

Here is the latest edition of the Sepsis Bulletin. The bulletin covers the latest information on sepsis and comes out fortnightly. Next edition is due 22 November 2018. Older editions are available as pdfs on the Keeping Up To Date library guide ([http://libguides.bodleian.ox.ac.uk/Keeping\\_up\\_to\\_date](http://libguides.bodleian.ox.ac.uk/Keeping_up_to_date))

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## SEPSIS BULLETIN

### 13 November 2018

#### Neonatal, paediatric and maternal sepsis

[Elevated Serum Total Bilirubin Level Is Associated with Poor Outcomes in Pediatric Patients with Sepsis-Associated Liver Injury](#)

Cui, Y. et al

**Canadian Journal of Infectious Diseases and Medical Microbiology**, vol. 2018,

The aim of this study was to assess the prognostic value of the serum total bilirubin (TBIL) level in pediatric patients with sepsis-associated liver injury (SALI). Elevated serum TBIL level is associated with poor outcomes in pediatric SALI.

[Fluid Bolus Therapy in Pediatric Sepsis: Current Knowledge and Future Direction](#)

Ben Gelbart

**Front Pediatr.** 2018; 6: 308. Published online 2018 Oct 25.

Sepsis is a leading cause of morbidity and mortality in children with a worldwide prevalence in pediatric

#### Adult sepsis (cont.)

Viewpoint - [Antibiotics for Sepsis-Finding the Equilibrium](#)

Klompas, M. et al

**JAMA**, Oct 9, 2018, Vol.320(14), p.1433

Sepsis is medicine's last remaining preserve for unrestrained antibiotic prescribing. The Surviving Sepsis Campaign guidelines recommend empirical broad-spectrum therapy within one hour of triage for both sepsis and septic shock.<sup>1</sup> This recommendation, and mandates that compel it, encourage clinicians to adopt an approach of "treat first, ask questions later" for patients with any possibility of serious infection. This approach fails to account for the difficulties clinicians face with diagnosing infection, especially when patients initially present to care, and the high rate of overdiagnosis of sepsis, and thus risks promoting excess antibiotic use and causing unintended harm.

intensive care units of approximately 8%. Fluid bolus therapy (FBT) is a first line therapy for resuscitation of septic shock and has been a recommendation of international guidelines for nearly two decades. The evidence base supporting these guidelines is based on limited data including animal studies and case control studies. In recent times, evidence suggesting harm from fluid in terms of morbidity and mortality has generated interest in evaluating FBT. In view of this, studies of fluid restrictive strategies in adults and children have emerged. The complexity of studying FBT relates to several points. Firstly, the physiological and haemodynamic response to FBT including magnitude and duration is not well described in children. Secondly, assessment of the circulation is based on non-specific clinical signs and limited haemodynamic monitoring with limited physiological targets. Thirdly, FBT exists in a complex myriad of pathophysiological responses to sepsis and other confounding therapies. Despite this, a greater understanding of the role of FBT in terms of the physiological response and possible harm is warranted. This review outlines current knowledge and future direction for FBT in sepsis.

[The most common causative bacteria in maternal sepsis-related deaths in Japan were group A Streptococcus: A nationwide survey](#)

Tanaka, H. et al

**Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy**, 27 October 2018

The present retrospective study provides an in-depth analysis of the maternal sepsis-related deaths reported in Japan, and aims to guide future care regarding maternal sepsis. This is a nationwide, retrospective, descriptive cohort study. Data were retrospectively analyzed on all maternal death cases related to sepsis reported in Japan from 2010 through 2016. The most common causative bacteria in to maternal sepsis-related death were GAS. When encountering severe sepsis during the peripartum period, we recommend considering severe GAS infection and early intervention.

