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SEPSIS BULLETIN July/August 2020

Sepsis

<u>Clinical outcomes of continuous vs intermittent meropenem infusion for the treatment of sepsis: A systematic review</u> and meta-analysis

Chen, P. et al.

Adv Clin Exp Med, 29, 993-1000, 2020

The antibiotic meropenem is commonly administered to patients with sepsis and septic shock. The aim of this study was to conduct a meta-analysis to evaluate the clinical efficacy and safety of continuous compared to intermittent meropenem infusion for the treatment of sepsis. Compared with intermittent dosing, administration of meropenem antibiotics through continuous infusion in patients with sepsis is associated with decreased hospital mortality, increased clinical cure rates and greater microbiological eradication. Further high-quality studies should be conducted to confirm our findings.

The challenge of recognising sepsis: Future nanotechnology solutions

Claxton, A. et al.

J Intensive Care Soc, 21, 241-246, 2020

The urgent need to start anti-infective therapeutic interventions in suspected sepsis, and the lack of specific time-critical diagnostic information often lead to the widespread administration of broad-spectrum antimicrobial therapies, increasing the risk of unwanted patient harms and contributing to rising pathogen antimicrobial resistance. Nanotechnology, which involves engineering at the nanoscale, allows for the bespoke development of diagnostic

solutions with multi-functionality and high sensitivity that has the potential to help provide time-critical information to make more accurate diagnoses and treatment decisions for sepsis. Nanotechnologies also have the potential to improve upon the current strategies used for novel biomarker discovery. Here we describe some of the current limitations to identifying sepsis and explore the potential role for nanotechnology solutions.

The Surviving Sepsis Campaign: Basic/Translational Science Research Priorities

Deutschman, C. S. et al.

Crit Care Med, 48, 1217-1232, 2020

Expound upon priorities for basic/translational science identified in a recent paper by a group of experts assigned by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. In the first of a series of follow-up reports to the original paper, several members of the original task force with specific expertise provided a more in-depth analysis of the five identified priorities directly related to basic/translational science. This analysis expounds on what is known about the question and what was identified as priorities for ongoing research. It is hoped that this analysis will aid the development of future research initiatives.

<u>Incidence</u> and <u>mortality</u> of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis

Fleischmann-Struzek, C. et al.

Intensive Care Med, 46, 1552-1562, 2020

We investigate the global burden of sepsis in hospitalized adults by updating and expanding a systematic review and meta-analysis and to compare findings with recent Institute for Health Metrics and Evaluation (IHME) sepsis estimates. Compared to results from the IHME study, we found an approximately 50% lower incidence of hospital-treated sepsis. The majority of studies included were based on administrative data, thus limiting our ability to assess temporal trends and regional differences. The incidence of sepsis remains unknown for the vast majority of LMICs, highlighting the urgent need for improved epidemiological sepsis surveillance.

Biology of Interleukin-17 and Its Pathophysiological Significance in Sepsis

Ge, Y. et al.

Front Immunol, 11, 1558, 2020

The interleukin (IL)-17 family includes six structure-related cytokines (A-F). To date, majority of studies have focused on IL-17A. IL-17A plays a pivotal role in various infectious diseases, inflammatory and autoimmune disorders, and cancer. Several recent studies have indicated that IL-17A is a biomarker as well as a therapeutic target in sepsis. In the current review, we summarize the biological functions of IL-17, including IL-17-mediated responses and signal transduction pathways, with particular emphasis on clinical relevance to sepsis.

<u>Pulmonary Innate Immune Response Determines the Outcome of Inflammation During Pneumonia and Sepsis-</u> Associated Acute Lung Injury

Kumar, V.

Front Immunol, 11, 1722, 2020

The lung is a primary organ for gas exchange in mammals that represents the largest epithelial surface in direct contact with the external environment. It also serves as a crucial immune organ, which harbors both innate and adaptive immune cells to induce a potent immune response. Due to its direct contact with the outer environment, the lung serves as a primary target organ for many airborne pathogens, toxicants (aerosols), and allergens causing pneumonia, acute respiratory distress syndrome (ARDS), and acute lung injury or inflammation (ALI). The current review describes the immunological mechanisms responsible for bacterial pneumonia and sepsis-induced ALI. It highlights the immunological differences for the severity of bacterial sepsis-induced ALI as compared to the pneumonia-associated ALI. The immune-based differences between the Gram-positive and Gram-negative bacteria-induced pneumonia show different mechanisms to induce ALI. The role of pulmonary epithelial cells (PECs), alveolar macrophages (AMs), innate lymphoid cells (ILCs), and different pattern-recognition receptors (PRRs, including Toll-like receptors (TLRs) and inflammasome proteins) in neutrophil infiltration and ALI induction have been described during pneumonia and sepsis-induced ALI. Also, the resolution of inflammation is frequently observed during ALI associated with pneumonia, whereas sepsis-associated ALI lacks it. Hence, the review mainly describes the different immune mechanisms responsible for pneumonia and sepsis-induced ALI. The differences in immune response

depending on the causal pathogen (Gram-positive or Gram-negative bacteria) associated pneumonia or sepsis-induced ALI should be taken in mind specific immune-based therapeutics.

<u>Biomaterial-Driven Immunomodulation: Cell Biology-Based Strategies to Mitigate Severe Inflammation and Sepsis</u> Lasola, J. J. M. et al.

Front Immunol, 11, 1726, 2020

Inflammation is an essential component of a wide variety of disease processes and oftentimes can increase the deleterious effects of a disease. Finding ways to modulate this essential immune process is the basis for many therapeutics under development and is a burgeoning area of research for both basic and translational immunology. In addition to developing therapeutics for cellular and molecular targets, the use of biomaterials to modify innate and adaptive immune responses is an area that has recently sparked significant interest. In particular, immunomodulatory activity can be engineered into biomaterials to elicit heightened or dampened immune responses for use in vaccines, immune tolerance, or anti-inflammatory applications. We propose that nanoparticles represent a potential polypharmacological strategy to simultaneously modify multiple aspects of dysregulated immune responses where single target therapies have fallen short for these applications. This review intends to serve as a resource for immunology labs and other associated fields that would like to apply the growing field of rationally designed biomaterials into their work.

The severe COVID-19: A sepsis induced by viral infection? And its immunomodulatory therapy

Lin, H.Y.

