SEPSIS BULLETIN
September/October 2020

Sepsis

Proenkephalin Compared to Conventional Methods to Assess Kidney Function in Critically Ill Sepsis Patients
Beunders R et al
Shock. 2020;54(3):308-14
BACKGROUND: The assessment of renal function in clinical practice remains challenging. Using creatinine to assess the glomerular filtration rate (GFR) is notoriously inaccurate, and determination of the true GFR, e.g., using inulin or iohexol, is laborious and not feasible in daily practice. Proenkephalin (PENK) is a novel candidate biomarker for kidney function that is filtrated in the glomerulus, has shown to represent steady-state GFR in patients with different severities of renal insufficiency. In this pilot study in non-steady-state critically ill patients, we compared plasma PENK concentrations with creatinine-based GFR assessments and validated both against the "true GFR" measured using a gold standard method: iohexol plasma clearance. CONCLUSIONS: In this pilot study in non-steady-state critically ill sepsis patients, GFR appears to be more accurately reflected by plasma PENK concentrations compared to conventional creatinine-based methods. Therefore, PENK holds promise as an accurate and feasible biomarker to determine kidney function during non-steady-state conditions in the critically ill.

Sequential Changes of NLRP3 Inflammasome Activation in Sepsis and its Relationship With Death
Garnacho-Montero J et al
Shock. 2020;54(3):294-300
INTRODUCTION: Inflammasomes are recognized as key components of the innate immune response in sepsis. We aimed to describe the transcriptional expression of nucleotide-binding domain, leucine-rich repeat-containing receptor, pyrin domain-containing-3 (NLRP3), and serum interleukin-1beta (IL-1 beta) in critically ill patients, their changes over the first week and their prognostic value in septic patients. CONCLUSIONS: NLRP3 is activated in critically ill patients but this up-regulation is more intense in patients with sepsis. In sepsis, a sustained NLRP3 activation during the first week is protective and sepsis. An increased caspase-1 protein expression with reduced expression caspase-3 is the pattern observed in septic shock patients who survive.

The Value of Serum Uncoupling Protein-2 Level for the Patients With Sepsis
Huang W et al
Shock. 2020;54(3):301-7
BACKGROUND: To investigate the potential utility of serum uncoupling protein-2 (UCP2) level as a biomarker in septic

patientsCONCLUSION: Serum UCP2 levels at admission were markedly increased in patients with sepsis, which is useful for early diagnose and prognostic prediction. UCP2 is a potential biomarker for sepsis, or even a subtype of sepsis.

Hemodynamic Impact of Cardiovascular Antihypertensive Medications in Patients With Sepsis-Related Acute Circulatory Failure

de Roquetaillade C et al

Shock. 2020;54(3):315-20

BACKGROUND: Impact of prior cardiovascular antihypertensive medication during the initial phase of septic shock in terms of catecholamine requirements and mortality has been poorly investigated and remains unclear. OBJECTIVES: To investigate the association between chronic prescription of cardiovascular antihypertensive medication prior to intensive care unit (ICU) admission, catecholamine requirement, and mortality in patients with septic shock. CONCLUSION: In patients admitted with septic shock, prior cardiovascular antihypertensive medication seems to have limited impact on initial hemodynamic failure and catecholamine requirement.

Evaluation of the Initiation Timing of Hydrocortisone in Adult Patients With Septic Shock

Sacha GL et al

Shock. 2020;Publish Ahead of Print

INTRODUCTION: Clinical studies evaluating the use of hydrocortisone in patients with septic shock are heterogeneous in design with conflicting results. The appropriate time in which to initiate hydrocortisone after shock onset is unknown. This study sought to compare clinical outcomes including vasopressor duration and mortality in patients with septic shock who received hydrocortisone based on timing of initiation after shock onset. CONCLUSIONS: In patients in whom hydrocortisone is prescribed for vasopressor-dependent septic shock, timing is crucial and hydrocortisone should be started within the first 12 hours after shock onset.

Presepsin Values Predict Septic Acute Kidney Injury, Acute Respiratory Distress Syndrome, Disseminated Intravascular Coagulation, and Shock

Shimoyama Y et al

Shock. 2020;Publish Ahead of Print

BACKGROUND: Sepsis remains a major cause of mortality in critically ill patients. This study aimed determine whether presepsin is a predictor of septic AKI, ARDS, DIC, and shock. CONCLUSION: Presepsin is a predictor of septic AKI, ARDS, and DIC. Combining presepsin values with GPS improved the specificity for predicting septic ARDS relative to using baseline presepsin values alone.

