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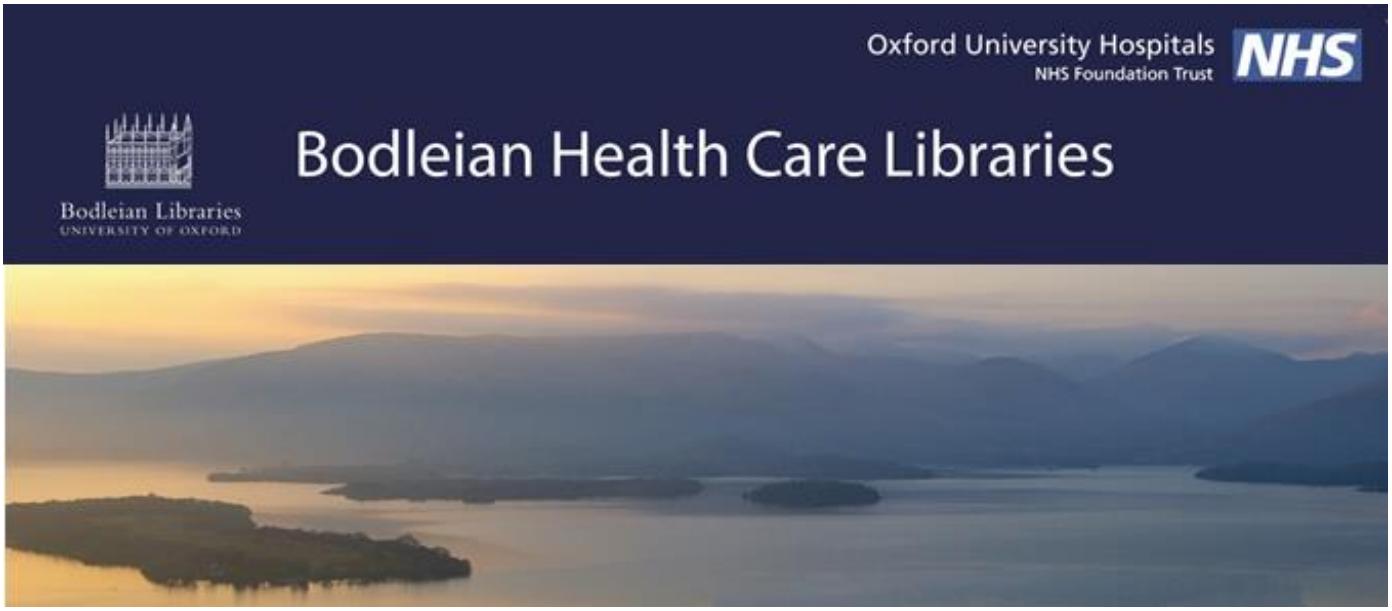

SEPSIS BULLETIN
May/June 2020

Adult sepsis

Evaluation on the effect of acupuncture on patients with sepsis-induced myopathy (ACU-SIM pilot study): A single center, propensity-score stratified, assessor-blinded, prospective pragmatic controlled trial
Chen, W. T. et al.
Medicine (Baltimore); 99; e20233
Sepsis-induced myopathy (SIM) is a disease that causes motor dysfunction in patients with sepsis. There is currently no targeted treatment for this disease. Acupuncture has shown considerable efficacy in the treatment of sepsis and muscle weakness. Therefore, our research aims to explore the effects of acupuncture on the improvement of muscle structure and function in SIM patients and on activities of daily living. There is currently no research on the therapeutic effects of acupuncture on SIM. The results of this study may contribute to new knowledge regarding early muscle atrophy and the treatment effect of acupuncture in SIM patients, and the results may also direct new approaches and interventions in these patients. This trial will serve as a pilot study for an upcoming multicenter real-world study.

Outcome of Immediate Versus Early Antibiotics in Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis
Rothrock, S. G. et al.

Ann Emerg Med;
Debate exists about the mortality benefit of administering antibiotics within either 1 or 3 hours of sepsis onset. We performed this meta-analysis to analyze the effect of immediate (0 to 1 hour after onset) versus early (1 to 3 hours after onset) antibiotics on mortality in patients with severe sepsis or septic shock. We found no difference in mortality between immediate and early antibiotics across all patients. Although the quality of evidence across studies was low, these findings do not support a mortality benefit for immediate compared with early antibiotics across all patients with sepsis.

Changes in Self-Rated Health After Sepsis in Older Adults: A Retrospective Cohort Study
Carey, M. R. et al.
Chest;
As more individuals survive sepsis, there is an urgent need to understand its effects on patient-reported outcomes. What is the effect of sepsis on self-rated health, and what role, if any, does functional disability play in mediating this effect? Mitigating sepsis-related functional disability may play a key role in improving self-rated health after sepsis.

Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019- results from a systematic review and meta-analysis
Bauer, M. et al.
Crit Care; 24; 239
Sepsis and septic shock remain drivers for mortality in critically ill patients. The heterogeneity of the syndrome hinders the generation of reproducible numbers on mortality risks. Consequently, mortality rates range from 15 to 56%. We aimed to update and extend the existing knowledge from meta-analyses and estimate 30- and 90-day mortality rates for sepsis and septic shock separately, stratify rates by region and study type and assess mortality rates across different sequential organ failure assessment (SOFA) scores. Trends of lower sepsis and continuous septic shock mortality rates over time and regional disparities indicate a remaining unmet need for improving sepsis management. Further research is needed to investigate how trends in the burden of disease influence mortality rates in sepsis and septic shock at 30- and 90-day mortality over time.

Clinical- and surgery-specific risk factors for post-operative sepsis: a systematic review and meta-analysis of over 30 million patients
Plaeke, P. et al.
Surg Today; 50; 427-439
Post-operative sepsis is a severe complication of surgery, which often worsens the clinical outcomes. While several risk factors have been identified, the importance of others remains uncertain. This systematic review and meta-analysis aimed to determine patient and surgery-related risk factors for post-operative sepsis. We reviewed Medline, the Web of Science, and the Cochrane library, systematically, for articles describing risk factors for sepsis. The role of eligible risk factors was investigated using a random-effects model, while analyzing univariate and multivariate data separately. In conclusion, multiple-patient and surgery-related risk factors are associated with the development of post-operative sepsis. Recognizing these risk factors could assist in the pre-operative identification of patients at risk of post-operative sepsis.

Timing of Initiation of Renal Replacement Therapy in Sepsis-Associated Acute Kidney Injury
Agapito Fonseca, J. et al.
J Clin Med; 9;
Sepsis-associated acute kidney injury (SA-AKI) is a major issue in medical, surgical and intensive care settings and is an independent risk factor for increased mortality, as well as hospital length of stay and

cost. SA-AKI encompasses a proper pathophysiology where renal and systemic inflammation play an essential role, surpassing the classic concept of acute tubular necrosis. No specific treatment has been defined yet, and renal replacement therapy (RRT) remains the cornerstone supportive therapy for the most severe cases. The timing to start RRT, however, remains controversial, with early and late strategies providing conflicting results. This article provides a comprehensive review on the available evidence on the timing to start RRT in patients with SA-AKI.

Repositioned Drugs for Inflammatory Diseases such as Sepsis, Asthma, and Atopic Dermatitis
Prakash, A. V. et al.
Biomol Ther (Seoul); 28; 222-229
The process of drug discovery and drug development consumes billions of dollars to bring a new drug to the market. Drug development is time consuming and sometimes, the failure rates are high. Thus, the pharmaceutical industry is looking for a better option for new drug discovery. Drug repositioning is a good alternative technology that has demonstrated many advantages over de novo drug development, the most important one being shorter drug development timelines. In the last two decades, drug repositioning has made tremendous impact on drug development technologies. In this review, we focus on the recent advances in drug repositioning technologies and discuss the repositioned drugs used for inflammatory diseases such as sepsis, asthma, and atopic dermatitis.

Sepsis Associated Delirium
Atterton, B. et al.
Medicina (Kaunas); 56;
Sepsis is a potentially life-threatening condition caused by a systemic dysregulated host response to infection. The brain is particularly susceptible to the effects of sepsis with clinical manifestations ranging from mild confusion to a deep comatose state. Sepsis-associated delirium (SAD) is a cerebral manifestation commonly occurring in patients with sepsis and is thought to occur due to a combination of neuroinflammation and disturbances in cerebral perfusion, the blood brain barrier (BBB) and neurotransmission. The usefulness of biomarkers, neuroimaging and electroencephalopathy (EEG) in the diagnosis of SAD remains controversial. The Society of Critical Care Medicine (SCCM) guidelines advise against the use of medications to treat delirium unless distressing symptoms are present or it is hindering the patient's ability to wean from organ support.

Sepsis-Induced Cardiomyopathy: a Comprehensive Review
L'Heureux, M. et al.
Curr Cardiol Rep; 22; 35
To briefly review epidemiology and pathophysiology of SICM and provide a more extensive review of the data on diagnostic and management strategies. Sepsis is a significant cause of mortality, and sepsis-induced cardiomyopathy has both prognostic and management implications for these patients. Individualized work-up and management of these patients is crucial to improving outcomes.

