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Sepsis

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May 2024

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1. **A Comprehensive Review of the Immunomodulatory Effects of Vitamin D in Sepsis**

Authors: Ahuja, Abhinav;Agrawal, Sachin;Acharya, Sourya and Kumar, Sunil

Publication Date: Feb ,2024

Journal: Cureus 16(2), pp. e53678

Abstract: Sepsis remains a critical global health challenge characterised by a dysregulated immune response to infection, leading to systemic inflammation and organ dysfunction. This review examines the immunomodulatory effects of Vitamin D in sepsis, focusing on its regulation of immune cell function, modulation of cytokine production, and enhancement of antimicrobial responses. While the potential of Vitamin D as an adjunctive therapy in sepsis management is evident, challenges such as variability in Vitamin D status, uncertainties regarding optimal dosages and patient heterogeneity, and potential adverse effects require careful consideration. The review highlights the implications for future research and clinical practice, emphasising the need for standardised measurement protocols, elucidation of optimal supplementation strategies, and integration of Vitamin D assessments into routine care. Despite the complexities, Vitamin D emerges as a promising avenue for personalised interventions in sepsis, necessitating ongoing research collaboration and evidence-based guidelines to harness its full therapeutic potential and improve clinical outcomes. Copyright © 2024, Ahuja et al.

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2. **Determining the Association Between the Origin of Sepsis and the Severity of Sepsis in Intensive Care Unit (ICU) Patients Using Acute Physiology and Chronic Health Evaluation (APACHE) IV.**

Authors: Arumairaj, Antony J.;Habtes, Imnett;Park, Hansang;Valencia-Manrique, Julio C.;Arzu, Jennifer;Mattana, Joseph;Chaudhari, Shobhana;Trenard, Natoushka and Newman, Thomas

Publication Date: Feb ,2024

Journal: Cureus 16(2), pp. e54653

Abstract: Objective The objective of this study is to compare the outcomes of hospital mortality, the requirement of invasive ventilation, vasopressor requirement, duration of vasopressor requirement, and duration of intensive care unit (ICU) stay among the different causes of sepsis and to determine which cause of sepsis had the most severe outcomes. Methods A retrospective chart review was done in critically ill adult patients who were admitted with sepsis to the ICU from July 2017 until July 2019. Acute Physiology and Chronic Health Evaluation (APACHE) IV scores were calculated on patients admitted to ICU on day one of ICU admission. Each patient was then evaluated for outcomes of hospital mortality, need for invasive ventilation, requirement of vasopressors, duration of vasopressors, and duration of ICU stay. The outcomes were then compared between the different sources of sepsis to determine which source of sepsis had the highest severity. Results In total, 176 patients were included in the study. Ninety-three patients were admitted with respiratory sepsis, 26 patients were admitted with gastrointestinal sepsis, 31 patients were admitted with urosepsis, and 26 patients were admitted with other miscellaneous causes of sepsis. The hospital mortality was highest in the respiratory sepsis group at 32%, with a trend towards statistical significance with a P value of 0.057. ICU stay duration was highest in patients with respiratory sepsis at six days, with a statistically significant P value of Copyright © 2024, Arumairaj et al.

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3. **Exploring ncRNA-mediated pathways in sepsis-induced pyroptosis**

Authors: Bhat, Asif Ahmad;Riadi, Yassine;Afzal, Muhammad;Bansal, Pooja;Kaur, Harpreet;Deorari, Mahamedha;Ali, Haider;Shahwan, Moyad;Almalki, Waleed Hassan;Kazmi, Imran;Alzarea, Sami I.;Dureja, Hairsh;Singh, Sachin Kumar;Dua, Kamal and Gupta, Gaurav

Publication Date: Apr ,2024

Journal: Pathology, Research & Practice 256, pp. 155224

Abstract: Sepsis, a potentially fatal illness caused by an improper host response to infection, remains a serious problem in the world of healthcare. In recent years, the role of ncRNA has emerged as a pivotal aspect in the intricate landscape of cellular regulation. The exploration of ncRNA-mediated regulatory networks reveals their profound influence on key molecular pathways orchestrating pyroptotic responses during septic conditions. Through a comprehensive analysis of current literature, we navigate the diverse classes of ncRNAs, including miRNAs, lncRNAs, and circRNAs, elucidating their roles as both facilitators and inhibitors in the modulation of pyroptotic processes. Furthermore, we highlight the potential diagnostic and therapeutic implications of targeting these ncRNAs in the context of sepsis, aiming to cover the method for novel and effective strategies to mitigate the devastating consequences of septic pathogenesis. As we unravel the complexities of this regulatory axis, a deeper understanding of the intricate crosstalk between ncRNAs and pyroptosis emerges, offering promising avenues for advancing our approach to sepsis intervention. The intricate pathophysiology of sepsis is examined in this review, which explores the dynamic interaction between ncRNAs and pyroptosis, a highly regulated kind of programmed cell death. Copyright © 2024 Elsevier GmbH. All rights reserved.

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

Authors: Boscarino, Giovanni;Romano, Rossana;Iotti, Carlotta;Tegoni, Francesca;Perrone, Serafina and Esposito, Susanna

Publication Date: Mar 10 ,2024

Journal: Antibiotics 13(3)

Abstract: 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.