Effect of Early Central Venous Catheterization On Mortality Among Patients with Severe Sepsis: A Nationwide Inpatient Database Study

Edakubo S et al

Shock. 2020;Publish Ahead of Print

BACKGROUND: Clinical guidelines for the management of sepsis have accelerated the utilization of central venous catheterization (CVC). However, risks associated with CVC may be high in the initial phase of severe sepsis because of patient instability. The timing of CVC itself has not been fully evaluated. Therefore, we aimed to assess the association between CVC in the initial care of patients with severe sepsis and corresponding mortality rates. CONCLUSIONS: Among patients with severe sepsis, early CVC was not associated with improved in-hospital mortality rates.

Temporal Differential Expression of Physiomarkers Predicts Sepsis in Critically Ill Adults

Mohammed A et al

Shock. 2020;Publish Ahead of Print

BACKGROUND: Sepsis is a life-threatening condition with high mortality rates. Early detection and treatment are critical to improving outcomes. Our primary objective was to develop artificial intelligence capable of predicting sepsis earlier using a minimal set of streaming physiological data in real-time. CONCLUSIONS: This study demonstrates that salient physiomarkers derived from continuous bedside monitoring are temporally and differentially expressed in septic patients. Using this information, minimalistic artificial intelligence models can be developed to predict sepsis earlier in critically ill patients.

Single Cell RNA-SEQ of Human Myeloid Derived Suppressor Cells in Late Sepsis Reveals Multiple Subsets with Unique Transcriptional Responses: A Pilot Study

Darden DB et al

Shock. 2020;Publish Ahead of Print

BACKGROUND: Increased circulating myeloid-derived suppressor cells (MDSCs) are independently associated with poor long-term clinical outcomes in sepsis. Studies implicate subsets of MDSCs having unique roles in lymphocyte suppression; however, characterization of these cells after sepsis remains incomplete. We performed a pilot study to determine the transcriptomic landscape in MDSC subsets in sepsis using single-cell RNAseq (scRNA-seq).
CONCLUSION: This pilot study successfully demonstrated that MDSCs maintain a transcriptomic profile that is immunosuppressive in late sepsis. Interestingly, the landscape in chronic critical illness is partially dependent on the original septic insult. Preliminary data would also indicate immunosuppressive MDSCs from late sepsis patients appear to have a somewhat unique transcriptome from cancer and/or other inflammatory diseases.

Lymphocyte Immunosuppression and Dysfunction Contributing to Persistent Inflammation, Immunosuppression and Catabolism Syndrome (PICS)

Bergmann CB et al

Shock. 2020;Publish Ahead of Print

Persistent Inflammation, Immune Suppression and Catabolism Syndrome (PICS) is a disease state affecting patients who have a prolonged recovery after the acute phase of a large inflammatory insult. Trauma and sepsis are two pathologies after which such an insult evolves. In this review, we will focus on the key clinical determinants of PICS: Immunosuppression and cellular dysfunction. Currently, relevant immunosuppressive functions have been attributed to both innate and adaptive immune cells. However, there are significant gaps in our knowledge, as for trauma and sepsis the immunosuppressive functions of these cells have mostly been described in acute phase of inflammation so far, and their clinical relevance for the development of prolonged immunosuppression is mostly unknown. It is suggested that the initial immune imbalance determines the development of PCIS. Additionally, it remains unclear what distinguishes the onset of immune dysfunction in trauma and sepsis and how this drives immunosuppression in these cells. In this review we will discuss how regulatory T cells (Tregs), innate lymphoid cells (ILCs), natural killer T cells (NKT cells), TCR-a CD4 CD8 double-negative T cells (DN T cells) and B cells can contribute to the development of post-traumatic and septic immunosuppression. Altogether, we seek to fill a gap in the understanding of the contribution of lymphocyte immunosuppression and dysfunction to the development of chronic immune disbalance. Further, we will provide an overview of promising diagnostic and therapeutic interventions, whose potential to overcome the detrimental immunosuppression after trauma and sepsis is currently being tested.

Calpain Activation and Organ Failure in Sepsis: Molecular Insights and Therapeutic Perspectives

Huang Y et al

Shock. 2020;Publish Ahead of Print

Sepsis is a severe systemic response to infection; its ensuing organ failure commonly portends an unfavourable prognosis. Despite the fact that sepsis has been studied for decades, the molecular mechanisms underlying sepsis-induced organ dysfunction remain elusive and more complex than previously thought, and effective therapies are extremely limited. Calpain is a type of calcium-dependent cysteine protease that includes dozens of isoforms. Calpain, as well as its endogenous specific inhibitor calpastatin, have been implicated in the pathogenesis of sepsis-induced organ dysfunction. Further, there is an accumulating body of evidence supporting the beneficial effect of calpain inhibition or regulation on multiple organ failure in sepsis. Better understanding of the underlying molecular mechanisms is helpful in the development of calpain/calpastatin-targeted therapeutic strategies to protect against sepsis-induced organ injury. The aim of this review is to summarize the recent literature and evidence surrounding the role of the calpain/calpastatin system in the process of organ dysfunction caused by sepsis-including regulation of cell death, modulation of inflammatory response, and disruption of critical proteins-to provide guidance for future research and therapy development.

