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Sepsis
Current Awareness Bulletin

June 2019

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Title: Modified Sequential Organ Failure Assessment sepsis score in an emergency department setting: Retrospective assessment of prognostic value.

Citation: Emergency Medicine Australasia; Jun 2019; vol. 31 (no. 3); p. 339-346

Author(s): Raymond, Nigel J; Nguyen, Mai; Allmark, Sandra; Woods, Lisa; Peckler, Brad

Objective: Use of the Sequential Organ Failure Assessment (SOFA) score has been proposed by the Third International Consensus Definitions for Sepsis and Septic Shock. The utility in the ED is not yet well established. We retrospectively studied the application of a modified SOFA (mSOFA) score, to assess its ability to predict mortality.

Methods: At our urban tertiary teaching hospital staff recorded patients with probable sepsis in the ED Information System (EDIS). Data was analysed for the year of July 2015 to June 2016. For a sample of the suspected sepsis patients, ED and inpatient clinical records were manually reviewed to ascribe an mSOFA score and assess its performance in predicting mortality, with a primary outcome of death by 30 days.

Results: There were 474 patients recorded over the 1 year with probable sepsis, of whom 228 were manually reviewed. The mSOFA was a significant predictor of mortality at all the time points tested. The 30 day mortality was 22/88 (25%) for those with a positive mSOFA score and 3 out of 140 (2.1%) of those with a negative mSOFA score (OR 15.2, 95% CI [4.4, 52.7]; P < 0.001). This equated to a negative predictive value of 97.9% (95% exact CI 93.9–99.6%).

Conclusion: For ED patients thought likely to have sepsis, the mSOFA score distinguished those with a high or low mortality risk. The high negative predictive value could be practically useful. Prospective study of the mSOFA score used in ED will be needed to validate these observations.

Title: Immature granulocytes index as early marker of sepsis.

Source: International Journal of Laboratory Hematology; Jun 2019; vol. 41 (no. 3); p. 392-396

Author(s): Ayres, Laura S.; Sgnaolin, Vanessa; Munhoz, Terezinha P.

Introduction: Sepsis induces the recruitment of immature neutrophils into the circulation. An immature granulocyte percentage (IG%) count greater than 3% has been shown to be an indicator for the risk of sepsis. The aim of this study was to evaluate the IG% as predictor of sepsis compared to blood culture results and sepsis diagnostic confirmation.

Methods: The study included individuals (n = 301) of both sexes aged ≥18 years who underwent Hospital São Lucas examinations between January and November 2017. For all the patients, IG%, as well as blood culture results, were evaluated. All examinations were obtained from Clinical Laboratory database. Data were analyzed through the SPSS program version 18.0.

Results: There was statistical association between blood culture and IG% results (P = 0.009) and between sepsis confirmation and IG% on Pearson chi-square test (P < 0.001). An IG% cutoff point of 2.0% was able to exclude sepsis based on clinical diagnosis with a specificity of 90.9% and a sensitivity of 38.5%. The cutoff value in ROC analyses of IG% based on blood culture results was 0.3% and 0.4% based on clinical diagnosis.

Conclusion: Our study demonstrated that IG% <2.0% are helpful on the exclusion of sepsis diagnosis with a very high specificity (90.9%). The IG% is a useful additional marker for sepsis diagnosis allowing the early initiation of therapy and better possibilities of recovery.

Title: Risk Factors at Index Hospitalization Associated With Longer-term Mortality in Adult Sepsis Survivors.

Citation: JAMA Network Open; May 2019; vol. 2 (no. 5)

Author(s): Shankar-Hari, Manu; Harrison, David A.; Ferrando-Vivas, Paloma; Rubenfeld, Gordon D.; Rowan, Kathryn

Question: Which generic and sepsis-specific patient characteristics, known during index critical care admission for sepsis, are independently associated with long-term mortality in sepsis survivors?

Findings: In this cohort study of 94 748 adult sepsis survivors, age, male sex, 1 or more severe comorbidities, prehospitalization dependency, nonsurgical status, acute severity of illness, site of infection, and organ dysfunction were independently associated with long-term mortality.

Meaning: Generic and sepsis-specific risk factors, known during index critical care admission for sepsis, could be used to identify a higher-risk sepsis survivor population for targeted strategies aimed at reducing the excess risk of long-term mortality. This cohort study investigates the generic and sepsis-specific patient characteristics that are associated with long-term mortality in patients who survive hospitalization for sepsis.

Importance: Sepsis survivors, defined as adult patients who survived to hospital discharge following a critical care unit admission for sepsis, are at increased risk of long-term mortality. Identifying factors independently associated with long-term mortality, known during critical care admission for sepsis, could inform targeted strategies to reduce this risk.

Objective: To assess, in adult sepsis survivors, factors independently associated with long-term mortality, known during their index critical care admission for sepsis, meeting Third International Consensus Definitions for Sepsis and Septic Shock criteria.

Design, Setting, and Participants: This cohort study included a nationally representative sample of 94 748 adult sepsis survivors from 192 critical care units in England. Participants were identified from consecutive critical care admissions between April 1, 2009, and March 31, 2014, with survival status ascertained as of March 31, 2015. Statistical analyses were completed in June 2017.

Exposures: Generic patient characteristics (age, sex, ethnicity, severe comorbidities [defined using the Acute Physiology and Chronic Health Evaluation II method], dependency, surgical status, and acute illness severity [scored using the Acute Physiology and Chronic Health Evaluation II acute physiology component]) and sepsis-specific patient characteristics (site of infection, number of organ dysfunctions, and septic shock status) known during index critical care admission for sepsis. Main Outcomes and Measures: Long-term mortality in adult sepsis survivors with maximum follow-up of 6 years. Adjusted hazard ratios (HRs) were estimated using Cox regression for both generic and sepsis-specific patient characteristics.

Results: Sepsis survivors had a mean (SD) age of 61.3 (17.0) years, 43 584 (46.0%) were female, and 86 056 (90.8%) were white. A total of 46.3% had respiratory site of infection. By 1 year from hospital discharge, 15% of sepsis survivors had died, with 6% to 8% dying per year over the subsequent 5 years. Age, sex, race/ethnicity, severe comorbidities, dependency, nonsurgical status, and site of infection were independently associated with long-term mortality. Compared with single-organ dysfunction, having 2 or 3 organ dysfunctions was associated with increased risk of long-term mortality (adjusted HR, 1.07; 95% CI, 1.01-1.13; and adjusted HR, 1.18; 95% CI, 1.03-1.14, respectively), while having 4 organ dysfunctions or more was not associated with increased risk. Unexpectedly, the Acute Physiology and Chronic Health Evaluation acute physiology component score had an incremental association with long-term mortality (adjusted HR, 1.11 for every 5-point increase; 95% CI, 1.08-1.13). The adjusted HR for septic shock was 0.89 (95% CI, 0.85-0.92).

Conclusions and Relevance: This study suggests that generic and sepsis-specific risk factors, known during index critical care admission for sepsis, could identify a high-risk sepsis survivor population for biological characterization and designing interventions to reduce long-term mortality.

Title: Sepsis from a cardiovascular perspective.

Citation: British Journal of Cardiac Nursing; May 2019; vol. 14 (no. 5); p. 1-3

Author(s): Cowan, Helen

Abstract: The author focuses on several important issues to consider with regards to sepsis from a cardiovascular perspective, including fluid therapy as a crucial intervention during initial treatment of sepsis, the impact of corticosteroids on death at one month in patients with sepsis, and the safety and efficacy of procalcitonin as a biomarker for sepsis.

Title: Acute kidney injury following contrast media administration in the septic patient: A retrospective propensity-matched analysis

Citation: Journal of Critical Care; Jun 2019; vol. 51 ; p. 111

Author(s): Hinson, Jeremiah S; Nour Al Jalbout; Ehmann, Michael R; Klein, Eili Y

Purpose: To determine the risk for acute kidney injury (AKI) attributable to intravenous contrast media (CM) administration in septic patients.

Materials and methods: This was a single-center retrospective propensity matched cohort analysis performed in the emergency department (ED) of an academic medical center. All visits for patients ≥18 years who met sepsis diagnostic criteria and had serum creatinine (SCr) measured both on arrival to the ED and again 48 to 72 h later were included. Of 4171 visits, 1464 patients underwent contrast-enhanced CT (CECT), 976 underwent unenhanced CT and 1731 underwent no CT at all.

