Supplementary Material 2- Supplemental Table 1

All questions initially submitted by research committee members

TOPIC 1 - INFECTIONS

1) Nosocomial infections and antibiotic performance. Lower rates of VAP but same with antibiotic prescription? As VAP is the most frequent ICU infection, it can be used as a surrogate for this purpose.
2) Fungal infection in ICU. In the last years Infection guidelines are more and more straightforward for empirical recommending broad (and very expensive) spectrum antifungals in ICU but papers conducted does not totally support change in outcomes
3) Source Control. Weak evidence of SSC recommendations.
4) Recognition of infection / optimal antibiotic therapy (combination? relevance of pkpd? even duration in patients with persisting sepsis)
5) Antibiotic monotherapy versus combination therapy for septic shock
6) Duration of antimicrobial therapy
7) Timing of source control
8) What is the role (if any) of combination antibiotic therapy for septic shock?
9) Evaluate the clinical impact of microbiological rapid diagnostic tests in sepsis. Information regarding RDT are mainly about diagnostic accuracy but information about the clinical impact in terms of escalation, de-escalation, and other outcomes is scarce.
10) We have been having big (sic) discussions within the guidelines group and with the IDSA about the role of combination (versus monotherapy) antibiotics
11) Duration of antibiotic courses
12) double coverage for gram negatives
13) Impact of antimicrobial pharmacokinetic optimization in sepsis and septic shock particularly with respect to continuous/extended infusion of β-lactams
14) Impact of early empiric combination therapy on outcome of sepsis and septic shock in contrast to other infections without sepsis and organ failure in immunocompetent patients
15) The use of biomarkers and clinical strategies/algorithms to support antimicrobial de-escalation and their impact on outcome in sepsis and septic shock.
16) Antimicrobial management: explore broad versus directed coverage from an epidemiologic standpoint (e.g., does it make sense not to use carbepenems until your cephalosporin resistance rate (or case mortality) crosses a threshold value?)

TOPIC 2 - FLUIDS/RESUSCITATION/HEMODYNAMICS

1) Comparison of fluid type: role of albumin vs crystalloid in early sepsis resuscitation (despite some studies, this question has not yet been answered)
2) Comparison of fluid type: role of normal saline vs. balanced crystalloid solution (would not advocate as strongly since evidence for deleterious effects of high volume chloride infusion in other areas is not definitive, but septic shock is a good model to test this hypothesis)
3) How much fluid to give – could compare either two different fixed volumes (30cc/kg compared to another fixed volume) or compare targeted volumes (individualized therapy)
4) Do chloride rich or poor crystalloid solutions change outcome in septic shock when

significant resuscitation is needed?
5) Evaluate a resuscitation protocol based in dynamic parameters (PLR, VVS, PPV, etc.) on relevant clinical outcomes. The goals are more physiological and discriminate better responders and no-responders but the clinical benefit is not well established.
6) How much volume to give sepsis patient in initial resuscitation
7) Does the initial resuscitation from sepsis-induced hypoperfusion, by using at least 30ml/kg of intravenous crystalloid fluid given within the first 3 hours work in the ward and in the ICU other than in the emergency
8) How septic patients with brain injury or abdominal hypertension should be resuscitated?
9) Is the repeated fluid challenge better than the 30 ml/kg crystalloids bolus resuscitating patients from sepsis?
10) Where do we stand with GDT (is it over or need to be adapted?)
11) Resuscitation endpoints: using venous capacitance/mean systemic pressure as a better surrogate for volume responsiveness or even the elusive "volume status" metric.
12) Vasopressor choice, dosing, and titration schemes. Role of phenylephrine for septic shock (or vasopressin, but that has already been studied, even though questions remain)
13) Is the regional hemodynamics better the systemic to predict sepsis evolution?
14) Recognition and management of new-onset AF in the setting of septic shock (therapy goals, anticoagulation strategies, long-term outcomes).