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5. **Early switch from intravenous to oral antibiotic therapy in patients with cancer who have low-risk neutropenic sepsis: the EASI-SWITCH RCT.**

Authors: Coyle, Vicky;Forde, Caroline;Adams, Richard;Agus, Ashley;Barnes, Rosemary;Chau, Ian;Clarke, Mike;Doran, Annmarie;Grayson, Margaret;McAuley, Danny;McDowell, Cliona;Phair, Glenn;Plummer, Ruth;Storey, Dawn;Thomas, Anne;Wilson, Richard and McMullan, Ronan

Publication Date: Mar ,2024

Journal: Health Technology Assessment (Winchester, England) 28(14), pp. 1-101

Abstract: Background: Neutropenic sepsis is a common complication of systemic anticancer treatment. There is variation in practice in timing of switch to oral antibiotics after commencement of empirical intravenous antibiotic therapy. Objectives: To establish the clinical and cost effectiveness of early switch to oral antibiotics in patients with neutropenic sepsis at low risk of infective complications. Design: A randomised, multicentre, open-label, allocation concealed, non-inferiority trial to establish the clinical and cost effectiveness of early oral switch in comparison to standard care. Setting: Nineteen UK oncology centres. Participants: Patients aged 16 years and over receiving systemic anticancer therapy with fever (>= 38degreeC), or symptoms and signs of sepsis, and neutropenia (: Patients aged 16 years and over receiving systemic anticancer therapy with fever (>= 38degreeC), or symptoms and signs of sepsis, and neutropenia (9/l) within 24 hours of randomisation, with a Multinational Association for Supportive Care in Cancer score of >= 21 and receiving intravenous piperacillin/tazobactam or meropenem for /l) within 24 hours of randomisation, with a Multinational Association for Supportive Care in Cancer score of >= 21 and receiving intravenous piperacillin/tazobactam or meropenem for Intervention: Early switch to oral ciprofloxacin (750 mg twice daily) and co-amoxiclav (625 mg three times daily) within 12-24 hours of starting intravenous antibiotics to complete 5 days treatment in total. Control was standard care, that is, continuation of intravenous antibiotics for at least 48 hours with ongoing treatment at physician discretion. Main outcome measures: Treatment failure, a composite measure assessed at day 14 based on the following criteria: fever persistence or recurrence within 72 hours of starting intravenous antibiotics; escalation from protocolised antibiotics; critical care support or death. Results: The study was closed early due to under-recruitment with 129 patients recruited; hence, a definitive conclusion regarding non-inferiority cannot be made. Sixty-five patients were randomised to the early switch arm and 64 to the standard care arm with subsequent intention-to-treat and per-protocol analyses including 125 (intervention n = 61 and control n = 64) and 113 (intervention n = 53 and control n = 60) patients, respectively. In the intention-to-treat population the treatment failure rates were 14.1% in the control group and 24.6% in the intervention group, difference = 10.5% (95% confidence interval 0.11 to 0.22). In the per-protocol population the treatment failure rates were 13.3% and 17.7% in control and intervention groups, respectively; difference = 3.7% (95% confidence interval 0.04 to 0.148). Treatment failure predominantly consisted of persistence or recurrence of fever and/or physician-directed escalation from protocolised antibiotics with no critical care admissions or deaths. The median length of stay was shorter in the intervention group and adverse events reported were similar in both groups. Patients, particularly those with care-giving responsibilities, expressed a preference for early switch. However, differences in health-related quality of life and health resource use were small and not statistically significant. Conclusions: Non-inferiority for early oral switch could not be proven due to trial under-recruitment. The findings suggest this may be an acceptable treatment strategy for some patients who can adhere to such a treatment regimen and would prefer a potentially reduced duration of hospitalisation while accepting increased risk of treatment failure resulting in re-admission. Further research should explore tools for patient stratification for low-risk de-escalation or ambulatory pathways including use of biomarkers and/or point-of-care rapid microbiological testing as an adjunct to clinical decision-making tools. This could include application to shorter-duration antimicrobial therapy in line with other antimicrobial stewardship studies. Trial registration: This trial is registered as ISRCTN84288963. Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 13/140/05) and is published in full in Health Technology Assessment; Vol. 28, No. 14. See the NIHR Funding and Awards website for further award information.; plain-language-summary Neutropenic sepsis, or infection with a low white blood cell count, can occur following cancer treatment. Usually patients receive treatment with intravenous antibiotics (antibiotics delivered into a vein) for two or more days. Patients at low risk of complications from their infection may be able to have a shorter period of intravenous antibiotics benefitting both patients and the NHS. The trial compared whether changing from intravenous to oral antibiotics (antibiotics taken by mouth as tablets or liquid) 12-24 hours after starting antibiotic treatment ('early switch') is as effective as usual care. Patients could take part if they had started intravenous antibiotics for low-risk neutropenic sepsis. Patients were randomly allocated to 'early switch' or to usual care. The main outcome measured was treatment failure. Treatment failure happened if fever persisted or recurred despite antibiotics, if patients needed to change antibiotics, if they needed to be re-admitted to hospital or needed to be admitted to intensive care within 14 days or died. We had originally intended that 628 patients would take part, but after review of the design of the study the number needed to take part was revised to 230. We were not able to complete the trial as planned as unfortunately only 129 patients took part. As the trial was smaller than expected we were