Chin J Traumatol, 23, 190-195, 2020

COVID-19 is known for its magical infectivity, fast transmission and high death toll based on the large number of infected people. From the perspective of the clinical manifestation, autopsy examination and pathophysiology, the essence of COVID-19 should be viewed as a sepsis induced by viral infection, and has the essential characteristics as sepsis induced by other pathogens. Therefore, in addition to etiological and supportive treatment, immunomodulatory therapy is also appropriate to severe COVID-19. Although there is still a lack of consensus on immunotherapy for sepsis so far, relatively rich experiences have been accumulated in the past decades, which will help us in the treatment of severe COVID-19. This article will elaborate immunotherapy of sepsis, though it may not be consistent.

<u>Sepsis-Induced Myocardial Dysfunction (SIMD): the Pathophysiological Mechanisms and Therapeutic Strategies</u> Targeting Mitochondria

Lin, Y. et al.

Inflammation, 43, 1184-1200, 2020

Sepsis is a lethal syndrome with multiple organ failure caused by an inappropriate host response to infection. Cardiac dysfunction is one of the important complications of sepsis, termed sepsis-induced myocardial dysfunction (SIMD), which is characterized by systolic and diastolic dysfunction of both sides of the heart. The current review briefly introduces the mechanism of SIMD, highlights how mitochondrial dysfunction contributes to SIMD, and discusses the role of metabolic resuscitation in the treatment of SIMD.

Immune Response and COVID-19: A mirror image of Sepsis

Lopez-Collazo, E. et al.

Int J Biol Sci, 16, 2479-2489, 2020

The emergence of SARS-CoV-2 virus and its associated disease COVID-19 have triggered significant threats to public health, in addition to political and social changes. An important number of studies have reported the onset of symptoms compatible with pneumonia accompanied by coagulopathy and lymphocytopenia during COVID-19. Increased cytokine levels, the emergence of acute phase reactants, platelet activation and immune checkpoint expression are some of the biomarkers postulated in this context. As previously observed in prolonged sepsis, T-cell exhaustion due to SARS-CoV-2 and even their reduction in numbers due to apoptosis hinder the response to the infection. In this review, we synthesized the immune changes observed during COVID-19, the role of immune molecules as severity markers for patient stratification and their associated therapeutic options.

<u>Epidemiology</u> and <u>burden</u> of <u>sepsis</u> acquired in hospitals and intensive care units: a systematic review and metaanalysis

Markwart, R. et al.

Intensive Care Med, 46, 1536-1551, 2020

Sepsis is recognized as a global public health problem, but the proportion due to hospital-acquired infections remains unclear. We aimed to summarize the epidemiological evidence related to the burden of hospital-acquired (HA) and ICU-acquired (ICU-A) sepsis. HA sepsis is of major public health importance, and the burden is particularly high in ICUs. There is an urgent need to improve the implementation of global and local infection prevention and management strategies to reduce its high burden among hospitalized patients.

CD4 T Cell Responses and the Sepsis-Induced Immunoparalysis State

Martin, M. D. et al.

Front Immunol, 11, 1364, 2020

Sepsis remains a major cause of death in the United States and worldwide, and costs associated with treating septic patients place a large burden on the healthcare industry. This review will focus on the current understanding of how sepsis impacts the CD4 T cell responses, including numerical representation, repertoire diversity, phenotype and effector functionality, subset representation (e.g., Th1 and Treg frequency), and therapeutic efforts to restore CD4 T cell numbers and function following sepsis. Additionally, we will discuss recent efforts to model the acute sepsis phase and resulting immune dysfunction using mice that have previously encountered infection, which more accurately reflects the immune system of humans with a history of repeated infection throughout life. A thorough understanding of how sepsis impacts CD4 T cells based on previous studies and new models that accurately reflect the human immune system may improve translational value of research aimed at restoring CD4 T cell-mediated immunity, and overall immune fitness following sepsis.

Complement in sepsis-when science meets clinics

Mollnes, T. E. and M. Huber-Lang

FEBS Lett, 594, 2621-2632, 2020

Sepsis as life-threatening organ dysfunction caused by microorganisms represents a dreadful challenge for the immune system. The role of the complement system as major column of innate immunity has been extensively studied in various sepsis models, but its translational value remains in the dark. Complement activation products, such as C3a and C5a, and their corresponding receptors provide useful diagnostic tools and promising targets to improve organ function and outcome. However, a monotherapeutic complement intervention irrespective of the current immune function seems insufficient to reverse the complex sepsis mechanisms. Indeed, sepsis-induced disturbances of cross talking complement, coagulation, and fibrinolytic cascades lead to systemic 'thromboinflammation', ultimately followed by multiple-organ failure. We propose to reliably monitor the complement function in the patient and to re-establish the immune balance by patient-tailored combined therapies, such as complement and Toll-like receptor inhibition. Our working hypothesis aims at blocking the 'explosive' innate immune recognition systems early on before downstream mediators are released and the inflammatory response becomes irreversible, a strategy that we name 'upstream approach'.

<u>Venoarterial Extracorporeal Membranous Oxygenation: Treatment Option for Sepsis-Induced Cardiogenic Shock? A</u>
Systematic Review

Sato, R. and A. Kuriyama

Crit Care Med, 48, e722-e729, 2020

Clinicians often encounter adult patients with septic shock who fail to respond to fluid therapy and vasopressors. There is an increasing interest in venoarterial extracorporeal membranous oxygenation in the treatment of patients with septic shock, but its outcomes and safety remain unclear. The aim of this study is to describe in-hospital mortality and complication rate in adult patients with septic shock who underwent venoarterial extracorporeal membranous oxygenation, and to identify patients who may potentially benefit from venoarterial extracorporeal membranous oxygenation remains a controversial treatment strategy in septic shock. The reported in-hospital mortality rates in patients with sepsis-induced cardiogenic shock who underwent venoarterial extracorporeal membranous oxygenation were quite inconsistent. There is a need for

well-designed studies to assess the benefit and safety of venoarterial extracorporeal membranous oxygenation in patients with sepsis-induced cardiogenic shock.