Results: The primary outcome was incidence of AKI. Logistic regression and between-groups odds ratios with and without propensity-score matching were used to test for an independent association between CM administration and AKI. Incidence of AKI was 7.2%, 9.4% and 9.7% in those who underwent CECT, unenhanced CT and no CT. CM administration was not associated with increased incidence of AKI.

Conclusions: Sepsis is a medical emergency proven to benefit from early diagnosis and rapid initiation of treatment, which is often aided by CECT. Our findings argue against withholding CM for fear of precipitating AKI in potentially septic patients.

Title: Adherence to fluid resuscitation guidelines and outcomes in patients with septic shock: Reassessing the "one-size-fits-all" approach

Citation: Journal of Critical Care; Jun 2019; vol. 51 ; p. 94

Author(s): Truong, Tuyet-Trinh N; Dunn, Andrew S; McCardle, Ken; Glasser, Allison; Huprikar, Shirish; Poor, Hooman; Raucher, Beth; Poeran, Jashvant

Objective: The Surviving Sepsis Campaign and Centers for Medicare and Medicaid Services (CMS) Severe Sepsis and Septic Shock Management Bundle (SEP-1) recommend rapid crystalloid infusion (≥30 mL/kg) for patients with sepsis-induced hypoperfusion or septic shock. We aimed to assess compliance with this recommendation, factors associated with non-compliance, and how compliance relates to mortality.

Design: Retrospective, observational study.Setting1136-bed academic and 235-bed community hospital (January 2015–June 2016).

Patients: Patients with septic shock.InterventionsCrystalloid infusion (≥30 mL/kg) within 6 h of identification of septic shock as required by CMS.MeasurementsAssociations with compliance and how compliance associates with mortality; odds ratios (OR) and 95% confidence intervals (CI) reported.

Main results: Overall, 1027 septic shock patients were included. Of these, 486 (47.3%) met the 6-hour 30 ml/kg fluid requirement. Compliance was lower in patients with congestive heart failure (CHF) (40.9%), chronic kidney disease (CKD) (42.3%) or chronic liver disease (38.5%) and among those that were identified in the inpatient setting (35.4%) rather than in the emergency department (51.7%). When adjusting for relevant covariates, compliance (compared to non-compliance) was not associated with in-hospital mortality: OR 1.03 CI 0.76–1.41.

Conclusions: These findings question a "one-size-fits-all" approach to fluid administration and performance measures for patients with sepsis.

Title: The nitric oxide pathway antagonists in septic shock: Meta-analysis of controlled clinical trials

Citation: Journal of Critical Care; Jun 2019; vol. 51 ; p. 34

Author(s): Pascual-Ramirez, Javier; Koutrouvelis, Aristides

Abstract:[...]it showed a deleterious effect for this population in terms of mortality [4]. When this is the case, the use of a tool as meta-analysis may be particularly useful in obtaining meaningful conclusions.2 Methods Electronic searches in Medline, EMBASE and Google Scholar were carried out using the medical subject headings, text words and Boolean operators "nitric oxide synthase" and "clinical trial" and "distributive shock" or "septic shock" up to December 2016. The outcomes analyzed in these RCTs were: hemodynamic (blood pressure, heart rate, cardiac output, systemic vascular resistance, pulmonary vascular resistance, etc) survival, adverse events (acute respiratory or renal deterioration, significant liver damage, severe hematologic abnormalities, cardiac failure, ischemia or dysrhythmia) and disposition issues (length of stay in ICU and/or hospital). Study Action – Agent Target population N = 841 scorestudy N = 791 score control Centers Description Outcomes Petros [11] NOS inhibitor Septic shock 5 6 1 0.3 mg·kg−1 plus 1 mg·kg−1 plus 1 mg·kg−1·h−1 × 6 h Main: hemodynamics NG-monomethyl-L-arginine APACHE II 31 APACHE II 27 Others: survival Bakker/Watson [12,13] NOS inhibitor Septic shock 156 156 48 5 mg·kg−1·h−1 titrated to a maximum 20 mg·kg−1·h−1 × 72 h Main: efficacy as ROS NG-methyl-L-arginine hydrochloride SAPS II 51 SAPS II 55 Others: organ dysfunction, survival López [14] NOS inhibitor Septic shock 439 381 126 2.5 mg·kg−1·h−1 titrated to a maximum 20 mg·kg−1·h−1 × 7–14 days Main: survival NG-methyl-L-arginine hydrochloride SAPS II 52 SAPS II 52 Others: ROS, adverse events Kirov [15] Guanylate cyclase inhibitor Methylene blue Septic shock 10 10 1 2 mg·kg−1 plus 0.25 mg·kg−1·h−1 titrated to a maximum 2 mg·kg−1·h−1 Main: hemodynamics SAPS II 57.8 SAPS II 57.7 Others: ROS, survival, LOS ICU Memis [16] Guanylate cyclase inhibitor Methylene blue Severe sepsis 15 15 1 0.5 mg·kg−1·h−1 × 6 h Main: cytokine levels APACHE II APACHE II Others: Blood pressure, survival 13 14 SOFA 6.2 SOFA 7.06 Kinasewitz [17] NO scavenger Pyridoxilated hemoglobin polyoxyethylene Distributive shock 33 29 15 0.25 ml·kg−1·h−1 for a maximum 100 h Main: survival APACHE II 33 APACHE II 30 Others: hemodynamics, adverse events, LOS ICU Vincent [18] NO scavenger Pyridoxilated hemoglobin polyoxyethylene Distributive shock 183 194 61 0.25 ml·kg−1·h−1 for a maximum 150 h Main: survival SOFA 13.8 SOFA 12.8 Others: adverse events, ROS Table 2 Summary of the included studies.

Title: Risk Factors for Mortality in Pediatric Postsurgical versus Medical Severe Sepsis

Citation: Journal of Surgical Research; Oct 2019; vol. 242 ; p. 100-110

Author(s): Thakkar R.K.; Weiss S.L.; Fitzgerald J.C.; Nadkarni V.M.; Keele L.; Thomas N.J.; Muszynski J.A.; Hall M.W.; et al

Background: Sepsis is a leading cause of morbidity and mortality after surgery. Most studies regarding sepsis do not differentiate between patients who have had recent surgery and those without. Few data exist regarding the risk factors for poor outcomes in pediatric postsurgical sepsis. Our hypothesis is pediatric postsurgical, and medical patients with severe sepsis have unique risk factors for mortality.

Method(s): Data were extracted from a secondary analysis of an international point prevalence study of pediatric severe sepsis. Sites included 128 pediatric intensive care units from 26 countries. Pediatric patients with severe sepsis were categorized into those who had recent surgery (postsurgical sepsis) versus those that did not (medical sepsis) before sepsis onset. Multivariable logistic regression models were used to determine risk factors for mortality.

Result(s): A total of 556 patients were included: 138 with postsurgical and 418 with medical sepsis. In postsurgical sepsis, older age, admission from the hospital ward, multiple organ dysfunction syndrome at sepsis recognition, and cardiovascular and respiratory comorbidities were independent risk factors for death. In medical sepsis, resource-limited region, hospital-acquired infection, multiple

organ dysfunction syndrome at sepsis recognition, higher Pediatric Index of Mortality-3 score, and malignancy were independent risk factors for death.

Conclusion(s): Pediatric patients with postsurgical sepsis had different risk factors for mortality compared with medical sepsis. This included a higher mortality risk in postsurgical patients presenting to the intensive care unit from the hospital ward. These data suggest an opportunity to develop and test early warning systems specific to pediatric sepsis in the postsurgical population.

Title: The Liverpool Peritonsillar abscess Score: Development of a predictive score through a prospective multicentre observational study

Citation: Clinical Otolaryngology; May 2019; vol. 44 (no. 3); p. 293-298

Author(s): Lau A.S.; Ridley P.; Carmichael N.; Selwyn D.M.; Yang D.; Swainbank L.; Metcalfe C.; Watson G.; Emerson H.

Objectives: While uncommon in the population at large, peritonsillar abscess (PTA) is a common subject of ENT referrals. Missed or uncertain diagnosis is a source of concern for non-specialist referrers. In line with the NHS England Second Sepsis Action Plan, we aimed to develop a predictive score for the presence of PTA. This would help to improve non-specialist colleagues' diagnostic certainty as well as to support ENT surgeons' triage of these referrals.

Design(s): Prospective, multicentre observational study. Setting(s): Primary and secondary care. Participant(s): Patients >16 years with symptoms of sore throat.

