

Here is the latest edition. The bulletin covers the latest information on sepsis and comes out monthly. Next edition is due April 2020. Older editions are available as pdfs on the Keeping Up To Date library guide (http://libguides.bodleian.ox.ac.uk/Keeping_up_to_date)

COVID-19 NEWS You may already be aware that the Bodleian Libraries are closed. We are still able to allow you to enter the Cairns Library at the John Radcliffe Hospital for now but there are no staff on duty. The OUH Trust may decide to close the library completely for physical access at some point. However we have plenty of services that we can offer you online. In the first instance, please email me back with any questions or queries about anything you need. Or you can email our enquiries email: hcl-enquiries@bodleian.ox.ac.uk. We are all working from home so we are keen for you to let us know how we can help.



SEPSIS BULLETIN

March 2020

Adult sepsis

[Sepsis therapies: learning from 30 years of failure of translational research to propose new leads.](#)

Cavaillon JM, Singer M, Skirecki T.

EMBO Mol Med. 2020 Mar 16:e10128.

Sepsis has been identified by the World Health Organization (WHO) as a global health priority. There has been a tremendous effort to decipher underlying mechanisms responsible for organ failure and death, and to develop new treatments. Despite saving thousands of animals over the last three decades in multiple preclinical studies, no new effective drug has emerged that has clearly improved patient outcomes. In the present review, we analyze the reasons for this failure, focusing on the inclusion of inappropriate patients and the use of irrelevant animal models. We advocate against repeating the same mistakes and propose changes to the research paradigm. We discuss the long-term consequences of surviving sepsis and, finally, list some putative approaches-both old and new-that could help save lives and improve survivorship.

[Immune Consequences of Endothelial Cells' Activation and Dysfunction During Sepsis.](#)

Pons S, et al.

Crit Care Clin. 2020 Apr;36(2):401-413.

The vascular endothelium provides a direct interface between circulating blood cells and parenchymal cells. Thus, it has a key role in vasomotor tone regulation, primary hemostasis, vascular barrier, and immunity. In the case of systemic inflammation, endothelial cell (EC) activation initiates a powerful innate immune response to eliminate the pathogen. In some specific conditions, ECs may also contribute

to the activation of adaptive immunity and the recruitment of antigen-specific lymphocytes. However, the loss of EC functions or an exaggerated activation of ECs during sepsis can lead to multiorgan failure.

[The Inflammatory and Hemostatic Response in Sepsis and Meningococemia.](#)

Boeddha NP, et al.

Crit Care Clin. 2020 Apr;36(2):391-399.

Meningococemia is notorious for evasion of the host immune system and its rapid progression to fulminant disease, and serves as a unique model for pediatric sepsis. Illness severity is determined by complex interplays among host, pathogen, and environment. The inflammatory host response, including proinflammatory and anti-inflammatory responses in innate and adaptive immunity, skews toward a proinflammatory state. This leads to endothelial dysfunction and activation of the hemostatic response, which may lead to disseminated intravascular coagulation. This article reviews the pathogenesis of sepsis, in particular the inflammatory and hemostatic response in meningococcal sepsis

[Role of Antithrombin III and Tissue Factor Pathway in the Pathogenesis of Sepsis.](#)

Sungurlu S, Kuppy J, Balk RA.

Crit Care Clin. 2020 Apr;36(2):255-265.

The pathobiology of the septic process includes a complex interrelationship between inflammation and the coagulations system. Antithrombin (AT) and tissue factor are important components of the coagulation system and have potential roles in the production and amplification of sepsis. Sepsis is associated with a decrease in AT levels, and low levels are also associated with the development of multiple organ failure and death. Treatment strategies incorporating AT replacement therapy in sepsis and septic shock have not resulted in an improvement in survival or reversal of disseminated intravascular coagulation.

[Biomarkers for Point-of-Care Diagnosis of Sepsis.](#)

Teggert A, Datta H, Ali Z.

Micromachines (Basel). 2020 Mar 10;11(3):E286.

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. In 2017, almost 50 million cases of sepsis were recorded worldwide and 11 million sepsis-related deaths were reported. Therefore, sepsis is the focus of intense research to better understand the complexities of sepsis response, particularly the twin underlying concepts of an initial hyper-immune response and a counter-immunological state of immunosuppression triggered by an invading pathogen. Diagnosis of sepsis remains a significant challenge. Prompt diagnosis is essential so that treatment can be instigated as early as possible to ensure the best outcome, as delay in treatment is associated with higher mortality. In order to address this diagnostic problem, use of a panel of biomarkers has been proposed as, due to the complexity of the sepsis response, no single marker is sufficient. This review provides background on the current understanding of sepsis in terms of its epidemiology, the evolution of the definition of sepsis, pathobiology and diagnosis and management. Candidate biomarkers of interest and how current and developing point-of-care testing approaches could be used to measure such biomarkers is discussed.

[Sepsis-Associated Encephalopathy: From Delirium to Dementia?](#)

Chung HY, et al.

J Clin Med. 2020 Mar 5;9(3):E703.

Sepsis is a major cause of death in intensive care units worldwide. The acute phase of sepsis is often accompanied by sepsis-associated encephalopathy, which is highly associated with increased mortality. Moreover, in the chronic phase, more than 50% of surviving patients suffer from severe and long-term cognitive deficits compromising their daily quality of life and placing an immense burden on primary caregivers. Due to a growing number of sepsis survivors, these long-lasting deficits are increasingly relevant. Despite the high incidence and clinical relevance, the pathomechanisms of acute and chronic stages in sepsis-associated encephalopathy are only incompletely understood, and no specific therapeutic options are yet available. Here, we review the emergence of sepsis-associated

encephalopathy from initial clinical presentation to long-term cognitive impairment in sepsis survivors and summarize pathomechanisms potentially contributing to the development of sepsis-associated encephalopathy.

