SEPSIS 2011 Beijing

Symposium Program & Abstract Book

Venue - China National Convention Center, Beijing
27-28 October 2011

Sepsis 2011 Beijing
in association with the
Chinese Society of Critical Care Medicine

An International Symposium Hosted by The International Sepsis Forum Inc, a non profit organization

www.sepsisforum.org
Ce n’est pas assez d’avoir l’esprit bon, mais le principal est de l’appliquer bien.

translated: “It’s not enough to have a good mind; the most important thing is to use it well”

René Descartes (1596—1650)
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Dear friends, colleagues, and fellow participants,

On behalf of the entire Council of the International Sepsis Forum (ISF), it is my pleasure and distinct honor to welcome you to the 2011 edition of our annual SEPSIS symposium. This is our fifth consecutive international sepsis meeting organized by the ISF in collaboration with our sponsors. This year’s meeting is unique in that it is our first meeting held in Asia and is held in partnership with, and in close cooperation with, the Chinese Society of Critical Care Medicine’s annual meeting held this year in Beijing.

We wish to thank this year’s meeting organizers, Simon Finfer from Sydney, Australia, and Mervyn Singer from London, UK, for putting together a superb 2-day scientific symposium. This meeting features an entire spectrum of new information relating to sepsis from basic discoveries in inflammation research to practical recommendations about specific management strategies for septic patients.

We are especially thankful to Professor Du Bin and his colleagues here in Beijing for working closely with us in developing this joint program with the Chinese Society of Critical Care Medicine. Their willingness to work with us, their shared expertise, and their generosity and hospitality are very much appreciated.

We are delighted to be here and trust you that will enjoy the opportunity to participate in the scientific sessions. Please visit the poster presentations, interact with the researchers and clinical investigators, and enjoy the allure and history of this magnificent city.

The ISF is dedicated to improving the care of the septic patient through basic and applied research, education of health care providers and patients, and increasing public awareness of the problem of sepsis.

This Sepsis 2011 meeting points to the worldwide relevance of sepsis and supports the view that sepsis should be recognized as a global health emergency.

Thank you for joining us and please enjoy the scientific sessions and the social events that make up SEPSIS 2011-Beijing.

Sincerely,

S. Opal
Chair of the ISF
The International Sepsis Forum

Introduction

Improving Sepsis Outcomes
The International Sepsis Forum (ISF) is a unique collaborative effort between industry and academia. It is the first initiative to focus solely on the management of patients with sepsis. While sepsis and its sequelae are still associated with high morbidity and mortality rates, new data on patient management are emerging that may ultimately improve the current situation. Such findings need to be evaluated and incorporated, where appropriate, into existing treatment protocols. Headed by a Council of international experts and opinion leaders, the ISF is focused exclusively on improving the management of sepsis by developing consensus on the latest understanding of key scientific and clinical issues and disseminating emerging practice guidelines to researchers, intensivists, and other critical care professionals.

The ISF is a 501(c) (3) non-profit charity, based in the USA.

Vision, Mission, and Core Values
The vision of the ISF is to reduce the global toll of morbidity and mortality from sepsis.

The mission of the ISF is to improve the care of critical care patients by:
• Promoting an improved understanding of the basic biology and pathology of sepsis
• Enhancing the understanding of the epidemiology of sepsis
• Improving the design and conduct of clinical research to improve the management of septic patients
• Educating health professionals in the optimal management of patients with sepsis
• Raising the profile of sepsis as a global health challenge with the public, with healthcare practitioners, with industry, and with global health agencies

Core Values of the ISF
Integrity, responsibility, and accountability to ourselves and to the patients and communities we serve. Respectful, collegiate, and transparent relationships within our group, with the scientific and clinical communities, and with our academic and industry collaborators. Courage, compassion, justice, and innovative thought in combating the global challenge of sepsis.

Council Members:

STEVEN OPAL - ISF CHAIR
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Weill Cornell Medical School of Cornell University
Infectious Disease Division
The Memorial Hospital of Rhode Island
Pawtucket, Rhode Island, USA

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Head, Infectious Diseases Service
Department of Medicine
Centre Hospitalier Universitaire Vaudois
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Senior Staff Specialist in Intensive Care
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Professor of Medicine
Academic Medical Center
Center for Infection and Immunity
Amsterdam, The Netherlands

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Department of Surgery
David Geffen School of Medicine, UCLA
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Senior Associate in Critical Care Medicine
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Erasmus University Hospital
Universite Libre de Bruxelles
Brussels, Belgium

www.sepsisforum.org
Sepsis 2011: 
General Information

Venue
China National Convention Center  
No 7 Tianchen East Road, Chaoyang District  
Beijing 100105 China

Registration Desk
The registration desk for non-Chinese participants will be in the main entrance on Level 1 and will be open during the following hours:

- **Wednesday 26 October 2011**  15:00 – 18:00
- **Thursday 27 October 2011**  06:00 – 19:00
- **Friday 28 October 2011**  08:00 – 16:00

Badges
Name badges will be issued to all participants on arrival at registration. Participants are kindly requested to wear their name badges at all times for security. Access to all scientific events, catering, and the exhibition areas will only be possible with your name badge. Replacement badges can be obtained from the registration desk in case of loss.

Catering
Morning and afternoon breaks will be served from the service points on Level 3 of the conference center.

Lunches on 27 and 28 October will be served in B1 of the conference center.

Certificates of Attendance
Pre-registered delegates will receive a Certificate of Attendance with their materials on arrival. This conference operates on the basis that participants declare openly to their accrediting organization how much of the conference they attended.

Feedback Forms
The organizers need feedback to help direct future events. Please take your time to complete the feedback forms daily and return to the registration desk.

Poster Presentations
A listing of all the posters is on pages 36 - 37. Posters should be fixed to the boards using tape during registration on 27 October on Level 3 of the congress center and will be displayed for the duration of Sepsis 2011. Each poster has an allocated board with a number. This number cannot be moved or the poster swapped for any other. Authors are invited to stand by their posters.
during the welcome reception on October 27.

Please remember to take your poster home with you!

Poster Awards
A selection of abstracts has been chosen for best abstract awards and they will be presented in both poster and oral presentations. Please refer to page 34 for information on these awards.

The 2011 Stephen F. Lowry Young Investigator Award
This prestigious award will be presented during one of the best abstract sessions. Please refer to page 33 for more information. Award certificates will be given by Steven Opal and Daniel Traber.

Publication of Abstracts
ISF has included all accepted abstracts in the program book. A selection of abstracts has also been published as a supplement to the journal Critical Care. Abstracts chosen for publication in this journal are under the editorial control of the journal and not the ISF.

Welcome Reception
Thursday 27 October
Welcome Reception will be held from 16:30 – 19:00 on Level 1. You are welcome to take your refreshments to Level 3 to view the posters.

Poster Viewing
Poster will be available throughout Sepsis 2011, but poster presenters have been asked to stand by their posters during the welcome reception which will be held on 27 October 16:30-19:00 will be held on Level 3.

Smoking
Sepsis 2011 is a non-smoking conference.

Mobile Phones
We appreciate that delegates need to be available for calls. We kindly ask that all mobile phones be placed in mute or vibrate mode during the sessions.
# Sepsis 2011: Scientific Program 26-27 October

## Wednesday 26 October

**16.00 – 18.00**
Registration open Level 1

## Thursday 27 October

**06.00 – 08.00**
Registration open Level 1

**08.00 – 08.30**
**OPENING CEREMONY**

**08.30 – 10.00**
**SESSION I: PLENARY LECTURES**
- What do we mean by sepsis? – definitions and new paradigms **STEVEn OPal**
- The burden of sepsis in the Developed World **DEREk ANgUS**
- The burden of sepsis in China **XIu-Ming XI**
- Emerging infections, antibiotic resistance and pandemics – should we be afraid? **THIERRY CALANDRA**

**10.00 – 10.30**
**COFFEE BREAK**

**10.30 – 12.00**
**SESSION II: PLENARY LECTURES**
- Host recognition – the innate and adaptive immune response **TOM VAN DER POll**
- Genetics, sepsis and inflammation **JEAn-PaUL MiRA**
- Fever control – does controlling temperature increase mortality **MORITOkI EGI**
- The Surviving Sepsis bundles – a pragmatic approach to treatment **R. PHIlIP DEllINGER**

**12.00 – 13.00**
**LUNCH BREAK**

## 13.00 – 16.30

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## 14.30 – 15.00
**COFFEE BREAK**

## 15.00 – 16.30

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## Sepsis 2011: Scientific Program 28 October

### Friday 28 October

**Registration open Level 1**

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Coming Soon…

**BD BACTEC™ Plus PRIME**
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BD introduces the next generation blood culture media with three resins. It is called PRIME. The PRIME resin has a unique dark red hue that can easily be seen throughout the BACTEC blood culture bottles. BACTEC Plus PRIME offers a triplex of cationic adsorption and hydrophobic attraction resins. BACTEC Plus PRIME builds on the proven effectiveness of BACTEC Plus resin media, which have been shown to neutralize a wide variety of antimicrobials improving recovery and shortening time to detection.

With BACTEC Plus PRIME, BD demonstrates its dedication and leadership in continuing to bring innovative and quality diagnostic products and systems to the diagnostic sciences.
What do we mean by sepsis? – Definitions and new paradigms

Steven Opal  The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

The seemingly straightforward process of defining the clinical manifestations of sepsis is more challenging than originally envisioned. The primary care provider, the hospitalist, the critical care specialist, clinical trialist, and laboratory scientist all have a general understanding of what sepsis implies, but they have remarkably disparate opinions about what sepsis really is when attempting to write its meaning. To clarify the situation and to provide a more unified definition of sepsis, a North American advisory board met in 1991 and proposed a series of standardized definitions to be used in sepsis trials. These definitions primarily revolved around the concept of systemic inflammatory response (SIRS) as a unifying principle that was common to all patients with sepsis. These criteria were so simple and logical that they rapidly became accepted as the standard definition for sepsis. These criteria or variants of them have been used to essentially all sepsis studies over the last 2 decades, despite the recognized shortcomings with this simple clinical definition of sepsis. The primary problem with this definition is the SIRS criteria were very non-specific and overly sensitive. The majority of patients admitted to acute care hospital wards through the emergency room will have SIRS criteria. Many of these patients will have a localized infection such as uncomplicated pneumonia or urinary tract infection and are treated in the conventional manner with generally excellent outcomes. By strict interpretation of the definition of sepsis (ie, sepsis is the host response to infection) all these patients would be classified as septic. Even patients treated as outpatients for infections such as otitis media or uncomplicated influenza would also meet the sepsis criteria. This definition of sepsis is misleading and has created confusion over terminology.

The burden of sepsis in the developed world

Derek Angus  University of Pittsburgh, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

In recent years, a number of large-scale studies have estimated the incidence or prevalence of severe sepsis in many industrialized nations. Most of the studies are focused on patients admitted to an ICU, and most report that 5-15% of ICU patients either have severe sepsis on admission or develop severe sepsis during admission. However, the number of ICU beds per population varies widely across countries, and thus the number of cases per population varies widely. Whether this wide variation represents true differences in severe sepsis or, rather, represents the fact that many countries provide care for severe sepsis at variable rates outside the ICU is unclear.

Severe sepsis is defined as infection complicated by acute organ dysfunction, but many measures of acute organ dysfunction require provision of life support (eg, acute respiratory failure is often defined as requirement for mechanical ventilation). Thus, the number of ventilators and number of staffed ICU beds will affect the number of cases that meet severe sepsis criteria. This interaction highlights both methodologic challenges when measuring the epidemiology of severe sepsis and potential public health challenges. Specifically, one wonders about the fate of patients who develop severe infections in countries with limited access to ICU beds.

In my talk, I will discuss these findings and their implications. With these caveats in mind, I will also review the use of healthcare resources for severe sepsis and patient outcome.

The burden of sepsis in China

Xiu-Ming Xi  President, Chinese Society of Critical Care Medicine, China

Sepsis remains a highly prevalent syndrome throughout the world. Most studies have reported an occurrence rate of severe sepsis ranging between 6% and 14% in the western countries and 8.68% in China among critical care admissions. With the aging of the population, the incidence of severe sepsis is predicted to increase.
Mammals are armed with innate and adaptive immune systems. The innate immune system provides rapid (ie, within hours) defense against invading microbes. Cells of the innate immune system recognize microbial structures called pathogen-associated molecular patterns (PAMPs) via pattern-recognition receptors, among which Toll-like receptors (TLRs) occupy a prominent role. Examples of PAMPs include lipopolysaccharides (LPS; expressed by all Gram-negative bacteria), lipopeptides (constituents of many pathogens), lipoteichoic acid (a cell wall component of Gram-positive bacteria), and flagellin (factor in the mobility of bacteria). The interaction between PAMPs and TLRs triggers the innate immune response and secretion of inflammatory cytokines that more efficiently prime T cells and help to guide the subsequent adaptive response.

The adaptive immune response provides the host with the ability to recognize and remember specific pathogens (to generate immunity) and to mount stronger attacks each time the pathogen is encountered. Lymphocytes (T and B cells) are the cells classically involved in adaptive immune responses. Activated adaptive immune cells can activate innate immune responses during infection, for example by the release of type 1 cytokines by T cells (which activate macrophages) and the secretion of antibodies by B cells (that activate complement proteins and immune cells). The host needs to respond to infection with a balanced immune response, on the one hand sufficient to eradicate invading pathogens, while on the other hand not causing damage to surrounding tissues. Excessive activation of immune cells, such as occurs during overwhelming sepsis, can lead to tissue injury, organ failure, and even death. The host utilizes various mechanisms to maintain the delicate balance between allowing the immune response to target the pathogen and preventing widespread over-activation leading to injury. Recent evidence indicates that T lymphocytes (that according to the current dogma normally take days to become activated) can regulate innate cells in the very early phase of infection. This lecture will discuss current insight in the interaction between cells classically involved in innate and adaptive immunity in the very early phase of severe infection.

Emerging infections, antibiotic resistance, and pandemics – should we be afraid?

Thierry Calandra
Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Abstract not available

Host recognition – The innate and adaptive immune response

Tom van der Poll
Division of Infectious Diseases & The Center of Experimental and Molecular Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

Severe sepsis continues to be a major and increasing health care burden worldwide. Despite aggressive organ support and optimal microbial therapy, sepsis remains the most common cause of death in ICUs with an overall mortality rate of 25-40%. The relative failure of conventional therapeutic strategies has stimulated...
a major interest in the development of new research axes, such as identification of genetic factors that influence sepsis susceptibility, therapeutic response, or outcome. Genetically-determined differences in host immune responses against pathogens might explain why some people get sick and die when they encounter a pathogen, whereas others stay perfectly healthy. Explosion of knowledge both in human genomics and in host inflammatory response explains the increasing interest in immunogenetics over the last 15 years. Indeed, twin and adoptee studies have suggested more than 20 years ago that host genetic factors are major determinants of susceptibility to infectious diseases in humans. Recently, candidate gene studies and human genome wide analysis have been used to identify infectious diseases susceptibility and resistance genes. Rarely, a single gene defect has been directly related to devastating consequences such as interferon-gamma receptor mutations leading to fatal infections with ubiquitous mycobacteria. For clinical practice, gene polymorphisms of specific immunological or physiological mediators appear to be of major importance. These genetic variants, which modify the regulation or function of either pathogen recognition receptors or inflammatory mediators, have been associated with susceptibility and/or outcome of severe sepsis and septic shock. All steps of the host response to bacteria clearance have been shown to be potentially affected by genetic factors. However, genetic studies in sepsis have produced contradictory results related in part to methodological faults. Improved adherence to published guidelines of good study design will help to ensure that genetic epidemiology contributes to a better classification of the heterogeneous septic population. The impact of these findings on the understanding of infectious disease pathogenesis and on the design of future preventive and therapeutic strategies should also be considerable.

**Fever control – does controlling temperature increase mortality?**

Moritoki Egi  
Department of Anesthesiology and Resuscitology, Okayama University Hospital, Okayama, Japan

A fever is common in critically ill patients. It is usually a physiological expression of the host’s response to an infective or inflammatory pathology, and is accompanied by changes in metabolic and immune function. There is no clear recommendation for antipyretic treatments in febrile non-neurological intensive care patients. Since many ICU patients are febrile, it is desirable to understand the possible benefit and harm of fever for non-neurologically critically ill patients.

We conducted a prospective observational study to assess the association of fever and antipyretic with mortality in 1,425 non-neurologically critically ill patients in 25 ICUs in Korea and Japan. Using multivariate logistic analysis, we found a significant relationship between BT_{Max} and 28-day mortality (odds ratio 1.69; p = 0.05). This result was accounted for by patients with BT_{Max} >39.5°C. Antipyretic treatments were administered in 749 patients (52.5%). For the 672 patients (47.1%) who received physical cooling, it was initiated at median 38.1°C (IQR 37.8°C–38.5°C). Antipyretic drug administration was started for 290 patients (20.3%) at median 38.6°C (IQR 38.2°C–39.0°C). We also found that administration of antipyretic drugs was independently associated with increased 28-day mortality.

We plan to conduct a phase II RCT to compare the effects of 2 temperature targets on outcomes in non-neurologically-injured critically ill patients with a temperature of ≥ 38.0°C. The null hypothesis is that there is no difference in ICU-free survival at day 28 in those patients assigned a temperature target of < 38°C and those assigned a temperature target of < 39.6°C. The proposed study is a multicenter, unblinded, phase 2b randomized controlled trial. Critically ill patients with a core temperature ≥ 38.0°C will be randomized to permissive temperature management or to the intensive temperature management arm. The primary endpoint will be the number of days of intensive carefree survival measured at 28 days. Secondary endpoints will include temperature indices, potential complications of a permissive strategy, analgæsic and sedative requirements, need for intensive care support, and recruitment and protocol violation rates.

The proposed sample size is based on an absolute increase of 3.08 days on the number of days of ICU-free survival calculated at day 28, from a baseline of 15.4 ± 9.6 ICU-free days (calculated using information of 989 patients with medical admission or emergency surgery admission in FACE). A total of 310 patients will give this study an 80% power to detect a 20% relative increase in the number of days of ICU-free survival to day 28 at an alpha of 0.05 (increase to 18.4 days). For the FACE II trial, patients will be recruited from 8-10 ICUs throughout Korea, Japan, and other countries. Potential participants will be identified by ICU clinicians.

**The surviving sepsis bundles – a pragmatic approach to treatment and performance improvement**

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The Surviving Sepsis Campaign Guidelines for the Management of Severe Sepsis and Septic Shock were first published in 2004 with a revision in 2008. The second revision is scheduled to be published in 2012 with 26 sponsoring organizations. Guidelines are a useful compilation of knowledge and provide organized thought around treatment. However, guidelines themselves do not produce much change in patient care at the bedside. What is needed to change healthcare provider behavior are protocols, performance improvement programs, and especially audit and feedback.

The Sepsis Bundles were created from the guidelines and include indicators of quality, which can be scored as having been achieved or not achieved with chart review. The severe sepsis resuscitation bundle (Fig 1.) is to be completed within 6 hours of identifying severe sepsis and includes measuring serum lactate, obtaining blood cultures, administering broad spectrum antibiotics, giving fluid bolus for hypotension or evidence of tissue hyperperfusion, and initiation of early goal-directed therapy in the appropriate patient population. Patients are identified for database entry based on presence of infection, evidence of systemic manifestations of infection, and an infection-induced organ dysfunction. In 2010 the Surviving Sepsis Campaign published the results of a global performance evaluation program.
improvement initiative using the sepsis bundles and demonstrated an improvement in compliance with the bundles that was associated with a reduction in mortality from 37% to 30.8%.

