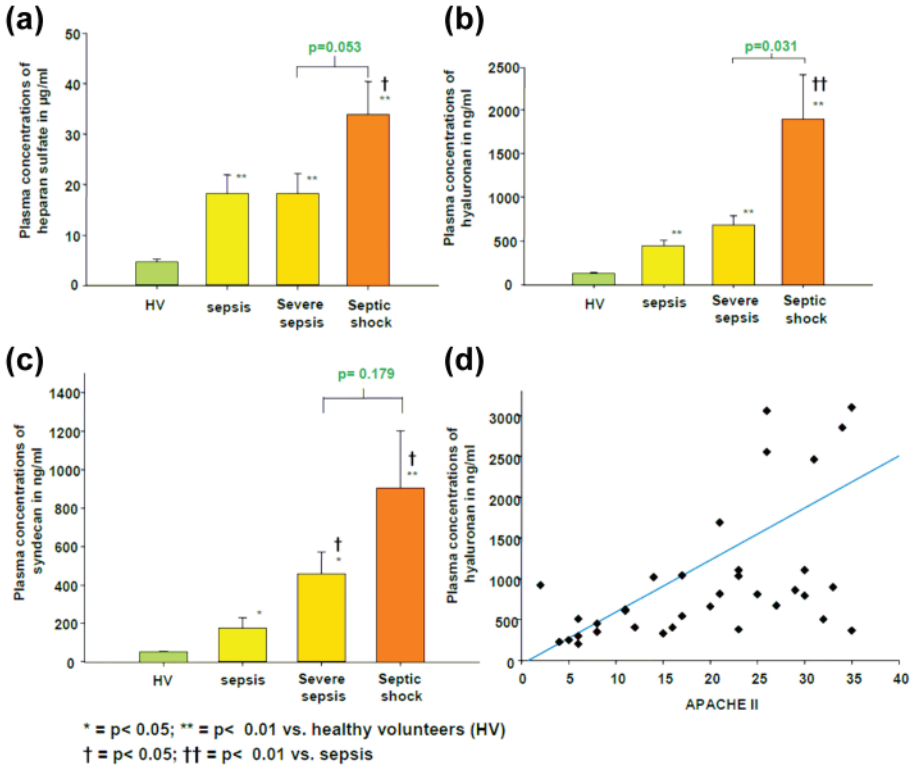

Figure 1 (abstract P22). (a) to (c) Increase in the glycocalyx components in plasma of healthy volunteers (HV) and of patients with increasing sepsis severity. **(d)** Correlation between APACHE II score of septic patients and hyaluronan plasma concentrations.

Table 1 (abstract P22). Demographic data

	Healthy volunteers ($n = 8$)	Sepsis ($n = 10$)	Severe sepsis ($n = 9$)	Septic shock ($n = 18$)
Age (years)	29.1 ± 2.9	51.6 ± 19.7	63.3 ± 23.5	63.3 ± 21.4
APACHE II	n.b.	7.6 ± 3.9	17.8 ± 6.9	27.9 ± 5.3
MOD	n.b.	2.1 ± 1.6	6.9 ± 3.2	9.4 ± 3.6
SOFA	n.b.	4.1 ± 2.8	9.0 ± 3.0	13.3 ± 3.4

Table 2 (abstract P22). Correlation between the glycocalyx components (hyaluronan, syndecan) and the APACHE II, SOFA and MOD score of septic patients

	APACHE II	SOFA	MOD
Hyaluronan	$r^2 = 0.583$, $P = 0.000$	$r^2 = 0.529$, $P = 0.001$	$r^2 = 0.435$, $P = 0.008$
Syndecan	$r^2 = 0.425$, $P = 0.010$	$r^2 = 0.476$, $P = 0.003$	$r^2 = 0.529$, $P = 0.001$

Table 3 (abstract P22). Correlation between the glycocalyx components (heparan sulfate, hyaluronan) and the C-reactive protein, procalcitonin and IL-6 in plasma of septic patients

	CRP	PCT	IL-6
Heparan sulfate	$r^2 = -0.63$, $P = 0.714$	$r^2 = 0.20$, $P = 0.928$	$r^2 = 0.505$, $P = 0.012$
Hyaluronan	$r^2 = 0.398$, $P = 0.016$	$r^2 = 0.723$, $P = 0.000$	$r^2 = 0.468$, $P = 0.021$

24 hours after onset of sepsis. Informed consent was obtained from all patients or their legal representatives, respectively.

Results Plasma levels of the glycocalyx components were significantly higher in septic patients than in healthy volunteers and even more pronounced in patients with severe sepsis and septic shock (all $P < 0.05$; Figure 1). Hyaluronan and syndecan plasma levels correlated positively with the APACHE II, SOFA and MOD scores (Figure 1 and Table 2). Hyaluronan displayed a positive correlation with the C-reactive protein, procalcitonin and IL-6 in plasma (Table 3). The PMN dysfunction – characterized by an increase in cytotoxic capability and a decrease in microbicidity – showed a parallel course to the heparan sulfate plasma levels.

Conclusion Elevated plasma levels of hyaluronan, syndecan and heparan sulfate are suggestive of a glycocalyx shedding from endothelium with increasing sepsis severity. This process might contribute to the vascular dysfunction and development of edema in septic patients.

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P23

Abstract withdrawn

P24

Early peak temperature and mortality in critically ill patients with or without infection

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Introduction The febrile response in the context of infection may be linked to a protective host response through enhanced immune function at elevated body temperatures [1-9]. Alternatively the use of antipyretics may reduce metabolic expense, patient discomfort, or protect against neurological injury.

Objective To determine whether fever is associated with reduced risk of death in patients admitted to an ICU with infection compared with other patients.

Methods A retrospective cohort study using a database of Australian and New Zealand (ANZ) ICU admissions as a development cohort and a database of UK ICU admissions as a validation cohort. The sample included 129 ICUs in ANZ and 201 ICUs in the UK. The ANZ development cohort consisted of 269,078 patients and the UK validation cohort consisted of 366,973 patients. All patients were admitted to an ICU between 2005 and 2009. A total of 29,083/269,078 (10.8%) ANZ patients and 103,191/366,973 (28.1%) UK patients were categorised as having an infection at the time of ICU admission. The main outcome measures were the association between peak temperature in the first 24 hours after ICU admission and in-hospital mortality in patients admitted with or without infection.

Results In the ANZ cohort, adjusted in-hospital mortality risk progressively decreased with increasing peak temperature in patients with infection. Relative to 36.5 to 36.9°C, the lowest risk was at 39 to 39.4°C (adjusted OR = 0.56; 95% CI = 0.48 to 0.66). In patients without infection, the adjusted mortality risk progressively increased above 39.0°C (adjusted OR = 2.07 at ≥40.0°C; 95% CI = 1.68 to 2.55). In the UK cohort, findings were similar with adjusted odds ratios at corresponding temperatures of 0.77 (95% CI = 0.71 to 0.85) and 1.94 (95% CI = 1.60 to 2.34) for the infection and non-infection groups, respectively. See Figures 1 and 2.

Conclusion Peak temperature in the first 24 hours in the ICU is associated with decreased in-hospital mortality in critically ill patients with an infection; randomised trials are needed to compare the effect on mortality of controlling fever against a permissive approach to fever management in such patients.

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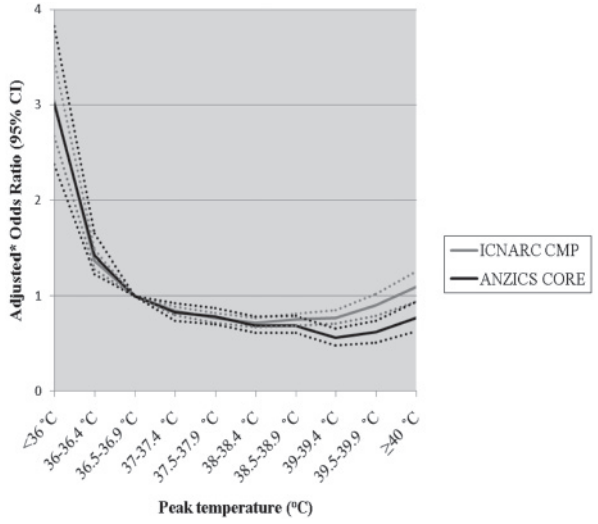

Figure 1 (abstract P24). Adjusted* odds ratios for in-hospital mortality versus peak temperature in the first 24 hours in the ICU for patients in the infection group. *Odds ratios adjusted for illness severity using the ICNARC (2009) model predicted log odds of acute hospital mortality with the temperature component removed for the UK data and the APACHE III predicted log odds risk of death with the temperature component removed for the ANZ data.

