

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 18 January 2019. 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

### 4 January 2019

#### Neonatal, paediatric and maternal sepsis

[Effects of prebiotics on sepsis, necrotizing enterocolitis, mortality, feeding intolerance, time to full enteral feeding, length of hospital stay, and stool frequency in preterm infants: a meta-analysis.](#)

Chi, C. et al

**European journal of clinical nutrition** December 19, 2018

Prebiotics are increasingly recognized as an effective measure to promote health and prevent adverse health outcomes in preterm infants. We aimed to systematically review the randomized controlled trials (RCTs) in this area. The results showed that the use of prebiotics with preterm infants is safe and can decrease the incidence of sepsis, mortality, length of hospital stay, and time to full enteral feeding but not NEC.

#### Adult sepsis (cont.)

[The 2018 Surviving Sepsis Campaign's Treatment Bundle: When Guidelines Outpace the Evidence Supporting Their Use](#)

Spiegel, R. et al

**Ann Emerg Med.** 2018 Aug 30. pii: S0196-0644(18)30607-3

Although well intentioned, the current sepsis bundles and the potential penalties associated with noncompliance lay a heavy weight on ED care absent evidence that a net benefit will follow. The proposed Surviving Sepsis Campaign abbreviated bundle heightens the burden by further restricting the time allotted for the identification and treatment of patients with suspected sepsis, all without any evidence of benefit or knowledge of the logistic consequences or cost. A more thoughtful approach to both the identification and management of patients with sepsis is needed, one that engages all

[Sepsis prediction during outbreaks at neonatal intensive care units through body surface screening for Gram-negative bacteria: systematic review and meta-analysis.](#)

Harder, T. et al

**BMC research notes**, December 22, 2018, Vol.11(1), p.917

This systematic review focusses on the prognostic accuracy of neonatal body surface screening during outbreaks caused by Gram-negative bacteria for prediction of sepsis. In a previous systematic review we reported that only limited evidence of very low quality exists regarding the predictive value of this screening under routine conditions. We aimed to investigate whether this is different in outbreak settings. Extending a previously published systematic review, we show here that in contrast to routine settings sensitivity of body surface screening for sepsis prediction is very high, while specificity is still insufficient. Surface screening appears to be a useful component of bundles of interventions used during outbreaks, but the evidence base is still limited.

[Immunologic biomarkers for diagnostic of early-onset neonatal sepsis.](#)

Memar, M.Y. et al

**The journal of maternal-fetal & neonatal medicine**  
January 2019, Vol.32(1), pp.143-153

Accurate identification of early onset neonatal sepsis (EOS) is challenging. Blood culture has been considered as a gold standard method but the identification of EOS is intricate by a high false-negative results. This review provides an overview of biomarkers as indicators for the diagnosis of EOS. There is an affluence of studies appraising diagnostic indicators in the identification of EOS. Acute-phase reactants, cytokines, and cell surface antigens have been investigated as indicators for EOS, but none of them are presently in routine clinical setting. Despite the promising data for some immunologic biomarkers, present evidence shows that none of them can constantly diagnose 100% of infections. IL-6 is the most potent marker for evaluation of EOS prognosis. Procalciton (PCT) and C-reactive protein (CRP) are appropriate indicators for the detection and monitoring of antibiotics therapy. A panel of sepsis biomarkers along with presently routine

stakeholders and experts, including the emergency medicine clinicians who treat most patients hospitalized with sepsis and who will be responsible for implementing these recommendations. A better strategy will identify more meaningful time stamps, focus less on the exact volume of fluid administered, and concentrate on identifying the subgroup of septic patients who will benefit from timely, appropriate care while limiting the diagnostic noise and logistic burdens that come with oversensitive screening tools.