Glucocorticoids in Sepsis: To Be or Not to Be

Vandewalle, J. and C. Libert

Front Immunol, 11, 1318, 2020

Sepsis is a highly lethal syndrome resulting from dysregulated immune and metabolic responses to infection, thereby compromising host homeostasis. Activation of the hypothalamic-pituitary-adrenal (HPA) axis and subsequently adrenocortical glucocorticoid (GC) production during sepsis are important regulatory processes to maintain homeostasis. Multiple preclinical studies have proven the pivotal role of endogenous GCs in tolerance against sepsis by counteracting several of the sepsis characteristics, such as excessive inflammation, vascular defects, and hypoglycemia. Sepsis is however often complicated by dysfunction of the HPA axis, resulting from critical-illness-related corticosteroid insufficiency (CIRCI) and GC resistance. Therefore, GCs have been tested as an adjunctive therapy in sepsis and septic shock in different randomized clinical trials (RCTs). Nonetheless, these studies produced conflicting results. Interestingly, adding vitamin C and thiamin to GC therapy enhances the effects of GCs, probably by reducing GC resistance, and this results in an impressive reduction in sepsis mortality as was shown in two recent preliminary retrospective before-after studies. Multiple RCTs are currently underway to validate this new combination therapy in sepsis.

Antibiotics administered within 1 hour to adult emergency department patients screened positive for sepsis: a systematic review

Xantus, G. et al.

Eur J Emerg Med, 27, 260-267, 2020

The 2018 Surviving Sepsis Campaign update recommended instigating the Sepsis-6 bundle within 1 h; however, the supporting evidence is weak. The objective was to systematically review the literature to determine whether there is mortality benefit (hospital or 28/30-day survival) associated with administration of antibiotics <1 h to adult emergency department (ED) patients screened positive for sepsis using systemic inflammatory response system criteria.: There is equivocal evidence of in-hospital or 28/30-day survival benefit associated with antibiotics administered </=1 h after presentation to the ED for patients who screened positive for sepsis. Further research is needed to identify the exact patient group, which would truly benefit from initiation of antibiotics <1 h after ED presentation.

Use of Intravenous Immunoglobulins in Sepsis Therapy-A Clinical View

Jarczak, D. et al.

Int J Mol Sci, 21, , 2020

Sepsis is a life-threatening organ dysfunction, defined by a dysregulated host immune response to infection. During sepsis, the finely tuned system of immunity, inflammation and anti-inflammation is disturbed in a variety of ways. Both pro-inflammatory and anti-inflammatory pathways are upregulated, activation of the coagulation cascade and complement and sepsis-induced lymphopenia occur. Due to the manifold interactions in this network, the use of IgM-enriched intravenous immunoglobulins seems to be a promising therapeutic approach. Unfortunately, there is still a lack of evidence-based data to answer the important questions of appropriate patient populations, optimal timing and dosage of intravenous immunoglobulins. With this review, we aim to provide an overview of the role of immunoglobulins, with emphasis on IgM-enriched formulations, in the therapy of adult patients with sepsis and septic shock.

Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis: A Randomized Trial

Kyriazopoulou, E. et al.

Am J Respir Crit Care Med, 2020, , 2020

Although early antimicrobial discontinuation guided by procalcitonin (PCT) has showed decreased antibiotic consumption in lower respiratory tract infections (LRTIs), the outcomes in long-term sepsis sequelae remain unclear. We investigate if PCT-guidance may reduce the incidence of long-term infection-associated adverse events in sepsis. In sepsis, PCT-guidance was effective in reducing infection-associated adverse events, 28-day mortality, and cost of hospitalization. Clinical trial registration available at www.clinicaltrials.gov, ID: NCT03333304. This article is open

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An Explainable Artificial Intelligence Predictor for Early Detection of Sepsis

Yang, M. et al.

Crit Care Med, 2020, , 2020

Early detection of sepsis is critical in clinical practice since each hour of delayed treatment has been associated with an increase in mortality due to irreversible organ damage. This study aimed to develop an explainable artificial intelligence model for early predicting sepsis by analyzing the electronic health record data from ICU provided by the PhysioNet/Computing in Cardiology Challenge 2019. Explainable artificial intelligence sepsis predictor model achieves superior performance for predicting sepsis risk in a real-time way and provides interpretable information for understanding sepsis risk in ICU.

Coronavirus (Covid-19) sepsis: revisiting mitochondrial dysfunction in pathogenesis, aging, inflammation, and mortality

Shenoy, S.

Inflamm Res, 2020, 01-Sep, 2020

Decline in mitochondrial function occurs with aging and may increase mortality. We discuss mitochondrial contribution to Covid-19 sepsis, specifically the complex interaction of innate immune function, viral replication, hyper-inflammatory state, and HIF-alpha/Sirtuin pathways. Aging is associated with worse outcomes in sepsis. Modulating Sirtuin activity is emerging as therapeutic agent in sepsis. HIF-alpha, levels of mitochondrial DNA, and other mitochondrial DAMP molecules may also serve as useful biomarker and need to be investigated. These mechanisms should be explored specifically for Covid-19-related sepsis. Understanding newly discovered regulatory mechanisms may lead to the development of novel diagnostic and therapeutic targets.

Effect of dexmedetomidine on inflammation in patients with sepsis requiring mechanical ventilation: a sub-analysis of a multicenter randomized clinical trial

Ohta, Y. et al.

Crit Care, 24, 493, 2020

Administration of dexmedetomidine has been reported to improve inflammatory response in animals. We explored the effects of administering dexmedetomidine on the levels of C-reactive protein (CRP) and procalcitonin, and thus on inflammation, in patients with sepsis enrolled in a randomized clinical trial. Sedation using dexmedetomidine reduced inflammation in patients with sepsis requiring mechanical ventilation.

Sepsis-Associated Brain Dysfunction: A Review of Current Literature

Czempik, P. F. et al.

Int J Environ Res Public Health, 17, , 2020

Sepsis-associated brain dysfunction (SABD) may be the most common type of encephalopathy in critically ill patients. SABD develops in up to 70% of septic patients and represents the most frequent organ insufficiency associated with sepsis. It presents with a plethora of acute neurological features and may have several serious long-term psychiatric consequences. SABD might cause various pathological changes in the brain through numerous mechanisms. Clinical neurological examination is the basic screening method for SABD, although it may be challenging in subjects receiving with opioids and sedative agents. As electrographic seizures and periodic discharges might be present in 20% of septic patients, screening with electroencephalography (EEG) might be useful. Several imaging techniques have been suggested for non-invasive assessment of structure and function of the brain in SABD patients; however, their usefulness is rather limited. Although several experimental therapies have been postulated, at the moment, no specific treatment exists. Clinicians should focus on preventive measures and optimal management of sepsis. This review discusses epidemiology, clinical presentation, pathology, pathophysiology, diagnosis, management, and prevention of SABD.