Key items in a performance improvement program include identifying a properly motivated team and educating that team and the other healthcare providers, followed by mechanisms for patient identification, data collection, and feedback. The role of the nurse is important in patient identification. Utilization of a protocol that is tied to the sepsis bundles is needed. “Time zero” is used to score the time-limited indicators. Reasons for failure of a sepsis performance improvement program include undersupplied resources, mediocre education, overly-complex algorithms and protocols, and barriers between hospital administration and clinicians. Clinical buy-in from healthcare providers may be challenging.

Figure 1. Severe Sepsis Resuscitation Bundle

Complete tasks within 6 hours of identifying severe sepsis

1. Measure serum lactate
2. Obtain blood cultures prior to antibiotic administration
3. Administer broad spectrum antibiotic within 3 hours of ED admission and within 1 hour of non-ED admission
4. In the event of hypotension and/or serum lactate >4 mmol/L:
   a. Deliver an initial minimum of 20mL/kg of crystalloid or equivalent
   b. Begin vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP > 65 mm Hg
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/L:
   a. Achieve a central venous pressure (CVP) of >8 mm/Hg
   b. Achieve a central venous oxygen saturation (ScvO₂) >70%, or mixed venous oxygen saturation (SmvO₂) >65%

Early Goal Directed Therapy

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More than 10 years ago, Rivers et al published a highly interesting single center study suggesting that an algorithm to protocolize resuscitation, with decisions guided by central venous pressure and oxygen saturation, could significantly improve mortality from septic shock. The algorithm, dubbed Early Goal Directed Therapy (EGDT), drove decisions for the first 6 hours of care, initiated in the Emergency Department. EGDT included a number of traditional steps relating to use of fluids and vasopressors. In addition, it also involved use of a proprietary central venous catheter, which allowed continuous measurement of central venous oxygen saturation, and the oxygenation parameters drove instructions for blood transfusion and use of inotropes, steps that are a little less traditional for septic shock.

In the wake of the trial, many centers around the world have attempted to adopt EGDT, often reporting success in before-and-after study designs. However, there were no confirmatory randomized trials and a number of logistic and conceptual issues have been raised. I will discuss the Rivers trial, the rationale for EGDT, and the case for whether further study is necessary.

Choice of vasopressor and fluids

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Fluids and vasopressors are the mainstay for hemodynamic stabilization and the achievement of an adequate cellular oxygen supply in patients with septic shock. Vasopressors should be used only after an adequate volume challenge did not result in a mean arterial pressure of at least 65 mm Hg. On the basis of currently available data, a clear-cut recommendation cannot be made for the use of a specific vasopressor agent. Recent guideline recommendations suggest norepinephrine or epinephrine rather than dopamine or vasopressin as a first choice vasopressor. In life-threatening hypotension, short-term vasopressor therapy may also be required in the case where the potentials of volume therapy have not yet been completely exhausted. There are indications that epinephrine exerts negative effects on gastrointestinal perfusion. However, a randomized, multicenter trial involving 330 patients revealed no differences with respect to the 28-day mortality between a combination therapy with dobutamine/epinephrine and epinephrine. A combination of epinephrine and dobutamine is not recommended.

The routine use of vasopressin is not recommended. Vasopressin may lead to a significant reduction in cardiac output and a redistribution of regional blood flow. With dosages of > 0.04 U/min, myocardial ischemia, a drop in cardiac output, cardiac arrest, and ischemic skin lesions were reported. According to the results of the VASST trial, vasopressin was beneficial in patients with a low noradrenaline delivery dose (< 15 µg per minute).

Fluids: Use of starches in comparison to crystalloids and to 3% gelatins in severe sepsis patients has resulted in an increased incidence of renal failure and cannot be recommended. This is also true for 6% HES 130/0.4 for which there are also data on increased
The use of steroids in septic shock patients has been controversial for decades. High dose corticosteroids were standard therapy in the 1970’s and 1980’s. During the late 1980’s and 1990’s, however, the consensus was that corticosteroids should not be used in sepsis/septic shock after studies did not show an improved survival for patients treated with steroids. Studies in the late 1990’s and early 2000’s demonstrated hemodynamic benefits with lower doses of steroids for longer periods of time.

Ammann et al. evaluated low dose hydrocortisone in patients with severe septic shock in a multicenter, randomized, placebo-controlled, double-blind study. Randomization of patients occurred within 8 hours of shock and patients received intravenous hydrocortisone (50 mg) every 6 hours plus enteral fludrocortisone for 7 days. Response to a 250μg corticotropin stimulation test defined whether patients were “non-responders” or “responders.” 299 patients were analyzed and the lungs were the primary source of infection. Shock reversal was more common (57%) in steroid-treated patients than patients receiving placebo (40%) and more rapid. 28-day mortality was decreased by steroid therapy in all patients (61% versus 55%) and the non-responders (63% versus 53%). Based principally on the Ammann study, the Surviving Sepsis Campaign recommended the use of low dose hydrocortisone for septic shock and steroid use for patients in septic shock once again became common.

Hydrocortisone use and corticotropin testing in septic shock patients was evaluated in a subsequent multicenter, randomized, placebo-controlled, double-blind study – Cortics®. Patients were septic and in shock for up to 72 hours. A total of 499 patients were analyzed and the gastrointestinal tract was the primary source of infection. At enrollment, 99% of patients received vaspressors and study drug usually commenced within 12 hours. There were no differences in 28-day mortality for patients receiving hydrocortisone or placebo respectively in nonresponders (35% vs. 36%), responders (29% versus 29%) or all patients (34% versus 32%). In patients reversing shock, shock reversal was faster in patients receiving hydrocortisone rather than placebo in all three groups. Hydrocortisone did not increase the percentage of patients with shock reversal. Hydrocortisone-treated patients had more episodes of superinfection, new sepsis, and septic shock.

Despite these 2 recent, large, well-performed studies, steroid use in septic shock patients remains controversial. The updated Surviving Sepsis Campaign has given the recommendation, “We suggest intravenous hydrocortisone be given only to adult septic shock patients after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy” and that steroid therapy should not be guided by corticotropin test results.

References:
Hyperglycemia in critically ill patients: Hyperglycemia is a common finding in patients who are acutely ill even in the absence of a prior diagnosis of diabetes mellitus. In acutely ill patients, hyperglycemia is associated with a worse outcome. For example, patients suffering an acute myocardial infarction who have a blood glucose concentration above 8 mmol/L have a 3-fold increase in mortality and a greater risk of developing cardiac failure.

As hyperglycemia is consistently associated with increased morbidity and mortality, critical care researchers have conducted a number of trials to investigate whether tighter control of blood glucose in critically ill patients is beneficial. In 2001 Van den Berghe and colleagues reported a randomized controlled trial of 1548 patients admitted to a surgical ICU and found a significant reduction in hospital mortality in patients in whom a blood glucose concentration target of 4.4 - 6.1 mmol/L was compared to a blood glucose target of 10.0 – 11.1 mmol/L. The reported absolute risk reduction was 3.7%; the relative risk of death with tight blood glucose control was 0.66 (95%CI 0.48-0.92, P=0.04). The mechanism proposed for the reduction in mortality was largely through a reduction in deaths due to multiple organ failure and sepsis. In 2006 Van Den Berghe and colleagues reported a second trial, which recruited 1200 patients admitted to a medical intensive care unit. Overall, this trial did not report a significant reduction in 90-day mortality (tight glucose control 35.9% versus 37.7% for conventional control, P=0.53). The widespread interest in Van Den Berghe’s results has led other investigators to conduct trials of tight glucose control almost all of which have failed to confirm Van Den Berghe’s findings.

To date there have been more than 30 randomized controlled trials of glucose control in critical care settings and most studies have reported non-significant results. In part this is because many of the trials have been too small and when considered alone had insufficient statistical power to examine the effects of tight glucose control on mortality. In 2008, a meta-analyses of trials involving a total of 8315 critically ill patients from 25 studies found that tight glucose control (defined in the meta-analysis as maintaining a blood glucose target of <8.3 mmol/L) did not significantly affect the overall risk of in-hospital death (RR=0.93, 95%CI 0.95-1.03), although tight glucose control was associated with a reduction in the risk of septicemia (RR=0.76, 95%CI 0.59-0.97) and an increased risk of hypoglycemia, RR=5.13 (95%CI 4.09-6.43)1. When the trials of tight glucose control with a target blood glucose of ≤6.1mmol/L were considered alone, the meta-analysis still reported a non-significant reduction in the relative risk of in-hospital mortality (RR 0.90, 95%CI 0.77-1.04).

In March 2009, the largest trial of tight glycemic control in critically ill patients to date reported its findings. The NICE-SUGAR study was a 6104-patient international multicenter trial, which examined the effect of targeting normoglycemia (blood glucose 4.5 - 6.0 mmol/L) compared to conventional glucose control (blood glucose ≤10.0mmol/L) on 90-day mortality in critically ill adults. The study found increased mortality in patients treated with tight glucose control; absolute increase in 90-day mortality of 2.6% (RR=1.10, 95%CI 1.01-1.20, P=0.02). An updated meta-analysis including the NICE-SUGAR data and studies with tight and moderately tight glycemic control demonstrates significant heterogeneity between studies but no overall effect of tight glycemic control on mortality (RR 0.93, 95%CI 0.83, 1.04).

Trials have also reported inconsistent effects of tight glucose control on other important outcomes such as the incidence of septicemia, renal failure, and the length of ICU and hospital stay. Furthermore, whether tight glucose control affects cause-specific mortality, which individual trials have inadequate statistical power to examine, is unknown.

Possible explanations for the discrepancies in the evidence: There are a number of potential reasons why the studies that have been performed to date have reported discrepant findings. Some trials were multicenter and included a heterogroup of ICU patients, while others had only surgical or medical patients and were conducted in single hospitals, or included only patients with a particular diagnosis such as sepsis. Different effects in different patient groups are possible but unlikely to prove the predominant reason for differing results. In Van Den Berghe’s trials, most calories administered to patients were given as intravenous glucose or parenteral nutrition and the control group did not receive insulin until the blood glucose exceeded 12mmol/L. Both of these are in marked contrast to the treatment of patients included in the NICE-SUGAR Study in whom more than 70% of calories were delivered by the enteral route and patients in the control group receive insulin as soon as the blood glucose concentration exceeded 10mmol/L. Recently the same investigators have reported a trial comparing outcomes using the nutrition strategy of their trials (early parenteral nutrition supplemented with enteral nutrition as possible) versus enteral nutrition with no supplementary parenteral nutrition for the first 7 days2. Although there was no difference in landmark mortality between the 2 groups, the patients with late initiation of parenteral nutrition increased the likelihood of being discharged alive early from the ICU, had fewer ICU infections, fewer were treated with mechanical ventilation for more than 2 days, and both the median duration of renal replacement therapy and healthcare costs were reduced4.

The VISEP study specifically examined the effect of an intensive glucose control in patients with severe sepsis5; the investigators found no evidence of benefit from intensive glucose control. The NICE SUGAR study enrolled 1299 patients who had severe sepsis at baseline and these patients constitute an a priori subgroup in the trial6; the treatment effect observed in patients with severe sepsis was the same as in those without severe sepsis, namely an increase in mortality in patients assigned to receive intensive glucose control.

Conclusions: The reasons for differing results in trials of intensive insulin therapy or intensive glucose control remain to be fully elucidated. Ultimately the ideal target range for blood glucose and the optimum method to achieve that target range can only be determined through additional large-scale trials. To do this safely we must define quality standards for intensive glucose control, find affordable methods of frequent and highly accurate blood glucose measurement in the ICU, and then conduct multicenter “efficacy” studies to determine if intensive glucose control can reduce mortality under optimum trial conditions; only then should we consider further large scale “effectiveness” trials. These conclusions apply to patients in general admitted to intensive care units and this includes patients with severe sepsis.

References:
Which antibiotics and for how long?

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Treatment of patients with sepsis necessitates a multifaceted approach combining the use of optimal diagnostic tools, prompt initiation of appropriate antimicrobial therapy, and adequate supportive care. Numerous studies performed since the 1960’s have shown that early, appropriate antimicrobial therapy reduced the mortality of patients with bacterial sepsis. Whenever indicated, drainage of abscesses and removal of infected necrotic tissues or prosthetic material also are essential for recovery. Recommendations for antibiotic therapy in patients with severe sepsis and septic shock have been based largely on the results of multicenter studies performed in neutropenic cancer patients treated with extended-spectrum penicillins, third- or fourth-generation cephalosporins, or carbapenem antibiotics. However, critically ill patients with sepsis differ considerably from febrile neutropenic cancer patients. Indeed, capillary leak syndrome and multi-organ dysfunctions are encountered more often in patients with severe sepsis and septic shock and are likely to affect pharmacokinetics and pharmacodynamics parameters and may affect the efficacy and toxicity of antibiotics.

For many years combination therapy with a beta-lactam and an aminoglycoside was considered standard therapy for patients with Gram-negative bacteremia, severe sepsis, or septic shock. However, monotherapy with carbapenems, third-generation and fourth-generation cephalosporins, or extended-spectrum penicillins has been shown to be as efficacious as and less toxic than aminoglycoside-containing antibiotic combinations. This was confirmed by 2 meta-analyses that did not reveal a benefit of combination therapy in immunocompetent hosts presenting with Gram-negative bloodstream infections, severe sepsis, or septic shock. Moreover, the results of a meta-analysis suggested that superinfections or the emergence of resistant bacteria were also not more frequent in patients treated with single antibiotics than in those on combination therapy. Yet, these results should be interpreted with some caution for several reasons. Firstly, very few studies have used the same beta-lactam antibiotic in both treatment arms, which affects the interpretation of the intrinsic effect of the second agent of the combined therapy. Secondly, many studies conducted in critically ill patients with severe sepsis or septic shock have included fewer than 200 patients, which limits the statistical power of these studies. Recently, 3 retrospective studies, 1 of which was a meta-analytic/meta-regression study, appeared to support the superiority of combination therapy in sepsis, Gram-negative sepsis, or septic shock. Combination therapy improved the appropriateness of initial antimicrobial therapy and survival, especially in patients with a risk of death >25%, but was detrimental when the risk of death was <15%. However, given their retrospective nature, these studies are not devoid of important limitations and prospective clinical trials are needed to try to resolve the ongoing controversy about the pro’s and con’s of monotherapy versus combination therapy.

While waiting the results of such studies, combination therapy may still be preferred as empirical treatment of Gram-negative sepsis in centers with a high incidence of multi-resistant Gram-negative bacilli. Whatever the choice of initial empirical antibiotics, it is of paramount importance to reassess the appropriateness of antibiotic therapy within 24-48 hours, at a time when bacteriological data become available and the initial clinical response can be evaluated. De-escalation therapy should be strongly encouraged with the goal to use the least expensive antibiotic with the narrowest possible spectrum of activity in order to lessen the “ecological” pressure and minimize the risk of selecting resistant organisms. Monitoring of antibiotic blood levels is also an integral part of the management of the severely ill septic patient as both under- and overdosing are well-recognized causes of treatment failure or toxicity. Finally, few studies have addressed the issue of the optimal duration of antibiotic therapy. The 2008 international guidelines of the Surviving Sepsis Campaign suggest a duration of 3 to 5 days for combination therapy and of 7 to 10 days in total recognizing that a longer therapy may be required depending on the type and site of infection and the underlying conditions.

References:
6. Galeski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Critical Care Medicine 2010;38:1045-53.
How do I ventilate a patient with severe sepsis?

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Ventilation is an essential function of life and one of the first to be replaced by artificial means in the ICU patient. Mechanical ventilation is the second most common therapeutic intervention in the intensive care unit after treatment of cardiac arrhythmias. Mechanical ventilation with an endotracheal tube is associated with an increased risk of pneumonia, impaired cardiac performance, and lung injury. Mechanical ventilation may induce lung injury referred to as ventilator induced lung injury (VILI). VILI resembles acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). It occurs due to mechanical stress from over inflation (likely with any increase in plateau pressure, but a commonly used threshold is >30 cm H2O), not utilizing minimal PEEP to prevent collapse of lung at end expiration and with tidal hyperinflation. VILI is associated with release of inflammatory mediators. The current recommendation is to use a lung protection strategy in patients with ALI and ARDS with an initial tidal volume of 8 ml/kg which is then decreased to 6 ml/kg over 1-2 hours and even lower if necessary (down to 4 ml/kg PVD) to achieve a Pplat of 30 cm H2O. Most pulmonary cells express a large repertoire of genes under transcriptional control that are modulated by biomechanical forces and bacterial infections. It should be noted that obese patients, edematous patients, and patients with increased intra-abdominal pressure can be allowed to have higher Pplat based on the magnitude of these findings. It is difficult to identify precisely what this allowance should be.

Ventilator associated pneumonia (VAP) is a frequent complication during mechanical ventilation of severe sepsis patients and is an important cause of morbidity and mortality. Bedside care practices such as elevation of head and bed as well as anti-bacterial mouth care can decrease the incidence of VAP. Mechanical ventilation may be responsible for the translocation of bacteria related toxin into the blood stream and contribute to multiple organ dysfunction syndrome (MODS).

Morbidly obese patients are at less risk for surgical wound infection with an end tidal CO2 of 50 mm Hg versus 40 mm Hg. This is thought to be due to the beneficial effects of CO2 on increasing cardiac output and causing peripheral vasodilation. Hypercapnic acidosis attenuates the inflammatory response and may worsen acute lung injury. Hypercapnia should be avoided in patients with elevated intracranial pressure.

Which biomarkers do I use?

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More than 100 distinct molecules have been proposed to be potentially useful biologic markers of sepsis and so to aid in improved stratification of patients for research and clinical decision-making1. At the bedside a sepsis marker is only useful if it adds value to the physician’s clinical judgment. Ideally, an infection/sepsis marker should meet the following demands: to shorten the time to and improve the diagnosis; to facilitate the differentiation between infectious and non-infectious causes of inflammation and its sequelae, organ dysfunction or shock; to allow the differentiation between viral and bacterial infections; and to represent the effectiveness of antimicrobial treatment and other measures of source control more accurately than conventional clinical and laboratory signs. The sepsis markers that have been investigated most in respect to their potential clinical utility are CRP, IL 6, IL 8, LBP, and procalcitonin (PCT).

A number of studies indicate that sensitivity and specificity of PCT for sepsis is better than that of CRP, IL6, IL8, and conventional parameters like leucocyte count and body temperature. The use of biomarkers might help to avoid antibiotic misuse and overuse and to curb the rising incidence of microbial resistance2. Among >100 biomarkers proposed for use as infection/sepsis markers, procalcitonin is the most frequently evaluated. It has been tested in 11 randomized controlled trials with more than 3500 patients and resulted in a considerable, 35–70%, reduction in antibiotic use without an apparent negative impact on patient outcome. Testing was carried out in hospital, intensive care unit, emergency, and primary care settings; most of the patients had lower respiratory tract infections, and only smaller studies exist in surgical patients with infectious complications, immunocompromis ed patients, and patients with sepsis. There are, however, concerns since trials designed to show non-inferiority of procalcitonin to standard management allowed rather large differences for mortality rates, in the range of 7.5–10%, thus clinically relevant excess mortality by procalcitonin-guided antibiotic therapy cannot be completely ruled out.