[A Comparison of the Quick Sequential \(Sepsis-Related\) Organ Failure Assessment Score and the National Early Warning Score in Non-ICU Patients With/Without Infection](#)

Redfern, O.C. et al

**Critical Care Medicine**: December 2018 - Volume 46 - Issue 12 - p 1923–1933

The Sepsis-3 task force recommended the quick Sequential (Sepsis-Related) Organ Failure Assessment score for identifying patients with suspected infection who are at greater risk of poor outcomes, but many hospitals already use the National Early Warning Score to identify high-risk patients, irrespective of diagnosis. We sought to compare the performance of quick Sequential (Sepsis-Related) Organ Failure Assessment and National Early Warning Score in hospitalized, non-ICU patients with and without an infection. The National Early Warning Score outperforms the quick Sequential (Sepsis-Related) Organ Failure Assessment score, irrespective of infection status. These findings suggest that quick Sequential (Sepsis-Related) Organ Failure Assessment should be re-evaluated as the system of choice for identifying non-ICU patients with suspected infection who are at greater risk of poor outcome.

[A Retrospective Review of the Sepsis Definition after Publication of Sepsis-3.](#)

Braun, Derek

**The American journal of medicine**, November 22, 2018

Two and a half years after the introduction of Sepsis-3, clinicians continue not to document Sequential Organ Failure Assessment (SOFA) scores. The purpose of this

tests will make easy earlier identification, appropriate management, and improved outcome may be more efficient than single indicator.

[Screening for colonisation with gentamicin-resistant Gram-negative organisms on the neonatal unit: does positive screening predict sepsis?](#)

Walker, O. et al

**Archives of disease in childhood. Fetal and neonatal edition**, January 2019, Vol.104(1), pp.F113-F114

At our tertiary-level neonatal unit, surface swabs have been taken weekly to screen for gentamicin-resistant GNB. We conducted a retrospective analysis to investigate whether colonisation screening in our unit is effective at predicting LOS.

[Severe group A streptococcal infections in mothers and their newborns in London and the South East, 2010–2016: assessment of risk and audit of public health management](#)

Leonard, A. et al

**BJOG : an international journal of obstetrics and gynaecology**, January 2019, Vol.126(1), pp.44–53.

Are public health guidelines being followed in the management of mothers and their newborns to reduce the risk of iGAS infection? We describe cases of invasive group A Streptococcus (iGAS) in mothers or neonates and assess management according to national guidelines, which recommend administering antibiotics to both mother and neonate if either develops iGAS infection within 28 days of birth and investigation of clusters in maternity units. iGAS infection remains a potential postpartum risk. Prophylaxis among neonates and storage of isolates from maternity cases can be improved.

[Genetic polymorphisms and sepsis in premature neonates.](#)

Esposito, S. et al

PloS one, 2014, Vol.9(7), p.e101248

Identifying single nucleotide polymorphisms (SNPs) in the genes involved in sepsis may help to clarify the

review is to determine if the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were being utilized in defining sepsis in the clinical setting. There continue to be variations in what standard is accepted by both commercial payers and the Centers for Medicare and Medicaid (CMS) in diagnosing sepsis. Due to Sepsis-3 criteria not being accepted by CMS or the Infectious Disease Society of America, along with it not being able to be operationalized for use in the clinical setting, it is recommended to continue utilizing systemic inflammatory response syndrome criteria plus infection while Sepsis-3 continues to be evaluated. It will also allow for some time to study any effect it may have on patient outcomes. There is also a need for a uniform definition of sepsis.

[Early Post-Intensive Care Syndrome among Older Adult Sepsis Survivors Receiving Home Care.](#)

Riegel, B. et al

**Journal of the American Geriatrics Society**, November 30, 2018

New or worsened disabilities in functional, cognitive, or mental health following an intensive care unit (ICU) stay are referred to as post-intensive care syndrome (PICS). PICS has not been described in older adults receiving home care. Our aim was to examine the relationship between length of ICU stay and PICS among older adults receiving home care. We expected that patients in the ICU for 3 days or longer would demonstrate significantly more disability in all three domains on follow-up than those not in the ICU. A secondary aim was to identify patient characteristics increasing the odds of disability. Older adults receiving home care who develop sepsis and are in an ICU for 3 days or longer, are likely to develop new or worsened physical disabilities. Whether these disabilities remain after the early post-discharge phase requires further study.