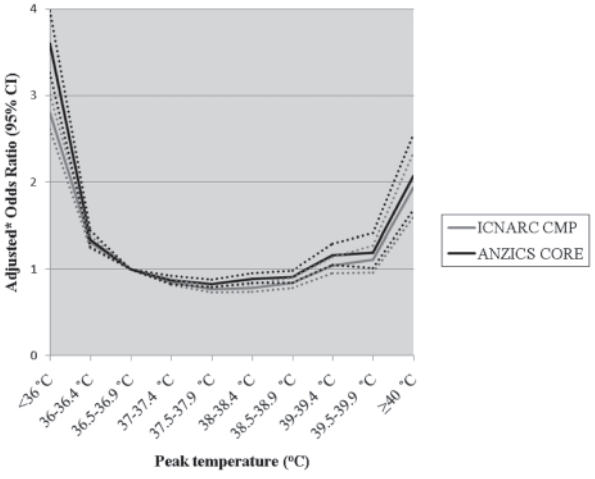

Figure 2 (abstract P24). Adjusted* odds ratios for in-hospital mortality versus peak temperature in the first 24 hours in the ICU for patients in the non-infection group. *Odds ratios adjusted for illness severity using the ICNARC (2009) model predicted log odds of acute hospital mortality with the temperature component removed for the UK data and the APACHE III predicted log odds risk of death with the temperature component removed for the ANZ data.

P25

Role of procalcitonin and high-sensitivity C-reactive protein in sepsis: a prospective study

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Introduction Sepsis is the most common cause of morbidity and mortality in ICU patients. The clinical signs of infection and routine laboratory tests are not specific and at times misleading. Even the bacteriological evidence of infection is not sensitive enough. In view of this diagnostic and therapeutic dilemma, an effective and specific marker is needed that can support or exclude the diagnosis of infection. Hence we evaluated the usefulness of biochemical markers such as procalcitonin (PCT) and high-sensitivity C reactive protein (hsCRP) in monitoring the therapeutic response to treatment in patients with sepsis.
Methods Fifty-seven patients admitted to the ICU of Sir Ganga Ram Hospital, New Delhi, India from July 2010 to April 2011 with a fresh episode of sepsis were included in the study. PCT and hsCRP were analyzed in serum samples at 0 hours, 24 hours and 72 hours. Blood cultures were performed on the day of admission (0 hours) and the patients were categorized as culture positive or culture negative. Patients were followed up for 28 days and were then grouped as survivors and nonsurvivors.
Results During the observation period of 28 days, 44 patients survived and 13 expired. Over a period of 0 to 72 hours the PCT level decreased in 86% survivors as compared with 46% nonsurvivors (P =0.001), whereas it increased in 13.6% survivors as compared with 53.8% nonsurvivors (P = 0.001). The change in the levels of hsCRP in both surviving and nonsurviving patients was not significant. The 0-hour blood culture was positive in 24 out of 57 patients. The PCT levels at 0 hours was significantly high in culture-positive patients (P = 0.002) as compared with culture-negative patients, whereas there was no significant difference in the hsCRP levels in the above-mentioned groups. The area under the curve of PCT and hsCRP in culture-positive and culture-negative patients was 0.743 (95% CI = 0.608 to 0.878, P = 0.002) and 0.564 (95% CI = 0.414 to 0.715, P = 0.405), respectively.
Conclusion These observations indicate that PCT is a better prognostic indicator than hsCRP and is also a better predictor of bacteremia in the newly admitted critically ill patients of sepsis. Hence, routine use of PCT as a monitoring tool may aid in appropriate therapeutic intervention in patients with sepsis.
Acknowledgements The authors thank the Indian Council of Medical Research, New Delhi, India for financial support.

P26

Prehospital identification of sepsis patients and alerting of receiving hospitals: impact on early goal-directed therapy

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Introduction Over the past several years, the early identification and aggressive treatment of sepsis patients has become a standard of care in the hospital setting. A relatively small number of emergency medical service (EMS) systems have started programs to screen for sepsis; an even smaller number provide treatment based on that screening process in the prehospital setting.
Objective The purpose of this study is twofold. First, the study aims to determine how effectively paramedics working in the county EMS system can use a screening tool to identify potential sepsis patients and provide an alert to the receiving hospital. Second, the study will examine whether or not an early identification process in the field leads to improved treatment of sepsis. The end goal is to reduce morbidity and mortality of sepsis patients in the hospital setting.
Methods This is a multi-site prospective observational study with comparison to retrospective cohort. Patient data will be collected to determine whether or not the alert process leads to early obtaining of a serum lactate measurement and early goal-directed therapy.
Results Data points being analyzed from prehospital care reports: criteria from the sepsis screening tool include evidence of infection, temperature, heart rate, respiratory rate; and EMS field clinical impression (for comparison with emergency department (ED) admitting diagnosis). Data points being analyzed in the hospitals include the following: ED admitting diagnosis; serum lactate values, blood culture, timestamps; evidence of early goal-directed therapy – timestamps/values for fluid and antibiotic administration; hospital admitting diagnosis; and discharge diagnosis. The results of the study will be available by 2012/2013.
Conclusion Preliminary anecdotal and early data analysis reports from EMS and hospital staff suggest that patients are being identified as septic prior to ED arrival and have lower lactate levels. Patients are also treated more timely on arrival to the ED for sepsis. Final data analysis will shed more light on our hypothesis. Early identification of septic patients has implications for further research both in the field and hospital settings.

P27

Abstract withdrawn

P28

Thalidomide in combination with augmentin (amoxicillin with clavulanic acid) protects BALB/c mice suffering from *Klebsiella pneumoniae* B5055-induced sepsis

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Introduction Despite extensive research in the field of sepsis pathogenesis and its management, mortality associated with sepsis in hospitals remains very high. For example, more than 18 million people are affected by sepsis worldwide and have an expected 1% increase annually in ICUs. Sepsis is the outcome of a deregulated immune system occurring during systemic bacterial (that is, Gram-negative or Gram-positive) infection. So modulating the immune system by an immunomodulatory approach may prove beneficial to sepsis patients. In the present study, we evaluated the protective immunomodulatory effect of thalidomide alone or with augmentin in *Klebsiella pneumoniae* B5055-induced sepsis in BALB/c mice.
Methods The mouse model of sepsis was developed by placing *K. pneumoniae* B5055 entrapped in fibrin and thrombin clots in the peritoneal cavity of mice. The septic mice were treated with thalidomide alone (30 mg/kg/day p.o.), with augmentin alone (20 μg/ml i.p.) and with their combination. The bacterial load in blood was estimated by blood culture on MacConkey's agar plates along with measuring the other systemic inflammatory parameters. For example, lipid peroxidation was measured in terms of malondialdehyde (MDA) and nitric oxide (NO) levels in serum by biochemical methods. Levels of proinflammatory cytokines (that is, TNFα and IL-1α) and anti-inflammatory cytokine (that is, IL-10) levels in serum were measured by ELISA.
Results The thalidomide-alone-treated mice showed 75% survival whereas 60% of the augmentin-alone-treated group survived. However, their combination (thalidomide + augmentin) treatment provided 100% survival. Treatment with thalidomide alone significantly (P <0.05) decreased TNFα, IL-1α, NO and MDA levels in the serum without significantly (P <0.05) decreasing the bacterial count in blood. However, levels of IL-10 in serum were found to be significantly (P <0.05) elevated upon thalidomide treatment. Augmentin alone only decreased the bacterial load in blood significantly (P <0.05), while no significant decrease was observed on inflammatory mediators studied. However, a combination thalidomide with augmentin significantly (P <0.05) decreased both the bacterial count as well as inflammatory mediators (that is, TNFα, IL-1α, NO and MDA) and provided 100% protection to animals.
Conclusion Thalidomide can be used as an immunomodulatory agent along with antibiotics for sepsis management.

P29

A novel DDAH-1 inhibitor improved sepsis-induced impairment in vasoreactivity to noradrenaline in a rat endotoxaemia model

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Introduction In septic shock, iNOS activation and nitric oxide (NO) overproduction contribute to vascular hyporeactivity to adrenergic vasopressors. The consequent hypotension often necessitates high doses of catecholamine administration. However, this may lead to detrimental effects on tissue perfusion, immune function and myocardial function. Asymmetric dimethlyarginine (ADMA), an endogenous inhibitor of NO synthase, is extensively metabolised by dimethylarginine dimethylaminohydrolase (DDAH). Competitive inhibition of the DDAH-1 isoform should thus reverse hypotension but, as this isoform is absent in immune cells, it should not compromise the immune effects of NO. Hence, we investigated whether L257, a novel DDAH-1 inhibitor, could spare norepinephrine dosing in a rat endotoxic shock model.
Methods Anaesthetised, spontaneously breathing male Wistar rats (body weight 270 to 330 g) had their left carotid artery and right internal jugular vein cannulated for arterial pressure monitoring and fluid infusion, respectively. Then 40 mg/kg *Klebsiella pneumoniae* lipopolysaccharide was administered intravenously over 30 minutes followed by fluid resuscitation at a rate of 10 ml/kg/hour thereafter. When the mean arterial pressure fell over 20% below baseline, they received norepinephrine titrated to maintain arterial pressure at ±10% baseline. Thirty minutes post commencement of norepinephrine, animals were randomized to receive either L-257 (3 mg/kg bolus then infusion of 125 μg/hour) or, in controls, an equivalent volume of saline. Experiments were terminated 3 hours post commencement of norepinephrine titration, before which echocardiography was performed and serum samples were collected for biochemistry.
Results L-257-treated animals ($n = 8$) required a significantly lower total dose of noradrenaline over 3 hours compared with the eight control animals (38 ± 9 vs. 48 ± 4 μg, $P < 0.05$). The heart rate was significantly lower in the treatment group ($P < 0.05$), which associated with a trend of increased stroke volume and cardiac output. Serum BUN and urea were also significantly lower in the treatment group ($P < 0.05$, Table 1).
Conclusion In this acute endotoxic rat model, we demonstrate that DDAH-1 inhibition by L-257 could reduce norepinephrine dosage and ameliorate its harmful effects. This agent warrants further study as a putative therapy for septic shock.
Acknowledgements This study was funded by Wellcome Trust in the UK.