Procalcitonin was also shown to be helpful to differentiate infectious from non-infectious causes of systemic inflammation. Although in this respect it performs better than conventional markers of infection such as CRP, there are a number of non-infectious causes that may result in elevated procalcitonin levels. This is very common after major trauma and was observed in patients treated with anti-T-cell antibodies, alemtuzumab, interleukin 2, or granulocyte transfusions, and patients with acute graft-versus-host disease or liver metastasis.

Marker panels derived from transcriptomic or proteomic profiling hold promise in overcoming the limitations of procalcitonin for differentiating non-infectious from infection-associated inflammation. However, the utility of these novel diagnostic tools in the clinical setting remains to be proven. For the time being, procalcitonin is the best-evaluated and most useful sepsis marker. Currently, large clinical trials are ongoing to further assess its clinical utility and cost effectiveness in severe sepsis and other groups of ICU patients.

References:
The elderly population is increasing around the world. By 2030, 25% of Western Europeans will be at least 65 years of age. By 2050, the overall population will increase 50%, whereas the population over age 65 will increase by more than 120%. ICU use increases with age and currently approximately half of ICU days are required for elderly patients.

Sepsis in children

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Learning Objectives

Sepsis is the most common cause of death in infants and children worldwide. The learning objectives for this session include:

2. An overview of the epidemiology of sepsis in children including infecting organisms and host susceptibility factors. A comparison will be made between sepsis in adults, adolescents, children, infants and neonates.
3. The Surviving Sepsis Guidelines as they relate to infants and children will be discussed updated with evidence from recently published studies. Fluid management, use of steroids, ECMO and other treatment interventions as they relate specifically to pediatric populations will be addressed.
4. Secondary or nosocomial sepsis in critically ill children leads to additional morbidity and mortality and is often preventable. I will review evidence-based recommendations for the prevention of hospital acquired infections including central venous catheter related infections, urinary tract infections, ventilator associated pneumonia, enterocolitis caused by Clostridium difficile, and nosocomial viral infections.

At the conclusion of this session, participants will have a stronger grasp of how to diagnose, treat and prevent sepsis in infants, children and adolescents.

Sepsis in the elderly ICU patient

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The elderly population is increasing around the world. By 2030, 25% of Western Europeans will be at least 65 years of age. By 2050, the overall population will increase 50%, whereas the population over age 65 will increase by more than 120%. ICU use increases with age and currently approximately half of ICU days are required for elderly patients.

Hemodynamic monitoring forms an important part of patient management in the intensive care unit, but patients require different types and degrees of monitoring depending on their diagnosis and severity of disease. Importantly, monitoring is of little value if the data it gathers cannot help in diagnosis or be influenced by therapies that will improve patient status. The choice of monitoring technique will, therefore, be determined by the parameters one is interested in for the patient in question. Generally, and wherever possible, we are tending toward less invasive monitoring techniques; but in certain complex patients, the advantages offered by invasive monitoring, for example, the simultaneous measurement of multiple variables including mixed venous oxygen saturation (SvO2), can still be of benefit. In the patient with severe sepsis, arterial pressure, cardiac output, cardiac filling pressures (central venous pressure) and some surrogate of tissue oxygenation, eg, blood lactate levels, SvO2 (or ScvO2), would be a minimum requirement.

Having decided which monitoring technique to use and what to monitor, we then need to decide what targets to fix for the parameters being monitored. The key goal of treatment of the patient with severe sepsis or septic shock is to restore adequate tissue perfusion. Which targets need to be set to achieve that goal are difficult to define without a specific, direct means of monitoring tissue perfusion. Clinically, our targets for all patients should be: Well perfused skin, maintained or restored urine output, and adequate mentation, ie, no confusion. However, for hemodynamic variables, there is no one-size-fits-all level for any measure and targets must be adapted according to the individual patient. For example, a mean arterial pressure of 65 mm Hg may be acceptable in most patients but in some patients with a history of hypertension, a higher MAP, nearer 80 mm Hg, may be more appropriate. Likewise for central venous pressure, the Surviving Sepsis Campaign guidelines suggested a range (8-12 mm Hg), but this is just a guide.

Cardiac output values are particularly difficult to interpret and optimal levels will vary according to circumstances, much like the speed of a car must vary according to where the car is being driven and for what purpose. SvO2 can be useful when measured, but again there is no optimal value that fits everyone; ScvO2 is just an approximation of SvO2 and carries its own limitations. For evaluations over longer periods of time (to see if we are heading in the right direction), repeated lactate measurements provide a useful indicator of ongoing patient status and response to therapy (optimally we should see a 20% decrease over a 2-hour period). In summary then, what I monitor and what I target will vary in each patient. In most patients, several variables need to be monitored and the values obtained integrated to provide a full picture of that patient’s ongoing status and response to therapy—no simple protocol will be applicable to everybody.
used by patients more than 65 years. The problem will only become more severe in the future as the elderly will use more ICU resources.

Sepsis is a disease of the elderly. US hospitals noted a mean age of 64 years of severe sepsis patients, with severe sepsis increasing with age [3]. In Europe, ICU patients with severe sepsis had a median age of 65 years [3]. In the Angus study [4], the incidence of sepsis was high in infants (5.5/1,000 aged 0–1 years), lower in older children (0.2/1,000 aged 5–14 years), rose slowly during adulthood (5.3/1,000 aged 60–64 years), and increased dramatically in the elderly (26.2/1,000 aged > 65 years) [5]. Excluding HIV patients, the incidence rate of sepsis for women was similar to that of men [5]. The age-specific incidence rate, however, was lower in women than in men; and from 30 years on, women had a rate similar to that of men 5 years younger [6]. In the Martin study [6], the incidence of sepsis increased across all age deciles, from 30 cases per 100,000 individuals in the 10–99 age decile to 2,422 cases per 100,000 in the 90–99 age decile. The relative risk for sepsis was 13 times higher for those patients 65 or older [6]. During the 24-year study period of the Martin study [6], patients greater than 65 years accounted for 37% of hospitalizations and 65% of sepsis cases with sepsis occurring in 2.5% of these hospitalizations. These patients contributed disproportionately to the increases in the incidence of sepsis, with incidence rates increasing 20% faster than rates in the younger cohort (mean increase 11.5% versus 9.5% per year, P < 0.001) [6]. Sepsis developed later in life in female patients than in male patients; the mean age among women was 62 years, as compared with 57 years among men [7]. Most important, however, is the fact that the average age of septic patients is increasing over time [3]. In the US, the average age of patients with sepsis increased consistently over time from 57 years in 1979 to 1984 to 60 years in 1995 to 2007. In another study, the mean age increased over time from 64 to 68 years (P < 0.001) [8].

In the Martin study [6], of the patients with cultured microorganisms, 51% of infections were from Gram-positive bacteria, 43% from Gram-negative bacteria, 2% anaerobes, and 4% fungi. Patients more than 65 years were 1.3 times more likely to have Gram-negative infections and patients less than 65 years were 1.2 times more likely to have Gram-positive infections and 1.8 times more likely to have fungal infections. Respiratory infections caused the most sepsis (34%); gastroenteritis infections 12.4%; skin, soft tissue, and bone 5.5%; and other sources 23% [5]. Patients more than 65 years had a greater risk for respiratory infections and gastroenteritis infections as the causes of sepsis and gastrointestinal infections were less common compared to younger patients [6]. Pneumonia appears to be more common in the elderly population and pneumonia more frequently leads to a septic physiologic response [7].

In the Angus study [4], the overall hospital mortality rate was 28.6%. Mortality increased with age from 10% in children to 38% in patients greater than 85 years [4]. This trend was most pronounced in patients without underlying comorbidities. Mortality was higher and changed very little throughout most of adult life for patients who did have underlying comorbidities [4]. Although the likelihood of developing sepsis differed for men and women by age, the likelihood of dying from sepsis was the same for men and women after adjusting for age, underlying comorbidities, and site of infection [7].

In the Martin study [6], the case fatality rate for sepsis patients was 24%. Mortality increased linearly across age deciles averaging 28% for patients greater than 65 years and 18% for those less than 65 years (P < 0.001) [6]. A multivariate logistic regression model adjusting for several variables demonstrated that age greater than 65 years was independently associated with a 2.3 times higher risk of death among septic patients [4]. Among sepsis non-survivors, patients greater than 65 years were 26% more likely to die the first week in the hospital [8]. Among septic survivors, the elderly were less likely to return home (54% versus 76%, P < 0.001) and more likely to require non-acute health care facilities after hospital discharge (37% versus 15%, P < 0.001).

The reason that age is strongly associated with both risk and outcome from sepsis is most likely related to several factors [4]. This may be secondary to age-related differences in immune function ranging from failed antigen processing by leukocytes [9] to altered inflammatory cytokine expression [10]. Age-related conditions such as dementia or immobility can certainly add to these risks and outcomes [11]. The fact that age has been shown to be an independent predictor of death in septic patients may also relate to differences in health care access and delivery of health care including limitations [12] and patient and provider preferences [13]. Increasing life expectancy combined with greater rates of sepsis in the elderly population will certainly increase the need for intensive care resources in the future.

In summary, despite the fact that individuals greater than 65 years account for only 1/8 of the US population, they account for 2/3 of all sepsis cases. Increases in the incidence of sepsis are weighted toward the elderly population where incidence rates are rising the fastest [6]. Age is an independent predictor of death in septic patients; elderly patients die earlier during sepsis-related hospitalizations and elderly survivors require more skilled nursing or rehabilitative care after hospitalization [6].

References:

Neutropenic sepsis

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Severe sepsis defined as infection-induced organ dysfunction predispose to septic shock and increased mortality in neutropenic patients. In particular, bacteremia still causes significant mortality among neutropenic patients with cancer. As neutropenia in cancer patients has been associated with higher mortality in several studies, intensivists became reluctant to admit neutropenic patients with septic shock. However, recent studies have reevaluated outcomes of cancer patients with sepsis and focused on neutropenic cancer patients with severe sepsis or septic shock. They demonstrated that survival of septic shock patients with malignancies and neutropenia markedly increased over the recent years. This might be ascribed both to a better selection of patients and to improvements in the care and management of septic shock, including new therapeutic strategies for sepsis. Similarly to non-neutropenic patients, Simplified Acute
Physiology Score II, invasive mechanical ventilation, renal replacement therapy, fungal infections, and unknown microorganism were identified as poor prognostic factors. More specifically, early combination antibiotic therapy including an aminoglycoside, and early indwelling catheter removal seem to be associated with a better outcome.

Furthermore, case volume as appears to be a major prognostic factor in this setting, admission in a high-volume unit being associated with a marked decrease in mortality as compared to low-volume units (adjusted odds ratio 0.63; 95% confidence interval [0.46-0.87], P = .002).

In conclusion, even if mortality rate of neutropenic septic patients is still very high, recent data support a large admission of these patients essentially in specialized ICUs.

H1N1 and other “new” viruses

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Influenza is a major cause of morbidity and mortality; annually, influenza causes over 200,000 hospitalizations and approximately 41,000 deaths in the United States. Influenza viruses can be classified as A, B or C. Influenza A is found in humans, other mammals and birds and is the only influenza virus which is known to have caused pandemics, including the three 20th century pandemics and the recent H1N1 influenza pandemic. Although most of influenza A related mortality can be attributed to secondary bacterial pneumonia, the virus itself is also an important cause of community-acquired pneumonia (CAP), causing 5-10% of CAP-cases in various case series. As such, influenza infection is a major concern for pulmonologists and intensive care physicians.

More generally, viral infections of the lower respiratory tract cause an enormous disease burden in various age groups, in particular and older adults. New diagnostic multiplex tests, commonly PCR based, have the potential to detect a wider range of established and newly discovered viruses with greater sensitivity. Important causes of pneumonia are (besides influenza) parainfluenza, respiratory syncytial virus, human metapneumovirus and adenovirus; the role of rhinoviruses and some of the newly described viruses, including human coronaviruses and bocavirus, is not totally clear yet.

The role of the neutrophil

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Learning Objectives

After this session, participants should be able to:

1. To understand the mechanisms through which circulating neutrophils are able to identify and kill invading micro-organisms.

2. To understand how these same mechanisms can cause injury to host tissues.

3. To understand the mechanisms through which neutrophil-mediated inflammation is terminated through the apoptosis or programmed cell death of the neutrophil, and how this process is impaired in sepsis.

Pharmacological modulation of inflammation

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There is consensus among experts that the pathophysiology of sepsis is driven by dysregulated inflammation. It is apparent, however, that mediators of the inflammatory response should not be viewed in a narrowly dichotomous way as being purely “pro-inflammatory” or “anti-inflammatory.” Similarly, it is largely impossible to view pharmacological agents, which modulate the inflammatory response, as being simply “pro-inflammatory” or “anti-inflammatory.”

Notwithstanding the common use of many agents, such as corticosteroids, beta-adrenergic agonists, insulin, and statins, which have some immunomodulating actions, in the clinical practice of critical care medicine, the intentional manipulation of inflammatory or immune responses in the management of patients with severe sepsis or related conditions, such as acute respiratory distress syndrome (ARDS), is in its infancy.

The relative absence of purposeful pharmacological modification of immune responses in critical care medicine is striking, since immune-modulating agents are widely employed in other fields of medicine for the management of a variety of chronic conditions, such as rheumatoid arthritis and inflammatory bowel disease. The failure to
incorporate immune-modulating agents into the practice of critical care medicine is not due to lack of interest in this concept. Rather, despite promising pre-clinical data in many instances, disappointing results have been obtained when immunomodulating pharmacological approaches have been evaluated for the treatment of sepsis or ARDS in prospective clinical trials. Numerous reasons might account for the difficulty, which is associated with translating positive pre-clinical results into the development of new practical immunomodulating strategies for use in the management of sepsis or ARDS.

Among these reasons, however, 2 stand out as being most important. First, in contrast to many chronic diseases, the immunological derangements in sepsis are quite dynamic and evolve rapidly over the span of minutes to days, leading to myriad clinical phenotypes. Thus, it is unlikely that any single agent will be appropriate for all of the various phenotypic manifestations of sepsis. Indeed, the same agent might be beneficial for some patients but deleterious for others. Second, most currently available animal models of human sepsis, including those using mice, rats, and non-human primates, may be inappropriate due to key differences among species in immunological responses to lipopolysaccharide and other pathogen-associated molecular pattern (PAMP) molecules. Thus, therapeutic efficacy, which is demonstrated in pre-clinical studies, using animal models, may fail to predict the results of a clinical trial, which enrolls human subjects.

Activated protein C – a critical look

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Activated protein C (drotrecogin alfa [activated], DAA) was the first immunomodulatory agent to be shown in a randomized controlled trial to significantly reduce mortality in patients with severe sepsis. After that pivotal PROWESS trial, DAA was licensed by many regulatory authorities, including the FDA and EMEA, for use in severely ill patients with severe sepsis. Although initially developed for its effects on the coagulation system, further scientific study has revealed that it has many other actions, including protective effects on the endothelium, effects on leukocyte chemotaxis and adhesion, and anti-apoptotic effects. It may also have beneficial effects on the microcirculation. Nevertheless, controversy has surrounded the drug because of potential effects of protocol changes during the PROWESS trial, its high costs, and increased risks of bleeding. Subsequent trials in the pediatric and less severely ill patient populations failed to show benefit, and finally another phase III trial was demanded to clarify the efficacy of this drug in its target population.

This study, PROWESS-SHOCK, which randomized patients with persistent (at least 4 hours) vasopressor-dependent septic shock has recently been completed and the results will be presented at the 32nd ISICEM in Brussels in March 2012. In theory, these results should help resolve some of the controversy behind activated protein C. However, there are ethical and practical problems with the protocol related to the fact that the drug under investigation is actually licensed for use. Patients in whom DAA was clearly indicated could be prescribed the drug, and hence were not available for randomization in the study. The study population would therefore be composed of patients who were anyway less likely to benefit, thus limiting the reliability of the results. To try to reduce this effect, only centers in which the physicians considered that there was equipoise between activated protein C and placebo were enrolled, but it will be interesting to see whether the results of the study can finally put an end to the ongoing controversy that has surrounded activated protein C in the last 10 years since the first PROWESS study.

Extra-corporeal therapies of severe sepsis/septic shock

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Continuous hemofiltration is now a widely accepted treatment modality for acute renal failure. New insights into severe sepsis and septic shock pathogenesis have led to hemofiltration intervention as a potential immunomodulatory therapy for severe sepsis and septic shock. Numerous animal and human studies have investigated the effect of antibiotic therapy targeting at specific infection associated toxins and mediators. Another possible immunotherapy is removal of various inflammatory substances including endotoxin, cytokines, oxygen free radicals, and arachidonic acids by hemofiltration. Removal of so-called middle molecules by hemofiltration is a convective process and when higher volumes of ultrafiltration are used (high volume hemofiltration or HVHF) improvement in hemodynamic status can be demonstrated in animal study animals. Human studies with small numbers of patients have reported improvement in pathophysiology to include cardiac index, venous oxygen saturation, arterial pH, and norepinephrine requirements.

Endotoxemia is well reported in patients with septic shock and, as levels rise, is associated with increasing mortality. Sources of endotoxin include Gram-negative infection and the gut, the latter sometimes described as the motor driving septic shock. Polymyxin B is an avid anti-endotoxin compound and is available as a Polymyxin embedded polysulfonere hemoperfusion cartridge. This device is approved for use in Japan where it has been used almost 90,000 times with a very good safety profile. Meta analysis of the effect of the PMX cartridges in patients with septic shock demonstrates improvement in hemodynamics in patients with initial MAP <70 as well as those >70. This study by Cruz, et al. published in 2006 was a metaanalysis of 12 papers. The EUPHAS study was published in the New England Journal of Medicine in 2010 and was a randomized placebo controlled study (although not blinded) comparing Polymyxin B hemoperfusion and conventional therapy. There were 34 patients in the Polymyxin group and 30 in the conventional therapy population. Populations were similar at baseline. The 30-day mortality was greater in the conventional therapy group with the PMX group showing improvement in MAP, isotropic score and vasopressor dependency index. There was also a significant difference in the SOFA score over time that favored the PMX group (total, cardiovascular, and renal SOFA).

Trials are ongoing in the US using both the hemofiltration approach for severe sepsis (B Braun) as well as hemoperfusion (Polymyxin embedded canister) endotoxin removal in septic shock (Spectral).
The latter EUPHRATES trial is unique in severe sepsis trials to date in that the first step of patient enrollment includes confirming that septic shock patients have high endotoxin acuity with a rapid turnaround measurement (EAA). Only patients with high endotoxin activity are randomized to either conventional therapy or endotoxin removal with the Polymyxin embedded hemoperfusion cartridge.

**SESSION IV Parallel Session IVa**

**Should I use pro- or anti-inflammatory treatment for severe sepsis?**

**Steven Opal** The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

**Learning Objectives**

After this session, participants should be able to:

1. Define the role of pro-inflammatory and anti-inflammatory molecules in the pathogenesis of sepsis as it is currently understood

2. Define the potential roles and possible pitfalls of inhibitors of either the pro- or the anti-inflammatory aspects of sepsis pathophysiology

3. Present a strategy for the rational delivery of immunomodulators in severe sepsis in keeping with the reality of the complexity of sepsis and the problem of non-resolving inflammation in the pathophysiology of septic shock

**SESSION IV Parallel Session IVa**

**Is there a role for hormonal and metabolic manipulation?**

**Mervyn Singer** Intensive Care Medicine, University College London, London, UK

There is a marked effect of critical illness on hormone levels. Apart from the usual suspects, (ie, stress hormones such as adrenaline, cortisol, and vasopressin) circulating levels of many other hormones are affected, including sex hormones (eg, estrogen, testosterone, DHEA), gut hormones (eg, insulin, ghrelin, PYY), growth hormone, and thyroid hormones. In general, these have not been well characterized over time though change is more marked with individual patient severity. With many hormones, there appears to be a temporal relationship with elevated plasma levels in the early phases of critical illness that often fall to subnormal levels as organ failure becomes established. There may be modifications of the hormone itself, with a greater increase in inactive hormone (eg, reverse tri-iodothyronine). Furthermore, receptors for these hormones (and/or downstream processes) are also affected, with resistance to glucocorticoids, catecholamines and insulin being well recognized. Overall body metabolism follows a similar pattern, with an early increase in oxygen consumption, followed by a fall during the established phase, and then a rebound increase during the recovery phase. This relationship is not surprising as hormones are major regulators of metabolism and mitochondrial activity.

