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Sepsis Bulletin

January – February 2024

Sepsis

[Neonatal, paediatric and maternal sepsis]

[PAMPs and DAMPs in Sepsis: A Review of Their Molecular Features and Potential Clinical Implications]
Cicchinelli, S., et al.
Int J Mol Sci. (2024) Vol.25 (2)
Sepsis is a serious organ dysfunction caused by a dysregulated immune host reaction to a pathogen. The innate immunity is programmed to react immediately to conserved molecules, released by the pathogens (PAMPs), and the host (DAMPs). We aimed to review the molecular mechanisms of the early phases of sepsis, focusing on PAMPs, DAMPs, and their related pathways, to identify potential biomarkers. We included studies published in English and searched on PubMed(®) and Cochrane(®). After a detailed discussion on the actual knowledge of PAMPs/DAMPs, we analyzed their role in the different organs affected by sepsis, trying to elucidate the molecular basis of some of the most-used prognostic scores for sepsis. Furthermore, we described a chronological trend for the release of PAMPs/DAMPs that may be useful to identify different subsets of septic patients, who may benefit from targeted therapies. These findings are preliminary since these pathways seem to be strongly influenced by the peculiar characteristics of different pathogens and host features. Due to these reasons, while initial findings are promising, additional studies are necessary to clarify the potential involvement of these molecular patterns in the natural evolution of sepsis and to facilitate their transition into the clinical setting.

[The Impact of Pathogens on Sepsis Prevalence and Outcome]
Dyck, B., et al.
Pathogens. (2024) Vol.13 (1)
Sepsis, a severe global healthcare challenge, is characterized by significant morbidity and mortality.

The 2016 redefinition by the Third International Consensus Definitions Task Force emphasizes its complexity as a “life-threatening organ dysfunction caused by a dysregulated host response to infection”. Bacterial pathogens, historically dominant, exhibit geographic variations, influencing healthcare strategies. The intricate dynamics of bacterial immunity involve recognizing pathogen-associated molecular patterns, triggering innate immune responses and inflammatory cascades. Dysregulation leads to immunothrombosis, disseminated intravascular coagulation, and mitochondrial dysfunction, contributing to the septic state. Viral sepsis, historically less prevalent, saw a paradigm shift during the COVID-19 pandemic, underscoring the need to understand the immunological response. Retinoic acid-inducible gene I-like receptors and Toll-like receptors play pivotal roles, and the cytokine storm in COVID-19 differs from bacterial sepsis. Latent viruses like human cytomegalovirus impact sepsis by reactivating during the immunosuppressive phases. Challenges in sepsis management include rapid pathogen identification, antibiotic resistance monitoring, and balancing therapy beyond antibiotics. This review highlights the evolving sepsis landscape, emphasizing the need for pathogen-specific therapeutic developments in a dynamic and heterogeneous clinical setting.

Hospital-Onset Sepsis Warrants Expanded Investigation and Consideration as a Unique Clinical Entity

Ginestra, J.C., et al.

Chest. (2024)

Sepsis causes more than a quarter million deaths among hospitalized adults in the United States each year. Although most cases of sepsis are present on admission, up to one quarter of patients with sepsis develop this highly morbid and mortal condition while hospitalized. Compared with patients with community-onset sepsis (COS), patients with hospital-onset sepsis (HOS) are twice as likely to require mechanical ventilation and ICU admission, have more than two times longer ICU and hospital length of stay, accrue five times higher hospital costs, and are twice as likely to die. Patients with HOS differ from those with COS with respect to underlying comorbidities, admitting diagnosis, clinical manifestations of infection, and severity of illness. Despite the differences between these patient populations, patients with HOS sepsis are understudied and warrant expanded investigation. Here, we outline important knowledge gaps in the recognition and management of HOS in adults and propose associated research priorities for investigators. Of particular importance are questions regarding standardization and reporting of research methods, understanding of clinical heterogeneity among patients with HOS, development of tailored management recommendations, optimization of care delivery and quality metrics, identification and correction of disparities in care and outcomes, and how to ensure goal-concordant care for patients with HOS.

Multidrug-Resistant Sepsis: A Critical Healthcare Challenge

Kumar, N.R., et al.

Antibiotics (Basel). (2024) Vol.13 (1)

Sepsis globally accounts for an alarming annual toll of 48.9 million cases, resulting in 11 million deaths, and inflicts an economic burden of approximately USD 38 billion on the United States healthcare system. The rise of multidrug-resistant organisms (MDROs) has elevated the urgency surrounding the management of multidrug-resistant (MDR) sepsis, evolving into a critical global health concern. This review aims to provide a comprehensive overview of the current epidemiology of (MDR) sepsis and its associated healthcare challenges, particularly in critically ill hospitalized

patients. Highlighted findings demonstrated the complex nature of (MDR) sepsis pathophysiology and the resulting immune responses, which significantly hinder sepsis treatment. Studies also revealed that aging, antibiotic overuse or abuse, inadequate empiric antibiotic therapy, and underlying comorbidities contribute significantly to recurrent sepsis, thereby leading to septic shock, multi-organ failure, and ultimately immune paralysis, which all contribute to high mortality rates among sepsis patients. Moreover, studies confirmed a correlation between elevated readmission rates and an increased risk of cognitive and organ dysfunction among sepsis patients, amplifying hospital-associated costs. To mitigate the impact of sepsis burden, researchers have directed their efforts towards innovative diagnostic methods like point-of-care testing (POCT) devices for rapid, accurate, and particularly bedside detection of sepsis; however, these methods are currently limited to detecting only a few resistance biomarkers, thus warranting further exploration. Numerous interventions have also been introduced to treat MDR sepsis, including combination therapy with antibiotics from two different classes and precision therapy, which involves personalized treatment strategies tailored to individual needs. Finally, addressing MDR-associated healthcare challenges at regional levels based on local pathogen resistance patterns emerges as a critical strategy for effective sepsis treatment and minimizing adverse effects.

