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Sepsis Bulletin

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Sepsis

Neonatal, paediatric and maternal sepsis

Adverse Effects Related to Corticosteroid Use in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis

Chaudhuri, D., et al.

Critical care explorations. (2024) Vol.6 (4); e1071.

OBJECTIVES: We postulate that corticosteroid-related side effects in critically ill patients are similar across sepsis, acute respiratory distress syndrome (ARDS), and community-acquired pneumonia (CAP). By pooling data across all trials that have examined corticosteroids in these three acute conditions, we aim to examine the side effects of corticosteroid use in critical illness. DATA SOURCES: We performed a comprehensive search of MEDLINE, Embase, Centers for Disease Control and Prevention library of COVID research, CINAHL, and Cochrane center for trials. STUDY SELECTION: We included randomized controlled trials (RCTs) that compared corticosteroids to no corticosteroids or placebo in patients with sepsis, ARDS, and CAP. DATA EXTRACTION: We summarized data addressing the most described side effects of corticosteroid use in critical care: gastrointestinal bleeding, hyperglycemia, hypernatremia, superinfections/secondary infections, neuropsychiatric effects, and neuromuscular weakness. CONCLUSIONS: In ARDS, sepsis, and CAP, corticosteroids are associated with hyperglycemia and probably with hypernatremia but likely have no effect on gastrointestinal bleeding or secondary infections. More data examining effects of corticosteroids, particularly on neuropsychiatric outcomes and neuromuscular weakness, would clarify the safety of this class of drugs in critical illness.

The chain of survival and rehabilitation for sepsis: concepts and proposals for healthcare trajectory optimization

Jouffroy, R., et al.

Annals of intensive care. (2024) Vol.14 (1); 58.

This article describes the structures and processes involved in healthcare delivery for sepsis, from the prehospital setting until rehabilitation. Quality improvement initiatives in sepsis may reduce both morbidity and mortality. Positive outcomes are more likely when the following steps are optimized: early recognition, severity assessment, prehospital emergency medical system activation when available, early therapy (antimicrobials and hemodynamic optimization), early orientation to an adequate facility (emergency room, operating theater or intensive care unit), in-hospital organ failure resuscitation associated with source control, and finally a comprehensive rehabilitation program. Such a trajectory of care dedicated to sepsis amounts to a chain of survival and rehabilitation for sepsis. Implementation of this chain of survival and rehabilitation for sepsis requires full interconnection between each link. To date, despite regular international recommendations updates, the adherence to sepsis guidelines remains low leading to a considerable burden of the disease. Developing and optimizing such an integrated network could significantly reduce sepsis related mortality and morbidity. Copyright © 2024. The Author(s).

Effect of delayed antibiotic use on mortality outcomes in patients with sepsis or septic shock: A systematic review and meta-analysis

Tang, F., et al.

International immunopharmacology. (2024) Vol.129; 111616.

BACKGROUND: The use of antibiotics is essential in the treatment of sepsis and septic shock, and delaying their administration may impact patient mortality outcomes. However, there is currently a controversial debate surrounding this issue. In this meta-analysis, we aimed to explore the association between delayed antibiotic use and mortality in patients with sepsis and septic shock. METHODS: A systematic search was conducted on PubMed, EMBASE, Web of Science, and Cochrane Library to identify relevant studies published from 2013 to 2023. These studies focused on patients with sepsis or septic shock and provided information on various antibiotic administration times and mortality rates. Two independent reviewers screened and extracted the data. The quality of each study was assessed using the Newcastle-Ottawa Scale, and the collected data were analyzed using STATA 15.1 software. CONCLUSION: The administration of antibiotics beyond 1 h after emergency triage or disease identification is strongly associated with an increased IHM in patients with sepsis or septic shock, and each hour of delay in antibiotic administration may be associated with an increase in the IHM. Furthermore, the use of antibiotics identification beyond 3 h after emergency triage / sepsis or septic shock may also increase the IHM. Copyright © 2024. Published by Elsevier B.V.

Efficacy and safety of levosimendan in patients with sepsis: a systematic review and network meta-analysis

Tan, R., et al.

Frontiers in pharmacology. (2024) Vol.15; 1358735.

Objective: We conducted a systematic review to assess the advantages and disadvantages of levosimendan in patients with sepsis compared with placebo, milrinone, and dobutamine and to explore the clinical efficacy of different concentrations of levosimendan. Methods: PubMed, Web of Science, Cochrane Library, Embase, CNKI, Wanfang data, VIP, and CBM databases were searched

using such keywords as simendan, levosimendan, and sepsis. The search time was from the establishment of the database to July 2023. Two researchers were responsible for literature screening and data collection respectively. After the risk of bias in the included studies was evaluated, network meta-analysis was performed using R software gemtc and rjags package. Conclusion: The existing evidence suggests that levosimendan can significantly improve CI and lactate levels in patients with sepsis, and levosimendan at 0.1 microg/kg/min might be the optimal dose. Unfortunately, all interventions in this study failed to reduce the 28-day mortality. Copyright © 2024 Tan, Guo, Yang, Yang, Li, Zhu and Du.

Hemodynamic goals in sepsis and septic shock resuscitation: An umbrella review of systematic reviews and meta-analyses with trial sequential analysis

Orso, D., et al.