Table 1 (abstract P29).

Variable	NE	NE + L-257	*P* value
SV (ml/minute)	0.18 ± 0.04	0.23 ± 0.04	0.07
HR (beats/minute)	500 ± 15	449 ± 37	0.03
CO (ml)	90 ± 18	102 ± 19	0.31
U (mM)	16.6 ± 1.2	12.8 ± 1.7	0.01
BUN (mg/dl)	44.8 ± 3.7	35.9 ± 4.8	0.03
Cr (μM)	51.3 ± 15.2	31.8 ± 4.3	0.08
ALT (IU/l)	98 ± 79.8	71.3 ± 48.3	0.6

P30

A novel DDAH-1 inhibitor improved cardiovascular function in a short-term anesthetized rat model of sepsis

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Introduction Excessive NOS activity and NO overproduction are believed to play an important role in sepsis-induced macrocirculatory and microcirculatory dysfunction. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthesis, is extensively metabolised by dimethylarginine dimethylaminohydrolase (DDAH).

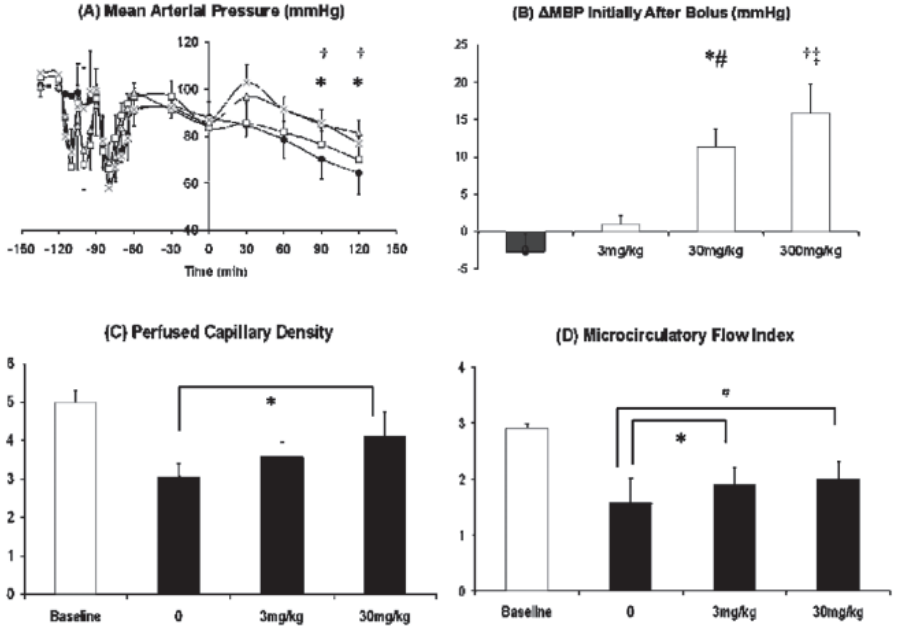

Figure 1 (abstract P30). (a) The effect of bolus doses of L-257 at 0 mg/kg, 3 mg/kg, 30 mg/kg and 300 mg/kg on the mean arterial pressure in the short-term organ function study on anaesthetized Wistar rats ($n = 6$ in the each group). The bolus L-257 was given at 0 minutes for 10-minute infusion. Animals treated with 300 mg/kg L-257, ×; animals treated with 30 mg/kg L-257, open triangle; animals treated with 3 mg/kg, open square; control animals, solid circle. **(b)** The initial change of mean arterial pressure 30 minutes after bolus injections among the four groups. *$P < 0.05$, 30 mg/kg vs. control; #$P < 0.05$, 30 mg/kg vs. 3 mg/kg; †$P < 0.05$, 300 mg/kg vs. control; ‡$P < 0.05$, 300 mg/kg vs. 3 m/kg. **(c), (d)** The effects of bolus doses of L-257 at 0 mg/kg, 3 mg/kg and 30 mg/kg on perfused capillary density and microcirculatory index ($n = 4$ in each group). *$P < 0.05$, 30 mg/kg vs. control; #$P < 0.05$, 30 mg/kg vs. 3 m/kg.

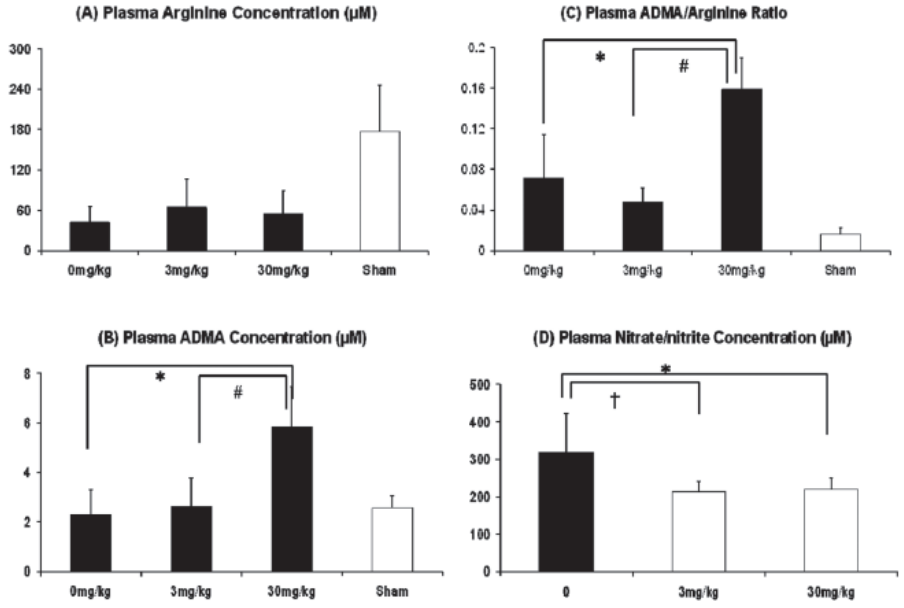

Figure 2 (abstract P30). The effect of bolus doses of L-257 at 0 mg/kg, 3 mg/kg and 30 mg/kg on **(a)** plasma arginine and **(b)** ADMA concentrations, **(c)** the ADMA/arginine ratio and **(d)** plasma nitrate/nitrite concentrations in the short-term organ function study on anaesthetized Wistar rats ($n = 6$ in each group). *P <0.05, 30 mg/kg vs. control; #P <0.05, 30 mg/kg vs. 3 m/kg; †P <0.05, 3 mg/kg vs. control.

The DDAH-1 isoform is present in vascular smooth muscle so its inhibition should theoretically reverse sepsis-induced hypotension. We thus investigated the dose-dependent cardiovascular effects of a novel DDAH-1 competitive inhibitor, L-257, in experimental sepsis.

Methods Anaesthetised, spontaneously breathing male Wistar rats (body weight 270 to 330 g) had their left carotid artery and right internal jugular vein cannulated for arterial pressure monitoring and fluid infusion, respectively. Then 40 mg/kg *Klebsiella pneumoniae* lipopolysaccharide was administered intravenously over 30 minutes followed by fluid resuscitation at a rate of 10 ml/kg/hour thereafter. When the mean arterial pressure fell over 20% below baseline, groups ($n = 6$) were randomized to receive a bolus dose of L-257 of 0 (control), 3, 30 or 300 mg/kg. Animals were sacrificed 2 hours later with prior measurement of gastrocnemius muscle microcirculatory perfusion and with collection of plasma samples for biochemistry, arginine, ADMA and nitrate/nitrite measurements.

Results The bolus doses of L-257 were given after approximately 60 to 90 minutes post endotoxin when the mean BP fell over 20%. Arterial pressure, perfused capillary density and microcirculatory flow index were better maintained than in controls, especially at higher doses (Figure 1, P <0.05). Significantly higher plasma ADMA concentrations and ADMA/arginine ratios were seen in the 30 mg/kg bolus group (Figure 2, P <0.05). Plasma nitrate/nitrite levels in the treated animals were significantly lower compared with those in controls (Figure 2, P <0.05).

Conclusion In this short-term rat model of endotoxaemia, we demonstrated protective dose-dependent effects of a novel DDAH-1 inhibitor, L-257, on cardiovascular function. This was associated with an elevation of plasma ADMA level and a resultant reduction of plasma nitrate/nitrite level.