[Sepsis: developing new alternatives to reduce neuroinflammation and attenuate brain injury.](#)

Meneses G. et al

**Ann N Y Acad Sci.** 2018 Nov 29.

pathophysiology of neonatal sepsis. The aim of this study was to evaluate the relationships between sepsis in pre-term neonates and genes potentially involved in the response to invasion by infectious agents. The results show that genetic variability seems to play a role in sepsis in pre-term neonates by influencing susceptibility to and the severity of the disease, as well as the risk of having disease due to specific pathogens.

#### [Earlier and more targeted treatment of neonatal sepsis.](#)

Özenci, V. et al

**Acta paediatrica** (Oslo, Norway : 1992), January 2019, Vol.108(1), pp.169-170

Neonatal sepsis occurs in 1–2 of the 1000 live born neonates and accounts for 3-5% of deaths in term and more than 30% in extremely preterm infants. These mortality rates due to neonatal infections are unacceptably high. Immediate and targeted antibiotic treatment is crucial in order to improve survival in this vulnerable population. Pilot study.

#### [Which biomarkers reveal neonatal sepsis?](#)

Wang K. et al

**PLoS One**. 2013 Dec 18;8(12):e82700.

We address the identification of optimal biomarkers for the rapid diagnosis of neonatal sepsis. We employ both canonical correlation analysis (CCA) and sparse support vector machine (SSVM) classifiers to select the best subset of biomarkers from a large hematological data set collected from infants with suspected sepsis from Yale-New Haven Hospital's Neonatal Intensive Care Unit (NICU). CCA is used to select sets of biomarkers of increasing size that are most highly correlated with infection. The effectiveness of these biomarkers is then validated by constructing a sparse support vector machine diagnostic classifier. We find that the following set of five biomarkers capture the essential diagnostic information (in order of importance): Bands, Platelets, neutrophil CD64, White Blood Cells, and Segs. Further, the diagnostic performance of the optimal set of biomarkers is significantly higher than that of isolated individual biomarkers. These results suggest an enhanced sepsis scoring system for neonatal sepsis that includes these five biomarkers. We demonstrate the robustness of our analysis by comp

Sepsis occurs when a systemic infection induces an uncontrolled inflammatory response that results in generalized organ dysfunction. The exacerbated peripheral inflammation can induce, in turn, neuroinflammation which may result in severe impairment of the central nervous system (CNS). Indeed, the ensuing blood-brain barrier disruption associated with sepsis promotes glial activation and starts a storm of proinflammatory cytokines in the CNS that leads to brain dysfunction in sepsis survivors. Endotoxic shock induced in mice by peripheral injection of lipopolysaccharides closely resembles the peripheral and central inflammation observed in sepsis. In this review, we provide an overview of the neuroinflammatory features in sepsis and of recent progress toward the development of new anti-neuroinflammatory therapies seeking to reduce mortality and morbidity in sepsis survivors.

#### [Autophagy and skeletal muscles in sepsis.](#)

Mofarrahi, M. et al

**PloS one**, 2012, Vol.7(10), p.e47265

Mitochondrial injury develops in skeletal muscles during the course of severe sepsis. Autophagy is a protein and organelle recycling pathway which functions to degrade or recycle unnecessary, redundant, or inefficient cellular components. No information is available regarding the degree of sepsis-induced mitochondrial injury and autophagy in the ventilatory and locomotor muscles. This study tests the hypotheses that the locomotor muscles are more prone to sepsis-induced mitochondrial injury, depressed biogenesis and autophagy induction compared with the ventilatory muscles. We conclude that locomotor muscles are more prone to sepsis-induced mitochondrial injury, decreased biogenesis and increased autophagy compared with the ventilatory muscles and that autophagy in skeletal muscles during sepsis is regulated in part through the NFκB transcription factor.

