Essentials of Sepsis Management

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KEYWORDS

- Sepsis • Sepsis syndrome • Surgical infection • Septic shock
- Goal-directed therapy

KEY POINTS

- Successful treatment of perioperative sepsis relies on the early recognition, diagnosis, and aggressive treatment of the underlying infection; delay in resuscitation, source control, or antimicrobial therapy can lead to increased morbidity and mortality.
- When sepsis is suspected, appropriate cultures should be obtained immediately so that antimicrobial therapy is not delayed; initiation of diagnostic tests, resuscitative measures, and therapeutic interventions should otherwise occur concomitantly to ensure the best outcome.
- Early, aggressive, invasive monitoring is appropriate to ensure adequate resuscitation and to observe the response to therapy.
- Any patient suspected of having sepsis should be in a location where adequate resources can be provided.

INTRODUCTION

Sepsis is among the most common conditions encountered in critical care, and septic shock is one of the leading causes of morbidity and mortality in the intensive care unit (ICU). Indeed, sepsis is among the 10 most common causes of death in the United States.[1] Martin and colleagues[2] showed that surgical patients account for nearly one-third of sepsis cases in the United States. Despite advanced knowledge in the field, sepsis remains a common threat to life in the perioperative period. Survival relies on early recognition and timely targeted correction of the syndrome's root cause as well as ongoing organ support. The objective of this article is to review strategies for detection and timely management of sepsis in the perioperative surgical patient. A comprehensive review of the molecular and cellular mechanisms of organ dysfunction and sepsis management is beyond the scope of this article. The information presented herein is divided into sections devoted to definitions and diagnosis, source

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control, fluid therapy, antibiotic therapy, and organ support for clarity of discussion, but the practitioner should understand that these approaches occur simultaneously at the bedside, and each action is related to, and should act in concert with, the others.

DEFINITION AND DIAGNOSIS

The most important aspect of intervention in sepsis is early recognition of the signs and symptoms of the condition. Reducing time to diagnosis and initiation of therapy for severe sepsis is considered a critical component of mortality reduction.[3] The Society of Critical Care Medicine and the American College of Chest Physicians proposed standard definitions of this illness spectrum in a consensus published in 1992. The systemic inflammatory response syndrome describes an immune response consisting of 2 or more of the following:

- Temperature greater than 38°C or less than 35°C
- Heart rate greater than 90 beats per minute
- Respiratory rate higher than 20 breaths per minute or a $Paco_2$ below 32 mm Hg
- Leukocytosis of 12,000/mm^3 or less than 4000/mm^3

This inflammatory reaction in the presence of infection is known as sepsis. Complications of organ failure and hypotension constitute severe sepsis. Finally, septic shock is defined by severe sepsis accompanied by hypoperfusion and organ failure refractory to fluid resuscitation.[4]

As with all clinical maladies, a focused history and physical examination can provide vital information about potential risk factors for infection and the most likely site of origin. Several clinical clues may support the clinician's suspicion of infection. For example, unexplained tachycardia is frequently the first indicator of inadequate organ perfusion or a hyperdynamic state of inflammation and should be thoroughly investigated in a perioperative patient. Septic patients, unlike those in cardiac failure or hemorrhagic shock, frequently have warm skin on examination because their peripheral vasculature is not constricted. Acute glucose elevation can be a predictor of infection and should raise the provider's suspicion when present.[5] Inadequate urine output, while useful in monitoring volume and perfusion status, is a late finding in sepsis and septic shock.