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P31

Early detection of serum enteric bacterial DNA with real-time PCR in patients with SIRS

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Introduction Sepsis remains a major and increasing healthcare problem with a mortality exceeding 25%. The early detection of infection is important in treating sepsis. Nucleic acid amplification methods have the potential to improve the timeliness, sensitivity, and accuracy of the tests used to detect respiratory pathogens. We used a quantitative real-time PCR (rt-PCR) to detect the enteric bacterial counts in blood from patients in the emergency room.

Methods EDTA samples were collected from patients with systemic inflammatory response syndrome (SIRS) presenting to the emergency room after obtaining informed consent. Enteric bacterial loads in blood samples were assayed by rt-PCR to quantitate the bacterial 23S rDNA and EB rDNA loads. Descriptive and clinical data were collected from the medical records and compared with 23S and EB rDNA results.

Results From January 2011 to April 2011, 39 patients (mean age 71.15 ± 17.12, range 22 to 93) were enrolled in the study. There was no correlation between serum lactate and enteric bacterial load in patients with SIRS. However, in a subgroup comprising patients presenting with respiratory distress and abnormal blood white cell count, the enteric bacterial rDNA load was higher and showed correlation with serum lactate level. The serum enteric bacterial rDNA loads were significantly higher in patients with positive cultures and in patients presenting with higher serum lactate. Correlations between serum lactate and enteric bacterial rDNA load were also significant in the patients with positive culture results.

Conclusion The quantitative assay for enteric bacterial rDNA could be a useful tool to detect early enteric bacterial translocation in patients presenting to the emergency room with elevated serum lactate level or with respiratory distress and abnormal white blood cell counts.

P32

Direct effects of esmolol, ultra-short-acting β-blockers, on cardiac function, ion channels, and coronary arteries in guinea pigs

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Introduction β_1-adrenergic antagonists have been recently used in septic patients to improve sepsis-induced immune, cardiovascular and coagulation dysfunction. But it is difficult and one is hesitant to use these drugs in septic shock patients who have already had hypotension

because these drugs sometimes trigger excessive hypotension due to direct effects on heart function in addition to their β_1 blocking effects. Since little is known about their acute direct effects on mammalian heart, we therefore evaluated the direct effects of esmolol, ultra-short-acting β-blockers, on cardiac performance and single cell-electrophysiology in guinea pig hearts, and compared these effects with those of landiolol.

Methods All animal experiments were approved by the University Animal Ethics Committee. Under deep anesthesia with pentobarbital, the heart was excised and mounted on a Langendorff apparatus to measure the coronary perfusion pressure (CPP). The saline-filled balloon was inserted into the left ventricle to measure the heart rate (HR) and systolic left ventricular pressure (sLVP). The coronary flow was maintained at a constant value during the experiments. Single ventricular cells were enzymatically isolated from hearts and cardiac ion currents were investigated by the patch clamp methods. Group comparisons were conducted by one-way repeated-measures analysis of variance with Dunnett's or Turkey's multiple comparison test. Differences at $P < 0.05$ were considered to denote significance.

Results Esmolol increased CPP in a concentration-dependent manner, and decreased both the sLVP and HR significantly at concentrations >10 μM. Esmolol also shortened the action potential duration (APD) in a concentration-dependent manner, and inhibited the inward rectifier K^+ current (I_{K1}), while the L-type Ca^{2+} current (I_{CaL}) and outward current (I_{Ks} and I_{Kr}) and ATP-sensitive K^+ current were hardly affected. Furthermore, with the application of BAPTA from patch pipettes, the chelation of intracellular calcium ion did not antagonize APD shortening by esmolol. On the other hand, landiolol had minimal effects on cardiac coronary perfusion, cardiac contractility, action potential, and cardiac ionic currents. In the Kyoto Model computer simulation, sole inhibition of I_{K1} or I_{CaL} failed to simulate APD shortening induced by esmolol.

Conclusion The present findings demonstrated that esmolol has more direct effects on the heart than landiolol; that is, the elevation of coronary perfusion pressure and negative inotropic action. The negative inotropic action is accompanied with the APD shortening in single cardiomyocytes. Inhibition of I_{K1} and I_{CaL}, and inhibition of ionic current systems other than those we identified may be involved in the APD shortening caused by esmolol.

P33

Abstract withdrawn

P34

Sepsis-induced lung fibrosis in baboons is reduced by the treatment with a complement inhibitor

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Introduction Pulmonary fibrosis is a major and common medical condition, characterized by progressive scaring and decline in lung function. Persistent inflammation and acute lung injury in response to sepsis are potential triggers of the fibrotic response. Recently, we have reported that *Escherichia coli* sepsis in baboons strongly induces procoagulant responses and affects the integrity of the lung. These effects are diminished by the treatment with compstatin, a C3 convertase complement inhibitor [1].

Methods Here we used the baboon model described [1] in conjunction with detailed gene expression analysis, as well as biochemical and histological assays to determine if *E. coli* sepsis triggered metabolic and signaling pathways related to lung remodeling and fibrosis, and whether complement inhibition could attenuate these pathways.

Results Microarray gene expression analysis shows that sepsis augments several fibrotic gene clusters in the lung as early as 24 hours post *E. coli* challenge. Immunochemical and biochemical analysis reveals enhanced collagen synthesis, induction of profibrotic factors and increased cell recruitment and proliferation. Compstatin treatment decreases sepsis-induced expression of extracellular matrix genes, including eight collagen genes. Sirius Red and immunofluorescence staining for procollagens 1 and 3 confirms the collagen deposition in the lung. Ingenuity® pathway analysis of transcriptomics data shows that compstatin treatment reduces sepsis-induced expression of genes involved in fibroblast transformation and connective tissue production, cell chemotaxis, migration and proliferation (see Table 1). Immunocytochemistry and pathway-oriented transcriptomics and phospho-proteomics analysis reveal changes of multiple processes mediated by transforming growth factor beta (TGF-β), connective tissue growth factor and other TGF-β controlled proteins. Immunostaining for cell proliferation markers demonstrates that compstatin treatment strongly reduces cell proliferation in fibroblastic foci. Moreover, biochemical analysis shows decreased production in the compstatin-treated group of two chemokines responsible for fibrocyte recruitment (CCL2 and CXCL12) and of the type 1 tissue inhibitor of metalloproteases that controls extracellular matrix remodeling.

Conclusion Our data demonstrate that bacterial sepsis initiates pulmonary collagen deposition, and complement inhibition effectively attenuates the fibrotic response. This suggests that complement inhibitors could be used for prevention of sepsis-induced pulmonary fibrosis.

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Table 1 (abstract P34).

	E. coli				*E. coli* + CS T+5			
	Modified genes				Modified genes			
	Up	Down	Total	*P* value	Up	Down	Total	*P* value
Fibroblast transformation	32	10	42	1.41×10^{-6}	12	69	81	1.09×10^{-7}
Connective tissue disorder	133	59	192	2.62×10^{-5}	92	341	434	3.1×10^{-7}
Chemotaxis	39	13	52	5.0×10^{-3}	31	92	123	1.98×10^{-5}
Cell migration	95	40	135	2.11×10^{-5}	80	250	330	9.36×10^{-8}
Cell proliferation	187	70	257	2.67×10^{-8}	118	466	584	5.83×10^{-13}
Fibroblast proliferation	23	7	30	4.80×10^{-3}	10	62	72	5.56×10^{-6}

CS T+5, compstatin-treated animals at T + 5 hours.

P35

AB103, a CD28 antagonist peptide: a new therapeutic agent in a model of severe sepsis

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Introduction AB103 is a novel CD28 antagonist peptide currently in clinical development that modulates CD28 signaling in T cells, without affecting the normal humoral immune response. In experimental models of Gram-positive, Gram-negative and polymicrobial sepsis, AB103 demonstrated significant activity, increasing overall survival.
Methods The AB103 activity and mode of action (MOA) were evaluated in a murine model of cecal ligation and puncture (CLP). AB103 (5 mg/kg) was administered to mice (Balb/c) at various times points following CLP (2 to 24 hours), together with moxifloxacin.
Results A single dose of AB103, given at 12 or 24 hours post CLP, rescued 100% and 62.2% of the animals (respectively) from sepsis-induced mortality, whereas moxifloxacin alone (LD_{90}, given at 12 hours) rescued only 25% (P <0.05) of the animals. In a separate set of experiments investigating the MOA, AB103 administration (5 mg/kg, given without antibiotics 2 hours post CLP) was associated with: a reduction in Th-1 cytokine levels in peritoneum (TNFα, IL-3, IL-17 and Rantes) and plasma (IL-3 and IL-6); a reduction in splenocyte proliferation, stimulated *ex vivo* with anti-CD3 and anti-CD28 antibodies; a reduction in neutrophil recruitment to the spleen, liver and kidney, as determined by MPO activity; and a reduced bacterial load in peritoneum, blood and tissues (kidney, liver, spleen).
Conclusion These data demonstrate that attenuation of CD28 signaling is a viable therapeutic approach to the treatment of sepsis. Due to its robust activity and good safety profile in humans already established in a phase 1 study, AB103 should be clinically evaluated in sepsis patients.