Muscle-Derived Mitochondrial Transplantation Reduces Inflammation, Enhances Bacterial Clearance, and Improves Survival in Sepsis

Zhang Z et al

Shock. 2020;Publish Ahead of Print

BACKGROUND: Mitochondrial transplantation is a promising strategy for the treatment of several diseases. However, the effects of mitochondrial transplantation on the outcome of polymicrobial sepsis remain unclear. CONCLUSIONS:

These data displayed that mitochondrial replenishment reduces systemic inflammation and organ injury, enhances bacterial clearance, and improves the survival rate in sepsis. Thus, extraneous mitochondrial replenishment may be an effective adjunctive treatment to reduce sepsis-related mortality.

Hyper-Activation of Endogenous GLP-1 System to Gram-Negative Sepsis is Associated with Early Innate Immune Response and Modulated by Diabetes

Bloch O et al

Shock. 2020;Publish Ahead of Print

BACKGROUND: Culture-positive Gram-negative sepsis induces greater magnitude of early innate immunity /inflammatory response compared with culture-negative sepsis. We previously demonstrated increased activation of anti-inflammatory Glucagon Like Peptide-1 (GLP-1) hormone in initial phase of sepsis more pronounced in diabetes patients. However, whether GLP-1 system is hyper-activated during the early innate immune response to Gram-negative sepsis and modulated by diabetes remains unknown. CONCLUSIONS: Early stage of Gram-negative sepsis is characterized by endogenous GLP-1 system hyperactivity associated with over activation of innate immune response and organ dysfunction, which are modulated by diabetes. Total GLP-1 may be novel marker for rapid diagnosis of Gram-negative sepsis and its severity.

Utilization of the Signature Method to Identify the Early Onset of Sepsis From Multivariate Physiological Time Series in Critical Care Monitoring

Morrill JH et al

Crit Care Med. 2020;48(10):e976-e81

OBJECTIVES: Patients in an ICU are particularly vulnerable to sepsis. It is therefore important to detect its onset as early as possible. This study focuses on the development and validation of a new signature-based regression model, augmented with a particular choice of the handcrafted features, to identify a patient's risk of sepsis based on physiologic data streams. The model makes a positive or negative prediction of sepsis for every time interval since admission to the ICU. MEASUREMENTS AND MAIN RESULTS: The algorithm yielded a utility function score which was the first placed entry in the official phase of the challenge.

Beneficial Effects of Vasopressin Compared With Norepinephrine on Renal Perfusion, Oxygenation, and Function in Experimental Septic Acute Kidney Injury

Okazaki N et al

Crit Care Med. 2020;48(10):e951-e8

OBJECTIVES: To compare the effects of restoring mean arterial pressure with vasopressin or norepinephrine on systemic hemodynamics, renal blood flow, intrarenal perfusion and oxygenation, and renal function in ovine septic acute kidney injury. CONCLUSIONS: In ovine septic acute kidney injury, restoration of mean arterial pressure with vasopressin induced a more sustained improvement in renal function than norepinephrine, without exacerbating renal medullary ischemia and hypoxia or reducing mesenteric blood flow below baseline values.

Culture-negative sepsis

Thorndike Jand Kollef MH

Curr Opin Crit Care. 2020;26(5):473-7

The traditional approach to sepsis treatment utilizes broad-spectrum antibiotics. Unfortunately, a significant proportion of infected patients have 'culture-negative' sepsis despite appropriate microbiologic assessment. There has been increased interest in the past decade on the treatment of culture-negative sepsis. Outcome data comparing culture-negative sepsis with culture-positive sepsis are mixed and it is unclear if culture-negative sepsis is a distinct entity. Recent recommendations promoting antibiotic de-escalation in culture-negative sepsis can be difficult to implement. A variety of strategies have been suggested for limiting antibiotic courses among patients with negative cultures, including limiting antibiotic durations, use of antibiotic stewardship programs, early consideration of narrow antibiotics, rapid diagnostic technology, and eliminating anti-MRSA therapy based on surveillance swabs. Owing to the difficulty inherent in studying the lack of positive data, and to the uncertainty surrounding diagnosis in patients with culture-negative sepsis, prospective data to guide antibiotic choices are lacking. However, antibiotic de-escalation in culture-negative sepsis is both recommended and feasible in patients showing clinical signs of improvement. Increased use of rapid diagnostics, careful consideration of antibiotic necessity, and antibiotic stewardship programs may result in less antibiotic days and better outcomes.