Data: We prospectively collected comprehensive data on patient demographics, symptoms and clinical status. We documented whether the patient had aspiration-proven PTA or not. We performed binary logistic regression analysis, iterative development of a predictive score which we validated internally.

Result(s): 100 patients were included (46 PTA and 54 tonsillitis). Five variables added significantly to the logistic regression model: unilateral sore throat; trismus; male gender; pharyngeal voice change; and uvular deviation. Using the odds ratio outputs, we developed the Liverpool Peritonsillar abscess Score (LPS) iteratively. We validated the latest (third) iteration of the LPS internally (ie, on the same sample), yielding sensitivity 96%; specificity 85%; positive predictive value 85%; and negative predictive value 96%. The area under the receiver operating characteristics (AUROC) curve was 0.970.

Conclusion(s): We have developed the first predictive score for PTA based on symptoms and signs that do not require the user to have specialist experience. Its high negative predictive value may be particularly helpful to non-specialist colleagues.

Title: Variations in infection sites and mortality rates among patients in intensive care units with severe sepsis and septic shock in Japan

Citation: Journal of Intensive Care; May 2019; vol. 7 (no. 1)

Author(s): Abe T.; Deshpande G.A.; Sugiyama T.; Uchida M.; Nagata I.; Ogura H.; Umemura Y.; Kushimoto S.; Shiraishi A.; Saitoh D.; Fujishima S.; Mayumi T.; Hifumi T.; Shiino Y.; Nakada T.-A.; Tarui T.; Otomo Y.; Okamoto K.; Kotani J.; Sakamoto Y.; Sasaki J.; Shiraishi S.-I.; Takuma K.; Tsuruta R.; Hagiwara A.; Yamakawa K.; Fujimi S.; Masuno T.; Takeyama N.; Yamashita N.; Ikeda H.; Ueyama M.; Gando S.

Background: Accurate and early identification of infection sites might help to drive crucial decisions regarding the treatment of sepsis. We aimed to determine the clinical and etiological features of infection according to sites among patients with severe sepsis in Japan.

Method(s): This secondary analysis of a multicenter, prospective cohort study included 59 intensive care units (ICU) and proceeded between January 2016 and March 2017. The study cohort comprised 1184 adults (>= 16 years) who were admitted to an ICU with severe sepsis and septic shock diagnosed according to the sepsis-2 criteria. Sites of infection diagnosed by physicians in charge at

the time of arrival comprised the lung, abdomen, urinary tract, soft tissue, bloodstream, central nervous system (CNS), and undifferentiated infections. The primary outcome was in-hospital mortality.

Result(s): The most common sites of infection were the lungs (31.0%), followed by intra-abdominal sites (26.3%), the urinary tract (18.4%), and soft tissue (10.9%). The characteristics of the patients with severe sepsis across seven major suspected infection sites were heterogeneous. Septic shock was more frequent among patients with intra-abdominal (72.2%) and urinary tract (70.2%) infections than other sites. The in-hospital mortality rate due to severe sepsis and septic shock of a pooled sample was 23.4% (range, 11.9% [urinary tract infection] to 47.6% [CNS infection]). After adjusting for clinical background, sepsis severity, and stratification according to the presence or absence of shock, variations in hospital mortality across seven major sites of infection remained essentially unchanged from those for crude in-hospital mortality; adjusted in-hospital mortality rates ranged from 7.7% (95%CI, - 0.3 to 15.8) for urinary tract infection without shock to 58.3% (95%CI, 21.0-95.7) for CNS infection with shock in a generalized estimating equation model. Intra-abdominal and urinary tract infections were statistically associated with less in-hospital mortality than pneumonia. Infections of the CNS were statistically associated with higher in-hospital mortality rates than pneumonia in a logistic regression model, but not in the generalized estimating equation model.

Conclusion(s): In-hospital mortality and clinical features of patients with severe sepsis and septic shock were heterogeneous according to sites of infection.

Title: Understanding and Enhancing Sepsis Survivorship: Priorities for Research and Practice.

Citation: American journal of respiratory and critical care medicine; Jun 2019

Author(s): Prescott, Hallie C; Iwashyna, Theodore J; Blackwood, Bronagh; Calandra, Thierry; Chlan, Linda L; Choong, Karen; Connolly, Bronwen; Dark, Paul; Ferrucci, Luigi; Finfer, Simon; Girard, Timothy D; Hodgson, Carol; Hopkins, Ramona O; Hough, Catherine L; Jackson, James C; Machado, Flavia R; Marshall, John C; Misak, Cheryl; Needham, Dale M; Panigrahi, Pinaki; Reinhart, Konrad; Yende, Sachin; Zafonte, Ross; Rowan, Kathryn M; Angus, Derek C; International Sepsis Forum

Abstract: An estimated 14.1 million patients survive sepsis each year. Many survivors experience poor long-term outcomes, including new or worsened neuropsychological impairment, physical disability, and vulnerability to further health deterioration, including recurrent infection, cardiovascular events, and acute renal failure. However, clinical trials and guidelines have focused on shorter-term survival, so there are few data on promoting longer-term recovery. To address this unmet need, the International Sepsis Forum convened a Colloquium in February 2018 on "Understanding and Enhancing Sepsis Survivorship". The goals were to identify (1) gaps and limitations of current research, (2) shorter-term priorities, and (3) longer-term priorities for understanding and enhancing sepsis survivorship. Twenty-six experts from eight countries participated. The top short-term priorities identified by nominal group technique culminating in formal voting were to better leverage existing databases for research, develop and disseminate educational resources on post-sepsis morbidity, and partner with sepsis survivors to define and achieve research priorities. The top longer-term priorities were to study mechanisms of long-term morbidity through large cohort studies with deep phenotyping, build a harmonized global sepsis registry to facilitate enrollment into cohorts and trials, and complete detailed longitudinal follow-up to characterize the diversity of recovery experiences. This Perspective reviews Colloquium discussions, the identified priorities, and current initiatives to address them.

Title: Factors influencing awareness of healthcare providers on maternal sepsis: a mixed-methods approach.

Citation: BMC public health; Jun 2019; vol. 19 (no. 1); p. 683

Author(s): Brizuela, Vanessa; Bonet, Mercedes; Souza, João Paulo; Tunçalp, Özge; Viswanath, Kasisomayajula; Langer, Ana

Background: An awareness campaign set to accompany the Global Maternal Sepsis Study (GLOSS) was launched in 2017. In order to better develop and evaluate the campaign, we sought to understand the factors that influence awareness of maternal sepsis by exploring healthcare providers' knowledge, perception of enabling environments, and perception of severity of maternal sepsis.

Methods: We used a mixed-methods approach that included 13 semi-structured interviews to GLOSS regional and country coordinators and 1555 surveys of providers working in GLOSS participating facilities. Directed content analysis and grounded theory were used for qualitative analysis, based on a framework including four overarching themes around maternal health conditions, determinants of maternal health, barriers and facilitators to sepsis identification and management, plus 24 additional sub-topics that emerged during the interviews. Descriptive statistics for frequencies and percentages were used for the quantitative analysis; significance was tested using Pearson $\chi 2$. Logistic regressions were performed to adjust for selected variables.

Results: Analysis of interviews described limited availability of resources, poor quality of care, insufficient training and lack of protocols as some of the barriers to maternal sepsis identification and management. Analysis from the quantitative survey showed that while 92% of respondents had heard of maternal sepsis only 15% were able to correctly define it and 43% to correctly identify initial management. Provider confidence, perceived availability of resources and of a supportive environment were low (33%, 38%, and 48% respectively). Overall, the predictor that most explained awareness was training. Respondents from the survey and interviewees identified sepsis among the main conditions affecting women at their facilities.

Conclusions: Awareness on maternal sepsis, while acknowledged as important, remains low. Healthcare providers need resources and support to feel confident about the correct identification and management of sepsis, as a prerequisite for the improvement of awareness of maternal sepsis. Similarly, providers need to know about maternal sepsis and its severity to understand the importance of reducing sepsis-related mortality and morbidity. Awareness raising campaigns can help bring neglected maternal health conditions, such as sepsis, to the forefront of global and local agendas.

Title: Soluble CD14 subtype (sCD14-ST) as biomarker in neonatal early-onset sepsis and late-onset sepsis: a systematic review and meta-analysis.

