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Surviving Sepsis Campaign: Research Opportunities for Infection and Blood Purification Therapies

OBJECTIVES: Patients with infection can develop sepsis, and their mortality can be high. An important aspect in the treatment of sepsis is adequate management of the infection.

DATA SOURCES: Using a modified Delphi approach, the Surviving Sepsis Campaign research committee recently published a series of 26 priorities for sepsis and septic shock.

STUDY SELECTION: Task force members with specific expertise were tasked with generating expanded reviews for all infection questions and a subset of adjunctive therapy questions from the larger list of sepsis priorities. Each question was addressed by one of the six task force members.

DATA EXTRACTION: In-depth reviews were then edited by the group as a whole, with added input from the committee coauthors.

DATA SYNTHESIS: Six questions were addressed: 1) should empiric antibiotic combination therapy be used in sepsis or septic shock? 2) does optimization of antimicrobial pharmacokinetics and pharmacodynamics impact patient outcomes in sepsis? 3) should viral reactivation resulting from sepsis-induced immunosuppression be treated with antiviral therapy in critically ill septic patients? 4) should rapid diagnostic tests be implemented in clinical practice? 5) what is the role of lung-protective ventilation in sepsis patients without acute respiratory distress syndrome? and 6) how do we determine the efficacy of “blood purification” therapies such as endotoxin absorbers, cytokine absorbers, and plasmapheresis.

CONCLUSIONS: The research committee members for the Surviving Sepsis Campaign aimed to explore research questions in order to provide existing evidence and highlight areas of uncertainty and future directions.

KEY WORDS: infection; intensive care unit; sepsis; septic shock; ventilator-associated pneumonia

Patients admitted to an ICU due to sepsis and with the need of organ support have a high mortality rate (1). The Surviving Sepsis Campaign (SSC) has previously made very specific recommendations to be implemented to fight sepsis (2). Treatment of severe infections is a top priority of sepsis management (3). Recommendations from the SSC have been shown to improve outcome, following implementation (4, 5). Despite the guidelines use of Grading of Recommendations, Assessment, Development, and Evaluation methodology, some recommendations from SSC have proven to be controversial due to either conflicting data or concerns from some inadequate data to drive recommendations. One example is that the SSC strongly recommends that empirical broad-spectrum antibiotics should be given within 1 hour of sepsis identification to patients with septic shock and also to those with sepsis and without shock (2). One of the main concerns voiced regarding this

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recommendation is the lack of randomized clinical trials in support of it. However, data from multiple observational studies and meta-analyses suggest that early antibiotic administration is associated with improved survival even among patients without shock (6). This and other controversies highlight the need for further research in multiple areas related to sepsis. Further, there are many questions in which inadequate data exist for SSC to yield a recommendation.

In an attempt to both drive clinical research and answer fundamental questions related to sepsis biology, the SSC created the SCC research committee to prioritize research needs. This led to the recent publication of 26 research priorities in sepsis and septic shock (7, 8). In the present article, we expand upon six research questions in the SSC priority list related to both infection and adjunctive therapy to provide evidence and delineate areas of uncertainty and future directions.

METHODS

The SSC research committee members initially had 88 suggestions from 18 task force members. Using a modified Delphi approach, this was narrowed down to 26 research priorities that were published in 2018 (7, 8). The methods for arriving at the final research priorities are described in the original publication. Further, although this publication had a broad overview for each question, a pre hoc decision was made that expanded versions would be published in subsequent manuscripts to examine each priority in depth. This has resulted in three subsequent publications on: 1) administration, scoring, epidemiology, and identification of sepsis (9); 2) fluid resuscitation and vasopressor therapy (10, 11); and 3) basic/translational science (12, 13). This work represents the fourth and final article expanding the original research priorities and focuses on infection and adjunctive therapy. Of note, the article includes all previously identified research priority questions on infection but only includes a subset of questions on adjunctive therapy as the committee did not feel that there was significant utility to expanding the discussion on some of the adjunctive priorities beyond what was already published.

