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Sepsis Pathophysiology and Anesthetic Consideration

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Abstract

Sepsis remains to be a significant health care issue associated with high mortality and healthcare cost, despite the extensive effort to better understand the pathophysiology of the sepsis. Recently updated clinical guideline for severe sepsis and septic shock, “Surviving Sepsis Campaign 2012”, emphasizes the importance of early goal-directed therapy, which can be implemented in intraoperative management of sepsis patients. Herein, we review the updates of current guideline and discuss its application to anesthetic management. Furthermore, we review the recent advance in knowledge of sepsis pathophysiology, focusing on immune modulation, which may lead to new clinical therapeutic approach to sepsis.

Introduction

The word “sepsis” was first introduced by Hippocrates in the medical literature to describe the diseases as a consequence of self-intoxication with harmful products derived from the colon [1]. Hugo Schottmuller introduced the modern definition in 1914, as “sepsis is a state of microbial invasion from a portal of entry into the blood stream which causes signs of illness” [2]. Since then, terms such as “bacteremia”, “septicemia”, “sepsis”, “sepsis syndrome”, and “septic shock” were used interchangeably to indicate patients exhibiting systemic responses to infection without any specific diagnostic criteria [3]. High mortality associated with sepsis motivated various clinical studies and mechanism researches. However, the lack of clear definition of sepsis made it difficult to interpret these studies. Starting at the consensus conference in 1992, the establishment of conceptual and practical definition of sepsis has been attempted to make early bedside detection and allow early therapeutic intervention, where sepsis was defined as systemic inflammatory response to the presence (documented) of infection [3]. Most recently in Surviving sepsis campaign 2012 (SSC 2012), sepsis is defined as “the presence (probable or documented) of infection together with systemic manifestations of infection”, detailed in (Table 1) [4]. Severe sepsis is defined as “sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion” as in (Table 2).

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Tissue hypoperfusion, if persists, leads into organ dysfunction and failure. No surprise severe sepsis is the leading cause of death in the non-cardiac intensive care unit (ICU) [5]. Angus *et al.* studied the incidence of severe sepsis selected by ICD-9 codes for both bacterial or fungal infectious process and a diagnosis of acute organ dysfunction at all the hospitals in 7 states. They estimated that about 751,000 sepsis cases occurred in 1995 with the hospital mortality rate of 28.6 % in the U.S. [6]. Teres *et al.* studied the outcome of severe sepsis using the 1992 consensus conference definition at 50 intensive care units from 1998 to 1999. The hospital mortality rate was even higher (36.3%) [7]. It remains to be a substantial health care burden with a high mortality, responsible for 40% of ICU expenditures. The costs are estimated to be about \$16.7 billion per year [6].

In parallel to the advancement of health care, the number of patients suffering from sepsis has been on rise due to the increasing number of aging patients infected with treatment-resistant organisms, with compromised immune systems, and undergoing prolonged high-risk surgery [8]. The incidence was projected to increase by about 1.5% yearly [6]. One of cardinal sepsis managements is to identify and treat the source of infection. Surgical intervention represents one of the “source control” methods, consisting of drainage of infected fluids, debridement of infected soft tissues, removal of infected devices or foreign bodies, and finally, definite measures to correct anatomic derangement. Given the increasing number of septic patients, surgical interventions in this population will be experienced more frequently. Here, we review the up-to-date knowledge of sepsis management, pathophysiology, and potential concerns in the intraoperative management.

Surviving Sepsis Campaign Guideline of Management of Severe Sepsis and Septic Shock: 2012

With extensive research, various pathophysiological derangements have been described in sepsis and more than 30 phase III randomized trials have been tested to address the efficacy of targeted drug therapies without success [9].

Due to the persistently high mortality associated with sepsis, a group of international critical care and infectious disease experts have developed guidelines that caregivers could use to improve the outcomes of septic patients. The resultant consensus guideline named “SSC guidelines for management of severe sepsis and septic shock” was published in 2004 [10]. The goal of sepsis management is to immediately achieve adequate control of the source of infection with the least physiological embarrassment. The third edition of SSC guidelines, namely SSC 2012 was published recently [4]. The current version reflects significantly growing literatures, where many recommendations in the original version were revised. These changes should be also reflected in the intraoperative care.

Initial Resuscitation (Early Goal-Directed Therapy; EGDT)

Rivers *et al.* showed that the implementation of EGDT improved survival in 263 patients who presented with septic shock (entry criteria: systemic blood pressure < 90 mmHg or lactate > 4 mmol/L) in the single center emergency department (ED) [11]. In this study, EGDT was defined as resuscitation with the goal of central venous pressure (CVP) 8- 12

mmHg, mean arterial pressure (MAP) $\geq$ 65 mmHg, and central venous or mixed venous oxygen saturation $\geq$ 70% during the first 6 hours following the identification of patients. These goals were aimed at *via* crystalloid resuscitation to restore preload, vasopressors to maintain adequate mean arterial pressure, administration of packed red blood cells (targeting hematocrit of 30%) and/or dobutamine to achieve a goal mixed venous oxygen saturation. Overall, the EGDT arm achieved less hospital mortality compared to the control arm (30.5 % vs 46.5%, respectively). The clinical benefit of EGDT was validated in several studies [12-15]. Because the earliest, effective therapeutic interventions allow survival benefit to patients, now sepsis is recognized as a time-sensitive emergency. SSC guidelines in 2004 already recommended this early resuscitation goal. Thereafter, the reduction of lactate value as a surrogate marker of tissue hypoperfusion, was validated in two clinical studies [16, 17]. The new resuscitation bundle of SSC 2012 reflects this information as listed in (Table 3). The resuscitation bundles of SSC 2012 were rearranged into two parts shown in (Table 3).