[Biomarker Phenotype for Early Diagnosis and Triage of Sepsis to the Pediatric Intensive Care Unit](#)

Mickiewicz, B. et al

**Scientific Reports** volume 8, Article number: 16606 (2018)

Early diagnosis and triage of sepsis improves outcomes. We aimed to identify biomarkers that may advance

[Assessing Variability in Hospital-Level Mortality Among U.S. Medicare Beneficiaries With Hospitalizations for Severe Sepsis and Septic Shock](#)

Hatfield, K.M. et al

**Critical Care Medicine**. 46(11):1753-1760, November 2018.

Objectives were to assess the variability in short-term sepsis mortality by hospital among Centers for Medicare and Medicaid Services beneficiaries in the United States during 2013–2014. In a large study of present at admission sepsis among Medicare beneficiaries, we showed that mortality was most strongly associated with underlying comorbidities and measures of illness on arrival. However, after adjusting for patient characteristics, mortality also modestly depended on where a patient with sepsis received care, suggesting that efforts to improve sepsis outcomes in lower performing hospitals could impact sepsis survival.

[Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis](#)

Barbar, S.D. et al.

**New England Journal Of Medicine**, 2018 Oct 11, Vol.379(15), pp.1431-1442

Acute kidney injury is the most frequent complication in patients with septic shock and is an independent risk factor for death. Although renal-replacement therapy is the standard of care for severe acute kidney injury, the ideal time for initiation remains controversial. Among patients with septic shock who had severe acute kidney injury, there was no significant difference in overall mortality at 90 days between patients who were assigned to an early strategy for the initiation of renal-replacement therapy and those who were assigned to a delayed strategy

[Validation of diagnostic gene sets to identify critically ill patients with sepsis](#)

Maslove, D.M. et al.

**Journal of Critical Care**, February 2019, Vol.49, pp.92-98

Gene expression diagnostics have been proposed to identify critically ill patients with sepsis. Three expression-based scores have been developed (1) the Sepsis MetaScore (SMS); 2) the SeptiCyte™ Lab; and 3) the FAIM3:PLAC8 ratio), but have not been compared in a prospective validation. We sought to validate these scores using an independent dataset and analysis. All three scores distinguished septic from non-septic ICU patients, with the SMS showing the best performance overall in our cohort. Our results suggest that models

diagnosis and triage of pediatric sepsis. The metabolic-based biomarkers predicted which sepsis patients required care in a PICU versus those that could be safely cared for outside of a PICU. This has potential to inform appropriate triage of pediatric sepsis, particularly in EDs with less experience evaluating children.

#### [What to do if your child is unwell](#)

##### **The Meningitis Research Foundation (MRF)**

The Meningitis Research Foundation (MRF) has launched a resource highlighting the importance of information for patients at risk of serious infections such as meningitis and sepsis. MRF has launched a newly updated GP handbook which includes a section on safety netting and can be downloaded or ordered free from the website. Doctors can direct patients to this, or download documents for patients to take home so that they know what to do if symptoms progress

#### [Assessment and comparison of bacterial load levels determined by quantitative amplifications in blood culture-positive and negative neonatal sepsis](#)

Stranieri, I. et al

**Rev Inst Med Trop Sao Paulo.** 2018 Oct 25; 60:e61.

Bacterial sepsis remains a major cause of mortality and blood cultures are the gold standard of laboratory diagnosis even though they lack sensitivity in neonates. Culture negative sepsis, also known as clinical sepsis, has long been considered a diagnosis in neonatal intensive care units because, as well as culture-positive infants, culture-negative neonates have worse prognosis in comparison with non-infected ones. Quantitative amplifications are used to detect bacterial infections in neonates but results are considered only in a qualitative way (positive or negative). The aim of the present study was to determine and compare bacterial load levels in blood culture-positive and culture-negative neonatal sepsis. The present study has shown that blood culture-negative neonates have lower bacteria load levels in their bloodstream when compared to blood culture-positive infants.