[Time to stop randomized and large pragmatic trials for intensive care medicine syndromes: the case of sepsis and acute respiratory distress syndrome.](#)

Girbes ARJ, de Grooth HJ.

J Thorac Dis. 2020 Feb;12(Suppl 1):S101-S109.

In this paper we discuss the limitations of large randomized controlled trials with mortality endpoints in patients with critical illness associated diagnoses such as sepsis. When patients with the same syndrome diagnosis do not share the pathways that lead to death (the attributable risk), any therapy can only lead to small effects in these populations. Using Monte Carlo simulations, we show how the syndrome-attributable risks of critical illness-associated diagnoses are likely overestimated using common statistical methods. This overestimation of syndrome-attributable risks leads to a corresponding overestimation of attainable treatment effects and an underestimation of required sample sizes. We demonstrate that larger and more 'pragmatic' randomized trials are not the solution because they decrease therapeutic and diagnostic precision, the therapeutic effect size and the probability of finding a beneficial effect. Finally, we argue that the most logical solution is a renewed focus on mechanistic research into the complexities of critical illness syndromes.

[Sepsis trends: increasing incidence and decreasing mortality, or changing denominator?](#)

Rhee C, Klompas M.

J Thorac Dis. 2020 Feb;12(Suppl 1):S89-S100.

Numerous studies suggest that the incidence of sepsis has been steadily increasing over the past several decades while mortality rates are falling. However, reliably assessing trends in sepsis epidemiology is challenging due to changing diagnosis and coding practices over time. In this review, we summarize the major epidemiologic studies of sepsis trends, potential biases in these analyses, and the recent change in the surveillance paradigm toward using objective clinical data from electronic health records to more accurately characterize sepsis trends.

[Vitamin C: an essential "stress hormone" during sepsis.](#)

Marik PE.

J Thorac Dis. 2020 Feb;12(Suppl 1):S84-S88

The stress response is a preserved evolutionary response that functions to enhance the survival of the species. In mammals, the stress response is characterized by activation of the HPA axis and sympathoadrenal system (SAS) as well as the increased synthesis and secretion of vitamin C. Cortisol, catecholamines, and vitamin C act synergistically to increase hemodynamic reserve, maintain immune function and protect the host against excessive oxidant injury. Humans (and anthropoid apes) have lost the ability to synthesize vitamin C and therefore have an impaired stress response. The inability to produce vitamin C has serious implications in septic humans. Treatment with vitamin C appears to restore the stress response and improve the survival of stressed humans.

[Timeliness of antibiotics for patients with sepsis and septic shock.](#)

Schinkel M, et al.

J Thorac Dis. 2020 Feb;12(Suppl 1):S66-S71.

For many years, sepsis guidelines have focused on early administration of antibiotics. While this practice may benefit some patients, for others it might have detrimental consequences. The increasingly shortened timeframes in which administration of antibiotics is recommended, have forced physicians to sacrifice diagnostic accuracy for speed, encouraging the overuse of antibiotics. The evidence supporting this practice is based on retrospective data, with all the limitations attached, while the only randomized trial on this subject does not show a mortality benefit from early administration of antibiotics in a population of patients with sepsis as often seen in the emergency department (ED). Physicians are challenged to treat patients suspected of having sepsis within a short period of time, while the real

challenge should be to identify patients who would not be harmed by withholding treatment with antibiotics until the diagnosis of infection with a bacterial origin is confirmed and the appropriateness of a course of antibiotics can be evaluated more adequately. Therefore, in the general population of patients with sepsis, taking the time to gather additional data to confirm the diagnosis should be encouraged without a specific timeframe, although physicians should be encouraged to perform an adequate work-up as soon as possible. Patients with suspected sepsis and signs of shock should immediately be treated with antibiotics, as there is no margin for error.

[Melatonin for the treatment of sepsis: the scientific rationale.](#)

Colunga Biancatelli RML, et al.

J Thorac Dis. 2020 Feb;12(Suppl 1):S54-S65.

Sepsis affects 30 million people worldwide, leading to 6 million deaths every year (WHO), and despite decades of research, novel initiatives are drastically needed. According to the current literature, oxidative imbalance and mitochondrial dysfunction are common features of septic patients that can cause multiorgan failure and death. Melatonin, alongside its traditionally accepted role as the master hormonal regulator of the circadian rhythm, is a promising adjunctive drug for sepsis through its anti-inflammatory, antiapoptotic and powerful antioxidant properties. Several animal models of sepsis have demonstrated that melatonin can prevent multiorgan dysfunction and improve survival through restoring mitochondrial electron transport chain (ETC) function, inhibiting nitric oxide synthesis and reducing cytokine production. The purpose of this article is to review the current evidence for the role of melatonin in sepsis, review its pharmacokinetic profile and virtual absence of side effects. While clinical data is limited, we propose the adjunctive use of melatonin in patients with severe sepsis and septic shock.

[The origins of the Lacto-Bolo reflex: the mythology of lactate in sepsis.](#)

Spiegel R, Gordon D, Marik PE.

J Thorac Dis. 2020 Feb;12(Suppl 1):S48-S53.

The use of lactate as a marker of the severity of circulatory shock was popularized by Dr. Weil in the 1970's. Dr. Weil promoted the idea that blood lactate concentration increased in circulatory shock due to anaerobic metabolism following decreased oxygen delivery. This concept becomes entrenched with 1992 ACCP/SCCM consensus conference definition of sepsis. Since then, the central role of lactate in the definition and management of septic shock has only been expanded and become more ingrained. This review will discuss the wisdom of such an approach, an updated model describing the origins of hyperlactatemia in sepsis, and how such improvements in our knowledge of the underlying physiology should change our approach to resuscitation in patients presenting with septic shock.