Perhaps far from being purely pathological events, these changes may actually represent an adaptive response to critical illness. The consequent decreases in muscular activity, anabolic processes, appetite, and so forth may allow the body to focus its attempts more fully on dealing with the systemic inflammatory response. This may explain why therapeutic attempts to manipulate hormonal levels have ended in failure (eg, corticosteroids), if not outright harm, as demonstrated by randomized controlled trials of growth hormone, thyroxine, and insulin (to achieve tight glycemic control). There are now increasing data to suggest high-dose catecholamine therapy is harmful.

The benefits and risks of direct manipulation of metabolism are also uncertain. This can range from temperature regulation (eg, cooling of pyrexic patients or active therapeutic hypothermia) to induction of “suspended animation” (eg, with hydrogen sulphide).

In conclusion, there are likely to be opportunities to manipulate hormones or metabolic activity but until we have a better understanding of how these change in critical illness, and to have markers that could indicate the correct timing, dosage, and duration for such an intervention, we should not be interfering excessively.

**SESSION IV Parallel Sessions**

**Parallel Session IVb**

**MEET-THE-PROFESSOR**

**How do I feed patients with septic shock**

**Charles Sprung** General Intensive Care Unit, Department of Anesthesiology and Critical Care Medicine, Hadassah Hebrew University Medical Center, Jerusalem, Israel

**Learning Objectives**

After this session, participants should be able to describe:

1. What are the pros and cons of using enteral versus total parenteral nutrition in septic patients

2. What are the latest guidelines for nutrition in septic patients

3. How to feed patients with septic shock
Where do I look when the source is unclear

Gavin Joynt  Hong Kong

Abstract not available

How did I manage patients with SARS

Gavin Joynt  Hong Kong

Abstract not available

Cardiovascular quiz

Jean-Louis Vincent  Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Belgium

Cardiovascular dysfunction is frequent in patients with severe sepsis and septic shock. In this session, we will discover key aspects of this dysfunction, including its effects on cardiac output, SvO2, and blood lactate levels, in a quiz format.

Fungal sepsis

Thierry Calandra  Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Invasive mycoses are life-threatening opportunistic infections and have emerged as a major cause of morbidity and mortality in critically ill patients. Over the last 2 decades, the incidence of fungal sepsis has increased 3-fold in the US. Candida species are the most frequent cause of fungal infections (70-80% of cases) and account for 5-5% of health-care associated infections and for 5-10% of the cases of severe sepsis and septic shock. Candida is the fourth most common cause of bloodstream infections in the US, but is a much less common cause of bloodstream infections in Europe. In a recent survey conducted by the Fungal Infection Network of Switzerland (FUNGtOS) in tertiary care hospitals, ICU s and surgical wards accounted for about 2/3 of all episodes of candidemia. Invasive Candida infections have also become the 3rd most common cause of late onset infection in most neonatal ICUs with an incidence ranging from 7-20% among low birth weight infants with a crude mortality rate of 30-60%. Invasive candidiasis is associated with high overall mortality (25-80%). Invasive Candida infections are therefore a rapidly growing medical challenge with unmet needs. Critically ill and severely immunocompromised patients are at particularly high risk of invasive candidiasis. Loss of integrity of skin and mucosal barriers, surgery, prolonged broad-spectrum antibiotic therapy, colonization with Candida, parenteral nutrition, and treatment with immunosuppressive agents are major risk factors for invasive Candida infections. Infections of the bloodstream, of intravascular devices, of the abdominal cavity, of the urinary tract, and disseminated infections are the most frequent clinical presentations of invasive candidiasis in ICU patients.

Early initiation of appropriate antifungal therapy thus plays a key role for reducing morbidity and mortality associated with invasive candidiasis. Dissemination of infection to multiple organs is an independent prognostic factor of fatal outcome in patients with candidiasis. Despite the high mortality associated with invasive Candida infections, few prophylactic or pre-emptive studies have been performed in either surgical or ICU patients to date and several of these studies were underpowered to demonstrate an impact of antifungal prophylaxis. In surgical or ICU patients, fluconazole prophylaxis was found to prevent intra-abdominal candidiasis in high-risk surgical patients with recurrent gastro-intestinal perforations or anastomotic leaks and to prevent candidiasis in patients expected to stay in the ICU for more than 3 days or to be ventilated for more than 5 days. Rigorous selection of patients at high risk of invasive candidiasis is necessary to maximize the chances of reducing the morbidity and mortality of fungal infections, while minimizing treatment costs and the exposure of low risk patients to adverse events and emergence of resistant fungal strains. For decades, amphotericin B deoxycholate has been standard therapy for invasive fungal infections. In recent years, several new antifungal agents have become available offering additional therapeutic options for the management of invasive fungal infections. These include lipid formulations of amphotericin B, azoles (fluconazole, voriconazole, posaconazole) and echinocandins (caspofungin, micafungin and anidulafungin). Clinical trials have shown that triazoles and echinocandins are at least as efficacious as and under most circumstances better tolerated than polyenes as first line or salvage therapy of oropharyngeal or esophageal candidiasis, candidemia or invasive candidiasis. Recently, the Infectious Diseases Society of America (IDSA) and the Fungal Infection Study Group of the European Society for Clinical Microbiology and Infectious Diseases have published or presented their guidelines on the management of candidiasis.
Influenza and other respiratory infections in children

Adrienne Randolph

Learning Objectives

Respiratory tract infections are the most common cause of death from sepsis in infants and children. The learning objectives for this session include to give an overview of life-threatening respiratory infections in children. This will include the following topics:

1. A review of the proposed diagnostic criteria for bronchiolitis and pneumonia in pediatrics and their complications including hypoxia, respiratory failure, empyema, pneumothorax, and acute lung injury.

2. Respiratory syncytial virus (RSV) and influenza account for a high proportion of lower respiratory tract infections in children admitted to the intensive care unit (ICU). This talk will include an overview of the features of these two viruses which allow them to escape the host immune response and cause life-threatening respiratory infections.

3. Unpublished findings from two large multicenter pediatric registries of critically ill children with life-threatening influenza will be reviewed. Investigators have used these registries to develop risk adjustment models identifying children at highest risk for ICU admission and worse clinical outcomes from life-threatening influenza infection.

4. A major risk factor for death from influenza and other viral pneumonia is bacterial coinfection, especially in otherwise healthy children. Diagnosis of bacterial coinfection can be challenging. Some bacterial organisms, including Methicillin-resistant Staphylococcus aureus (MRSA), often lead to a fulminant and necrotizing pneumonia. The rising prevalence, diagnostic and treatment implications of MRSA infection in children admitted to the ICU will be reviewed.

5. Features of the immune response in children with life-threatening influenza and other viral infections have been associated with worse clinical outcomes. Paradoxically, children who die from life-threatening influenza have high levels of systemic inflammation consistent with a “cytokine storm” but their innate immune system’s ability to fight infection is suppressed. The implications of this finding for the treatment of severe respiratory infections in children will be discussed.

At the conclusion of this session, participants will have a stronger grasp of how to diagnose and treat life-threatening respiratory infections and their complications in children.

The liver in sepsis

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Liver dysfunction is common in sepsis and can be attributed to diverse factors, including overwhelming inflammation and poor perfusion but also drug-induced injury or total parental nutrition. Liver damage ranges from small self-limited abnormalities in liver chemistry to fulminant organ failure. As a result, cholestasis induced by inflammation is a common complication in patients with extrahepatic infections and sepsis accounts for approximately 20% of cases of hyperbilirubinemia in community hospitals. The incidence of liver dysfunction is underestimated when traditional “static” measures such as serum-transaminases or bilirubin as opposed to “dynamic” tests, such as clearance tests, are used to diagnose liver dysfunction. Hepatobiliary transport systems are essential for the uptake and excretion of a variety of compounds including bile acids but also xenobiotics, and this partial function is monitored by dye excretion. Disruption and dysregulation of this excretory pathway results in cholestasis, leading to the intrahepatic accumulation of bile acids and other toxic compounds with progression of liver pathology. While fulminant liver failure in previously healthy septic patients is rare, a deterioration of a pre-existing liver disease is common and causes substantial morbidity and mortality.

Infections are involved in the pathogenesis of many episodes of decompensated cirrhosis, such as the hemodynamic alterations of cirrhosis, variceal bleeding, renal insufficiency, and encephalopathy. Primary prophylaxis with antibiotics, eg, quinolones, has evolved as an effective strategy in preventing infections and is associated with lower incidence of sepsis and mortality in a selected population of patients with liver cirrhosis. Thus, mortality from acute- or chronic liver dysfunction has recently decreased but infections with multiresistant microorganisms are recently on the rise contributing again to greater disease burden and mortality.

Early recognition, supportive care, and effective treatment of the underlying disease process as well as avoidance of hepatotoxic drugs is cornerstone in the management of liver dysfunction in the critical care setting.
Abdominal sepsis

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Complicated intra-abdominal infections (IAIs) are the second most common underlying cause of death due to severe sepsis among intensive care unit (ICU) patients. Complicated IAIIs are “complicated” when the infectious process extends beyond the hollow viscus of origin into the peritoneal cavity. IAIIs are associated with abscess formation and/or peritonitis. “Source control” is any procedure, or series of procedures, that eliminates infectious foci, controls factors that promote on-going infection, and corrects or controls anatomic derangements to restore normal physiologic function. Certain factors increase the likelihood that efforts to achieve satisfactory source control will be unsuccessful. These factors include: delayed intervention (ie, >24 h after the onset of IAI), higher severity of illness (eg, APACHE II score ≥15), advanced age (>70 years), pre-existing chronic medical conditions, poor nutritional status, and extensive peritoneal involvement.

The risk of treatment failure also is increased when the IAI developed in a health care facility, such as a hospital or nursing home. Accordingly, most experts recommend very broad empiric antimicrobial coverage for such “health care-associated” IAIIs. For cases in this category, appropriate regimens include: meropenem, imipenem/cilastatin, doripenem, piperacillin/tazobactam, ciprofloxacin plus metronidazole, ceftazidime or cefepime plus metronidazole, and aztreonam plus metronidazole plus vancomycin.

Empiric antibiotic therapy for hospital-acquired intra-abdominal infections should be guided by knowledge of the flora seen at the particular hospital and the hospital’s antimicrobial susceptibility pattern. At some institutions, the empiric regimen should consist of multiple antibiotics designed to provide coverage against non-fermenting Gram-negative bacilli, notably Pseudomonas aeruginosa and Acinetobacter spp, extended spectrum β-lactamase-producing Klebsiella spp and Escherichia coli, Enterobacter spp, Proteus spp, methicillin resistant Staphylococcus aureus, enterococci, and Candida spp. Such broad-spectrum antimicrobial therapy should be tailored when culture and susceptibility reports become available to reduce the number and spectra of administered agents.

In uncomplicated cases, most experts recommend a short course of antimicrobial chemotherapy (≤7 days). However, many cases are not straightforward and are complicated by multisystem organ dysfunction as well as secondary proven or suspected extra-abdominal infections (eg, ventilator-associated pneumonia). In these situations, strict guidelines regarding duration of antimicrobial chemotherapy are nearly impossible to formulate, and management must be individualized.

The epithelium in sepsis

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The multiple organ dysfunction syndrome (MODS) is the most common cause of death among patients requiring care in an intensive care unit. There is widespread agreement that MODS is the clinical manifestation of a dysregulated inflammatory response. Indeed, most of the published research regarding the pathogenesis of MODS has focused on the various signaling pathways that lead to the activation of the innate immune system and the elaboration of cytokines, oxidants, tissue-destructive enzymes and other pro-inflammatory mediators. Interestingly, however, the biochemical and cell biological basis for organ dysfunction per se remains very poorly understood. It is clear, however, that the histopathology of MODS in humans is remarkably bland; massive cell death, whether due to necrosis or apoptosis, is almost certainly not the cause of MODS. Rather, the final step in the development of MODS is probably the widespread dysfunction of parenchymal cells in multiple organs as a result of the deleterious effects of a poorly controlled systemic inflammatory response. Thus, an under-explored area of research can be summarized by this question: How does the inflammatory response lead to cellular dysfunction that translates into dysfunction of those organs (ie, the lungs, liver, kidneys, and intestine) that are most commonly and profoundly affected by sepsis?

The answer to this question, of course, remains elusive. Nevertheless, data exist to support the view that derangements in the formation and/or function of specialized structures in epithelial cells–tight junctions (TJs)–may be a key factor leading to lung, liver, gut and, perhaps, kidney dysfunction associated with conditions, such as sepsis and acute lung injury syndrome (ARDS), that are caused by dysregulated inflammatory processes.

Bioenergetics and metabolism

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How systemic inflammation leads to multiple organ failure is an unanswered yet crucial question. A better understanding of this mechanism will accelerate the development of directed therapies that should prove more effective than the current emphasis on immunomodulatory approaches that have repeatedly...
failing to show unambiguous improvements in patient outcome. Increasing evidence in both patients and animal models has implicated mitochondrial dysfunction as playing a key role in organ failure induced by sepsis and other systemic insults. This concept is supported by (i) a lack of gross histological derangement with minimal cell death in failed organs; (ii) an early increase in overall body metabolism, followed by a fall during the established phase, and then a rebound increase during the recovery phase; (iii) an elevation in local tissue oxygen tension, implying availability but non-utilization of oxygen; and (iv) rapid and often full recovery of functionality of these failed organs, even in those organs that are considered poorly regenerative.

A major mitochondrial function is the generation of energy (ATP) through oxidative phosphorylation, a process responsible for utilizing >90% of total oxygen consumed by the body. Sepsis can (i) directly inhibit and/or damage the electron transport chain (that generates the energy needed to phosphorylate ADP) via excess generation of oxygen and nitrogen reactive species; (ii) modulate the activity of hormones that modulate mitochondrial function; and (iii) affect transcription of genes encoding for proteins within the ETC. There may also be a direct inhibition of metabolism that, by negative feedback, decreases the need for energy generation. Organ (and whole body) recovery is preceded by an increase in turnover of new mitochondrial protein and by an increase in energy utilization. Therapeutic avenues include mitochondrial protection, eg. enhancement of mitochondrial antioxidants, or stimulation of mitochondrial recovery once the inflammatory stimulus has abated.

### Cardiac dysfunction and vascular hyporeactivity

**Mervyn Singer** Intensive Care Medicine, University College London, London, UK

Sepsis is associated with a transient and sometimes profound depression of myocardial function, excessive vasodilatation and capillary leak, and a decreased ability to respond to catecholamines (‘vascular hyporeactivity’). These differing factors create a difficult scenario for the treating clinician — filling the dilated and leaky intravascular compartment, though not excessively so; generating an adequate blood flow to the tissues; and maintaining an adequate blood pressure that, traditionally, has often required high doses of catecholamines which, in themselves, are likely to be injurious.

Multiple mechanisms exist to explain both the cardiac and vascular abnormalities. These include impaired intracellular handling of calcium, excess production of nitric oxide, decreased production of vasopressin, excessive activation of potassium channels, decreased sensitivity of adrenoreceptors, and altered contraction and relaxation (affecting myosin-actin cross-linking). In the heart, both systolic and diastolic functions are affected.

An ever-increasing awareness of the underlying pathophysiology has allowed new therapies to be investigated. These include the use of vasopressin or analogues such as terlipressin, nitric oxide modulation (eg. by inhibiting nitric oxide synthase or scavenging NO), calcium sensitizers (such as levosimendan), or drugs with inhibitory effects on potassium channels such as the sulphhydryl agents. Though promise has been shown by some of these approaches, others have been detrimental (eg. NO modulation). We still do not understand the optimal parameters of flow, pressure, and organ perfusion that we should be targeting but there is a greater appreciation of the need to reduce sedation, minimize catecholamine dosing, and to tolerate lower blood pressures provided adequate tissue perfusion is maintained.

### Coagulation and the endothelium

**Tom van der Poll** Division of Infectious Diseases & The Center of Experimental and Molecular Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

Patients with sepsis almost invariably show evidence for activation of the coagulation system. Hemostatic disorders in patients with infection may range from subtle activation of coagulation that can only be detected by sensitive markers for coagulation factor activation to somewhat more robust coagulation activation that may be evident by modestly decreased platelet counts and slight prolongation of clotting times to fulminant disseminated intravascular coagulation (DIC). DIC is commonly seen in sepsis and in particular in septic shock where the incidence is somewhere between 30-50%. Bacteria and proinflammatory cytokines promote fibrin deposition through 3 main pathways: tissue factor (TF)-mediated thrombin generation, dysfunctional physiological anticoagulant mechanisms, and impaired fibrin removal due to depression of the fibrinolytic system. It is now evident that reciprocal interactions exist between coagulation and inflammation, and that the crosstalk between these historically separated pathways is a critical determinant of the outcome of sepsis.

The main route by which inflammation triggers coagulation is via TF. Coagulation is triggered when TF expression is induced on the surface of mononuclear cells and endothelial cells upon stimulation by bacterial products or pro-inflammatory cytokines, or when circulating blood comes into contact with extravascular cells that constitutively express TF. TF binds and activates clotting factor VII, which via factor X results in the generation of thrombin and fibrin. Strategies that prevent the activation of the TF/Factor VIIa pathway in humans and non-human primates abrogated the activation of the common pathway of coagulation elicited by administration of LPS or bacteria. In lethal sepsis models in baboons, TF inhibition prevented multiple organ failure and mortality.

Three important anticoagulant pathways protect us from excessive clotting, ie, antithrombin, TF pathway inhibitor (TTP), and the protein C system. Severe infection impairs the function of all of these pathways, thereby further facilitating the widespread formation of fibrin. The Protein C system represents an important anticoagulant mechanism by virtue of the capacity of activated protein C (APC) to proteolytically inactivate the coagulation cofactors Va and Vlla. Many studies have supported the anticoagulant potency of the protein C system in vivo. Recombinant APC has been found to exert protective effects in many preclinical models of sepsis. Besides acting as an anticoagulant, APC can mediate cytoprotective effects via triggering protease activated receptor-1 (PAR1). Of interest, the protective APC effects observed in sepsis models do not rely on the anticoagulant properties of this protein: APC mutants that lack anticoagulant properties but retain the capacity to activate PAR1 are promising new drugs for sepsis treatment.
Sepsis has been defined as the host response to infection. Treatment of infection with appropriate antimicrobials and/or source control is a mainstay of its successful management, as is correction of the physiologic derangements that result from this powerful response. Over the past three decades, remarkable advances have been made in understanding the complex array of host-derived molecules that contribute to the expression of a septic response. Literally hundreds of mediators have been implicated, and manipulation of dozens of these can prevent the lethality associated with endotoxin challenge in a mouse, suggesting that these may be promising targets for human therapies. Yet clinical trials in humans have been almost universally disappointing in introducing new therapies for a disorder that is one of the leading causes of death on the planet. The failure is not a result of failed drugs, but a much more fundamental failure of concept and imagination on the part of those of us who have been involved in this endeavor.