Sepsis in the surgical patient is likely an underappreciated cause of morbidity and mortality in the perioperative period. In the postoperative period beyond 24 hours, sepsis is by far the most common cause of shock. Sources include surgical site infections, catheter-related bloodstream infections (CRBSI), pneumonia, and urinary tract infections. Moore and colleagues[6] found that the abdomen was the most common site of infection in their general surgery ICU population, accounting for 63% of cases, followed by the lungs (17%), wound/soft tissue (10%), urinary tract (7%), and all other sites (4%). In fact, the authors demonstrated that the incidence of sepsis and septic shock exceeded those of pulmonary embolism and myocardial infarction by 10-fold. Gram-negative species were the most prevalent culprits, particularly in abdominal sources of sepsis.[6] An understanding of the patient's recent clinical trajectory is invaluable, particularly in the perioperative period. Host defense mechanisms can be compromised by many factors, including surgery, implanted devices, or previous antibiotic use. Knowledge of the patient's surgical history can give clues to mental status changes, increased minute ventilation, decreased urine output, glucose intolerance, thrombocytopenia, or gastrointestinal failure.

Appropriate cultures should be obtained before initiating antimicrobial therapy, provided the antimicrobials are not delayed. These cultures should include one set

of blood cultures drawn from any indwelling device, and a separate set drawn peripherally. If the site of origin is not clear, prompt imaging studies should be performed, as required, to investigate suspected sources of infection, and any potential source should be sampled.

Any patient suspected of being in septic shock should be immediately moved to the ICU and administered antibiotics within 1 hour. Septic shock, a result of infection and the attendant inflammatory response, is composed of metabolic derangements attributable to inadequate perfusion, resulting in the buildup of lactic acid and the disruption of normal cellular function. However, the other significant challenge of the shock syndrome consists of the organism's neuroendocrine responses aimed at restoring adequate perfusion. One of these responses, glucose dysregulation, is a common clue to the presence of an infectious source. One prospective study of 2200 trauma patients admitted to the ICU revealed a 91% positive predictive value of acute glucose elevation in the diagnosis of infection.[5] This stress-induced hyperglycemia is generally seen as a transient plasma glucose level greater than 200 mg/dL and is thought to occur following increases in cortisol, glucagon, and epinephrine. Acute glucose elevation should stimulate clinicians to search for a new source of infection.

When septic shock is diagnosed, fluid bolus should be given, unless there is indisputable evidence of acute left heart failure. Electrocardiogram tracing should be obtained immediately to determine the likelihood of cardiac dysfunction. Arterial blood gas should be measured, as pH will drop below neutral due to anaerobic metabolism and lactic acid accumulation, if a shock state exists.

After the syndrome is recognized and resuscitation is begun, a review of the patient's medical history is paramount to determine causation. Surgical sites must be quickly examined for erythema, drainage, bullous changes, or other signs of infection. Surgeons and those caring for surgical patients should have specific knowledge of any operative procedure a patient has undergone, because this will surely help them focus on possible causes for sepsis and septic shock. If sepsis occurs in the first 24 hours after surgery, surgical site infection should be entertained. A streptococcal wound infection can quickly progress to myofascial necrosis. If this is present, radical debridement in the operating room is mandatory, supported by antibiotic therapy.

SOURCE CONTROL

A specific, treatable source of sepsis should always be aggressively sought and addressed as rapidly as possible. Specifically, abscess drainage, wound exploration, debridement of necrotic tissue, removal of infected implanted device, or surgical control of infectious source should occur simultaneously with resuscitation and antibiotic administration. An identified source should always be sampled and cultured for targeted therapy. A rare exception for surgical intervention exists with pancreatic necrosis, in which delayed surgical intervention has been shown to produce better outcomes.[7] Without adequate source control, resuscitative efforts will not be successful. Definitive operation in the case of abdominal sepsis is not as important as limiting the ongoing physiologic insult. A damage-control approach is appropriate for septic shock from abdominal sources using the same principles as the damage-control approach to trauma care.[8]