[Fluid resuscitation in sepsis: the great 30 mL per kg hoax.](#)

Marik PE, Byrne L, van Haren F.

J Thorac Dis. 2020 Feb;12(Suppl 1):S37-S47.

Large volume fluid resuscitation is currently viewed as the cornerstone of the treatment of septic shock. The surviving sepsis campaign (SSC) guidelines provide a strong recommendation to rapidly administer a minimum of 30 mL/kg crystalloid solution intravenously in all patients with septic shock and those with elevated blood lactate levels. However, there is no credible evidence to support this recommendation. In fact, recent findings from experimental, observational and randomized clinical trials demonstrate improved outcomes with a more restrictive approach to fluid resuscitation. Accumulating evidence suggests that aggressive fluid resuscitation is harmful. Paradoxically, excess fluid administration may worsen shock. In this review, we critically evaluate the scientific evidence for a weight-based fluid resuscitation approach. Furthermore, the potential mechanisms and consequences of harm associated with fluid resuscitation are discussed. Finally, we recommend an individualized, conservative and physiologic guided approach to fluid resuscitation.

[Role of procalcitonin use in the management of sepsis.](#)

Gregoriano C, et al.

J Thorac Dis. 2020 Feb;12(Suppl 1):S5-S15.

Important aspects of sepsis management include early diagnosis as well as timely and specific treatment in the first few hours of triage. However, diagnosis and differentiation from non-infectious causes often cause uncertainties and potential time delays. In this context, the use of the blood infection marker procalcitonin (PCT) has gained much attention. There is still no gold standard for the detection of sepsis and use of conventional diagnostic approaches are restricted by some limitations. Therefore, additional tests are necessary to enable early and reliable diagnosis. PCT has good discriminatory properties to differentiate between bacterial and viral inflammations with rapidly available results. To date, PCT is the best studied biomarker regarding antibiotic stewardship. Still, further research is needed to understand optimal use of PCT, also in combination with other reemerging diagnostic tests for most efficient sepsis care.

[Interventions for rapid recognition and treatment of sepsis in the emergency department - A narrative review.](#)

Uffen JW, et al.

Clin Microbiol Infect. 2020 Feb 28;S1198-743X(20)30105-1.

Sepsis is a major cause of morbidity and mortality worldwide. Early recognition and treatment of sepsis is associated with improved outcome. Emergency departments (EDs) are the main department where patients with sepsis are presented. But recognition in the ED remains difficult. Different alert and triage systems, screening scores and intervention strategies have been developed to assist clinicians in early recognition of sepsis and to optimize management. This narrative review describes currently applied interventions or interventions we can start using today such as screening scores, (automated) triage systems, sepsis teams, and clinical pathways in sepsis care, and summarizes evidence for the effect of implementation of these interventions in the ED on patient management and outcomes. Severity and poor outcome of sepsis and the frequency of presentation in EDs. make a structured, protocolled approach towards these patients essential, preferably as part of a clinical pathway.

[\[Update in immune regulatory dysfunction of dendritic cells in sepsis\].](#)

Fei X, Sheng ZY, Yao YM.

Zhonghua Shao Shang Za Zhi. 2020 Feb 20;36(2):150-155.

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Further development of sepsis usually leads to septic shock or even death. Many previous studies have focused on the abnormal reactions of monocytes/macrophages, neutrophils, complement system, or cytokine inflammation in sepsis. Many evidences in recent years suggest that dendritic cells, as the most powerful antigen-presenting cells in innate immune system of body, play important role during the process of immune disorders of sepsis. In this article, I review the main classification, immune function, monitoring method, regulatory pathways of dendritic cells and their clinical significance in immune disorders of sepsis, so as to find new strategies for immune regulation of sepsis.

[Treating sepsis with vitamin C, thiamine, and hydrocortisone: Exploring the quest for the magic elixir.](#)

Obi J, Pastores SM, Ramanathan LV, Yang J, Halpern NA.

J Crit Care. 2020 Jan 8;S0883-9441(19)31610-7.

The administration of ascorbic acid (vitamin C) alone or in combination with thiamine (vitamin B1) and corticosteroids (VCTS) has recently been hypothesized to improve hemodynamics, end-organ function, and may even increase survival in critically ill patients. This review aims to explore the current evidence and potential benefits and adverse effects of the VCTS regimen for the treatment of sepsis.

[Nutritional support in sepsis: when less may be more.](#)

van Niekerk G, Meaker C, Engelbrecht AM.

Crit Care. 2020 Feb 14;24(1):53.

Despite sound basis to suspect that aggressive and early administration of nutritional support may hold therapeutic benefits during sepsis, recommendations for nutritional support have been somewhat underwhelming. Current guidelines (ESPEN and ASPEN) recognise a lack of clear evidence demonstrating

the beneficial effect of nutritional support during sepsis, raising the question: why, given the perceived low efficacy of nutritional support, are there no high-quality clinical trials on the efficacy of permissive underfeeding in sepsis? Here, we review clinically relevant beneficial effects of permissive underfeeding, motivating the urgent need to investigate the clinical benefits of delaying nutritional support during sepsis.

[Association of IL-6 -174G > C Polymorphism with Susceptibility to Childhood Sepsis: A Systematic Review and Meta-Analysis.](#)

Ferdosian F, et al.

Fetal Pediatr Pathol. 2020 Feb 14:1-15.

This meta-analysis evaluates the correlation between the IL-6-174 G > C polymorphism and susceptibility of childhood sepsis. There was no significant association of the IL-6-174G > C polymorphism with susceptibility to sepsis in childhood overall, but there was an association with the Caucasian and African ethnic subgroups.