Citation: BMC immunology; Jun 2019; vol. 20 (no. 1); p. 17

Author(s): van Maldeghem, Iris; Nusman, Charlotte M; Visser, Douwe H

Background: Early diagnosis of bacterial sepsis in neonates is hampered by non-specific symptoms and the lack of rapid responding laboratory measures. The biomarker soluble CD14 subtype (sCD14-ST) seems promising in the diagnostic process of neonatal sepsis. In order to evaluate the differences in diagnostic accuracy of sCD14-ST between early onset sepsis (EOS) and late onset sepsis (LOS) we assessed this systematic review and meta-analysis.

Results: Twelve articles were included in the systematic review and 10 in the meta-analysis. There was a high risk of bias on patient selection, index test and/or flow and timing. The overall quality of the included studies was moderate. At sepsis onset a consequently higher level of sCD14-ST was found in septic neonates compared to healthy controls with significant higher levels in LOS compared to EOS. In the first 24 h after sepsis onset a significant increase in pooled means of plasma sCD14-ST levels was seen in EOS ($t(71.6) = 7.3$, $p < .0001$) while this was not seen in LOS or healthy controls. Optimal cut-off values ranged from 305 to 672 ng/l for EOS cases versus healthy controls. The pooled sensitivity was 81% (95%CI: 0.76-0.85), the pooled specificity was 86% (0.81-0.89) with an AUC of 0.9412 (SE 0.1178). In LOS optimal cut-off values ranged from 801 to 885 ng/l with a pooled sensitivity of 81% (0.74-0.86) and a pooled specificity of 100% (0.98-1.00). An AUC and SROC was not estimable in LOS because of the low number of studies.

Conclusions: sCD14-ST is a promising and rapid-responding diagnostic biomarker for EOS and LOS. The difference in pooled means between EOS and LOS underlines the importance to consider EOS and LOS as two different disease entities, requiring separate analysis in original articles and systematic reviews.

Title: Role of disseminated intravascular coagulation in severe sepsis.

Citation: Thrombosis research; Jun 2019; vol. 178 ; p. 182-188

Author(s): Gando, Satoshi; Shiraishi, Atsushi; Yamakawa, Kazuma; Ogura, Hiroshi; Saitoh, Daizoh; Fujishima, Seitaro; Mayumi, Toshihiko; Kushimoto, Shigeki; Abe, Toshikazu; Shiino, Yasukazu; Nakada, Taka-Aki; Tarui, Takehiko; Hifumi, Toru; Otomo, Yasuhiro; Okamoto, Kohji; Umemura, Yutaka; Kotani, Joji; Sakamoto, Yuichiro; Sasaki, Junichi; Shiraishi, Shin-Ichiro; Takuma, Kiyotsugu; Tsuruta, Ryosuke; Hagiwara, Akiyoshi; Masuno, Tomohiko; Takeyama, Naoshi; Yamashita, Norio; Ikeda, Hiroto; Ueyama, Masashi; Fujimi, Satoshi; Japanese Association for Acute Medicine (JAAM) Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis and Trauma (FORECAST) Study Group

Background: Disseminated intravascular coagulation (DIC) associated with multiple organ dysfunction syndrome (MODS) plays pivotal roles in severe sepsis.

Objectives: We performed a multicenter, prospective data collection study and retrospectively analyzed the data to confirm the role of DIC in severe sepsis.

Methods: Eligible patients were ICU patients who met the definitions of severe sepsis, and 1013 patients were included. DIC scores as well as disease severity and the development of MODS on the day of the diagnosis of severe sepsis (day 0) and at day 3 were evaluated. The primary outcome was hospital mortality, and MODS on days 0 and 3 was the secondary outcomes.

Results: The overall mortality rate of severe sepsis was 21.5%, and the prevalence of DIC was 50.9% (516/1013). DIC patients were more seriously ill and exhibited a higher prevalence of MODS (32.0% vs. 13.1%) on day 0 and worse mortality rate (24,8% vs. 17.5%) than non-DIC patients. DIC patients also showed a lower survival probability than non-DIC patients (Log rank p = 0.028). Logistic regression analyses after propensity score adjustment for potential confounders confirmed a significant association between DIC and MODS and hospital death in the patients with severe sepsis. The new development of DIC and persistent DIC from days 0 to 3 were associated with a high incidence of MODS and low survival probability.

Conclusions: The mortality rate of severe sepsis has been improved; however, DIC is still associated with the poor prognosis of these patients. Evaluating the dynamic changes in the DIC status may improve the prediction capability.

Title: Red cell distribution width and its association with mortality in neonatal sepsis.

Citation: The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians; Jun 2019; vol. 32 (no. 12); p. 1925-1930

Author(s): Martin, Snehal L; Desai, Saumil; Nanavati, Ruchi; Colah, Roshan B; Ghosh, Kanjaksha; Mukherjee, Malay B

Objective: Neonatal sepsis is a major cause of mortality in the developing countries. However, with current severity scores and laboratory parameters, predicting outcomes of neonatal sepsis is a serious challenge. Red cell distribution width (RDW) is a readily available pragmatic means to predict outcomes of various comorbidities in adults and children, without causing any additional blood loss. However, its utility in neonates remains unexplored. Hence, the objective of the present study was to evaluate the association of RDW with neonatal sepsis and its role as a predictive marker for mortality.

Methods: This Prospective observational study was carried out in a Level IIIB NICU for a period of 3 years. It involved comparison of RDW values of septic neonates with those of controls (matched for gestational age and birth weight) with an equal allocation ratio. A total of 251 septic neonates along with 251 controls >28 weeks of gestational age were enrolled. The RDW was derived from complete blood count done within first 6 hours of life. After arranging the RDW (median; interquartile range (IQR)), the values were categorized as those above the 50th percentile i.e. ≥20% and those below the 50th percentile i.e. <20%. The cumulative survival rates of the above two groups were assessed using the Kaplan-Meier curve and the log rank test.

Results: RDW levels were significantly higher among the neonatal sepsis cases (19.90%) as compared to the controls (18.90%) with a p value of < .001. RDW was significantly higher amongst the nonsurvivors than survivors (p < .003). Kaplan-Meier curve showed that septic neonates having RDW values ≥20% had significantly increased mortality (p < .02) with a hazard ratio of 0.5.

Conclusions: High RDW is associated with neonatal sepsis and is an independent outcome predictor for mortality associated with neonatal sepsis.

Title: Health-Related Quality of Life Among Survivors of Pediatric Sepsis.

Citation: Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies; Jun 2019; vol. 20 (no. 6); p. 501-509

Author(s): Killien, Elizabeth Y; Farris, Reid W D; Watson, R Scott; Dervan, Leslie A; Zimmerman, Jerry J

Objectives: Mortality from pediatric sepsis has steadily declined over the past several decades; however, little is known about morbidity among survivors. We aimed to determine the prevalence of and risk factors for failure to recover to baseline health-related quality of life following community-acquired pediatric sepsis.DESIGNRetrospective cohort study.

Setting: Seattle Children's Hospital.

Patients: Children aged 1 month to 21 years admitted to the inpatient wards or ICUs from 2012 to 2015 who met 2005 consensus sepsis criteria within 4 hours of hospitalization and were enrolled in the hospital's Outcomes Assessment Program with baseline, admission, and post-discharge health-related quality of life data available.

Interventions: None.

Measurements and Main Results: We assessed health-related quality of life with the Pediatric Quality of Life Inventory for pre-admission baseline, admission, and post-discharge (median, 31 d) status. We determined associations between patient and illness characteristics with failure to recover within 4.5 points of baseline at follow-up (the minimum clinically significant difference between two scores). Of 790 patients, 23.8% failed to recover to baseline health-related quality of life at follow-up. Factors associated with failure to recover were septic shock, older age, private insurance, complex chronic disease, immune compromise, CNS infection or bacteremia, ICU admission, and longer length of stay. On multivariable analysis controlling for time to follow-up, failure to recover was independently associated with septic shock (relative risk, 1.79; 95% CI, 1.24-2.58), older age (relative risk, 1.02/yr; 95% CI, 1.01-1.05), immune compromise (relative risk, 1.83; 95% CI, 1.40-2.40), and length of stay (relative risk, 1.03/d; 95% CI, 1.01-1.04).

Conclusions: Nearly one-quarter of children surviving hospitalization for community-acquired sepsis experienced a clinically significant deterioration in health-related quality of life. We identify risk factors for poor outcomes following sepsis and highlight the need for ongoing evaluation and treatment by primary and specialty care providers for pediatric sepsis survivors after hospital discharge.

Title: The protective role of autophagy in sepsis.