Immunosuppression in Sepsis: Biomarkers and Specialized Pro-Resolving Mediators

Padovani, C.M. and K. Yin

Biomedicines. (2024) Vol.12 (1)

Severe infection can lead to sepsis. In sepsis, the host mounts an inappropriately large inflammatory response in an attempt to clear the invading pathogen. This sustained high level of inflammation may cause tissue injury and organ failure. Later in sepsis, a paradoxical immunosuppression occurs, where the host is unable to clear the pre-existing infection and is susceptible to secondary infections. A major issue with sepsis treatment is that it is difficult for physicians to ascertain which stage of sepsis the patient is in. Sepsis treatment will depend on the patient's immune status across the spectrum of the disease, and these immune statuses are nearly polar opposites in the early and late stages of sepsis. Furthermore, there is no approved treatment that can resolve inflammation without contributing to immunosuppression within the host. Here, we review the major mechanisms of sepsis-induced immunosuppression and the biomarkers of the immunosuppressive phase of sepsis. We focused on reviewing three main mechanisms of immunosuppression in sepsis. These are lymphocyte apoptosis, monocyte/macrophage exhaustion, and increased migration of myeloid-derived suppressor cells (MDSCs). The biomarkers of septic immunosuppression that we discuss include increased MDSC production/migration and IL-10 levels, decreased lymphocyte counts and HLA-DR expression, and increased GPR18 expression. We also review the literature on the use of specialized pro-resolving mediators (SPMs) in different models of infection and/or sepsis, as these compounds have been reported to resolve inflammation without being immunosuppressive. To obtain the necessary information, we searched the PubMed database using the keywords sepsis, lymphocyte apoptosis, macrophage exhaustion, MDSCs, biomarkers, and SPMs.

Sepsis in elderly patients: the role of neutrophils in pathophysiology and therapy

Ramoni, D., et al.

Intern Emerg Med. (2024)

Sepsis is among the most important causes of mortality, particularly within the elderly population. Sepsis prevalence is on the rise due to different factors, including increasing average population

age and the concomitant rise in the prevalence of frailty and chronic morbidities. Recent investigations have unveiled a “trimodal” trajectory for sepsis-related mortality, with the ultimate zenith occurring from 60 to 90 days until several years after the original insult. This prolonged temporal course ostensibly emanates from the sustained perturbation of immune responses, persevering beyond the phase of clinical convalescence. This phenomenon is particularly associated with the aging immune system, characterized by a broad dysregulation commonly known as “inflammaging.” Inflammaging associates with a chronic low-grade activation of the innate immune system preventing an appropriate response to infective agents. Notably, during the initial phases of sepsis, neutrophils-essential in combating pathogens-may exhibit compromised activity. Paradoxically, an overly zealous neutrophilic reaction has been observed to underlie multi-organ dysfunction during the later stages of sepsis. Given this scenario, discovering treatments that can enhance neutrophil activity during the early phases of sepsis while curbing their overactivity in the later phases could prove beneficial in fighting pathogens and reducing the detrimental effects caused by an overactive immune system. This narrative review delves into the potential key role of neutrophils in the pathological process of sepsis, focusing on how the aging process impacts their functions, and highlighting possible targets for developing immune-modulatory therapies. Additionally, the review includes tables that outline the principal potential targets for immunomodulating agents.

The role of platelets in sepsis: A review

Xu, X., et al.

Biomol Biomed. (2024)

Sepsis, a life-threatening condition characterized by organ dysfunction, results from a complex series of pathophysiological mechanisms including immune dysfunction, an uncontrolled inflammatory response, and coagulation abnormalities. It is a major contributor to global mortality and severe disease development. Platelets, abundant in the circulatory system, are sensitive to changes in the body’s internal environment and are among the first cells to respond to dysregulated pro-inflammatory and pro-coagulant reactions at the onset of sepsis. In the initial stages of sepsis, the coagulation cascade, inflammatory response, and endothelial tissue damage perpetually trigger platelet activation. These activated platelets then engage in complex inflammatory and immune reactions, potentially leading to organ dysfunction. Therefore, further research is essential to fully understand the role of platelets in sepsis pathology and to develop effective therapeutic strategies targeting the associated pathogenic pathways. This review delves into the involvement of platelets in sepsis and briefly outlines the clinical applications of associated biomarkers.

The Changes in the Quantity of Lymphocyte Subpopulations during the Process of Sepsis

Yang, J., et al.

Int J Mol Sci. (2024) Vol.25 (3)

Sepsis remains a global challenge, especially in low- and middle-income countries, where there is an urgent need for easily accessible and cost-effective biomarkers to predict the occurrence and prognosis of sepsis. Lymphocyte counts are easy to measure clinically, and a large body of animal and clinical research has shown that lymphocyte counts are closely related to the incidence and prognosis of sepsis. This review extensively collected experimental articles related to lymphocyte counts since the unification of the definition of sepsis. The article categorizes and discusses the relationship between absolute lymphocyte counts, intrinsic lymphocyte subsets, effector T-

lymphocytes, B-lymphocytes, dendritic cells, and the incidence and prognosis of sepsis. The results indicate that comparisons of absolute lymphocyte counts alone are meaningless. However, in addition to absolute lymphocyte counts, innate lymphocyte subsets, effector T-cells, B-lymphocytes, and dendritic cells have shown certain research value in related studies.

The critically ill older patient with sepsis: a narrative review

Ibarz, M., et al.

Ann Intensive Care. (2024) Vol.14 (1); 6.

Sepsis is a significant public health concern, particularly affecting individuals above 70 years in developed countries. This is a crucial fact due to the increasing aging population, their heightened vulnerability to sepsis, and the associated high mortality rates. However, the morbidity and long-term outcomes are even more notable. While many patients respond well to timely and appropriate interventions, it is imperative to enhance efforts in identifying, documenting, preventing, and treating sepsis. Managing sepsis in older patients poses greater challenges and necessitates a comprehensive understanding of predisposing factors and a heightened suspicion for diagnosing infections and assessing the risk of sudden deterioration into sepsis. Despite age often being considered an independent risk factor for mortality and morbidity, recent research emphasizes the pivotal roles of frailty, disease severity, and comorbid conditions in influencing health outcomes. In addition, it is important to inquire about the patient's preferences and establish a personalized treatment plan that considers their potential for recovery with quality of life and functional outcomes. This review provides a summary of the most crucial aspects to consider when dealing with an old critically ill patient with sepsis.