[Natriuretic Peptides to Predict Short-Term Mortality in Patients With Sepsis: A Systematic Review and Meta-analysis.](#)

Vallabhajosyula S, et al.

Mayo Clin Proc Innov Qual Outcomes. 2020 Jan 8;4(1):50-64.

Data are conflicting regarding the optimal cutoffs of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) to predict short-term mortality in patients with sepsis. In this hypothesis-generating analysis, BNP and NT-proBNP cutoffs of 622 pg/mL and 4000 pg/mL optimally predicted short-term mortality in patients with sepsis. The applicability of these results is limited by the heterogeneity of included patient populations.

[Protective effect of rhubarb combined with ulinastatin for patients with sepsis.](#)

Meng F, et al.

Medicine (Baltimore). 2020 Feb;99(7):e18895.

Sepsis is the leading cause of death in critically ill patients. Ulinastatin (UTI), a protease inhibitor, and rhubarb, used as a traditional Chinese medication, are proved to be effective in treating sepsis, but the effect of the combination therapy of these two drugs on sepsis remains unclear. This study aimed to investigate the effect of the combination treatment of UTI and rhubarb on sepsis patients. This study suggested that the combination of UTI and rhubarb may be a promising therapeutic scheme to ameliorate sepsis.

[Dyadic post-traumatic stress after intensive care: Case report of a sepsis patient and his wife.](#)

Gawlytta R, et al.

Intensive Crit Care Nurs. 2020 Feb 6:102806.

Following intensive care treatment, patients and their spouse often report traumatic memories that are frequently associated with post-traumatic stress symptoms. In this case report, we describe the case of a sepsis survivor and his wife who both suffered concurrently from intensive care associated post-traumatic stress symptoms as long-term sequelae. Both were treated with internet-based cognitive-behavioral writing therapy (iCBT) for post-traumatic stress disorder (PTSD) after intensive care. Experiences of critical illness and intensive care can lead to post-traumatic stress in patients and their partners. Hence, it may be useful to offer mental health screening and psychotherapeutic treatment options to both ICU patients and their partners.

[Pancreatic stone protein - sepsis and the riddles of the exocrine pancreas.](#)

Graf R.

Pancreatology. 2020 Feb 1:S1424-3903(20)30034-X.

Pancreatic stone protein (PSP), discovered in the 1970ies, was first associated with stone formation during chronic pancreatitis. Later, the same protein was independently detected in islet preparations and named regenerating protein 1 (REG1). Additional isoforms of PSP, including pancreatitis-associated

protein (PAP), belong to the same protein family. Although the names indicate a potential function in stone formation or islet regeneration, involvements in cellular processes were only suggestive and never unequivocally proven. We established an association between PSP levels in patient blood samples and the development of sepsis. In this review, written in connection with receiving the Lifetime Achievement Award of the European Pancreatic Club, the evolution of the sepsis aspect of PSP is described. We conclude that the true functional properties of this fascinating pancreatic protein still remain an enigma.

[Glycocalyx in Endotoxemia and Sepsis.](#)

Goligorsky MS, Sun D.

Am J Pathol. 2020 Feb 6:S0002-9440(20)30071-7.

Along with the recognition of a crucial role played by endothelial dysfunction secondarily igniting cardiovascular, pulmonary, and renal complications, investigational focus has extended toward endothelial glycocalyx. This delicate coating of cells, including the vascular endothelium, regulates permeability, leukocyte traffic, nitric oxide production, and coagulation, and harbors diverse growth and survival factors. In this brief overview, we discuss the metabolic signatures of sepsis as they relate to the loss of glycocalyx integrity and highlight the contribution of several proteases, heparanase, and hyaluronidase to the shedding of glycocalyx. Clinical manifestations of glycocalyx degradation in unraveling acute respiratory distress syndrome and the cardiovascular, microcirculatory, and renal complications of sepsis are concisely presented. Finally, we list therapeutic strategies for preventing the degradation of, and for restoration of, the glycocalyx.

[A Novel Role for CETP as Immunological Gatekeeper: Raising HDL to Cure Sepsis?](#)

Blauw LL, et al.

Trends Endocrinol Metab. 2020 Feb 4:S1043-2760(20)30003-5.

Raising HDL using cholesteryl ester transfer protein (CETP) inhibitors failed to show a clinically relevant risk reduction of cardiovascular disease in clinical trials, inviting reconsideration of the role of CETP and HDL in human physiology. Based on solid evidence from studies with isolated macrophages, rodents, and humans, we propose that a major function of CETP may be to modulate HDL in order to help resolve bacterial infections. When gram-negative bacteria invade the blood, as occurs in sepsis, Kupffer cells lose their expression of CETP to increase HDL levels. This rise in HDL prevents systemic endotoxemia by binding lipopolysaccharide and induces a systemic proinflammatory response in macrophages to mediate bacterial clearance. This raises the interesting possibility to repurpose CETP inhibitors for the treatment of sepsis.

[Nutrition in Sepsis: A Bench-to-Bedside Review.](#)

De Waele E, Malbrain MLNG, Spapen H.

Nutrients. 2020 Feb 2;12(2):E395.

Nutrition therapy in sepsis is challenging and differs from the standard feeding approach in critically ill patients. The dysregulated host response caused by infection induces progressive physiologic alterations, which may limit metabolic capacity by impairing mitochondrial function. Hence, early artificial nutrition should be ramped-up and emphasis laid on the post-acute phase of critical illness. This review aims to provide an overview and practical recommendations of all aspects of nutritional therapy in the setting of sepsis.