Australian critical care: official journal of the Confederation of Australian Critical Care Nurses. (2024)

OBJECTIVE: The objective of this study was to verify whether any parameter among those used as the target for haemodynamic optimisation (e.g., mean arterial pressure, central venous oxygen saturation, systolic or diastolic dysfunction, CO2 gap, lactates, right ventricular dysfunction, and PvaCO2/CavO2 ratio) is correlated with mortality in an undifferentiated population with sepsis or septic shock. METHODS: An umbrella review, searching MEDLINE, the Cochrane Database of Systematic Reviews, Health Technology Assessment Database, and the JBI Database of Systematic Reviews and Implementation Reports, was performed. We included systematic reviews and meta-analyses enrolling a population of unselected patients with sepsis or septic shock. The main outcome was mortality. Two authors conducted data extraction and risk-of-bias assessments independently. We used a random-effects model to pool binary and continuous data and summarised estimates of effect using equivalent odds ratios (eORs). We used the ROBIS tool to assess risk of bias and the assessment of multiple systematic reviews 2 score to assess global quality. CONCLUSIONS: According to this umbrella review, diastolic dysfunction is the haemodynamic variable that is most closely linked to the prognosis of septic patients. The PvaCO2/CavO2 ratio and the CO2gap are significantly related to the mortality of septic patients, but the poor quality of evidence or the low number of cases, studied so far, limit their clinical applicability. Copyright © 2024 Australian College of Critical Care Nurses Ltd. Published by Elsevier Ltd. All rights reserved.

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.

IL-1beta, the first piece to the puzzle of sepsis-related cognitive impairment?

Zhu, Q., et al.

Frontiers in neuroscience. (2024) Vol.18; 1370406.

Sepsis is a leading cause of death resulting from an uncontrolled inflammatory response to an infectious agent. Multiple organ injuries, including brain injuries, are common in sepsis. The underlying mechanism of sepsis-associated encephalopathy (SAE), which is associated with neuroinflammation, is not yet fully understood. Recent studies suggest that the release of interleukin-1beta (IL-1beta) following activation of microglial cells plays a crucial role in the development of long-lasting neuroinflammation after the initial sepsis episode. This review provides a comprehensive analysis of the recent literature on the molecular signalling pathways involved in microglial cell activation and interleukin-1beta release. It also explores the physiological and pathophysiological role of IL-1beta in cognitive function, with a particular focus on its contribution to long-lasting neuroinflammation after sepsis. The findings from this review may assist healthcare providers in developing novel interventions against SAE.

Immunomodulatory drugs in sepsis: a systematic review and meta-analysis

Robey, R.C., et al.

Anaesthesia. (2024)

Dysregulation of the host immune response has a central role in the pathophysiology of sepsis. There has been much interest in immunomodulatory drugs as potential therapeutic adjuncts in sepsis. We conducted a systematic review and meta-analysis of randomised controlled trials evaluating the safety and clinical effectiveness of immunomodulatory drugs as adjuncts to standard care in the treatment of adults with sepsis. Our primary outcomes were serious adverse events and all-cause mortality. Fifty-six unique, eligible randomised controlled trials were identified, assessing a range of interventions including cytokine inhibitors; anti-inflammatories; immune cell stimulators; platelet pathway inhibitors; and complement inhibitors. At 1-month follow-up, the use of cytokine inhibitors was associated with a decreased risk of serious adverse events, based on 11 studies involving 7138 patients. The only immunomodulatory drugs associated with an increased risk of serious adverse events were toll-like receptor 4 antagonists. Based on 18 randomised controlled trials, involving 11,075 patients, cytokine inhibitors reduced 1-month mortality. Mortality reduction was also shown in the subgroup of 13 randomised controlled trials that evaluated anti-tumour necrosis factor alpha intervention. Anti-inflammatory drugs had the largest apparent effect on mortality at 2 months at any dose. These data indicate that, except for toll-like receptor 4 antagonists, there is no evidence of safety concerns for the use of immunomodulatory drugs in sepsis, and they may show some short-term mortality benefit for selected drugs.

Improving sepsis classification performance with artificial intelligence algorithms: A comprehensive overview of healthcare applications

G, A., et al.

Journal of critical care. (2024) Vol.83; 154815.

PURPOSE: This study investigates the potential of machine learning (ML) algorithms in improving sepsis diagnosis and prediction, focusing on their relevance in healthcare decision-making. The primary objective is to contribute to healthcare decision-making by evaluating the performance of various supervised and unsupervised models. MATERIALS AND METHODS: Through an extensive literature review, optimal ML models used in sepsis research were identified. Diverse datasets from relevant sources were employed, and rigorous evaluation metrics, including accuracy, specificity, and sensitivity, were applied. Innovative techniques were introduced, such as a Stacked Blended Ensemble Model and Skopt Optimization with Blended Ensemble, incorporating Bayesian optimization for hyperparameter tuning. RESULTS: ML algorithms demonstrate efficacy in sepsis diagnosis, presenting an improved balance between specificity and sensitivity, critical for effective clinical decision-making. Classifier ensemble models show enhanced accuracy and efficiency, with novel optimization techniques contributing to improved adaptability. CONCLUSION: The study emphasizes the potential benefits of ML algorithms in sepsis management, advocating for ongoing research to optimize performance and ensure ethical utilization in healthcare decision-making. Ethical considerations, interpretability, and transparency are crucial factors in implementing these algorithms in clinical practice.

Inflammaging in Multidrug-Resistant Sepsis of Geriatric ICU Patients and Healthcare Challenges

Kumar, N.R., et al.