Prognosis and rescue therapy for sepsis-related severe thrombocytopenia in critically ill patients

Zhou, Z. et al.

Cytokine, 136, 155227, 2020

Sepsis is the most common critical disease with high mortality in intensive care unit. Platelet count (PC) frequently altered in sepsis patients and implicated in the pathogenesis of multi-organ failure. It is also worth mentioning that thrombocytopenia was closely associated with poor outcomes in sepsis patients. However, whether drug intervention aimed at correcting thrombocytopenia would improve the prognosis of sepsis patients and which kind of sepsis patients could benefit from this therapy is still unclear. This study aims to explore the effect of severe thrombocytopenia on the prognosis of sepsis and the impact of a platelet-elevating drug (recombinant human thrombopoietin, rhTPO) for these sepsis patients. These results suggested that sepsis patients with severe thrombocytopenia, not mild-moderate thrombocytopenia, had a poorer prognosis. RhTPO, probably as effective rescue therapy, could quickly recover PC and improve the prognosis in these sepsis patients.

Sepsis and Coronavirus Disease 2019: Common Features and Anti-Inflammatory Therapeutic Approaches

Beltran-Garcia, J. et al.

Crit Care Med, 2020, , 2020

Great efforts are being made worldwide to identify the specific clinical characteristics of infected critically ill patients that mediate the associated pathogenesis, including vascular dysfunction, thrombosis, dysregulated inflammation, and respiratory complications. Recently, coronavirus disease 2019 has been closely related to sepsis, which suggests that most deaths in ICUs in infected patients are produced by viral sepsis. Understanding the physiopathology of the disease that lead to sepsis after severe acute respiratory syndrome coronavirus 2 infection is a current clinical need to improve intensive care-applied therapies applied to critically ill patients. Although the whole representative data characterizing the immune and inflammatory status in coronavirus disease 2019 patients are not completely known, it is clear that hyperinflammation and coagulopathy contribute to disease severity. Here, we present some common features shared by severe coronavirus disease 2019 patients and sepsis and describe proposed anti-inflammatory therapies for coronavirus disease 2019 which have been previously evaluated in sepsis.

<u>Combined Treatment With Hydrocortisone, Vitamin C, and Thiamine for Sepsis and Septic Shock: A Randomized</u> Controlled Trial

Chang, P. et al.

Chest, 158, 174-182, 2020

We review the question of whether hydrocortisone, vitamin C, and thiamine treatment can reduce the mortality of patients with sepsis is controversial. We evaluate the efficacy and safety of hydrocortisone, vitamin C, and thiamine combination treatment for patients with sepsis or septic shock (HYVCTTSSS). The study was terminated after the midterm analysis. Among patients with sepsis or septic shock, the combination of hydrocortisone, vitamin C, and thiamine did not reduce mortality compared with placebo. TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT03258684; URL: www.clinicaltrials.gov.

COVID-19 Sepsis and Microcirculation Dysfunction

Colantuoni, A. et al.

Front Physiol, 11, 747, 2020

The spreading of Coronavirus (SARS-CoV-2) pandemic, known as COVID-19, has caused a great number of fatalities all around the World. Up to date (2020 May 6) in Italy we had more than 28,000 deaths, while there were more than 205.000 infected. The majority of patients affected by COVID-19 complained only slight symptoms: fatigue, myalgia or cough, but more than 15% of Chinese patients progressed into severe complications, with acute respiratory distress syndrome (ARDS), needing intensive treatment. We tried to summarize data reported in the last months from several Countries, highlighting that COVID-19 was characterized by cytokine storm (CS) and endothelial dysfunction in severely ill patients, where the progression of the disease was fast and fatal. Endothelial dysfunction was the fundamental mechanism triggering a pro-coagulant state, finally evolving into intravascular disseminated coagulation, causing embolization of several organs and consequent multiorgan failure (MOF). The Italian Society of Clinical Hemorheology and Microcirculation was aimed to highlight the role of microcirculatory dysfunction in the pathogenetic mechanisms of COVID-19 during the spreading of the biggest challenges to the World Health.

Sepsis and Septic Shock - Basics of diagnosis, pathophysiology and clinical decision making

Font, M. D. et al.

Med Clin North Am, 104, 573-585, 2020

Sepsis and septic shock are major causes of mortality among hospitalized patients. The sepsis state is due to dysregulated host response to infection, leading to inflammatory damage to nearly every organ system. Early recognition of sepsis and appropriate treatment with antibiotics, fluids, and vasopressors is essential to reducing organ system injury and mortality. This review summarizes the current understanding of the epidemiology, pathophysiology, diagnosis, and treatment of sepsis and septic shock.

The Multifaceted Function of Granzymes in Sepsis: Some Facts and a Lot to Discover

Garzon-Tituana, M. et al.

Front Immunol, 11, 1054, 2020

Sepsis is a serious global health problem. In addition to a high incidence, this syndrome has a high mortality and is responsible for huge health expenditure. The pathophysiology of sepsis is very complex and it is not well-understood yet. However, it is widely accepted that the initial phase of sepsis is characterized by a hyperinflammatory response while the late phase is characterized by immunosuppression and immune anergy, increasing the risk of secondary infections. Granzymes (Gzms) are a family of serine proteases classified according to their cleavage specificity. In this review, we provide a comprehensive overview on the contribution of these novel functions of Gzms to sepsis and the new therapeutic opportunities emerging from targeting these proteases for the treatment of this serious health problem.

Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis: The ORANGES Trial

Iglesias, J. et al.

Chest, 158, 164-173, 2020

Sepsis is a major public health burden resulting in 25% to 30% in-hospital mortality and accounting for over 20 billion dollars of US hospital costs. Does hydrocortisone, ascorbic acid, thiamine (HAT) therapy improve clinical outcomes in sepsis and septic shock?: Our results suggest that the combination of IV ascorbic acid, thiamine, and hydrocortisone significantly reduced the time to resolution of shock. Additional studies are needed to confirm these findings and assess any potential mortality benefit from this treatment. TRIAL REGISTRATION: ClinicalTrials.gov; No.: NCT03422159; URL: www.clinicaltrials.gov.

Targeting of G-protein coupled receptors in sepsis

Rehman, A. et al.