#### [Comparison of Methods for Identification of Pediatric Severe Sepsis and Septic Shock in the Virtual Pediatric Systems Database](#)

Lindell, R.B. et al

**Critical care medicine,** 31 October 2018

Objectives were to compare the performance of three methods of identifying children with severe sepsis and septic shock from the Virtual Pediatric Systems

developed from the co-analysis of multiple cohorts are more generalizable. Further work is needed to identify expression-based biomarkers of response to specific therapies.

#### [An update on membranes and cartridges for extracorporeal blood purification in sepsis and septic shock](#)

Honoré, P.M. et al.

**Current opinion in critical care,** December 2018, Vol.24(6), pp.463-468

This review aims to summarize the most recent advances on different membranes and cartridges used for extracorporeal blood purification in critically ill patients with sepsis or septic shock. None of the discussed specific membranes or cartridges can currently be recommended as sole adjunctive treatment in sepsis and septic shock. Any available technique should be timely initiated and adapted to the patient's status. Sickest patients seem to benefit more from blood purification. Patient selection is thus of crucial importance and may be optimized by focusing on disease severity and degree of organ failure. Measurement of endotoxin activity and plasma procalcitonin levels can support the selection process but ideal cutoff values need to be defined. Well-designed prospective randomized clinical trials assessing or comparing the various available membranes and cartridges are eagerly awaited.

#### [Adherence to Mediterranean-style diet and risk of sepsis in the REasons for Geographic and Racial Differences in Stroke \(REGARDS\) cohort](#)

Gray, M.S. et al

**The British journal of nutrition,** 30 October 2018, pp.1-7

Sepsis - syndrome of infection complicated by organ dysfunction - is responsible for over 750 000 hospitalisations and 200 000 deaths in the USA annually. Despite potential nutritional benefits, the association of diet and sepsis is unknown. Therefore, we sought to determine the association between adherence to a Mediterranean-style diet (Med-style diet) and long-term risk of sepsis in the REasons for Geographic Differences in Stroke (REGARDS) cohort. High Med-style diet adherence is associated with lower risk of sepsis. Dietary modification may potentially provide an option for reducing sepsis risk.

database to prospective screening using consensus criteria. Children with severe sepsis and septic shock are best identified in the Virtual Pediatric Systems database using explicit diagnosis codes for severe sepsis and septic shock. The accuracy of these codes and level of clinical detail available in the Virtual Pediatric Systems database allow for sophisticated epidemiologic studies of pediatric severe sepsis and septic shock in this large, multicenter database.

[Assessment of blood enterovirus PCR testing in paediatric populations with fever without source, sepsis-like disease, or suspected meningitis: a prospective, multicentre, observational cohort study](#)

Lafolie, J. et al.

**The Lancet. Infectious diseases**, 30 October 2018

Enteroviruses are the most frequent cause of acute meningitis and are seen increasingly in sepsis-like disease and fever without source in the paediatric population. Detection of enterovirus in cerebrospinal fluid (CSF) specimens by PCR is the gold standard diagnostic test. Our aim was to assess a method of detecting enterovirus in blood specimens by PCR. Testing for enterovirus in blood by PCR should be an integral part of clinical practice guidelines for infants aged 2 years or younger. This testing could decrease the length of hospital stay and reduce exposure to antibiotics for low-risk patients admitted to the emergency department with febrile illness.

[Increased surfactant protein-D levels in the airways of preterm neonates with sepsis indicated responses to infectious challenges](#)

Mackay, R-M.A. et al

**Acta paediatrica** (Oslo, Norway : 1992), 29 October 2018

Sepsis is multifactorial and potentially devastating for preterm neonates. Changes in surfactant protein-D (SP-D), phosphatidylcholine (PC) and PC molecular species during infection may indicate innate immunity or inflammation during sepsis. We aimed to compare these important pulmonary molecules in ventilated neonates without or with sepsis. Increased SP-D levels and changes in PC molecular species during sepsis were consistent with direct or indirect pulmonary inflammatory processes. Very preterm neonates were able to mount an acute inflammatory innate immune response to infectious challenges, despite low levels of surfactant proteins at birth.