#### [Interleukin 38 Protects Against Lethal Sepsis.](#)

Xu, F. et al

**The Journal of infectious diseases**, August 24, 2018, Vol.218(7), pp.1175-1184

[Mupirocin for Staphylococcus aureus Decolonization of Infants in Neonatal Intensive Care Units.](#)

Kotloff, K.L. et al

**Pediatrics**. 2019 Jan;143(1). pii: e20181565.

Staphylococcus aureus (SA) is the second leading cause of late-onset sepsis among infants in the NICU. Because colonization of nasal mucosa and/or skin frequently precedes invasive infection, decolonization strategies, such as mupirocin application, have been attempted to prevent clinical infection, but data supporting this approach in infants are limited. We conducted a phase 2 multicenter, open-label, randomized trial to assess the safety and efficacy of intranasal plus topical mupirocin in eradicating SA colonization in critically ill infants. Application of mupirocin to multiple body sites was safe and efficacious in eradicating SA carriage among infants in the NICU; however, after 2 to 3 weeks, many infants who remained hospitalized became recolonized.

[Management of Neonates Born at  \$\geq 35\$  0/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis](#)

Puopolo, K. et al

**Pediatrics**, Dec 2018, Vol.142(6), p.1

The incidence of neonatal early-onset sepsis (EOS) has declined substantially over the last 2 decades, primarily because of the implementation of evidence-based intrapartum antimicrobial therapy. However, EOS remains a serious and potentially fatal illness. Laboratory tests alone are neither sensitive nor specific enough to guide EOS management decisions. Maternal and infant clinical characteristics can help identify newborn infants who are at risk and guide the administration of empirical antibiotic therapy. The incidence of EOS, the prevalence and implications of established risk factors, the predictive value of commonly used laboratory tests, and the uncertainties in the risk/benefit balance of antibiotic exposures all vary significantly with gestational age at birth.

**Adult sepsis**

Interleukin 38 (IL-38) is the most recently characterized cytokine of the interleukin 1 family. However, its role in sepsis remains unknown. Our findings suggest that IL-38 attenuates sepsis by decreasing inflammation and increasing bacterial clearance, thus providing a novel tool for antiseptic therapy.

[Sepsis-The "Gift" That Keeps on Giving, Regardless of Age.](#)

Simpson, S.Q.

**Critical care medicine**, August 2018, Vol.46(8), pp.1378-1380

There is little doubt that sepsis is an affliction associated with aging. Editorial

[A minimal set of physiometers in continuous high frequency data streams predict adult sepsis onset earlier](#)

van Wyk, F. et al

**International Journal of Medical Informatics**, 02/2019, Vol.122, C, pp.55-62

Sepsis is a life-threatening condition with high mortality rates and expensive treatment costs. To improve short- and long-term outcomes, it is critical to detect at-risk sepsis patients at an early stage. A random forest classifier was trained to discriminate between sepsis and non-sepsis patients. The use of machine learning algorithms on continuous streams of physiological data can allow for early identification of at-risk patients in real-time with high accuracy.

[Exploring the Pathways Revealed by International Sepsis Benchmarking.](#)

Walkey, A.J.

**Critical care medicine**, January 2019, Vol.47(1), pp.135-137

Editorial

[Sepsis programme successes are responsible for the increased detection of bacteraemia.](#)

[Association of Corticosteroid Treatment With Outcomes in Adult Patients With Sepsis: A Systematic Review and Meta-analysis.](#)

Fang, F. et al

**JAMA internal medicine**, December 21, 2018

Although corticosteroids are widely used for adults with sepsis, both the overall benefit and potential risks remain unclear. We conducted a systematic review and meta-analysis of the efficacy and safety of corticosteroids in patients with sepsis. The findings suggest that administration of corticosteroids is associated with reduced 28-day mortality compared with placebo use or standard supportive care. More research is needed to associate personalized medicine with the corticosteroid treatment to select suitable patients who are more likely to show a benefit.

