

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 20 December 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)

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SEPSIS BULLETIN 7 December 2018

Neonatal, paediatric and maternal sepsis

[Interleukin-6 for early diagnosis of neonatal sepsis with premature rupture of the membranes: A meta-analysis.](#)

Qiu, X. et al

Medicine (Baltimore). 2018 Nov;97(47):e13146.

Premature rupture of the membranes (PROM) is the principal risk factor for neonatal sepsis. Interleukin-6 (IL-6) has been investigated for early diagnosis of neonatal sepsis, but not for diagnosis of neonatal sepsis with PROM. The objective of this study is to investigate the early diagnostic value of IL-6 for neonatal sepsis with PROM. IL-6 is therefore a sensitive and specific diagnostic marker for the early diagnosis of neonatal sepsis with PROM.

[Identification and treatment of paediatric sepsis: getting the balance right](#)

Carter, M. et al

Adult sepsis (cont.)

[Latent class analysis of ARDS subphenotypes: a secondary analysis of the statins for acutely injured lungs from sepsis \(SAILS\) study](#)

Sinha, Pratik et al

Intensive Care Medicine, 2018, Vol.44(11), pp.1859-1869

Using latent class analysis (LCA), we have consistently identified two distinct subphenotypes in four randomized controlled trial cohorts of ARDS. One subphenotype has hyper-inflammatory characteristics and is associated with worse clinical outcomes. Further, within three negative clinical trials, we observed differential treatment response by subphenotype to randomly assigned interventions. The main purpose of this study was to identify ARDS subphenotypes in a contemporary NHLBI Network trial of infection-associated ARDS (SAILS) using LCA and to test for differential treatment response to rosuvastatin

Archives of Disease in Childhood, Dec 2018, Vol.103(12), p.1185

Recent National Institute for Health and Care Excellence (NICE) guidance on sepsis defines clinical criteria to guide the management of a child presenting with suspected infection. In children with suspected infection, presence of a 'high-risk' criterion should lead to intravenous access, parenteral antibiotic administration and consideration of intravenous fluid boluses, unless a senior decision-making doctor (DMD; defined as a Specialist Trainee (ST) 4 paediatrician, or ST4 emergency physician for older children) makes an alternative diagnosis. Since clinical screening criteria for sepsis are non-specific, many children without sepsis may receive antibiotic treatment for each case of true sepsis. Early review by senior paediatricians of children presenting to emergency departments (ED) with serious bacterial infection has previously been associated with better outcome. The consistent presence of DMDs in EDs may therefore maintain NICE guideline compliance, reduce costs and improve care of children with febrile illnesses.

[Association of Bacteremic Sepsis With Long-term Neurocognitive Dysfunction in Pediatric Patients With Acute Lymphoblastic Leukemia](#)

Cheung, Y. et al

JAMA Pediatrics, Nov 2018, Vol.172(11), p.1092
Although long-term survival in children with acute lymphoblastic leukemia (ALL) now exceeds 90%, survivors are at risk for treatment-related neurocognitive dysfunction that can persist into adulthood. We hypothesized that bacteremic sepsis during treatment for ALL contributes to long-term neurocognitive dysfunction and tested this hypothesis in a cohort study, using a propensity score-weighted model to adjust for potential confounders. The finding that sepsis was associated with impaired long-term neurocognitive function has practice-changing implications for cancer survivorship. Prevention of infection, early recognition and appropriate management of sepsis, and preemptive neurocognitive interventions should be prioritized, because these might prevent or ameliorate neurologic damage. Future research could aim to validate this finding independently and evaluate mechanisms of brain injury.

[Burden and factors associated with clinical neonatal sepsis in urban Uganda: a community cohort study](#)

therapy in the subphenotypes. LCA using a two-subphenotype model best described the SAILS population. The subphenotypes have features consistent with those previously reported in four other cohorts. Addition of new class-defining variables in the LCA model did not yield additional subphenotypes. No treatment effect was observed with rosuvastatin. These findings further validate the presence of two subphenotypes and demonstrate their utility for patient stratification in ARDS.