not able to draw conclusions as to whether 'early switch' is no less effective than usual care. Our findings suggest that 'early switch' might result in a shorter time in hospital initially; however, treatment failure was more likely to occur, meaning some patients had to return to hospital for further antibiotics. There were no differences in side effects and no serious complications from treatment or treatment failure (such as intensive care admission or death) among the 65 patients in the 'early switch' group. Patients were satisfied with 'early switch'. Early switch may be a treatment option for some patients with low-risk neutropenic sepsis who would prefer a shorter duration of hospital admission but accept a risk of needing hospital re-admission. Language: English

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

Authors: De Rose, Domenico Umberto;Ronchetti, Maria Paola;Santisi, Alessandra;Bernaschi, Paola;Martini, Ludovica;Porzio, Ottavia;Dotta, Andrea and Auriti, Cinzia

Publication Date: Mar 19 ,2024

Journal: Tropical Medicine & Infectious Disease 9(3)

Abstract: 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.

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7. **Compliance with maternal sepsis guidelines in a tertiary hospital in the Netherlands.**

Authors: de Vries, B. S.;Verschueren, K. J. C.;Jansen, S.;Bekker, V.;Veenhof, M. B. and van den Akker, T.

Publication Date: 2024

Journal: Hospital Practice (1995) , pp. 1-5

Abstract: OBJECTIVES: Sepsis is a common cause of maternal mortality and morbidity. Early detection and rapid management are essential. In this study, we evaluate the compliance with the implemented maternity-specific Early Warning Score (EWS), Rapid Response Team (RRT) protocol and the Surviving Sepsis Campaign (SSC) Hour-1 Bundle in a tertiary hospital in the Netherlands. METHOD(S): We performed a retrospective patient chart review from July 2019 to June 2020 at the Leiden University Medical Centre. We included women who received therapeutic antibiotics and were admitted for at least 24hours. RESULT(S): We included 240 women: ten were admitted twice and one woman three times, comprising 252 admissions. A clinical diagnosis of sepsis was made in 22 women. The EWS was used in 29% (n=73/252) of admissions. Recommendations on the follow-up of the EWS were carried out in 53% (n=46/87). Compliance with the RRT protocol was highest for assessment by a medical doctor within 30minutes (n = 98/117, 84%) and lowest for RRT involvement (n=7/23, 30%). In women with sepsis, compliance with the SSC Bundle was highest for acquiring blood cultures

(n=19/22, 85%), while only 64% (n=14/22) received antibiotics within 60minutes of the sepsis diagnosis. CONCLUSION(S): The adherence to the maternity-specific EWS and the SSC Hour-1 bundle was insufficient, even within this tertiary setting in a high-income country.

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8. **Developments and Trends of Nanotechnology Application in Sepsis: A Comprehensive Review Based on Knowledge Visualization Analysis**

Authors: Fu, Jiaji;Cai, Wentai;Pan, Shangwen;Chen, Lang;Fang, Xiaowei;Shang, You and Xu, Jiqian

Publication Date: Mar 19 ,2024

Journal: Acs Nano 18(11), pp. 7711-7738

Abstract: Sepsis, a common life-threatening clinical condition, continues to have high morbidity and mortality rates, despite advancements in management. In response, significant research efforts have been directed toward developing effective strategies. Within this scope, nanotechnology has emerged as a particularly promising field, attracting significant interest for its potential to enhance disease diagnosis and treatment. While several reviews have highlighted the use of nanoparticles in sepsis, comprehensive studies that summarize and analyze the hotspots and research trends are lacking. To identify and further promote the development of nanotechnology in sepsis, a bibliometric analysis was conducted on the relevant literature, assessing research trends and hotspots in the application of nanomaterials for sepsis. Next, a comprehensive review of the subjectively recognized research hotspots in sepsis, including nanotechnology-enhanced biosensors and nanoscale imaging for sepsis diagnostics, and nanoplatforms designed for antimicrobial, immunomodulatory, and detoxification strategies in sepsis therapy, is elucidated, while the potential side effects and toxicity risks of these nanomaterials were discussed. Particular attention is given to biomimetic nanoparticles, which mimic the biological functions of source cells like erythrocytes, immune cells, and platelets to evade immune responses and effectively deliver therapeutic agents, demonstrating substantial translational potential. Finally, current challenges and future perspectives of nanotechnology applications in sepsis with a view to maximizing their great potential in the research of translational medicine are also discussed.