FLUID THERAPY AND HEMODYNAMIC SUPPORT

The ultimate goal of any hemodynamic intervention is the improvement of tissue perfusion and oxygenation. Subtle changes in a patient's condition are valuable signs in early recognition of hypoxemia or acidosis. Adequate fluid resuscitation should ideally

be achieved before the use of vasopressors, although these are sometimes necessary earlier in severe cases. Initial fluid resuscitation should consist of crystalloid resuscitation of 30 mL/kg per ideal body weight. Patients with evidence of tissue hypoperfusion after initial fluid challenge, or those with persistent blood lactate concentration of 4 mmol/L or less, should receive ongoing, protocolized resuscitation. Evidence of hypoperfusion can appear in many ways, and treatment requires the physician to be at the bedside observing the effects of current therapy. Patients with early sepsis, whose vital signs may still fall within an expected range, might display metabolic derangements, such as confusion, a change in their state of wakefulness, or decreased urine output. If raising the blood pressure with volume or vasopressors mitigates these derangements, then central nervous system responsiveness or urine volume can be a good indicator of the adequacy of tissue perfusion.[9]

The Surviving Sepsis Campaign (SSC) suggests goals of this resuscitation are central venous pressure of 8 to 12 mm Hg, mean arterial pressure (MAP) of 65 mm Hg or more, urine output of 0.5 mL/kg/h or more, mixed venous oxygen saturation of at least 65%, or superior vena cava oxygen saturation of 70% (grade 1C recommendation).[10] A randomized controlled trial targeting these goals in the initial 6-hour period demonstrated a 15.9% reduction in 28-day mortality. This strategy was termed *early goal-directed therapy*.[11] Although the SSC demonstrated that adherence to fluid resuscitation targets was low, the goals remain a strong recommendation endorsed by the SSC.[12] Further study has determined goal-directed therapy is both clinically sound and economically beneficial.[13]

No clear benefit has been shown from the use of colloid solution over crystalloid in resuscitation for sepsis. A low-level recommendation comes from the SSC for the consideration of albumin in severe sepsis and septic shock.[10] The SAFE trial showed albumin to be as safe and effective as normal saline.[14] In a meta-analysis of 17 randomized trials, albumin administration showed small and variable benefit across different protocols. Although its use remains controversial, it can be considered in severe sepsis and septic shock in patients who have received large-volume crystalloid resuscitation.

Commonly, patients in septic shock decompensate to a point whereby their endogenous mechanisms can no longer maintain adequate oxygen delivery. In refractory shock, vasopressors are desirable aids to help compensate for distributive shock. If vasopressors are needed to reach the target of MAP of 65 or greater, norepinephrine is the first choice with strong α-1 and β-1 characteristics, and epinephrine may be added. Vasopressin (0.03 U/min) may be combined with norepinephrine but should not be used as the initial medication.[10,15] Clinicians must be aware, however, that these vasopressors are associated with serious adverse events, including dysrhythmias, chest pain, myocardial infarction, limb ischemia, mesenteric ischemia, and stroke. Patients who have such adverse events may also have significantly increased mortality.[16]

Phenylephrine is not recommended for use in septic shock unless norepinephrine is associated with severe dysrhythmia or as salvage therapy when other vasopressors have failed to achieve the target MAP.[17] Low-dose dopamine is not recommended for the purpose of maintaining renal function.[18] In the setting of myocardial dysfunction or ongoing hypoperfusion, despite intravascular volume replacement and adequate MAP, dobutamine should be considered at a rate up to 20 μm/kg/min.

Measurement of blood flow and intravascular volume status at the bedside can be assisted with multiple available technologies.[19] The use of these tools requires knowledge of their methods and limitations, however, so the data they generate can be correctly interpreted. The efficacy of these monitoring technologies requires further

study before these tools are deemed standard of care in sepsis management. An arterial catheter for monitoring and continuous analysis should be placed in any patient requiring vasopressors and aggressive blood pressure management. Pulmonary artery catheters, while used much less frequently than in past decades, may still be considered in shock management. A large meta-analysis of randomized controlled trials concluded that use of a pulmonary artery catheter did not increase overall mortality or days in the hospital, nor did it confer any other benefit.[20] Use of these technologies is based on clinician judgment and experience in interpreting data. Ultimately, the goal remains the same: to restore circulation to a normal state and reverse hypoperfusion while inflicting no further harm on the patient.