Geriatrics (Basel, Switzerland). (2024) Vol.9 (2)

Multidrug-resistant sepsis (MDR) is a pressing concern in intensive care unit (ICU) settings, specifically among geriatric patients who experience age-related immune system changes and comorbidities. The aim of this review is to explore the clinical impact of MDR sepsis in geriatric ICU patients and shed light on healthcare challenges associated with its management. We conducted a comprehensive literature search using the National Center for Biotechnology Information (NCBI) and Google Scholar search engines. Our search incorporated keywords such as "multidrug-resistant sepsis" OR "MDR sepsis", "geriatric ICU patients" OR "elderly ICU patients", and "complications", "healthcare burdens", "diagnostic challenges", and "healthcare challenges" associated with MDR sepsis in "ICU patients" and "geriatric/elderly ICU patients". This review explores the specific risk factors contributing to MDR sepsis, the complexities of diagnostic challenges, and the healthcare burden faced by elderly ICU patients. Notably, the elderly population bears a higher burden of MDR sepsis (57.5%), influenced by various factors, including comorbidities, immunosuppression, age-related immune changes, and resource-limited ICU settings. Furthermore, sepsis imposes a significant economic burden on healthcare systems, with annual costs exceeding $27 billion in the USA. These findings underscore the urgency of addressing MDR sepsis in geriatric ICU patients and the need for tailored interventions to improve outcomes and reduce healthcare costs.

The Interplay between Antibiotics and the Host Immune Response in Sepsis: From Basic Mechanisms to Clinical Considerations: A Comprehensive Narrative Review

Tosi, M., et al.

Antibiotics (Basel, Switzerland). (2024) Vol.13 (5) Sepsis poses a significant global health challenge due to immune system dysregulation. This narrative review explores the complex relationship

between antibiotics and the immune system, aiming to clarify the involved mechanisms and their clinical impacts. From pre-clinical studies, antibiotics exhibit various immunomodulatory effects, including the regulation of pro-inflammatory cytokine production, interaction with Toll-Like Receptors, modulation of the P38/Pmk-1 Pathway, inhibition of Matrix Metalloproteinases, blockade of nitric oxide synthase, and regulation of caspase-induced apoptosis. Additionally, antibiotic-induced alterations to the microbiome are associated with changes in systemic immunity, affecting cellular and humoral responses. The adjunctive use of antibiotics in sepsis patients, particularly macrolides, has attracted attention due to their immune-regulatory effects. However, there are limited data comparing different types of macrolides. More robust evidence comes from studies on community-acquired pneumonia, especially in severe cases with a hyper-inflammatory response. While studies on septic shock have shown mixed results regarding mortality rates and immune response modulation, conflicting findings are also observed with macrolides in acute respiratory distress syndrome. In conclusion, there is a pressing need to tailor antibiotic therapy based on the patient's immune profile to optimize outcomes in sepsis management.

Methylene blue in sepsis and septic shock: a systematic review and meta-analysis

Ballarin, R.S., et al.

Frontiers in medicine. (2024) Vol.11; 1366062.

Background: Methylene blue is an interesting approach in reducing fluid overload and vasoactive drug administration in vasodilatory shock. The inhibition of guanylate cyclase induced by methylene blue infusion reduces nitric oxide production and improves vasoconstriction. This systematic review and meta-analysis aimed to assess the effects of methylene blue administration compared to placebo on the hemodynamic status and clinical outcomes in patients with sepsis and septic shock. Methods: The authors specifically included randomized controlled trials that compared the use of methylene blue with placebo in adult patients with sepsis and septic shock. The outcomes were length of intensive care unit stay, hemodynamic parameters [vasopressor use], and days on mechanical ventilation. We also evaluated the abnormal levels of methemoglobinemia. This systematic review and meta-analysis were recorded in PROSPERO with the ID CRD42023423470. Conclusion: Administering methylene blue to patients with sepsis and septic shock leads to reduced time to vasopressor discontinuation, length of intensive care unit stay, and days on mechanical ventilation.

Naringin: A flavanone with a multifaceted target against sepsis-associated organ injuries

Bajgai, B., et al.

Phytomedicine : international journal of phytotherapy and phytopharmacology. (2024) Vol.130; 155707.

BACKGROUND: Sepsis causes multiple organ dysfunctions and raises mortality and morbidity rates through a dysregulated host response to infection. Despite the growing research interest over the last few years, no satisfactory treatment exists. Naringin, a naturally occurring bioflavonoid with vast therapeutic potential in citrus fruits and Chinese herbs, has received much attention for treating sepsis-associated multiple organ dysfunctions. PURPOSE: The review describes preclinical evidence of naringin from 2011 to 2024, particularly emphasizing the mechanism of action mediated by naringin against sepsis-associated specific injuries. The combination therapy, safety profile, drug interactions, recent advancements in formulation, and future perspectives of naringin

are also discussed. METHODS: In vivo and in vitro studies focusing on the potential role of naringin and its mechanism of action against sepsis-associated organ injuries were identified and summarised in the present manuscript, which includes contributions from 2011 to 2024. All the articles were extracted from the Medline database using PubMed, Science Direct, and Web of Science with relevant keywords. CONCLUSION: Naringin might be a promising therapeutic approach for preventing sepsis-induced multiple organ failure. Naringin should be used alongside other therapeutic therapies with caution despite its great therapeutic potential and lower toxicity. Nonetheless, clinical studies are required to comprehend the therapeutic benefits of naringin against sepsis.

The Omics Complexity in Sepsis: The Limits of the Personalized Medicine Approach

Isac, S., et al.