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9. **Characterisation of Cardiovascular Function**

Authors: Garrity, K., Docherty, C., Mangion, K., McPeake, J. and McCall, P.
Intensive Care Unit Survivors of Sepsis (Conduct-Icu): Early Pilot Phase Results

Publication Date: 2024

Publication Details: Heart. Conference: British Society of Cardiovascular Magnetic Resonance Annual Congress, BSCMR 2023. Glasgow United Kingdom. 110(Supplement 1) (pp A16); BMJ Publishing Group,

Abstract: Background Sepsis is one of the leading causes of Intensive Care Unit (ICU) and hospital admission in the UK. It is now increasingly recognised that admission with sepsis is associated with a long-term risk of adverse cardiovascular events that is comparable to other major risk factors such as hypertension or dyslipidaemia. Many survivors of critical illness are burdened with significant functional impairments following admission. The extent to which chronic cardiovascular dysfunction may play a role in these functional impairments is unclear. Here we report early results from the first few patients participating in CONDUCT-ICU, an observational cohort study examining the role of cardiac dysfunction in functional impairments following admission to intensive care. Methods CONDUCT-ICU is a pilot, prospective observational cohort study combining cardiac magnetic resonance (CMR) imaging, biomarkers and functional outcome measures. We aim to explore the feasibility of CMR imaging in this population, the prevalence of right ventricular (RV) and left ventricular (LV) dysfunction, mechanisms of long-term cardiac injury and dysfunction following critical illness and the relationship between CMR imaging findings, biomarkers and functional outcomes. Patients admitted to ICU with sepsis without previously known cardiovascular disease were prospectively recruited at the point of ICU discharge and subsequently followed up 6-10 weeks following discharge from hospital. CMR imaging was

undertaken at follow-up in addition to the collection of patient-reported outcome measures and inflammatory and cardiac biomarkers. We explored the prevalence of left and right ventricular systolic dysfunction and compared to local control populations. Results 27 patients were recruited to the study, of which 15 were able to attend follow-up and complete CMR imaging. 8 participants were male and 7 participants female. Median left ventricular ejection fraction (LVEF) was 56% (IQR 50-59). Median right ventricular ejection fraction was 52.5% (IQR 44-57). 6 patients (40%) had persisting evidence of left or right ventricular systolic dysfunction despite resolution of their index illness. Conclusion In this small pilot study of ICU survivors without previously diagnosed cardiac dysfunction, sepsis was associated with persisting LV or RV dysfunction in over one third of patients.

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10. **Prehospital early warning scores for adults with suspected sepsis: the PHEWS observational cohort and decision-analytic modelling study.**

Authors: Goodacre, Steve;Sutton, Laura;Ennis, Kate;Thomas, Ben;Hawksworth, Olivia;Iftikhar, Khurram;Croft, Susan J.;Fuller, Gordon;Waterhouse, Simon;Hind, Daniel;Stevenson, Matt;Bradburn, Mike J.;Smyth, Michael;Perkins, Gavin D.;Millins, Mark;Rosser, Andy;Dickson, Jon and Wilson, Matthew

Publication Date: Mar ,2024

Journal: Health Technology Assessment (Winchester, England) 28(16), pp. 1-93

Abstract: Background: Guidelines for sepsis recommend treating those at highest risk within 1 hour. The emergency care system can only achieve this if sepsis is recognised and prioritised. Ambulance services can use prehospital early warning scores alongside paramedic diagnostic impression to prioritise patients for treatment or early assessment in the emergency department. Objectives: To determine the accuracy, impact and cost-effectiveness of using early warning scores alongside paramedic diagnostic impression to identify sepsis requiring urgent treatment. Design: Retrospective diagnostic cohort study and decision-analytic modelling of operational consequences and cost-effectiveness. Setting: Two ambulance services and four acute hospitals in England. Participants: Adults transported to hospital by emergency ambulance, excluding episodes with injury, mental health problems, cardiac arrest, direct transfer to specialist services, or no vital signs recorded. Interventions: Twenty-one early warning scores used alongside paramedic diagnostic impression, categorised as sepsis, infection, non-specific presentation, or other specific presentation. Main outcome measures: Proportion of cases prioritised at the four hospitals; diagnostic accuracy for the sepsis-3 definition of sepsis and receiving urgent treatment (primary reference standard); daily number of cases with and without sepsis prioritised at a large and a small hospital; the minimum treatment effect associated with prioritisation at which each strategy would be cost-effective, compared to no prioritisation, assuming willingness to pay 20,000 per quality-adjusted life-year gained. Results: Data from 95,022 episodes involving 71,204 patients across four hospitals showed that most early warning scores operating at their pre-specified thresholds would prioritise more than 10% of cases when applied to non-specific attendances or all attendances. Data from 12,870 episodes at one hospital identified 348 (2.7%) with the primary reference standard. The National Early Warning Score, version 2 (NEWS2), had the highest area under the receiver operating characteristic curve when applied only to patients with a paramedic diagnostic impression of sepsis or infection (0.756, 95% confidence interval 0.729 to 0.783) or sepsis alone (0.655, 95% confidence interval 0.63 to 0.68). None of the strategies provided high sensitivity (> 0.8) with acceptable positive predictive value (> 0.15). NEWS2 provided combinations of sensitivity and specificity that were similar or superior to all other early warning scores. Applying NEWS2 to paramedic diagnostic impression of sepsis or infection with thresholds of > 4, > 6 and > 8 respectively provided sensitivities and positive predictive values (95% confidence interval) of 0.522 (0.469 to 0.574) and 0.216 (0.189 to 0.245), 0.447 (0.395 to 0.499) and 0.274 (0.239 to 0.313), and 0.314 (0.268 to 0.365) and 0.333 (confidence interval 0.284 to 0.386). The mortality relative risk reduction from prioritisation at which each strategy would be cost-effective exceeded 0.975 for all strategies analysed. Limitations: We estimated accuracy using a sample of older patients at one hospital. Reliable evidence was not available to estimate the effectiveness of prioritisation in the decision-analytic modelling. Conclusions: No strategy is ideal but using NEWS2, in patients with a paramedic diagnostic impression of infection or sepsis could identify one-third to half of sepsis cases