[The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care](#)

Komorowski, M. et al

Nature Medicine, 2018 Nov, Vol.24(11), pp.1716-+
Sepsis is the third leading cause of death worldwide and the main cause of mortality in hospitals, but the best treatment strategy remains uncertain. In particular, evidence suggests that current practices in the administration of intravenous fluids and vasopressors are suboptimal and likely induce harm in a proportion of patients. To tackle this sequential decision-making problem, we developed a reinforcement learning agent, the Artificial Intelligence (AI) Clinician, which extracted implicit knowledge from an amount of patient data that exceeds by many-fold the life-time experience of human clinicians and learned optimal treatment by analyzing a myriad of (mostly suboptimal) treatment decisions. We demonstrate that the value of the AI Clinician's selected treatment is on average reliably higher than human clinicians. In a large validation cohort independent of the training data, mortality was lowest in patients for whom clinicians' actual doses matched the AI decisions. Our model provides individualized and clinically interpretable treatment decisions for sepsis that could improve patient outcomes.

[Severe sepsis 3-hour bundle compliance and mortality](#)

Lynn, Nb ; Gupta, C ; Vaaler, M ; Held, J ; Leon, L

American Journal Of Infection Control, 2018 Nov, Vol.46(11), pp.1299-1300

Severe sepsis is a major cause of mortality among hospitalized patients. We tracked severe sepsis 3-hour bundle compliance and mortality over time. Those patients with severe sepsis who received the entire bundle had improved in-hospital survivability over those patients who did not receive the bundle.

Violet Okaba Kayom ; Jamiir Mugalu ; Abel Kakuru ; Sarah Kiguli ; Charles Karamagi

BMC Pediatrics, 01 November 2018, Vol.18(1), pp.1-8

Neonatal sepsis is one of the most important causes of mortality in developing countries and yet the most preventable. In developing countries clinical algorithms are used to diagnose clinical neonatal sepsis because of inadequate microbiological services. Most information on incidence and risk factors of neonatal sepsis are from hospital studies which may not be generalized to communities where a significant proportion of mothers do not deliver from health facilities. This study, conducted in urban Uganda, sought to determine the community based incidence of clinical neonatal sepsis and the factors associated. The high incidence of clinical neonatal sepsis in this urban community with high rates of antenatal care attendance and health facility delivery places a demand on the need to improve the quality of antenatal, perinatal and postnatal care in health facilities with regards to infection prevention including promoting simple practices like hand washing. The astoundingly low mortality rate is most likely because this was a low risk cohort. However it may also suggest that the neonatal mortality in developing countries may be reduced with promotion of simple low cost interventions like community follow up of neonates using village health teams or domiciliary care.

[Implementation of the sepsis risk score for chorioamnionitis-exposed newborns](#)

Gievers, LI ; Sedler, J ; Phimoi, Ca ; Dukhovny, D ; Geddes, J ; Graven, P ; Chan, B ; Khaki, S

Journal Of Perinatology, 2018 Nov, Vol.38(11), pp.1581-1587

To prevent early onset sepsis (EOS), ~10% of neonates receive antibiotics based on CDC recommendations regarding chorioamnionitis exposure. A sepsis risk score (SRS) predicts EOS and spares unnecessary evaluation and treatment. Algorithm implementation decreased antibiotic and resource utilization without missing cases of EOS.