Journal of personalized medicine. (2024) Vol.14 (3)

Sepsis is one of the most common causes of morbidity and mortality worldwide. Despite the remarkable advances in modern medicine throughout the last century, the mortality rates associated with sepsis have remained significantly elevated, both in high- and low-income countries. The main difficulty in the diagnosis and treatment of septic patients is the tremendous heterogeneity of this condition. The vast heterogeneity that characterizes sepsis ranges from the clinical presentation to the biological aspects of the disease. Evidence-based medicine approaches sepsis as a homogenous syndrome and does not consider the individual discrepancies between septic patients. This approach may contribute to the poor outcomes of septic patients. In recent years, personalized medicine has gained significant interest. This novel form of medicine underlines the importance of understanding the genetic, epigenetic, and molecular basis of a disease in order to provide a more tailored approach for the patient. The study of "omics", such as cytomics, genomics, epigenomics, transcriptomics, proteomics, and metabolomics, provides a deeper comprehension of the complex interactions between the host, the disease, and the environment. The aim of this review is to summarize the potential role of a personalized approach in sepsis management, considering the interactions between various "omics".

The possible mechanisms of ferroptosis in sepsis-associated acquired weakness

Yang, J., et al.

Frontiers in physiology. (2024) Vol.15; 1380992.

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, and its morbidity and mortality rates are increasing annually. It is an independent risk factor for intensive care unit-acquired weakness (ICU-AW), which is a common complication of patients in ICU. This situation is also known as sepsis-associated acquired weakness (SAW), and it can be a complication in more than 60% of patients with sepsis. The outcomes of SAW are often prolonged mechanical ventilation, extended hospital stays, and increased morbidity and mortality of patients in ICUs. The pathogenesis of SAW is unclear, and an effective clinical treatment is not available. Ferroptosis is an iron-dependent type of cell death with unique morphological, biochemical, and genetic features. Unlike other forms of cell death such as autophagy, apoptosis, and necrosis, ferroptosis is primarily driven by lipid peroxidation. Cells undergo ferroptosis during sepsis, which further enhances the inflammatory response. This process leads to increased cell death, as well as multi-organ dysfunction and failure. Recently, there have been sporadic reports suggesting that SAW is associated with ferroptosis, but the exact pathophysiological mechanisms remain unclear.

Therefore, we reviewed the possible pathogenesis of ferroptosis that leads to SAW and offer new strategies to prevent and treat SAW. Copyright © 2024 Yang, Yan, Chen, Li, Miao, Ma, Zeng and Xie.

Post-sepsis psychiatric disorder: Pathophysiology, prevention, and treatment

Li, D., et al.

Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. (2024)

Post-sepsis psychiatric disorder, encompassing anxiety, depression, post-traumatic stress disorder and delirium, is a highly prevalent complication secondary to sepsis, resulting in a marked increase in long-term mortality among affected patients. Regrettably, psychiatric impairment associated with sepsis is frequently disregarded by clinicians. This review aims to summarize recent advancements in the understanding of the pathophysiology, prevention, and treatment of post-sepsis mental disorder, including coronavirus disease 2019-related psychiatric impairment. The pathophysiology of post-sepsis psychiatric disorder is complex and is known to involve blood-brain barrier disruption, overactivation of the hypothalamic-pituitary-adrenal axis, neuroinflammation, oxidative stress, neurotransmitter dysfunction, programmed cell death, and impaired neuroplasticity. No unified diagnostic criteria for this disorder are currently available; however, screening scales are often applied in its assessment. Modifiable risk factors for psychiatric impairment post-sepsis include the number of experienced traumatic memories, the length of ICU stay, level of albumin, the use of vasopressors or inotropes, daily activity function after sepsis, and the cumulative dose of dobutamine. To contribute to the prevention of post-sepsis psychiatric disorder, it may be beneficial to implement targeted interventions for these modifiable risk factors. Specific therapies for this condition remain scarce. Nevertheless, non-pharmacological approaches, such as comprehensive nursing care, may provide a promising avenue for treating psychiatric disorder following sepsis. In addition, although several therapeutic drugs have shown preliminary efficacy in animal models, further confirmation of their potential is required through follow-up clinical studies. Copyright © 2024. The Author(s).

Recent Advances in Immunomodulatory Therapy in Sepsis: A Comprehensive Review

Jain, A., et al.

Cureus. (2024) Vol.16 (3); e57309.

Sepsis remains a critical healthcare challenge, characterized by dysregulated immune responses to infection, leading to organ dysfunction and high mortality rates. Traditional treatment strategies often fail to address the underlying immune dysregulation, necessitating exploring novel therapeutic approaches. Immunomodulatory therapy holds promise in sepsis management by restoring immune balance and mitigating excessive inflammation. This comprehensive review examines the pathophysiology of sepsis, current challenges in treatment, and recent advancements in immunomodulatory agents, including biologics, immunotherapy, and cellular therapies. Clinical trial outcomes, safety profiles, and future research and clinical practice implications are discussed. While immunomodulatory therapies show considerable potential in improving sepsis outcomes, their successful implementation requires further research, collaboration, and integration into standard clinical protocols. Copyright © 2024, Jain et al.

Recent Data about the Use of Corticosteroids in Sepsis-Review of Recent Literature

Lazar, A.