The pathophysiology of sepsis and precision-medicine-based immunotherapy

Giamarellos-Bourboulis, E.J., et al.

Nat Immunol. (2024) Vol.25 (1); 19-28.

Sepsis remains a major cause of morbidity and mortality in both low- and high-income countries. Antibiotic therapy and supportive care have significantly improved survival following sepsis in the twentieth century, but further progress has been challenging. Immunotherapy trials for sepsis, mainly aimed at suppressing the immune response, from the 1990s and 2000s, have largely failed, in part owing to unresolved patient heterogeneity in the underlying immune disbalance. The past decade has brought the promise to break this blockade through technological developments based on omics-based technologies and systems medicine that can provide a much larger data space to describe in greater detail the immune endotypes in sepsis. Patient stratification opens new avenues towards precision medicine approaches that aim to apply immunotherapies to sepsis, on the basis of precise biomarkers and molecular mechanisms defining specific immune endotypes. This approach has the potential to lead to the establishment of immunotherapy as a successful pillar in the treatment of sepsis for future generations.

Molecular antimicrobial susceptibility testing in sepsis

Martin-Loeches, I., et al.

Future Microbiol. (2024) Vol.19; 61-72.

Rapidly detecting and identifying pathogens is crucial for appropriate antimicrobial therapy in patients with sepsis. Conventional diagnostic methods have been a great asset to medicine, though

they are time consuming and labor intensive. This work will enable healthcare professionals to understand the bacterial community better and enhance their diagnostic capacity by using novel molecular methods that make obtaining quicker, more precise results possible. The authors discuss and critically assess the merits and drawbacks of molecular testing and the added value of these tests, including the shift turnaround time, the implication for clinicians' decisions, gaps in knowledge, future research directions and novel insights or innovations. The field of antimicrobial molecular testing has seen several novel insights and innovations to improve the diagnosis and management of infectious diseases. Sepsis is a life-threatening reaction to an infection. This infection is normally caused by [a] bacteria. Identifying the bacteria that has caused the infection is very important to choosing the best treatment. This is usually done using molecular testing. This article discusses the advantages and disadvantages of molecular testing, which tests are available and the value of these tests in clinical practice, the implication of molecular tests for clinicians' decisions and the gaps in our knowledge. It also discusses future innovations in molecular testing.

Destabilisation of T cell-dependent humoral immunity in sepsis

Davies, K. and J.E. McLaren

Clin Sci (Lond). (2024) Vol.138 (1); 65-85.

Sepsis is a heterogeneous condition defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For some, sepsis presents as a predominantly suppressive disorder, whilst others experience a pro-inflammatory condition which can culminate in a 'cytokine storm'. Frequently, patients experience signs of concurrent hyper-inflammation and immunosuppression, underpinning the difficulty in directing effective treatment. Although intensive care unit mortality rates have improved in recent years, one-third of discharged patients die within the following year. Half of post-sepsis deaths are due to exacerbation of pre-existing conditions, whilst half are due to complications arising from a deteriorated immune system. It has been suggested that the intense and dysregulated response to infection may induce irreversible metabolic reprogramming in immune cells. As a critical arm of immune protection in vertebrates, alterations to the adaptive immune system can have devastating repercussions. Indeed, a marked depletion of lymphocytes is observed in sepsis, correlating with increased rates of mortality. Such sepsis-induced lymphopenia has profound consequences on how T cells respond to infection but equally on the humoral immune response that is both elicited by B cells and supported by distinct CD4+ T follicular helper (TFH) cell subsets. The immunosuppressive state is further exacerbated by functional impairments to the remaining lymphocyte population, including the presence of cells expressing dysfunctional or exhausted phenotypes. This review will specifically focus on how sepsis destabilises the adaptive immune system, with a closer examination on how B cells and CD4+ TFH cells are affected by sepsis and the corresponding impact on humoral immunity.

Biomarker Enrichment in Sepsis-Associated Acute Kidney Injury: Finding High-Risk Patients in the Intensive Care Unit

Baeseman, L., et al.

Am J Nephrol. (2024) Vol.55 (1); 72-85.

BACKGROUND: Sepsis-associated acute kidney injury (AKI) is a leading comorbidity in admissions to the intensive care unit. While a gold standard definition exists, it remains imperfect and does not allow for the timely identification of patients in the setting of critical illness. This review will discuss the use of biochemical and electronic biomarkers to allow for prognostic and predictive enrichment of patients with sepsis-associated AKI over and above the use of serum creatinine and urine output.

SUMMARY: Current data suggest that several biomarkers are capable of identifying patients with sepsis at risk for the development of severe AKI and other associated morbidity. This review discusses these data and these biomarkers in the setting of sub-phenotyping and endotyping sepsis-associated AKI. While not all these tests are widely available and some require further validation, in the near future we anticipate several new tools to help nephrologists and other providers better care for patients with sepsis-associated AKI. KEY MESSAGES: Predictive and prognostic enrichment using both traditional biomarkers and novel biomarkers in the setting of sepsis can identify subsets of patients with either similar outcomes or similar pathophysiology, respectively. Novel biomarkers can identify kidney injury in patients without consensus definition AKI (e.g., changes in creatinine or urine output) and can predict other adverse outcomes (e.g., severe consensus definition AKI, inpatient mortality). Finally, emerging artificial intelligence and machine learning-derived risk models are able to predict sepsis-associated AKI in critically ill patients using advanced learning techniques and several laboratory and vital sign measurements.

Therapeutic Strategies Targeting Mitochondrial Dysfunction in Sepsis-induced Cardiomyopathy

Salami, O.M., et al.

Cardiovasc Drugs Ther. (2024) Vol.38 (1); 163-180.