Citation: Microbial pathogenesis; Jun 2019; vol. 131 ; p. 106-111

Author(s): Feng, Ying; Liu, Boyi; Zheng, Xiang; Chen, Li; Chen, Wei; Fang, Zhicheng

Abstract: Sepsis is characterized by life-threatening organ dysfunction caused by a deregulated host response to infection. Autophagy is one of the innate immune defense mechanisms against microbial attack. Previous studies have demonstrated that autophagy is activated initially in sepsis, followed by a subsequent phase of impairment. A number of sepsis-related studies have shown that autophagy plays a protective role in multiple organ injuries partly by clearing pathogens, regulating inflammation and metabolism, inhibiting apoptosis and suppressing immune reactions. In this review, we present a

general overview of and recent advances in the role of autophagy in sepsis and consider the therapeutic potential of autophagy activators in treating sepsis.

Title: Sepsis Presenting in Hospitals versus Emergency Departments: Demographic, Resuscitation, and Outcome Patterns in a Multicenter Retrospective Cohort.

Citation: Journal of hospital medicine; Jun 2019; vol. 14 (no. 6); p. 340-348

Author(s): Leisman, Daniel E; Angel, Catalina; Schneider, Sandra M; D'Amore, Jason A; D'Angelo, John K; Doerfler, Martin E

Background: Differences between hospital-presenting sepsis (HPS) and emergency department-presenting sepsis (EDPS) are not well described.

Objectives: We aimed to (1) quantify the prevalence of HPS versus EDPS cases and outcomes; (2) compare HPS versus EDPS characteristics at presentation; (3) compare HPS versus EDPS in process and patient outcomes; and (4) estimate risk differences in patient outcomes attributable to initial resuscitation disparities.

Design: Retrospective consecutive-sample cohort.

Setting: Nine hospitals from October 1, 2014, to March 31, 2016.PATIENTSAll hospitalized patients with sepsis or septic shock, as defined by simultaneous (1) infection, (2) ≥2 Systemic Inflammatory Response Syndrome (SIRS) criteria, and (3) ≥1 acute organ dysfunction criterion. EDPS met inclusion criteria while physically in the emergency department (ED). HPS met the criteria after leaving the ED.

Measurements: We assessed overall HPS versus EDPS contributions to case prevalence and outcomes, and then compared group differences. Process outcomes included 3-hour bundle compliance and discrete bundle elements (eg, time to antibiotics). The primary patient outcome was hospital mortality.

Results: Of 11,182 sepsis hospitalizations, 2,509 (22.4%) were hospital-presenting. HPS contributed 785 (35%) sepsis mortalities. HPS had more frequent heart failure (OR: 1.31, CI: 1.18-1.47), renal failure (OR: 1.62, CI: 1.38-1.91), gastrointestinal source of infection (OR: 1.84, CI: 1.48-2.29), euthermia (OR: 1.45, CI: 1.10-1.92), hypotension (OR: 1.85, CI: 1.65-2.08), or impaired gas exchange (OR: 2.46, CI: 1.43-4.24). HPS were admitted less often from skilled nursing facilities (OR: 0.44, CI: 0.32-0.60), had chronic obstructive pulmonary disease (OR: 0.53, CI: 0.36-0.78), tachypnea (OR: 0.76, CI: 0.58-0.98), or acute kidney injury (OR: 0.82, CI: 0.68-0.97). In a propensity-matched cohort (n = 3,844), HPS patients had less than half the odds of 3-hour bundle compliant care (17.0% vs 30.3%, OR: 0.47, CI: 0.40-0.57) or antibiotics within three hours (66.2% vs 83.8%, OR: 0.38, CI: 0.32-0.44) vs EDPS. HPS was associated with higher mortality (31.2% vs 19.3%, OR: 1.90, CI: 1.64-2.20); 23.3% of this association was attributable to differences in initial resuscitation (resuscitation-adjusted OR: 1.69, CI: 1.43-2.00).

Conclusions: HPS differed from EDPS by admission source, comorbidities, and clinical presentation. These patients received markedly less timely initial resuscitation; this disparity explained a moderate proportion of mortality differences.

Title: Admission characteristics predictive of in-hospital death from hospital-acquired sepsis: A comparison to community-acquired sepsis.

Citation: Journal of critical care; Jun 2019; vol. 51 ; p. 145-148

Author(s): Padro, Teresa; Smotherman, Carmen; Gautam, Shiva; Gerdik, Cynthia; Gray-Eurom, Kelly; Guirgis, Faheem W

Purpose: Healthcare associated (HA) sepsis is associated with increased resource utilization and mortality compared with community acquired (CA) sepsis. The purpose of this study was to identify independent predictors of in-hospital mortality from HA-sepsis.

Materials And Methods: Retrospective study of adult patients admitted with HA or CA-sepsis. Predictors were identified using logistic regression.

Results: There were 3917 sepsis encounters, of which 3186 were CA and 731 were HA. History of stroke (83/731, 11%) and myocardial infarction (70/731, 10%) were higher in HA than CA-sepsis (stroke: 258/3186, 8%, p = .005; myocardial infarction: 213/3186, 7%, p = .007). HA-sepsis patients required more mechanical ventilation (153/731, 21%) than CA-patients (218/3186, 7%, p < .001) and had a higher rate of vasopressor use (334/731, 46%) than CA patients (832/3186, 26%, p < .001). The HA group had longer ICU lengths of stay (LOS) than CA patients did at 9 days and 2.8 days, respectively (p < .0001). Moderate to severe liver disease (OR = 27, 95%CI 1.4, 513, p = .031) and congestive heart failure (CHF, 5.81, 95% CI 1.3, 26, p = .025) were predictive of in-hospital mortality from HA-sepsis.

Conclusions: Liver disease and CHF were independent predictors of in-hospital mortality in HA-sepsis. HA-sepsis patients had increased prevalence of previous stroke, myocardial infarction, and liver disease.

Title: A worldwide perspective of sepsis epidemiology and survival according to age: Observational data from the ICON audit.

Citation: Journal of critical care; Jun 2019; vol. 51 ; p. 122-132

Author(s): Kotfis, Katarzyna; Wittebole, Xavier; Jaschinski, Ulrich; Solé-Violán, Jordi; Kashyap, Rahul; Leone, Marc; Nanchal, Rahul; Fontes, Luis E; Sakr, Yasser; Vincent, Jean-Louis; ICON Investigators

Purpose: To investigate age-related differences in outcomes of critically ill patients with sepsis around the world.

Methods: We performed a secondary analysis of data from the prospective ICON audit, in which all adult (>16 years) patients admitted to participating ICUs between May 8 and 18, 2012, were included, except admissions for routine postoperative observation. For this sub-analysis, the 10,012 patients with completed age data were included. They were divided into five age groups - ≤50, 51-60, 61-70, 71-80, >80 years. Sepsis was defined as infection plus at least one organ failure.

Results: A total of 2963 patients had sepsis, with similar proportions across the age groups (≤50 = 25.2%; 51-60 = 30.3%; 61-70 = 32.8%; 71-80 = 30.7%; >80 = 30.9%). Hospital mortality increased with age and in patients >80 years was almost twice that of patients ≤50 years (49.3% vs 25.2%, p 70 years was independently associated with increased risk of dying.

Conclusions: The odds for death in ICU patients with sepsis increased with age with the maximal rate of increase occurring between the ages of 71 and 77 years.

Title: Usefulness of qSOFA and SIRS scores for detection of incipient sepsis in general ward patients: A prospective cohort study.

Citation: Journal of critical care; Jun 2019; vol. 51 ; p. 13-18

Author(s): Luo, Jingchao; Jiang, Wei; Weng, Li; Peng, Jinmin; Hu, Xiaoyun; Wang, Chunyao; Liu, Guangyun; Huang, Huibin; Du, Bin

Purpose: To prospectively assess the diagnostic value of quick Sequential Organ Failure Assessment (qSOFA) and systemic inflammatory response syndrome (SIRS) scores for sepsis in ward patients with infections.

Materials And Methods: Consecutive patients admitted with infection or developing infection during hospital stay were included. All variables for calculating qSOFA, SIRS, and SOFA scores were collected, and the maximum scores were determined until hospital discharge, death, or day 28, whichever occurred earlier. The primary outcome was sepsis at 28 days. Diagnostic and prognostic values were assessed using the area under the receiver operating characteristic curve (AUROC) with the conventional cutoff value of 2.