Biomedicines. (2024) Vol.12 (5)

Sepsis, characterized by life-threatening organ dysfunction due to a maladaptive host response to infection, and its more severe form, septic shock, pose significant global health challenges. The incidence of these conditions is increasing, highlighting the need for effective treatment strategies. This review explores the complex pathophysiology of sepsis, emphasizing the role of the endothelium and the therapeutic potential of corticosteroids. The endothelial glycocalyx, critical in maintaining vascular integrity, is compromised in sepsis, leading to increased vascular permeability and organ dysfunction. Corticosteroids have been used for over fifty years to treat severe infections, despite ongoing debate about their efficacy. Their immunosuppressive effects and the risk of exacerbating infections are significant concerns. The rationale for corticosteroid use in sepsis is based on their ability to modulate the immune response, promote cardiovascular stability, and potentially facilitate organ restoration. However, the evidence is mixed, with some studies suggesting benefits in terms of microcirculation and shock reversal, while others report no significant impact on mortality or organ dysfunction. The Surviving Sepsis Campaign provides cautious recommendations for their use. Emerging research highlights the importance of genomic and transcriptomic analyses in identifying patient subgroups that may benefit from corticosteroid therapy, suggesting a move toward personalized medicine in sepsis management. Despite potential benefits, the use of corticosteroids in sepsis requires careful consideration of individual patient risk profiles, and further research is needed to optimize their use and integrate genomic insights into clinical practice. This review underscores the complexity of sepsis treatment and the ongoing need for evidence-based approaches to improve patient outcomes.

Reliability of IL-6 Alone and in Combination for Diagnosis of Late Onset Sepsis: A Systematic Review

Eichberger, J., et al.

Children (Basel, Switzerland). (2024) Vol.11 (4)

Diagnosis of neonatal sepsis is difficult due to nonspecific signs and symptoms. Interleukin-6 (IL-6) is a promising marker for neonatal sepsis. We aimed to test the accuracy of IL-6 in neonates after 72 h of life in case of late onset sepsis (LOS). We searched for studies regarding IL-6 accuracy for the diagnosis of LOS between 1990 and 2020 using the PubMed database. Following study selection, the reported IL-6 sensitivities and specificities ranged between 68% and 100% and 28% and 100%, with median values of 85.7% and 82% and pooled values of 88% and 78% (respectively) in the 15 studies including 1306 infants. Subgroup analysis revealed a better sensitivity (87% vs. 82%), but not specificity (both 86%), in preterm infants compared to term infants or mixed populations. Early sample collection revealed the highest sensitivity (84%), but had the lowest specificity (86%). To assess quality, we used a STARD checklist adapted for septic neonates and the QUADAS criteria. Limitations of this review include the heterogeneous group of studies on the one side and the small number of studies on the other side that analyzed different combinations of biomarkers. We concluded that IL-6 demonstrated good performance especially in the preterm infant population and the best results were achieved by measurements at the time of LOS suspicion.

The Role of Biomarkers in Diagnosis of Sepsis and Acute Kidney Injury

Ferreira, G.S., et al.

Biomedicines. (2024) Vol.12 (5)

Sepsis and acute kidney injury (AKI) are two major public health concerns that contribute significantly to illness and death worldwide. Early diagnosis and prompt treatment are essential for achieving the best possible outcomes. To date, there are no specific clinical, imaging, or biochemical indicators available to diagnose sepsis, and diagnosis of AKI based on the KDIGO criterion has limitations. To improve the diagnostic process for sepsis and AKI, it is essential to continually evolve our understanding of these conditions. Delays in diagnosis and appropriate treatment can have serious consequences. Sepsis and AKI often occur together, and patients with kidney dysfunction are more prone to developing sepsis. Therefore, identifying potential biomarkers for both conditions is crucial. In this review, we talk about the main biomarkers that evolve the diagnostic of sepsis and AKI, namely neutrophil gelatinase-associated lipocalin (NGAL), proenkephalin (PENK), and cell-free DNA.

The role of platelets in sepsis: A review

Xu, X., et al.

Biomolecules & biomedicine. (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.

Role of serum neuron-specific enolase levels in the early diagnosis and prognosis of sepsis-associated encephalopathy: a systematic review and meta-analysis

Pei, M., et al.

Frontiers in neurology. (2024) Vol.15; 1353063.

Background: Sepsis-associated encephalopathy (SAE) is one of the most ubiquitous complications of sepsis and is characterized by cognitive impairment, poor prognosis, and a lack of uniform clinical diagnostic criteria. Therefore, this study investigated the early diagnostic and prognostic value of serum neuron-specific enolase (NSE) in SAE. Methods: This systematic review and meta-analysis systematically searched for clinical trials with serum NSE information in patients with sepsis in the PubMed, Web of Science, Embase, and Cochrane databases from their inception to April 10, 2023. Included studies were assessed for quality and risk of bias using The Quality Assessment of Diagnostic Accuracy-2 tool. The meta-analysis of the included studies was performed using Stata 17.0 and Review Manager version 5.4. Findings: Eleven studies were included in this meta-analysis involving 1259 serum samples from 947 patients with sepsis. Our results showed that the serum NSE levels of patients with SAE were higher than those of the non-encephalopathy sepsis group, and the serum NSE levels of patients with sepsis who died were higher than those of survivors. Conclusion: Elevated serum NSE levels in patients with sepsis are

associated with the early diagnosis of SAE and mortality; therefore, serum NSE probably is a valid biomarker for the early diagnosis and prognosis of patients with SAE. Copyright © 2024 Pei, Yang, Zhang, Huang, Fang, Xu, Lin and He.

Sepsis as a Potential Risk Factor for Upper Gastrointestinal Bleeding in Critically Ill Patients: A Systematic Review and Meta-analysis

Yao, Y., et al.

Journal of intensive care medicine. (2024); 8850666241252048.