P36

Cardiovascular effects of β-blockade in a sheep model of severe sepsis

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Introduction In sepsis, sympathetic nerve activity is differentially increased in individual organs. The increased cardiac sympathetic nerve activity is partly responsible for the increase in heart rate (HR) and cardiac output (CO) opposing the development of hypotension [1]. Recently, in a rat septic model, β-blockade appeared safe and decreased the inflammatory response and mortality [2]. Accordingly, we sought to investigate the cardiovascular effects of selective β1-receptor blockade in a sheep model of sepsis.
Methods Eight merino ewes were studied in a university-affiliated research institute in Melbourne. The study design was a prospective interventional crossover animal study. The animals had renal and cardiac flow probes implanted to continuously measure CO and renal blood flow (RBF). Every animal was randomly allocated to receive sepsis and atenolol (atenolol group, AG) or sepsis alone (control group, CG) and then crossed over. After 24 hours of baseline period, sepsis was induced through a bolus of live *Escherichia coli* by a continuous infusion for a total 24 hours of sepsis. After the first 8 hours of sepsis (development sepsis period, DS), a bolus of atenolol (10 mg bolus) was given followed by a continuous infusion of 0.125 mg/kg/hours for 16 hours. Two-way repeated-measure ANOVA was performed to compare the average of periods and group interaction. P <0.05 was considered significant (not significant (NS), P >0.05).
Results Animals in the AG and CG had similar baseline values and developed a similar hyperdynamic state in the DS (Figure 1 and Table 1). Atenolol reduced CO and HR without changes in stroke volume. Hypotension was slightly greater in the AG than in the CG (MAP: 81.5 vs. 86.1 mmHg) with a greater decrease in total peripheral conductance (16.8 vs. 22.1 l/minute/mmHg). Changes in lactate level were similar. Similar increases in RBF and in renal vascular conductance (RVC) were observed in the AG and CG and after an initial increase in diuresis in the DS, oliguria similarly subsequently developed in both groups. Creatinine clearance decreased in a similar way in the AG and CG from 59.2 (± 2.8) to 32 (± 5.7) ml/minute and from 65.2 (± 9.9) to 36 (± 7) ml/minute, respectively (P = 0.381). One animal in the AG and two in the CG died in the 24 hours after the end of sepsis.
Conclusion β-blockade in hyperdynamic sepsis appears safe. It results in only limited decreases in mean arterial pressure, and does not increase lactate levels or worsen renal function.

Table 1 (abstract P36). Hemodynamic and renal findings during baseline, development (DS) and intervention sepsis periods in the CG and AG groups

	Group	Baseline period	Development sepsis period (DS)	Sepsis intervention period	*P* value
CO	CG	3.68 (0.29)	3.68 (0.29)	4.12 (0.29)	**<0.001**
	AG	3.21 (0.22)	3.21 (0.22)	5.63 (0.53)	
HR	CG	66.0 (6.5)	66.0 (6.5)	108.8 (8.6)	**<0.001**
	AG	59.7 (6.4)	59.7 (6.4)	111.6 (8.4)	
MAP	CG	93.7 (5.1)	102.5 (3.6)	86.1 (4.1)	**0.035**
	AG	96.3 (5.0)	102.5 (3.8)	81.5 (4.3)	
RBF	CG	217.3 (14.8)	217.3 (14.8)	324.8 (19.7)	0.194
	AG	214.7 (19.9)	214.7 (19.9)	292.3 (27.4)	
UO	CG	31.1 (7.1)	84.1 (20.4)	22.1 (4.8)	0.097
	AG	34.8 (7.0)	52.3 (17.4)	16.8 (11.0)	
TPC	CG	38.2 (3.4)	38.9 (3.4)	63.9 (6.8)	0.084
	AG	34.3 (3.1)	37.3 (3.2)	51.4 (6.8)	<0.001
SV	CG	51.4 (3.7)	39.1 (3.6)	35.5 (8.2)	0.147
	AG	51.2 (4.6)	36.7 (3.5)	39.6 (3.6)	
RVC	CG	2.39 (0.18)	3.26 (0.26)	3.74 (0.41)	0.55
	AG	2.23 (0.16)	2.88 (0.26)	3.53 (0.44)	

Values are the mean (± standard error). *P* value: two-way repeated-measures ANOVA interaction between treatment group and time (see text for definitions).

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P37

A sepsis progression model in humans: characterization of biomarkers descriptive of sepsis progression

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Introduction Previously our group has developed neural net progression models to characterize the development of organ failure in an ovine only as well as an integrated human/ovine model of acute lung injury using early clinical information. The goal of this study was to expand our model of disease progression using clinically available

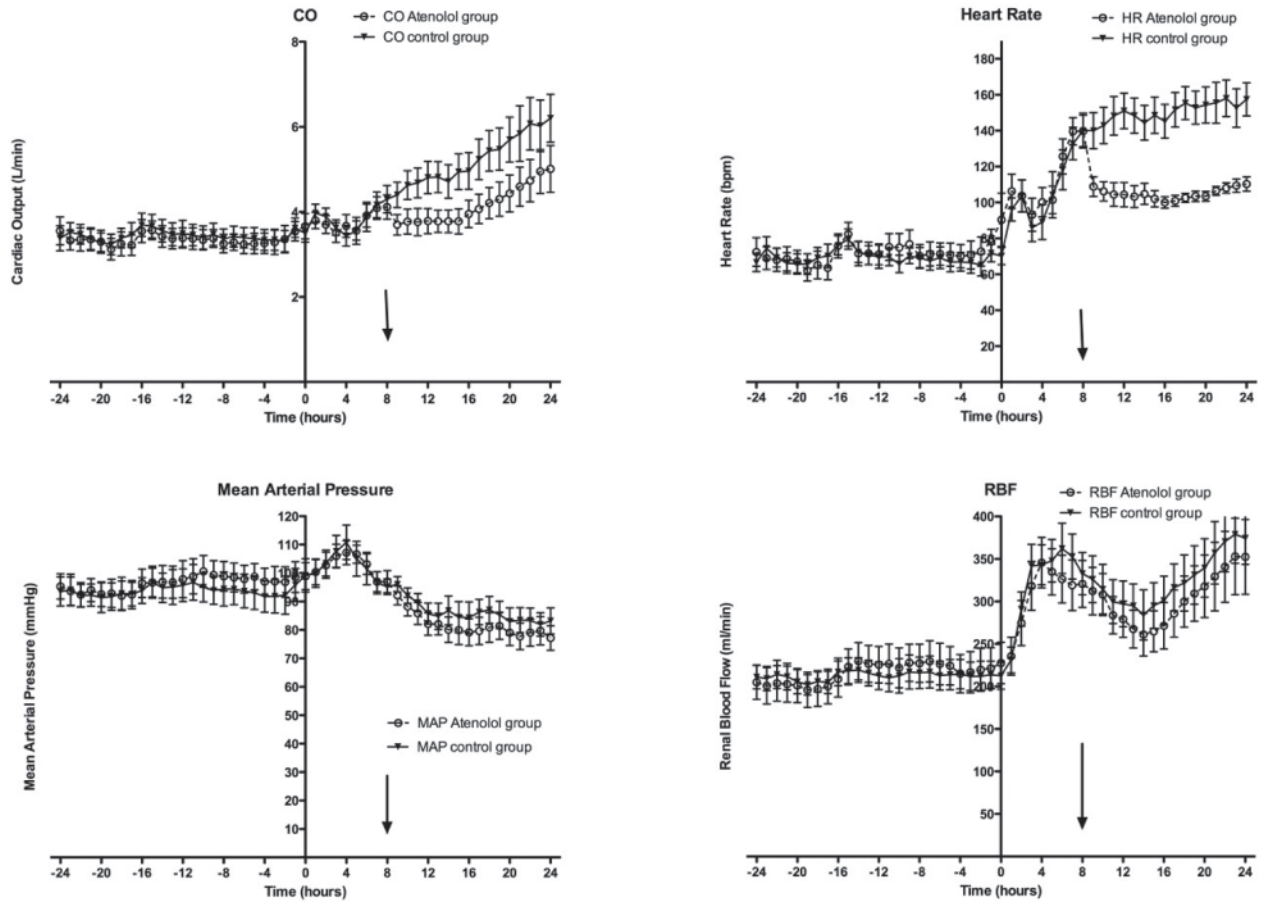

Figure 1 (abstract P36). Hemodynamic variables during baseline and sepsis in the atenolol (AG, white circles, dotted line) and control (CG, black triangles, continuous line) groups.

data as well as more exploratory biomarkers, such as the endotoxin activity assay (EAA), cytokines, D-dimer, copeptin, and procalcitonin, in an adult population with sepsis.