If hemodynamic targets can be met and perfusion restored with volume and vasopressors, additional corticosteroids provide no real benefit.[10] However, there may be a role for hydrocortisone supplementation in refractory hypotension, dosed at 200 mg per day. The CORTICUS trial, a large European multicenter trial, failed to show benefit from steroid therapy in patients with septic shock, although it included patients whether or not they were responsive to vasopressors.[21] Several other randomized trials have shown significant shock reversal with steroid therapy.[22–25] Random cortisol levels and adrenocorticotropic hormone stimulation testing have not been demonstrated to be useful or predictive of patients who will benefit from steroid supplementation.[21,22]

ANTIMICROBIAL THERAPY

The timely administration of appropriate antimicrobials is critically important to reduce morbidity and mortality from sepsis.[26–29] The choice of agents is based on multiple factors, including patient history, details and timing of surgical procedures, previous antibiotic exposure, and hospital antimicrobial susceptibility patterns. Cultures of blood, urine, pulmonary secretions, wound drainage, or other potential infectious sites should be performed *before* initiation of antibiotics. Broad-spectrum antimicrobial therapy should begin within 1 hour of recognizing the presence of severe sepsis or septic shock.[10]

The initiation of broad-spectrum antibiotics, meant to cover a host of possible culprit organisms, should be able to contain the most common infectious agents in a given hospital or ICU and be effective at limiting superinfection and resistant organisms. The prevalence of methicillin-resistant *Staphylococcus aureus* should be considered, and initial antimicrobial therapy should include agents active against this strain. In addition, antifungal therapy should be considered if candidemia is a likely pathogen. Recent Infectious Diseases Society of America guidelines recommend antifungal therapy in immunosuppressed or neutropenic patients, those who have received prior antibiotic therapy, or those who have fungal colonization.[30] Combination therapy including an extended-spectrum β-lactam and an aminoglycoside or fluoroquinolone should be used if complicated or multidrug-resistant infections such as *Acinetobacter* and *Pseudomonas* species are suspected.[10] Combination therapy for suspected or known *Pseudomonas aeruginosa* or other multidrug-resistant gram-negative pathogens increases the likelihood that at least one agent will be effective.[31]

Daily assessments of the antibiotic regimen should examine clinical progress of the patient, culture data to guide de-escalation of the broad-spectrum regimen and target specific culprit organisms as soon as they are known, and compliance with antibiotic stewardship guidelines to ensure appropriate combinations and length of therapy. Such stewardship programs are in place to prevent resistance, reduce toxicity, and

reduce costs.[10] Once the causative pathogen is identified, the most appropriate and cost-effective regimen should be implemented. This practice reduces the likelihood of superinfection with opportunistic organisms such as *Candida* species, *Clostridium difficile*, or vancomycin-resistant *Enterococcus* species, which can all be sources of septic shock and subsequent mortality. Once started, antimicrobial therapy should generally not exceed 7 to 10 days. Certainly, variables exist that necessitate longer therapy including certain patient factors relating to response and immune susceptibility, undrained foci of infection, and some fungal infections.

A common challenge in critical care is determining when to stop antibiotics. Occasionally, patients appear septic, and broad-spectrum antibiotics are initiated, but culture data never identify causative pathogens. Clinicians are then presented with the conundrum of continuing antibiotics in a patient who might be clinically improving, although there is no specific infection identified, or stopping the regimen to prevent opportunistic infection, resistance, and wasted resources. Multidrug resistance increases the cost of antimicrobial treatment by as much as 50%.[32] The use of biomarkers such as C-reactive protein and procalcitonin to differentiate between infection and inflammation without an infectious source remains undefined.[33] Procalcitonin levels might aid in the decision to discontinue antibiotics in this scenario, although available evidence remains conflicting.[33–35] Clinicians should recognize that even though bacterial and fungal sources are likely, blood cultures may be negative in as many as half the cases of severe sepsis if empiric therapy is administered.[10] The decision to continue, narrow, or stop antimicrobial therapy is made on clinician judgment with available information. Antimicrobial agents should not be used in states of severe inflammation determined to be of noninfectious cause.