For this article, a systematic review process was put in place for each question with the author of each question being responsible for the individual data search. We searched Medline and Embase databases

for studies published in English from inception until April 02, 2021, including data from meta-analyses, randomized controlled trials, and any recent interventional or observational studies considered relevant for the topic. No methodologists were employed. The search strategy consisted of controlled vocabulary (i.e., Medical Subject Headings), keywords, and free-text words for the main search, which covered the concepts underlying each section. Six committee members with specific expertise were tasked with generating expanded reviews of the six infection and adjunctive therapy questions for this article. Committee members were chosen from the entire 18-member SSC research committee based upon expertise topics related to severe infection or adjunctive therapy in sepsis. In keeping with a commitment to diversity on the overall committee, diversity (broadly defined but including geographic, gender, profession, specialty, socioeconomic) was expressly considered when populating the committee. After each committee member wrote an expanded review of each question, these were subsequently edited by the group as a whole. The coauthors of the SSC research committee (D.D.B., C.M.C.) oversaw the entire process and also edited the article as a whole.

Conflict of Interest Policy

No industry input was obtained in the committee's previous identification of the research priorities or in their expanded description in this article. No industry representatives were involved at any point in the process, and no financial compensation or honoraria was received for participation on the committee. Each committee member provided a personal disclosure, and no attempt was made by the group to seek additional information on self-reported conflict of interest.

RESULTS

Should Empiric Antibiotic Combination Therapy Be Used in Sepsis or Septic Shock?

What Is Known? Early administration of antimicrobials is associated with improved mortality in patients with sepsis (14, 15). In the setting of diagnostic uncertainty, antimicrobial selection must be empiric and suitable to cover the most likely pathogens. There are several rationales for combining agents (16). Expanding coverage with combinations of antimicrobials with

complementary spectra increases the likelihood of covering the causative pathogen when the diagnosis is uncertain. Evidence suggests such coverage provides better suppression of bacteria likely to have some antibiotic resistance (17) and better cure in *Pseudomonas aeruginosa* infections (18). In neither case was mortality affected, but there may be a mortality benefit with efficient empirical therapy from combination antibiotics (19). It is a theoretical consideration that agents with different tissue penetration might be helpful in sepsis of unknown origin. Combination therapy could enhance killing and clearance of bacteria in severe infection. This could be beneficial in terms of speeding source control or limiting the triggers of a dysregulated host response to infection. From a clinical and research perspective, these are fundamentally different questions but can be difficult ones to disentangle in the literature, as methodologies do not exclude multiple mechanisms, most commonly proposing broad empiric coverage and synergy as plausible (4, 9, 10, 12, 15). Even in studies that purport to address coverage alone (8, 11) or synergy alone (13, 14), the other hypothesis is a confounding one. Analyses investigating combination therapy suggest no benefit (16, 20–24) or improved mortality (25–27). Of note, only one large randomized trial has addressed combination therapy, with negative results (16). Given the trade-off of potential toxicities and benefit, there may be benefit in only the most severely ill or immunocompromised patients (21). A recent meta-analysis (22) found no differences in mortality, secondary infections, length of stay (LOS), or duration of mechanical ventilation. Subgroup analysis of higher illness severity (including comparing sepsis with septic shock) suggested no difference in mortality or secondary infections. Existing literature is limited to mostly observational studies and combinations that do not share similar agents with monotherapy.

Other potential sources of benefit for combination therapies include secondary effects of additional agents on bacterial pathogenicity (such as toxin production inhibition with ribosome-active antibiotics) or immunomodulatory properties (28). Care of necrotizing soft-tissue infections has exploited these properties, although supporting evidence is limited (29). Such mechanisms of benefit could be explored in animal models. Harms from combination therapy include direct drug toxicities (30–33), alterations in the microbiome, or the prospect of mitochondrial toxicities (34). Each of these

might be underrepresented in available literature, as studies are usually not powered for complications.