The concept of sepsis should alert the clinician to the possibility of infection, and prompt efforts to diagnose a site and organism, and to treat rapidly and appropriately with antibiotics, source control, and supportive care. However it provides no information on the nature of the host response that might enable the clinician to make an informed decision regarding adjuvant treatments. The innate host immune response that is responsible for the clinical syndrome of sepsis is complex, and highly variable in its expression. For examples, levels of circulating TNF can differ by a factor of 7000 in patients with clinical sepsis. A decision to neutralize TNF presupposes that it is present in excess: the concept of sepsis and its current definition tells us nothing about the presence or levels of the mediator targeted. Furthermore, the host response to infection is adaptive, and in many infections, essential for survival. Neutralizing TNF increases survival in animal models of endotoxin or systemic challenge with Gram-negative organisms, but increases mortality in models of infection with S. pneumoniae. Finally an inflammatory mediator response is not specific to infection, but can occur with other acute insults such as trauma or pancreatitis, thus there is no a priori reason to only study patients with infection.

Ten fundamental changes in approach are needed if we are to realize the potential for adjuvant treatments that target the host response. First, we must study these only in those patients in who the target of the intervention is shown to be present. If the therapy neutralizes TNF or endotoxin, then these must be shown to be present in excessive amounts; if it replenishes activated protein C or interferon gamma, then these must be shown to be deficient. Second, we should include all acutely ill patients who meet these criteria, and not only those in whom the cause is infection. Third, we should exclude those who might plausibly be harmed by the therapy (eg patients with pneumococcal infection if the treatment is anti-TNF) – a requirement that presupposes a robust pre-clinical portfolio to detect harm. Fourth, we should stage patients so that those who are treated are those most likely to benefit. Fifth, early phase studies should demonstrate that the intervention does alter the target of therapy. Sixth, early studies should be designed to show rescue of patients who are refractory to conventional therapy. Seventh, dose and duration of therapy should be titrated to levels of the target or a surrogate biomarker. Eighth, we must explore data from earlier unsuccessful trials to generate plausible hypotheses that can inform future research. Ninth, we must undertake large studies of the clinical and biochemical natural history of critically ill patients to better understand and stratify the disease we are treating. Tenth, we must do all this in the context of a professional initiative to improve the survival of septic patients, rather than the context of a commercial clinical trial seeking to develop and market a new therapy.

The challenge is far from simple. But as Einstein once commented, “The definition of insanity is doing the same thing over and over and expecting different results.”

Clinical research in China

Yangfeng Wu

To serve the most populous nation in the world, China’s healthcare system probably faces the most challenging situation in the world too. Although clinical research in China can be traced back to thousands years ago with the Sheng Nong’s story of his tests on hundreds herbs, “Shen Nong Chang Bai Cao”, and the first book on Chinese herbal medicine, the modern clinical research conducted in a manner of systematic operation with special scientific disciplines of theory and methodology took place only in the recent decades.

This presentation will briefly introduce the major challenges in healthcare, the needs of clinical research, the regulation of clinical trials, the current clinical research status and government initiatives in China. It will also analyze the strengths, weakness, opportunities, and threats (SWOT) for conducting clinical research in China.

ACCESS- Eritoran, TLR4 antagonists in severe sepsis

Steven Opal

ACCESS stands for “A Controlled Comparison of Eritoran vs. Placebo in Patients with Severe Sepsis” which was a phase III international randomized clinical trial investigating the survival benefit of Eritoran (a specific lipid A antagonist) which functions as a competitive inhibitor of endotoxin at the level of the MD2:TLR4 complex. This was the first phase III trial that specifically targeted a toll-like receptor in a major systemic inflammatory state. The study randomized
1,984 patients in a 2:1 randomization process with 1,322 patients receiving Eritoran and 662 receiving placebo in this double blind comparative trial. The study consisted of a 6-day treatment course of Eritoran given twice daily compared with vehicle control. Patients needed to be randomized within 12 hours of the onset of sepsis-induced organ dysfunction. All patients enrolled needed to receive approval by a clinical coordinating center, have objective evidence of infection, meet all entry and exclusion criteria, and have a calculated APACHE II score between 21 and 37 points.

The primary endpoint of this study was 28-day all cause mortality with a secondary endpoint of all-cause mortality after 1 year of enrollment. There were a number of other secondary endpoints that analyzed specific organ dysfunctions, cytokines, quality of life measures, and incidence of infection subsequent to randomization. Study enrollment ended in September of 2010 and the primary study results were presented in a press release 4 months later. The study failed to meet its primary endpoint of reduction in 28-day mortality or its 1-year endpoint of reduced mortality after 12 months of randomization. None of the secondary endpoints analyzed in this study showed statistically significant differences between placebo and the treated arms. The drug proved to be exceedingly well tolerated with no increased incidence of severe adverse reactions or treatment emergent or non-treatment related adverse reactions. They were no observed increases in incidence of secondary infections. The reasons for the failure of this highly potent TLR4 inhibitor to improve outcome in these severely septic patients remains unclear. A number of potential explanations could have played a role in the failure of this compound to improve the outcome in severely septic patients. A careful analysis of this study will be needed to understand the nature of endotoxin-mediated pathology in human sepsis, and to inform investigators before embarking of sepsis trials with other TLR inhibitors or other endotoxin blocking agents.

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**PROWESS-Shock**: activated protein C in septic shock

The history of the development of effective adjuvant treatments for sepsis has been a frustrating one. Numerous interventions have shown promise in early phase clinical research, only to fail to show a sufficiently robust mortality benefit in phase III trials to achieve regulatory approval. An exception to this sorry narrative was the PROWESS study of recombinant activated protein C for patients with severe sepsis. Published in 2001, the PROWESS study reported a statistically and clinically significant 6.1% improvement in the survival of patients treated with the agent, and although the FDA review panel was split, activated protein C was licensed for use under the commercial name of Xigris®.

Yet the subsequent course was far from smooth. Vocal opposition decreed multiple aspects of the launch of the drug, from the validity of the trial results (focused on early termination of the trial and interim changes in its conduct) to the perception of overly aggressive marketing by the manufacturer of the drug. Moreover although observational studies suggested benefit for treatment, randomized controlled trials in children, and in adults with a lower severity of illness, failed to replicate the initial benefit. The ongoing controversy led the EMEA in Europe to mandate a new placebo-controlled clinical trial as a condition of ongoing regulatory approval. PROWESS-Shock differs in many respects from prior sepsis trials. It was designed and is run by a Steering Committee independent from the study sponsor, and the relationship between the investigators and Eli Lilly is laid out in detail in a published memorandum of agreement. The Steering Committee is notable for including investigators who have not had a long history of ties to the company, including some who have been openly skeptical about the drug.
The statistical analysis plan was also developed and published in advance of the trial, and the primary analysis will be undertaken by an independent academic statistical unit. The trial is also unusual in that it is being conducted in an environment where the agent is commercially available, raising concerns that the appropriate study population might not be recruited.

Nonetheless, the target population comprises patients who, based on available data, should be maximally likely to benefit from intervention—those with refractory septic shock. The challenges of selective open label treatment are minimized, though not eliminated, by conducting the trial in sites where use of the drug is low.

Recruitment of the planned 1696 study subjects concluded in late August, and so the last patient will have completed 28 day followup by the end of September. Data cleanup and analysis will occur in October, and the first results will be reviewed on October 31, although the plan is to defer full presentation until 90 day mortality data are available.

PROWeSS-Shock is an important study—not just for the future of a promising drug, but for the future of sepsis research. We wait with anticipation.

**Clinical Trials**

### Early Goal Directed Therapy: ProCESS, ARISE, and ProMISE

**Derek Angus** University of Pittsburgh, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

In response to worldwide speculation about the role of early goal directed therapy (EGDT) for septic shock, 3 large government-funded randomized trials have been initiated. In Australia and New Zealand, EGDT is being tested against usual care for septic shock in 1300 patients (850 per arm) in a trial known as ARISE. In the US, EGDT is being tested in a 3-arm trial (ProCESS) against usual care and a protocolized usual care arm that does not involve use of the central venous catheter and does not include blood transfusion or inotrope instructions. This trial will also study 850 patients per arm.

Finally, in the UK, in a trial entitled ProMISE, EGDT is being tested against British usual care in a 2-arm trial similar in size to ARISE. All 3 trials will administer EGDT via a standardized trained team, akin to trauma teams. All 3 trial investigator groups have collaborated to ensure similar data collection and delivery of EGDT, thus facilitating a post-trial individual patient meta-analysis. In this talk, I will review the design and status of these trials.

### China survey of candidiasis in ICUs (China-SCAN study)

**Haibo Qiu** China

**Abstract not available**

### European revival of albumin in sepsis: EARSS and ALBIOS

**Jean-Paul Mira** Cochin-St.Vincent de Paul University Hospital, Paris, France

The efficacy of albumin administration on survival in the critical care setting remains controversial. Hence, several meta-analyses have reported negative, neutral, or beneficial effects of albumin administration. To clarify this controversy, the Saline versus Albumin Fluid Evaluation (SAFE) study has been performed, comparing the effects of 4% albumin vs saline for volume replacement in critically ill patients. The results demonstrated no differences in 28-day mortality between the 2 randomized groups, but confirmed the safety of albumin administration in acutely ill patients. Furthermore, a predefined subgroup analysis has shown a trend of longer survival in albumin-treated septic patients treated. Moreover, hypoalbuminemia is common in critically ill patients such as septic patients and is associated with worse outcomes. However, it is not known if hypoalbuminemia is just an excellent biomarker or if correcting hypoalbuminemia has beneficial effects on survival of septic patients, because albumin has several important physiological effects with potentially beneficial effects in critical illness. Thus, further studies are needed to clarify what precise role albumin has in today’s ICU.

Two current large multicenter European clinical trials try to understand the place of 20% albumin in severe sepsis treatment. These studies have similar endpoints but different methodologies. Their main common objective is to analyze if 20% albumin administration in the early course of severe sepsis/septic shock reduces the 28th day mortality with a further control at 90th day. The secondary objectives are to verify the differences in organ dysfunctions (as assessed by the Sequential Organ Failure Assessment score), hospital and intensive care unit (ICU) length of stay between the treated and control group. The French study (EARSS) will include 800 patients and compare administration of 300 mL 20% albumin per day from D1 to D3 of septic shock to the same volume of saline. Albumin administration will not been allowed in the control group during the study. The Italian study (ALBIOS) aims to verify whether volume replacement with 20% albumin and its maintenance
within plasmatic physiologic range (≥30 g/l) improves survival of patients with severe sepsis of septic shock, as compared to crystalloids. ALBIOS will include about 1350 patients with severe sepsis or septic shock, who will be randomized to receive either albumin or crystalloids as fluid therapy. Volume replacement will be performed for both groups according to the early goal-directed therapy. Treated group will receive 60 g albumin infusion after randomization, and 40-60 g albumin daily infusion to maintain serum album level ≥30 g/l. Control group will receive crystalloids for the entire study; albumin administration will be allowed only when daily serum albumin level will be lower than 15 g/l. Patients will be treated until the 28th day after randomization or until ICU discharge.

The results of these 2 European studies will be available in 2010/2011 and will clarify the effects of 20% albumin in the settings of severe sepsis/septic shock.

A large trial of corticosteroid treatment of septic shock - the ESCAPE study

The accepted principles of therapy for septic shock include prompt resuscitation and administration of antibiotics, source control, intravenous fluid therapy, and organ system support with vasopressor drugs, mechanical ventilation, and renal replacement therapy as required. There is an established biological rationale for the administration of adjunctive corticosteroids in the management of patients with septic shock. Septic shock arises as a result of inflammation and vasoplegia from a complex, biological cascade that is dependent on inter- and intracellular signalling. Treatment with exogenous corticosteroids has long been advocated as a possible means to modulate the inflammatory process. In the last 30 years, 17 randomized trials (n=2138) of adjunctive therapy with corticosteroids for septic shock have been conducted. Despite these, there is no consensus as to the effectiveness of corticosteroid therapy and their use in clinical practice varies among clinicians. Two recent trials dominate current thinking on the use of corticosteroids in septic shock: the first trial was the French study of 299 patients published in 2002. This trial studied hydrocortisone 200 mg per day compared with placebo in patients with septic shock. Shock was reversed more rapidly in patients receiving hydrocortisone and although overall landmark mortality was not reduced, the investigators reported improved survival in patients with a reduced response to corticortin (83% versus 53%, CI 0.47-0.95, P=0.02). The trial had a number of limitations that raised concerns over the external validity of its findings: a) Benefit was only demonstrated in patients who failed to respond to corticortin. These comprised 76.6% of the study population, a percentage that was much larger than the 40% the investigators expected. Statistical significance was only obtained in a survival analysis after adjustment for baseline covariates; in contrast, in-hospital mortality was higher in patients who responded to corticortin who received hydrocortisone. b) Additionally, patients who were assigned to receive hydrocortisone also received fludrocortisone. The importance of this additional mineralocorticoid is unclear, and this part of the protocol has not been broadly adopted by clinicians. The second study was the 2008 European multicenter study, the largest randomized controlled trial reported to date. The Corticosteroid Therapy of Septic Shock (CORTICUS) study examined the efficacy of low dose hydrocortisone (200 mg/day) compared to placebo in 499 patients with septic shock. The study was stopped prematurely when lower than expected recruitment resulted in termination of funding and expiry of the study drug supply. As a result, the trial was significantly underpowered to detect a clinically important treatment effect. The main findings of this trial were: a) The mortality in the steroid group was 34% versus 31% in controls (P=0.51). b) Shock was reversed more rapidly in patients receiving hydrocortisone. c) In contrast to the French study, the corticotropin stimulation test did not identify a subgroup of patients who benefited from treatment with hydrocortisone.

Neither the CORTICUS trial (N = 499) nor the French study (N = 299) had adequate statistical power to demonstrate a clinically significant reduction in the risk of death from current baseline mortality rate of around 30%.

The Surviving Sepsis Campaign Guidelines of 2008 provided qualified support for the use of low dose hydrocortisone in septic shock (weak, low grade recommendation) based on the publication of the CORTICUS study. They recommend that “intravenous hydrocortisone be given only to adult septic shock patients after it has been confirmed that their blood pressure is poorly responsive to fluid and vasopressor therapy.” The Australian and New Zealand Intensive Care Society (ANZICS) published a position statement commenting they were unable to sponsor the guidelines in general as some components did not have clear supportive evidence. With regard to the recommendations on steroid therapy they noted “the literature does not provide clear guidance, and practice varies widely among Australian and New Zealand intensive care physicians. This practice variation seems likely to continue until more definitive clinical data are published.”

As a result of the contradictory evidence and marked variation in clinical practice in Australia and New Zealand, the ANZICS clinical trials group has obtained a National Health and Medical Research Council grant to conduct a trial of hydrocortisone in patients with persistent septic shock. The study will be a multicenter double blind randomized controlled trial. Critically ill patients with septic shock will be randomized to receive 200 mg of hydrocortisone or placebo in addition to conventional treatment. The primary endpoint will be 90-day all cause mortality, secondary endpoints will include shock resolution, organ failure, 28-day mortality, and quality adjusted life years (QALY’s). To avoid further uncertainty, the investigators decided that the sample size should substantially exceed the total number of patients who have been studied so far. To that end, recruitment of 3800 is planned; this will provide 90% power to detect a 15% reduction in relative risk; 5% absolute risk reduction) from an estimated baseline mortality rate of 33%.

Recruitment to the trial should commence early in 2012 and international collaborations are likely required to ensure that this number of patients can be recruited in a reasonable timeframe. Successful completion of this trial should resolve one of the longest standing debates regarding the management of patients with septic shock.

References:
Applying Best Practices to Sepsis Diagnostics

*Presented by Steven Opal, Pawtucket, USA*

This symposium will include a review of current diagnostic tools and how they impact care of sepsis patients.

The objectives of the symposium include a clearer understanding of guidelines for diagnostic testing, how variables such as the volume of blood tested impacts positivity rates, and how other diagnostic tests other than blood culture contribute the diagnosis of sepsis.

The 2011 **Stephen F. Lowry Young Investigator Award**

This award is given in honor and memory of our former ISF colleague and friend Stephen F. Lowry to the Young Investigator who presented the best research presentation relating to the care of sepsis patients at our annual international SEPSIS symposium. This year’s award recipient is **Sophie Mwinsa Chimese**, from the Department of Internal Medicine, University of Zambia, Lusaka, Zambia for her study:

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

Congratulations, we trust that you will continue to make important contributions to the field of sepsis research in the future.
Sepsis 2011:
Best Abstract Awards

Authors of the 6 best abstracts will present their work as oral presentations on 27 October from 15:00 -16:30.

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Early vasopressin application in shock
Sandro Oliveira Albert Schweitzer Hospital, Bangu Hospital, Rio de Janeiro, Brazil

P24
Early peak temperature and mortality in critically ill patients with or without infection
Manoj Saxena1,2, Paul Young1,4, Richard Beasley1,4, Michael Bailey2, Rinaldo Bellomo3, David Pilcher1, Simon Finfer1,3, David Harrison4, John Myburgh2,3, Kathryn Rowan6
1Division of Critical Care and Trauma, George Institute for Global Health, Sydney, New South Wales, Australia; 2St George Clinical School, University of New South Wales, New South Wales, Australia; 3Intensive Care Unit, Wellington Regional Hospital, Capital and Coast District Health Board, Wellington, New Zealand; 4Medical Research Institute of New Zealand, Wellington, New Zealand; 5Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; 6Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation, Melbourne, Victoria, Australia.