Adult sepsis

[The use of procalcitonin in the determination of severity of sepsis, patient outcomes and infection characteristics](#)

Yunus, Iram

PLoS One, Nov 2018, Vol.13(11), p.e0206527

[Mechanical ventilation enhances extrapulmonary sepsis-induced lung injury: role of WISP1- \$\alpha\$ v \$\beta\$ 5 integrin pathway in TLR4-mediated inflammation and injury](#)

Xibing Ding et al

Critical Care, 01 November 2018, Vol.22(1), pp.1-11

High tidal volume ventilation of healthy lungs or exacerbation of existing acute lung injury (ALI) by more moderate mechanical ventilation (MTV) produces ventilator-induced lung injury. It is less clear whether extrapulmonary sepsis sensitizes the lung to MTV. These data show for the first time that otherwise noninjurious mechanical ventilation can exacerbate ALI due to extrapulmonary sepsis underscoring a potential interactive contribution of common events (sepsis and mechanical ventilation) in critical care, and that a WISP1-TLR4-integrin β 5 pathway contributes to this phenomenon.

[Hydrocortisone, Ascorbic Acid and Thiamine \(HAT Therapy\) for the Treatment of Sepsis. Focus on Ascorbic Acid](#)

Paul E. Marik

Nutrients, 01 November 2018, Vol.10(11), p.1762

Sepsis is a devastating disease that carries an enormous toll in terms of human suffering and lives lost. Over 100 novel pharmacologic agents that targeted specific molecules or pathways have failed to improve the outcome of sepsis. Preliminary data suggests that the combination of Hydrocortisone, Ascorbic Acid and Thiamine (HAT therapy) may reduce organ failure and mortality in patients with sepsis and septic shock. HAT therapy is based on the concept that a combination of readily available, safe and cheap agents, which target multiple components of the host's response to an infectious agent, will synergistically restore the dysregulated immune response and thereby prevent organ failure and death. This paper reviews the rationale for HAT therapy with a focus on vitamin C.

[Abnormal neutrophil traps and impaired efferocytosis contribute to liver injury and sepsis severity after binge alcohol use](#)

Bukong, T. et al

Journal of Hepatology, Nov 2018, Vol.69(5), p.1145

Disease severity in alcoholic liver disease (ALD) is associated with a significant presence of neutrophils (a type of immune cell) in the liver. It remains unknown how alcohol affects the capacity of neutrophils to

The primary objective of this study was to determine the correlation between procalcitonin values and illness severity by evaluating the degree of end organ dysfunction using the Sequential Organ Failure Assessment score, length of stay and the severity of sepsis (sepsis alone vs. septic shock), The hypothesis that procalcitonin values would be higher in sicker patients was formulated before data collection began. Secondary outcomes studied in relation to procalcitonin levels included infection characteristics such as the site of infection, microbial agent and dialysis dependent CKD. Procalcitonin has a higher specificity for bacterial infections than other acute phase reactants. Although initial procalcitonin value may be helpful in the determination of illness severity, it is not always a reliable prognostic indicator and carries little significance as a standalone value. Procalcitonin values may be influenced by preexisting comorbid conditions such as chronic kidney disease, which are associated with higher procalcitonin values at baseline. Procalcitonin can provide invaluable information when viewed as one piece of a clinical puzzle, and is most powerful when the interpreting physician is aware of how values are influenced by the different clinical scenarios presented in this article.

[The host response in critically ill sepsis patients on statin therapy : a prospective observational study](#)

Wiewel, M. et al

Annals of Intensive Care, 2018, Vol.8(1), pp.urn:issn:2110-5820

Statins can exert pleiotropic anti-inflammatory, vascular protective and anticoagulant effects, which in theory could improve the dysregulated host response during sepsis. We aimed to determine the association between prior statin use and host response characteristics in critically ill patients with sepsis. In conclusion, statin therapy is not associated with a modified host response in sepsis patients on admission to the ICU.

[Early Administration of Intravenous Fluids in Sepsis: Pros and Cons.](#)

Bonanno LS.

Crit Care Nurs Clin North Am. 2018 Sep;30(3):323-332.