There are several modifications in hemodynamic support for EGDT in SSC 2012. First, crystalloids are recommended as the initial resuscitation fluid. When patients receive substantial amount of crystalloids, the administration of albumin is suggested. The administration of hydroxyethyl starches (HES) is no longer recommended. This is based on the results of several randomized trials where HES did not show survival benefit, and even associated with increased risk of acute kidney injury [18-20]. Second, clear orders of recommendation was given in the choice of vasopressors to achieve target MAP $>$ 65 mmHg. The initial SSC guideline advocates dopamine or norepinephrine as a primary vasoactive drug [10]. However, the analysis of five randomized trials comparing norepinephrine to dopamine by SSC committee showed favor of norepinephrine in the short-term mortality [4]. Also a meta-analysis showed that dopamine was associated with an increased risk of arrhythmias [21]. The recommendations of SSC 2012 are 1) norepinephrine as the first-choice vasopressor, 2) epinephrine as the first alternative to norepinephrine, 3) vasopressin up to 0.03-0.04 unit/min can be used only if a patient does not respond to other vasopressor agents, but not as a solo agent, and 4) dopamine for only highly selected patients such as patients with absolute or relative bradycardia.

The practice of targeting hematocrit of 30% to attain the target mixed venous saturation was advocated in the original EGDT protocol and included in SSC 2008. The landmark study of ICU patients by Hebert *et al.* demonstrated that the restrictive red cell transfusion (transfusion at hemoglobin $<$ 7 g/dL, maintaining hemoglobin of 7-9 g/dL) was at least as effective as and possibly superior to the liberal transfusion (transfusion at hemoglobin $<$ 10 g/dL, maintaining 10-12 g/dL) [22]. Wu *et al.* retrospectively studied the intraoperative transfusion threshold for patients aged 65 years or above presenting to general surgical procedures. Transfusion was associated with a lower 30-day postoperative mortality in the case of substantial operative blood loss or low preoperative hematocrit level ($<$ 24 %). However, transfusion was associated with increased mortality risks when preoperative hematocrit levels between 30 % and 35.9 % and/or blood loss $<$ 500 mL [23]. In various critical care literatures, the overall consensus of blood transfusion threshold is around hemoglobin 7(- 9) g/dL [24]. SSC 2012 recommends that red blood cell transfusion should

occur when the hemoglobin concentration decreases to < 7.0 g/dL to target a hemoglobin concentration of 7.0 to 9.0 g/dL.

Diagnosis

Diagnostic testing such as cultures and diagnostic imaging is indispensable. SSC 2012 recommends obtaining appropriate cultures before antimicrobial therapy is initiated (Table 3). Two or more blood cultures (both aerobic and anaerobic bottles) should be sent, at least one drawn percutaneously. Culture should be sent from each port if the indwelling catheter(s) is placed > 48 hours. The diagnostic imaging is increasingly important in confirming the sites of infection, excluding alternative pathology, and guiding radiological or surgical source control procedure. This should be performed promptly.

Source Control and Antimicrobial Therapy

Rapid, adequate infection source control with the least physiological embarrassment is a cardinal component in sepsis management. Source control measures include the administration of appropriate antibiotics and interventions including drainage of infected fluids, surgical debridement of infected soft tissues, removal of infected devices or foreign bodies, and finally, definite measures to correct anatomic derangement. The drainage can be performed percutaneously under imaging guidance or by an open surgical approach. The current guideline states that interventions should take place for source control within the first 12 hours after the diagnosis is made [4]. Unfortunately, they are not risk-free. Surgical intervention may cause further complications such as bleeding, fistulas, or inadvertent organ injury. Or surgical manipulation may potentially release infective materials systemically, worsening patients' hemodynamics and requiring further resuscitation. In the case of peripancreatic necrosis as a potential source of infection, definitive intervention should be delayed until adequate demarcation of viable and nonviable tissues has occurred [25].

Intravenous antibiotics should be started as early as possible after the diagnosis of severe sepsis and septic shock. Broad-spectrum agents should be used initially against all likely bacterial pathogens. Antifungal coverage may be considered at high-risk patient population (immunocompromized patients etc). The resuscitation bundle proposed that this should be accomplished within 3 hours (Table 3), ideally within one hour [4]. The rationale behind is that a number of studies demonstrated each hour delay in administration of effective antimicrobial agents increased mortality by 7.6 % [26, 27]. It is worth mentioning that common culprits of sepsis have shifted from gram negative organisms to gram positive organisms and fungi over the years [28]. In addition, a spectrum of causative organisms and their anti-biograms in each institution should be taken into account when choosing antibiotics coverage. Once causative organism(s) is isolated and susceptibilities determined, de-escalation of the initial broad-spectrum therapy is necessary while minimizing antimicrobial exposure that otherwise may lead to the development of antibiotic resistance, and lead to overgrowth of *Clostridium difficile* in gastrointestinal tract. In the setting requiring surgical intervention, there is some debate over whether broad-spectrum antibiotics should be withheld until appropriate, intraoperative cultures are obtained, and may need case-by-case discussion among multidisciplinary teams.