P29
A novel DDAH1 inhibitor improved sepsis-induced impairment in vasoreactivity to noradrenaline in a rat endotoxaemia model
Zhen Wang Valerie Taylor, Ray Stidwill, James Leiper, Mervyn Singer
Bloomsbury Institute of Intensive Care Medicine, Department of Medicine, University College, London, United Kingdom

P39
Interplay between angiopoietin-2, VEGF and peroxynitrite is an important determinant of vascular hyperpermeability during methicillin-resistant Staphylococcus aureus sepsis
Perenlei Enkhbaatar Yong Zhu, Lillian Traber, Daniel Traber
Department of Anesthesiology, University of Texas Medical Branch, Galveston, Texas, USA

P40
Clinical characteristics, management, and outcomes of sepsis in Lusaka, Zambia
Sophie Mwinsa Chimese1, Ben Andrews1,2, Shabir Lakhi1,3
1Department of Internal Medicine, University of Zambia, Lusaka, Zambia; 2Institute for Global Health, Vanderbilt University, Nashville, Tennessee, USA; 3Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia

P41
AZD9773, a novel anti-tumour necrosis factor-α immune Fab in development for severe sepsis and septic shock: Demonstration of safety and efficacy in a murine CLP sepsis model
Peter Newham1, Peter Ceuppens2, Shampa Das1, James WT Yates3, Richard Knight1, Jennifer S McKay2
1Global Safety Assessment, AstraZeneca, Macclesfield, Cheshire, UK; 2Discovery Enabling Capabilities and Sciences, AstraZeneca, Macclesfield, Cheshire, UK; 3Clinical Pharmacology & DMPK, AstraZeneca, Macclesfield, Cheshire, UK; 4Oncology iMed DMPK, AstraZeneca, Macclesfield, Cheshire, UK

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Sepsis 2011: Acknowledgments

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Special thanks go to BD Diagnostics for sponsoring a satellite

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Educational Grant:

Special thanks go to CSL Behring for their unrestricted educational grant to support delegate travel bursaries for Sepsis 2011 Beijing

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The Organizing Committee would also like to thank:

• The Chinese Society of Critical Care Medicine for their help and guidance with this year’s Symposium

• Prof Simon Finfer and Mervyn Singer for their organization of the program and speakers

• The ISF Executive Director – Elaine Rinicker

• Lily Wang and Shining Guo for their local expertise, help, and assistance

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Sepsis 2011

Beijing, China, 26–28 October 2011

Published: 27 October 2011

P1
Thrombin-activatable fibrinolysis inhibitor and organ dysfunction in disseminated intravascular coagulation associated with sepsis
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1Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, Sappora, Japan; 2Division of Gene Therapeutics, National Center for Global Health and Medicine, Tokyo, Japan


Introduction
Fibrinolytic shutdown plays a pivotal role 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
O Butyrsky, V Starosek
Department of Surgery, Crimean Medical University, Simferopol, Ukraine


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 PHA method. Escherichia coli K30 LPS was used as antigen for AE antibody detection. The level of general immunoglobulin was determined by 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)

<table>
<thead>
<tr>
<th></th>
<th>AEI</th>
<th>HI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgA</td>
<td>IgG</td>
</tr>
<tr>
<td>Peritonitis patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.28 ± 0.01, 0.45 ± 0.02</td>
<td>0.12 ± 0.01, 0.13 ± 0.02</td>
<td>0.21 ± 0.03, 0.29 ± 0.04</td>
</tr>
<tr>
<td>P &lt; 0.05</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Donors</td>
<td>0.35 ± 0.05</td>
<td>0.16 ± 0.01</td>
</tr>
</tbody>
</table>

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P3  
Presepsin (sCD14-ST) as a new diagnostic biomarker of sepsis: development of diagnostic tools using the whole blood  
T Shozushima  
Department of Critical Care Medicine, Iwate Medical University, School of Medicine, Morioka, Japan  

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, 611.3 pg/ml; SIRS, 333.5 ± 130.6 pg/ml; sepsis, 817.9 ± 572.7 pg/ml; and normal (non-infection), 294.2 ± 121.4 pg/ml; local infection, 721.0 ± 229.4 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 showed 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  
N Matsumoto, G Takahashi, M Kojika, Y Ishibe, S Tatsuyori, S Yasushi, SK Inada, S Endo  
Department of Critical Care Medicine, School of Medicine, Iwate Medical University, Morioka, Japan  

Introduction  
Endotoxin activity assay (EAA) levels were compared with endotoxin levels determined by the turbidimetric kinetic method. 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  
The Yale insulin protocol was effective and safe in sepsis patients admitted to the ICU.

P5  
Yale insulin protocol infusion in sepsis patients  
S Oliveira  
Albert Schweitzer and Hospital Bangu Hospital, Rio de Janeiro – RJ, Brazil  

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  
We 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 < 0.001). 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  
S Oliveira  
Albert Schweitzer and Hospital Bangu Hospital, Rio de Janeiro – RJ, Brazil  

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. 25.9%, 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
S Zieliński
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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 group 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 PaO2 /FiO2 (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.

Acknowledgements
The authors declare no conflict of interest related to this work. The study was supported by the Wroclaw Medical University. LPS adsorbers were kindly provided by Alteco Medical AB, Lund, Sweden.

P8

Urinary hepcidin is potentially a marker of systemic infection rather than inflammation, in the setting of preserved renal function
NJ Glassford1, AG Schneider1, G Eastwood1, L Peck1, H Young1, M Westerman1, V Ostdahl1, R Bellomo1
1Department of Intensive Care, Austin Hospital, VIC, Australia; 2Intrinsic LifeSciences LLC, La Jolla, CA, USA

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 delineate 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
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum Cr</th>
<th>CRP</th>
<th>Serum Cr</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary hepcidin</td>
<td>−0.272</td>
<td>0.204</td>
<td>−0.225</td>
<td>0.506</td>
</tr>
<tr>
<td>(P = 0.013)</td>
<td>(P = 0.064)</td>
<td>(P = 0.314)</td>
<td>(P = 0.016)</td>
<td></td>
</tr>
<tr>
<td>1/urinary hepcidin</td>
<td>0.287</td>
<td>−0.19</td>
<td>0.225</td>
<td>−0.506</td>
</tr>
<tr>
<td>(P = 0.009)</td>
<td>(P = 0.087)</td>
<td>(P = 0.314)</td>
<td>(P = 0.016)</td>
<td></td>
</tr>
</tbody>
</table>

| Urinary hepcidin      | 0.146    | 0.241 | −0.276   | 0.418 |
| corrected for         |          |      |          |      |
| serum creatinine      | (P = 0.019) | (P = 0.029) | (P = 0.227) | (P = 0.06) |
| 1/urinary hepcidin    | 0.158    | −0.228 | 0.276    | −0.418 |
| corrected for         |          |      |          |      |
| urinary creatinine    | (P = 0.159) | (P = 0.041) | (P = 0.227) | (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.

References

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
NJ Glassford, AG Schneider, G Eastwood, L Peck, H Young, R Bellomo
Department of Intensive Care, Austin Hospital, Heidelberg, VIC, Australia

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.

**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.

**References**

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum Cr</th>
<th>CRP</th>
<th>Cramer’s V</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Sepsis (n = 22)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Urinary NGAL</td>
<td>0.349</td>
<td>0.302</td>
<td>0.391</td>
<td>0.057</td>
</tr>
<tr>
<td>(P = 0.116)</td>
<td>(P = 0.173)</td>
<td>(P &lt; 0.001)</td>
<td>(P = 0.61)</td>
<td></td>
</tr>
<tr>
<td>Urinary NGAL corrected for urine creatinine</td>
<td>0.311</td>
<td>0.235</td>
<td>0.514</td>
<td>0.070</td>
</tr>
<tr>
<td>(P = 0.171)</td>
<td>(P = 0.305)</td>
<td>(P &lt; 0.001)</td>
<td>(P = 0.532)</td>
<td></td>
</tr>
<tr>
<td>Serum NGAL corrected for urine creatinine</td>
<td>0.244</td>
<td>0.411</td>
<td>0.661</td>
<td>-0.034</td>
</tr>
<tr>
<td>(P = 0.274)</td>
<td>(P = 0.057)</td>
<td>(P &lt; 0.001)</td>
<td>(P = 0.763)</td>
<td></td>
</tr>
<tr>
<td><strong>No sepsis (n = 83)</strong></td>
<td></td>
<td></td>
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**Table 1 (abstract P10). Relationships between NGAL, FENa and AKI**

<table>
<thead>
<tr>
<th>FENa</th>
<th>n</th>
<th>Urinary NGAL</th>
<th>Serum NGAL</th>
<th>Urine: serum NGAL ratio</th>
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<tbody>
<tr>
<td><strong>Nonseptic AKI</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>43</td>
<td>0.153</td>
<td>0.328</td>
<td>0.587</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>AKI</strong></td>
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</tr>
<tr>
<td>33</td>
<td>-0.039</td>
<td>0.830</td>
<td>0.438</td>
<td>0.011</td>
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<tr>
<td><strong>RIFLE R-F</strong></td>
<td></td>
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</tr>
<tr>
<td>14</td>
<td>0.015</td>
<td>0.958</td>
<td>0.235</td>
<td>0.418</td>
</tr>
<tr>
<td><strong>Septic AKI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>-0.168</td>
<td>0.602</td>
<td>-0.007</td>
<td>0.983</td>
</tr>
<tr>
<td><strong>RIFLE R-F</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-0.300</td>
<td>0.624</td>
<td>0.500</td>
<td>0.391</td>
</tr>
</tbody>
</table>

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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 determined the need for organ support, length of ICU stay and mortality. Severity of illness was assessed by APACHE II 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

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.

References


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

<table>
<thead>
<tr>
<th>Test result variable</th>
<th>RIFLE R, I or F</th>
<th>ROC AUC</th>
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<tbody>
<tr>
<td></td>
<td>Septic</td>
<td>Nonseptic</td>
</tr>
<tr>
<td></td>
<td>Area (SE)</td>
<td>Area (SE)</td>
</tr>
<tr>
<td>Urinary NGAL</td>
<td>0.367 (0.136)</td>
<td>0.561 (0.068)</td>
</tr>
<tr>
<td>Urinary NGAL corrected for urinary creatinine</td>
<td>0.417 (0.136)</td>
<td>0.578 (0.066)</td>
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<tr>
<td>Serum NGAL</td>
<td>0.375 (0.162)</td>
<td>0.639 (0.065)</td>
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<tr>
<td>Serum NGAL positivity</td>
<td>0.492 (0.158)</td>
<td>0.611 (0.066)</td>
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<tr>
<td>Urine-serum NGAL ratio</td>
<td>0.483 (0.140)</td>
<td>0.498 (0.068)</td>
</tr>
<tr>
<td>1 / urinary hepcidin</td>
<td>0.508 (0.153)</td>
<td>0.624 (0.066)</td>
</tr>
<tr>
<td>1 / urinary hepcidin corrected for urinary creatinine</td>
<td>0.483 (0.156)</td>
<td>0.598 (0.067)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Test result variable</th>
<th>RIFLE I or F</th>
<th>ROC AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Septic</td>
<td>Nonseptic</td>
</tr>
<tr>
<td></td>
<td>Area (SE)</td>
<td>Area (SE)</td>
</tr>
<tr>
<td>Serum NGAL positivity</td>
<td>0.492 (0.158)</td>
<td>0.674 (0.082)</td>
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<tr>
<td>Urine-serum NGAL ratio</td>
<td>0.483 (0.140)</td>
<td>0.543 (0.081)</td>
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<tr>
<td>1 / urinary hepcidin</td>
<td>0.508 (0.153)</td>
<td>0.611 (0.080)</td>
</tr>
<tr>
<td>1 / urinary hepcidin corrected for urinary creatinine</td>
<td>0.483 (0.156)</td>
<td>0.578 (0.083)</td>
</tr>
</tbody>
</table>

SE, standard error.
Use of plasma protein fraction in patients with septic shock admitted to the ICU

D Juneja, O Singh, P Nasa, Y Javeri, R Dang
Department of Critical Care Medicine, Max Super Speciality Hospital, Saket, New Delhi, India

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 = 0.276), 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

<table>
<thead>
<tr>
<th>Parameter of interest</th>
<th>Control group (n = 87)</th>
<th>PPF group (n = 99)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.11 ± 15.4</td>
<td>67.28 ± 14.8</td>
<td>0.154</td>
</tr>
<tr>
<td>Sex, male</td>
<td>50 (57.3%)</td>
<td>63 (63.6%)</td>
<td>0.479</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>20.69 ± 6.2</td>
<td>21.64 ± 7.6</td>
<td>0.356</td>
</tr>
<tr>
<td>PDR</td>
<td>39.51 ± 19.2</td>
<td>42.47 ± 22.5</td>
<td>0.341</td>
</tr>
<tr>
<td>SOFA score</td>
<td>9.53 ± 3.5</td>
<td>10.38 ± 3.7</td>
<td>0.105</td>
</tr>
<tr>
<td>RBC transfusions</td>
<td>32 (36.8%)</td>
<td>33 (33.3%)</td>
<td>0.735</td>
</tr>
<tr>
<td>Renal support</td>
<td>31 (35.6%)</td>
<td>38 (38.4%)</td>
<td>0.814</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>50 (57.3%)</td>
<td>60 (60.1%)</td>
<td>0.776</td>
</tr>
<tr>
<td>Time taken to stop vasopressors (hours)</td>
<td>70.69 ± 55.2</td>
<td>51.29 ± 64.5</td>
<td>0.030*</td>
</tr>
</tbody>
</table>

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.
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
G Gursel
Department of Pulmonary Critical Care Medicine, Gazi University School of Medicine, Ankara, Turkey

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
X Forceville1, D Vitoux, W Wasowicz2, M Dehoux3, P Van Antwerpeen4, D Annane5, E Plouvier1, A Bontem6, J Gromadzinska7, B Lavoliere8, A Combiez1, E Bellissant9
1Réanimation Polyvalente, CH de Meaux, France; 2Biochimie A, CHU St Louis, Paris, France; 3Toxicology and Carcinogenesis, Nofer Institute, Lodz, Poland; 4Biochimie métabolique et cellulaire, CHU Bichat, Paris, France; 5Chimie pharmaceutique organique, Université Libre de Bruxelles, Belgium; 6Réanimation, CHU Poincaré, Garches, France; 7Biochimie CH de Meaux, France; 8Recherche – Santé Publique, CIC Inserm 0203, CHU Pontchaillou, Rennes, France

Introduction
Sodium selenite (Na2SeO3) 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 Na2SeO3 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 Na2SeO3 toxicity, especially on the lung, under continuous administration of high-dose Na2SeO3 in the SERENITE study.

Methods
In a randomized, double-blind multicenter study performed in 60 septic shock patients [2], the efficacy and tolerance of Na2SeO3 (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 Na2SeO3 especially on the lung was observed for any clinical or biological variables. PaO2/FiO2 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 Na2SeO3 (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 Na2SeO3 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 Na2SeO3 opening a new field in septic shock treatment based on oxidant selenocompounds.

Table 1 (abstract P16). PaO2/FiO2 according to group and time

<table>
<thead>
<tr>
<th>Baseline (D0)</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D7</th>
<th>D10</th>
<th>D14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na2SeO3</td>
<td>20 ± 15</td>
<td>23 ± 12</td>
<td>24 ± 10</td>
<td>25 ± 14</td>
<td>26 ± 11</td>
<td>30 ± 13</td>
</tr>
<tr>
<td>Placebo</td>
<td>22 ± 13</td>
<td>21 ± 11</td>
<td>25 ± 13</td>
<td>26 ± 11</td>
<td>28 ± 14</td>
<td>33 ± 17</td>
</tr>
<tr>
<td>P value</td>
<td>0.60</td>
<td>0.37</td>
<td>0.92</td>
<td>0.81</td>
<td>0.65</td>
<td>0.52</td>
</tr>
</tbody>
</table>

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.
Acknowledgements The authors thank all the investigators, biochemists, pharmacists and clinical research team involved in the SERENITE Study, the Minister of Health for financing, and Meaux Hospital as promoter. XF is the co-inventor with DV of patent FR 98 10889, PCT N/FR 99/02.66 (delivered: US 6,844,012 B1, Au 760 534; EP 1107767), and has ownership of the corresponding patent. XF is the main shareholder of a small start-up named SERENITE-Forceville devoted to early diagnosis and treatment of septic shock especially by selenocompounds.

References

P17
Temperature management of patients with sepsis and inflammation in Australian and New Zealand ICUs: a point prevalence study
NE Hammond1,2,*, MK Saxena1,3, C Taylor4, I Seppelt4,5, P Glass1, J Myburgh1,2,3
1The George Institute for Global Health, Sydney, NSW, Australia; 2St George Hospital, Sydney, NSW, Australia; 3St George Clinical School, University of NSW, Sydney, NSW, Australia; 4Sydney Medical School, University of Sydney, NSW, Australia

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.

References

Figure 1 (abstract P17). Type of antipyretic and physical cooling used on the study day (n = 311).
P18
A survey of fever management in febrile intensive care patients without neurological injury
MK Saxena1,2, NE Hammond3, C Taylor4, P Young5, MC Reade6, R Bellomo6, J Myburgh1,2,3
1The George Institute for Global Health, Sydney, NSW, Australia; 2St George Hospital, Sydney, NSW, Australia; 3St George Clinical School, University of New South Wales, Sydney, NSW, Australia; 4St George Clinical School, University of Sydney, NSW, Australia; 5Sydney Medical School, University of Sydney, NSW, Australia; 6Medical Research Institute of New Zealand, Wellington, New Zealand; 6Austin Hospital & University of Melbourne, VIC, Australia

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

<table>
<thead>
<tr>
<th>First line (n = 418)</th>
<th>Second line (n = 409)</th>
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<tr>
<td><strong>Nurse</strong></td>
<td><strong>Doctor</strong></td>
</tr>
<tr>
<td>Pharmacological only</td>
<td>23</td>
</tr>
<tr>
<td>Physical only</td>
<td>13</td>
</tr>
<tr>
<td>Pharmacological and physical</td>
<td>64</td>
</tr>
</tbody>
</table>
T Nishida1, H Ishikura1, A Murai1, Y Irie1, T Umemura1, T Kamitani1, S Endo2
1Department of Emergency and Critical Care Medicine, Fukushima University Hospital, Fukushima, Japan; 2Department of Critical Care Medicine, School of Medicine, Iwate Medical University, Iwate, Japan

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 (r² = 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.
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 PRISMA-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 PRISMA-III score. There was a positive association between vitamin D level (OR = 1.13, 95% CI = 1.01, 1.27, P = 0.03) and the overall prevalence of vitamin D deficiency in critically ill children was 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 vitamin D axis in sepsis and hemodynamic instability that deserves further investigation.

References
Sepsis 2011  China National Convention Center, Beijing  27-28 October 2011

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.

References

Table 1 (abstract P22). Demographic data

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

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

<table>
<thead>
<tr>
<th></th>
<th>APACHE II</th>
<th>SOFA</th>
<th>MOD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronan</td>
<td>( r^2 = 0.583, ) ( P = 0.000 )</td>
<td>( r^2 = 0.529, ) ( P = 0.001 )</td>
<td>( r^2 = 0.435, ) ( P = 0.008 )</td>
<td></td>
</tr>
<tr>
<td>Syndecan</td>
<td>( r^2 = 0.425, ) ( P = 0.010 )</td>
<td>( r^2 = 0.476, ) ( P = 0.003 )</td>
<td>( r^2 = 0.529, ) ( P = 0.001 )</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>PCT</th>
<th>IL-6</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparan sulfate</td>
<td>( r^2 = -0.63, ) ( P = 0.714 )</td>
<td>( r^2 = 0.20, ) ( P = 0.928 )</td>
<td>( r^2 = 0.505, ) ( P = 0.012 )</td>
<td></td>
</tr>
<tr>
<td>Hyaluronan</td>
<td>( r^2 = 0.398, ) ( P = 0.016 )</td>
<td>( r^2 = 0.723, ) ( P = 0.000 )</td>
<td>( r^2 = 0.468, ) ( P = 0.021 )</td>
<td></td>
</tr>
</tbody>
</table>

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.

Table 1 (abstract P22). Demographic data

<table>
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<th>Healthy volunteers (n = 8)</th>
<th>Sepsis (n = 10)</th>
<th>Severe sepsis (n = 9)</th>
<th>Septic shock (n = 18)</th>
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<td>Age (years)</td>
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</table>
P24

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

M Saxena1,2, P Young3, R Beasley4, M Bailey2, R Bellomo3, D Pilcher5, S Finfer1,2, D Hansson6, J Myburgh1,3, K Rowan8

1George Institute for Global Health, Sydney, NSW, Australia; 2Intensive Care Unit, Wellington Regional Hospital, Capital and Coast District Health Board, Wellington, New Zealand; 3Medical Research Institute of New Zealand, Wellington, New Zealand; 4Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia; 5Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation, Melbourne, VIC, Australia; 6Sydney Medical School, University of Sydney, NSW, Australia; 7Sydney Medical School, University of New South Wales, Sydney, NSW, Australia; 8Intensive Care National Audit and Research Centre, London, UK


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.