Sepsis is an increasingly worldwide problem; it is currently regarded as a complex life-threatening dysfunction of one or more organs as a result of dysregulated host immune response to infections. The heart is one of the most affected organs, as roughly 10% to 70% of sepsis cases are estimated to turn into sepsis-induced cardiomyopathy (SIC). SIC can be defined as a reversible myocardial dysfunction characterized by dilated ventricles, impaired contractility, and decreased ejection fraction. Mitochondria play a critical role in the normal functioning of cardiac tissues as the heart is highly dependent on its production of adenosine triphosphate (ATP), its damage during SIC includes morphology impairment, mitophagy, biogenesis disequilibrium, electron transport chain disturbance, molecular damage from the actions of pro-inflammatory cytokines and many other different impairments that are major contributing factors to the severity of SIC. Although mitochondria-targeted therapies usage is still inadequate in clinical settings, the preclinical study outcomes promise that the implementation of these therapies may effectively treat SIC. This review summarizes the different therapeutic strategies targeting mitochondria structure, quality, and quantity abnormalities for the treatment of SIC.

The Apelin/APJ System: A Potential Therapeutic Target for Sepsis

Song, Q., et al.

J Inflamm Res. (2024) Vol.17; 313-330.

Apelin is the native ligand for the G protein-coupled receptor APJ. Numerous studies have demonstrated that the Apelin/APJ system has positive inotropic, anti-inflammatory, and anti-apoptotic effects and regulates fluid homeostasis. The Apelin/APJ system has been demonstrated to play a protective role in sepsis and may serve as a promising therapeutic target for the treatment of sepsis. Better understanding of the mechanisms of the effects of the Apelin/APJ system will aid in the development of novel drugs for the treatment of sepsis. In this review, we provide a brief overview of the physiological role of the Apelin/APJ system and its role in sepsis.

Platelet P2Y(12) signalling pathway in the dysregulated immune response during sepsis

Amoafo, E.B., et al.

Br J Pharmacol. (2024) Vol.181 (4); 532-546.

Sepsis is a complicated pathological condition in response to severe infection. It is characterized by a strong systemic inflammatory response, where multiple components of the immune system are involved. Currently, there is no treatment for sepsis. Blood platelets are known for their role in haemostasis, but they also participate in inflammation through cell-cell interaction and the secretion of inflammatory mediators. Interestingly, an increase in platelet activation, secretion, and aggregation with other immune cells (such as monocytes, T-lymphocytes and neutrophils) has been detected in septic patients. Therefore, antiplatelet therapy in terms of P2Y(12) antagonists has been evaluated as a possible treatment for sepis. It was found that blocking P2Y(12) receptors decreased platelet marker expression and limited attachment to immune cells in some studies, but not in others. This review addresses the role of platelets in sepsis and discusses whether antagonizing P2Y(12) signalling pathways can alter the disease outcome. Challenges in studying P2Y(12) antagonists in sepsis also are discussed. LINKED ARTICLES: This article is part of a themed issue on Platelet purinergic receptor and non-thrombotic disease. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v181.4/issuetoc.

Machine learning algorithms in sepsis

Agnello, L., et al.

Clin Chim Acta. (2024) Vol.553; 117738.

Sepsis remains a significant global health challenge due to its high mortality and morbidity, compounded by the difficulty of early detection given its variable clinical manifestations. The integration of machine learning (ML) into laboratory medicine for timely sepsis identification and outcome forecasting is an emerging field of interest. This comprehensive review assesses the current body of research on ML applications for sepsis within the realm of laboratory diagnostics, detailing both their strengths and shortcomings. An extensive literature search was performed by two independent investigators across PubMed and Scopus databases, employing the keywords “Sepsis,” “Machine Learning,” and “Laboratory” without publication date limitations, culminating in January 2023. Each selected study was meticulously evaluated for various aspects, including its design, intent (diagnostic or prognostic), clinical environment, demographics, sepsis criteria, data gathering period, and the scope and nature of features, in addition to the ML methodologies and their validation procedures. Out of 135 articles reviewed, 39 fulfilled the criteria for inclusion. Among these, the majority (30 studies) were focused on devising ML algorithms for diagnosis, fewer (8 studies) on prognosis, and one study addressed both aspects. The dissemination of these studies across an array of journals reflects the interdisciplinary engagement in the development of ML algorithms for sepsis. This analysis highlights the promising role of ML in the early diagnosis of sepsis while drawing attention to the need for uniformity in validating models and defining features, crucial steps for ensuring the reliability and practicality of ML in clinical setting.

Exploring post-SEPSIS and post-COVID-19 syndromes: crossovers from pathophysiology to therapeutic approach

Holmes, D., et al.

Front Med (Lausanne). (2023) Vol.10; 1280951.

Sepsis, driven by several infections, including COVID-19, can lead to post-sepsis syndrome (PSS) and post-acute sequelae of COVID-19 (PASC). Both these conditions share clinical and

pathophysiological similarities, as survivors face persistent multi-organ dysfunctions, including respiratory, cardiovascular, renal, and neurological issues. Moreover, dysregulated immune responses, immunosuppression, and hyperinflammation contribute to these conditions. The lack of clear definitions and diagnostic criteria hampers comprehensive treatment strategies, and a unified therapeutic approach is significantly needed. One potential target might be the renin-angiotensin system (RAS), which plays a significant role in immune modulation. In fact, RAS imbalance can exacerbate these responses. Potential interventions involving RAS include ACE inhibitors, ACE receptor blockers, and recombinant human ACE2 (rhACE2). To address the complexities of PSS and PASC, a multifaceted approach is required, considering shared immunological mechanisms and the role of RAS. Standardization, research funding, and clinical trials are essential for advancing treatment strategies for these conditions.

Cell death proteins in sepsis: key players and modern therapeutic approaches

Yang, C.S., et al.

Front Immunol. (2023) Vol.14; 1347401.

Cell death proteins play a central role in host immune signalling during sepsis. These interconnected mechanisms trigger cell demise via apoptosis, necroptosis, and pyroptosis while also driving inflammatory signalling. Targeting cell death mediators with novel therapies may correct the dysregulated inflammation seen during sepsis and improve outcomes for septic patients.

Global trends in research on endothelial cells and sepsis between 2002 and 2022: A systematic bibliometric analysis

Shi, Y., et al.

Heliyon. (2024) Vol.10 (1); e23599.