Sepsis Unmasking Fahr's Disease
Mandal, A. K. J. et al.
Am J Med Sci;
Fahr's disease is a sporadic or familial neurodegenerative disorder characterized by symmetrical calcification of cerebral structures, particularly the basal ganglia, cerebellar dentate nuclei and surrounding white matter, in the absence of metabolic causes of calcification. We report the case of a previously fit, high functioning 58-year-old man who developed catastrophic irreversible neuropsychiatric collapse after sepsis despite appropriate antimicrobial treatment. Important diagnostic considerations in the septic patient who develops neurological complications, namely sepsis-associated encephalopathy

and antibiotic-associated encephalopathy, are discussed. The patient remains severely handicapped 6 months after the acute event. Patients with clinically silent neurodegenerative/neuropsychiatric conditions, such as Fahr's disease, may present with florid and unpredicted neurological features in the context of systemic illness.

Enhancing sepsis management through machine learning techniques: A review
Ocampo-Quintero, N. et al.
Med Intensiva;
Sepsis is a major public health problem and a leading cause of death in the world, where delay in the beginning of treatment, along with clinical guidelines non-adherence have been proved to be associated with higher mortality. Machine Learning is increasingly being adopted in developing innovative Clinical Decision Support Systems in many areas of medicine, showing a great potential for automatic prediction of diverse patient conditions, as well as assistance in clinical decision making. In this context, this work conducts a narrative review to provide an overview of how specific Machine Learning techniques can be used to improve sepsis management, discussing the main tasks addressed, the most popular methods and techniques, as well as the obtained results, in terms of both intelligent system accuracy and clinical outcomes improvement.

Significance of body temperature in elderly patients with sepsis
Shimazui, T. et al.
Crit Care; 24; 387
Elderly patients have a blunted host response, which may influence vital signs and clinical outcomes of sepsis. This study was aimed to investigate whether the associations between the vital signs and mortality are different in elderly and non-elderly patients with sepsis. In septic patients, we found mortality in non-elderly sepsis patients was increased with hypothermia and decreased with fever. However, mortality in elderly patients was not associated with BT. These results illuminate the difference in the inflammatory response of the elderly compared to non-elderly sepsis patients.

Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)
Alhazzani, W. et al.
Crit Care Med; 48; e440-e469
The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of a rapidly spreading illness, Coronavirus Disease 2019 (COVID-19), affecting thousands of people around the world. Urgent guidance for clinicians caring for the sickest of these patients is needed. The Surviving Sepsis Campaign COVID-19 panel issued several recommendations to help support healthcare workers caring for critically ill ICU patients with COVID-19. When available, we will provide new evidence in further releases of these guidelines.

Effect of IV Push Antibiotic Administration on Antibiotic Therapy Delays in Sepsis
Gregorowicz, Alex J. et al.
Critical Care Medicine; 48; 1175-1179
Timeliness of antibiotic administration is recognized as an important factor in reducing mortality associated with sepsis. According to guidelines, antibiotics should be administered within 1 hour of sepsis presentation and the Centers for Medicare & Medicaid Services mandates administration within 3 hours. This study evaluates the difference in time from sepsis diagnosis to first-dose completion of beta-lactam antibiotics between IV push and IV piggyback administration. Use of an IV push strategy may safely facilitate more rapid administration of beta-lactam antibiotics and may allow for better compliance with sepsis management guidelines.

The Metabolic Basis of Immune Dysfunction Following Sepsis and Trauma
McBride, M. A. et al.
Front Immunol; 11; 1043
Critically ill, severely injured and high-risk surgical patients are vulnerable to secondary infections during hospitalization and after hospital discharge. This review will define current knowledge of leukocyte metabolic dysfunction during and after sepsis and trauma. We will further discuss therapeutic strategies that target leukocyte mitochondrial function and might have value in preventing or reversing sepsis- and trauma-induced immune dysfunction.

Summer, sun and sepsis-The influence of outside temperature on nosocomial bloodstream infections: A cohort study and review of the literature
Schwab, F. et al.
PLoS One; 15; e0234656
The incidence of many infections is seasonal e.g. surgical site infections, urinary tract infection and bloodstream infections. We questioned whether there is seasonal variation even in climate-controlled hospitalized patients, and analyzed the influence of climate parameters on nosocomial bloodstream infections. A better understanding of the etiology of these infections is needed to provide guidance for future infection control strategies.