Steroids

For patients suffering from adrenal insufficiency, steroid may be potentially helpful. One of the effects is to improve vascular tone that is mediated by increasing the sensitivity of smooth muscle to catecholamines and reducing nitric oxide formation [29]. Hydrocortisone is indicated only for patients with septic shock where fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability. SSC 2012 recommends intravenous hydrocortisone alone at a dose of 200 mg/day. This principle can be applicable intraoperatively.

Recombinant Activated Protein C (rhAPC)

rhAPC is no longer recommended in sepsis based on the result of the recombinant human activated protein C worldwide evaluation of severe sepsis (PROWESS)-SHOCK trial. The study did not show any benefit in patients with septic shock [30]. The drug is no longer available in the market.

Mechanical Ventilation (Lung Protective Ventilation)

Acute lung injury often complicates sepsis, and lung protective ventilation should be performed. Lung protective ventilation consists of low tidal volumes with the goal of maintaining end-inspiratory plateau pressures less than 30 cmH₂O. The study by Eisner *et al.*, who compared the use of low tidal volume (6 mL/kg) versus traditional tidal volume (12 mL/kg), demonstrated that the low tidal volume ventilation group had the reduction of mortality in sepsis with acute lung injury [31]. To avoid pulmonary venous desaturation with the use of low tidal volume ventilation, positive end-expiratory pressure can be used and will help to decrease oxygen requirement. This ventilatory strategy can be applied intraoperatively.

Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

SSC 2012 recommends minimization of continuous or intermittent sedation in mechanically ventilated septic patients. The rationale is that the protocol-based sedation was shown to be associated with reduced duration of mechanical ventilation, length of stay, and tracheostomy rates [32]. However, whether or not daily sedation interruption is beneficial is still not conclusive. Earlier studies supported the benefit [33, 34], but the recent study did not show any benefit except surgical patients who demonstrated shortened intubation period with daily sedation interruption [35].

Skeletal muscle weakness, especially respiratory muscle weakness, has been reported in critically ill patients likely due to muscle wasting and disuse secondary to prolonged bedrest, especially in those following the use of intermediate and long-acting neuromuscular blockades (NMBs). Critical illness neuropathies and myopathies have been reported to be associated with NMB use based on case series and nonrandomized observational studies, the causality of which is still to be determined. A recent study of continuous infusion of cisatracurium in patients with early adult respiratory distress syndrome (ARDS) and PaO₂/FiO₂ < 150 mmHg (ACURASYS study) showed improved survival rates and more

organ failure free days without weakness [36]. Based on this, the guideline states that NMBs should be avoided if possible in the septic patients without ARDS.

Pros and Cons of SSC Guidelines

Although SSC 2012 is too soon to be evaluated, there are promising results from the performance of earlier guidelines. The implementation of earlier guidelines has been shown to improve the outcome of patients [12-15]. In addition, it may be financially favorable. The implementation of protocol-driven sepsis management was substantial cost-saving in one study [37]. The simulation study based on the existing data also supported the reduction of cost, attributed mostly to shortening the length of hospital stay [38].

However, the adherence to all applicable elements of the bundles in SSC2008 still seems to be not accomplished as people would hope [39]. The adherence to CVP and ScvO₂ targets for initial resuscitation was low [12, 40]. There often seems to exist the lack of agreement on the protocol, including the concern over the potential harm of central line insertion and question on predicting preload status based on CVP value and targeting CVP of 8- 12 mmHg [41]. The location where this protocol is initiated may also matter. There are concerns of initiating this protocol in the ED due to potential ED overcrowding and inadequate staffing [38] and equipment in availability [41]. Earlier guideline recommended blood transfusion up to hematocrit of 30 % to meet ScvO₂ goal if necessary. There was a concern about this practice. In SSC 2012, this practice is no longer recommended as stated above. In addition, bundled therapies are not tailored individually to particular patients' needs. The adherence to SSC 2012 and mortality improvement is to be re-evaluated hereafter.

Anesthetic Management

Problems of Septic Patients who Present to Surgical Procedures

Patients with severe sepsis may have significant respiratory and cardiovascular embarrassment. Early sepsis is accompanied by a decrease in systemic vascular resistance and high cardiac output [42]. In advanced sepsis, myocardial contractile failure can be seen. In the absence of vigorous fluid resuscitation, the cardiac output is decreased and the patients can be cold and clammy. Early resuscitation referring to SSC 2012 is, therefore, quite important. The resuscitation should be tailored to adjust preload, contractility, and afterload prior to surgical procedures. The first 6 hours of resuscitation phase frequently coincide with the time for emergency surgery. Consideration should be given before moving patients to the operating room whether patients are stable enough for transport.