Pharmacol Ther, 211, 107529, 2020

The Third International Consensus Definitions (Sepsis-3) define sepsis as life-threatening multi-organ dysfunction caused by a dysregulated host response to infection. Sepsis can progress to septic shock-an even more lethal condition associated with profound circulatory, cellular and metabolic abnormalities. Septic shock remains a leading cause of death in intensive care units and carries a mortality of almost 25%. In this review, we summarize the diverse roles played by various subfamilies of GPCR in the pathogenesis of sepsis and identify potential targets for pharmacotherapy through these novel approaches.

Efficacy and safety of recombinant human soluble thrombomodulin in patients with sepsis-associated coagulopathy: A systematic review and meta-analysis

Valeriani, E. et al.

J Thromb Haemost, 18, 1618-1625, 2020

The efficacy and safety of recombinant human soluble thrombomodulin (rhsTM) have not been definitively proven. The effects may depend on the presence of sepsis-associated coagulopathy (SAC). The aim of this systematic review and meta-analysis was to evaluate the efficacy and safety of rhsTM in patients with SAC defined by high international normalized ratio and low platelet count. In patients with sepsis, SAC is associated with higher 28-day mortality. The administration of rhsTM reduced 28-day mortality in patients with SAC, but not in those without SAC.

<u>Development of a nomogram to predict 30-day mortality of patients with sepsis-associated encephalopathy: a retrospective cohort study</u>

Yang, Y. et al.

J Intensive Care, 8, 45, 2020

Sepsis-associated encephalopathy (SAE) is related to increased short-term mortality in patients with sepsis. We aim to establish a user-friendly nomogram for individual prediction of 30-day risk of mortality in patients with SAE. SAE is related to increased 30-day mortality of patients with sepsis. The nomogram presents excellent performance in predicting 30-day risk of mortality in SAE patients, which can be used to evaluate the prognosis of patients with SAE and may be more beneficial once specific treatments towards SAE are developed.

Efficacy and Safety of Recombinant Human Thrombopoietin on Sepsis Patients With Thrombocytopenia: A Systematic Review and Meta-Analysis

Zhang, J. et al.

Front Pharmacol, 11, 940, 2020

The efficacy and safety of the administration of recombinant human thrombopoietin (rhTPO) in sepsis patients with thrombocytopenia were still inconclusive. Objectives: To investigate whether rhTPO is a benefit for sepsis patients with thrombocytopenia. Current evidence shown that rhTPO could increase PCs on 7(th) day of treatment and reduce the transfusion volume of blood products in sepsis-related thrombocytopenia during hospitalization. The conclusions are needed to be verified indeed by more multicenter RCTs due to the limitation of the included studies.

The Role of Brain Natriuretic Peptide as a Prognostic Marker for Sepsis

Bhandari, B. and J. Cunningham

Cureus, 12, e8954, 2020

Brain natriuretic peptide (BNP) is a neurohormone released in response to volume expansion and increased pressure. It is commonly used to assist in the diagnosis and management of heart failure. BNP can also play an important role as a biomarker in septic shock; however, elevations of BNP in conditions other than sepsis or cardiac dysfunction limits its use as the sole prognostic marker in patients hospitalized with sepsis. Further relationships regarding laboratory value and correlation with severity of illness need to be established with larger prospective studies to develop consensus regarding a cut-off point for optimum sensitivity and specificity in predicting in-hospital mortality related to sepsis.

Assessment of Health Care Exposures and Outcomes in Adult Patients With Sepsis and Septic Shock

Fay, K. et al.

JAMA Netw Open, 3, e206004, 2020

Current information on the characteristics of patients who develop sepsis may help in identifying opportunities to improve outcomes. Most recent studies of sepsis epidemiology have focused on changes in incidence or have used administrative data sets that provided limited patient-level data. Objective: To describe sepsis epidemiology in adults. Most adults experienced sepsis onset outside of the hospital and had recent encounters with the health care system. A sepsis-associated pathogen was identified in more than half of patients. Future efforts to improve sepsis outcomes may benefit from examination of health maintenance practices and recent health care exposures as potential opportunities among high-risk patients.

<u>Prognostic role of red blood cell distribution width in patients with sepsis: a systematic review and meta-analysis</u> Zhang, L. et al.

BMC Immunol, 21, 40, 2020

Outcome prediction for patients with sepsis may be conductive to early aggressive interventions. Numerous biomarkers and multiple scoring systems have been utilized in predicting outcomes, however, these tools were either expensive or inconvenient. We performed a meta-analysis to evaluate the prognostic role of red blood cell distribution width (RDW) in patients with sepsis. For patients with sepsis, baseline RDW may be a useful predictor of mortality, patients with increased RDW are more likely to have higher mortality.

The use of fecal microbiota transplant in sepsis

Keskey, R. et al.

Transl Res, 2020, , 2020

Sepsis is defined as a dysregulated inflammatory response, which ultimately results from a perturbed interaction of both an altered immune system and the biomass and virulence of involved pathogens. This response has been tied to the intestinal microbiota, as the microbiota and its associated metabolites play an essential role in regulating the host

immune response to infection. In turn, critical illness as well as necessary health care treatments result in a collapse of the intestinal microbiota diversity and a subsequent loss of health-promoting short chain fatty acids, such as butyrate, leading to the development of a maladaptive pathobiome. These perturbations of the microbiota contribute to the dysregulated immune response and organ failure associated with sepsis. Several case series have reported the ability of fecal microbiota transplant (FMT) to restore the host immune response and aid in recovery of septic patients. Additionally, animal studies have revealed the mechanism of FMT rescue in sepsis is likely related to the ability of FMT to restore butyrate producing bacteria and alter the innate immune response aiding in pathogen clearance. However, several studies have reported lethal complications associated with FMT, including bacteremia. Therefore, FMT in the treatment of sepsis is and should remain investigational until a more detailed mechanism of how FMT restores the host immune response in sepsis is determined, allowing for the development of more fine-tuned microbiota therapies.

Heart Dysfunction in Sepsis

Poveda-Jaramillo, R.

J Cardiothorac Vasc Anesth, 2020, , 2020

Cardiac involvement during sepsis frequently occurs. A series of molecules induces a set of changes at the cellular level that result in the malfunction of the myocardium. The understanding of these molecular alterations has simultaneously promoted the implementation of diagnostic strategies that are much more precise and allowed the advance of the therapeutics. The heart is a vital organ for survival. Its well-being ensures the adequate supply of essential elements for organs and tissues.