without prioritising unmanageable numbers. No other score provided clearly superior accuracy to NEWS2. Research is needed to develop better definition, diagnosis and treatments for sepsis. Study registration: This study is registered as Research Registry (reference: researchregistry5268). Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 17/136/10) and is published in full in Health Technology Assessment; Vol. 28, No. 16. See the NIHR Funding and Awards website for further award information.; plain-language-summary Sepsis is a life-threatening condition in which an abnormal response to infection causes heart, lung or kidney failure. People with sepsis need urgent treatment. They need to be prioritised at the emergency department rather than waiting in the queue. Paramedics attempt to identify people with possible sepsis using an early warning score (based on simple measurements, such as blood pressure and heart rate) alongside their impression of the patient's diagnosis. They can then alert the hospital to assess the patient quickly. However, an inaccurate early warning score might miss cases of sepsis or unnecessarily prioritise people without sepsis. We aimed to measure how accurately early warning scores identified people with sepsis when used alongside paramedic diagnostic impression. We collected data from 71,204 people that two ambulance services transported to four different hospitals in 2019. We recorded paramedic diagnostic impressions and calculated early warning scores for each patient. At one hospital, we linked ambulance records to hospital records and identified who had sepsis. We then calculated the accuracy of using the scores alongside diagnostic impression to diagnose sepsis. Finally, we used modelling to predict how many patients (with and without sepsis) paramedics would prioritise using different strategies based on early warning scores and diagnostic impression. We found that none of the currently available early warning scores were ideal. When they were applied to all patients, they prioritised too many people. When they were only applied to patients whom the paramedics thought had infection, they missed many cases of sepsis. The NEWS2, score, which ambulance services already use, was as good as or better than all the other scores we studied. We found that using the NEWS2, score in people with a paramedic impression of infection could achieve a reasonable balance between prioritising too many patients and avoiding missing patients with sepsis. Language: English

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11. **Meta-analysis of evaluating neuron specific enolase as a serum biomarker for sepsis-associated encephalopathy.**

Authors: Hu, Jiyun;Xie, Shucai;Xia, Weiping;Huang, Fang;Xu, Biaoxiang;Zuo, Zhihong;Liao, Ya;Qian, Zhaoxin and Zhang, Lina

Publication Date: Apr 20 ,2024

Journal: International Immunopharmacology 131, pp. 111857

Abstract: INTRODUCTION: Brain dysfunction in sepsis is known as Sepsis-associated encephalopathy (SAE), which often results in severe cognitive and neurological sequelae and increases the risk of death. Neuron specific enolase (NSE) may serve as an important neurocritical biomarker for detection and longitudinal monitoring in SAE patients. Our Meta-analysis aimed to explore the diagnostic and prognostic value of serum NSE in SAE patients. Currently, no systematic Review and Meta-analysis have been assessed that NSE as a biomarker of SAE. METHODS: The study protocol was registered in the PROSPERO database (CRD42023398736) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We conducted a systematic review and Meta-analysis to evaluate the serum NSE's diagnostic accuracy for SAE and prognostic strength for probability of death of septic patients. We systematic searched electronic bibliographic databases from PubMed, MEDLINE, Web of Science, Embase, Cochrane databases, CNKI, CQVIP, and WFSD. QUADAS-2 assessment tool was used to evaluate quality and risk of bias of the selected studies. Subgroup analyses, funnel plots, sensitivity analyses were also carried out. Review Manager version 5.4 and Stata16.0. was used for statistical analysis. RESULTS: This Meta-analysis included 22 studies with 1361 serum samples from SAE patients and 1580 serum samples from no-encephalopathy septic (NE) patients. The Meta-analysis showed that individuals with SAE had higher serum NSE level than NE controls (SMD 1.93 (95 % CI 1.51-2.35), P : This Meta-analysis included 22 studies with 1361 serum samples from SAE patients and 1580 serum samples from no-encephalopathy septic (NE) patients. The Meta-analysis showed that individuals with SAE had higher

serum NSE level than NE controls (SMD 1.93 (95 % CI 1.51-2.35), P : This Meta-analysis included 22 studies with 1361 serum samples from SAE patients and 1580 serum samples from no-encephalopathy septic (NE) patients. The Meta-analysis showed that individuals with SAE had higher serum NSE level than NE controls (SMD 1.93 (95 % CI 1.51-2.35), P CONCLUSION: Our Meta-analysis reveals a significant association between elevated NSE concentrations and the increased likelihood of concomitant SAE and mortality during septic patients. This comprehensive analysis will equip ICU physicians with up-to-date insights to accurately identify patients at risk of SAE and implement appropriate intervention strategies to mitigate morbidity and improve neurological outcomes. However, it is important to note that the presence of substantial heterogeneity among studies poses challenges in determining the most effective discrimination cutoff values and optimal sampling collection time. Copyright © 2024 Elsevier B.V. All rights reserved.