Sepsis is a systemic syndrome involving physiological, pathological, and biochemical abnormalities precipitated by infection and is a major global public health problem. Endothelial cells (ECs) dysfunction is a major contributor to sepsis-induced multiple organ failure. This bibliometric analysis aimed to identify and characterize the status, evolution of the field, and new research trends of ECs and sepsis over the past 20 years. For this analysis, the Web of Science Core Collection database was searched to identify relevant publications on ECs in sepsis published between January 1, 2002, and December 31, 2022. Microsoft Excel 2021, VOSviewer software, CiteSpace software, and the online analysis platform of literature metrology (http://bibliometric.com) were used to visualize the trends of publications' countries/regions, institutions, authors, journals, and keywords. In total, 4200 articles were identified and screened, primarily originating from 86 countries/regions and 3489 institutions. The USA was the leading contributor to this research field, providing 1501 articles (35.74 %). The journals that published the most articles were SHOCK, CRITICAL CARE MEDICINE, and PLOS ONE, accounting for 10.79 % of the total. The current emerging hotspots are concentrated on "endothelial glycocalyx," "NLRP3 inflammasome," "extracellular vesicle," "biomarkers," and "COVID-19," among others. In conclusion, this study provides a comprehensive overview of the scientific productivity and emerging research trends in the field of ECs in sepsis. The evidence supporting the significant role of ECs in both physiological and pathological responses to sepsis is continuously growing. More in-depth studies of the molecular mechanisms underlying sepsis-induced endothelial dysfunction and EC-targeted therapies are warranted in the future.

Neonatal, paediatric and maternal sepsis

Use of transcriptomics for diagnosis of infections and sepsis in children: A narrative review
Casini, F., et al.
Acta Paediatr. (2024)
AIM: The aim of this review was to summarise the most recent evidence about the use of omics-based techniques as an instrument for a more rapid and accurate characterisation of respiratory tract infections, neurological infections and sepsis in paediatrics. METHODS: We performed a narrative review using PubMed and a set of inclusion criteria: English language articles, clinical trials, meta-analysis and reviews including only paediatric population inherited to this topic in the last 15 years. RESULTS: The examined studies suggest that host gene expression signatures are an effective method to characterise the different types of infections, to distinguish infection from colonisation and, in some cases, to assess the severity of the disease in children. CONCLUSIONS: 'Omics-based techniques' may help to define the aetiology of infections in paediatrics, representing a useful tool to choose the most appropriate therapies and limit antibiotic resistance.

Efficacy and safety of short- vs. standard-course antibiotics for culture-negative neonatal sepsis: a systematic review and meta-analysis
Devi, R., et al.
J Trop Pediatr. (2024) Vol.70 (2)
OBJECTIVES: To conduct a systematic review and meta-analysis of evidence from randomized controlled trials (RCTs) comparing a short course of antibiotics (2-4 days), to a standard course (5-7 days), for the treatment of culture-negative neonatal sepsis. METHODS: Relevant databases were searched for RCTs comparing short- vs. standard-course of antibiotics for culture-negative sepsis. The primary outcomes were mortality and treatment failure, defined as the reappearance of clinical signs suggestive of sepsis within 7 days of stoppage of antibiotics. Secondary outcomes included neurological impairment, duration of hospital stay, need for oxygen, respiratory support and double-volume exchange transfusion (DVET). CONCLUSION: Very-low certainty evidence suggests that a short antibiotic course, compared to a standard course, does not affect treatment failure rates in culture-negative neonatal sepsis. There is a need for well-designed RCTs powered enough to assess critical outcomes such as mortality and neurological sequelae to generate stronger evidence and inform guidelines. PROSPERO REGISTRATION NUMBER: CRD42023437199. Prolonged antibiotic usage has been associated with increased mortality and morbidity in neonates. The standard practice in culture-negative neonatal sepsis has been to administer antibiotics for 5-7 days, based on expert consensus. In this systematic review, a short course of antibiotics (2-4 days), in comparison to a standard course (5-7 days), did not affect the treatment failure rates in culture-negative neonatal sepsis. However, the certainty of evidence was too low to make robust conclusions. There is a need for well-designed large trials to generate stronger evidence and inform guidelines.

Prebiotics and sepsis in infants: An updated systematic review and meta-analysis
Qin, Y. and L. Pan
Adv Clin Exp Med. (2024)
BACKGROUND: Sepsis is a critical situation, and its treatment and reduction are important clinical issues. Antibiotics are a routine treatment option, but their adverse effects are a concern in

pediatric patients, especially infants. Prebiotics might be an alternative option. OBJECTIVES: The aim of this study was to provide an updated systemic review and meta-analysis of randomized controlled trials (RCTs) on the use of prebiotics for sepsis in infants, which could assist clinicians in deciding whether to use this treatment. METHODS: The study included RCTs related to prebiotics and sepsis in infants. A random effects model and the odds ratio (OR) were applied to estimate the effect of prebiotic use and the incidence of sepsis in infants. The analysis included 16 studies with a total of 6,438 infants. The primary outcome was the OR of sepsis for infants who received prebiotics. RESULTS: The results of the meta-analysis demonstrated that the pooled OR of sepsis was significantly lower for infants who used prebiotics. However, the results indicated a medium level of heterogeneity. CONCLUSION: The results showed that the use of prebiotics might be associated with a reduction of sepsis in infants. The standardized application of this treatment might be an intriguing topic for future clinical research.

Role of diagnostic tests for sepsis in children: a review

Rodgers, O., et al.

Arch Dis Child. (2024)

Paediatric sepsis has a significant global impact and highly heterogeneous clinical presentation. The clinical pathway encompasses recognition, escalation and de-escalation. In each aspect, diagnostics have a fundamental influence over outcomes in children. Biomarkers can aid in creating a larger low-risk group of children from those in the clinical grey area who would otherwise receive antibiotics 'just in case'. Current biomarkers include C reactive protein and procalcitonin, which are limited in their clinical use to guide appropriate and rapid treatment. Biomarker discovery has focused on single biomarkers, which, so far, have not outperformed current biomarkers, as they fail to recognise the complexity of sepsis. The identification of multiple host biomarkers that may form a panel in a clinical test has the potential to recognise the complexity of sepsis and provide improved diagnostic performance. In this review, we discuss novel biomarkers and novel ways of using existing biomarkers in the assessment and management of sepsis along with the significant challenges in biomarker discovery at present. Validation of biomarkers is made less meaningful due to methodological heterogeneity, including variations in sepsis diagnosis, biomarker cut-off values and patient populations. Therefore, the utilisation of platform studies is necessary to improve the efficiency of biomarkers in clinical practice.