[Cannabis Sativa Revisited-Crosstalk between microRNA Expression, Inflammation, Oxidative Stress, and Endocannabinoid Response System in Critically Ill Patients with Sepsis.](#)

Dinu AR, et al.

Cells. 2020 Jan 28;9(2):E307.

Critically ill patients with sepsis require a multidisciplinary approach, as this situation implies multiorgan distress, with most of the bodily biochemical and cellular systems being affected by the condition. Moreover, sepsis is characterized by a multitude of biochemical interactions and by dynamic changes of the immune system. The aim of this review paper was to present, in detail, the important mechanisms modulated by the endocannabinoid signaling pathway, as well as of the molecular and cellular links it has

with sepsis. At the same time, we wish to present the possible implications of cannabinoids in the most important biological pathways involved in sepsis, such as inflammation, redox activity, immune system, and epigenetic expression.

[Perioperative Management of Patients with Sepsis and Septic Shock, Part II: Ultrasound Support for Resuscitation.](#)

Bughrara N, Diaz-Gomez JL, Pustavoitau A.

Anesthesiol Clin. 2020 Mar;38(1):123-134.

Point-of-care ultrasound is capable of identifying the precise causes of hemodynamic failure in patients with septic shock. Patients in shock demonstrate complex alterations in their circulation, including changes in loading conditions (preload and afterload), right and left ventricular function, and development of obstructive physiology, and some of them have a burden of underlying cardiac disease. We provide a systematic approach to the evaluation of this patient population using qualitative assessment of myocardial performance, fluid responsiveness, and fluid tolerance. Our approach is based on a limited number of ultrasound views: subcostal, inferior vena cava (IVC), and lung views are obtained in rapid succession. A combination of findings in these views is grouped into distinct hemodynamic phenotypes, each of them requiring their own approach to management.

[Perioperative Management of Patients with Sepsis and Septic Shock, Part I: Systematic Approach.](#)

Bughrara N, et al.

Anesthesiol Clin. 2020 Mar;38(1):107-122.

Point-of-care ultrasound is capable of identifying the precise causes of hemodynamic failure in patients with septic shock. Patients in shock demonstrate complex alterations in their circulation, including changes in loading conditions (preload and afterload), right and left ventricular function, and development of obstructive physiology, and some of them have a burden of underlying cardiac disease. We provide a systematic approach to the evaluation of this patient population using qualitative assessment of myocardial performance, fluid responsiveness, and fluid tolerance. Our approach is based on a limited number of ultrasound views: subcostal, inferior vena cava (IVC), and lung views are obtained in rapid succession. A combination of findings in these views is grouped into distinct hemodynamic phenotypes, each of them requiring their own approach to management.

[Sepsis Management in the Emergency Department.](#)

McVeigh SE.

Nurs Clin North Am. 2020 Mar;55(1):71-79.

Sepsis is a deadly and costly condition, but effectively managing sepsis in the emergency department (ED) can help to improve patient outcomes. A key part of sepsis management is improving compliance with sepsis bundles, which can be challenging in the ED setting. Bedside nurses in the ED have a unique opportunity to facilitate early identification and treatment of patients with sepsis, which increases sepsis bundle compliance and improves patient outcomes. Interventions reviewed in this article can help to improve early identification and treatment, along with ways to standardize care, provide education, and implement feedback.

Neonatal, paediatric and maternal sepsis

[Unusual presentation of late-onset disseminated staphylococcal sepsis in a preterm infant.](#)

Khattak SG, Dady I, Mukherjee D.

BMJ Case Rep. 2019 Mar 15;12(3).

An ex-30-week gestation, preterm male baby was admitted to a tertiary neonatal unit and noted to have increased ventilator requirements and diagnosed with sepsis. The baby also developed an abscess over the left elbow and over the xiphisternum along with a decrease in movement of the left hand and the right leg. Panton-Valentine leukocidin (PVL)-producing *Staphylococcus aureus* (SA) was isolated from the blood culture. A whole body MRI showed disseminated abscess with multiple foci in the lung, left elbow and over the xiphisternum. Disseminated sepsis with multiple septic foci has not been previously

reported in neonates. We would like to highlight the fact that sepsis due to PVL toxin-producing SA can cause significant morbidity and mortality in neonates. Proper screening should be done to rule out septic foci in neonates. MRI is a good non-invasive investigation to document septic foci in a neonate and rule out multiorgan involvement.

[Preclinical Detection of Non-catheter Related Late-onset Sepsis in Preterm Infants by Fecal Volatile Compounds Analysis: A Prospective, Multi-center Cohort Study.](#)

Berkhout DJC1, et al.

Pediatr Infect Dis J. 2020 Apr;39(4):330-335.

Late onset sepsis (LOS) in preterm infants is preceded by fecal volatile organic compound (VOC) alterations, suggesting an etiologic role of gut microbiota in LOS rather than being primarily caused by central venous catheters (CVC). To increase our knowledge about the involvement of the gut microbiota in LOS, we analyzed fecal samples from septic infants without a CVC. Fecal VOC profiles of preterm LOS infants without a CVC differed from matched controls underlining the increasing notion that aberrations in gut microbiota composition and activity may play a role in LOS etiology.

[Progranulin as a novel biomarker in diagnosis of early-onset neonatal sepsis.](#)

Rao L, et al.

Cytokine. 2020 Apr;128:155000.

Infections are leading causes of morbidity and mortality in neonates and may also have severe long-term consequences. As early diagnosis of neonatal sepsis improves prognosis, identification of new or complementary biomarkers is of great importance. In this study, we have evaluated the diagnostic value of progranulin (PGRN) in early-onset neonatal sepsis (EOS) and compare its effectiveness with other commonly used biomarkers, such as procalcitonin (PCT) and C-reactive protein (CRP). PGRN may be used as a promising biomarker for the diagnosis of EOS, and the combined use of PGRN and PCT could improve the diagnosis of sepsis.