Purpose: Sepsis is a common and critical condition in intensive care units (ICUs) known to complicate patient outcomes. Previous studies have indicated an association between sepsis and various ICU morbidities, including upper gastrointestinal bleeding (UGIB). However, the extent of this relationship and its implications in ICU settings remain inadequately quantified. This study aims to elucidate the association between sepsis and the risk of UGIB in ICU patients. Methods: A comprehensive meta-analysis was conducted, encompassing nine studies with a total of nearly 9000 participants. These studies reported events for both sepsis and nonsepsis patients separately. Pooled odds ratios (ORs) were calculated to assess the risk of UGIB in septic versus nonseptic ICU patients. Subgroup analyses were conducted based on age and study design, and both unadjusted and adjusted ORs were examined. Conclusion: This meta-analysis reveals a significant association between sepsis and an increased risk of UGIB in ICU patients, particularly in adults. These findings highlight the need for vigilant monitoring and proactive management of septic ICU patients to mitigate the risk of UGIB. Future research should focus on understanding the underlying mechanisms and developing tailored preventive strategies.

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

Ramoni, D., et al.

Internal and emergency medicine. (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. Copyright © 2024. The Author(s).

Sepsis-Related Lung Injury and the Complication of Extrapulmonary Pneumococcal Pneumonia

Darkwah, S., et al.

Diseases (Basel, Switzerland). (2024) Vol.12 (4)

Globally, sepsis and pneumonia account for significant mortality and morbidity. A complex interplay of immune-molecular pathways underlies both sepsis and pneumonia, resulting in similar and overlapping disease characteristics. Sepsis could result from unmanaged pneumonia. Similarly, sepsis patients have pneumonia as a common complication in the intensive care unit. A significant percentage of pneumonia is misdiagnosed as septic shock. Therefore, our knowledge of the clinical relationship between pneumonia and sepsis is imperative to the proper management of these syndromes. Regarding pathogenesis and etiology, pneumococcus is one of the leading pathogens implicated in both pneumonia and sepsis syndromes. Growing evidence suggests that pneumococcal pneumonia can potentially disseminate and consequently induce systemic inflammation and severe sepsis. Streptococcus pneumoniae could potentially exploit the function of dendritic cells (DCs) to facilitate bacterial dissemination. This highlights the importance of pathogen-immune cell crosstalk in the pathophysiology of sepsis and pneumonia. The role of DCs in pneumococcal infections and sepsis is not well understood. Therefore, studying the immunologic crosstalk between pneumococcus and host immune mediators is crucial to elucidating the pathophysiology of pneumonia-induced lung injury and sepsis. This knowledge would help mitigate clinical diagnosis and management challenges.

Severe mental illness and mortality in sepsis and septic shock: a systematic review and meta-analysis

Lakbar, I., et al.

Molecular psychiatry. (2024)

BACKGROUND: There have been conflicting reports regarding the case-fatality outcomes associated with sepsis and septic shock in patients with severe mental illness (SMI). METHODS: We searched Medline R, Web of Science R and the Cochrane Library R databases (from inception to 4-July-2023) for papers reporting outcomes associated with sepsis and septic shock in adult with (cases) vs. without SMI (controls). The main study outcome was the unadjusted case-fatality rate at hospital discharge, or 30 days if unavailable. Secondary outcomes included the rates of adjusted case-fatality at hospital discharge. CONCLUSION: In conclusion, our study reveals a survival advantage of SMI patients over their non-SMI counterparts. Further research is needed to fully elucidate the mechanisms involved and to develop targeted interventions that can improve the prognosis of both SMI and non-SMI patients facing sepsis.

Therapeutic Effects of Mesenchymal Stem Cell-Derived Extracellular Vesicles in sepsis: a Systematic Review and Meta-Analysis of Preclinical Studies

Aghayan, A.H., et al.

Stem cell reviews and reports. (2024)

BACKGROUND: Sepsis is a life-threatening disorder with no definitive cure. Preclinical studies suggest that extracellular vesicles derived from mesenchymal stromal cells (EV-MSCs) can mitigate inflammatory conditions, potentially leading to increased survival and reduced organ dysfunction during sepsis. Our aim to conduct this systematic review and meta-analysis is assessing the EV-MSCs therapeutic efficacy in sepsis. METHODS: PubMed, Embase, Scopus, WOS and ProQuest databases and also Google Scholar search engine were searched for published articles. We used

hazard ratio (HR) and standardized mean difference (SMD) as effect sizes to evaluate the therapeutic effect of EV-MSCs on survival rate and determine their effect on reducing organ dysfunction, respectively. Finally, we employed GRADE tool for preclinical animal studies to evaluate certainty of the evidence. CONCLUSION: Our results indicate that EV-MSCs can be as promising therapy for sepsis management in animal models and leading to increased survival rate and reduced organ dysfunction. Furthermore, our study introduces a novel tool for risk of bias assessment and provides recommendations based on various analysis. Future studies with aiming to guide clinical translation can utilize the results of this article to establish stronger evidence for EV-MSC effectiveness. Copyright © 2024. The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature.

Unraveling the Intricate Web: Complement Activation Shapes the Pathogenesis of Sepsis-Induced Coagulopathy

Wei, X., et al.