Effects of Fusu mixture (Wen-Shen-Qian-Yang Method) on sepsis-induced acute respiratory distress syndrome Zhang, L. et al.

Medicine (Baltimore), 99, e21066, 2020

Sepsis is the most common etiology of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Capillary leakage caused by lung endothelial injury is the central cause of ARDS. The results of research in modern medicine in reducing endothelial damage and restoring endothelial functions are limited. In the previous clinical observations, we found that the Fusu mixture not only improves the clinical symptoms but also reduces the leakage of pulmonary capillaries. Therefore, the purpose of this study is to determine the clinical efficacy of the Fusu mixture combined with Western medicine in the treatment of ARDS caused by sepsis and to explore the mechanism of traditional Chinese medicine. The purpose of this study is to evaluate the clinical efficacy of Fusu mixture in the treatment of sepsis-induced ARDS and explore its possible mechanism of action. If successful, it will provide evidence-based adjuvant therapy for the clinical treatment of ARDS.

<u>Neuroendocrine Modulation of the Immune Response after Trauma and Sepsis: Does It Influence Outcome?</u> Kobbe, P. et al.

J Clin Med, 9, , 2020

Although the treatment of multiple-injured patients has been improved during the last decades, sepsis and multiple organ failure (MOF) still remain the major cause of death. Following trauma, profound alterations of a large number of physiological systems can be observed that may potentially contribute to the development of sepsis and MOF. This includes alterations of the neuroendocrine and the immune system. A large number of studies focused on posttraumatic changes of the immune system, but the cause of posttraumatic immune disturbance remains to be established. However, an increasing number of data indicate that the bidirectional interaction between the neuroendocrine and the immune system may be an important mechanism involved in the development of sepsis and MOF. The aim of this article is to highlight the current knowledge of the neuroendocrine modulation of the immune system during trauma and sepsis.

How well are sepsis and a sense of urgency documented throughout the acute care chain in the Netherlands? A prospective, observational study

Latten, G. et al.

BMJ Open, 10, e036276, 2020

We investigate the documentation of sepsis and a sense of urgency throughout the acute care chain. Our study shows that in prehospital and ED medical records, sepsis and a sense of urgency are documented in one out of five

patients. In only 1 out of 20 patients sepsis or a sense of urgency is documented by all involved professionals. It is possible that poor documentation causes harm, due to delayed diagnosis or treatment. Hence, it could be important to raise awareness among professionals regarding the importance of their documentation.

Iron Homeostasis and Ferritin in Sepsis-Associated Kidney Injury

McCullough, K. and S. Bolisetty

Nephron, 2020, 01-May, 2020

Sepsis associated acute kidney injury (SA-AKI) is a common clinical syndrome that occurs among hospitalized patients and significantly impacts mortality. Furthermore, survival after sepsis is intricately dependent on recovery of kidney function. In this review, we discuss the role of iron imbalance in mediating the pathogenic events during sepsis. Intracellular ferritin serves as a repository for iron and prevents iron-mediated injury and may limit the availability of iron to pathogens. Circulating levels of ferritin also increase during sepsis and often correlate with severity of sepsis. Herein, we examine preclinical and clinical data and discuss recent findings that suggest immunomodulatory roles for ferritin. We also discuss the possible mechanistic roles for ferritin in mitigating the pathogenic sequelae of sepsis and highlight current gaps in knowledge.

Rates, predictors, and mortality of sepsis-associated acute kidney injury: a systematic review and meta-analysis Liu, J. et al.

BMC Nephrol, 21, 318, 2020

Due to the high incidence and mortality of sepsis-associated acute kidney injury, a significant number of studies have explored the causes of sepsis-associated acute kidney injury (AKI). However, the opinions on relevant predictive risk factors remain inconclusive. This study aimed to provide a systematic review and meta-analysis to determine the predisposing factors for sepsis-associated AKI. Risk factors of S-AKI arise from a wide range of sources, making it difficult to predict and prevent this condition. Comorbidities, and certain drugs, are the main risk factors for S-AKI. Our review can provide guidance on the application of interventions to reduce the risks associated with sepsis-associated acute kidney injury and can also be used to tailor patient-specific treatment plans and management strategies in clinical practice.

Neonatal, Child and maternal sepsis

<u>Transcranial Doppler Can Predict Development and Outcome of Sepsis-Associated Encephalopathy in Pediatrics With Severe Sepsis or Septic Shock</u>

Algebaly, HA. et al.

Frontiers in Pediatrics, 8, 450, 2020

Sepsis is a common cause of pediatric intensive care unit (ICU) admission. Sepsis-associated encephalopathy (SAE) may occur owing to brain dysfunction in those patients and may be related to impaired cerebral microcirculation. Transcranial Doppler (TCD) can be used to detect this impairment. In this study, we aimed to assess the role of TCD in prediction of SAE and mortality in patients with severe sepsis or septic shock admitted to PICU. In children with SAE, cerebrovascular resistance is high and is associated with increased mortality.

Enteral Lactoferrin Supplementation for Preventing Sepsis and Necrotizing Enterocolitis in Preterm Infants: A MetaAnalysis With Trial Sequential Analysis of Randomized Controlled Trials

Gao, Y. et al.

Front Pharmacol, 11, 1186, 2020

Several clinical trials investigated the effects of enteral lactoferrin supplementation on the prevention of sepsis and necrotizing enterocolitis (NEC) in preterm infants, but the efficacy and safety remain disputed. Therefore, we systematically evaluated the effect of enteral lactoferrin supplementation in preterm infants through a metaanalysis with trial sequential analysis (TSA). Limited evidence suggested that enteral lactoferrin supplementation was associated with a reduction of late-onset sepsis in infants with a birth weight below 1500g, however, did not decrease the incidence of NEC stage II or III, all-cause mortality, and other adverse events in preterm infants. The present evidence was insufficient to inform clinical practice.

<u>Screening-based and Risk-based Strategy for the Prevention of Early-onset Group B Streptococcus/Non-group B Streptococcus Sepsis in the Neonate: A Systematic Review and Meta-analysis</u>

Li, Q. Y. et al.

Pediatr Infect Dis J, 39, 740-748, 2020

Screening-based and risk-based strategies are the 2 strategies for preventing group B streptococcus (GBS) diseases in neonates. We aimed to compare the effects of these 2 strategies in reducing the incidence of early-onset GBS sepsis (GBS-EOS) and their effects on the incidence of non-GBS sepsis. Compared with risk-based strategy, screening-based prophylaxis was associated with a reduced risk of GBS-EOS.