Anesthetic Management Based on Currently Available Clinical Literatures

Patients undergoing source control procedures are in an inherently unstable cardiovascular state. The majorities of anesthetics not only have direct cardiovascular depressant effects, but also inhibit compensatory hemodynamic responses such as baroreflex. These drugs can further aggravate the reduction of preload and afterload. Every attempt should be made to adequately volume-resuscitate before the induction of anesthesia.

General anesthesia is usually indicated during surgical procedures for sepsis. General anesthetics are composed of intravenous and inhalational anesthetics. Intravenous anesthetics include propofol, etomidate, and ketamine. Inhalational anesthetics include isoflurane, sevoflurane and desflurane. The induction of general anesthesia is typically performed using intravenous anesthetics. Etomidate has minimal effect on cardiovascular profiles and deems ideal for induction. However, etomidate can inhibit adrenal mitochondrial 11- β -hydroxylase activity and may induce adrenal suppression. Two recent studies demonstrated that the use of etomidate was associated with increased mortality and adrenal insufficiency in sepsis [43, 44]. Therefore, etomidate may not be a preferred option.

There is no literature that studied the outcome benefit in sepsis when anesthesia is maintained inhalationally or intravenously. One study which compared propofol versus isoflurane anesthesia in patients undergoing abdominal surgeries demonstrated that isoflurane arm had increased incidence of postoperative tracheobronchitis and pneumonia within a month [45]. This was a rather small study in patients for elective procedures, but it will be interesting to evaluate in the future whether or not the maintenance by different anesthetics has any impact on the outcome of sepsis.

Sepsis may alter both the pharmacokinetics and the pharmacodynamics of drugs. For example, the requirement of inhalational anesthetic was reduced in severe sepsis [46]. Monitoring the depth of anesthesia by bispectral index monitoring may optimize the level of anesthesia and alleviate hemodynamic compromise from anesthetic overdose.

Hemodynamic and respiratory management during surgery should be referred to the recommendation of SSC 2012. Resuscitation effort should be continued intraoperatively to meet the resuscitation bundle target. A couple of things may be specific intraoperatively. First, the hemodynamic state may be further compromised due to blood loss or systemic release of bacteria or endotoxins. Transfusion of blood products should be done without delay if there is significant bleeding. Second, CVP of 8-12 mmHg as recommended as a goal in the resuscitation bundle may not be appropriate intraoperatively. CVP values may undergo dynamic change, depending on the change of intra-thoracic or –abdominal pressures through surgical manipulation. Markers such as pulse pressure variation can be valuable tools to estimate volume responsiveness in this case.

Pathophysiology of Sepsis and Consideration of Anesthetics' Choice in the Future

Sepsis is a time-sensitive condition and the implementation of EGDT reinforced this concept. Although these interventions have improved the outcomes of septic patients, severe sepsis still carries a high mortality rate. The persistently high mortality rate despite early aggressive resuscitation suggests a need for novel therapeutic interventions to further improve survival, requiring thorough understanding of sepsis pathophysiology. EGDT sets “6 hours” as a golden period of intervention. However, patients are at the similar physiological state during this “6 hours” window?

Hotchkiss *et al.* suggested that immunological responses could be different among patients [47]. A certain subset of patients may have a very short hyperinflammatory stage before experience a hypoinflammatory response. Extensive research has been done to understand the pathophysiology of sepsis. While our understanding is still far from complete, sepsis turns out to be quite heterogeneous and complex, involving multiple systems. In this section, we review the known pathophysiology of sepsis. And then in next section, we review the immune-modulatory effects by anesthetics.

“Exaggeration of Inflammatory Response” Theory

Lewis Thomas popularized the theory that the host defense, rather than the microorganisms was responsible most for the morbidity and mortality from sepsis [48]; Systemic activation of our innate immune system becomes too excessive to damage our own body. Immune cells recognize not only microorganisms (pathogen-associated molecular patterns; PAMPs) but also damaged tissues (damage-associated molecular patterns; DAMPs) [28]. A significant amount of DAMPs, derived from both invading microorganisms and damaged host tissues, highly stimulate host immune system and create uncontrolled proinflammatory responses, often described as “cytokine storm” [28]. Various animal sepsis models (lypopolysaccharide (LPS) injection, bacterial injection, cecal ligation and puncture (CLP), etc) have recapitulated this process. Besides, the genetic deletion or antagonizing some of proinflammatory mediators improved the survival of septic animals [9]. These findings led to many clinical trials of anti-inflammatory agents based on the assumption that uncontrolled pro-inflammatory responses caused organ injuries and ultimately the death of patients [49]. Anti-tumor necrosis factor (TNF)- α antibody and interleukin (IL)-1 receptor antagonist were among the agents tested. Overall, they did not demonstrate any clinical benefit [49-51].