Best practice: antibiotic decision-making in ICUs
Brink AJand Richards G
Curr Opin Crit Care. 2020;26(5):478-88
PURPOSE OF REVIEW: A major challenge in the ICU is optimization of antibiotic use. This review assesses current understanding of core best practices supporting and promoting astute antibiotic decision-making. SUMMARY: Multiple challenges and research priorities for antibiotic optimization remain; however, the best stewardship practices should be identified and entrenched in daily practice. Reducing unnecessary exposure remains a vital strategy to limit resistance development.

A Comparison of Sepsis-2 (Systemic Inflammatory Response Syndrome Based) to Sepsis-3 (Sequential Organ Failure Assessment Based) Definitions-A Multicenter Retrospective Study
Engoren M et al
Crit Care Med. 2020;48(9):1258-64
OBJECTIVES: Recently, the definition of sepsis has changed from a physiologic derangement (Sepsis-1 and -2) to organ dysfunction (Sepsis-3) based. We sought to determine the concordance between the different sepsis phenotypes and how that affected mortality. CONCLUSIONS: We found that Sepsis-2 and Sepsis-3-based sepsis diagnoses represent separate phenotypes with poor agreement. Patients who have both phenotypes are at increased risk of mortality compared with having either phenotype alone. Inclusion of both systemic inflammatory response syndrome and Sequential Organ Failure Assessment criteria in the same model improves the discrimination of mortality.

Trends, Cost, and Mortality From Sepsis After Trauma in the United States: An Evaluation of the National Inpatient Sample of Hospitalizations, 2012-2016
Eguia E et al
Crit Care Med. 2020;48(9):1296-303
OBJECTIVES: Identification and outcomes in patients with sepsis have improved over the years, but little data are available in patients with trauma who develop sepsis. We aimed to examine the cost and epidemiology of sepsis in patients hospitalized after trauma. CONCLUSIONS: While national trends for sepsis mortality have improved over the years, our analysis of National Inpatient Sample did not support this trend in the trauma population. The odds risk for death after sepsis and the cost of care remained high regardless of severity of injury. More rigor is needed in tracking sepsis after trauma and evaluating the effectiveness of hospital mandates and policies to improve sepsis care in patients after trauma.

Sepsis and the Obesity Paradox: Size Matters in More Than One Way
Jagan N et al
Crit Care Med. 2020;48(9):e776-e82
OBJECTIVES: Multiple studies have demonstrated an obesity paradox such that obese ICU patients have lower mortality and better outcomes. We conducted this study to determine if the mortality benefit conferred by obesity is affected by baseline serum lactate and mean arterial pressure. CONCLUSIONS: Our retrospective analysis suggests that although patient size (i.e., body mass index) is a predictor of in-hospital death among all-comers with sepsis-providing further evidence to the obesity paradox-it adds that illness severity is critically important whether quantified as higher lactate or by Acute Physiology and Chronic Health Evaluation III score. Our results highlight that the obesity paradox is more than a simple association between body mass index and mortality and reinforces the importance of illness severity.

Evaluation of Vasopressor Exposure and Mortality in Patients With Septic Shock
Roberts RJ et al
Crit Care Med. 2020;48(10):1445-53
OBJECTIVES: The objectives of this study were to: 1) determine the association between vasopressor dosing intensity during the first 6 hours and first 24 hours after the onset of septic shock and 30-day in-hospital mortality; 2) determine whether the effect of vasopressor dosing intensity varies by fluid resuscitation volume; and 3) determine whether the effect of vasopressor dosing intensity varies by dosing titration pattern. CONCLUSIONS: Increasing vasopressor dosing intensity during the first 24 hours after septic shock was associated with increased mortality. This association varied with the amount of early fluid administration and the timing of vasopressor titration.

Normothermia in Patients With Sepsis Who Present to Emergency Departments Is Associated With Low Compliance With Sepsis Bundles and Increased In-Hospital Mortality Rate

Park S et al
Crit Care Med. 2020;48(10):1462-70
OBJECTIVES: To investigate the impact of normothermia on compliance with sepsis bundles and in-hospital mortality in patients with sepsis who present to emergency departments. DESIGN: Retrospective multicenter observational study. CONCLUSIONS: Normothermia at emergency department triage was significantly associated with an increased risk of in-hospital mortality and a lower rate of compliance with the sepsis bundle. Despite several limitations, our findings suggest a need for new strategies to improve sepsis outcomes in this group of patients.