TOPIC 3 - ADJUNCTIVE THERAPIES (VENTILATION, NUTRITION, ENDOCRINE)
1) Role of lung protective ventilation in sepsis patients *without* ARDS
2) Enteral nutrition support in septic shock
3) Effects of aspects of care we haven't been collecting data on – protocols on vent weaning, sedation, SBTs, ambulation.
4) Timing of metabolic (nutritional) support – does early or late matter?
5) Composition of macronutrient support – sugar, fat, protein – does it matter?
6) Are steroids actually indicated in septic shock? If so, when?
7) Does blockade of co-inhibitors (such as PD1, PDL1, BTLA, CTLA4) improve outcomes in sepsis (not sure if this is a basic science or clinical question)?
8) Does ECMO improve outcomes in ARDS? Does proning? Does paralysis?
9) Evaluation of the different technologies for absortion of mediators: endotoxin absorbers, cytokine absorbers.
10) PK/PD of antibiotics is sepsis + CRRT or Absortion or ECMO or hypoalbuminemia.
11) Volume versus pressure limitation in sepsis induced ARDS
12) Ventilation of patients with sepsis without ARDS
13) Use of esophageal monitors to guide ventilator settings in sepsis induced ARDS
14) The present glucose control guidelines target an upper blood glucose level ≤ 180 mg/dL without a lower target other than hypoglycemia. Future research should identify whether the upper blood glucose level target should remain ≤ 180 mg/dL or ≤ 150 mg/dL. In addition, a lower target other than hypoglycemia may be more appropriate.
15) In view of the FDA statement "critically ill patients should not be tested with a glucose meter because results may be inaccurate," more accurate glucometers utilizing capillary blood must be developed or a much quicker central laboratory turnaround for results

16) Further study should develop validated, safe, and effective protocols and closed-loop systems for controlling blood glucose concentrations and variability while avoiding hypoglycemia.
17) In the general realm of adjunctive therapies, I think there are many unanswered questions in the realm of nutrition in addition to those you propose regarding management of hyperglycemia. Implementing both of these therapies (management of hyperglycemia, and institution of early nutritional support) generate a substantial body of work for our ICU caregivers, at a time when there are many other competing demands. Despite our recommendations, I think there remain a lot of unanswered or poorly answered questions regarding timing and even utility of early nutritional therapy, as most studies have been carried out in a general critical care cohort, and not specifically in patients with sepsis/septic shock. Moreover, many of the studies have less than optimal methodology and are underpowered. One question that still generates far more smoke than light among my colleagues is when to start enteral nutrition in patients on vasopressor infusions; opinions seem to range all over the map on this one.

TOPIC 4 - SCORING SYSTEM/IDENTIFICATION/SCREENING

Recognition of Sepsis

1) Recognition of sepsis and which would be the best scorings? Differences for Emergency vs Wards. I think that we should better define an immunoscore. Last SEPSIS 3 recommended lactate that is not available in all the places but there is no immunoscore including lymphopenia surprisingly not for predisposition
2) Application of Sepsis-3 criteria to SSC database – does it miss people who are septic? Does it omit people who aren't really septic?
3) Does differentiating severe sepsis/sepsis from septic shock have any effect on process or outcome? That is, does an initial designation of septic shock result in more rapid institution of the bundles? And does that effect mortality/morbidity etc?
4) Is qSOFA (or sepsis-3) or MEWS superior for diagnosing and predicting outcomes in sepsis?
5) Risk stratification in sepsis based in biomarkers
6) Does the qSOFA perform well also in the emergency room?
7) Compare qSOFA prospectively to SIRS as screening tool for sepsis in the ED and hospital floors.
8) Can big data be used to either predict decompensation or predict clinical trajectories in real time in the ICU
9) Use of artificial intelligence or self-learning computing systems for predictive/prognostic scores.

Evaluation of organ dysfunction

1) Building a better SOFA
2) Can we come up with a better marker of organ dysfunction than SOFA?

Diagnosis of infections

1) Improving the sensitivity/specificity of potential point-of-care testing. Possibilities include metabolomics, inflammatory molecules, or RNA sequencing for detection of transcription of virulence factors. Over-arching goal: shorten time to diagnosis. Secondary benefits: improve overall epidemiology and enrollment in clinical trials
2) Isolation of new bacterial, viral, fungal even parasitic pathogens in sepsis and

characterization of how these might differ from a bacteria-centric model Main goal: expand diagnosis and therapy to a potential population of sub-clinical patients. Secondary: explore possibilities of multi-pathogen infection. Characterize "normal' versus pathogenic bacteremia

Sepsis Outside the Hospital

1) Routine screening for sepsis in long term care facilities
2) Pre-hospital management of sepsis

TOPIC 5 - ADMINISTRATION/EPIDEMIOLOGY

1) Organizational aspects.
2) Epidemiology of sepsis susceptibility. Main goal: characterize the risk factors (host, pathogen phenotype, response) to tailor therapy, even prophylaxis to specific combinations. Secondary: improve understanding of host-pathogen interactions to look for novel therapeutics.
3) Patient/family values and preferences regarding sepsis – explicitly not addressed in newest guidelines
4) Component analysis of bundles – does fluid matter more than antibiotics? Does anything else matter at all?
5) Evaluate the impact of a secondary evaluation of sepsis treatment at ICU admission. A structured evaluation of the sepsis treatment at ICU admission or after several hours could help to improve antibiotic treatment, source control and hemodynamic resuscitation. Quality improvement intervention.
6) Cost-effectiveness of sepsis interventions.
7) Do quality metrics improve care: Cluster RCT for comparing metrics/bundles to usual care.
8) Risk stratification with biomarker panels

TOPIC 6 - POST-ICU OUTCOMES

1) Long term outcomes in septic patients and economic burden.
2) Incidence of long term sequelae (add some stuff to the database)
3) Effects of institution (timing, use) of bundles on long term sequelae
4) Prevention of organ failure at long term. Analyze the impact of the sepsis treatment on renal or lung function at 1 year.
5) What is the outcome and recovery of the QoL of elderly patients with sepsis?
6) Prognostic/Predictive score at ICU discharge.