Methods Three North American study sites enrolled adult patients within 24 hours of meeting at least two SIRS criteria with clinical evidence of infection. Biomarker sampling occurred daily on days 1 to 7 and on days 14, 21, and 28. Clinical data from the 24 hours preceding the first sampling point as well as the baseline biomarker values were used as model inputs. Model outputs were serum creatinine (Scr) and organ metric (OM) over the study duration. OM is a composite parameter similar to the SOFA score with the CNS category removed and a continuous rather than categorical value. A neural net was used to perform a multiple parameter logistic regression while allowing for non-linear (usually sigmoidal) dependence on input parameters. Input parameters are first used individually to model the output and are then ranked based on the minimum mean squared error (MMSE) in these single-parameter models. The two parameters with the lowest MMSE are used to create the final multi-parametric model, which yields a lower modeling error than the original single-parameter models.

Results Thirty patients were enrolled with the two most common infection types being pneumonia and bloodstream. Seventy per cent of patients had at least one organ failure at enrollment. Diastolic blood pressure (DBP), red blood cell count (RBC), and copeptin had the smallest MMSE when individually predicting OM. Combining DBP and RBC yielded good agreement between the modeled and actual OM value ($r^2 = 0.60$). Individually, the prothrombin time (PT), copeptin, and phosphorus had the smallest MMSE when modeling Scr. The r^2 value between the model and actual Scr was 0.64 when combining PT and copeptin.

Conclusion When analyzed using a neural net model, changes in overall organ dysfunction and serum creatinine were predicted from early clinical data in a population of adult patients with sepsis. Identifying predictive biomarker patterns and coupling this information with known drug/intervention response could aid in optimizing treatment timing for greatest clinical benefit.

P38

Abstract withdrawn

P39

Interplay between angiopoietin-2, vascular endothelial growth factor and peroxynitrite is an important determinant of vascular hyperpermeability during methicillin-resistant *Staphylococcus aureus* sepsis

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Introduction We have reported that nitric oxide (NO) production and microvascular hyperpermeability were significantly higher in septic sheep with methicillin-resistant *Staphylococcus aureus* (MRSA) than with *Pseudomonas aeruginosa*. We hypothesize that peroxynitrite, a byproduct of NO, causes vascular hyperpermeability in MRSA sepsis via promoting vascular endothelial growth factor (VEGF) and

angiopoietin-2 (Ang-2). The hypothesis was tested, using both a well-established ovine sepsis model and cultured human umbilical endothelial cells (HUVECs).

Methods Female ewes were chronically instrumented with multiple catheters and live MRSA (USA300, 10^{11} CFU) was instilled into the both lungs by bronchoscope under deep isoflurane anesthesia. The sheep were then randomly allocated to control and treated (nonspecific NOS inhibitor L-NAME, 25 mg/kg, i.v., every 12 hours) groups and monitored for 24 hours for cardiopulmonary hemodynamics. The cells were challenged with 10^5 CFU of live MRSA or 50 μM peroxynitrite and co-incubated with or without L-NAME, peroxynitrite scavenger FeTMPyP, Tie-2 and Ang-2 antibody, and VEGF and its antibody. At different times after the treatment, the permeability was measured by quantifying the amount of FITC-Dextran that passed through the confluent HUVEC monolayer (n = 4). Ang-2 mRNA was determined by RT-PCR in those cells with or without treatment as well (n = 4). Statistical analysis: one-way ANOVA (Bonferroni).

Results *In vivo*, L-NAME significantly reduced MRSA-induced fluid accumulation and requirement, as well as expression of VEGF. HUVEC permeability was time-dependently increased following MRSA co-incubation, reaching a plateau at 2 and 4 hours. These permeability changes (73 ± 4 RFUs) were significantly (P <0.001) inhibited by 1 mM L-NAME (28 ± 1), 5 μM FeTMPy (34 ± 2), 5 μg/ml Tie-2 antibody (32 ± 2), and 5 μg/ml Ang-2 antibody (30 ± 1). In HUVECs, the Ang-2 mRNA was time-dependently (picks at 30 minutes) and dose-dependently increased by peroxynitrite (highest at 50 μM). Treatment of HUVECs with 5 μM VEGF augmented the MRSA-induced Ang-2 mRNA increases. The latter was reversed with FeTMPyP and 5 μM VEGF antibody.

Conclusion Ang-2 and VEGF, Tie-2 receptor, NO and its byproduct peroxynitrite play an important role in MRSA-induced vascular hyper-permeability. The results strongly suggest that peroxynitrite increases vascular hyper-permeability by promoting Ang-2 release through stimulating the VEGF expression during MRSA-induced Gram-positive sepsis.

P40

Clinical characteristics, management, and outcomes of sepsis in Lusaka, Zambia

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Introduction Although infectious diseases are the leading causes of death in sub-Saharan Africa, there are few studies describing sepsis in the region. Available data suggest that HIV prevalence is disproportionately high among septic patients and that treatment, particularly fluid administration, may be suboptimal [1]. Our study evaluated the clinical characteristics, management, and hospital outcomes of patients admitted with sepsis in Zambia. We hypothesized that patients with bacteremia have higher in-hospital mortality than those without.

Methods We conducted a prospective observational study of patients admitted with sepsis to the Adult Filter Clinic (medical ER) of the University Teaching Hospital (UTH) in Lusaka Zambia. Sepsis was defined as two or more SIRS criteria and clinically suspected infection. Baseline characteristics and laboratory results were recorded, as was the timing of antibiotics and fluid administration. Patients were followed until discharge or death.

Results In 3 months, 161 septic patients were enrolled. One hundred and ten (68%) patients were HIV positive; 23 (14%) had unknown HIV status. Ninety-one (57%) had severe sepsis. Organ dysfunction included altered mentation (31%), renal dysfunction (16%), severe respiratory distress (respiratory rate ≥40) (11%), thrombocytopenia (11%), and hepatic dysfunction (7%). Multiple organ dysfunction occurred in 26%. After excluding contaminants, blood cultures were positive in 29 (18%) patients. *Staphyloccoccus aureus*, salmonella species, *Streptococcus pneumoniae*, and *Klebsiella pneumoniae* were the most common pathogens. Only 29% of patients received intravenous fluids within 1 hour of presentation. Eighty-four percent of patients received ≤1 l within the first 6 hours of presentation, and 55% received ≤1 l in the first 24 hours. Overall in-hospital mortality was 40.4% (65/161). In-hospital mortality for severe sepsis was 54.9% (50/91). Important predictors for in-patient mortality (Table 1) were low Glasgow Coma Scale on admission (adjusted odds ratio (AOR) 16.0 (2.9 to 87.1)), positive blood culture (AOR 4.8 (1.5 to 15.0)), and positive and unknown HIV status (AOR 4.20 (1.0 to 17.0) and AOR 7.7 (1.2 to 47.7), respectively).

Table 1 (abstract P40). Risk factors for in-hospital death

Variable	Adjusted OR	Crude OR
Anemia, Hb <9 g/dl	0.91 (0.74 to 4.93)	1.05 (0.56 to 1.80)
Blood culture positive	**4.8 (1.50 to 15.0)**	**2.38 (1.14 to 4.95)**
GCS		
≥13	1	1
9 to 12	**5.50 (1.90 to 16.20)**	**3.60 (1.60 to 8.11)**
<9	**16.00 (2.90 to 87.10)**	**11.2 (3.50 to 36.4)**
HIV		
Negative	1	1
Positive	**4.20 (1.00 to 17.00)**	**2.35 (0.88 to 6.28)**
Unknown	**7.70 (1.20 to 47.70)**	**8.38 (2.36 to 29.7)**
<1 hour to IVF	0.40 (0.10 to 1.10)	0.86 (0.43 to 1.72)
MAP <65	2.10 (0.70 to 6.80)	1.25 (0.56 to 2.81)
IVF in first 6 hours		
0	1	1
1	0.80 (0.30 to 2.00)	0.81 (0.41 to 1.61)
2 or more	0.30 (0.10 to 1.10)	0.60 (0.23 to 1.58)

Statistically significant ORs in bold.

Conclusion In-hospital mortality due to sepsis is higher in Zambia than in most studies from the developed world. Low Glasgow Coma Scale and positive blood cultures are associated with increased in-hospital mortality. Insufficient i.v. fluid administration probably contributes to the high overall mortality. Standardized management including early fluids and antibiotics might improve outcomes of sepsis and severe sepsis in sub-Saharan Africa.