A Time-Phased Machine Learning Model for Real-Time Prediction of Sepsis in Critical Care
Li X et al
Crit Care Med. 2020;48(10):e884-e8
OBJECTIVES: As a life-threatening condition, sepsis is one of the major public health issues worldwide. Early prediction can improve sepsis outcomes with appropriate interventions. With the PhysioNet/Computing in Cardiology Challenge 2019, we aimed to develop and validate a machine learning algorithm with high prediction performance and clinical interpretability for prediction of sepsis onset during critical care in real-time. CONCLUSIONS: The proposed Time-phAsed machine learning model for Sepsis Prediction model is accurate and interpretable for real-time prediction of sepsis onset in critical care, which holds great potential for further evaluation in prospective studies.

Inhibitory Immune Checkpoint Molecule Expression in Clinical Sepsis Studies: A Systematic Review
Busch LM et al
Crit Care Med. 2020;48(9):1365-74
OBJECTIVES: Checkpoint inhibitors have been proposed for sepsis following reports of increased checkpoint molecule expression in septic patients. To determine whether clinical studies investigating checkpoint molecule expression provide strong evidence supporting trials of checkpoint inhibitors for sepsis. CONCLUSIONS: Although sepsis may increase some checkpoint molecule expression compared with healthy controls, the data are limited and inconsistent. Further, data from the more informative patient comparisons are potentially confounded by severity of illness. These clinical checkpoint molecule expression studies do not yet provide a strong rationale for trials of checkpoint inhibitor therapy for sepsis.

Cost Analysis of Adjunctive Hydrocortisone Therapy for Septic Shock: U.S
Oh M et al
Crit Care Med. 2020;48(10):e906-e11
OBJECTIVES: To conduct a cost analysis of adjunctive hydrocortisone therapy for severe septic shock from the perspective of a third-party payer in the United States. CONCLUSIONS: Using adjunctive hydrocortisone therapy yields a significant monetized benefit based on inputs from the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock and Activated Protein C and Corticosteroids for Human Septic Shock trials.

Right Ventricular Dysfunction in Early Sepsis and Septic Shock
Lanspa MJ et al
Chest. 2020
BACKGROUND: Sepsis is a frequently lethal state, commonly associated with left ventricular (LV) dysfunction. Right ventricular (RV) dysfunction in sepsis is less well understood. RESEARCH QUESTION: In septic patients, how common is RV dysfunction, and is it associated with worse outcomes? INTERPRETATION: Right ventricular dysfunction is present in nearly half of studied septic patients and is associated with over threefold higher 28-day mortality.

Adjunctive therapy with vitamin c and thiamine in patients treated with steroids for refractory septic shock: A propensity matched before-after, case-control study
Coloretti I et al
J Crit Care. 2020;59:37-41
PURPOSE: Triple therapy with steroids, vitamin C and thiamine has been recently proposed as a safe and beneficial in patients with sepsis. In 2017, we added the use of intravenous vitamin C and thiamine in septic shock patients receiving low dose hydrocortisone because poorly responsive to vasopressors. Aim of this study is to verify whether triple therapy rather than steroids alone can improve outcome in patients with refractory shock. CONCLUSIONS: Although with significant limitations, our experience indicated that triple therapy seems to provide an improvement of clinical outcomes in patients with refractory septic shock.

Excess mortality risk from sepsis in patients with HIV - A meta-analysis
Pyarali FF et al
J Crit Care. 2020;59:101-7
PURPOSE: Differences in HIV prevalence, access to antiretrovirals and ICU resources may result in wide variation in sepsis mortality in HIV patients. The aim of this study was to perform a meta-analysis to quantify the excess risk of sepsis mortality in HIV patients. CONCLUSIONS: HIV increases the risk of sepsis mortality compared to seronegative individuals across all time periods and geographic areas. We note that this effect is more pronounced in patients with organ dysfunction.

Triage of patients with fever: The Manchester triage system's predictive validity for sepsis or septic shock and seven-day mortality
Zaboli A et al
J Crit Care. 2020;59:63-9
OBJECTIVE: Up to 15% of patients arrive in the emergency department suffering from fever. Triage is their first contact and is responsible for the stratification of patients according to the severity of the condition for which they are presenting at the emergency department. The aim of this study is to assess the predictive validity of the Manchester Triage System in patients with fever for sepsis or septic shock and seven-day mortality. CONCLUSION: The Manchester Triage System has demonstrated high sensitivity and negative predictive value in patients with fever diagnosed with sepsis or septic shock. For patients with sepsis or septic shock one-third of cases with an incorrectly assigned priority code were caused by incorrect application of the Manchester Triage System.