Clinicians should also consider sepsis of viral origin, and antivirals should be initiated similar to antimicrobials. Viruses such as influenza, cytomegalovirus, and other herpes viruses can all induce septic shock and should be considered in cases with no clear bacterial infection. The role of some viruses in sepsis remains unclear, and active viremia may act as a marker of disease severity rather than an actual agent of organ injury and death in septic patients.[36]

ORGAN SUPPORT AND MONITORING

A comprehensive discussion of the mechanism and therapies for shock is beyond the scope of this review, but the practitioner's understanding of the essentials of managing septic shock is critical to patient survival. Knowledge of the shock syndrome has increased dramatically over the past several decades, and all advances point to the goal of prompt restoration of oxygen delivery. Invasive devices such as arterial blood pressure monitors, central venous catheters, and urinary catheters are helpful to guide therapy, although their placement should not detract from focusing on ongoing resuscitation of the patient.

Tachypnea is common in the septic patient, as is mental status deterioration. Intubation and mechanical ventilation might be warranted, depending on clinical findings. Resuscitation should be ongoing while intubation is performed. Ventilation strategies should be based on lung-protective strategies that have been supported by clinical trials and widely accepted. The precise choice of ventilator mode and tidal volume varies according to degree of respiratory distress and hypoxemia, sedation required, volume status, and other factors that make ventilator support in the septic patient a dynamic and individualized process. Positive end-expiratory pressure, recruitment maneuvers for hypoxemia due to acute respiratory distress syndrome (ARDS), and prone positioning in sepsis-induced ARDS with Pa_{O_2}/Fi_{O_2} ratio less than or equal to

100 are all available adjunctive tools to improve oxygenation in the septic patient. Rescue therapies such as high-frequency oscillatory ventilation, airway pressure release ventilation, and extracorporeal membrane oxygenation require experienced personnel with significant expertise.[37]

Although the optimum hemoglobin concentration in sepsis is not defined, red blood cell transfusion is an important tool in organ support. The American College of Critical Care Medicine Taskforce of the Society of Critical Care Medicine and the Canadian Critical Care Trials Group endorse evidence-based transfusion for hemoglobin concentration less than 7 g/dL.[38,39] In patients with ongoing myocardial ischemia, hemorrhage, ischemic coronary disease, or other comorbidities, this transfusion trigger may be altered based on clinician judgment.

Immediately available indicators of global tissue perfusion include arterial pH and lactic acid. These indicators of the metabolic state are important, and mortality is as high as 46.1% in patients with both hypotension and lactate greater than 4.[12] Once resuscitation has restored adequate oxygen delivery, lactate should be metabolized and pH should return to normal. Persistent acidosis indicates inadequate source control such as ongoing bleeding or tissue necrosis. Lactic acid can be used as a marker of hypoperfusion and the depth of the shock state.

NUTRITION AND GLUCOSE CONTROL

Nutrition management in critically ill patients is an important and frequently overlooked aspect of care. Nutrition strategies that take into account information specific to the patient's perioperative condition, first-hand knowledge of the patient's operative history, and available nutritional access and support options should be in place. It is preferable that patients be fed enterally, which can be accomplished orally or via gastric or enteric feeding tube. If enteral feeding is not possible, total parenteral nutrition can be instituted per hospital protocols. Nutrition is frequently withheld in the perioperative period because of ileus and intestinal surgery, among other reasons. No direct evidence defines benefit or harm of parenteral nutrition in the first 48 hours in sepsis.[10] An adjunct to nutritional regimens is stress-ulcer prophylaxis. Patients with severe sepsis or septic shock who have bleeding risk factors should be placed on H2-blocker or proton pump inhibitor. Patients who are not coagulopathic, do not require mechanical ventilation for at least 48 hours, and are normotensive do not require stress-ulcer prophylaxis.[10] In addition, those receiving enteral nutrition do not need prophylaxis, and some evidence suggests that ulcer prophylaxis in this group might increase the risk of pneumonia and death.[40]