Results: Of 409 general ward patients, 146 patients and 371 patients met qSOFA and SIRS criteria, 229 patients developed sepsis. Although qSOFA score had a better overall diagnostic performance of sepsis (AUROC 0.75 vs. 0.69), it had a much lower sensitivity (53% vs. 98%) and higher specificity (87% vs. 18%) than SIRS score. In addition, qSOFA score had a better prognostic value than SIRS score (AUROC 0.86 vs. 0.67).

Conclusions: Neither SIRS score nor qSOFA score could serve as an ideal screening tool for early identification sepsis, whereas qSOFA score might help to identify patients with higher risk of poor clinical outcome.

Trial Registration: clinicaltrials.gov Identifier: NCT02930070.

Title: Prediction of bloodstream infection caused by extended-spectrum β-lactamase-producing Enterobacterales in patients with suspected community-onset sepsis.

Citation: International journal of antimicrobial agents; Jun 2019; vol. 53 (no. 6); p. 820-829

Author(s): Fröding, Inga; Valik, John Karlsson; Bolinder, Ludvig; Nauclér, Pontus; Giske, Christian G

Objectives: In severe infections, time to appropriate therapy is decisive for survival. Patients with bloodstream infection caused by extended-spectrum β-lactamase-producing Enterobacterales (EPE-BSI) often receive inadequate empirical treatment. This study aimed to identify risk factors, to evaluate a previously suggested risk score and to suggest a new score for facilitating empirical treatment choice.

Methods: Predictors for EPE-BSI were assessed through a retrospective case-control design. The diagnostic performance of the two scores was evaluated. Included patients had blood cultures sampled at four EDs in Stockholm (2012-2015), were admitted, and received antibiotics with activity against Gram-negative bacilli.

Results: A total of 277 EPE-BSI cases and 400 controls were included. The strongest predictor of EPE-BSI was prior EPE-positive culture (cases 33% vs. controls 3%; multivariate (MV) OR = 19.1). Recent EPE-positivity within ≤3 months had a univariate OR of 32.8. Other major predictors were recent prostate biopsy (14% vs. 1%; MV OR = 22.2) and healthcare abroad (6% vs. 2%; MV OR = 3.9). Several previously suggested risk factors were not associated with EPE-BSI. The previously developed Utrecht score had a sensitivity of 54% and a specificity of 77%. The Stockholm score suggested herein (prior EPE-positive culture/prostate biopsy/healthcare abroad) showed comparable sensitivity (50%) but better specificity (96%). Prediction in patients lacking major predictors was difficult and caused high false-positive rates, which would cause unnecessary overtreatment.

Conclusions: Prior EPE-positive culture, especially recently sampled, prostate biopsy and healthcare abroad were the strongest risk factors for community-onset EPE-BSI in Stockholm. Local data are needed when evaluating risk-scoring models before implementation.

Title: SIRS or qSOFA? Is that the question? Clinical and methodological observations from a meta-analysis and critical review on the prognostication of patients with suspected sepsis outside the ICU.

Citation: Internal and emergency medicine; Jun 2019; vol. 14 (no. 4); p. 593-602

Author(s): Franchini, Stefano; Scarallo, Luca; Carlucci, Michele; Cabrini, Luca; Tresoldi, Moreno

Abstract: The purpose of the study was to assess the prognostic performances, in terms of in-hospital mortality, of the quick sequential organ failure assessment (qSOFA) score and the systemic inflammatory response syndrome (SIRS) criteria applied to patients with suspected infection outside the ICU, and to critically reappraise the results and the clinical impact of the SEPSIS-3 study and of the subsequent trials. We performed bivariate meta-analysis, evaluation of the Bayesian post-test probabilities of death, and computation of the unidentified deaths for every 1000 screened cases (UDS1000). The use of qSOFA for screening instead of the SIRS implies a relevant increase in the

UDS1000. However, this difference appears far smaller in the SEPSIS-3 study, largely due to an underestimation of SIRS sensitivity. The increment in the pre-test probability of death implied by a positive qSOFA is higher than that implied by a positivity of the SIRS. However, the included studies use highly variable definitions of "suspected sepsis" and carry very high levels of heterogeneity. SIRS overperforms qSOFA as a rule-out tool for mortality, while qSOFA shows a higher rule-in power. However, the evident lack of consistency across the published studies undermines the significance of both the meta-analytic approach and the reproducibility of the outcomes, and demands for a standardized definition of the target population.

Title: Sepsis patients with complication of hypoglycemia and hypoalbuminemia are an early and easy identification of high mortality risk.

Citation: Internal and emergency medicine; Jun 2019; vol. 14 (no. 4); p. 539-548

Author(s): Furukawa, Makoto; Kinoshita, Kosaku; Yamaguchi, Junko; Hori, Satoshi; Sakurai, Atsushi

Abstract: Either hypoglycemia or hypoalbuminemia alone is an independent condition associated with increased risk of mortality in critical illness. This study evaluates whether the mortality risk increases in septic patients if these conditions are combined. Patients admitted to our hospital from 2008 to 2015 who satisfied the definition of sepsis were targeted (n = 336). We classified cases into three groups based on blood glucose (BG) level measured at admission: hypoglycemia (Hypo-G; BG < 80 mg/dl), intermediate glycemia (Inter-G; 80-199 mg/dl), and hyperglycemia (Hyper-G; ≥ 200 mg/dl) group, and then estimated mortality. We also compared the clinical data of these glycemic groups in combination with hypoalbuminemia (Hypo-A) or Inter-G with non-hypoalbuminemia (Inter-G + Nonhypo-A), as a secondary analysis. Diagnostic cut-off level of Hypo-A (< 2.8 mg/dl) was determined using the ROC curve between blood albumin and mortality. In Hypo-G group (n = 40), APACHE II/SOFA scores are significantly higher than in the Inter-G (n = 196) and Hyper-G groups (n = 100). Mortality is 52.5% in the Hypo-G and 60.0% in the Hypo-G with Hypo-A (Hypo-G + Hypo-A) groups. Significantly higher APACHE II or SOFA scores and mortality are observed in the Hypo-G + Hypo-A group compared to the Inter-G + Nonhypo-A group. A higher mortality risk is observed in cases with Hypo-G + Hypo-A (OR 5.065) than those with Hypo-G (OR 3.503), Inter-G (OR 1.175), Hyper-G (OR 1.756) or Hypo-A (OR 3.243), calculated by a single logistic-regression analysis. Hypo-G + Hypo-A in patients with sepsis is related to higher ICU mortality. Physicians should be keenly aware of these conditions to provide immediate intensive treatment after admission of septic patients.

Title: Immunometabolism: Another Road to Sepsis and Its Therapeutic Targeting.

Citation: Inflammation; Jun 2019; vol. 42 (no. 3); p. 765-788

Author(s): Kumar, Vijay

Abstract: Sepsis is a major health problem all over the world. Despite its existence since the time of Hippocrates (470 BC), sepsis is still a serious medical problem for physicians working in both pediatric and adult intensive care units. The most current US FDA-approved drug called recombinant human activated protein C or Drotrecogin-α is also failed in clinical trials and showed similar effects as placebo. The epidemiological data and studies have indicated sepsis as a major socioeconomic burden all over the world. Advances in immunology and genomic medicine have established different immunological mechanisms as major regulators of the pathogenesis of the sepsis. These immunological mechanisms come into action upon activation of several components of the immune system including innate and adaptive immunity. The activation of these immune cells in response to the pathogens or pathogen-associated molecular patterns (PAMPs) responsible for the onset of sepsis is regulated by the metabolic stage of the immune cells called immunometabolism. An alternation in the immunometabolism is responsible for the generation of dysregulated immune response during sepsis and plays a very important role in the process. Thus, it becomes vital to understand the immunometabolic reprograming during sepsis to design future target-based therapeutics depending on the severity. The current review is designed to highlight the importance of

immune response and associated immunometabolism during sepsis and its targeting as a future therapeutic approach.

Title: Pharmacological management of sepsis in adults with a focus on the current gold standard treatments and promising adjunctive strategies: evidence from the last five years.