[Identification of subclasses of sepsis that showed different clinical outcomes and responses to amount of fluid resuscitation: a latent profile analysis.](#)

Zhang, Z. et al

**Critical care (London, England)**, December 18, 2018, Vol.22(1), p.347

Sepsis is a heterogeneous disease and identification of its subclasses may facilitate and optimize clinical management. This study aimed to identify subclasses of sepsis and its responses to different amounts of fluid resuscitation. The study identified four subphenotypes of sepsis, which showed different mortality outcomes and responses to fluid resuscitation. Prospective trials are needed to validate our findings.

[Effect of cytomegalovirus reactivation on the time course of systemic host response biomarkers in previously immunocompetent critically ill patients with sepsis: a matched cohort study.](#)

van de Groep, K. et al

**Critical care (London, England)**, December 18, 2018, Vol.22(1), p.348

Cytomegalovirus (CMV) reactivation in previously immunocompetent critically ill patients is associated with increased mortality, which has been hypothesized to result from virus-induced immunomodulation. Therefore, we studied the effects of CMV reactivation

Simmons, M D et al

**The Journal of hospital infection**, January 2019, Vol.101(1), pp.93-99

Escherichia coli bacteraemia reduction targets are challenging but, in West Wales, this was the key infection surrogate measure set by the local health board in 2013, prior to the introduction of a Welsh Government target. The initial plateau of cases was not maintained and prompted this review. Success in one area (sepsis management) conflicts with 'failure' in reducing E. coli bacteraemia. It is argued that targets need to be considered carefully in the light of all available

[Sepsis: Early Recognition and Optimized Treatment.](#)

Kim, H.I. et al

**Tuberculosis and respiratory diseases**, January 2019 Vol.82(1), pp.6-14

Sepsis is a life-threatening condition caused by infection and represents a substantial global health burden. Recent epidemiological studies showed that sepsis mortality rates have decreased, but that the incidence has continued to increase. Although a mortality benefit from early-goal directed therapy (EGDT) in patients with severe sepsis or septic shock was reported in 2001, three subsequent multicenter randomized studies showed no benefits of EGDT versus usual care. Nonetheless, the early administration of antibiotics and intravenous fluids is considered crucial for the treatment of sepsis. In 2016, new sepsis definitions (Sepsis-3) were issued, in which organ failure was emphasized and use of the terms "systemic inflammatory response syndrome" and "severe sepsis" was discouraged. However, early detection of sepsis with timely, appropriate interventions increases the likelihood of survival for patients with sepsis. Also, performance improvement programs have been associated with a significant increase in compliance with the sepsis bundles and a reduction in mortality. To improve sepsis management and reduce its burden, in 2017, the World Health Assembly and World Health Organization adopted a resolution that urged governments and healthcare workers to implement appropriate measures to address sepsis. Sepsis should be considered a medical

on the temporal course of host response biomarkers in patients with sepsis. CMV reactivation was not independently associated with changes in the temporal trends of host response biomarkers in comparison with non-reactivating patients. Therefore, these markers should not be used as surrogate clinical endpoints for interventional studies evaluating anti-CMV therapy.