Biomarkers and Associated Immune Mechanisms for Early Detection and Therapeutic Management of Sepsis
Trzeciak, A. et al.
Immune Netw; 20; e23
Sepsis is conceptually defined as life-threatening organ dysfunction that is caused by a dysregulated host response to infection. This review summarizes recent advances in sepsis prognosis research and discusses progress made in elucidating the underlying causes of prolonged health deficits experienced by patients surviving the early phases of sepsis.

A narrative review of heart rate and variability in sepsis
Wee, B. Y. H. et al.
Ann Transl Med; 8; 768
Clinicians face challenges in the timely diagnosis and management of pediatric sepsis. Pediatric heart rate has been incorporated into early warning systems and studied as a predictor for critical illness. We aim to review. (I) the role of heart rate in pediatric warning systems and (II) the role of heart rate variability (HRV) in adult and neonatal sepsis, with a focus on its potential applications in pediatrics. With further studies to explore its role, HRV analysis has the potential to add to current tools in the diagnosis and prognosis of pediatric sepsis.

The gut microbiome's role in the development, maintenance, and outcomes of sepsis
Adelman, M. W. et al.
Crit Care; 24; 278
The gut microbiome regulates a number of homeostatic mechanisms in the healthy host including immune function and gut barrier protection. Loss of normal gut microbial structure and function has been associated with diseases as diverse as Clostridioides difficile infection, asthma, and epilepsy. Recent evidence has also demonstrated a link between the gut microbiome and sepsis. In this review, we focus on three key areas of the interaction between the gut microbiome and sepsis. While much of the evidence linking the gut microbiome and sepsis has been established in pre-clinical studies, clinical evidence is lacking in many areas. To address this, we outline a potential research agenda for further investigating the interaction between the gut microbiome and sepsis.

The Story of Nitric Oxide, Sepsis and Methylene Blue: A Comprehensive Pathophysiologic Review
Saha, B. K. and S. L. Burns
Am J Med Sci;
Methylene blue (MB) is considered to be the first synthetic medication ever used in humans. There are many indications for MB, including vasoplegic shock. Nitric oxide (NO), the central mediator of sepsis, promotes vasoplegia by enhancing the guanylate cyclase cyclic guanosine monophosphate second messenger system, the effect of which is attenuated by MB. Therefore, the use of MB represents a unique pharmacologic approach towards treating the underlying pathophysiology of vasoplegia in sepsis. There are numerous reports of the successful use of MB in refractory shock in the literature. This manuscript describes the historical aspects of the identification of NO as the endothelial derived relaxation factor and its role in the pathogenesis of vasoplegia in septic shock. An analysis of the existing evidence for the use of MB as an inhibitor of NO in vasodilatory shock is provided. The adverse effects associated with the use of MB and an approach to optimal dosing in septic shock are also addressed.

The cellular basis of organ failure in sepsis-signaling during damage and repair processes
Bauer, M. and R. Wetzker
Med Klin Intensivmed Notfmed; 115; 04-Sep
Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The review introduces key signaling processes involved in infection-induced "resistance" and "tolerance". We propose that elaboration of these signaling pathways allows novel insights into sepsis-associated tissue damage and repair processes.

Role of beta2 Integrins in Neutrophils and Sepsis
Yuki, K. and L. Hou
Infect Immun; 88;
Sepsis remains medically challenging, with high morbidity and mortality. A novel intervention is urgently needed in the absence of specific, targeted therapy. Neutrophils act as double-edged swords in sepsis; they can help to eradicate microbes, but they also contribute to tissue injury. beta2 integrins are critical adhesion molecules that regulate a number of neutrophil functions. beta2 integrins consist of four members, namely, alphaLbeta2, alphaMbeta2, alphaXbeta2, and alphaDbeta2. Here, we review the role of each beta2 integrin in neutrophils and sepsis and consider future direction for therapeutic intervention.

Is lactoferrin still a treatment option to reduce neonatal sepsis?
Ochoa, T. J.
The Lancet Child and Adolescent Health; 4; 411-412
Lactoferrin, a glycoprotein present in milk, tears, saliva, and in the specific granules of the neutrophils, is part of the innate immune system. Lactoferrin has antimicrobial and immunomodulatory properties that might potentially protect the newborn against infection, mainly by three mechanisms: modulation of bacterial growth in the gastrointestinal tract, promotion of intestinal-cell proliferation, differentiation and maturation, and regulation of the host immune response. Clinical trials have been done in preterm infants to determine the effect of bovine lactoferrin supplementation on prevention of late-onset sepsis, with controversial results.