[Serial clinical observation for management of newborns at risk of early-onset sepsis.](#)

Berardi A, et al.

Curr Opin Pediatr. 2020 Apr;32(2):245-251. doi: 10.1097/MOP.0000000000000864.

Current management approaches for asymptomatic neonates at risk of early onset sepsis remain controversial. Strategies based entirely on clinical observation (SCO, serial clinical observation) have gained consensus. SCO strategy may require changes in the processes of newborn care at birthing centers. Nonetheless, SCO is safe and is associated with fewer laboratory evaluations and unnecessary antibiotics. Thoughtful and thorough practices related to the care of all newborns will benefit any birthing centre. VIDEO ABSTRACT: <http://links.lww.com/MOP/A40>.

[Comparison of the management recommendations of the Kaiser Permanente neonatal early-onset sepsis risk calculator \(SRC\) with NICE guideline CG149 in infants \$\geq\$ 34 weeks' gestation who developed early-onset sepsis.](#)

Morris R, et al.

Arch Dis Child Fetal Neonatal Ed. 2020 Mar 13. pii: fetalneonatal-2019-317165.

To compare the management recommendations of the Kaiser Permanente neonatal early-onset sepsis risk calculator (SRC) with National Institute for Health and Care Excellence (NICE) guideline CG149 in infants \geq 34 weeks' gestation who developed early-onset sepsis (EOS). While both tools were poor in identifying EOS within 4 hours, NICE was superior to SRC in identifying asymptomatic cases. Currently, four out of five EOS have symptoms at first identification, the majority of whom present within 24 hours of birth. Antibiotic stewardship programmes using SRC should include enhanced observation for infants currently treated within NICE guidance.

[Meropenem vs standard of care for treatment of neonatal late onset sepsis \(NeoMero1\): A randomised controlled trial.](#)

Lutsar I, et al.

PLoS One. 2020 Mar 4;15(3):e0229380.

The early use of broad-spectrum antibiotics remains the cornerstone for the treatment of neonatal late onset sepsis (LOS). However, which antibiotics should be used is still debatable, as relevant studies were conducted more than 20 years ago, recruited in single centres or countries, evaluated antibiotics not in clinical use anymore and had variable inclusion/exclusion criteria and outcome measures. Moreover, antibiotic-resistant bacteria have become a major problem in many countries worldwide. We hypothesized that efficacy of meropenem as a broad-spectrum antibiotic is superior to standard of care regimens (SOC) in empiric treatment of LOS and aimed to compare meropenem to SOC in infants aged <90 days with LOS. Within this study population, we found no evidence that meropenem was superior to SOC in terms of success at TOC, short term hearing disturbances, safety or mortality were similar in both treatment arms but the study was underpowered to detect the planned effect. Meropenem treatment did not select for colonization with CRGNOs. We suggest that meropenem as broad-spectrum antibiotic should be reserved for neonates who are more likely to have Gram-negative LOS, especially in NICUs where microorganisms producing extended spectrum- and AmpC type beta-lactamases are circulating.

[Challenges in developing a consensus definition of neonatal sepsis.](#)

McGovern M, et al.

Pediatr Res. 2020 Mar 3.

Sepsis remains a leading cause of morbidity and mortality in the neonatal population, and at present, there is no unified definition of neonatal sepsis. Existing consensus sepsis definitions within paediatrics are not suited for use in the NICU and do not address sepsis in the premature population. Many neonatal research and surveillance networks have criteria for the definition of sepsis within their publications though these vary greatly and there is typically a heavy emphasis on microbiological culture. The concept of organ dysfunction as a diagnostic criterion for sepsis is rarely considered in neonatal literature, and it remains unclear how to most accurately screen neonates for organ dysfunction. We discuss common themes and potential shortcomings in sepsis definitions within neonatology. We highlight the need for a consensus definition of neonatal sepsis and the challenges that this task poses.

[Neonatal Outcomes Following Culture-negative Late-onset Sepsis Among Preterm Infants.](#)

Jiang S, et al.

Pediatr Infect Dis J. 2020 Mar;39(3):232-238.

Culture-negative late-onset sepsis (LOS) is commonly diagnosed in neonatal intensive care units, while the outcomes of neonatal culture-negative LOS are not reported for large cohorts. This study aimed to examine the incidence and neonatal outcomes for culture-negative LOS in a contemporary multicenter cohort of preterm infants. Culture-negative LOS was frequently diagnosed in preterm infants and was associated with increased risks of adverse outcomes. There is an emerging need for more precise diagnosis and treatment strategies for culture-negative LOS.

[Screening for early onset neonatal sepsis: NICE guidance-based practice versus projected application of the Kaiser Permanente sepsis risk calculator in the UK population.](#)

Goel N, et al.

Arch Dis Child Fetal Neonatal Ed. 2020 Mar;105(2):118-122.

To compare management recommendations of the National Institute for Health and Care Excellence (NICE) guidelines with the Kaiser Permanente sepsis risk calculator (SRC) for risk of early onset neonatal sepsis (EONS). The judicious adoption of SRC in UK clinical practice for screening and management of EONS could potentially reduce interventions and antibiotic usage in three out of four term or near-term infants and promote earlier discharge from hospital in >50%. We did not identify any EONS case missed by SRC when compared with NICE. These results have significant implications for healthcare resources.

[Antenatal corticosteroids for women at risk of preterm delivery: the "Emperor's New Clothes" tale in medical practice.](#)

Beksac MS, et al

J Matern Fetal Neonatal Med. 2020 Feb 24:1-8.