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

Authors: Isac, Sebastian;Isac, Teodora;Tanasescu, Maria Daniela;Pavel, Bogdan;Andreescu, Cristina Veronica;Badea, Andrada-Georgiana;Ojog, Damiana;Teodorescu, Geani-Danut;Laceanu, Anca;Trifan, Cristian-Bogdan and Droc, Gabriela

Publication Date: Feb 20 ,2024

Journal: Journal of Personalized Medicine 14(3)

Abstract: 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".

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13. **Obesity Is Associated with Improved Early Survival but Increased Late Mortality in Surgical Patients with Sepsis: A Propensity Matched Analysis.**

Authors: Jalilvand, A.;Ireland, M.;Collins, C.;Kellett, W.;Strassel, S.;Tamer, R.;Wahl, W. and Wisler, J.

Publication Date: 2024

Journal: The Journal of Trauma and Acute Care Surgery (pagination), pp. Date of Publication: 14 Mar 2024

Abstract: INTRODUCTION: While obesity is a risk factor for post-operative complications, its impact following sepsis is unclear. The primary objective of this study was to evaluate the association between obesity and mortality following admission to the surgical ICU (SICU) with sepsis. METHOD(S): We conducted a single center retrospective review of SICU patients grouped into obese (n = 766, BMI >=30 kg/m2) and non-obese (n = 574, BMI 18-29.9 kg/m2) cohorts. Applying 1:1 propensity matching for age, sex, comorbidities, SOFA, and transfer status, demographic data, comorbidities, and sepsis presentation were compared between groups. Primary outcomes included in-hospital and 90-day mortality, ICU length of stay (LOS), need for mechanical ventilation (IMV) and renal replacement therapy (RRT). P METHOD(S): We conducted a single center retrospective review of SICU patients grouped into obese (n = 766, BMI >=30 kg/m2) and non-obese (n = 574, BMI 18-29.9 kg/m2) cohorts.

Applying 1:1 propensity matching for age, sex, comorbidities, SOFA, and transfer status, demographic data, comorbidities, and sepsis presentation were compared between groups. Primary outcomes included in-hospital and 90-day mortality, ICU length of stay (LOS), need for mechanical ventilation (IMV) and renal replacement therapy (RRT). P RESULT(S): Obesity associates with higher median ICU LOS (8.2 vs 5.6, p RESULT(S): Obesity associates with higher median ICU LOS (8.2 vs 5.6, p RESULT(S): Obesity associates with higher median ICU LOS (8.2 vs 5.6, p RESULT(S): Obesity associates with higher median ICU LOS (8.2 vs 5.6, p RESULT(S): Obesity associates with higher median ICU LOS (8.2 vs 5.6, p CONCLUSION(S): Obesity is an independent risk factor for 90-day mortality for surgical patients with sepsis, but its impact appeared later in hospitalization. Understanding differences in systemic responses between these cohorts may be important for optimizing critical care management.III.Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

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14. **Sepsis-Associated Acute Kidney Injury: Where Are We Now?**

Authors: Kounatidis, Dimitris;Vallianou, Natalia G.;Psallida, Sotiria;Panagopoulos, Fotis;Margellou, Evangelia;Tsilingiris, Dimitrios;Karampela, Irene;Stratigou, Theodora and Dalamaga, Maria

Publication Date: 2024

Journal: Medicina (Kaunas, Lithuania)

Abstract: Worldwide, sepsis is a well-recognized cause of death. Acute kidney injury (AKI) may be related to sepsis in up to 70% of AKI cases. Sepsis-associated AKI (SA-AKI) is defined as the presence of AKI according to the Kidney Disease: Improving Global Outcomes criteria in the context of sepsis. SA-AKI is categorized into early, which presents during the first 48 h of sepsis, and late, presenting between 48 h and 7 days of sepsis. SA-AKI is associated with a worse prognosis among patients with sepsis. However, there are different SA-AKI phenotypes as well as different pathophysiological pathways of SA-AKI. The aim of this review is to provide an updated synopsis of the pathogenetic mechanisms underlying the development of SA-AKI as well as to analyze its different phenotypes and prognosis. In addition, potential novel diagnostic and prognostic biomarkers as well as therapeutic approaches are discussed. A plethora of mechanisms are implicated in the pathogenesis of SA-AKI, including inflammation and metabolic reprogramming during sepsis; various types of cell death such as apoptosis, necroptosis, pyroptosis and ferroptosis; autophagy and efferocytosis; and hemodynamic changes (macrovascular and microvascular dysfunction). Apart from urine output and serum creatinine levels, which have been incorporated in the definition of AKI, several serum and urinary diagnostic and prognostic biomarkers have also been developed, comprising, among others, interleukins 6, 8 and 18, osteoprotegerin, galectin-3, presepsin, cystatin C, NGAL, proenkephalin A, CCL-14, TIMP-2 and L-FABP as well as biomarkers stemming from multi-omics technologies and machine learning algorithms. Interestingly, the presence of long non-coding RNAs (lncRNAs) as well as microRNAs (miRNAs), such as PlncRNA-1, miR-22-3p, miR-526b, LncRNA NKILA, miR-140-5p and miR-214, which are implicated in the pathogenesis of SA-AKI, may also serve as potential therapeutic targets. The combination of omics technologies represents an innovative holistic approach toward providing a more integrated view of the molecular and physiological events underlying SA-AKI as well as for deciphering unique and specific phenotypes. Although more evidence is still necessary, it is expected that the incorporation of integrative omics may be useful not only for the early diagnosis and risk prognosis of SA-AKI, but also for the development of potential therapeutic targets that could revolutionize the management of SA-AKI in a personalized manner.