Game changer or gimmick: inflammatory markers to guide antibiotic treatment decisions in neonatal early-onset sepsis

Stocker, M. and E. Giannoni

Clin Microbiol Infect. (2024) Vol.30 (1); 22-27.

BACKGROUND: The diagnosis of neonatal early-onset sepsis (EOS) is challenging, and inflammatory markers are widely used to guide decision-making and therapies. OBJECTIVES: This narrative review presents the current state of knowledge regarding the diagnostic value and potential pitfalls in the interpretation of inflammatory markers for EOS. SOURCES: PubMed until October 2022 and searched references in identified articles using the search terms: neonatal EOS, biomarker or inflammatory marker, and antibiotic therapy or antibiotic stewardship. CONTENT: In situations with a high or low probability of sepsis, the measurements of inflammatory markers have no impact on the decision to start or stop antibiotics and are just gimmick, whereas they may be a game changer for neonates with intermediate risk and therefore an unclear situation. There is no single or combination of inflammatory markers that can predict EOS with high probability, allowing us to

make decisions regarding the start of antibiotics based only on inflammatory markers. The main reason for the limited accuracy is most probably the numerous non-infectious conditions that influence the levels of inflammatory markers. However, there is evidence that C-reactive protein and procalcitonin have good negative predictive accuracy to rule out sepsis within 24 to 48 hours. Nevertheless, several publications have reported more investigations and prolonged antibiotic treatments with the use of inflammatory markers. Given the limitations of current strategies, using an algorithm with only moderate diagnostic accuracy may have a positive impact, as reported for the EOS calculator and the NeoPInS algorithm. IMPLICATIONS: As the decision regarding the start of antibiotic therapy is different from the process of stopping antibiotics, the accuracy of inflammatory markers needs to be evaluated separately. Novel machine learning-based algorithms are required to improve accuracy in the diagnosis of EOS. In the future, inflammatory markers included in algorithms may be a game changer reducing bias and noise in the decision-making process.

Early-versus late-onset sepsis in neonates - time to shift the paradigm?

Russell, N., et al.

Clin Microbiol Infect. (2024) Vol.30 (1); 38-43.

BACKGROUND: Neonatal sepsis is traditionally classified as early-onset sepsis (EOS) and late-onset sepsis (LOS) disease categories. This paradigm was based on observed epidemiological data from high income settings. However, increasing availability of microbiology results from diverse settings challenges these assumptions, necessitating re-examination of neonatal sepsis classifications. OBJECTIVES: To review the literature describing the aetiology of EOS and LOS in hospitalized neonates with stratification of pathogen spectrum by low- (LIC), middle- (MIC) and high-income (HIC) country settings, to critically re-examine the continued appropriateness of the 'EOS vs. LOS' sepsis paradigm in all settings. SOURCES: PubMed was searched for peer-reviewed English full-text articles published from inception up until 8 August 2022. CONTENT: Studies often report on either EOS or LOS, rather than both. We identified only 49 original articles reporting on pathogen distribution of both EOS and LOS in the same hospital setting. Clear differences in sepsis aetiology were shown between LIC, MIC and HIC settings, with increasing importance of Klebsiella pneumoniae and decreasing importance of Group B Streptococcus in the first 72 hours of life in LIC and MIC. IMPLICATIONS: The concept of 'EOS vs. LOS' may be less useful for predicting the pathogen spectrum of neonatal sepsis in LIC and MIC, but the paradigm has shaped reporting of neonatal sepsis, and our understanding. Future neonatal sepsis reporting should utilize strengthening the reporting of observational studies in epidemiology for newborn infection (STROBE-NI) reporting guidelines and clearly describe timing of infection by day, and variation in pathogen spectrum across the neonatal period. Data identified in this review challenge the generalizability of the prevailing EOS/LOS paradigm in LIC and MIC.

Antimicrobial stewardship and targeted therapies in the changing landscape of maternal sepsis

Shah, N.M., et al.

J Intensive Med. (2024) Vol.4 (1); 46-61.

Pregnant and postnatal women are a high-risk population particularly prone to rapid progression to sepsis with significant morbidity and mortality worldwide. Moreover, severe maternal infections can have a serious detrimental impact on neonates with almost 1 million neonatal deaths annually attributed to maternal infection or sepsis. In this review we discuss the susceptibility of pregnant women and their specific physiological and immunological adaptations that contribute to their

vulnerability to sepsis, the implications for the neonate, as well as the issues with antimicrobial stewardship and the challenges this poses when attempting to reach a balance between clinical care and urgent treatment. Finally, we review advancements in the development of pregnancy-specific diagnostic and therapeutic approaches and how these can be used to optimize the care of pregnant women and neonates.

Short course of intravenous antibiotics in the treatment of uncomplicated proven neonatal bacterial sepsis: A systematic review

Aljarbou, A., et al.

Acta Paediatr. (2024) Vol.113 (1); 56-66.

AIM: To evaluate the efficacy and harms of a short (7-10 days) compared with a standard (10-14 days) duration of antibiotics in culture-proven neonatal sepsis for reducing all-cause mortality, treatment failure and duration of hospitalisation. METHODS: Medline, EMBASE and Cochrane CENTRAL were searched for randomised trials. RESULTS: We included five studies, all conducted in India (447 infants with a gestational age greater than 32 weeks). Except for one study, all studies were at high risk of bias. All-cause mortality was reported in three studies with only one death reported in the standard duration regimen arm (243 patients, very low certainty). A meta-analysis showed no evidence of the effect on treatment failure (RR of 1.47 [95% CI 0.48-4.50], 440 patients, five studies, very low certainty) of short-term antibiotics. Short-term antibiotic regimen shortened the duration of hospitalisation by 4 days (mean difference of -4.04 days [95% CI -5.47 to -2.61]; 4 studies; 371 patients; very low certainty). CONCLUSION: Among studies focused on infants born with a gestational age greater than 32 weeks, short-term administration of antibiotics may shorten the duration of hospitalisation, but the evidence is very uncertain. The evidence on other predefined outcomes is very uncertain to draw definite conclusions.