Gaps in Knowledge and Future Directions. The science behind this process remains unsettled, especially considering potential sources of either benefit or harm from combination antimicrobial therapy. There are several potential confounding factors and unresolved questions in the published literature. The severity of illness may be incompletely addressed; so too might the sensitivity of specific organisms to combination therapy. Discussions of spectrum and clearance should include nonbacterial pathogens. Further, ways to isolate testing adequate coverage from testing synergy are limited. Specific combinations (e.g., double beta-lactam vs beta-lactam plus aminoglycoside) may merit specific investigation (35). Dosing strategies may be as important for cure and mortality benefit as the use of combinations (36, 37).

There is opportunity for well-constructed trials to substantively improve the current state of knowledge about combination antibiotic therapies in sepsis. Open questions of specific agent combinations, purpose of combined coverage (with appropriately selected endpoints), patient selection, dosing, and monitoring are topics worth direct investigation in tightly controlled studies. Trials should ideally compare one agent as monotherapy with combination therapy in order to isolate the effect of combination therapy. Basic science investigations into mechanisms, such as toxin production inhibition and immunomodulation, may inform clinical research. Larger datasets that allow for appropriate risk stratification and analysis of the details of dosing strategies and complications could enhance low quality of evidence that currently exists.

Does Optimization of Antimicrobial Pharmacokinetics and Pharmacodynamics Impact Patient Outcomes in Sepsis?

What Is Known? The pathophysiologic changes observed during the course of sepsis and multisystem organ failure are known to alter the pharmacokinetics/pharmacodynamics (PK/PD) of antimicrobial agents. Although pharmacokinetics refers to the movement of drugs through the body, pharmacodynamics is defined as the biological response to drugs by the critically ill patient (38). Because of alterations to PK/PD in sepsis, traditional approaches to antimicrobial prescription

may result in suboptimal in vivo concentration (39, 40). Furthermore, septic patients may be more susceptible to experiencing adverse drug events from antimicrobial agents, due to the complex interplay between drug, host, and disease progression.

Clinical modifications that occur during sepsis such as increased cardiac output, capillary leak, and reduced protein levels such as albumin result in substantial changes in the volume of distribution (Vd) and clearance of antibiotics, both of which may affect the PK/PD of a drug (38). Derangements in Vd may be attributable to vasodilation, worsening endothelial integrity, and the large volume administration of IV fluids (40). An increase in Vd results in a corresponding decrease in antimicrobial serum concentrations. Alterations in drug clearance, primarily through renal dysfunction or augmented renal clearance, may significantly affect antimicrobial serum concentrations. Given the frequency of changes to Vd and clearance alterations in sepsis, it is likely that many patients experience significant deviations in antimicrobial PK/PD, possibly compromising microbial clearance and recovery from sepsis. Since there is no readily observable method to determine the effects of antimicrobial agents as opposed to other drugs (e.g., vasopressors), inadequate antimicrobial dosing may not be apparent to the clinician in real time.

Attempts at optimizing antimicrobial PK/PD have largely focused on prolonging infusion times in an effort to provide sufficient antimicrobial peak concentrations in relation to the minimum inhibitory concentrations (MICs) (peak:MIC) (41, 42). A recent meta-analysis of 13 studies with 1,957 participants was insufficient to recommend continuous infusion of IV antibiotics compared with intermittent infusions of antibiotics at routine clinical care (43), consistent with prospective studies evaluating prolonged antimicrobial infusions failing to improve mortality (44, 45).

Antimicrobial PK/PD optimization should also reduce toxicity. Recent meta-analyses suggest that the combination of piperacillin/tazobactam and vancomycin increases the risk of acute kidney injury (AKI) (31, 46). These studies were limited by the definition of AKI used and retrospective design. Importantly, meta-analyses of retrospective studies may intensify the bias in the underlying studies. Nevertheless, these studies highlight the importance of efforts at optimizing antimicrobial PK/PD with a goal of minimizing harm as an outcome.