Neonatal, infant and maternal sepsis

Sustainability of a Clinical Examination-Based Approach for Ascertainment of Early-Onset Sepsis in Late Preterm and Term Neonates
Frymoyer, A. et al.
J Pediatr;
We demonstrated the sustained impact over a 5-year period of a clinical examination-based approach to

identification of early-onset sepsis in late preterm and term neonates at our hospital. To date, more than 20 000 neonates have been safely managed using this approach, resulting in a 63% reduction in antibiotic use.

Disseminated Intravascular Coagulation Is an Independent Predictor of Adverse Outcomes in Children in the Emergency Department with Suspected Sepsis
Slatnick, L. R. et al.
J Pediatr;
To evaluate the impact of early disseminated intravascular coagulation (DIC) on illness severity in children using a database of emergency department ED encounters for children with suspected sepsis, in view of similar associations in adults. A DIC score of >/=3 was an independent predictor for both vasopressor use and mortality in this pediatric cohort, distinct from the adult overt DIC score cutoff of >/=5.

Gene Expression Profiles in Children With Suspected Sepsis
Balamuth, F. et al.
Ann Emerg Med; 75; 744-754
Sepsis recognition is a clinical challenge in children. We aim to determine whether peripheral blood gene expression profiles are associated with pathogen type and sepsis severity in children with suspected sepsis. The study demonstrates feasibility of evaluating gene expression profiling data in children evaluated for sepsis in the pediatric emergency department setting. Our results suggest that gene expression profiling may facilitate identification of source pathogen in children with suspected sepsis, which could ultimately lead to improved tailoring of sepsis treatment and antimicrobial stewardship.

Association of Histological and Clinical Chorioamnionitis With Neonatal Sepsis Among Preterm Infants: A Systematic Review, Meta-Analysis, and Meta-Regression
Villamor-Martinez, E. et al.
Front Immunol; 11; 972
Chorioamnionitis (CA) is considered a key risk factor for very preterm birth and for developing early onset sepsis (EOS) in preterm infants, but recent data suggest that CA might be protective against late onset sepsis (LOS). In conclusion, our data suggest that the positive association between chorioamnionitis and LOS may be modulated by the effect of chorioamnionitis on gestational age.

Utility of Procalcitonin as a Biomarker for Sepsis in Children
Downes, K. J. et al.
J Clin Microbiol; 58;
Sepsis is a complex process defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. It is associated with significant morbidity and mortality rates in both adults and children, and emphasis has been placed on its early recognition and prompt provision of antimicrobials. Owing to limitations of current diagnostic tests (i.e., poor sensitivity and delayed results), significant research has been conducted to identify sepsis biomarkers. Ideally, a biomarker could reliably and rapidly distinguish bacterial infection from other, noninfectious causes of systemic inflammatory illness. In doing so, a sepsis biomarker could be used for earlier identification of sepsis, risk stratification/prognostication, and/or guidance of antibiotic decision-making. In this minireview, we review one of the most common clinically used sepsis biomarkers, procalcitonin, and its roles in sepsis management in these three areas. We highlight key findings in the adult literature but focus the bulk of this review on pediatric sepsis. The challenges and limitations of procalcitonin measurement in sepsis are also discussed.

Impact of Early-Onset Sepsis and Antibiotic Use on Death or Survival with Neurodevelopmental Impairment at 2 Years of Age among Extremely Preterm Infants
Mukhopadhyay, S. et al.

J Pediatr; 221; 39-46 e5
To evaluate the hypothesis that early-onset sepsis increases risk of death or neurodevelopmental impairment (NDI) among preterm infants; and that among infants without early-onset sepsis, prolonged early antibiotics alters risk of death/NDI. Early-onset sepsis was associated with increased risk of death/NDI among extremely preterm infants. Among matched infants without culture-confirmed infection, prolonged early antibiotic administration was not associated with death/NDI.

Pediatric Sepsis Definition-A Systematic Review Protocol by the Pediatric Sepsis Definition Taskforce
Menon, K. et al.
Crit Care Explor; 2; e0123
Sepsis is responsible for a substantial proportion of global childhood morbidity and mortality. However, evidence demonstrates major inaccuracies in the use of the term "sepsis" in clinical practice, coding, and research. Current and previous definitions of sepsis have been developed using expert consensus but the specific criteria used to identify children with sepsis have not been rigorously evaluated. Therefore, as part of the Society of Critical Care Medicine's Pediatric Sepsis Definition Taskforce, we will conduct a systematic review to synthesize evidence on individual factors, clinical criteria, or illness severity scores that may be used to identify children with infection who have or are at high risk of developing sepsis-associated organ dysfunction and separately those factors, criteria, and scores that may be used to identify children with sepsis who are at high risk of progressing to multiple organ dysfunction or death.