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15. **Sepsis-associated acute kidney injury: recent advances in enrichment strategies, sub-phenotyping and clinical trials**

Authors: Legrand, Matthieu;Bagshaw, Sean M.;Bhatraju, Pavan K.;Bihorac, Azra;Caniglia, Ellen;Khanna, Ashish K.;Kellum, John A.;Koyner, Jay;Harhay, Michael O.;Zampieri, Fernando G.;Zarbock, Alexander;Chung, Kevin;Liu, Kathleen;Mehta, Ravindra;Pickkers, Peter;Ryan, Abigail;Bernholz, Juliane;Dember, Laura;Gallagher, Martin;Rossignol, Patrick, et al

Publication Date: 03 21 ,2024

Journal: Critical Care (London, England) 28(1), pp. 92

Abstract: Acute kidney injury (AKI) often complicates sepsis and is associated with high morbidity and mortality. In recent years, several important clinical trials have improved our understanding of sepsis-associated AKI (SA-AKI) and impacted clinical care. Advances in sub-phenotyping of sepsis and AKI and clinical trial design offer unprecedented opportunities to fill gaps in knowledge and generate better evidence for improving the outcome of critically ill patients with SA-AKI. In this manuscript, we review the recent literature of clinical trials in sepsis with focus on studies that explore SA-AKI as a primary or secondary outcome. We discuss lessons learned and potential opportunities to improve the design of clinical trials and generate actionable evidence in future research. We specifically discuss the role of enrichment strategies to target populations that are most likely to derive benefit and the importance of patient-centered clinical trial endpoints and appropriate trial designs with the aim to provide guidance in designing future trials. Copyright © 2024. The Author(s).

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16. **Vascular leak in sepsis: physiological basis and potential therapeutic advances**

Authors: McMullan, Ross R.;McAuley, Daniel F.;O'Kane, Cecilia M. and Silversides, Jonathan A.

Publication Date: 03 23 ,2024

Journal: Critical Care (London, England) 28(1), pp. 97

Abstract: Sepsis is a life-threatening condition characterised by endothelial barrier dysfunction and impairment of normal microcirculatory function, resulting in a state of hypoperfusion and tissue oedema. No specific pharmacological therapies are currently used to attenuate microvascular injury. Given the prominent role of endothelial breakdown and microcirculatory dysfunction in sepsis, there is a need for effective strategies to protect the endothelium. In this review we will discuss key mechanisms and putative therapeutic agents relevant to endothelial barrier function. Copyright © 2024. The Author(s).

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17. **Navigating the Complexity of Scoring Systems in Sepsis Management: A Comprehensive Review**

Authors: Reddy, Venkat;Reddy, Harshitha;Gemnani, Rinkle;Kumar, Sunil and Acharya, Sourya

Publication Date: Feb ,2024

Journal: Cureus 16(2), pp. e54030

Abstract: This comprehensive review navigates the intricate landscape of sepsis scoring systems, aiming to provide healthcare professionals and researchers with a nuanced understanding of their role in contemporary sepsis management. Beginning with a succinct overview of sepsis, the review emphasizes the significance of scoring systems in standardizing assessments and guiding clinical decision-making. Through a detailed analysis of prominent systems such as SOFA, APACHE, and qSOFA, the review delineates their unique attributes, strengths, and limitations. The implications for sepsis management and patient outcomes are discussed, highlighting the potential for these tools to enhance early detection and intervention. The review concludes with a compelling call to action, urging healthcare professionals to integrate scoring systems into routine practice and researchers to explore novel approaches. By synthesizing current knowledge and addressing future directions, this review serves as a valuable resource for those seeking clarity and guidance in the dynamic landscape of sepsis management. Copyright © 2024, Reddy et al.