Gaps in Knowledge and Future Directions. In spite of the recognition of pathophysiologic alterations affecting key antimicrobial PK/PD variables, there is a lack of higher level clinical data (e.g., prospective data) describing the relationship between antimicrobial serum concentrations and concentrations at the site of infection with outcomes in septic patients. Therefore, the concept of antimicrobial PK/PD optimization needs to be rigorously evaluated in clinical trials.

The current regulatory approval process for antimicrobials necessitates uniform dosing in a heterogeneous cohort of patients to demonstrate noninferiority to established treatments. Although this has been the standard approach for decades, it is unknown if uniform dosing is optimal in a patient cohort as dynamic as septic patients. Already, personalized drug dosing has expanded in other therapeutic arenas (47, 48). In contrast, evaluations of personalized antimicrobial PK/PD resource utilization in the clinical setting are lacking for septic patients.

In an era of personalized medicine, research efforts may also be directed at personalizing antimicrobial dosing to be more dynamic and reflective of pathophysiologic alterations in patient PK/PD variables. Work has been done in this field with studies of adjusted aminoglycoside daily dosing given their pharmacokinetics characteristics, but there is greater opportunity for expanding adjusted dosing to other antimicrobials (49, 50). Allowing for a more personalized dosing approach necessitates a change in regulatory requirements of antimicrobial research from the current approach of standardized dosing and noninferiority design. Conceivably, antimicrobial dosing can be adjusted in real time to match the physiologic needs of the septic patient, although to test this process for drug approval requires reforms to the existing review process.

Importantly, there is a need for the evaluation of resource utilization and healthcare delivery if the concept of personalized antimicrobial dosing in septic patients is to move from hypothesis to clinical practice. Estimating resource needs would be necessary for stakeholder support.

Should Viral Reactivation Resulting From Sepsis-Induced Immunosuppression Be Treated With Antiviral Therapy in Critically Ill Septic Patients?

What Is Known? Sepsis-induced immunosuppression in previously immunocompetent patients contributes

to poor outcomes, including organ failure and death. Studies have shown sepsis-induced deficits in the innate and adaptive immune system, including T-cell exhaustion (51–57). Evidence supports a contributing role for sepsis-induced immunosuppression, including T-cell exhaustion in development of secondary infections and in the reactivation of latent viral infections (58–60).

Multiple studies have documented reactivation of viruses in patients with sepsis, including cytomegalovirus, herpes simplex virus-1 (HSV-1), human herpes virus-6, Epstein-Barr virus (EBV), torque teno virus, and the polyomaviruses, BK virus and John Cunningham virus (57, 60–65). Although most studies detect reactivation in between 15% and 40% of patients with sepsis, some report levels up to 70% (65, 66). Associations have also been demonstrated between reactivation of viruses such as cytomegalovirus and EBV and increased secondary bacterial and fungal infections, with higher morbidity and mortality in patients with sepsis and critical illness (60, 67–69).

There are minimal conclusive data on antiviral therapy in patients with sepsis and critical illness. A recent placebo-controlled multicenter randomized control trial in critically ill cytomegalovirus-seropositive patients treated with either placebo or with ganciclovir followed by IV ganciclovir or oral valganciclovir did not show a difference in the primary outcome of change in interleukin (IL)–6 from day 1 to 14 (70). At 28 days, the ganciclovir group had significantly less cytomegalovirus reactivation and more ventilator free days, but there were no differences in mortality, mechanical ventilation days, ICU LOS, or secondary infection (70). One single-center, open-label randomized controlled trial tested the effects of anticytomegalovirus prophylaxis with valacyclovir or low-dose valganciclovir on cytomegalovirus reactivation in cytomegalovirus-seropositive patients (71). Although the study was underpowered for efficacy, results indicated that both antiviral agents suppressed cytomegalovirus reactivation in critically ill patients. Importantly, however, there was increased mortality in patients receiving valacyclovir which led to the study being halted (71). A retrospective analysis suggests that antiviral therapy may be beneficial in severe cytomegalovirus disease in previously immunocompetent individuals, but the rarity of severe cytomegalovirus in this context makes large randomized controlled trials difficult (72). Despite the

frequency with which ICU patients have HSV-1 reactivation in the oropharynx—as well as the association between HSV-1 reactivation and worse outcomes of critically ill patients—there are no definitive data on the efficacy of antiviral therapy for HSV-1 reactivation. Small studies have not shown improved outcomes with acyclovir (73).