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P41

AZD9773, a novel anti-TNFα immune Fab in development for severe sepsis and septic shock: demonstration of safety and efficacy in a murine CLP sepsis model

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Introduction TNFα is thought to play a central role in the pathogenesis of sepsis and septic shock. AZD9773 is an ovine polyclonal anti-human TNFα immune Fab comprising TNFα-directed and nonspecific Fab populations. AZD9773 potency and pharmacokinetic attributes such as a shorter half-life distinguish it from anti-TNF monoclonal antibodies, which have been assessed previously in clinical sepsis models. Here we explore the preclinical safety/efficacy of AZD9773 in a mouse cecal ligation puncture (CLP) model. There are currently no reports of anti-TNF agent efficacy in mouse CLP; rather, TNFα neutralization

is associated with minimal/no effect or increased mouse mortality. As AZD9773 is differentiated from other anti-TNFα agents based on neutralizing potency and pharmacokinetic attributes, we studied both the safety and efficacy of this product in mouse CLP models.
Methods We studied AZD9773 (plus imipenem) effects in two mouse CLP models: a mild-grade model to explore the potential for AZD9773 to compromise mouse survival, and a severe-grade model to test AZD9773 efficacy. CLP (mild-grade sepsis) comprised 100% cecal ligation and single 20-gauge needle puncture, while CLP (severe-grade sepsis) comprised 100% cecal ligation and single 18-gauge needle puncture. Saline resuscitation and imipenem administration were included in both models. Since AZD9773 does not bind or neutralize murine TNFα, the CLP models were established in Tg1278/–/– (human TNFα transgene/mouse TNFα null) mice. An equivalent protein dose of DigiFab (plus imipenem) served as an irrelevant Fab control. Survival was monitored for 5 days.
Results The control severe-grade model resulted in approximately 20% survival at 5 days. Therapeutic i.p. dosing of AZD9773 bid from 24 to 60 hours (first dose 4,000 units/kg, second to fourth doses 2,000 units/kg) resulted in statistically significant increases in survival (>70%) compared with i.p. DigiFab control (n = 15 per group). The mild-grade model resulted in 63% survival with imipenem alone, 65% survival with AZD9773 and 69% survival with DigiFab at 5 days. Thus, therapeutic dosing of AZD9773 bid from 24 to 60 hours (schedule/dose/route as previously) did not result in significantly different survival outcomes versus either DigiFab or imipenem alone (n = 60 per group).
Conclusion These data demonstrate for the first time that TNFα neutralization in a murine CLP model improves survival in a severe sepsis setting. Moreover, contrasting with previous reports, TNF suppression in mild-grade CLP models is not associated with increased mortality. These findings support the hypothesis that AZD9773 has potential to be differentiated from other anti-TNF agents as a therapeutic intervention in sepsis.
Conflicts of interest All authors are employees of AstraZeneca.

P42

Efficacy of endotoxin absorption therapy on sepsis by polymyxin B-attached fibers

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Introduction Endotoxin plays a role in the development of Gram-negative bacterial sepsis. In Japan, polymyxin B-attached fibers (PMX-B) are used clinically as an endotoxin absorption therapy to neutralize the biological activity of lipid A, the immunomodulatory center of lipopolysaccharide (LPS) endotoxin. Because hemodynamic improvement is not seen in all cases, it cannot be assumed that this therapy will be effective against all cases of sepsis.
Hypothesis Endotoxin absorption therapy is effective against abdominal infection. Moreover, the mortality rate significantly improved in endotoxin-positive cases of abdominal infection.
Methods Between 1997 and April 2008, endotoxin absorption therapy was performed on 105 septic patients in the ICU of Hyogo College of Medicine and the Osaka City General Hospital. The 105 cases were divided into an abdominal infection group (n = 45) and a nonabdominal infection group (n = 60). Before and after therapy, the endotoxin level was measured in patients using the limulus amoebocyte lysate (LAL) and endotoxin activity assay (EAA) methods. Moreover, we measured blood pressure, cardiac index, and the administered dose of catecholamine. Using a retrospective analysis, we compared Sequential Organ Failure Assessment (SOFA) scores; the Risk, Injury, Failure, Loss, and End stage (RIFLE) criteria; and the 28-day survival rate between the two groups.
Results After the endotoxin absorption therapy, mean blood pressure increased significantly from 67.9 ± 11.4 to 86.4 ± 6.3 mmHg in the abdominal infection group, whereas there was no change in the nonabdominal infection group. After the therapy, the SOFA scores and RIFLE criteria improved in both groups, but they improved significantly in the abdominal infection group. Patients in the abdominal infection group, especially the endotoxin-positive cases, recovered earlier from shock and had a significantly higher rate of survival than the abdominal infection group.
Conclusion In endotoxin-positive patients with an abdominal infection, absorption therapy improved survival rate and cardiac and renal dysfunction due to sepsis or septic shock. However, further studies are required to verify the effectiveness of endotoxin absorption therapy.

P43

Lactate clearance as a simple bedside instrument to predict short-term mortality of severe septic patients

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Introduction Severe sepsis is major health problem with a high mortality rate, and still its incidence continues to rise [1-5]. Lactate clearance, measurement of the lactate level at two consecutive times, is an inexpensive and simple clinical parameter that can be obtained by a minimally invasive means [6-8]. This parameter represents kinetic alteration of the anaerobic metabolism that makes it a potential parameter to evaluate disease severity and intervention adequacy. Lactate clearance early in the hospital course may indicate a resolution of global tissue hypoxia and is associated with improved outcome [7-9]. Nevertheless, the relationship between lactate clearance and short-term mortality in severe septic patients is still poorly understood. Understanding the presence of confounder factors is also important to strengthen the role of lactate clearance in the treatment of severe septic patients.
Objective To evaluate the clinical course between lactate clearance groups, and determine the role of confounder variables that influence its relationship.
Methods This is a prospective cohort study conducted in Ciptomangunkusumo Hospital, from March to May 2011. Patients were categorized into the high lactate clearance group if there were differences in 6-hour lactate levels ≥10%, and conversely were categorized into the low lactate clearance group [7,8]. Deaths were observed within the first 10 days. After data collection, the statistical methods were analyzed using survival analysis. Analysis of confounder variables was performed by multivariate Cox regression test.
Results During the research period there were 60 patients recruited, consisting of 30 patients grouped into high lactate clearance and the remainder grouped into low lactate clearance. The survival rates in high and low lactate clearance groups were 60.0% versus 26.7% (see Figure 1). In the low lactate clearance group the median survival was 3 days, while the mortality rate did not reach 50% in the high lactate clearance group. The first interquartile was 1 day and 4 days. The hazard ratio between groups was 2.87 (95% CI = 1.41 to 5.83). Steps taken to analyze the role of variables that potentially act as confounder factors

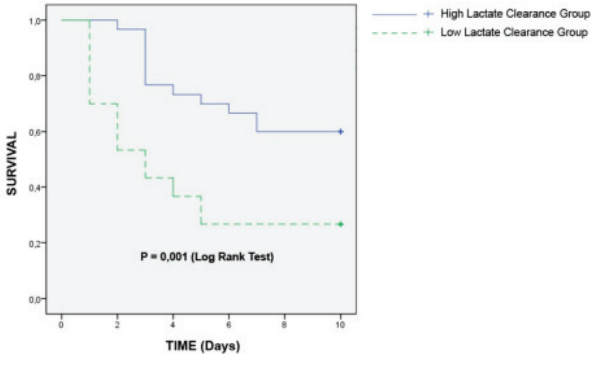

Figure 1 (abstract P43). Kaplan–Meier curves between lactate clearance groups.

Table 1 (abstract P43). Variables that potentially act as confounder factors

Variable	Nonsurvivors	Survivors	*P* value	Adjusted HR (95% CI)	HR change (%)
Septic shock within 6 hours					
With septic shock	11	4	0.081	3.083 (1.505 to 6.317)	7.4
Without septic shock	23	22			
Initial SOFA score					
>9	11	3	0.038	2.919 (1.388 to 6.138)	1.7
≤9	19	21			
Vasoactive drugs within 6 hours					
Without vasoactive drugs	22	23	0.013	2.988 (1.462 to 6.106)	4.1
With vasoactive drugs	12	3			
Invasive ventilation within 6 hours[a]					
Without mechanical ventilation	31	23	0.777	–	–
With mechanical ventilation	3	3			
PRC transfusion within 6 hours					
Without transfusion	29	25	0.069	3.077 (1.493 to 6.340)	7.2
With transfusion	5	1			
Fluid resuscitation within 6 hours					
<1,000 cm^3	15	18	0.166	2.942 (1.444 to 5.994)	2.5
≥1,000 cm^3	19	8			

HR, hazard ratio; SOFA, Sequential Organ Failure Assessment; PRC, packed red cells. [a]Invasive ventilation parameter not included in multivariate analysis, because *P* <0.25.

were by using bivariate analysis, in which variables that influenced the occurrence of deaths (indicated by *P* <0.25) underwent multivariate analysis subsequently. On multivariate analysis the presence of septic shock, degree of organ dysfunction, vasoactive drug usage, blood transfusion, and fluid resuscitation change the hazard ratio by no more than 10% (Table 1). For that reason, these parameters were not considered as confounders.

Conclusion Severe septic patients with high lactate clearance have a better survival rate compared with the low lactate clearance group, and its relationship is not influenced by the presence of confounder variables.

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P44

Effect of low-dose steroid on NF-κB and caspase-3 intestinal expression in a sepsis mouse model

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Introduction The use of low-dose corticosteroids in sepsis early stages is still debated. The association of LPS–LBP complexes to CD14 receptors and will interact with TLR4 to induce NF-κB as a signal and transcription of proinflammatory cytokines [1,2]. Excessive production of inflammatory cytokines will cause activation of SIRS, especially in gut-associated lymphoid tissues [3], which induces metabolic changes leading to apoptosis network, MOF, septic shock and death [3-5]. Changes in apoptosis are mediated by caspases, including caspase-3 that acts as an effector caspase [6,7]. Low-dose corticosteroids can inhibit the production of proinflammatory cytokines, production of inflammatory mediators, and lower adhesion of leukocytes to the endothelium [8].