Intrapartum azithromycin to prevent maternal and neonatal sepsis and deaths: A systematic review with meta-analysis

Kuitunen, I., et al.

Bjog. (2024) Vol.131 (3); 246-255.

OBJECTIVES: A systematic review with met-analysis was performed to summarise the evidence on the effect of intrapartum azithromycin on maternal and neonatal infections and deaths. SEARCH STRATEGY: PubMed, Scopus and Web of Science databases were searched in March 2023. SELECTION CRITERIA: Randomised controlled trials comparing intrapartum single-dose of azithromycin with placebo. DATA COLLECTION AND ANALYSIS: Maternal infections, maternal mortality, neonatal sepsis, neonatal mortality. We used the random-effects Mantel-Haenszel method to calculate risk ratios (RR) with 95% confidence intervals (95% CI). We assessed risk of bias of the included studies and estimated the evidence certainty using the GRADE approach. MAIN RESULTS: After screening 410 abstracts, five studies with 44 190 women and 44 565 neonates were included. The risk of bias was low in four and had some concerns in one of the studies. The risk of endometritis was 1.5% in the azithromycin group and 2.3% in the placebo group (RR 0.64, 95% CI 0.55-0.75), and the evidence certainty was high. The respective risk for chorioamnionitis was 0.05% and 0.1% (RR 0.50, 95% CI 0.22-1.18; evidence certainty moderate). The wound infection rate was lower in the azithromycin group (1.6%) than in the placebo group (2.5%), RR 0.52 (95% CI 0.30-0.89; moderate certainty evidence). The maternal sepsis rate was 1.1% in the azithromycin group and 1.7% in the placebo group (RR 0.66, 95% CI 0.56-0.77; evidence certainty high). Mortality rates did not show evidence of a difference (0.09% versus 0.08%; RR 1.26, 95% CI 0.65-2.42; moderate

certainty evidence). The neonatal mortality rate was 0.7% in the azithromycin group and 0.8% in the placebo group (RR 0.94, 95% CI 0.76-1.16; moderate certainty evidence). The neonatal sepsis rate was 7.6% in the azithromycin group and 7.4% in the placebo group (RR 1.02, 95% CI 0.96-1.09; moderate certainty evidence). CONCLUSIONS: Intrapartum administration of azithromycin to the mother reduces maternal postpartum infections, including sepsis. Impact on maternal mortality remains undecided. Azithromycin does not reduce neonatal sepsis or mortality rates.

Balanced crystalloids versus isotonic saline in pediatric sepsis: a comprehensive systematic review and meta-analysis

Mhanna, A., et al.

Proc (Bayl Univ Med Cent). (2024) Vol.37 (2); 295-302.

PURPOSE: We conducted a comprehensive meta-analysis to compare the effects of balanced crystalloids (BC) and isotonic saline (IS) in pediatric sepsis. METHODS: A systematic search was performed for studies comparing BC and IS in pediatric sepsis. Outcomes included mortality, acute kidney injury (AKI), need for renal replacement therapy (RRT), hospital length of stay (LOS), and pediatric intensive care unit (PICU) LOS. A random-effect models was used to calculated pooled odds ratios (OR) and mean differences (MD) with 95% confidence intervals (CIs). RESULTS: The analysis included six studies with 8753 children. BC demonstrated significant reductions in overall mortality (OR 0.84, 95% CI 0.71 to 0.98, P = 0.03, I(2) = 0%) and AKI (OR 0.74, 95% CI 0.57 to 0.96, P = 0.03, I(2) = 37%) compared to IS. RRT need was similar between the BC and IS groups (OR 0.79, 95% CI 0.60 to 1.02, P = 0.07, I(2) = 0%). Hospital and PICU LOS did not differ significantly. However, subgroup analysis of randomized controlled trials revealed significantly shorter hospital LOS in the BC group (mean difference -0.66 days, 95% CI -1.10 to -0.23, P = 0.003, I(2) = 0%). CONCLUSION: Our meta-analysis demonstrates that using BC in pediatric sepsis is associated with reduced mortality, AKI, and hyperchloremia rates compared to IS, while maintaining similar hospital and PICU LOS. Large-scale randomized controlled trials are needed to validate these findings.

Association between vitamin D receptor gene variants and neonatal sepsis: A systematic review and meta-analysis

Darnifayanti, D., et al.

J Infect Public Health. (2024) Vol.17 (3); 518-526.

The objective of this systematic review and meta-analysis was elucidating the association of VDR SNPs (FokI, TaqI, BsmI, BglI, and ApaI) with neonatal sepsis. Literature search was performed to retrieve records published until August 2nd, 2023 (PROSPERO registration: CRD42023451355). Meta-analysis was carried out to determine the pooled estimates for Odds Ratio (OR). A total of four studies were included with 500 neonates (250 sepsis cases and 250 healthy controls). There was an association observed between TaqI SNP with neonatal sepsis for CT vs. CC+TT (OR=1.95) and TT vs CT+CC (OR=0.40). Moreover, the pooled estimates also suggested that CC vs. CT+TT (OR= 0.37) and C vs. T (OR=0.66) of FokI SNP were significantly associated with neonatal sepsis. SNP of BglI was found to be significantly associated with neonatal sepsis, but only reported in a single study.

Neonatal sepsis and its predictors in Ethiopia: umbrella reviews of a systematic review and meta-analysis, 2023

Eyeberu, A., et al.

Ann Med Surg (Lond). (2024) Vol.86 (2); 994-1002.