Gaps in Knowledge and Future Directions. The role of testing for viral reactivation in patients with sepsis is not clear. Although studies have shown associations between viral reactivation and sepsis outcomes, there is uncertainty as to whether or not viral reactivation is causally related to poor sepsis outcomes. It is also unclear if coinfection with multiple viruses worsens sepsis outcomes compared with individual viruses. The efficacy of antiviral therapy in patients with sepsis-induced immunosuppression prophylactically to prevent viral reactivation and improve the outcome of patients with sepsis-induced immunosuppression is unknown. The role of antiviral therapy for known viral reactivation has also not yet been established. Furthermore, if antivirals are administered, it is not clear which viruses should be targeted.

Continued investigation is necessary to determine if viral reactivation promotes versus is associated with worse sepsis outcomes. Understanding the relationship between viral reactivation and outcomes would lay the groundwork for determining whether or not antivirals should be administered to previously immunocompetent patients with sepsis-induced immunosuppression. Furthermore, if viral reactivation is pathogenically important in sepsis outcomes, it will be necessary to determine which specific viruses play a pathogenic role in order to guide the design-targeted diagnostics and therapies. Finally, given potential toxicities of some antivirals, the risk-benefit ratio of treating patients with sepsis-induced immunosuppression for either the prevention of viral reactivation or the treatment of known viral reactivation still needs to be established.

Should Rapid Diagnostic Tests Be Implemented in Clinical Practice?

What Is Known? In sepsis, an untreated bacterial (or fungal) load increases exponentially over time (74). The toxic burden may thus increase in a similar fashion (75). There is concern that early use of antibiotics in patients with suspected sepsis but without shock might lead to antibiotic overuse. A proper assessment of the

risk of sepsis is needed as borderline patients may benefit less from aggressive early intervention than patients with shock. However, mortality rates for sepsis without shock at presentation are still high, especially in resource-limited settings (76, 77). Risk assessments should take into consideration baseline mortality rates and the balance between cost and benefit (78). Although the potential harm caused by an incorrect sepsis diagnosis or by the infusion of a single dose of antibiotics has not been established, observational data suggest there is a significant hazard of postponing recognition (79–83). The concern that overuse of antimicrobial agents will increase resistance is justified, but bedside decision-making is nuanced and often complex (84, 85). Antibiotics, if used appropriately, can be lifesaving. However, there is a threat from the rise in antibiotic resistance in many regions of the world. There are many explanations to this problem including the misuse and overuse of antibiotics. Notably, almost three-quarters of antibiotic use in the United States is with animals rather than patients (86). Additionally, antibiotic overprescribing is a common problem in primary care, where viruses cause most infections (87). Self-medication with antibiotics is also unregulated and available over-the-counter without a prescription in many parts of the world (88). Two major determinants of increasing antibiotic resistance are prolonged courses of antibiotics and subinhibitory and subtherapeutic antibiotic concentrations (89). Both promote the selection of pathogen strains and virulence.