Association between sepsis at ICU admission and mortality in patients with ICU-acquired pneumonia: An infectious second-hit model
Esperatti M et al
J Crit Care. 2020;59:207-14
PURPOSE: We explore the hypothesis that critically ill patients developing ICU-acquired pneumonia (ICU-AP) have worse outcomes and an altered inflammatory response if their ICU admission was sepsis-related. CONCLUSIONS: Previous sepsis does not appear to predispose to higher mortality nor worse outcomes in patients who develop ICU-acquired pneumonia.

Mean amplitude of glycemic excursions in septic patients and its association with outcomes: A prospective observational study using continuous glucose monitoring
Furushima N et al
J Crit Care. 2020
PURPOSE: To apply continuous glucose monitoring (CGM) and determine the mean amplitude of glycemic excursions (MAGE) in septic patients and to assess the associations of MAGE with outcomes and oxidative stress. CONCLUSIONS: In the current study, MAGE for the first 48 h of treatment that was obtained by using CGM was associated with 90-day all-cause mortality, 90-day ICU-free days and urinary 8-isoprostaglandinF2alpha level in septic patients.

Assessment of fluid resuscitation on time to hemodynamic stability in obese patients with septic shock
Kiracofe-Hoyte BR et al
J Crit Care. 2020
PURPOSE: Assess time to hemodynamic stability (HDS) in obese patients with septic shock who received <30 vs. >/=30 ml/kg of initial fluid resuscitation based on actual body weight (ABW). CONCLUSIONS: Obese patients given >/=30 ml/kg based on ABW had a shorter time to HDS and a lower risk of in-hospital death. Exploratory results suggest improved outcomes resuscitating by ABW vs. IBW; ABW showed no strong benefit over AdjBW. Further prospective studies are needed to confirm the optimal fluid dosing in obese patients.

Effectiveness of polymyxin B-immobilized hemoperfusion against sepsis and septic shock: A systematic review and meta-analysis
Li X et al
J Crit Care. 2020
PURPOSE: To evaluate the efficacy and safety of Polymyxin B-immobilized hemoperfusion (PMX-HP) against sepsis or septic shock. CONCLUSION: Using PMX-HP to treat patients with less severe sepsis can reduce overall mortality and is safe. Treatment efficacy may benefit from the reduction of endotoxin level and the improvement of hemodynamics.

More high quality RCTs are required to further evaluate the clinical role of PMX-HP against severe sepsis or septic shock.

Plasma Cortisol, Aldosterone, and Ascorbic Acid Concentrations in Patients with Septic Shock Do Not Predict Treatment Effect of Hydrocortisone on Mortality
Cohen J et al
Am J Respir Crit Care Med. 2020;202(5):700-7
Rationale: Whether biomarkers can identify subgroups of patients with septic shock with differential treatment responses to hydrocortisone is unknown. Objectives: To determine if there is heterogeneity in effect for hydrocortisone on mortality, shock resolution, and other clinical outcomes based on baseline cortisol, aldosterone, and ascorbic acid concentrations. Conclusions: In patients with septic shock, there was no heterogeneity in effect of adjunctive hydrocortisone on mortality, shock resolution, or other clinical outcomes based on cortisol, aldosterone, and ascorbic acid concentrations. Plasma aldosterone and ascorbic acid concentrations are not associated with outcome.

How I Do It: Dosing Fluids in Early Septic Shock
Chaudhuri D et al
Chest. 2020
Early IV fluid administration remains one of the modern pillars of sepsis treatment; however, questions regarding amount, type, rate, mechanism of action, and even the benefits of fluid remain unanswered. Administering the optimal fluid volume is important, because overzealous fluid resuscitation can precipitate multiorgan failure, prolong mechanical ventilation, and worsen patient outcomes. After the initial resuscitation, further fluid administration should be determined by individual patient factors and measures of fluid responsiveness. This review describes various static and dynamic measures that are used to assess fluid responsiveness and summarizes the evidence addressing these metrics. Subsequently, we outline a practical approach to the evaluation of fluid responsiveness in early septic shock and explore further areas crucial to ongoing research examining this topic.