[Transcriptomic Signatures in Sepsis and a Differential Response to Steroids: From the VANISH Randomized Trial](#)

Antcliffe, D.B. et al

**American journal of respiratory and critical care medicine**, 26 October 2018

There remains uncertainty about the role of corticosteroids in sepsis with clear beneficial effects on shock duration but conflicting survival effects. Two transcriptomic sepsis response signatures (SRS) have been identified. SRS1 is relatively immunosuppressed whilst SRS2 is relatively immunocompetent.

Transcriptomic profile at onset of septic shock was associated with response to corticosteroids. Those with the immuno-competent SRS2 endotype had significantly higher mortality when given corticosteroids compared to placebo.

[Prevalence and Predictors of Sepsis Death in Patients With Chronic Heart Failure and Reduced Left Ventricular Ejection Fraction](#)

Walker, A.M.N. et al

**Journal of the American Heart Association**, 16 October 2018, Vol.7(20), pp.e009684

Noncardiovascular death is increasingly common in people with chronic heart failure (CHF), yet its causes remain poorly characterized. We aimed to define the prevalence of sepsis death in people with CHF and to ascertain its risk marker profile. Sepsis is a major contributor to death in people with CHF and has a different risk marker profile from other modes of death, suggesting that it may be amenable to targeted preventative strategies

[Restricted fluid resuscitation in suspected sepsis associated hypotension \(REFRESH\): a pilot randomised controlled trial](#)

Macdonald, S. et al

**Intensive Care Medicine**, Oct 2018, pp.1-9

To determine if a regimen of restricted fluids and early vasopressor compared to usual care is feasible for initial resuscitation of hypotension due to suspected sepsis. A regimen of restricted fluids and early vasopressor in ED patients with suspected sepsis and hypotension appears feasible. Illness severity was moderate and mortality rates low. A future trial is necessary with recruitment of high-risk patients to determine effects on clinical outcomes in this setting.

## **Adult sepsis**

### [Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis.](#)

Barbar SD

**N Engl J Med.** 2018 Oct 11;379(15):1431-1442. doi: 10.1056/NEJMoa1803213.

Acute kidney injury is the most frequent complication in patients with septic shock and is an independent risk factor for death. Although renal-replacement therapy is the standard of care for severe acute kidney injury, the ideal time for initiation remains controversial. Among patients with septic shock who had severe acute kidney injury, there was no significant difference in overall mortality at 90 days between patients who were assigned to an early strategy for the initiation of renal-replacement therapy and those who were assigned to a delayed strategy.

### [Sepsis in mechanically ventilated patients with spinal cord injury: a retrospective analysis](#)

Weiterer, S. et al

#### **Spinal Cord** (2018)

Sepsis, one of the most frequent and life-threatening complications on intensive care units (ICUs), is associated with a need for mechanical ventilation (MV) as well as adverse respiratory outcomes in hospitalized individuals. However, it has poorly been investigated in patients with spinal cord injury (SCI); a population at high risk for pulmonary and infectious complications. Sepsis predominantly occurs as a secondary complication after SCI and is associated with detrimental outcomes. Although the lung is frequently affected as a failing organ, not all sepsis foci are pulmonary. Awareness of both actual sepsis focus and causative pathogen is central to initiate an adequate sepsis treatment.

### [The surviving sepsis controversy: a call to action for hospital medicine.](#)

Choi, J.J. et al

**Expert Rev Anti Infect Ther.** 2018 Nov 9. [Epub ahead of print]

There remains significant controversy behind the Surviving Sepsis Campaign Guidelines, as evidenced by the Infectious Diseases Society of America refusing to endorse the latest iteration put forth by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. An important stakeholder in this debate has not yet been adequately represented: hospitalists. Areas covered: In this perspective piece we review the key points in this controversy, specifically

### [Ascorbic acid, corticosteroids, and thiamine in sepsis: a review of the biologic rationale and the present state of clinical evaluation](#)