Fluid resuscitation in the management of patients with sepsis and severe sepsis has been considered the standard of care for almost 2 decades. The rationale for fluid resuscitation is related to improvement in cardiac output and organ perfusion. Recent research evidence

control infection, a major hallmark of ALD. We found that binge alcohol drinking impaired important strategies used by neutrophils to contain and resolve infection, resulting in increased liver injury during ALD. Neutrophil extracellular traps (NETs) are an important strategy utilized by neutrophils to immobilize and kill invading microorganisms. Herein, we studied NET formation and the process of neutrophil cell death (NETosis), as well as the clearance of NETs by macrophages (MΦ) (efferocytosis) in acute sepsis following binge drinking. Dysfunctional NETosis and efferocytosis following binge drinking exacerbate liver injury associated with sepsis.

[Clinical characteristics and prognosis of serous body cavity effusions in patients with sepsis: a retrospective observational study](#)

Xing, Ling-You et al

BMC Anesthesiology, 01 November 2018, Vol.18(1), pp.1-9

Cavity effusion is common in patients with infectious diseases. However, the incidence rate and characteristics of serous cavity effusions (SCE) in septic patients are not clear to date. The objective of this study was to investigate the incidence and characteristics of SCE in septic patients and to explore the correlations between the bloody effusions and the illness severity/prognosis in septic patients. The incidence of serous cavity effusion is high in patients with sepsis. The septic patients with bloody effusions suffer a more inflammatory burden and a worse prognosis compared to septic patients with non-bloody effusions.

[Protein kinase C-delta inhibition protects blood-brain barrier from sepsis-induced vascular damage](#)

Tang, Y. et al

Journal of Neuroinflammation, 01 November 2018, Vol.15(1), pp.1-12

Neuroinflammation often develops in sepsis leading to activation of cerebral endothelium, increased permeability of the blood-brain barrier (BBB), and neutrophil infiltration. We have identified protein kinase C-delta (PKCδ) as a critical regulator of the inflammatory response and demonstrated that pharmacologic inhibition of PKCδ by a peptide inhibitor (PKCδ-i) protected endothelial cells, decreased sepsis-mediated neutrophil influx into the lung, and prevented tissue damage. The objective of

challenges the use of fluid resuscitation in patients diagnosed with sepsis. Research is needed to determine the timing of fluid administration, as well as the volume and type of fluid to achieve positive patient outcomes. This article discusses the pros and cons of early fluid administration in the management of patients with sepsis.

[Emerging Adjunctive Approach for the Treatment of Sepsis: Vitamin C and Thiamine.](#)

Badeaux J.E. et al

Crit Care Nurs Clin North Am. 2018 Sep;30(3):343-351.

Evidence is emerging that parenteral administration of high-dose vitamin C and thiamine may be a beneficial adjuvant therapy of severe sepsis and septic shock. Despite modern practices in critical care medicine, sepsis and severe sepsis remain a leading cause of morbidity and mortality in the critical care unit.

[Hospital Costs Associated with Sepsis Compared with Other Medical Conditions.](#)

Danna DM.

Crit Care Nurs Clin North Am. 2018 Sep;30(3):389-398.

Sepsis is a condition that has become a main focus for health care organizations owing to the alarming cost of caring for patients, as well as the disturbing mortality rates, that accompany this condition. Sepsis is one of the costliest conditions billed to all payer groups: Medicare, Medicaid, private insurance, and uninsured patients. Health care organizations have implemented multiple strategies and best practices to improve the outcomes of patients with a diagnosis of sepsis.

[Etomidate as an Induction Agent in Sepsis.](#)

Devlin, R. et al

Crit Care Nurs Clin North Am. 2018 Sep;30(3):e1-e9.

Sepsis is a life-threatening response to infection often times requiring endotracheal intubation in critically ill patients. Etomidate is routinely used as an intravenous induction agent to provide sedation and amnesia before placing an endotracheal tube. Although etomidate has many favorable qualities, there is a major concern regarding the predictable adrenal insufficiency that follows its use. Controversy continues to this day as to whether etomidate should be avoided in the setting of sepsis or septic shock.