If there is a suspicion of sepsis, clinicians rely on clinical symptoms only, rather than on a positive identification of a causative organism. This results in initially prescribing broad-spectrum, nonspecific antibiotic treatment since current methods used to identify and characterize an infecting organism require waiting 2–6 days for pathogen identification (90). There has been some work done with the use of viral nucleic acid amplification testing in ICU patients with promising results. Whole blood analysis with nucleic acid detection (including multiplex polymerase chain reaction assays and microarrays), rapid antigen detection, novel methods of pathogen detection (e.g., T2 magnetic resonance) and susceptibility testing (e.g., morphokinetic cellular analysis), and application of direct metagenomics on clinical samples have all been proposed as techniques superior to current methods. Unfortunately, the evidence about the real-life impact of these assays

on patient management is scarce (91, 92). This is a significant problem considering the patient mortality in septic shock has been reported to increase by 7.8% every hour for the first 6 hours that treatment is not administered (15). By the time a patient receives their diagnosis, they may already have tissue damage, organ failure, and death. Although early diagnosis and early targeted treatment can improve survival, current diagnostic products are insensitive (~30% to 65% failure rate) and take several days to obtain clinical diagnosis (93). Frequent contamination (> 50%) causes confusion and potentially inappropriate treatment (94).

Gaps in Knowledge and Future Directions. There is a clear unmet clinical need for a rapid diagnostic test to enable physicians to diagnose infection and administer the optimum antibiotic rapidly based on pathogen identification (95). To our knowledge, sepsis detection from whole blood within the desired time frame has not been investigated/reported within the healthcare setting. Projects should be developed for cost-effective early detection of sepsis-causing pathogens in whole blood. This would reduce the existing adverse effects of delayed or misdirected sepsis therapy. Although this could reduce a major growing public health concern, it is unknown if rapid diagnostics would improve patient outcomes and how rapid they need to be in order to have a clinically significant impact.

Antibiotic stewardship strategies rely on the results of microbiological cultures (96). Currently, the turnaround time for culture results is unacceptably long, taking more than 72 hours, in many cases. The appearance and development of rapid diagnostics would aid in developing stronger, clinically feasible antibiotic stewardship programs. Future research should look into placing this equipment in ICU and/or emergency departments.

What Is the Role of Lung-Protective Ventilation in Adult Septic Patients Without Acute Respiratory Distress Syndrome?

What Is Known? The use of low tidal volume combined with a sliding scale of positive end-expiratory pressure (PEEP) and F_{iO_2} combinations as a form of lung-protective ventilation (LPV) is effective at decreasing mortality and shortening the duration of mechanical ventilation in patients with established acute respiratory distress syndrome (ARDS) (97). Because ARDS is an inflammatory form of acute lung injury that may

be exacerbated by injurious mechanical ventilation, the mechanisms for LPV efficacy in established ARDS may also apply to prevent ARDS (98). Observational studies have demonstrated associations between the development of ARDS and several aspects of mechanical ventilation including higher tidal volumes, inspiratory airway and driving pressures, mechanical power, and the failure to apply LPV (99–102). The use of low tidal volume ventilation during major abdominal surgery seems to reduce perioperative complications, including reducing by 71% the risk of postoperative respiratory failure and ARDS and decreasing hospital stay by 2.5 days (103). In a comparison study, the perioperative use of high PEEP and recruitment maneuvers failed to prevent postoperative complications and led to greater intraoperative hypotension compared with lower PEEP without recruitment maneuvers (104). Another trial found no improvement in outcomes with high PEEP and recruitment maneuvers for obese patients undergoing surgery (105). Meta-analyses suggest the use of LPV in critically ill patients may prevent pulmonary infections, reduce the development of ARDS, shorten the duration of mechanical ventilation, and decrease mortality (106, 107). Studies suggest reduced inflammation with low tidal volumes (target 6 mL/kg predicted body weight [PBW]), compared with intermediate tidal volumes (target 10 mL/kg PBW) (108). Patients had reductions in IL-6 levels and less development of ARDS (2.6% vs 13.5%; $p = 0.01$). In another trial, the use of lower tidal volumes did not favorably impact the development of ARDS, infectious pulmonary complications, the duration of mechanical ventilation or ICU stay, or mortality at either 28 or 90 days (109).