<u>Extracorporeal Membrane Oxygenation for Group B Streptococcal Sepsis in Neonates: A Retrospective Study of the Extracorporeal Life Support Organization Registry</u>

Schlapbach, L. J. et al.

Pediatr Crit Care Med, 21, e505-e512, 2020

Neonatal group B streptococcal sepsis remains a leading cause of neonatal sepsis globally and is characterized by unique epidemiologic features. Extracorporeal membrane oxygenation has been recommended for neonatal septic shock refractory to conventional management, but data on extracorporeal membrane oxygenation in group B streptococcal sepsis are scarce. We aimed to assess outcomes of extracorporeal membrane oxygenation in neonates with group B streptococcal sepsis. This large registry-based study indicates that treatment with extracorporeal membrane oxygenation for neonatal group B streptococcal sepsis is associated with survival in the majority of patients. Future quality improvement interventions should aim to reduce the burden of major extracorporeal membrane oxygenation-associated complications which affected four out of five neonatal group B streptococcal sepsis extracorporeal membrane oxygenation patients.

Association between vitamin D level and community-acquired late-onset neonatal sepsis

Siyah Bilgin, B. and D. Gonulal

Arch Argent Pediatr, 118, 265-272, 2020

The objective was to determine the relationship between mother and infant vitamin D levels and late onset sepsis. In this study, 25-hydroxyvitamin D levels were found to be lower in term infants with late-onset sepsis and among their mothers compared to the control group. Positive correlation was found between serum 25(OH)D levels of infants and their mothers.

Shock Severity Modifies Associations Between RBC Transfusion in the First 48 Hours of Sepsis Onset and the Duration of Organ Dysfunction in Critically III Septic Children

Srouji, L. S. et al.

Pediatr Crit Care Med, 21, e475-e484, 2020

We test the hypothesis that early RBC transfusion is associated with duration of organ dysfunction in critically ill septic children. In agreement with previous studies, early RBC transfusion was independently associated with longer duration of organ dysfunction. Ours is among the first studies to document different transfusion-associated risks based on clinically available measures of shock severity, demonstrating greater transfusion-associated risks in children with less severe shock. Larger multicenter studies to verify these interaction effects are essential to plan much-needed RBC transfusion trials for critically ill septic children.

Effects of oropharyngeal administration of colostrum on the incidence of necrotizing enterocolitis, late-onset sepsis, and death in preterm infants: a meta-analysis of RCTs

Tao, J. et al.

Eur J Clin Nutr, 74, 1122-1131, 2020

Necrotizing enterocolitis (NEC) and late-onset sepsis (LOS) are two major contributors to death among preterm infants. Oropharyngeal administration of colostrum (OAC) has been proved as an easy, safe, and economically viable technique to help preterm neonates to build up their immunity. In this review, we assessed the effects of OAC on preterm infants. The results show that OAC does not reduce the incidences of NEC, LOS, and death in preterm infants, but there is a trend toward a positive effect. It is therefore recommended as routine care for preterm infants in the NICU.

<u>C-reactive protein as a predictor of meningitis in early onset neonatal sepsis: a single unit experience</u> Durrani, N. U. R. et al.

J Perinat Med, 2020, , 2020

We determine whether there is a cut off value of serum C-reactive protein (CRP) associated with a higher risk of meningitis in suspected early onset sepsis (EOS) (onset birth to seven days of life). Serum CRP values have poor discriminatory power to distinguish between subjects with and without meningitis, in symptomatic EOS.

Diagnostic value of mean platelet volume for neonatal sepsis: A systematic review and meta-analysis

Wang, J. et al.

Medicine (Baltimore), 99, e21649, 2020

An increasing number of studies in recent years have identified mean platelet volume (MPV) as a predictive marker for neonatal sepsis. However, most of these studies focused on single regions, and therefore, the findings remain inconclusive. We, in this study, aimed to evaluate the potential of MPV as a biological indicator of neonatal sepsis through a systematic review and meta-analysis.: MPV was significantly higher in the neonatal sepsis group compared to the control group. Therefore, in clinical practice, MPV could be used as an indicator for the early diagnosis of neonatal sepsis.

Admission platelet count and indices as predictors of outcome in children with severe Sepsis: a prospective hospital-based study

Sayed, S. Z. et al.

BMC Pediatr, 20, 387, 2020

Sepsis is still one of the main causes of infants and children mortality especially in developing, economically challenged countries with limited resources. Our objective in this study was to determine, the prognostic value of platelet count, mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT) in critically ill infants and children with severe sepsis, as they are readily available biomarkers, that can guide clinicians during managing of severe sepsis. Thrombocytopenia, platelet indices and their ratios, especially plateletcrit and MPV/PCT, are readily available, sensitive, prognostic markers, that can identify the severe sepsis patients with poorest outcome.

Clinical prediction models to diagnose neonatal sepsis: a scoping review protocol

Neal, S. R. et al.

BMJ Open, 10, e039712, 2020

Neonatal sepsis is responsible for significant morbidity and mortality worldwide. Diagnosis is often difficult due to non-specific clinical features and the unavailability of laboratory tests in many low-income and middle-income countries (LMICs). Clinical prediction models have the potential to improve diagnostic accuracy and rationalise antibiotic usage in neonatal units, which may result in reduced antimicrobial resistance and improved neonatal outcomes. In this paper, we outline our scoping review protocol to map the literature concerning clinical prediction models to diagnose neonatal sepsis. We aim to provide an overview of existing models and evidence underlying their use and compare prediction models between high-income countries and LMICs. The nature of the scoping review methodology means that this study does not require ethical approval. Results will be disseminated through peer-reviewed publications and conference presentations, as well as through engagement with peers and relevant stakeholders.

Association of Acute Kidney Injury With Subsequent Sepsis in Critically Ill Children

Formeck, C. L. et al.

Pediatr Crit Care Med, 2020, , 2020

Acute kidney injury is a major cause of morbidity and mortality in critically ill children. A growing body of evidence has shown that acute kidney injury affects immune function, yet little is known about the association between acute kidney injury and subsequent infection in pediatric patients. Our objective was to examine the association of non-septic acute kidney injury with the development of subsequent sepsis in critically ill children. DESIGN: A single-center retrospective cohort study.: Acute kidney injury is associated with an increased risk for subsequent infection in critically ill children. These results further support the concept of acute kidney injury as a clinically relevant immunocompromised state.