TOPIC 7 - BASIC SCIENCE

1) Cellular dysfunction (how to diagnose/ leave it or try to intervene?)
2) What are the mechanisms implicating /triggering recovery?
3) Energy failure research, looking at mitochondrial dysfunction and changes in metabolism Main goal: enhance diagnosis (lactate: pyruvate ratios may be worth bringing back into the discussion) Secondary: explore organ dysfunction and therapy in terms of energy failure.
4) Therapeutics that could cause phenotypic shifting. Could we turn off virulence?
5) How do we identify patients in the hypo-inflammatory state of sepsis?
6) Does altering the microbiome alter the outcome in sepsis? If so, how do we do it?

7) Identifying the mechanisms by which immune suppression/failure to have an appropriate cellular response lead to poor outcomes in sepsis
8) Pharmacogenomics and precision medicine: identification of specific genotypes that respond or not respond to available treatments like steroids, etc.
9) Does the microbiome influence the sepsis outcome? Understanding the role of lipid mediators (includes resolvins, lipoxins, prostanoids, etc) in sepsis outcomes. This could be broadened to the Lipidome and Metabolome (rather than lipid mediators).
10) How do basic ICU therapies used in humans affect sepsis outcomes? This would include: fluids, sedatives, opioids, transfusions, nutritional supplements, possibly classes of antibiotics
11) Role of non-leukocyte populations in sepsis outcomes (i.e.: neurons, endothelials, etc)
12) Continuing to advance the models to more closely recapitulate the human condition – Multicellular platforms using human cells, continued adaptation of the existing animal models, better defining where mouse models do and do not provide useful pre-clinical information

Newly designed CRRT membranes for sepsis and SIRS--a pragmatic approach for bedside intensivists summarizing the more recent advances: a systematic structured review.

Honore PM[1], Jacobs R, Joannes-Boyau O, De Regt J, De Waele E, van Gorp V, Boer W, Verfaillie L, Spapen HD.

Author information

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Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium. Patrick.Honore@uzbrussel.be

Abstract

In recent years, after all the attention has been focused on the dose for continuous renal replacement therapy (CRRT) in sepsis and systemic inflammation response syndrome (SIRS), the relatively negative results of all those studies did urge our expectations on new approaches regarding CRRT in sepsis and SIRS. So far, after the failure of the major randomized studies on dose, attention is now drawn to new membranes that could better eliminate massive amounts of unbound mediators in wider spectrum and also in greater magnitude Nevertheless, for septic acute kidney injury, the recommended dose will remain 35 ml/kg/h until the IVOIRE (hIgh VOlume in Intensive Care) study will be published. In this new armamentarium, we have distinguished the first tools that can still be called membranes ranging from AN69 Surface Treated (ST), SEPTEX, polymethylmetacrylate, to Oxiris that can still run with a CRRT device. Polymyxin B is still a kind of membrane although it has a larger surface, but it can run in a hemoperfusion system and is also much more selective. Adsorptive columns and sorbents are not anymore membranes but are seen as cartridges as the surface is extremely huge when

compared with that of membranes (more than 500 m). They can still run in a hemoperfusion device. At the very end, we do have apheresis or selective plasma exchange (also very close to sorbents and columns) but we have very few data up to now regarding sepsis. Regarding spectrum, CytoSorb seems to be very promising although it is not able to capture endotoxin and IL-10. Oxiris is also promising as it can capture endotoxin and cytokines. AN69 ST is very powerful to capture numerous cytokines and especially high-mobility group box 1 protein (a very upstream cytokine). Polymethylmetacrylate has also the power to capture endotoxin and numerous other cytokines probably with a larger magnitude than Oxiris although this is not proven. Lastly, high-porosity membranes (Septex) may play a role especially when used in continuous venovenous hemodialysis mode. At the end, if we look for a more enlarged spectrum and a higher magnitude, CytoSorb might be seen as the most promising although not having the ability to fix endotoxin. Future studies will tell us which membrane or sorbent will be most useful in the adjunctive treatment for sepsis.