Fluid Response Evaluation in Sepsis Hypotension and Shock: A Randomized Clinical Trial
Douglas IS et al
Chest. 2020;158(4):1431-45
BACKGROUND: Fluid and vasopressor management in septic shock remains controversial. In this randomized controlled trial, we evaluated the efficacy of dynamic measures (stroke volume change during passive leg raise) to guide resuscitation and improve patient outcome. RESEARCH QUESTION: Will resuscitation that is guided by dynamic assessments of fluid responsiveness in patients with septic shock improve patient outcomes? INTERPRETATION: Physiologically informed fluid and vasopressor resuscitation with the use of the passive leg raise-induced stroke volume change to guide management of septic shock is safe and demonstrated lower net fluid balance and reductions in the risk of renal and respiratory failure. Dynamic assessments to guide fluid administration may improve outcomes for patients with septic shock compared with usual care. CLINICAL TRIAL REGISTRATION: NCT02837731.

A Systematic Review of the Effect of Delayed Appropriate Antibiotic Treatment on the Outcomes of Patients With Severe Bacterial Infections
Zasowski EJ et al
Chest. 2020;158(3):929-38
BACKGROUND: Patients with severe bacterial infections often experience delay in receiving appropriate treatment. Consolidated evidence of the impact of delayed appropriate treatment is needed to guide treatment and improve outcomes. RESEARCH QUESTION: What is the impact of delayed appropriate antibacterial therapy on clinical outcomes in patients with severe bacterial infections? INTERPRETATION: Avoiding delayed appropriate therapy is essential to reduce mortality in patients with severe bacterial infections. CLINICAL TRIAL REGISTRATION: PROSPERO; No.: CRD42018104669; URL: www.crd.york.ac.uk/prospero/.

Health-related quality of life in survivors of septic shock: 6-month follow-up from the ADRENAL trial
Hammond NE et al
Intensive Care Med. 2020;46(9):1696-706
PURPOSE: To investigate the impact of hydrocortisone treatment and illness severity on health-related quality of life (HRQoL) at 6 months in septic shock survivors from the ADRENAL trial. CONCLUSIONS: Approximately one fifth of

septic shock survivors report moderate to extreme problems in HRQoL domains at 6 months. Hydrocortisone treatment for septic shock was not associated with improved HRQoL at 6 months. Female gender was associated with worse pain at 6 months.

NEWS2

The usefulness of NEWS2 at day 7 of hospitalization in predicting COVID-19 evolution and as an early endpoint in therapeutic trials
Sixt T et al
J Infect. 2020
There is a need for reliable tools to predict the evolution of hospitalized patients suffering from COVID-19. The likelihood of unfavourable evolution for patients hospitalized for COVID-19 with a National Early Warning Score 2 (NEWS2) below 7 at Day 7 of hospitalization is nearly non-existent. Such a score could thus be used to allow earlier discharge of the patients and as a judgement criterion in therapeutic trials.

Predictive Value of 5 Early Warning Scores for Critical COVID-19 Patients
Hu H et al
Disaster Med Public Health Prep. 2020:1-8
OBJECTIVES: A simple evaluation tool for patients with novel coronavirus disease 2019 (COVID-19) could assist the physicians to triage COVID-19 patients effectively and rapidly. This study aimed to evaluate the predictive value of 5 early warning scores based on the admission data of critical COVID-19 patients. CONCLUSIONS: SEWS, NEWS, NEWS2, and HEWS demonstrated moderate discriminatory power and, therefore, offer potential utility as prognostic tools for screening severely ill COVID-19 patients. However, MEWS is not a good prognostic predictor for COVID-19.

Using National Early Warning Score (NEWS) 2 to help manage medical emergencies in the dental practice
Jevon Pand Shamsi S
Br Dent J. 2020;229(5):292-6
If a medical emergency occurs in the dental practice, members of the dental team must be able to respond promptly, effectively and safely. Fundamental to this response is knowing when it is necessary to call 999 for an ambulance and communicating effectively with the ambulance service to ensure the timely arrival of the emergency services and timely transfer to hospital. This can be helped by using the Royal College of Physicians' (RCP's) National Early Warning Score (NEWS) 2, widely used by the ambulance service and in hospitals - it reliably detects deterioration in adults, triggering review, treatment and escalation of care. Although NEWS2 hasn't yet been validated for use in primary care, NHS England is encouraging its widespread use in this sector. Using NEWS2 in the dental practice will help the dental team to effectively, confidently and safely manage medical emergencies, including sepsis, should they arise. This will facilitate effective teamwork and help to ensure enhanced patient outcomes. This article provides an overview of NEWS2, including benefits for using it in the dental practice and guidance on how to implement it.