Journal of innate immunity. (2024)

Sepsis-associated coagulopathy specifically refers to widespread systemic coagulation activation accompanied by a high risk of hemorrhage and organ damage, which in severe cases manifests as disseminated intravascular coagulation (DIC), or even develops into multiple organ dysfunction syndrome (MODS). The complement system and the coagulation system as the main columns of innate immunity and hemostasis respectively undergo substantial activation after sepsis. Dysfunction of the complement, coagulation/fibrinolytic cascades caused by sepsis leads to "thromboinflammation", which ultimately amplifies the systemic inflammatory response and accelerates the development of MODS. Recent studies have revealed that massive activation of the complement system exacerbates sepsis-induced coagulation and even results in DIC, which suggests that inhibition of complement activation may have therapeutic potential in the treatment of septic coagulopathy. Sepsis-associated thrombosis involves the upregulation or activation of procoagulant factors, down-regulation or inactivation of anticoagulant factors, and impairment of the fibrinolytic mechanism. This review aims to summarize the latest literature and analyze the underlying molecular mechanisms of the activation of the complement system on the abnormal coagulation cascades in sepsis. Copyright The Author(s). Published by S. Karger AG, Basel.

Unraveling the Multifaceted Role of Glutathione in Sepsis: A Comprehensive Review

Tandon, R. and A. Tandon

Cureus. (2024) Vol.16 (3); e56896.

Sepsis remains a formidable challenge in healthcare, characterized by a dysregulated host response to infection, leading to organ dysfunction and high mortality rates. Glutathione, a critical antioxidant and regulator of cellular redox balance, has emerged as a key player in the pathophysiology of sepsis. This comprehensive review explores the multifaceted role of glutathione in sepsis, focusing on its involvement in oxidative stress, immune modulation, and organ dysfunction. Glutathione depletion exacerbates oxidative damage and inflammatory responses, thereby contributing to the progression of sepsis. Understanding the intricate mechanisms underlying glutathione dysregulation in sepsis offers potential therapeutic avenues, with strategies targeting glutathione pathways showing promise in mitigating septic complications. However, further research is needed to optimize therapeutic approaches and identify biomarkers for patient stratification. Overall, this review underscores the importance of elucidating glutathione's role in

sepsis management to improve clinical outcomes and reduce the global burden of this life-threatening condition. Copyright © 2024, Tandon et al.

Neonatal, paediatric and maternal sepsis

Application of Advanced Molecular Methods to Study Early-Onset Neonatal Sepsis
Kosmeri, C., et al.
International journal of molecular sciences. (2024) Vol.25 (4)
Early-onset sepsis (EOS) is a global health issue, considered one of the primary causes of neonatal mortality. Diagnosis of EOS is challenging because its clinical signs are nonspecific, and blood culture, which is the current gold-standard diagnostic tool, has low sensitivity. Commonly used biomarkers for sepsis diagnosis, including C-reactive protein, procalcitonin, and interleukin-6, lack specificity for infection. Due to the disadvantages of blood culture and other common biomarkers, ongoing efforts are directed towards identifying innovative molecular approaches to diagnose neonates at risk of sepsis. This review aims to gather knowledge and recent research on these emerging molecular methods. PCR-based techniques and unrestricted techniques based on 16S rRNA sequencing and 16S-23S rRNA gene interspace region sequencing offer several advantages. Despite their potential, these approaches are not able to replace blood cultures due to several limitations; however, they may prove valuable as complementary tests in neonatal sepsis diagnosis. Several microRNAs have been evaluated and have been proposed as diagnostic biomarkers in EOS. T2 magnetic resonance and bioinformatic analysis have proposed potential biomarkers of neonatal sepsis, though further studies are essential to validate these findings.

Diagnostic value of maternal, cord blood and neonatal biomarkers for early-onset sepsis: a systematic review and meta-analysis
van Leeuwen, L.M., et al.
Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. (2024)
BACKGROUND: An accurate diagnosis of early-onset sepsis (EOS) is challenging because of subtle symptoms and the lack of a good diagnostic tool, resulting in considerable antibiotic overtreatment. A biomarker, discriminating between infected and non-infected newborns at an early stage of the disease, could improve EOS prediction. Numerous biomarkers have been tested, but have never been compared directly. OBJECTIVES: We aimed to provide a comprehensive overview of early biomarkers and their diagnostic value in maternal samples, umbilical cord blood, and neonatal serum. DATA SOURCES: PubMed-Medline, EMBASE, The Cochrane Library, and Web of Science were searched up to 1 March 2023, without restrictions on publication date, population, or language. STUDY ELIGIBILITY CRITERIA: Articles describing the diagnostic value of at least one biomarker in the detection of EOS in neonates, independent of gestational age, were included. METHODS OF DATA SYNTHESIS: Three independent researchers assessed the articles using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Meta-analysis was performed with all manuscripts describing diagnostic accuracy using a random-effects model. CONCLUSIONS: A biomarker stand-alone test is currently not reliable for direct antibiotic stewardship in newborns, although several biomarkers show promising initial results. Further

research into biomarker combinations could lead to an improved EOS diagnosis, reduce antibiotic overtreatment, and prevent associated health-related problems.

Influence of an Early Human Milk Diet on the Duration of Parenteral Nutrition and Incidence of Late-Onset Sepsis in Very Low Birthweight (VLBW) Infants: A Systematic Review

Coyne, R., et al.