The discovery of one of pattern recognition receptor (PRR) Toll-like receptors (TLRs) further enhanced our understanding of sepsis [52]. TLRs recognize PAMPs and DAMPs, and stimulate intracellular signaling leading to the production of inflammatory cytokines. For example, TLR4 is a well-known PRR, recognizing LPS from Gram-negative bacteria (an example of PAMPs) and a late phase mediator of sepsis high-mobility group box 1 (HMGB1) (an example of DAMPs) [28]. TLR4 knockout mice demonstrated the survival benefit in endotoxemic model [53]. However, TLR4 knockout mice showed worsened survival over wild-type mice in pneumococcal infection [54]. These may suggest that the target therapy against TLR4 is case (organism)-sensitive. The phase II trial of TLR4 antagonist E5564 showed possible benefit in high risk patients, but harm in low risk patients [55]. Typically septic patients manage to survive the hyperinflammatory stage with the aid of resuscitation despite that their physiology is significantly affected. Therefore, attentions have been directed to the exploration of other pathophysiological alternation in sepsis.

Alternation of Leukocyte Recruitment

Adequate recruitment of leukocytes to the sites of infection is one of the early, important features of successful immune response. Leukocytes experience several steps; rolling on the blood vessels, adherence onto the vascular endothelial cells, and migration into the sites of infection. Adhesion molecules such as selectins, integrins, and intercellular adhesion

molecules (ICAMs) are among the key players [56]. The importance of leukocyte recruitment against infection is greatly appreciated in the rare genetic disorder leukocyte adhesion deficiency (LAD) [57-59]. LAD type I, where the functional loss of the $\beta 2$ integrins causes the profound impairment of neutrophil mobilization into the extracellular, inflammatory sites, is characterized by recurrent, severe soft tissue infections and chronic periodontitis. LAD type II, where the selectin ligand is deficient, shows the susceptibility to infection, although its symptom tends to be milder than that of LAD type I.

Knockout mice of various adhesion molecules have been generated to understand their contributions to leukocyte recruitment. Sepsis models have been tested in these transgenic mice. The results of intra-abdominal sepsis are summarized in (Table 4). The mortalities were worse in the majority of knockout mice. However, the result may not be simply attributed to the impairment of leukocyte recruitment to the site of infection. For example, in *S. pneumoniae*-induced abdominal sepsis model of αM integrin knockout mice, neutrophil recruitment to the peritoneal cavity was significantly enhanced [60]. αM knockout mice developed bacterial inoculation in livers and spleens earlier than wild-type mice. In line, the majority of deaths occurred within 24-48 hours in αM knockout mice. Likewise, E-selectin knockout mice did not show any reduction of neutrophil recruitment to the peritoneal cavity [61].

In mild local infection, leukocytes are activated and recruited locally at the site of infection. In septic patients, however, the chemotaxis is impaired and the leukocyte recruitment to the original sites of infection is rather decreased [62, 63]. In sepsis, a significant surge of inflammatory mediators can trigger leukocyte activation (priming) systemically. This priming may cause leukocyte sequestration outside the site of infection. For example, neutrophils, the front-line defense cells, enter the majority of tissues *via* the postcapillary venules. But in the pulmonary circulation, emigration occurs *via* the capillaries [64]. In severe infection where the primary infection does not originate from the lung, neutrophils can still be largely sequestered in the lung because these capillaries are very narrow and long for primed neutrophils to be trapped. Song *et al.* modeled the pattern of neutrophil trafficking in severe abdominal sepsis based on this assumption. Their model fitted very well with neutrophil behaviors in CLP model [65, 66]. The derangement of leukocyte trafficking in sepsis could impact on patients' outcome. The previous transgenic mice studies did not explore this aspect in details. Whether or not the genetic deletion of adhesion molecules affect on the systemic leukocyte distribution remains to be determined.

Additional question is whether or not the type of microorganism affects leukocyte trafficking. ICAM-1 and αM knockout mice demonstrated complete opposite results between gram positive and negative organisms [67, 68]. The fundamental difference between gram positive and negative sepsis has been suspected and reviewed [69-71]. The strain difference would be another topic and beyond the scope of this review.

At this point, the therapeutic values of systemic adhesion molecule blockade need further examinations. The blockade may further decrease the number of leukocytes recruited to the infection site. Rather if we can direct leukocytes to the site of infection appropriately, it will certainly help for patients to fight against infection.

“Apoptosis” Theory

Animal and clinical studies suggested that the initial hyperinflammatory response was quickly followed by the development of the sustained anti-inflammatory response. This complementary anti-inflammatory response can be exaggerated and immunosuppressive (“immunoparalysis”) [72]. Notably, the time frame of death mostly coincides with this immunosuppressive period [28].

The autopsy study of patients who died from sepsis by Hotchkiss and colleagues showed extensive apoptosis of lymphocytes and gastrointestinal epithelial cells [73]. The further studies by the same group demonstrated in spleens from patients with sepsis that B cells and CD4⁺ T cells were significantly reduced among lymphocytes, and follicular and interdigitating dendritic cells (DCs) were among antigen presenting cells [74, 75]. The potential of anti-apoptotic therapies has been investigated [76]. Mice overexpressing the antiapoptotic protein bcl-2 had better survival from sepsis induced by CLP [77, 78]. Caspase inhibition also improved survival in CLP model [79].