To introduce the effect of a single course of betamethasone for pregnant women at risk of preterm delivery (PTD). Single course antenatal betamethasone administration may be ineffective on the respiratory complications of preterm and very preterm infants while it may be unfavorable for extremely preterm infants.

[ECMO for Neonatal Sepsis in 2019.](#)

Butt WW, Chiletti R

Front Pediatr. 2020 Feb 21;8:50.

Sepsis and septic shock in newborns causes mortality and morbidity depending on the organism and primary site. ECMO provides cardiorespiratory support to allow adequate organ perfusion during the time for antibiotics and source control surgery (if needed) to occur. ECMO mode and cannulation site vary depending on support required and local preference. Earlier and more aggressive use of ECMO can improve survival.

[Neonatal and Neurodevelopmental Outcomes Following Linezolid for Coagulase-negative Staphylococcal Infection: Real World Evidence.](#)

Sicard M, et al.

Pediatr Infect Dis J. 2020 Feb 20.

Coagulase-negative staphylococci (CoNS) frequently causes late-onset sepsis in preterm infants. Vancomycin is the first-line therapy, but the emergence of reduced vancomycin-susceptibility strains has resulted in linezolid use, of which long-term safety in preterm infants is unknown. Linezolid exposure was not associated with composite outcome of death or sNDI at 18-21 months. The association between linezolid and death may be due to indication bias. Further studies are warranted.

[Phase 2 Study of the Safety, Pharmacokinetics and Efficacy of Ceftaroline Fosamil in Neonates and Very Young Infants With Late-onset Sepsis.](#)

Bradley JS, et al.

Pediatr Infect Dis J. 2020 Feb 20.

With increasing antimicrobial resistance, antibiotic treatment options for neonatal late-onset sepsis (LOS) are becoming limited. Primary objective of this study was assessment of the safety of ceftaroline fosamil in LOS. Safety in neonates and very young infants was consistent with the known ceftaroline fosamil safety profile. These results support the use of ceftaroline fosamil (6 mg/kg every 8 hours) as a potential treatment option for LOS.

[The Role of Low 25-Hydroxyvitamin D Levels in Preterm Infants with Late- Onset Sepsis.](#)

Dogan P, et al.

Fetal Pediatr Pathol. 2020 Feb 17:1-10

We investigated the association between low 25-hydroxyvitamin D (25-OHD) levels and late-onset sepsis (LOS) in preterm infants (<37 weeks). Low 25-OHD levels are associated with an increased risk of developing LOS development in preterm infants.

[When Do Newborns Die? Timing and Cause-Specific Neonatal Death in Neonatal Intensive Care Unit at Referral Hospital in Gedeo Zone: A Prospective Cohort Study.](#)

Eshete A, Abiy S.

Int J Pediatr. 2020 Feb 15;2020:8707652.

Maternal, newborn, and child health have a high stake in the global health agenda, however, neonates' risk of dying is unacceptable in the world. Ethiopia is one of the countries with high burden of neonatal morbidity and mortality. Yet, timing and cause-specific neonatal death are under-investigated. The present study aimed to determine the timing and cause-specific neonatal death. The timing and cause-specific neonatal deaths were varying among different time of the neonatal periods that needs to design context-based policy and interventions.

[Low vasopressin and progression of neonatal sepsis to septic shock: a prospective cohort study.](#)

Aradhya AS, et al.

Eur J Pediatr. 2020 Feb 15.

The study objective was to analyse the association between low plasma vasopressin and progression of sepsis to septic shock in neonates < 34 weeks gestation. Septic neonates of < 34 weeks gestation were consecutively enrolled; moribund neonates and those with major malformations were excluded. In animal sepsis models and adult septic patients, exuberant production of nitric oxide metabolites and low vasopressin levels have been reportedly associated with progression to septic shock. Vasopressin levels have been variably reported as low as well as elevated in children with septic shock.

[Association of IL-6 -174G > C Polymorphism with Susceptibility to Childhood Sepsis: A Systematic Review and Meta-Analysis.](#)

Ferdosian F, et al.

Fetal Pediatr Pathol. 2020 Feb 14:1-15

This meta-analysis evaluates the correlation between the IL-6 -174 G > C polymorphism and susceptibility of childhood sepsis. There was no significant association of the IL-6 -174G > C polymorphism with susceptibility to sepsis in childhood overall, but there was an association with the Caucasian and African ethnic subgroups.

[Is Lower Vitamin D Level Associated with Increased Risk of Neonatal Sepsis? A Prospective Cohort Study.](#)

Behera CK, et al.

Indian J Pediatr. 2020 Feb 13

To evaluate the effect of maternal/ neonatal vitamin D levels on culture positive neonatal sepsis. Neonates with vitamin D deficiency/insufficiency are at higher risk for developing sepsis than those with sufficient vitamin D levels. Lower vitamin D levels in mothers is also associated with increased risk of sepsis in the neonates.

[Performance of Pediatric Systemic Inflammatory Response Syndrome and Organ Dysfunction Criteria in Late-Onset Sepsis in a Quaternary Neonatal Intensive Care Unit: A Case-Control Study.](#)

Coggins S, et al.

J Pediatr. 2020 Apr;219:133-139.e1.

To evaluate accuracy of systemic inflammatory response syndrome (SIRS) criteria in identifying culture-proven late-onset neonatal sepsis and to assess prevalence of organ dysfunction and its relationship with SIRS criteria. SIRS criteria did not accurately identify culture-proven late-onset sepsis, with poorest accuracy in preterm infants. SIRS criteria did not predict later organ dysfunction or mortality.

[Synbiotic use for the prevention of sepsis and necrotizing enterocolitis in very low birth weight neonates: a randomized controlled trial.](#)

Serce Pehlevan O, et al.