[Prompt admission to intensive care is associated with improved survival in patients with severe sepsis and/or septic shock.](#)

this study was to elucidate the regulation and relative contribution of PKC δ in the control of individual steps in neuroinflammation during sepsis. The BBB on-a-chip (B3C) in vitro assay is suitable for the study of BBB function as well as screening of novel therapeutics in real-time. PKC δ activation is a key signaling event that alters the structural and functional integrity of BBB leading to vascular damage and inflammation-induced tissue damage. PKC δ -TAT peptide inhibitor has therapeutic potential for the prevention or reduction of cerebrovascular injury in sepsis-induced vascular damage.

[Clinical significance and prognosis of serum tenascin-C in patients with sepsis](#)

Yuan, W. et al

BMC Anesthesiology, 01 November 2018, Vol.18(1), pp.1-6

Tenascin-C is a pro-inflammatory glycoprotein with various biological functions. High expression of tenascin-C is found in inflammation, tissue remodeling, and autoimmune diseases. However, its expression and clinical significance in sepsis remain unclear. This study was designed to investigate the relationship between serum tenascin-C levels and disease severity and prognosis in patients with sepsis. Elevated serum tenascin-C was found in septic patients and associated with severity and poor prognosis.

[Evaluating the discriminating capacity of cell death \(apoptotic\) biomarkers in sepsis](#)

Duplessis, C. et al

Journal of Intensive Care, 01 November 2018, Vol.6(1), pp.1-11

Sepsis biomarker panels that provide diagnostic and prognostic discrimination in sepsis patients would be transformative to patient care. We assessed the mortality prediction and diagnostic discriminatory accuracy of two biomarkers reflective of cell death (apoptosis), circulating cell-free DNA (cfDNA), and nucleosomes. To our knowledge, this is the first head-to-head comparison of cfDNA and nucleosomes in diagnosing sepsis and predicting sepsis-related mortality. Both cfDNA and nucleosome concentrations demonstrated a modest ability to distinguish sepsis survivors and non-survivors and provided additive diagnostic predictive accuracy in differentiating sepsis from non-infectious SIRS when integrated into a diagnostic prediction model including PCT and APACHE II. A sepsis biomarker strategy incorporating measures

Li, Q. et al

J Int Med Res. 2018 Oct;46(10):4071-4081.

To investigate the association between time from hospital admission to intensive care unit (ICU) admission (door to ICU time) and hospital mortality in patients with sepsis. A shorter time from hospital door to ICU admission was shown to be independently associated with reduced hospital mortality in patients with severe sepsis and/or septic shock.

[Sepsis in the Burn Patient.](#)

Manning J.

Crit Care Nurs Clin North Am. 2018 Sep;30(3):423-430.

Sepsis is the leading cause of death in burn patients.

Interventions are challenging owing to a lack of specific guidelines. All burn types involve a risk for complications. Interventions should include care of the burn, medication administration, continuous monitoring for infection development, infection prevention measures, and (if necessary) treatment of sepsis. Sepsis in burn patients is different from the unburned population. Efforts are needed to develop more accurate diagnostic strategies and guidelines to trigger rapid treatment via specific sepsis bundles.

of the apoptotic pathway may serve as an important component of a sepsis diagnostic and mortality prediction tool.

[Factors Underlying Racial Disparities in Sepsis Management](#)

Dimeglio, M. et al

Healthcare, 01 November 2018, Vol.6(4), p.133

Sepsis, a syndrome characterized by systemic inflammation during infection, continues to be one of the most common causes of patient mortality in hospitals across the United States. While standardized treatment protocols have been implemented, a wide variability in clinical outcomes persists across racial groups. Specifically, black and Hispanic populations are frequently associated with higher rates of morbidity and mortality in sepsis compared to the white population. While this is often attributed to systemic bias against minority groups, a growing body of literature has found patient, community, and hospital-based factors to be driving racial differences. In this article, we provide a focused review on some of the factors driving racial disparities in sepsis. We also suggest potential interventions aimed at reducing health disparities in the prevention, early identification, and clinical management of sepsis.

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