How does anti-apoptotic therapy help the outcomes of patients? Some possibilities have been suggested. The interplay between innate and adaptive immunity is now well appreciated [80]. CD4⁺ T helper 1 (T_H1) cells and T_H2 cells are among adaptive immune cells involved in this cross talk and demonstrate distinctive cytokine profiles. During sepsis, the shift from T_H1 response (pro-inflammatory cytokines interferon (IFN) γ , IL-12, and TNF- β production) to T_H2 response (IL-4, IL-5, IL-10, and IL-13 production) occurs, leading into significant immunosuppression. Hotchkiss *et al.* proposed that the apoptosis of lymphocytes might further worsen this trend. They examined the effect of adoptive transferred apoptotic or necrotic splenocytes on the production of T_H1 and T_H2 cytokines and the survival in CLP model. Transfer of apoptotic cells greatly increased mortality with decreased IFN γ (T_H2 response), while transfer of necrotic cells increased survival with increased IFN γ (T_H1 response) [81]. Another possibility may have something to do with dendritic cells. Dendritic cells are the most potent antigen-presenting cells. Using mice expressing the diphtheria toxin receptor on the CD11c promotor (DCKO mice), Scumpia *et al.* demonstrated that the significant depletion of mature myeloid and lymphoid dendritic cells worsened the outcome of sepsis in CLP model without the change of bacteremia and plasma cytokine concentrations [82]. Furthermore, intravenous injection of dendritic cells improved survival in these mice with the mechanism so far undetermined.

Beyond “Apoptosis”

The autopsy studies by Hotchkiss *et al.* did not find any major cell death in the heart, lung, liver and kidney [73-75]. These organs often demonstrated significant dysfunction in advanced sepsis. For example, cardiac dysfunction can be seen in the stage of “cold shock.” Early sepsis is accompanied by a decrease in systemic vascular resistance and a metabolic acidosis with high cardiac output (warm shock) [42]. Once sepsis advances, myocardial contractile failure can occur. Interestingly, this dysfunction is rather reversible.

Then why do these dysfunctions occur without the sign of cell death? In sepsis, the distribution of microvascular flow is altered [83]. Therefore, the reduction of oxygen

delivery to tissues was suspected initially. Contrary to the prediction, tissue oxygen tension within organs rather increased [84, 85]. The study by Brealey *et al.* found that septic patients with organ dysfunction and poor outcomes had nitric oxide overproduction, antioxidant depletion, mitochondrial dysfunction, and decreased adenosine triphosphate (ATP) production in biopsied muscles [86]. Taken together, the idea emerged that organ dysfunction in sepsis derived from tissues' inability to consume oxygen and subsequent mitochondrial dysfunction [87, 88]. Oxidative phosphorylation is the major process to produce cellular energy source ATP available to the body. Levy *et al.* demonstrated that cytochrome c (complex IV in the respiratory chain) was inhibited in sepsis [89]. Cells may maintain their viability by decreasing oxygen consumption and ceasing nonessential cellular functions (hibernation). Moreover, the evidence of hibernation was described in the heart of septic patients [90, 91]. The underlying mechanism of cytochrome c inhibition needs further exploration. One candidate is hydrogen sulfide, which is an endogenously produced in sepsis and inhibits cytochrome c [92]. The dysfunction of other organs in septic patients may also stem from "cell hibernation" (or "cell stunning") [47].

The Potential Concerns on Inhalational Anesthetics

Inhalational anesthetics are unique in that the drug concentration at which these drugs exert pharmacological activities is high (0.1-1 mM) [93]. This property is different from that of intravenous anesthetics, whose effective concentrations are much lower. Inhalational anesthetics are very promiscuous small molecules and seem to have targets outside the central nervous system including immune system at their effective concentrations [94, 95]. Many investigators have examined their effects on immune function as well as mitochondrial function *in vitro* and *in vivo* animal models. We will review the available literature of inhalational anesthetics on pathological processes relevant to sepsis. As mentioned in section IV, understanding and correcting the pathological process of sepsis is important. Laboratory findings described here may be explored and considered in clinical settings including the selection of anesthetics in the future.

Effects on Proinflammatory Mediators and Survival

The administration of inhalational anesthetics right before or after sepsis induction reduced the level of proinflammatory cytokines in several studies. Chiang *et al.* demonstrated that isoflurane (1.4 MAC; minimum alveolar concentration) down-regulated a panel of proinflammatory cytokines and chemokines as well as proteins known to be active in cell migration and chemotaxis (IL-1 β , IL-6, IL-12, KC, JE, MIP-1 α , Rantes) in zymozan A-induced peritonitis [96]. In contrast, anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 were not affected in this study. Isoflurane (1-2 MAC) and sevoflurane (1 MAC) attenuated the pro-inflammatory cytokine response (TNF α , IL-1 β , IL-6, RANTES etc) in LPS-induced endotoxemic mice and rats [97-101]. Lee *et al.* demonstrated that isoflurane (1 MAC)-anesthetized mice had significantly prolonged and increased survival of mice with septic peritonitis from CLP compared with pentobarbital-anesthetized mice [102]. The mechanism of survival benefit in inhalational anesthetic treatment group is not completely clear. The reduction of proinflammatory response may be one explanation, which is in line

with some results of transgenic mice but further examination is necessary to have definite answer.