Clin Exp Pediatr. 2020 Feb 5

Probiotics and prebiotics have strain-specific effects on the host. Synbiotics, a mixture of probiotics and prebiotics, are proposed to enhance more beneficial effects on the host than when either agent is administered alone. The combination of synbiotic and lactoferrin did not reduce the severity of NEC, sepsis or mortality.

[Assessment of C-Reactive Protein Diagnostic Test Accuracy for Late-Onset Infection in Newborn Infants: A Systematic Review and Meta-analysis.](#)

Brown JVE, et al.

JAMA Pediatr. 2020 Feb 3.

Rapid and accurate diagnosis of late-onset infection in newborn infants could inform treatment decisions and avoid unnecessary administration of antibiotics. To compare the accuracy of serum C-reactive protein (CRP) with that of microbiological blood culture for diagnosing late-onset infection in newborns. The findings suggest that determination of serum CRP level at initial evaluation of an infant with suspected late-onset infection is unlikely to aid early diagnosis or to select infants to undergo further

investigation or treatment with antimicrobial therapy or other interventions.

[Current and emerging treatments for neonatal sepsis.](#)

Carbone F, Montecucco F, Sahebkar A

Expert Opin Pharmacother. 2020 Feb 3:1-8.

Breastfeeding is beneficial against sepsis. Knowledge of the neonatal immune system is indeed too limited to effectively strengthen immune response by exogenous interventions, especially in preterm and low-birth-weight infants. Awareness of this limitation should pave the way for future studies (e.g. gender- and omics-based) aimed at better characterizing the infant immune system and promoting a more tailored approach.

[Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children.](#)

Weiss SL, et al.

Pediatr Crit Care Med. 2020 Feb;21(2):e52-e106.

To develop evidence-based recommendations for clinicians caring for children (including infants, school-aged children, and adolescents) with septic shock and other sepsis-associated organ dysfunction. A large cohort of international experts was able to achieve consensus regarding many recommendations for the best care of children with sepsis, acknowledging that most aspects of care had relatively low quality of evidence resulting in the frequent issuance of weak recommendations. Despite this challenge, these recommendations regarding the management of children with septic shock and other sepsis-associated organ dysfunction provide a foundation for consistent care to improve outcomes and inform future research.

[Neonatal Sepsis: Treatment of Neonatal Sepsis in Multidrug-Resistant \(MDR\) Infections: Part 2.](#)

Dudeja S

Indian J Pediatr. 2020 Feb;87(2):122-124.

Sepsis is one of the major causes of neonatal deaths in India and worldwide. Pathogens encountered in neonatal sepsis vary worldwide; reports from developing countries more commonly show Gram negative organisms, most common being *Acinetobacter* spp., *Klebsiella* spp. and *Escherichia coli*. Recent studies show that the incidence of antimicrobial resistance, to third generation cephalosporins and carbapenems, has been on a rise. Because of widespread antimicrobial resistance, 'Higher' or 'Reserve' antibiotics are increasingly being used as first/second line antibiotics. In the past decade, there has been a resurgence in the use of colistin as a result of Extended-spectrum β -lactamase (ESBL)- producing Enterobacteriaceae and carbapenem resistant Enterobacteriaceae (CRE), which retain susceptibility only to colistin. The increasing burden of drug resistant Gram negative organisms, particularly *Acinetobacter* spp., *Klebsiella* spp., and *E. coli* might pose a formidable threat in coming years.

[Neonatal Sepsis: Mortality and Morbidity in Neonatal Sepsis due to Multidrug-Resistant \(MDR\) Organisms: Part 1.](#)

Wattal C, et al.

Indian J Pediatr. 2020 Feb;87(2):117-121

The major causes of emergence of multidrug-resistant organisms (MDRO) in neonatal sepsis include empiric antibiotic prescriptions, unregulated use of over-the-counter drugs, high incidence of healthcare associated infections (HAI), lack of awareness about antibiotic stewardship program and under staffing of neonatal intensive care units. In general, mortality due to MDRO sepsis is significantly higher as compared to non MDRO sepsis. Reported morbidities include prolonged use of total parenteral nutrition, need for central venous catheter, invasive ventilation, increased duration of hospital stay and neurologic sequelae.

[Adjunctive therapy to treat neonatal sepsis.](#)

Esposito S, Principi N.

Expert Rev Clin Pharmacol. 2020 Jan;13(1):65-73

NS remains a relevant problem despite the availability of antibiotics effective against the most common agents and the introduction of effective preventive measures such as group B Streptococcus prenatal screening and intrapartum antibiotic prophylaxis. This explains why attempts to introduce new prophylactic and therapeutic measures have been made. Unfortunately, none of the measures suggested and tested to date can be considered a definitive advance. It is highly likely that in the future, new measures will be proposed according to the increase in the knowledge of the characteristics of immune system function in preterm infants and the methods to modulate improper immune responses.

NEWS2

No new articles

Need further help? The outreach team at the Bodleian Health Care Libraries is here to support the information needs of all OUH Trust staff.

We're happy to help you with literature searches, search skills training and advice, keeping you up to date, and general references enquiries.

Contact us:

01865 221936

hcl-enquiries@bodleian.ox.ac.uk

www.bodleian.ox.ac.uk/nhs

Register for OpenAthens to access e-resources:

<https://openathens.nice.org.uk/>

Bulletin content based partly on CASH (Current Awareness Service for Health) [here](#)

To subscribe/unsubscribe from this bulletin please email library@ouh.nhs.uk or reply to this email.

Please see our privacy notice https://libguides.bodleian.ox.ac.uk/Keeping_up_to_date/privacynotice