Breastfeeding medicine: the official journal of the Academy of Breastfeeding Medicine. (2024)

Introduction: Human milk is the preferred source of enteral nutrition for very low birthweight (VLBW) infants, and it possibly decreases dependence on parenteral nutrition (PN) and reduces incidence of late-onset sepsis (LOS). No systematic review to date has specifically addressed the value of early versus late introduction of human milk diet (HMD) on duration of PN and incidence of LOS among VLBW infants. Objective: To review the evidence for an early versus late introduction of HMD on duration of PN and incidence of LOS in VLBW infants. Method: Preferred reporting items for systematic reviews and meta-analysis-guided search of EMBASE and PubMed/Medline databases was conducted for this systematic review using phrases addressing population, intervention, comparator, and outcome framework to identify articles published over the past two decades without language restrictions. Full-text articles (both observational and randomized) that studied an early versus late initiation of HMD were included. Mean difference (MD) and relative risk (RR) with 95% confidence intervals (CIs) were calculated for PN and LOS. Quality of evidence was analyzed using UK National Service Framework and the risk-of-bias was assessed using Robvis R. Conclusion: An early HMD may reduce the duration of PN for a growth-restricted VLBW cohort. Observational studies suggesting reduced PN and LOS from early HMD endorse the need for bioactivity-focused human milk research. Variations in feeding guidelines among VLBW infants have the potential to influence neonatal outcomes significantly.

An Overview of Antibiotic Therapy for Early- and Late-Onset Neonatal Sepsis: Current Strategies and Future Prospects

Boscarino, G., et al.

Antibiotics (Basel, Switzerland). (2024) Vol.13 (3)

Neonatal sepsis is a clinical syndrome mainly associated with a bacterial infection leading to severe clinical manifestations that could be associated with fatal sequalae. According to the time of onset, neonatal sepsis is categorized as early- (EOS) or late-onset sepsis (LOS). Despite blood culture being the gold standard for diagnosis, it has several limitations, and early diagnosis is not immediate. Consequently, most infants who start empirical antimicrobial therapy do not have an underlying infection. Despite stewardship programs partially reduced this negative trend, in neonatology, antibiotic overuse still persists, and it is associated with several relevant problems, the first of which is the increase in antimicrobial resistance (AMR). Starting with these considerations, we performed a narrative review to summarize the main findings and the future prospects regarding antibiotics use to treat neonatal sepsis. Because of the impact on morbidity and mortality that EOS and LOS entail, it is essential to start an effective and prompt treatment as soon as possible. The use of targeted antibiotics is peremptory as soon as the pathogen in the culture is detected. Although prompt therapy is essential, it should be better assessed whether, when and how to treat neonates with antibiotics, even those at higher risk. Considering that we are certainly in the worrying era defined as the "post-antibiotic era", it is still essential and urgent to define novel

strategies for the development of antibacterial compounds with new targets or mechanisms of action. A future strategy could also be to perform well-designed studies to develop innovative algorithms for improving the etiological diagnosis of infection, allowing for more personalized use of the antibiotics to treat EOS and LOS.

Prebiotics and sepsis in infants: An updated systematic review and meta-analysis

Qin, Y. and L. Pan

Advances in clinical and experimental medicine: official organ Wroclaw Medical University. (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.

Reintroduction of Legacy Antibiotics in Neonatal Sepsis: The Special Role of Fosfomycin and Colistin

Baltogianni, M., et al.

Antibiotics (Basel, Switzerland). (2024) Vol.13 (4)

Neonatal sepsis is a leading cause of morbidity and mortality in neonates, particularly in low- and middle-income countries. The emergence of antimicrobial resistance is a rapidly growing global problem. A significant proportion of the pathogens that commonly cause neonatal sepsis are resistant to multiple antibiotics. Therefore, for the empirical treatment of neonatal sepsis, the repurposing of older antibiotics that are effective against multidrug-resistant pathogens is being investigated. This review aims to provide an overview of current research and experience using the repurposed antibiotics colistin and fosfomycin for the empirical treatment of neonatal sepsis. Based on current knowledge, colistin and fosfomycin may be potentially helpful for the empirical treatment of sepsis in neonates due to their efficacy against a wide range of pathogens and acceptable safety profile.

Role of diagnostic tests for sepsis in children: a review

Rodgers, O., et al.

Archives of disease in childhood. (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.

Stop in Time: How to Reduce Unnecessary Antibiotics in Newborns with Late-Onset Sepsis in Neonatal Intensive Care

De Rose, D.U., et al.

Tropical medicine and infectious disease. (2024) Vol.9 (3)

The fear of missing sepsis episodes in neonates frequently leads to indiscriminate use of antibiotics, and prescription program optimization is suggested for reducing this inappropriate usage. While different authors have studied how to reduce antibiotic overprescription in the case of early onset sepsis episodes, with different approaches being available, less is known about late-onset sepsis episodes. Biomarkers (such as C-reactive protein, procalcitonin, interleukin-6 and 8, and presepsin) can play a crucial role in the prompt diagnosis of late-onset sepsis, but their role in antimicrobial stewardship should be further studied, given that different factors can influence their levels and newborns can be subjected to prolonged therapy if their levels are expected to return to zero. To date, procalcitonin has the best evidence of performance in this sense, as extrapolated from research on early onset cases, but more studies and protocols for biomarker-guided antibiotic stewardship are needed. Blood cultures (BCs) are considered the gold standard for the diagnosis of sepsis: positive BC rates in neonatal sepsis workups have been reported as low, implying that the majority of treated neonates may receive unneeded drugs. New identification methods can increase the accuracy of BCs and guide antibiotic de-escalation. To date, after 36-48 h, if BCs are negative and the baby is clinically stable, antibiotics should be stopped. In this narrative review, we provide a summary of current knowledge on the optimum approach to reduce antibiotic pressure in late-onset sepsis in neonates.

Please note that some of the abstracts presented above have been edited. Follow the links to see the full originals.

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