Effects on Leukocyte Adhesion and Infiltration

Inhalational anesthetics can alter leukocyte adhesion and infiltration. Mobert *et al.* demonstrated that preincubation of polymorphonuclear neutrophils (PMNs) with halothane, isoflurane, or sevoflurane (maximal effect at 1 MAC), abolished enhanced neutrophil adhesion to hydrogen peroxide-activated human umbilical vascular endothelial cells (HUVECs) and adhesion of N-formyl-methionyl-leucyl-phenylalanine (fMLP)-stimulated PMNs to unstimulated HUVECs [103]. However, adhesion did not change when only HUVECs were pretreated with inhalational anesthetics. They concluded that the inhibition of integrin $\alpha M\beta 2$ up-regulation on PMNs cell surface by anesthetics underlied their observations. The intravital studies using rat mesentery also supported the idea that inhalational anesthetics could impair leukocyte adhesion. Morisaki *et al.* noticed that sevoflurane (1-2 MAC) caused a dose-dependent increase in leukocyte rolling [104]. Hayes *et al.* demonstrated that isoflurane (1.4% ~1.1 MAC) pretreatment increased leukocyte rolling velocities (> 200% more rapid) in endotoxemia [105]. $\beta 2$ integrins are key players of leukocyte adhesion. Isoflurane (0.5-2 MAC) and sevoflurane (0.5-2 MAC) directly bind and inhibit $\beta 2$ integrins [106-110]. This can at least partly explain the reduction of leukocyte adhesion under inhalational anesthetics.

The number of infiltrated leukocytes is not solely determined by the degree of leukocyte adhesion. Resolution is another factor to be considered. The aforementioned study by Chiang *et al.* demonstrated that isoflurane (1.4 MAC) rather promoted resolution, diminishing the amplitude of neutrophils infiltration and shortening the resolution interval [96].

Effects on Apoptosis

The effect of inhalational anesthetics on lymphocytes has been examined. They have been shown to inhibit lymphocyte proliferation [111, 112]. In addition, isoflurane and sevoflurane (4- 5 MAC) directly induced apoptosis in human peripheral lymphocytes [113, 114]. Mitochondria-mediated apoptotic pathway is shown to be involved [114]. In this pathway, cytochrome c leaks from the mitochondria, interacts with various proteins in the cytosol including the members of bcl-2 family and induces apoptosis [115]. However, we should keep in mind that these anesthetic concentrations are well above the clinically relevant concentrations and cautions are needed in interpretation.

Effects on Mitochondrial Function

Inhalational anesthetics demonstrated the toxic (apoptotic) or inhibitory effects on lymphocytes possibly through the alternation of mitochondrial function as mentioned above. In contrast, they may precondition and protect myocytes by affecting mitochondrial function [116]. In both lymphocytes and myocytes, mitochondrial membrane potential is attenuated, the production of superoxide and reactive oxygen species is enhanced, protein kinase C and mitogen-activated protein kinase (MAPK) are activated. Kurosawa *et al.* suggested that these alternations might have different impacts on lymphocytes and myocytes [94]. In

lymphocytes, the reduced transcription of activator protein-1 and attenuated production of proinflammatory cytokines ensue. On the other hand, in myocytes, it may open K_{ATP} channel and reduce mitochondrial calcium load. This will reduce mitochondrial respiration and slow ATP depletion, keep myocyte viable while in hibernation. The effects of anesthetics on mitochondrial function in different organs need to be evaluated extensively. The illustration of inhalational anesthetic targets may help to develop organ specific agents to induce protection.

Conclusions

Despite extensive research, sepsis still remains to be a difficult condition to treat and is associated with high mortality. The current clinical guidelines can help to implement effective management to improve the outcomes of sepsis patients. From anesthesiological/surgical standpoint, early identification of infectious source and its control, as well as maintenance of hemodynamic measures during surgical procedures are the key to the improvement of outcomes. Intraoperative management based on better understanding of pathophysiology of sepsis would also be warranted. In parallel, the continuous efforts need to be made to enhance our understanding of the fundamental patho-physiology and causes of death. Sepsis is a rather heterogeneous disease. In the future, the strategy to classify sepsis in different categories may help to stratify as direct effective therapies.

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List of Abbreviations

CLP	cecal ligation and puncture
DAMPs	damage-associated molecular pattern
DC	dendritic cell
EGDT	early goal-directed therapy
fMLP	N-formyl-methionyl-leucyl-phenylalanine
HMGB1	high-mobility group box 1
HUVEC	human umbilical vascular endothelial cell
ICAM	intracellular adhesion molecule
LAD	leukocyte adhesion deficiency
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
PAMPs	pathogen-associated molecular pattern
PMN	polymorphonuclear neutrophil
PRR	pattern recognition receptor
SSC	surviving sepsis campaign
T_H1	T helper 1
T_H2	T helper 2
TLR	toll-like receptor
TNF	tumor necrosis factor