Pediatric Outcomes After Regulatory Mandates for Sepsis Care

Gigli, K. H. et al.

Pediatrics, 146, , 2020

In 2013, New York introduced regulations mandating that hospitals develop pediatric-specific protocols for sepsis recognition and treatment. Implementation of statewide sepsis regulations was generally associated with improved mortality trends in New York State, particularly in prespecified subpopulations of patients, suggesting that the regulations were successful in affecting sepsis outcomes.

<u>The Co-development and Feasibility-Testing of an Innovative Digital Animation Intervention (DAISI) to Reduce the Risk of Maternal Sepsis in the Postnatal Period</u>

Haith-Cooper, M. et al.

Matern Child Health J, 24, 837-844, 2020

Sepsis is one of the most common causes of mortality in postnatal women globally and many other women who develop sepsis are left with severe morbidity. Women's knowledge of postnatal sepsis and how it can be prevented by simple changes to behaviour is lacking. DAISI appears to be an innovative solution for use in maternity care to address difficulties with the postnatal hospital discharge process. We could find no evidence of digital animation being used in this context and recommend a study to test it in practice prior to adopting its use more widely. If effective, the DAISI principle could be used in other maternity contexts and other areas of the NHS to communicate health promotion information.

Neonatal early onset sepsis in Middle Eastern countries: a systematic review

Khalil, N. et al.

Arch Dis Child, 105, 639-647, 2020

Early onset neonatal sepsis (EOS) accounts for a significant portion of neonatal mortality, which accounts for 46% of global under five child mortality. This systematic review studies the bacterial aetiology of EOS in the Middle East, susceptibility patterns to recommended empirical antibiotic therapy and whether this differs between high-income and middle-income countries in the region. EOS in middle-income countries was more likely to be due to Gramnegative pathogens and less likely to be susceptible to empirical antibiotic therapy. This has important public health implications regarding neonatal mortality in the Middle East region.

<u>Implementation of a clinical guideline to decrease laboratory tests in newborns evaluated for early onset sepsis</u> Le, C. N. et al.

J Neonatal Perinatal Med, 12, 443-448, 2020

Creation of a clinical guideline to reduce the number of complete blood counts (CBCs) obtained on healthy term infants for early onset sepsis (EOS) evaluation secondary to maternal chorioamnionitis. The clinical guideline demonstrated a significant reduction in the number of CBCs obtained in well-appearing infants admitted to the NICU secondary to maternal chorioamnionitis.

Challenges in developing a consensus definition of neonatal sepsis

McGovern, M. et al.

Pediatr Res, 88, 14-26, 2020

There is currently no consensus definition of neonatal sepsis and the definitions that are currently in use are varied. A consensus definition of neonatal sepsis would benefit clinicians, patients and researchers. Recent progress in adults with publication of Sepsis-3 provides guidance on how a consensus definition and screening criteria for sepsis could be produced in neonatology. 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.

<u>Early-Onset Neonatal Sepsis 2015 to 2017, the Rise of Escherichia coli, and the Need for Novel Prevention Strategies</u> Stoll, B. J. et al.

JAMA Pediatr, 174, e200593, 2020

Early-onset sepsis (EOS) remains a potentially fatal newborn condition. Ongoing surveillance is critical to optimize prevention and treatment strategies. Objective: To describe the current incidence, microbiology, morbidity, and

mortality of EOS among a cohort of term and preterm infants. In this study, EOS incidence and associated mortality disproportionately occurred in preterm infants. Contemporary cases have demonstrated the limitations of current GBS prevention strategies. The increase in E coli infections among very low-birth-weight infants warrants continued study. Ampicillin and gentamicin remained effective antibiotics in most cases, but ongoing surveillance should monitor antibiotic susceptibilities of EOS pathogens.

<u>Human milk oligosaccharides and their association with late-onset neonatal sepsis in Peruvian very-low-birth-weight infants</u>

Torres Roldan, V. D. et al.

Am J Clin Nutr, 112, 106-112, 2020

Oligosaccharides are the third most abundant component in human milk. They are a potential protective agent against neonatal sepsis. OBJECTIVES: We aimed to explore the association between human milk oligosaccharides (HMOs) and late-onset sepsis in very-low-birth-weight infants, and to describe the composition and characteristics of HMOs in Peruvian mothers of these infants. These findings suggest that concentrations of different HMOs vary from one individual to another according to their lactation period and secretor status. We also found that FDSLNH might protect infants with very low birth weight from late-onset neonatal sepsis. Confirming this association could prove 1 more mechanism by which human milk protects infants against infections and open the door to clinical applications of HMOs. This trial was registered at clinicaltrials.gov as NCT01525316.

<u>Perspective of the Surviving Sepsis Campaign on the Management of Pediatric Sepsis in the Era of Coronavirus</u>
Disease 2019

Weiss, S. L. et al.

Pediatr Crit Care Med, 2020, , 2020

Severe acute respiratory syndrome coronavirus 2 is a novel cause of organ dysfunction in children, presenting as either coronavirus disease 2019 with sepsis and/or respiratory failure or a hyperinflammatory shock syndrome. Clinicians must now consider these diagnoses when evaluating children for septic shock and sepsis-associated organ dysfunction. The Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children provide an appropriate framework for the early recognition and initial resuscitation of children with sepsis or septic shock caused by all pathogens, including severe acute respiratory syndrome coronavirus 2. However, the potential benefits of select adjunctive therapies may differ from non-coronavirus disease 2019 sepsis.

Contemporary trends in global mortality of sepsis among young infants less than 90 days old: protocol for a systematic review and meta-analysis

Pek, J. H. et al.

BMJ Open, 10, e038815, 2020

Neonatal sepsis has a high mortality rate that varies across different populations. We aim to perform a contemporary global evidence synthesis to determine the case fatality rates of neonatal sepsis, in order to better delineate this public health urgency and inform strategies to reduce fatality in this high-risk population. Results will be synthesised qualitatively and pooled for meta-analysis. ETHICS AND DISSEMINATION: No formal ethical approval is required as there is no collection of primary data. This systematic review and meta-analysis will be disseminated through conference meetings and peer-reviewed publications. PROSPERO REGISTRATION NUMBER: CRD42020164321.

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