BACKGROUND: Although neonatal sepsis is acknowledged as the primary cause of newborn death in Ethiopia, data on its impact at the national level are limited. Strong supporting data are required to demonstrate how this affects neonatal health. This umbrella study was conducted to determine the overall prevalence of newborn sepsis and its relationship with maternal and neonatal factors. METHODS: This umbrella review included five articles from various databases. The AMSTAR-2 method was used to assess the quality of included systematic review and meta-analysis studies. STATA Version 18 software was used for statistical analysis. A random-effects model was used to estimate the overall effects. RESULTS: In this umbrella review, 9032 neonates with an outcome of interest were included. The overall pooled prevalence of neonatal sepsis was 45% (95% CI: 39-51%; I(2)=99.34). The overall pooled effect size showed that prematurity was significantly associated with neonatal sepsis [odds ratio=3.11 (95% CI: 2.22-3.99)]. Furthermore, maternal factors are strongly associated with neonatal sepsis. CONCLUSIONS: Nearly half of Ethiopian neonates are affected by neonatal sepsis. It is critical to reduce premature birth, low birth weight, and preterm membrane rupture to reduce the incidence of neonatal sepsis. Furthermore, it is preferable to design and strengthen policies and programs aimed at improving maternal nutritional status and treating maternal infections, which all contribute to lowering the burden of neonatal sepsis.

Neonatal sepsis as a cause of retinopathy of prematurity: An etiological explanation

Dammann, O. and B.K. Stansfield

Prog Retin Eye Res. (2024) Vol.98; 101230.

Retinopathy of prematurity (ROP) is a complex neonatal disorder with multiple contributing factors. In this paper we have mounted the evidence in support of the proposal that neonatal sepsis meets all requirements for being a cause of ROP (not a condition, mechanism, or even innocent bystander) by means of initiating the early stages of the pathomechanism of ROP occurrence, systemic inflammation. We use the model of etiological explanation, which distinguishes between two overlapping processes in ROP causation. It can be shown that sepsis can initiate the early stages of the pathomechanism via systemic inflammation (causation process) and that systemic inflammation can contribute to growth factor aberrations and the retinal characteristics of ROP (disease process). The combined contribution of these factors with immaturity at birth (as intrinsic risk modifier) and prenatal inflammation (as extrinsic facilitator) seems to provide a cogent functional framework of ROP occurrence. Finally, we apply the Bradford Hill heuristics to the available evidence. Taken together, the above suggests that neonatal sepsis is a causal inducer of ROP.

Prevalence and factors associated with maternal and neonatal sepsis in sub-Saharan Africa: a systematic review and meta-analysis

Traoré, F.B., et al.

Front Public Health. (2024) Vol.12; 1272193.

OBJECTIVES: This study aimed to determine the prevalence and factors associated with maternal and neonatal sepsis in sub-Saharan Africa. METHODS: This systematic review and meta-analysis used the PRISMA guideline on sepsis data in sub-Saharan Africa. The bibliographic search was carried out on the following databases: Medline/PubMed, Cochrane Library, African Index Medicus,

and Google Scholar. Additionally, the reference lists of the included studies were screened for potentially relevant studies. The last search was conducted on 15 October 2022. The Joanna Briggs Institute quality assessment checklist was applied for critical appraisal. Estimates of the prevalence of maternal and neonatal sepsis were pooled using a random-effects meta-analysis model. Heterogeneity between studies was estimated using the Q statistic and the I2 statistic. The funnel plot and Egger's regression test were used to assess the publication bias. RESULTS: A total of 39 studies were included in our review: 32 studies on neonatal sepsis and 7 studies on maternal sepsis. The overall pooled prevalence of maternal and neonatal sepsis in Sub-Saharan Africa was 19.21% (95% CI, 11.46-26.97) and 36.02% (CI: 26.68-45.36), respectively. The meta-analyses revealed that Apgar score < 7 (OR: 2.4, 95% CI: 1.6-3.5), meconium in the amniotic fluid (OR: 2.9, 95% CI: 1.8-4.5), prolonged rupture of membranes >12 h (OR: 2.8, 95% CI: 1.9-4.1), male sex (OR: 1.2, 95% CI: 1.1-1.4), intrapartum fever (OR: 2.4, 95% CI: 1.5-3.7), and history of urinary tract infection in the mother (OR: 2.7, 95% CI: 1.4-5.2) are factors associated with neonatal sepsis. Rural residence (OR: 2.3, 95% CI: 1.01-10.9), parity (OR: 0.5, 95% CI: 0.3-0.7), prolonged labor (OR: 3.4, 95% CI: 1.6-6.9), and multiple digital vaginal examinations (OR: 4.4, 95% CI: 1.3-14.3) were significantly associated with maternal sepsis. CONCLUSION: The prevalence of maternal and neonatal sepsis was high in sub-Saharan Africa. Multiple factors associated with neonatal and maternal sepsis were identified. These factors could help in the prevention and development of strategies to combat maternal and neonatal sepsis. Given the high risk of bias and high heterogeneity, further high-quality research is needed in the sub-Saharan African context, including a meta-analysis of individual data. Systematic review registration: PROSPERO (ID: CRD42022382050).

Antibiotic use at planned central line removal in reducing neonatal post-catheter removal sepsis: a systematic review and meta-analysis

Ji, R., et al.

Front Pediatr. (2023) Vol.11; 1324242.

BACKGROUND: Post-catheter removal sepsis (PCRS) is a notable complication of indwelling central venous catheters (CVCs) in neonates, which is postulated to be secondary to the disruption of biofilms formed along catheter tips up on CVCs removal. It remains controversial whether this could be prevented by antibiotic use upon CVCs removal. We aimed to evaluate the protective effect of antibiotic administration at the time of CVCs removal. METHODS: We searched through PubMed, EMBASE, Cochrane databases and reference lists of review articles for studies comparing the use of antibiotics versus no use within 12 h of CVCs removal. Risk of bias was assessed using the modified Newcastle-Ottawa Scale and Cochrane risk-of-bias tool accordingly. Results of quantitative analyses were presented as mean differences (MD) or odds ratio (OR). Subgroup and univariate meta-regression analyses were performed to identify heterogeneity. CONCLUSION: Antibiotic administration upon CVCs removal does not significantly reduce the incidence of PCRS but offers less post-catheter removal blood stream infection. Whether this will be converted to better clinical outcomes lacks evidential support. Further randomized controlled studies with longer follow-up are needed. SUMMARY: Results of our meta-analysis suggest that antibiotic use at planned central line removal removal does not significantly reduce the incidence of PCRS but offers less blood stream infection, which might contribute to future management of central lines in neonates. SYSTEMATIC REVIEW REGISTRATION: https://www.crd.york.ac.uk/, PROSPERO (CRD42022359677).

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