Objective The aim of this study was to analyse NF-κB and caspase-3 intestinal expression, and also survival from use of low-dose steroid in the early stages of sepsis in the Balb/C mouse model of sepsis.

Methods Male Balb/C mice were inoculated with lipopolysaccharide for the sepsis mouse model. Sepsis mouse model grouping was to a sepsis group (Group I) and to sepsis with steroid (methylprednisolone 1 to 1.5 mg/kg BW/day) (Group II). Detection of intestinal NF-κB and caspase-3 expression used the immunohistochemistry technique on days 1, 3, 5 and 7. Survival was seen until the 7th day. The two-tailed Fisher exact test for the analysis of mortality, independent-sample *t* test for intestinal NF-κB and caspase-3 expression, and *P* <0.05 were used to determine significant differences.

Results Acute inflammatory response occurs in the early stages of sepsis (the first 5 days of exposure) and the process of death occurs in advanced stages of sepsis (after the first 5 days of exposure) [9]. This study shows that the use of low-dose corticosteroids in sepsis early stages (first 5 days) significantly inhibited the expression of NF-κB (see Table 1), so cytokine production of proinflammatory cytokines was not excessive. Reduced product proinflammatory cytokines would reduce the expression of intestinal caspase-3 (see Table 2), which will reduce

Table 1 (abstract P44). NF-κB intestinal expression

	Amount of cell expression		
Day	Group I	Group II	*P* value
1	17.5 ± 4.7	10.8 ± 3.6	0.019
3	26.5 ± 4.4	15.8 ± 3.6	0.001
5	39.3 ± 4.1	31.2 ± 7.0	0.033
7	54.8 ± 9.6	50.5 ± 10.7	0.476

Data presented as mean ± standard deviation.

Table 2 (abstract P44). Caspase-3 intestinal expression

	Amount of cell expression		
Day	Group I	Group II	*P* value
1	8.5 ± 2.9	4.3 ± 1.9	0.014
3	14.7 ± 3.1	9.8 ± 2.2	0.012
5	33.2 ± 8.3	12.8 ± 4.5	0.000
7	42.3 ± 3.2	37.7 ± 8.2	0.336

Data presented as mean ± standard deviation.

the excessive apoptosis in the intestinal tract. Decreased expression of NF-κB and caspase-3 in the intestinal tract would further reduce the excessive mucosal cell death. This situation will block the destruction and disruption of mucosal defense function of the digestive tract, thereby increasing immune response. The end result will be seen that low-dose corticosteroids can reduce mortality. This study found dead animals for Group I were 70%, while Group II were 10% ($P = 0.020$).

Conclusion Low-dose steroids can reduce NF-κB and caspase-3 intestinal expression and also mortality in early sepsis.

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P45

Etiological agents of bacterial sepsis in a newly constructed medical center in Saint Petersburg, Russia

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Introduction Sepsis is one of the factors of high mortality in ICUs in critically ill patients. Annual mortality from this condition is estimated at 30 to 50 deaths per 100,000 population [1,2,4,5]. The aim of the present study was to reveal the spectrum and resistance to antibiotics of microorganisms, causing sepsis in hospitalized patients of the multidisciplinary medical center, that accumulates patients from all regions of Russia, during the first year from its foundation, with low possibility of local nosocomial strains formation.

Methods The diagnosis of sepsis was verified by isolation of bacteria from blood (only two or more positive results were considered) and the presence of two or more criteria of systemic inflammatory response syndrome [3]. The cultures were isolated from blood with BactAlert (BioMerieux, France). The identification was performed by routine phenotypic methods and sequencing of the 16sRNA gene (ABI Prism 3130, MicroSeq ID v2.0 Software, MicroSeq ID 16s rDNA500 Library v2.0). Resistance to routinely used antibiotics was investigated with the disc diffusion method and by dilution techniques for MIC determination on Muller–Hinton agar (Oxoid, UK).

Results Sepsis, associated with bloodstream infections, was revealed in 89 cases – Gram-positive cocci predominated. *Staphylococcus* spp. were responsible for 35 (39.3%) cases: *Staphylococcus aureus* was the causative agent in eight (8.9%), coagulase-negative staphylococci (*Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis novobiosepticus*) in 27 (30.3%) infections. Other Gram-positive cocci were *Enterococcus faecalis* in eight (8.9%), *Enterococcus faecium* in six (6.7%). Gram-negative microorganisms included *Acinetobacter baumannii* that was found in 11 (12.4%), *Klebsiella* spp. (*Klebsiella pneumonia*, *Klebsiella rhinoscleromatis*, *Klebsiella oxytoca*) in five (5.6%), *Escherichia coli* in eight (8.9%), *Enterobacter* spp. (*Enterobacter cloaceae*, *Enterobacter aerogenes*, *Enterobacter hormaechea*) in three (3.4%), *Pseudomonas aeruginosa* in two (2.2%) patients with sepsis. Rarely isolated bacteria were *Bacillus thuringiensis* in one (1.1%), *Stenotrophomonas maltophylia* in one (1.1%), *Pantoeae agglomerans* in one (1.1%), *Corynebacterium mucifaciensis* in one (1.1%) case. Two and more species were isolated from blood in seven (7.9%) patients. In total, 105 strains were isolated in sepsis cases. Resistance to antibiotics was observed in 96 (91.4%) bacterial isolates; 56 (53.3%) were multidrug-resistant strains. All *E. faecium*, and nine (81.8%) strains of *A. baumannii* were resistant to seven or more antibiotics. All *E. faecium* strains were susceptible to linezolide, *A. baumannii* to tigecycline. Methicillin resistance was detected in two (15.4%) strains of *S. aureus* and 18 (60.0%) strains of coagulase-negative staphylococci; four (66.7%) strains of *E. faecium* were vancomycin resistant.

Conclusion Gram-positive bacteria were the leading causative agents of sepsis, associated with bloodstream infections in the newly-constructed hospital in Saint Petersburg. The majority of strains (91.4%) were resistant to antibiotics, and more than half of the isolates were multidrug resistant. Methicillin resistance was observed predominantly in coagulase-negative staphylococci, vancomycin resistance in *E. faecium*. All polyresistant *E. faecium* strains were susceptible to linezolide, *A. baumannii* to tigecycline.

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P46

Efficacy and safety of gelatin for fluid therapy in hypovolemia: a systematic review and meta-analysis

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Introduction Gelatin is frequently used as volume expander. There are growing concerns about safety.
Objective To systematically assess clinical evidence concerning mortality, coagulation and renal function.
Methods Systematic review of randomised controlled trials (RCT) on gelatin in hypovolemia in comparison to any other fluid with a comprehensive search strategy (Ovid Medline (1948 to May 2011), EMBASE (1947 to May 2011), Cochrane Library). Data were independently extracted and risk of bias assessed using the 2010 Cochrane tool. Primary outcome was overall mortality. Secondary outcomes were the number of patients exposed to allogeneic transfusion, frequency of renal replacement therapy (RRT) or acute renal failure (ARF). Albumin and crystalloid solutions were defined as suitable, and other synthetic colloids as unsuitable control fluids since they carry similar risk of side effects. Relative risks (RR) and weighted mean differences with 95% CIs were calculated. Data were pooled using a random-effects model (RevMan 5.1, Cochrane Collaboration).
Results The search yielded 1,288 citations, 210 reports were read in full. The final sample contained 72 RCT in English, German, French and Italian, published between 1975 and 2010, with 5,915 patients overall, 2,523 of which received gelatin. The median sample size in the gelatin groups was 20 patients (range 10 to 249). In 53 RCT (74%), the study period was ≤24.0 hours. Total gelatin dose was 20 ml/kg (median, range 6 to 62). Only 38 RCT (53%) used suitable control fluids. Forty-nine RCT (68%) investigated elective surgical patients, mostly from cardiac surgery (32 RCT, 44%). Nine RCT (13%) investigated critically ill patients, six RCT (8%) were in emergency patients and seven RCT (10%) were in children. The RR for mortality was 1.02 (CI 0.87 to 1.19, data from 23 RCT with 2,694 patients which reported mortality). Numbers of patients exposed to allogeneic transfusions were provided in 11 RCT, n = 1,148 patients and the RR was 1.16 (0.94 to 1.44). When only studies with suitable control fluids were included, the RR for mortality was 1.13 (0.88 to 1.46, 10 RCT, 1,392 patients) and risk for transfusion exposure was 1.35 (0.88 to 2.08, seven RCT, n = 672), tending towards control. Only six RCT (n = 662 patients) reported the occurrence of RRT or ARF, five of them in comparison with HES solutions. Three RCT reported anaphylactoid events.
Conclusion Most published studies on gelatin are small and short-time, use unsuitable control fluids and report too few events to reliably assess the safety of gelatin.

Cite abstracts in this supplement using the relevant abstract number, e.g.:
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