Gaps in Knowledge and Future Directions. Current evidence is inconclusive for any benefit to the use of LPV in critically ill patients, and clinical trials that have shown benefit are primarily perioperative studies for a surgical population. The sepsis patient population is not specifically addressed in most studies despite sepsis patients being at higher risk of ARDS and sepsis being the most common cause of ARDS (110). In addition, evidence does not delineate which patient populations are most likely to benefit from LPV, or whether LPV would potentially benefit all sepsis patients or only those with high illness severity such as septic shock or those with other risk factors for ARDS such as chronic lung disease or alcoholism. The optimal tidal

volume is unknown for prevention of ARDS, as some studies compared modestly different tidal volumes and others employed potentially injurious ventilation strategies (103, 108). The results of one previously planned clinical trial are unknown (111).

Because of the frequency of respiratory failure in sepsis with adverse consequences of ARDS such as prolonged mechanical ventilation and mortality, optimizing the approach to mechanical ventilation could save thousands of lives and reduce healthcare costs through reductions in mechanical ventilation and ICU stay. A first step is to complete pilot studies to confirm and refine the optimal mechanical ventilation strategy for ARDS prevention in the appropriate patient population, followed by one or more clinical trials to definitively establish whether LPV may prevent ARDS or otherwise favorably benefit sepsis patients.

How Do We Determine the Efficacy of “Blood Purification” Therapies Such as Endotoxin Absorbers, Cytokine Absorbers, and Plasmapheresis?

What Is Known? Polymyxin B hemoperfusion is currently used in many Asian countries, especially in Japan. Many studies published from these countries suggest efficacy, but they do not constitute the high-quality data needed to advocate for this therapy as a standard of care.

A recent meta-analysis (112) found that very low-quality randomized evidence suggested that hemoperfusion, hemofiltration, or plasmapheresis may reduce mortality in sepsis or septic shock, whereas moderate quality evidence cannot provide any support for a difference in mortality using polymyxin B hemoperfusion. Evaluating Use of Polymyxin Hemoperfusion in a Randomized Controlled Trial of Adults treated for Endotoxemia and Septic Shock, the largest of randomized controlled trials, suggests that polymyxin B hemoperfusion does not reduce mortality (113), although post hoc analysis suggests a reduction in mortality in an extrapolated group with less severe endotoxemia. In this study, the dosing, timing, and duration of therapy are unclear and may not have been sufficient to clear circulating endotoxin or other disease mediators. Another trial is underway that may clarify this (114).

With respect to intra-abdominal sepsis, a large retrospective cohort study in 2014 (115) suggests

postoperative polymyxin B hemoperfusion did not confer any survival benefit for the overall study population or any of the studied subgroups of patients with abdominal septic shock. The pilot Early Use of Polymyxin B Hemoperfusion in Abdominal Septic shock trial of 64 patients who underwent emergency surgery for intra-abdominal infection showed that polymyxin B hemoperfusion added to conventional therapy improved hemodynamics and organ dysfunction and reduced 28-day mortality (116). In contrast, a randomized controlled trial of 243 patients with septic shock after emergency surgery for peritonitis related to organ perforation demonstrated a nonsignificant increase in mortality and no improvement in organ failure with polymyxin B hemoperfusion treatment compared with conventional treatment (117). Further, in a case-control study, hemoperfusion with polymyxin B added to continuous renal replacement therapy resulted in faster decrease in endotoxin levels, but no improvements in clinical, physiologic, or biological variables in adults patients with septic shock and suspected Gram-negative bacteria infection with elevated

plasma endotoxin activity (EAA > 0.6 endotoxin unit/mL) and AKI requiring continuous renal replacement therapy (118).

The use of cytokine absorbers seems to produce a reduction in IL-6 (119, 120). However, a small single-center study suggests CE marked extracorporeal cytokine adsorber (CytoSorb) therapy does not reduce plasma IL-6 levels and did not detect statistically significant differences in secondary outcomes of Multiple Organ Dysfunction Score, ventilation time, and time course of oxygenation (121). Other studies corroborate that early extracorporeal cytokine adsorption treatment in septic shock applied without renal replacement therapy might reduce clinical and metabolic variables, but neither of them demonstrates mortality benefit. Other observational data support the use of cytokine hemoadsorption as a way to remove endotoxin and cytokines in patients with septic shock-associated acute renal failure (122), reduce vasopressor dependence, or reduce organ dysfunction scores (123). There are no proper randomized trials of plasmapheresis although some nonrandomized studies suggest favorable clinical outcomes (124).