Moskowitz, A. et al

**Critical Care**, 01 October 2018, Vol.22(1), pp.1-7

The combination of thiamine, ascorbic acid, and hydrocortisone has recently emerged as a potential adjunctive therapy to antibiotics, infectious source control, and supportive care for patients with sepsis and septic shock. In the present manuscript, we provide a comprehensive review of the pathophysiologic basis and supporting research for each element of the thiamine, ascorbic acid, and hydrocortisone drug combination in sepsis. In addition, we describe potential areas of synergy between these therapies and discuss the strengths/weaknesses of the two studies to date which have evaluated the drug combination in patients with severe infection. Finally, we describe the current state of current clinical practice as it relates to the thiamine, ascorbic acid, and hydrocortisone combination and present an overview of the randomized, placebo-controlled, multi-center Ascorbic acid, Corticosteroids, and Thiamine in Sepsis (ACTS) trial and other planned/ongoing randomized clinical trials.

### [Tako-Tsubo Cardiomyopathy in Severe Sepsis: Nationwide Trends, Predictors, and Outcomes](#)

Vallabhajosyula, S. et al.

**Journal of the American Heart Association**, 18 September 2018, Vol.7(18), pp.e009160

There are limited data on the presentation of Takotsubo cardiomyopathy (TTC) in severe sepsis. **Methods and Results** This was a retrospective cohort study using the National Inpatient Sample database (2007-2013) of all adults with severe sepsis. TTC was identified in patients with severe sepsis using previously validated administrative codes. TTC is observed with increasing frequency in severe sepsis and was associated with a significantly lower in-hospital mortality compared with patients without TTC. Presentation in later years of the study period, middle age, female sex, and white race were independent predictors for the diagnosis of TTC in severe sepsis.

### [Development and validation of a modified quick SOFA scale for risk assessment in sepsis syndrome.](#)

Cag Y. et al.

**PLoS ONE** 13(9): e0204608. (2018)

Sepsis is a severe clinical syndrome owing to its high mortality. Quick Sequential Organ Failure Assessment



the current guidelines for the identification and management of sepsis. Expert commentary: We believe it is time for hospitalists to weigh in on this important issue by formally commenting on the new guidelines, establishing research priorities, and leading future research studies in the field to help achieve consensus among all clinicians in the appropriate management of sepsis.

[Metabolic resuscitation strategies to prevent organ dysfunction in sepsis](#)

Reitsema, V. et al

**Antioxidants & Redox Signaling** Published Online:7 Nov 2018

Sepsis is the main cause of death among patients admitted to the intensive care unit (ICU). As current treatment is limited to antimicrobial therapy and supportive care, mortality remains high, which warrants efforts to find novel therapies. Mitochondrial dysfunction is emerging as a key process in the induction of organ dysfunction during sepsis and metabolic resuscitation might reveal to be a novel cornerstone in the treatment of sepsis. Here, we review novel strategies to maintain organ function in sepsis by precluding mitochondrial dysfunction by lowering energetic demand to allow preservation of ATP-levels, while reducing free radical generation. As the most common strategy to suppress metabolism, i.e. cooling, does not reveal unequivocal beneficial effects and may even increase mortality, caloric restriction or modulation of energy sensing pathways (i.e. Sirtuins, AMPK) may offer safe alternatives. Similar effects may be offered when mimicking hibernation by hydrogen sulphide (H<sub>2</sub>S). In addition H<sub>2</sub>S may also confer beneficial effects through upregulation of anti-oxidant mechanisms, similar to the other gasotransmitters nitric oxide (NO) and carbon monoxide (CO), which display anti-oxidant and anti-inflammatory effects in sepsis. Additionally, oxidative stress may be averted by systemic or mitochondria-targeted anti-oxidants of which a wide range are able to lower inflammation, and reduce organ dysfunction and mortality from sepsis. Together, mitochondrial dysfunction plays a key role in the pathophysiology of sepsis. As a consequence, metabolic resuscitation might reveal to be a novel cornerstone in the treatment of sepsis.

[Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level: The EUPHRATES Randomized Clinical Trial.](#)

(qSOFA) score has been proposed for the prediction of fatal outcomes in sepsis syndrome in emergency departments. Due to the low predictive performance of the qSOFA score, we propose a modification to the score by adding age. We conducted a multicenter, retrospective cohort study among regional referral centers from various regions of the country.

Participants recruited data of patients admitted to emergency departments and obtained a diagnosis of sepsis syndrome. Crude in-hospital mortality was the primary endpoint. We propose the use of the modified qSOFA score for early risk assessment among sepsis patients for improved triage and management of this fatal syndrome.

[Cytomorphometric Neutrophil and Monocyte Markers May Strengthen the Diagnosis of Sepsis.](#)

Mammen, J. et al

**Journal of Intensive Care Medicine**, 33(12), 656–662 (2018).

The diagnosis of sepsis is challenging in the absence of a gold standard test. Recent studies have explored the role of neutrophil and monocyte volume, conductivity, and scatter (VCS), derived from automated hematology analyzers, in diagnosing sepsis. We assessed the diagnostic accuracy of VCS parameters in critically ill patients with sepsis. In critically ill patients with suspected sepsis, VCS parameters may help strengthen the diagnostic probability of sepsis. Future studies may explore the role of serial monitoring of VCS to track response to antimicrobial therapy.

[Prevalence and Predictors of Sepsis Death in Patients With Chronic Heart Failure and Reduced Left Ventricular Ejection Fraction.](#)

Walker, A.M.N. et al

**J Am Heart Assoc.** 2018 Oct 16;7(20):e009684. doi: 10.1161/JAHA.118.009684.

Noncardiovascular death is increasingly common in people with chronic heart failure (CHF), yet its causes remain poorly characterized. We aimed to define the prevalence of sepsis death in people with CHF and to ascertain its risk marker profile. Sepsis is a major contributor to death in people with CHF and has a different risk marker profile from other modes of death, suggesting that it may be amenable to targeted

[Consideration of Occult Infection and Sepsis Mimics in the Sick Patient Without an Apparent Infectious Source.](#)

Boushra M. et al

Dellinger, R.P. et al

**JAMA.** 2018 Oct 9;320(14):1455-1463.

Polymyxin B hemoperfusion reduces blood endotoxin levels in sepsis. Endotoxin activity can be measured in blood with a rapid assay. Treating patients with septic shock and elevated endotoxin activity using polymyxin B hemoperfusion may improve clinical outcomes. Objective was to test whether adding polymyxin B hemoperfusion to conventional medical therapy improves survival compared with conventional therapy alone among patients with septic shock and high endotoxin activity. Among patients with septic shock and high endotoxin activity, polymyxin B hemoperfusion treatment plus conventional medical therapy compared with sham treatment plus conventional medical therapy did not reduce mortality at 28 days.

**J Emerg Med.** 2018 Nov 2. pii: S0736-4679(18)30954-5. [Epub ahead of print]

Evaluation and treatment of the acutely ill patient is typically complicated by multiple comorbidities and incomplete medical histories. This is exemplified by patients with sepsis, whose care is complicated by variable presentations, shifting definitions, and a variety of potential sources. Many practitioners fail to consider and recognize less-common sources of infection in a timely manner. Additionally, multiple noninfectious conditions can present with the fever and tachycardia typical of the septic patient. The errors of anchoring and premature closure may lead to delay in, or failure of, diagnosis of these conditions. In the seemingly septic patient who does not respond to antimicrobials and fluids, the differential should be broadened to include acutely life-threatening conditions that can mimic sepsis. A review of the patient's medical history, medications, and recent exposures can assist in identifying the source of the patient's elevated body temperature and tachycardia. Consideration of potential sources and other mimics of sepsis is needed in the emergency department.

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