[APRIL and sTACI could be predictors of multiorgan dysfunction syndrome in sepsis.](#)

Lendak, D.F. et al

**Virulence**, December 31, 2018, Vol.9(1), pp.946-953

Although the role of B cells in sepsis immunoregulation has become an interesting topic, there is lack of data on the role of B cell function regulators in prediction of multiorgan dysfunction syndrome (MODS). The aim of this study was to evaluate the prognostic value of A Proliferation Inducing Ligand (APRIL) and soluble Transmembrane Activator and CAML Interactor Protein (sTACI), the main B cell function regulators, in prediction of MODS development within the first 48h after admission to intensive care unit, among septic patients. Elevated level of sTACI could be the alarm for the increased B cell apoptosis and development of immune paralysis. Including these biomarkers into predictive scores specific for septic patients may potentially improve their sensitivity and specificity. Measurement of their concentrations dynamics could contribute to better assessment of sepsis evolution and timely introduction of immunomodulatory therapy.

[Circulating adrenomedullin estimates survival and reversibility of organ failure in sepsis: the prospective observational multinational Adrenomedullin and Outcome in Sepsis and Septic Shock-1 \(AdrenOSS-1\) study.](#)

Mebazaa, A. et al

**Critical care (London, England)**, December 21, 2018, Vol.22(1), p.354

Adrenomedullin (ADM) regulates vascular tone and endothelial permeability during sepsis. Levels of circulating biologically active ADM (bio-ADM) show an inverse relationship with blood pressure and a direct relationship with vasopressor requirement. In the present prospective observational multinational

emergency, and increasing the level of awareness of sepsis is essential.

[Low D-dimer levels in sepsis: Good or bad?](#)

Semeraro, F. et al

**Thrombosis research**, Vol.174, pp.13-15 December 5, 2018

DIC is a serious complication of sepsis and increases the risk of death. D-dimer (DD) is the most used fibrin-related marker for DIC diagnosis. However, DD levels depend on both coagulation and fibrinolysis. Patients with severe sepsis and normal DD were shown to have the highest mortality. Allegedly, normal DD in sepsis masks a DIC form with strong fibrinolysis inhibition. Letter

[Effects of antiplatelet therapy on the mortality rate of patients with sepsis: A meta-analysis.](#)

Ouyang, Y. et al

**Journal of critical care**, Vol.50, pp.162-168 December 5, 2018

Abnormal platelet activation plays an important role in the development of sepsis. The effect of antiplatelet drugs on the outcome of patients with sepsis remains unclear. This meta-analysis aimed to determine the effect of antiplatelet drugs on the prognosis of patients with sepsis. Antiplatelet drugs, particularly aspirin, could be used to effectively reduce mortality in patients with sepsis.

[Doppler-defined pulmonary hypertension in sepsis and septic shock.](#)

Vallabhajosyula, S. et al

**Journal of critical care**, December 8, 2018, Vol.50, pp.201-206

The association of pulmonary hypertension (PH) in patients with sepsis is lesser understood. In patients with sepsis and septic shock, PH is common and is noted to be associated with higher short and long-term mortality. Further studies are needed to understand the mechanisms by which PH is associated with outcomes.

Adrenomedullin and Outcome in Sepsis and Septic Shock 1 (, AdrenOSS-1) study, we assessed relationships between circulating bio-ADM during the initial intensive care unit (ICU) stay and short-term outcome in order to eventually design a biomarker-guided randomized controlled trial. AdrenOSS-1 shows that early levels and rapid changes in bio-ADM estimate short-term outcome in sepsis and septic shock. These data are the backbone of the design of the biomarker-guided AdrenOSS-2 trial.

[An electronic warning system helps reduce the time to diagnosis of sepsis.](#)

Westphal, G. A. et al

**Revista Brasileira de terapia intensiva**, December 13, 2018

To describe the improvements of an early warning system for the identification of septic patients on the time to diagnosis, antibiotic delivery, and mortality. This was an observational cohort study that describes the successive improvements made over a period of 10 years using an early warning system to detect sepsis, including systematic active manual surveillance, electronic alerts via a telephonist, and alerts sent directly to the mobile devices of nurses. For all periods, after an alert was triggered, early treatment was instituted according to the institutional sepsis guidelines. Electronic systems help reduce the triage-to-diagnosis time and diagnosis-to-antibiotic time in patients with sepsis.

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