Citation: Expert opinion on pharmacotherapy; Jun 2019; vol. 20 (no. 8); p. 991-1007

Author(s): Kyriazopoulou, Evdoxia; Giamarellos-Bourboulis, Evangelos J

Introduction: The last five years, there have been considerable changes in our perception on the pathogenesis of sepsis. This review aims to summarize the current progress of the last five years in the management and research fields of sepsis in a holistic approach. To achieve this, accumulated evidence over the last five years coming from randomized clinical trials (RCTs) and observational studies in adults for the management of sepsis is provided. Areas covered: In this review, the authors discuss available strategies in sepsis, divided into standard-of-care and adjunctive therapies. Standard-of-care approaches comprise antimicrobials, fluids, vasoactive agents, steroids. Antimicrobials remain the mainstay of treatment. However, key-point of management is early recognition of the patient that guides early start of antimicrobials. Patients with suspected infection and any two of: an altered mental state, more than 22 breaths per minute and systolic blood pressure below 100 mmHg should receive early intervention with broad-spectrum antimicrobials and fluids. Expert opinion: Low dose hydrocortisone replacement and fludrocortisone seem promising for the patient at septic shock. Adjunctive macrolide treatment of severe CAP is also associated with survival benefit. Future studies will help to provide additional insight into the field.

Title: Near-infrared spectroscopy to predict organ failure and outcome in sepsis: the Assessing Risk in Sepsis using a Tissue Oxygen Saturation (ARISTOS) study.

Citation: European journal of emergency medicine : official journal of the European Society for Emergency Medicine; Jun 2019; vol. 26 (no. 3); p. 174-179

Author(s): Macdonald, Stephen P J; Kinnear, Frances B; Arendts, Glenn; Ho, Kwok M; Fatovich, Daniel M

Objectives: Sepsis is acute organ dysfunction in the setting of infection. An accurate diagnosis is important to guide treatment and disposition. Tissue oxygen saturation (StO2) can be estimated noninvasively by near-infrared spectroscopy (NIRS), and may be an indicator of microcirculatory dysfunction in early sepsis. We aimed to determine the utility of StO2 for sepsis recognition and outcome prediction among patients presenting to the emergency department (ED) with infection.

Patients and Methods: A multicentre, prospective, observational cohort study recruited patients who were being admitted to hospital with infection. StO2 was measured in the ED using a handheld NIRS device, Inspectra 300. Outcomes were sepsis, defined as an increase in sequential organ failure assessment score of at least 2 points within 72 h, and composite in-hospital mortality/ICU admission at least 3 days.

Results: A cohort of 323 participants, median age 64 (interquartile range: 47-77) years, was recruited at three Australian hospitals. 143 (44%) fulfilled the criteria for sepsis and 22 (7%) died within 30 days. The mean ± SD StO2 was 74 ± 8% in sepsis and 78 ± 7% in nonsepsis ($P < 0.0001$). StO2 correlated with the peak sequential organ failure assessment score (Spearman's ρ -0.27, $P < 0.0001$). Area under the receiver operating characteristic curve was 0.66 (95% confidence interval: 0.60-0.72) for sepsis and 0.66 (0.58-0.75) for the composite outcome. StO2 less than 75% had an odds ratio of 2.67 (1.45-4.94; $P = 0.002$), for the composite outcome compared with StO2 at least 75%.

Conclusion: NIRS-derived StO2 correlates with organ failure and is associated with outcome in sepsis. However, its ability to differentiate sepsis among ED patients with infection is limited. NIRS cannot be recommended for this purpose.

Title: Natural killer cells in sepsis: Underprivileged innate immune cells.

Citation: European journal of cell biology; Jun 2019; vol. 98 (no. 2-4); p. 81-93

Author(s): Kumar, Vijay

Abstract: Sepsis is a devastating health condition originating due to the dysregulated immune response in response to the severe systemic infection. The innate immune system serves as the first line of defense against invading pathogens, and the failure to clear the infection leads to the development of sepsis via generation of a proinflammatory immune response. Natural Killer (NK) cells are highly recognized potent innate immune cells that play a very important role in the generation of an antiviral and antitumor immune response. These are also unique innate immune cells due to the existence of NK cell-mediated memory due to the process of education and learning as shown by the cells of adaptive immunity. However, developing data has shown the importance of NK cells in mounting a potent immune response against invading bacterial pathogens that if not contained accordingly may lead to the development of sepsis. Thus, the present review article is designed to highlight the previously unrecognized function of NK cells during sepsis as indicated by both clinical and experimental animal-based findings. However, a brief introduction regarding their development, subtypes, and function is also mentioned before describing their role in sepsis. Thereafter, the subsequent section is included describing the NK cell immunometabolic reprogramming during homeostasis, infection, and sepsis. NK cell immune memory and their therapeutic targeting to manage the sepsis as a future therapeutic approach emphasized before closing the manuscript.

Title: Seizure comorbidity boosts odds of 30-day readmission after an index hospitalization for sepsis.

Citation: Epilepsy & behavior : E&B; Jun 2019; vol. 95 ; p. 148-153

Author(s): Fox, Jonah; Lekoubou, Alain; Bishu, Kinfe G; Ovbiagele, Bruce

Objective: The objective of this study was to evaluate the association between comorbid seizures and hospital readmissions within 30 days following an index hospitalization for sepsis.

Methods: We analyzed data from 445,489 adult discharges derived from the 2014 National Readmission Database, to evaluate the association of an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis of seizure during an index hospitalization for sepsis and 30-day readmission rates. We excluded patients who died during hospitalization and those who had missing information on the length of stay or were discharged in December 2014. Prespecified groups were compared by their 30-day readmission and seizure status. We applied a multivariable logistic regression analysis to assess the independent association between seizure and readmission.

Results: Nearly one out of 15 patients discharged with a primary diagnosis of sepsis had comorbid seizures, of which 97% were status epilepticus. Patients with sepsis and comorbid seizures were 30% more likely to be readmitted within 30-days postdischarge, compared to those with sepsis and no comorbid seizures. Additional factors associated with a significantly higher risk for hospital readmission included male sex, age 45-84 years, increased length of stay and cost of primary admission, greater medical comorbidities, and discharge destination. Patients with seizures during their index hospitalization were significantly more likely to have also had a concurrent stroke or the central nervous system (CNS) infection compared with patients without seizures.

Conclusions: Seizures are not uncommon, and patients with sepsis and comorbid seizures are 30% more likely to be readmitted within 30-days postdischarge, compared to those with sepsis and no comorbid seizures.

Title: Precision medicine in pediatric sepsis.

Citation: Current opinion in pediatrics; Jun 2019; vol. 31 (no. 3); p. 322-327

Author(s): Atreya, Mihir R; Wong, Hector R

Purpose of Review: Pediatric sepsis is a heterogeneous state associated with significant morbidity and mortality, but treatment strategies are limited. Clinical trials of immunomodulators in sepsis have shown no benefit, despite having a strong biological rationale. There is considerable interest in application of a precision medicine approach to pediatric sepsis to identify patients who are more likely to benefit from targeted therapeutic interventions.

Recent Findings: Precision medicine requires a clear understanding of the molecular basis of disease. 'Omics data' and bioinformatics tools have enabled identification of endotypes of pediatric septic shock, with corresponding biological pathways. Further, using a multibiomarker-based approach, patients at highest risk of poor outcomes can be identified at disease onset. Enrichment strategies, both predictive and prognostic, may be used to optimize patient selection in clinical trials and identify a subpopulation in whom therapy of interest may be trialed. A bedside-to-bench-to-bedside model may offer clinicians pragmatic tools to aid in decision-making.

Summary: Precision medicine approaches may be used to subclassify, risk-stratify, and select pediatric patients with sepsis who may benefit from new therapies. Application of precision medicine will require robust basic and translational research, rigorous clinical trials, and infrastructure to collect and analyze big data.

Title: Quality of Life and 1-Year Survival in Patients With Early Septic Shock: Long-Term Follow-Up of the Australasian Resuscitation in Sepsis Evaluation Trial.

Citation: Critical care medicine; Jun 2019; vol. 47 (no. 6); p. 765-773

Author(s): Higgins, Alisa M; Peake, Sandra L; Bellomo, Rinaldo; Cooper, D Jamie; Delaney, Anthony; Harris, Anthony H; Howe, Belinda D; Nichol, Alistair D; Webb, Steve A; Williams, Patricia J; Australasian Resuscitation in Sepsis Evaluation (ARISE) Investigators and the ANZICS Clinical Trials Group

Objectives: To examine long-term survival and quality of life of patients with early septic shock.

Design: Prospective, randomized, parallel-group trial.

Setting: Fifty-one hospitals in Australia, New Zealand, Finland, Hong Kong, and the Republic of Ireland.