References


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 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 of death with the temperature component removed for the ANZ data.

ICNARC CMP
ANZICS CORE

ACUTE

ICNARC CMP
ANZICS CORE

Peat temperature (°C)
0.0 0.5 1.0 1.5 2.0 2.5 3.0
34.0 34.5 35.0 35.5 36.0 36.5 37.0

Peat temperature (°C)
0.0 0.5 1.0 1.5 2.0 2.5 3.0
22.0 22.5 23.0 23.5 24.0 24.5 25.0

ICNARC CMP
ANZICS CORE

Peak temperature (°C)
0.0 0.5 1.0 1.5 2.0 2.5 3.0
28.0 28.5 29.0 29.5 30.0 30.5 31.0

ICNARC CMP
ANZICS CORE

Peak temperature (°C)
0.0 0.5 1.0 1.5 2.0 2.5 3.0
0.0 0.5 1.0 1.5 2.0 2.5 3.0

Adjusted* Odds Ratio (95% CI)

Adjusted* Odds Ratio (95% CI)
P26
Prehospital identification of sepsis patients and alerting of receiving hospitals: impact on early goal-directed therapy
K Halimi1, J Freeman-Garriock1, C Agcaoili1, K Choy1, F Claridge1, M Jacobs1, M Taigan2
1Department of Emergency Medicine and Intensive Care, Washington Hospital, Fremont, CA, USA; 2Highland Hospital, Oakland, CA, USA

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 alert providers 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
V Kumar, S Chhibber
Department of Microbiology, Panjab University, Chandigarh, India

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 mg/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 and NO levels in 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 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
Z Wang, V Taylor, R Stidwill, J Leiper, M Singer
Bloomsbury Institute of Intensive Care Medicine, Department of Medicine, University College London, UK

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 dimethylarginine (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).

<table>
<thead>
<tr>
<th>Variable</th>
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<th>NE + L-257</th>
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<tbody>
<tr>
<td>SV (ml/minute)</td>
<td>0.18 ± 0.04</td>
<td>0.23 ± 0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>HR (beats/minute)</td>
<td>500 ± 15</td>
<td>449 ± 37</td>
<td>0.03</td>
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<tr>
<td>CO (ml)</td>
<td>90 ± 18</td>
<td>102 ± 19</td>
<td>0.31</td>
</tr>
<tr>
<td>U (mm)</td>
<td>16.6 ± 1.2</td>
<td>12.8 ± 1.7</td>
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<tr>
<td>BUN (mg/dl)</td>
<td>44.8 ± 3.7</td>
<td>35.9 ± 4.8</td>
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<tr>
<td>Cr (μM)</td>
<td>513 ± 15.2</td>
<td>318 ± 4.3</td>
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<tr>
<td>ALT (IU/l)</td>
<td>98 ± 79.8</td>
<td>71.3 ± 48.3</td>
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</table>

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 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. 3 mg/kg; §P <0.05, 300 mg/kg vs. control. (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 mg/kg.
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 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.

**Acknowledgements** This study was funded by Wellcome Trust in the UK.

**P31**

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

JM-C Yang

Department of Surgery, Kaohsiung Veterans General Hospital, Taiwan, China


**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 16S rDNA loads. Descriptive and clinical data were collected from the medical records and compared with 23S and 16S 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

S Shibata

Akita University Graduate School of Medicine, Department of Cell Physiology, Akita, Japan


**Introduction** β-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 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 (IᵢKr), while the L-type Ca²⁺ current (Iᵥ) and outward current (Iᵥ) 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 ion currents. In the Kyoto Model computer simulation, sole inhibition of Iᵥ or IᵢKr 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 Iᵥ and IᵢKr, and inhibition of ion 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
F Lupu1, H Zhu, R Silasi-Mansat1, C Georgescu1, N Popescu1, G Peer1, C Lupu1, F Taylor1, G Kinasewitz1, J Lambiri2
1Cardiovascular Biology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA; 2Department of Pathology, Oklahoma University Health Sciences Center, Oklahoma City, OK, USA; 3Neuroscience Research Department, Mayo Clinic Jacksonville, FL, USA; 4Department of Medicine, Pulmonary and Critical Care Division, Oklahoma University Health Sciences Center, Oklahoma City, OK, USA; 5Department of Pathology and Laboratory Medicine, School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Introduction Pulmonary fibrosis is a major and common medical condition, characterized by progressive scarring 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. 

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, Sirtus 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).

Acknowledgements The authors thank Dr. Barton Frank (OMRF) for help with protein array scanning and quantitation. This work was supported by grants from the National Institutes of Health (GM097747-01 to FL and JL; 2P20RR018758-06A2 and 1RC1GM09739-02 to FL; AI068730 and GM062134 to JL).

Table 1 (abstract P34).

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<th>E. coli + CS T+S</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Up</td>
<td>Down</td>
<td>Total</td>
</tr>
<tr>
<td>Fibroblast transformation</td>
<td>32</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>Connective tissue disorder</td>
<td>133</td>
<td>59</td>
<td>192</td>
</tr>
<tr>
<td>Chemotaxis</td>
<td>39</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>Cell migration</td>
<td>95</td>
<td>40</td>
<td>135</td>
</tr>
<tr>
<td>Cell proliferation</td>
<td>187</td>
<td>70</td>
<td>257</td>
</tr>
<tr>
<td>Fibroblast proliferation</td>
<td>23</td>
<td>7</td>
<td>30</td>
</tr>
</tbody>
</table>

CS T+S, 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 (LD₅₀) 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.

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**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 (± 7.7) 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.

**References**


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

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline period</th>
<th>Development sepsis period (DS)</th>
<th>Sepsis intervention period</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG 3.68 (0.29)</td>
<td>3.68 (0.29)</td>
<td>4.12 (0.29)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CG 3.68 (0.29)</td>
<td>3.68 (0.29)</td>
<td>4.12 (0.29)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG 5.67 (0.45)</td>
<td>3.21 (0.22)</td>
<td>3.21 (0.22)</td>
<td>5.63 (0.53)</td>
<td></td>
</tr>
<tr>
<td>CG 6.60 (6.5)</td>
<td>66.0 (6.5)</td>
<td>66.0 (6.5)</td>
<td>108.8 (6.8)</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG 93.7 (5.1)</td>
<td>102.3 (5.6)</td>
<td>102.3 (5.6)</td>
<td>86.1 (4.1)</td>
<td></td>
</tr>
<tr>
<td>CG 97.3 (5.1)</td>
<td>102.3 (5.6)</td>
<td>102.3 (5.6)</td>
<td>86.1 (4.1)</td>
<td></td>
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<tr>
<td>RBF</td>
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<tr>
<td>AG 217.3 (14.8)</td>
<td>217.3 (14.8)</td>
<td>217.3 (14.8)</td>
<td>324.8 (19.7)</td>
<td></td>
</tr>
<tr>
<td>CG 217.3 (14.8)</td>
<td>217.3 (14.8)</td>
<td>217.3 (14.8)</td>
<td>324.8 (19.7)</td>
<td></td>
</tr>
<tr>
<td>UO</td>
<td></td>
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</tr>
<tr>
<td>AG 31.1 (7.1)</td>
<td>31.1 (7.1)</td>
<td>31.1 (7.1)</td>
<td>22.1 (4.8)</td>
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</tr>
<tr>
<td>CG 34.8 (7.0)</td>
<td>34.8 (7.0)</td>
<td>34.8 (7.0)</td>
<td>16.8 (11.0)</td>
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<td>TPC</td>
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</tr>
<tr>
<td>AG 34.3 (3.1)</td>
<td>34.3 (3.1)</td>
<td>34.3 (3.1)</td>
<td>63.9 (6.8)</td>
<td></td>
</tr>
<tr>
<td>CG 38.2 (3.4)</td>
<td>38.2 (3.4)</td>
<td>38.2 (3.4)</td>
<td>63.9 (6.8)</td>
<td></td>
</tr>
<tr>
<td>SV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG 51.2 (4.6)</td>
<td>51.2 (4.6)</td>
<td>51.2 (4.6)</td>
<td>51.4 (6.8)</td>
<td></td>
</tr>
<tr>
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<td>51.4 (3.7)</td>
<td>51.4 (3.7)</td>
<td>51.4 (6.8)</td>
<td></td>
</tr>
<tr>
<td>RVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG 2.39 (0.18)</td>
<td>2.39 (0.18)</td>
<td>2.39 (0.18)</td>
<td>3.74 (0.41)</td>
<td></td>
</tr>
<tr>
<td>CG 2.23 (0.16)</td>
<td>2.23 (0.16)</td>
<td>2.23 (0.16)</td>
<td>3.53 (0.44)</td>
<td></td>
</tr>
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</table>

Values are the mean (± standard error). P value: two-way repeated-measures ANOVA interaction between treatment group and time (see text for definitions).
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
angiopeptin-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, 10^10 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 10^8 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 FeTMPyP (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 increased (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. Staphylococcus 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).

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.

Reference

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

<table>
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<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>Crude OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia, Hb &lt;9 g/dl</td>
<td>0.91 (0.74 to 4.93)</td>
<td>1.05 (0.56 to 1.80)</td>
</tr>
<tr>
<td>Blood culture positive</td>
<td>4.8 (1.50 to 15.0)</td>
<td>2.38 (1.14 to 4.95)</td>
</tr>
<tr>
<td>GCS ≥13</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MAP ≤65</td>
<td>2.10 (0.70 to 6.80)</td>
<td>1.25 (0.56 to 2.81)</td>
</tr>
<tr>
<td>HIV</td>
<td>Negative</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>4.20 (1.00 to 17.00)</td>
<td>2.35 (0.88 to 6.28)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7.70 (1.20 to 47.70)</td>
<td>8.38 (2.36 to 29.7)</td>
</tr>
<tr>
<td>&lt;1 hour to IVF</td>
<td>0.40 (0.10 to 1.10)</td>
<td>0.86 (0.43 to 1.72)</td>
</tr>
<tr>
<td>&gt;1 hour to IVF</td>
<td>0.80 (0.30 to 2.00)</td>
<td>0.81 (0.41 to 1.61)</td>
</tr>
<tr>
<td>HIV in first 6 hours</td>
<td>0.30 (0.10 to 1.10)</td>
<td>0.60 (0.23 to 1.58)</td>
</tr>
</tbody>
</table>

Statistically significant ORs in bold.

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
P Newham1, P Ceuppens1, S Das1, JTV Yates1, R Knight1, JS McKay2
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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
Hypothesis
Endotoxin absorption therapy is effective against abdominal infection. 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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1Internal Medicine Department, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia; 2The Indonesian Society for the Study of Tropical Medicine and Infectious Diseases, Jakarta, Indonesia

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 (8,18). 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.
were by using bivariate analysis, in which variables that influenced the occurrence of deaths (indicated by \( P < 0.025 \)) 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.

**Acknowledgments** The authors thank the nurses and administrative staff in the Division of Tropical Medicine and Infectious Diseases, Department of Internal Medicine, Faculty Medicine, University of Indonesia for their assistance in this study.

### References


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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, resulting in the 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...
The apoptotic response of the lymphoid system

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

Results

Conclusion


data presented as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Day</th>
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<tr>
<td></td>
<td>Group I</td>
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<tr>
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<td>3</td>
<td>26.5 ± 4.4</td>
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<tr>
<td>5</td>
<td>39.3 ± 4.1</td>
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<td>7</td>
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Table 2 (abstract P44). Caspase-3 intestinal expression

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<th>Amount of cell expression</th>
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<td>Group I</td>
</tr>
<tr>
<td>1</td>
<td>8.5 ± 2.9</td>
</tr>
<tr>
<td>3</td>
<td>14.7 ± 3.1</td>
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<tr>
<td>5</td>
<td>33.2 ± 8.3</td>
</tr>
<tr>
<td>7</td>
<td>42.3 ± 3.2</td>
</tr>
</tbody>
</table>

References

1. Hongwei Q, Cynthia AW, Sun JL, Xueyan Z, Etty NB: Effect of low-dose corticosteroids on mortality. This study found dead animals for Group I were 70%, while Group II were 10% (P = 0.020).


3. Chung CS, Chaudry IH, Ayala A: Low-dose corticosteroids can reduce mortality. This study found dead animals for Group I were 70%, while Group II were 10% (P = 0.020).


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

6. Chung CS, Chaudry IH, Ayala A: Low-dose corticosteroids can reduce mortality. This study found dead animals for Group I were 70%, while Group II were 10% (P = 0.020).


Objective To systematically assess clinical evidence concerning mortality, coagulation and renal function.

Methods Systematic review of randomised controlled trials (RCT) on gelatin in hypovolemic 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 transfusion were provided in 11 RCT, n = 1,148 patients and the RR was 1.16 (CI 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.

Introduction Gelatin is frequently used as volume expander. There are growing concerns about safety.

P47 Disseminated infections, caused by yeast-like fungi
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Background Disseminated infections, caused by yeast-like fungi, are life-threatening, mostly nosocomial infections, predominantly in immunocompromised patients (hematological, transplant patients), with the incidence getting higher over the past decades [1,2,3]. Mortality in disseminated candidiasis infection could reach up to 60% of patients, mostly in the intensive care unit. Candida is the fourth most common cause of bloodstream infection in the US hospitals [4]. The aim of this study was to determine the most commonly isolated yeasts, responsible for disseminated infections in hospital patients in Saint-Petersburg, Russia, and to evaluate the effective therapeutic regimens.

Materials and methods Hospitalized immunocompromised patients, who met the sepsis criteria and did not respond to antibacterial treatment for 3 days, were evaluated for the presence of yeast-like fungi in blood with BactAlert system. The diagnosis of disseminated infection was confirmed by isolation of fungus from at least 2 consecutive blood samples and the evidence of deep-seated organ involvement (lungs, brains, etc.) or typical eyes / skin lesions. The isolated yeasts were identified with routine mycological methods (morphology of colonies; microscopic examination; tests of growth tubes formation, formation of chlamydospores, tests of assimilation and fermentation of hydrocarbons) and sequencing of D2 region (ABI Prism 3130, MicroSeq D2 fungal library v2.0). The sensitivity to antifungal agents was tested with the broth microdilution method. The antifungal preparations were administered on the empiric basis and corrections were made after the clinical effectiveness of the start regiment and in vitro sensitivity to antifungals were evaluated in 3 or more days.

Results Thirty-one patients with disseminated infections caused by yeast-like fungi were observed: 30 adults (mean age was 49.6±2.4 years, 17 men and 13 women), one male patient was under 1 year of age. Disseminated infections were predominantly caused by Candida spp. (Candida albicans, Candida parapsilosis, Candida krusei, Candida tropicalis), 1 patient (male, 56 years old, with acute leukemia) developed disseminated infection, caused by Trichosporon faealis. Disseminated C albicans, C parapsilosis and T faealis infections were treated with fluconazole in daily dose 400 mg after a loading dose 800 mg during 21-35 days. The treatment was successful in all cases except the sepsis in a newborn due to C parapsilosis. The starting regiment in this case was 6 mg/kg/day. Intermediate susceptibility to fluconazole and itraconazole was revealed in the isolate. The therapy was changed to micafungin (2 mg/kg/day) with favorable mycological and clinical outcome. In 2 cases of C tropicalis infections treatment with fluconazole was ineffective despite the sensitivity of isolates to fluconazole in vitro. Addition of caspofungin (70 mg loading dose followed by 50 mg daily dose) to the therapeutic regiment showed good clinical and mycological response. In one case of disseminated infection caused by C krusei the isolate was sensitive to itraconazole in vitro and the preparation was used successfully in daily dose 600 mg for 3 days followed by 39 days in daily dose 400 mg.

Conclusions Candida spp. dominate as the ethiological agents of sepsis, caused by yeast-like fungi in immunocompromised hospitalized patients in Saint-Petersburg, Russia, with C albicans being the most frequently isolated pathogen.

Modern antifungals allow successful treatment of disseminated candidiasis in all cases. Sepsis due to T faealis can be successfully treated with fluconazole.

References

P48 Low-dose corticosteroids effects on clinical improvement sepsis patients with APAACHE II score
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Jl Puri Pantai Dalam FK Universitas Sebelas Maret, Jl Ir Sutami No. 36a, Keningan, Jepara, Surakarta, Indonesia

Background Mortality rate in sepsis still remains higher both in developed and developing countries. Low dose corticosteroid has
beneficial effect to ameliorate adrenal function due to stress condition and lessen antiinflammation components [1,2]. APACHE II score is one of the most predictor factors for grading and evaluate the severity [3,4]. If APACHE II score combined with the sign of the disease is useful to grade acute disease based on prognosis and assist researcher to compare prospering of new therapy.

**Objectives** Objective of this study is offering clinical evaluation the effect of low dose corticosteroid for septic patient using APACHE II score.

**Materials and Methods** Type of this study is RCT (randomized clinical trial). The study is conducted in Department Internal Medicine-RSUD of Dr Moewardi, Surakarta, December 2008–May 2009. In the subjects with corticosteroid treatment obtain metylprednisolon i.v 20 mg/8 hours. The evaluation using APACHE II score on the admission day, 3rd, 5th, and the 7th day. Hypothesis test is using unpair t-test or Mann Whitney test for alternative.

**Results** There were 26 subjects with fully follow-up evaluation for 7 days. At the initial study were obtained the same condition between subject with corticosteroid treatment and without corticosteroid. There was 26 subjects with fully follow-up evaluation for 7 days. At the initial study were obtained the same condition between subject with corticosteroid treatment and without corticosteroid. There was no statistically significant result for APACHE II score and PDR (P =0.017) in the 7th day of follow-up (p >0.05) but there is significant result for APACHE II score and PDR (P =0.017) in the 7th day of follow-up (see Figures 1 and 2).

**Conclusion** Low dose corticosteroid can ameliorate clinical condition of the septic patients using APACHE II score.

**References**

**Table 1:**

<table>
<thead>
<tr>
<th>Etiologic agents</th>
<th>Antisepsis Center patient data</th>
<th>Center of Cardiology patient data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Streptococcus epidemidis</td>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td>Nontoxigen Pneumoniae</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>15%</td>
<td>40%</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>3%</td>
<td>-</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>-</td>
<td>5%</td>
</tr>
<tr>
<td>Candida</td>
<td>-</td>
<td>10%</td>
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</table>

While all patients from Cardiologic Center had leukocytosis, it was detected only in 38% of patients from Antisepsis Center and remaining 8% had leucopenia and 52% had normocytosis. In spite of the severe course all patients in Antisepsis Center recovered while mortality rate approached 20% among patients in Cardiologic Center. 

**Conclusions** Specifics of nosocomial infections depends on multiple environmental factors including hospital flora and underlying conditions. Identifying the spectrum of the most common pathogens in specific hospitals led to creation of effective strategy for empirical treatment. Although any bacteria can become a cause of nosocomial infections the most commonly isolated bacteria was Staphylococcus aureus usually as MRSA. After studying the resistance patterns the most effective antibiotic therapy was combination of imipenem and aminoglicoside, as well as piperacillin-tazobactam. Levofloxacin was effective in number of cases and vancomycin was used in infections with MRSA. The most important means of prevention was to minimize invasive procedures, the use of broad-spectrum antibiotics and use of thorough hygiene procedures. Such measures whenever possible were correlated with better outcome.
P50
The expression of HLA-DR at newborns monocytes with septic complications
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Scientific Institute of Obstetrics and Pediatrics, Russian Federation

Introduction In modern pediatrics the problem of early diagnostics of purulo-septic complications at newborns in critical states is complicated due to the development of systemic inflammatory reaction right after a birth of an infant manifesting in progressing respiratory insufficiency, increasing disturbance of hemodynamics and multiple organ failure. The immune system is sure to play the leading part in the development, clinical course, and results of pyoinflammatory diseases. Therefore the research of objective, highly sensitive and specific markers for the early diagnosis of sepsis in newborns remains to be proven.