Glucose regulation can be a challenge in the perioperative period when nutrition is variable, and an infection state complicates this further. The largest study to date addressing glucose control in ICU patients is the NICE-SUGAR trial, which used a glucose level of 180 mg/dL as the upper limit of control. Multiple consensus statements for glycemic control in hospitalized patients have emerged, generally targeting levels between 140 and 180 g/dL.[41–43] Goals should be within this range, and efforts should be made to avoid wide swings in glucose levels. Of note, clinicians should adjust insulin regimens when nutrition is withheld or discontinued, because this is a common risk factor for hypoglycemia and there are large variations in glucose levels.

SPECIFIC PERIOPERATIVE ISSUES

Surgeons and those caring for surgical patients such as rapid response teams or critical care support teams should be aware of hospital protocols for resuscitation of acutely ill patients. Patients in the perioperative period frequently require pain control,

and many agents can suppress respiratory drive if not closely monitored. Drug inter-actions can cause delirium, hypoxemia, tachycardia, and other signs similar to early sepsis that must be detected and treated appropriately to rescue patients from poten-tial decline.

Septic patients are at increased risk for deep venous thrombosis. Patients with sepsis need daily venous thromboembolism prophylaxis, usually with daily low-molecular-weight heparin unless there is a contraindication to heparin use. Consequences of pulmonary embolism, particularly if a septic patient is already hemodynamically compromised, can be fatal.

NOSOCOMIAL SEPSIS PREVENTION

Prevention of secondary sepsis remains an important goal in surgical critical care. The nosocomial contributors of in-hospital sepsis are widely known but still poorly controlled. Rigorous infection control practices, as recommended by the SSC, should be enforced in any health care environment.[44] Multiple well-designed studies have demonstrated efficacy of focused interventions to reduce nosocomial infections.[45,46] Many health care facilities have specific policies to reduce nosocomial infection, which should be strictly followed by all who enter patient care areas, including family members and visitors, although they are frequently not required to do so.

Ninety percent of nosocomial sepsis cases are associated with central lines,[47] and research in this area is accordingly active due to both the clinical implications and the fact that Medicare and private insurers are discontinuing reimbursement for treatment of CRBSI and hospitals are being forced to assume these costs.

Strategies for preventing CRBSIs include proper hand hygiene for providers, the use of sterile barrier precautions for placement of central venous catheters, including skin antiseptic preparation, early removal of catheters as soon as they are no longer required, and routine replacement of connector tubing.[45,48] Antibiotic-impregnated catheters have also been used as a CRBSI-prevention strategy, with multiple studies supporting their effectiveness in reducing CRBSI incidence and cost. The Institute for Healthcare Improvement has advocated for a central-line infection prevention bundle comprising 5 elements: optimal hand hygiene, maximal sterile barrier precautions for catheter insertion, optimal catheter site selection, chlorhexidine skin antisepsis, and the daily evaluation of central line necessity.[49]

SUMMARY

This review outlines essentials of sepsis management in the surgical patient across the spectrum of care. Early recognition, aggressive fluid resuscitation, source control, and antibiotic therapy result in the best possible survival for patients suffering from sepsis. The Surviving Sepsis Guidelines should be reviewed and understood by any clinician caring for perioperative patients. Sepsis bundles, or protocols to enact evidence-based best practice, should be structured so that they can be implemented in a timely fashion to improve care delivery.

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