Patients: One-thousand five-hundred ninety-one patients who presented to the emergency department with early septic shock between October 2008 and April 2014, and were enrolled in the Australasian Resuscitation in Sepsis Evaluation trial.

Interventions: Early goal-directed therapy versus usual care.

Measurements and Main Results: Long-term survival was measured up to 12 months postrandomization. Health-related quality of life was measured using the EuroQoL-5D-3L, Short Form 36 and Assessment of Quality of Life 4D at baseline, and at 6 and 12 months following randomization. Mortality data were available for 1,548 patients (97.3%) and 1,515 patients (95.2%) at 6 and 12 months, respectively. Health-related quality of life data were available for 85.1% of survivors at 12 months. There were no significant differences in mortality between groups at either 6 months (early goal-directed therapy 21.8% vs usual care 22.6%; p = 0.70) or 12 months (early goal-directed therapy 26.4% vs usual care 27.9%; p = 0.50). There were no group differences in health-related quality of life at either 6 or 12 months (EuroQoL-5D-3L utility scores at 12 mo early goal-directed therapy 0.65 ± 0.33 vs usual care 0.64 ± 0.34; p = 0.50), with the health-related quality of life of both groups being significantly lower than population norms.

Conclusions: In patients presenting to the emergency department with early septic shock, early goal-directed therapy compared with usual care did not reduce mortality nor improve health-related quality of life at either 6 or 12 months.

Title: Drugs for the Prevention and Treatment of Sepsis in the Newborn.

Citation: Clinics in perinatology; Jun 2019; vol. 46 (no. 2); p. 327-347

Author(s): Mukhopadhyay, Sagori; Wade, Kelly C; Puopolo, Karen M

Abstract: Antimicrobial medications are the most commonly used medications in the neonatal intensive care unit. Antibiotics are used for infection prophylaxis, empiric treatment, and definitive treatment of confirmed infection. The choice of medication should be informed by the epidemiology and microbiology of infection in specific clinical scenarios and by the clinical condition of the infant. Understanding evolving pathogen susceptibility to antimicrobials and key pharmacotherapy determinants in neonates can inform optimal antibiotic use.

Title: Neutrophil pyroptosis: new perspectives on sepsis.

Citation: Cellular and molecular life sciences : CMLS; Jun 2019; vol. 76 (no. 11); p. 2031-2042

Author(s): Liu, Lu; Sun, Bingwei

Abstract: Pyroptosis is a caspase-1 or caspase-4/5/11-dependent programmed cell death associated with inflammation, which is initiated by inflammasomes or cytosolic LPS in innate immunity. Sepsis is a life-threatening organ dysfunction caused by an imbalance in the body's response to infection. It is a complex interaction between the pathogen and the host's immune system. Neutrophils play the role of a double-edged sword in sepsis, and a number of studies have previously shown that regulation of neutrophils is the most crucial part of sepsis treatment. Pyroptosis is one of the important forms for neutrophils to function, which is increasingly understood as a host active immune response. There is ample evidence that neutrophil pyroptosis may play an important role in sepsis. In recent years, a breakthrough in pyroptosis research has revealed the main mechanism of pyroptosis. However, the potential value of neutrophil pyroptosis in the treatment of sepsis did not draw enough attention. A literature review was performed on the main mechanism of pyroptosis in sepsis and the potential value of neutrophils pyroptosis in sepsis, which may be suitable targets for sepsis treatment in future.

Title: Hypertonic Saline in Human Sepsis: A Systematic Review of Randomized Controlled Trials.

Citation: Anesthesia and analgesia; Jun 2019; vol. 128 (no. 6); p. 1175-1184

Author(s): Orbegozo, Diego; Vincent, Jean-Louis; Creteur, Jacques; Su, Fuhong

Abstract: The role of hypertonic saline in sepsis remains unclear because clinical data are limited and the balance between beneficial and adverse effects is not well defined. In this systematic literature review, we searched PubMed and Embase to identify all randomized controlled trials up until January 31, 2018 in which hypertonic saline solutions of any concentration were used in patients of all ages with sepsis and compared to a cohort of patients receiving an isotonic fluid. We identified 8 randomized controlled trials with 381 patients who had received hypertonic saline. Lower volumes of hypertonic saline than of isotonic solutions were needed to achieve the desired hemodynamic goals (standardized mean difference, -0.702; 95% CI, -1.066 to -0.337; P < .001; moderate-quality evidence). Hypertonic saline administration was associated with a transient increase in sodium and chloride concentrations without adverse effects on renal function (moderate-quality evidence). Some data suggested a beneficial effect of hypertonic saline solutions on some hemodynamic parameters and the immunomodulatory profile (very low-quality evidence). Mortality rates were not significantly different with hypertonic saline than with other fluids (odds ratio, 0.946; 95% CI, 0.688-1.301; P = .733; low-quality evidence). In conclusion, in our meta-analysis of studies in patients with sepsis, hypertonic saline reduced the volume of fluid needed to achieve the same hemodynamic targets but did not affect survival.

Title: Assessing Fluid Resuscitation in Adults with Sepsis Who Are Not Mechanically Ventilated: a Systematic Review of Diagnostic Test Accuracy Studies.

Citation: Journal of general internal medicine; May 2019

Author(s): Seccombe, Adam; McCluskey, Lauren; Moorey, Hannah; Lasserson, Daniel; Sapey, Elizabeth

Background: Fluid resuscitation is a widely used intervention that is mandated in the management of sepsis. While its use can be life-saving, its overuse is associated with harm. Despite this, the best means of assessing a need for fluid resuscitation in an acute medical setting is unclear.

Objective: To assess studies of diagnostic tests that identify the need for fluid resuscitation in adults with sepsis, as defined by the presence of fluid responsiveness.

Design: Protocol registration was performed in advance (PROSPERO:CRD42017048651). Research database searches were performed alongside additional searches to identify grey literature. Diagnostic test accuracy studies that assessed any fluid assessment tool were identified independently by two authors, before data extraction and quality assessments were performed.

Participants: Adults with sepsis, without intensive care organ support, who would be appropriate for admission to an acute medical unit.

Key Results: Of the 26,841 articles that were screened, 14 studies were identified for inclusion, involving a combined total of 594 patients. Five categories of index test were identified: inferior vena cava collapsibility index (IVCCI), haemodynamic change with passive leg raise, haemodynamic change with respiration, haemodynamic change with intravenous fluid administration, and static assessment tools. Due to the high level of clinical heterogeneity affecting all aspects of study design, quantitative analysis was not feasible. There was a lack of consensus on reference tests to determine fluid responsiveness.

Conclusion: While fluid resuscitation is considered a key part of the management of sepsis, evidence to support fluid assessment in awake adults is lacking. This review has highlighted a number of research recommendations that should be addressed as a matter of urgency if patient harm is to be avoided.

Title: The cancer control status and APACHE II score are prognostic factors for critically ill patients with cancer and sepsis.

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Background/Purpose: Patients with cancer are eligible for hospice care when their life expectancy is 180 days or shorter. This study investigated the prognostic factors of patients with cancer and sepsis who were admitted to an intensive care unit (ICU) to assist with clinical decisions of hospice care.

Methods: A series of 279 patients admitted to the medical ICU with cancer and sepsis were included. Another series of 109 patients with cancer and sepsis admitted to the other medical ICU in the different branch of our hospital was included to verify the results.

Results: Among 279 patients, the 30-, 90-, and 180-day mortality rates were 47.3%, 72.0%, and 81.0%, respectively. APACHE II score and the cancer control status (controlled or remission (CR), active newly diagnosed (AND) and active recurrent or progressive (ARP)) were significant predictors of 30- and 90-day mortality(30-day: AND(odds ratio: 5.66; 95% confidence interval: 2.12-15.15), ARP(6.24; 2.92-13.33), APACHE II(1.07; 1.03-1.11); 90-day: AND(4.78; 1.91-11.99), ARP(24.03; 11.11-51.99), APACHE II(1.07; 1.02-1.19)) and were associated with a poor 180-day outcome. The 180-day mortality were significantly different among the patients with different cancer control status in the series of 279 patients (CR: 29.8%; AND: 69.4%; and ARP: 98.9 %) and that of 109 patients (46.4%; 96.8%; and 94.0%).

Conclusion: APACHE II score and the cancer control status may be the prognostic factors for critically ill patients with cancer and sepsis, and they may be helpful for evaluating hospice care.

Sources Used:

The following databases are used in the creation of this bulletin: BNI, CINAHL, EMBASE & Medline.

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