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18. **Advances and Challenges in Sepsis Management: Modern Tools and Future Directions**

Authors: Santacroce, Elena;D'Angerio, Miriam;Ciobanu, Alin Liviu;Masini, Linda;Lo Tartaro,

Domenico;Coloretti, Irene;Busani, Stefano;Rubio, Ignacio;Meschiari, Marianna;Franceschini, Erica;Mussini, Cristina;Girardis, Massimo;Gibellini, Lara;Cossarizza, Andrea and De Biasi, Sara

Publication Date: Mar 02 ,2024

Journal: Cells 13(5)

Abstract: Sepsis, a critical condition marked by systemic inflammation, profoundly impacts both innate and adaptive immunity, often resulting in lymphopenia. This immune alteration can spare regulatory T cells (Tregs) but significantly affects other lymphocyte subsets, leading to diminished effector functions, altered cytokine profiles, and metabolic changes. The complexity of sepsis stems not only from its pathophysiology but also from the heterogeneity of patient responses, posing significant challenges in developing universally effective therapies. This review emphasizes the importance of phenotyping in sepsis to enhance patient-specific diagnostic and therapeutic strategies. Phenotyping immune cells, which categorizes patients based on clinical and immunological characteristics, is pivotal for tailoring treatment approaches. Flow cytometry emerges as a crucial tool in this endeavor, offering rapid, low cost and detailed analysis of immune cell populations and their functional states. Indeed, this technology facilitates the understanding of immune dysfunctions in sepsis and contributes to the identification of novel biomarkers. Our review underscores the potential of integrating flow cytometry with omics data, machine learning and clinical observations to refine sepsis management, highlighting the shift towards personalized medicine in critical care. This approach could lead to more precise interventions, improving outcomes in this heterogeneously affected patient population.

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

Authors: Tan, Ruimin;Guo, He;Yang, Zinan;Yang, Huihui;Li, Qinghao;Zhu, Qiong and Du, Quansheng

Publication Date: 2024

Journal: Frontiers in Pharmacology 15, pp. 1358735

Abstract: 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. Results: Thirty-two randomized controlled trials (RCTs) were included in the network meta-analysis. Meta-analysis results showed that while levosimendan significantly improved CI levels at either 0.1 microg/kg/min (mean difference [MD] [95%CrI] = 0.41 [-0.43, 1.4]) or 0.2 microg/kg/min (MD [95%CrI] =0.54 [0.12, 0.99]). Levosimendan, at either 0.075 microg/kg/min (MD [95% CrI] =0.033 [-0.75, 0.82]) or 0.2 microg/kg/min (MD [95% CrI] = -0.014 [-0.26, 0.23]), had no significant advantage in improving Lac levels. Levosimendan, at either 0.1 microg/kg/min (RR [95% CrI] = 0.99 [0.73, 1.3]) or 0.2 microg/kg/min (RR [95% CrI] = 1.0 [0.88, 1.2]), did not have a significant advantage in reducing mortality. 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. Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023441220. Copyrigh t © 2024 Tan, Guo, Yang, Yang, Li, Zhu and Du.

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20. **Association of hospital-treated infectious diseases and infection burden with cardiovascular diseases and life expectancy.**

Authors: Zheng, Jiazhen;Ni, Can;Lee, S. W. Ricky;Li, Fu-Rong;Huang, Jinghan;Zhou, Rui;Huang,

Yining;Lip, Gregory Y. H.;Wu, Xianbo and Tang, Shaojun

Publication Date: May ,2024

Journal: Journal of Internal Medicine 295(5), pp. 679-694

Abstract: BACKGROUND: The association of a broad spectrum of infectious diseases with cardiovascular outcomes remains unclear. OBJECTIVES: We aim to provide the cardiovascular risk profiles associated with a wide range of infectious diseases and explore the extent to which infections reduce life expectancy. METHODS: We ascertained exposure to 900+ infectious diseases before cardiovascular disease (CVD) onset in 453,102 participants from the UK Biobank study. Time-varying Cox proportional hazard models were used. Life table was used to estimate the life expectancy of individuals aged >=50 with different levels of infection burden (defined as the number of infection episodes over time and the number of co-occurring infections). RESULTS: Infectious diseases were associated with a greater risk of CVD events (adjusted HR [aHR] 1.79 [95% confidence interval {CI} 1.74-1.83]). For type-specific analysis, bacterial infection with sepsis had the strongest risk of CVD events [aHR 4.76 (4.35-5.20)]. For site-specific analysis, heart and circulation infections posed the greatest risk of CVD events [aHR 4.95 (95% CI 3.77-6.50)], whereas noncardiac infections also showed excess risk [1.77 (1.72-1.81)]. Synergistic interactions were observed between infections and genetic risk score. A dose-response relationship was found between infection burden and CVD risks (p-trend 1 led to a CVD-related life loss at age 50 by 9.3 years [95% CI 8.6-10.3]) for men and 6.6 years [5.5-7.8] for women. CONCLUSIONS: The magnitude of the infection-CVD association showed specificity in sex, pathogen type, infection burden, and infection site. High genetic risk and infection synergistically increased the CVD risk. Copyright © 2024 The Association for the Publication of the Journal of Internal Medicine.

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21. **Post-Sepsis Syndrome.**

Authors: Leviner, S.

Publication Date: 2021

Journal: Critical Care Nursing Quarterly 44(2), pp. 182-186

Abstract: Sepsis is both common and costly. Successful implementation of guidelines in the acute care setting has decreased mortality and increased the number of sepsis survivors. However, patients returning to the community continue to experience complications related to sepsis and many are poorly prepared to manage these long-term complications. These long-term complications are collectively referred to as post-sepsis syndrome. The purpose of this review is to increase knowledge about post-sepsis syndrome and to compare post-sepsis syndrome with post-intensive care unit syndrome. Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

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