Methods Fifty-six newborns with syndrome of respiratory disturbances and perinatal defeat of a central nervous system were examined, infants being at artificial pulmonary ventilation, receiving therapy in resuscitation department and intensive therapy. In 19 infants the level of HLA-DR expression on monocytes did not exceed 40%. Later in these patients neonatal sepsis was diagnosed, the disease being confirmed by laboratory and bacteriological analyses. Due to early diagnosis of the development of this disease and timely strengthening of antibacterial and intensive therapy only in 2 patients the lethal outcome was registered.

Results Pathological anatomy research in all the dead children revealed neonatal sepsis. In 37 infants HLA-DR expression on monocytes was not reduced below concentration of 40%. The course of the main disease in these patients was not complicated with the development of neonatal sepsis.

Conclusions Thus, due to our investigations it was established that monocytes of newborns with septic complications expressed HLA-DR + (43.6% and are lower) to considerable less degree, than monocytes of newborns without those (86.6%). The monitoring definition of relative content of HLA-DR + monocytes allows diagnosing with a high degree of probability the development of neonatal sepsis in newborns at a preclinical stage. The received findings allow optimizing intensive therapy in carrying out sound immunocorrection.

P51
Syrian measures and strategy of tuberculosis management
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Background Tuberculosis (TB) is one of the health priorities in Syria, with an estimated annual incidence of 18 new smear positive cases per 100,000. Each year 3,400 individuals develop active TB (smear positive TB). Of these new cases, only 1561 were detected and treated by the National Tuberculosis programme (NTP), while 1839 were either not treated or inadequately treated by other health sectors. The goal is to reduce TB burden in Syria particularly among the poor and vulnerable populations in line with the MDG.

Materials and methods Diagnostic measures to ensure full access to services, referral procedures, and patient treatment protocols are defined at all stages, by a series of regulatory documents of the Syrian Ministry of Health.

Results The average age of TB patient in Syria is approximately 33 years, and more than 82% of the cases are from the productive age group (15-54). While there is no large-scale surveillance mechanism, a preliminary study found that in cultures obtained from 295 patients, 215 (72.88%) were fully sensitive to first-line drugs, while 80 (27.12%) were resistant to one or more drugs, the main challenge reflects on one side the low access of TB diagnostic services outside the coverage of Ministry of Health facilities, the urgent need to deal comprehensively with the TB problem and involve all TB stakeholders in providing standardized TB care, on the other side there could be a need to revisit the estimate of new smear positive TB incidence.

Conclusions The programme has achieved the global target of 85% treatment success rate (TSR) but is still far behind the case detection target of 70%. In order to achieve the above goal, the program will give a special emphasis on TB care for poor and vulnerable populations, and will address the 5 gaps identified in the overall needs assessment.

P52
Pulmonary Embolism in Sepsis Patient Following Appendectomy Surgery
A Case Report, S Lardo1, A Arianne2, K Chen2
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Background Sepsis is one of the major causes of mortality in critically ill patients and develops as a result of the host response to infection. The endothelium is a major target of sepsis-induced events and endothelial cell damage accounts for deposition of fibrin and the occlusion of capillaries by microthrombi.

Case illustration A 43-year-old woman, who underwent appendectomy surgery 5 days before, presented with pain in the surgical site, progressive severe dyspnea, chest tightness, and fever. The physical examination findings were notable for tachycardia, tachypnea, temperature of 37.8°C, rales in the right lung, and viscous pus coming from the surgical site. Arterial blood gas measurements performed while the patient was breathing room air were as follows: pH 7.45, PaCO2 34.6 mmHg, PaO2 62.5 mmHg, and SaO2 92.5%. Hemostasis profile showed D Dimer: 3441.9 ng/ml, PT 15 (c: 14) sec, APTT 34(c: 32) sec, and fibrinogen 685 mg/dL. There was also increasing of leucocyte 14.400/mm3, CRP > 120 mg/L, and procalcitonin 0.92 µL. On chest radiograph there was pleuropneumonia with minimal effusion in right side. The CT angiography of the chest and CT abdomen showed intralumen emboli in medial lobe segment of right pulmonary artery, right pleuropneumonia with segmental lesion in segment 10 right lobe and inflammation process along right lateral wall of the abdomen. The pus culture showed Escherchia coli ESBL (+) sensitive to carbenapen. The patient was given enoxaparin 40mg sc twice daily and meropenem 1 gr with extended infusion three times daily. After 8 days of treatment, patient was free from symptoms, no pus at the surgical site, CRP level was 6 mg/L, procalcitonin level was < 0.05 µg/L, the blood culture sterile, and patient discharged from hospital.

Discussion Severe sepsis can occur as a result of infection at any body site, including the lungs, abdomen, skin, or soft tissue. Sepsis mediators damage the endothelial lining, leading to increased capillary leakage. As a result of sepsis inflammatory cytokines, tissue factor, the first step in the extrinsic pathway of coagulation, is also expressed on the surfaces of the endothelium and of monocytes. Tissue factor leads to the production of thrombin, which itself is a proinflammatory substance. Proinflammatory cytokines also disrupt the body’s naturally occurring modulators of coagulation and inflammation, activated protein C (APC) and antithrombin. This homeostasis imbalance leads to thrombo or microthrombi generation. This case showed that infection in surgical site at the abdomen can lead to sepsis and its complication, pulmonary embolism; therefore, infection control and prophylatic treatment of pulmonary embolism is important.

Conclusion As a result of the vicious cycle of inflammation and coagulation, and impairment in fibrinolysis, there was homeostasis loss in sepsis leading to thrombi and microthrombi development. Efforts to early detection and treatment of pulmonary emboli and sepsis control must be taken to prevent fatal outcome.
P53
Is a human sequential organ failure assessment scoring applicable in a porcine model of severe Staphylococcus aureus sepsis?
KE Soerensen1, OL Nielsen1, MM Birck1, DB Soerensen1, PS Leifsson1, HE Jensen1, B Aalbaek1, AT Kristensen1, B Winberg2, M Kjelgaard-Hansen2, PMH Heegaard3, Tim Iburg1.
1Department of Veterinary Disease Biology, Faculty of Life Sciences, University of Copenhagen, Copenhagen, Denmark; 2Department of Small Animal Clinical Sciences, Faculty of Life Sciences, University of Copenhagen, Copenhagen, Denmark; 3Innate Immunology Group, Division of Veterinary Diagnostics and Research, National Veterinary Institute, Technical University of Denmark, Copenhagen, Denmark

Background The human Sequential Organ Failure Assessment (SOFA) score is used in intensive care units for assessing the extent of organ dysfunction or failure in patients with severe sepsis [1]. SOFA scoring is based on evaluation of the respiratory, haemostatic, hepatic, cardiovascular, central nervous and renal systems by the following measurements: PaO2/FIO2 ratio, platelet count, bilirubin, mean arterial pressure (MAP), Glasgow coma score and creatinine levels. Treating severe sepsis is difficult and valid animal models are important for developing new treatment strategies. Pigs are prone to develop sepsis following intravenous inoculation of Staphylococcus aureus [2,3]. In this study, the human SOFA score was applied in a porcine model of severe S. aureus sepsis.

Materials and Methods Five pigs were intravenously inoculated with a saline suspension of S. aureus (1x108 CFU/kg body weight). Two control pigs were sham-inoculated. Prior to inoculation all animals were equipped with a telemetric pressure catheter in a. iliaca externa and vascular access ports in the left a. carotis interna and v. jugularis interna respectively for blood sampling. Blood were sampled 4 times before inoculation and every 6 hours post inoculation. By 48 hours all animals were euthanized, gross pathological changes recorded and tissue sampled for histology.

Results All inoculated animals developed severe sepsis. Decreasing PaO2/FIO2 ratio and increasing bilirubin levels corresponded to dysfunction/failure of the respiratory and hepatic system respectively. In three inoculated pigs, MAP values decreased over time indicating initial cardio–vascular dysfunction. No changes were seen in creatinine levels. Due to platelet aggregation, accurate platelet count was not found to be an applicable SOFA parameter in this model. Mental assessment by Glasgow coma score was not feasible in pigs.

Conclusions The human SOFA parameters were applicable in this porcine model, making SOFA a valuable tool in identifying dysfunctional/failing organs and increasing the comparative relevance of the model according to the daily evaluation of human patients with severe sepsis. The respiratory system was the first to be affected, corresponding with similar human findings [4]. However, the liver appeared to be previously affected in pigs than in humans [4-6]. Actual SOFA scores could not be obtained in this model, as porcine cut-off values to distinguish between dysfunction and failure were indefinable. In future porcine studies, changes in SOFA parameters could serve as a goal for monitoring the effect of therapeutic intervention, especially if a specific porcine SOFA score is established.

References

P54
The clinical course of a meningococcal septicemia complicated with shock in an unvaccinated population of Georgia
M Javakhadze, T Khuchua, M Ekvitnishvili, M Gigauri
Tbilisi State Medical University, Georgia

Background Meningococcal septicemia remains as an important cause for morbidity and mortality for an unvaccinated population. Neisseria meningitidis has a unique ability to evade the host defense mechanisms. Circulating in a bloodstream the bacteria with its toxins can trigger a cascade of changes towards proinflammation, procoagulation, and hypotension. Disturbances in a coagulation system are well recognized by visible hemorrhagic skin lesions. We aimed to study a clinical course of meningococcal septicemia with shock.

Materials and methods We retrospectively studied case histories of meningococcal septicemia complicated with shock admitted at the Infectious Diseases Hospital of Georgia through the years 2005-2010. The obtained data was statistically processed by the statistical package SPSS-11. We studied a clinical course of the illness emphasizing on the earliest symptoms revealed, the characterization of meningococcal rash, the course of shock and correlation of symptoms with disease outcome.

Results In 2005-2010 a total of 102 patients with meningococcal infection were registered. The meningococcal septicemia with shock was detected in 49 patients among whom 18 cases were lethal. The overall lethality was 17.6%. Distribution of 49 patients (female -27, male -22) with shock through years was as follows: 2005 – 17 patients, 2006 – 10 lethal cases, 2008 – 15 - 3 ; 2009 – 24 - 6 ; 2010 – 10 - 2. The age distribution of the patients were as follows: <=1 years – 10 lethal cases, 5 lethal cases, 1-14 years – 28 patients, 9 lethal cases, 14-65 patients – 9 patients, 4 lethal cases and no patients were more than 65 years old. Meningitis was detected in 28 patients, with 7 lethal cases. Hospitalization was on the 2.1 and 2.35 days of illness, respectively for non- survivors and survivors. Hemorrhagic skin lesions were detected in all patients and in a big majority were developed on the first day of illness. The first element of rash was elevated mostly on lower extremities in survivors and mostly on face in non-survivors. The frequently isolated serotype was N. meningitidis C.

Conclusion A peak incidence was detected in 2009 respectively with a highest mortality rate in Georgia. The morbidity is highest in patients 1-14 years old, but the mortality is higher in patients less than 1 years old and more than 14 years old. Meningitis developed in 57% of patients. The mortality was not induced by a late hospitalization.

P55
Clinical course and outcome of fatal fulminant meningococcemia
M Javakhadze, T Khuchua, M Ekvitnishvili, M Gigauri
Tbilisi State Medical University, Georgia

Background Fulminant meningococcemia is clinically expressed by a rapid septic shock with a prominent haemorrhagic skin lesions, which are the result of endothelial injury and coagulopathy. The extreme form of the disturbances in a coagulator system during meningococcemia is expressed as disseminated intravascular coagulation (DIC). Both shock or DIC, separately from each other, can cause mortality. Although the overlapping of these 2conditions may occur, fulminant meningococcemia is characterized with a high mortality rate. Our aim was to study the clinical course of fatal fulminant meningococcemia.

Materials and methods We retrospectively studied cases of fatal fulminant meningococcemia hospitalized at the Infectious Diseases, AIDS and Clinical Immunology Scientific Practical Center of Georgia

References

between 2005-2010. The obtained data was statistically processed by the statistical package SPSS-11.

**Results**

Eighteen fatal cases (17.6% of all hospitalized patients with meningococcal infection in the hospital) were studied, female-9, male-9. Age of patients was as follows: <1 year- 5 patients; 1-14 years- 9 patients, 14-65 years- 4 patients. Time of hospitalization from the onset of illness was as follows: first day – 5 patients, 2nd day – 6 patients, 3rd day – 4 patients, 4th day – 1 patient, 5th day – 1 patient. The disease began with nasopharyngitis in 6 patients, who were hospitalized on2nd to 5th days from the onset of illness. Shock was detected at the admittance in 18 patients, meningitis developed in 8 patients, DIC syndrome in 4 patients, acute lung injury in 6 patients, coma in 2 patients, encephalitis in 2 patients. Mechanical lung ventilation was needed in 5 patients. The rash was detected in all patients with fast or rapid progression beginning on the first day of illness in 10 patients; the first element was detected on face in 5 patients; a tendency to confluence was detected beginning on the first day of illness in 10 patients; the first element was not a reason for lethal outcome but the lethal outcome was induced by rapid onset, fulminant progress of the illness, and development of septic shock. The death was registered on the first day of hospitalization in 89%. Meningococcal encephalitis developed in 11% of patients with meningococcal infection in the hospital. The death was registered on the first day of hospitalization in 14%.

**Conclusion**

The rate of lethal outcome was 17.6%. Late hospitalization is not a reason for lethal outcome but the lethal outcome was induced by rapid onset, fulminant progress of the illness, and development of septic shock. The death was registered on the first day of hospitalization in 89%. Meningococcal encephalitis developed in 11% of patients with meningococcal infection in the hospital (were hospitalized on 2nd to 5th days from the onset of illness). Shock was detected at the admittance in 18 patients, meningitis developed in 8 patients, DIC syndrome in 4 patients, acute lung injury in 6 patients, coma in 2 patients, encephalitis in 2 patients. Mechanical lung ventilation was needed in 5 patients. The rash was detected in all patients with fast or rapid progression beginning on the first day of illness in 10 patients; the first element was detected on face in 5 patients; a tendency to confluence was detected beginning on the first day of illness in 10 patients; the first element was not a reason for lethal outcome but the lethal outcome was induced by rapid onset, fulminant progress of the illness, and development of septic shock. The death was registered on the first day of hospitalization in 89%. Meningococcal encephalitis developed in 11% of patients where coma was the reason of death.

**P56**

**Septic Arthritis in Newborns – the System Approach to the Diagnostics and Treatment**

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2Scientific Research Institute of Orthopedics of the Academy of Medical Sciences of Ukraine, Kiev, Ukraine

**Aim**

To show the effectiveness of the system approach to the treatment of septic arthritis in newborns. The approach is based on presented results of experimental investigations.

**Material and methods**

Presented resume of epiphyseal osteomyelitis (septic arthritis) in rabbits 2-4 months old, 20-years experience (1990-2010) of using system approach to the diagnostics and treatment of newborns and infants up to 3 months old with septic affection of hip, shoulder, elbow and ankle joints. The main role in the diagnosis was played by cytology of joint liquid smear, ultrasound and X-ray investigations, bacteriological and serological monitoring, a number of biochemical investigations, such as alkaline phosphatase, CRP, investigations of coagulation system, PCT. The treating complex included: joint lavage, antibiotics, anticitokines medicines, antifungal agents, probiotics and magnetic/laser therapy.

**Results**

During the cytological investigations of the joint liquid detected over 10 leukocytes, ultrasonic examination detected turbid liquid during 2-3 day from the onset of a decease, X-Ray - only in 10% became informative. During the serological investigations in 30-40% the different staphylococci were leading (CoMRSA, MRSA, MSSA), under 20% were enterococci (Streptococcus faecalis, Streptococcus faecium), a number of patients had Gram-negative and microflora and fungi, in 10% - bacterial and fungal flora could not be detected, in these patients the deceases were caused by TORCH infections, the most frequent there were Toxoplasma gondi, CMV, less common - Chlamidia trachomatis. The staphylococcus, streptococcus and Gram-negative microflora antibodies were detected by serologic investigations. The severity of infection process was reflected by impaired coagulation – PT over 16", APTT under 82" (normal feature is under 42), fibrin monomer complexes – over 3; PCT <0,5 ng/ml, CRP<10 mm/l. The most effective for the treatment were the combination of glycopeptides (vancomycin or targcocid) with clindamycin – for MRSA and carbapenems with anfotericin B for MSSA. These antibacterial complexes were always combined with local lavage of joints with pyrogen-free water, antiseptics, and for 5 last years – with antibiotic rifampin. Also, it was combined with system prescription of antifungal medicines – diflukan or Amphotericin B. Simultaneously the physiotherapy – magnetic laser or bione was carried out. Anti-inflammatory therapy was made for 3-4 weeks. The time of antibacterial therapy termination was detected by the absence of leukocytes in smears, by PCT, CRP level, ultrasonic and X-ray investigations data.

**Conclusion**

The results of the treatment depends on the term of the administration to hospital – the best results were obtained with the admisay – 1 day, patient, 4th day – within 3 days, the 5th day – patient, 5th day – 1 patient. The disease began with nasopharyngitis in 6 patients, who were hospitalized on2nd to 5th days from the onset of illness. Shock was detected at the admittance in 18 patients, meningitis developed in 8 patients, DIC syndrome in 4 patients, acute lung injury in 6 patients, coma in 2 patients, encephalitis in 2 patients. Mechanical lung ventilation was needed in 5 patients. The rash was detected in all patients with fast or rapid progression beginning on the first day of illness in 10 patients; the first element was detected on face in 5 patients; a tendency to confluence was detected beginning on the first day of illness in 10 patients; the first element was not a reason for lethal outcome but the lethal outcome was induced by rapid onset, fulminant progress of the illness, and development of septic shock. The death was registered on the first day of hospitalization in 89%. Meningococcal encephalitis developed in 11% of patients where coma was the reason of death.

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**Colloid treatment in sepsis patients in intensive care – use of albumin versus hydroxyethyl starch (HES) is cost-effective in a decision analysis model**

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**Introduction**

Sepsis is a major source of mortality and morbidity in intensive care patients, leading to significant hospital costs. Recent data from clinical trials [1] and meta-analysis [2] suggests that the administration of albumin in sepsis may be beneficial. Hydroxyethyl starch (HES), a synthetic colloid less costly than albumin on a unit basis has been proposed as an alternative. However, adverse effects on renal function [3] and an increased risk of bleeding [4] may play a role in the overall cost-effectiveness of this drug. In addition, a considerable part of the evidence base for its use has recently been retracted from the literature because of scientific fraud [5], leaving its efficacy under doubt.

**Materials and Methods**

We have therefore studied the cost-effectiveness of albumin and HES in a decision analysis model using commercial software (TreeAge Software Inc, MA, USA) and published data from peer-reviewed literature for the costs, probabilities and effectiveness measured as life years saved for a hypothetical cohort of sepsis patients drawn from the United States’ Healthcare Cost and Utilization Project (HCUP).

**Results**

Our preliminary results suggest that albumin in the context of colloid use in intensive care patients with sepsis is cost-effective, using accepted levels of willingness to pay (WTP) for years of life saved.

**Conclusions**

The details of the model, sensitivity analysis of the different variables and estimates of the costs for life years saved with the various colloids will be reported.

**References**


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

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