Table 1
Diagnostic criteria for sepsis

Infection, documented or suspected, and some of the following:	
General variables	
Fever (> 38.3°C)	
Hypothermia (core temperature < 36°C)	
Heart rate > 90/min or more than two S.D. above the normal value for age	
Tachypnea	
Altered mental status	
Significant edema or positive fluid balance (> 20 mL/kg over 24 hours)	
Hyperglycemia (plasma glucose > 140 mg/dL) in the absence of diabetes	
Inflammatory variables	
Leukocytosis (WBC count > 12,000/ μ L)	
Leukopenia (WBC count < 4,000/ μ L)	
Normal WBC count with greater than 10% immature forms	
Plasma C-reactive protein more than 2 S.D. above the normal value	
Plasma procalcitonin more than 2 S.D. above the normal value	
Hemodynamic variables	
Arterial hypotension (sBP < 90 mmHg, MAP < 70 mmHg, or sBP decrease > 40 mmHg in adults or less than 2 S.D. below normal for age)	
Organ dysfunction variables	
Arterial hypoxemia (PaO ₂ /FiO ₂ < 300)	
Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)	
Creatinine increase > 0.5 mg/dL	
Coagulation abnormalities (INR > 1.5 or aPTT > 60 sec)	
Ileus (absent bowel sounds)	
Thrombocytopenia (platelet count < 100,000/ μ L)	
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL)	
Tissue perfusion variables	
Hyperlactatemia	
Decreased capillary refill or mottling	

* WBC= white blood cell; sBP= systolic blood pressure; MAP =mean arterial pressure; INR= international normalized ratio

The criteria of severe sepsis

Table 2

Severe sepsis is defined if any of the following is thought to be due to the infection
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with PaO2/FiO2 < 250 in the absence of pneumonia as infection source
Acute lung injury with PaO2/FiO2 < 200 in the presence of pneumonia as infection source
Creatinine > 2.0 mg/dL
Bilirubin > 2 mg/dL
Platelet count < 100,000/ μ L
Coagulopathy (INR > 1.5)

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Table 3
Surviving sepsis campaign care bundles

To BE COMPLETED WITHIN 3 HOURS:	
1	Measure lactate level
2	Obtain blood cultures prior to administration of antibiotics
3	Administer broad spectrum antibiotics
4	Administer 30 mL/kg crystalloid for hypotension or lactate > 4 mmol/L
TO BE COMPLETED WITH 6 HOURS:	
5)	Apply vasopressors for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure > 65 mmHg
6)	In the event of persistent arterial hypotension despite volume resuscitation or initial lactate > 4 mmol/L
	- Measure central venous pressure (CVP), aim CVP 8-12 mmHg
	- Measure central venous oxygen saturation (ScvO ₂), aim ScvO ₂ > 70%
	*Dobutamine infusion and red cells transfusion as options in the setting of SCVO ₂ <70%.
7)	Remeasure lactate if initial lactate was elevated. Aim normalization of lactate.
8)	Aim urine output > 0.5 mL/kg/hr

Table 4
Phenotypes of various knockout mice in sepsis

Knockout Gene	Outcomes	Leukocyte Recruitment to the Abdominal Cavity	References
$\beta 2$ integrin *	<i>S. pneumoniae</i> i.p. WT 53% survival vs -/- 0% at day #10	At day #2, comparable numbers of neutrophils present in the abdominal cavity, emigration % reduced.	[117]
αL integrin *	<i>S. pneumoniae</i> i.p. WT 63% survival vs -/- 12 % at day #7	At 8 hour, peritoneal neutrophil emigration % is ~12.5%.	[60]
αM integrin *	<i>S. pneumoniae</i> i.p. WT 76% survival vs -/- 50% at day #7 <i>L. monocytogenes</i> (better survival)	At 8 hour, peritoneal neutrophil emigration % is ~500%.	[60, 67]
ICAM-1	LPS i.p. WT 21% survival vs -/- 95% at day #4 CLP. WT 55% survival vs -/- 5% at day #4 <i>S. pneumoniae</i> i.p. Better WT survival than -/- at 24 h <i>H. influenzae</i> type b, better survival in -/-	Less granulocyte infiltration of lung	[68, 118]
P-selectin	<i>S. pneumoniae</i> i.p. WT 57% survival vs -/- 19 % at day #4	Impaired leukocyte recruitment to the peritoneal cavity	[61]
E-selectin	<i>S. pneumoniae</i> i.p. WT 57% survival vs -/- 7 % at day #4	No impairment of leukocyte to the peritoneal cavity	[61]
E/P-selectin	<i>S. pneumoniae</i> i.p. WT 57% survival vs -/- 28 % at day #4	Impaired leukocyte recruitment to the peritoneal cavity	[61]

* Integrins are heterodimeric molecules of α - and β - subunits. $\beta 2$ integrins consists of 4 members ($\alpha L\beta 2$, $\alpha Mb2$, $\alpha Xb2$ and $\alpha Db2$). $\beta 2$ knockout mice do not express any of 4 members, whereas αL and αM knockout mice lack just $\alpha L\beta 2$ and $\alpha M\beta 2$, respectively.

In the table, WT denotes wild-type mice, while -/- corresponding knockout mice.