TABLE 1.
Overview of Key Research Opportunities for Infection and Blood Purification Therapies

Questions
Question 1: Should empiric antibiotic combination therapy be used in sepsis or septic shock?
Key recommendation: Perform well-designed trials to explore monotherapy vs combination therapy with appropriate risk stratification, dosing strategies, and analysis of complications.
Question 2: Does optimization of antimicrobial pharmacokinetics and pharmacodynamics impact patient outcomes in sepsis?
Key recommendation: Institute personalized antimicrobial dosing in real time to match the physiologic needs of the septic patient.
Question 3: Should viral reactivation resulting from sepsis-induced immunosuppression be treated with antiviral therapy in critically ill septic patients?
Key recommendation: Perform well-designed trials to understand the relationship between viral reactivation and outcomes in previously immunocompetent patients with sepsis-induced immunosuppression and which specific viruses should be targeted if a difference is found.
Question 4: Should rapid diagnostic tests be implemented in clinical practice?
Key recommendation: Determine cost-effective technology which can lead to earliest detection of sepsis-causing pathogens in whole blood and widely distribute devices in both emergency departments and ICU.
Question 5: What is the role of lung-protective ventilation in adult septic patients without ARDS?
Key recommendation: Determine optimal mechanical ventilation strategy for ARDS prevention and perform definitive clinical trials to prevent ARDS in septic patients.
Question 6: How do we determine the efficacy of “blood purification” therapies such as endotoxin absorbers, cytokine absorbers, and plasmapheresis?
Key recommendation: Perform clinical trials to determine both ideal patient selection and ideal technology in which blood purification interventions may improve outcomes.

ARDS = acute respiratory distress syndrome.

Gaps in Knowledge and Future Directions.

Considering two high-quality studies failed to produce any evidence of survival benefit, the current role of these therapies remains unclear. Most of the studies done are in patients with Gram-negative sepsis where endotoxin may play a major role in pathogenesis. There are no large randomized trials showing efficacy of endotoxin removal or plasmapheresis or in patients with septic shock as a whole group. The CytoSorb data are limited only to cytokine clearance rather than mortality benefits. Potential adverse effects of these therapies such as interference with anticoagulation strategies, impact on pharmacokinetics of other drugs (e.g., antimicrobials, sedatives, etc.), or anaphylactoid reactions are not yet studied. A single approach likely cannot be applied to all patients, and previous sepsis definitions may not be helpful in finding biologically similar patients to treat.

Gaps call for conducting large, well-designed, definitive studies in patients with sepsis or septic shock. Sepsis as a group is heterogenous, and group-specific studies are preferred. There should be more clarity in patient selection, and trials should be conducted in a specifically selected group that is most likely to respond to blood purification interventions.

CONCLUSIONS

An overview of key recommendations for the six research questions is provided in **Table 1**. Absent clear understanding of the mechanisms involved in sepsis and many infection control and adjunctive interventions offers promise by optimizing the timely and directed nature of therapies. Other interventions, such as hemoperfusion, could benefit from clarity in how they work to identify the best use (if any), especially in the context of expense and labor intensity. Ventilation strategies offer a good example of translating clinical science from other venues to treat sepsis patients, but even in this case, further clarity in this population is needed.

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APPENDIX

The Research Committee of the Surviving Sepsis Campaign group members: Ignacio Martin-Loeches, Craig M. Coopersmith, Daniel De Backer, Clifford S. Deutschman, Ricard Ferrer-Roca, Judith Hellman, Sameer Jog, Ishaq Lat, Flavia Machado, Greg Martin, Mark E. Nunnally.