Predictive value of National Early Warning Score 2 (NEWS2) for intensive care unit admission in patients with SARS-CoV-2 infection
Gidari A et al
Infect Dis (Lond). 2020;52(10):698-704
Background: From January 2020, Coronavirus disease 19 (COVID-19) has rapidly spread all over the world. An early assessment of illness severity is important for the stratification of patients. We analysed the predictive value of National Early Warning Score 2 (NEWS2) for intensive care unit admission (ICU) in patients with Severe Acute Respiratory Syndrome- Coronavirus-2 (SARS-CoV-2) infection. Conclusions: NEWS2 at hospital admission was a good predictor for ICU admission. Patients with severe COVID-19 were correctly and rapidly stratified.

Can capillary lactate improve early warning scores in emergency department? An observational, prospective, multicentre study
Lopez-Izquierdo R et al
Int J Clin Pract. 2020
AIMS: To determine the prognostic usefulness of the National Early Warning Score-2 (NEWS2) and quick Sepsis-related Organ Failure Assessment (qSOFA) scores, in isolation and combined with capillary lactate (CL), using the new NEWS2-L and qSOFA-L scores to predict the 30-day mortality risk. CONCLUSION: NEWS2 and qSOFA scores are a very useful tool for assessing the status of patients who come to the ED in general for all types of patients in triage

categories II and III and for detecting the 30-day mortality risk. CL determined systematically in the ED does not seem to provide information on the prognosis of the patients.

Neonatal, paediatric and maternal sepsis

Evaluating Pediatric Sepsis Definitions Designed for Electronic Health Record Extraction and Multicenter Quality Improvement

Scott HF et al

Crit Care Med. 2020;48(10):e916-e26

OBJECTIVES: To describe the Children's Hospital Association's Improving Pediatric Sepsis Outcomes sepsis definitions and the identified patients; evaluate the definition using a published framework for evaluating sepsis definitions. CONCLUSIONS: The Improving Pediatric Sepsis Outcomes Sepsis definitions demonstrated feasibility for large-scale data abstraction. The patients identified provide important information about children treated for sepsis. When operationalized, these definitions enabled multicenter identification and data aggregation, indicating practical utility for quality improvement.

Mitochondrial Dysfunction is Associated With an Immune Paralysis Phenotype in Pediatric Sepsis

Weiss SL et al

Shock. 2020;54(3):285-93

OBJECTIVE: Immune dysregulation is a defining feature of sepsis, but the role for mitochondria in the development of immunoparalysis in pediatric sepsis is not known. We sought to determine if mitochondrial dysfunction measured in peripheral blood mononuclear cells (PBMCs) is associated with immunoparalysis and systemic inflammation in children with sepsis. DESIGN: Prospective observational study. CONCLUSIONS: Children with sepsis had lower PBMC mitochondrial respiration when immunoparalysis was present compared with those without immunoparalysis. The subsets with immune paralysis and low mitochondrial respiration exhibited the highest levels of systemic inflammation.

COVID-19 and sepsis

Coronavirus disease 2019 as a particular sepsis: a 2-week follow-up of standard immunological parameters in critically ill patients

Monneret G et al

Intensive Care Med. 2020;46(9):1764-5

Since the emergence of coronavirus disease 2019 (COVID-19), the number of patients admitted to ICU has never ceased to rise. While awaiting effective antiviral treatments, the understanding of the appropriate host immune response to a virus totally unknown of immune surveillance is of major importance. At the forefront of immune alterations previously described in COVID-19, patients homogenously present severe lymphopenia. Interestingly, bacterial sepsis also deeply perturbs immune homeostasis by inducing a complex immune response that varies over time and associates a systemic inflammatory response and lymphopenia. The objective of the present study was thus to conduct immune monitoring over the first 15 days in COVID-19 patients admitted to ICU based on markers previously evaluated in bacterial sepsis

Microcirculatory, Endothelial and Inflammatory Responses in Critically Ill Patients with COVID-19 Are Distinct from Those Seen in Septic Shock: A Case Control Study

Hutchings S et al

SSRN Electronic Journal. 2020

Critically ill patients with COVID-19 infection frequently exhibit a hyperinflammatory response and develop organ failures, however the underlying mechanisms are unclear. We investigated the microcirculatory, endothelial and inflammatory responses in critically ill COVID-19 patients and compared them to a group of patients with septic shock. Compared to patients with bacterial sepsis an overt shock state with tissue hypoperfusion does not appear typical of COVID-19 infection. There was no evidence of significant sublingual microcirculatory impairment, widespread endothelial injury or marked inflammatory cytokine release in this group of critically ill COVID-19 patients. COVID-19 may have a different pathogenesis to bacterial induced septic shock.

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