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Severe sepsis and septic shock
Management and performance improvement

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Morbidity and mortality from sepsis remains unacceptably high. Large variability in clinical practice, plus the increasing awareness that certain processes of care associated with improved critical care outcomes, has led to the development of clinical practice guidelines in a variety of areas related to infection and sepsis. The Surviving Sepsis Guidelines for Management of Severe Sepsis and Septic Shock were first published in 2004, revised in 2008, and recently revised again and published in 2013. The first part of this manuscript is a summary of the 2013 guidelines with some editorial comment. The second part of the manuscript characterizes hospital based sepsis performance improvement programs and highlights the sepsis bundles from the Surviving Sepsis Campaign as a key component of such a program.

Introduction

Morbidity and mortality from sepsis remains unacceptably high.[1,2] Large variability in clinical practice, plus the increasing awareness that certain processes of care associated with improved critical care outcomes, has led to the development of clinical practice guidelines in a variety of areas related to infection and sepsis.[3] The Surviving Sepsis Guidelines for Management of Severe Sepsis and Septic Shock were first published in 2004, revised in 2008, and recently revised again and published in 2013.[4-6] The first part of this manuscript is a summary of the 2013 guidelines with some editorial comment. The second part of the manuscript characterizes hospital based sepsis performance improvement programs and highlights the sepsis bundles from the Surviving Sepsis Campaign as a key component of such a program.

Diagnostic Terminology

Sepsis is defined as infection plus systemic manifestations of infection[7] (**Table 1**). Severe sepsis is defined as infection plus infection induced organ dysfunction or tissue hypoperfusion[7] (**Table 2**). Sepsis induced hypotension is defined as infection induced decrease in blood pressure (systolic pressure <90 mmHg or mean arterial pressure <70 mmHg). Septic shock is defined as the requirement for vasopressors after initial fluid resuscitation fails to correct sepsis induced hypotension.[7]

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Management

Initial resuscitation

Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined as hypotension persisting after initial fluid challenge or a blood lactate concentration ≥4 mmol/L) is recommended.[8-15] For the initial resuscitation of these patients the goals during the first 6 h of resuscitation include a central venous pressure 8–12 mmHg,[16,17] a mean arterial pressure (MAP) ≥65 mmHg,[18,19] a urine output ≥0.5 mL/kg/h, and a superior vena cava venous oxygen saturation of ≥70%.[20]

In patients who are found to initially have elevated lactate levels, targeting resuscitation to normalize lactate is suggested. Normalization of lactate seems a more appropriate goal than a percent reduction in baseline elevated lactate, although the latter has been demonstrated to be an effective resuscitation target variable.[21,22] Where capability to measure central venous oxygen saturation does not exist, lactate clearance can be used as an alternative. Where both technologies are available, both targets are recommended.

Diagnosis of infection

Early diagnosis of sepsis, source of sepsis, and ideally causative organism is important.[23-25] Two sets of blood cultures (both aerobic and anaerobic bottles) should be obtained before initiation of antimicrobial therapy unless it induces a significant delay (greater than 45 min) in the administration of antimicrobials.[26,27] At least one of these blood cultures should be drawn percutaneously and one drawn through each vascular access device, unless the device was recently (less than 48 h) inserted. Imaging studies should be obtained promptly to confirm a potential infection source.

Prevention of selective oral decontamination and selective digestive decontamination should be considered as an ICU wide process to prevent the occurrence of sepsis and severe sepsis.[28-30] Oral chlorhexidine gluconate is suggested as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis.

Treatment of infection

Antimicrobials administered within the first hour of recognition of severe sepsis and septic shock should be the "goal" of therapy.[31-36] Although an admirable goal, this time window is not the current standard of clinical practice. Initial empiric anti-infective therapy should be broad and target all likely pathogens and

include antimicrobials that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis. The antimicrobial regimen should be reassessed daily with the potential for de-escalation. Combination empirical therapy for a particular known or suspected infecting organism may be considered in certain patient groups such as neutropenic patients; patients with difficult-to-treat, multidrug resistant bacterial pathogens; patients with severe infections associated with respiratory failure and septic shock and for septic shock from bacteremic pneumococcal infections.[37-39] Empiric combination therapy should not be administered for more than 3–5 d. De-escalation to the most appropriate single drug therapy should be performed as soon as the susceptibility profile is known.

Duration of antimicrobial therapy is typically 7–10 d; however, longer courses may be appropriate in patients who have a slow clinical response, an undrainable focus of infection, bacteremia with *Staphylococcus aureus*, *Pseudomonas* ventilator-acquired pneumonia, as well as some fungal and viral infections or immunologic deficiencies, including neutropenia. Antiviral therapy should be initiated as early as possible in patients with severe sepsis or septic shock of viral origin including targeting influenza during flu outbreaks, such as H1N1.[40]

Source control is paramount.[41,42] A specific anatomical diagnosis of infection requiring consideration for emergent source control should be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 h after the diagnosis is made, if feasible. When source control is needed the "effective" intervention associated with the least physiologic insult should be considered (e.g., percutaneous rather than surgical drainage of an abscess). If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after another vascular access has been established. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred.

Hemodynamic support

Crystalloids are the initial fluid of choice in the resuscitation of severe sepsis and septic shock.[43] Hydroxyethyl starches are not recommended.[44-46] Albumin is suggested to be added to crystalloid fluid resuscitation when patients require substantial amounts of crystalloids.[47] Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia should include a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients. Fluid challenge techniques should continue as long as there is hemodynamic improvement based either on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables. Methods to assess intravascular volume such as echocardiography for assessment of left ventricular size or ultrasound assessment of inferior vena cava may also be used. Direct measurement of flow with assessment of effect of fluid boluses on stroke volume may be potentially useful, where that technology is available, and may include pulmonary artery catheters for thermodilution cardiac output measurement, esophageal Doppler for assessment of aortic flow and estimation of stroke volume based on arterial pressure waveform assessment using minimally invasive cardiac output measurement technologies such as LiDCO™, PiCCO®, and Flo Trac™. All of these devices have risks and some limitations.

Vasopressor therapy should initially target a mean arterial pressure (MAP) of ≥65 mmHg. Norepinephrine is the first

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^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 h)
Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC >12 000 μL^{-1})
Leukopenia (WBC count <4000 μL^{-1})
Normal WBC count with greater than 10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than 2 SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP <90 mmHg, MAP <70 mmHG, or an SBP decrease >40 mmHg in adults or less than 2 SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (PaO_2/FiO_2 <300)
Acute oliguria (urine output <0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation)
Creatinine increase >0.5 mg/dL or 44.2 μmol/L
Coagulation abnormalities (INR >1.5 or aPTT >60 s)
Ileus (absent bowel sound)
Thrombocytopenia (platelet count <100 000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (>1 mmol/L)
Decreased capillary refill or mottling

WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial pressure; INR, international normalized ratio; aPTT, activated partial thromboplastin time. Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature 38.5 °C or <35 °C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses. Used with permission from reference 6 as adapted from reference 125.

Table 2. Severe sepsis

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output <0.5 mL/kg/h for more than 2 h despite adequate fluid resuscitation
Acute lung injury with PaO_2/FiO_2 <250 in the absence of pneumonia as infection source
Acute lung injury with PaO_2/FiO_2 <200 in the presence of pneumonia as infection source
Creatinine >2.0 mg/dL (176.8 μmol/L)
Bilirubin >2 mg/dL (34.2 μmol/L)
Platelet count <100 000 μL
Coagulopathy (international normalized ratio >1.5)

Used with permission from reference 6 as adapted from reference 125.

choice vasopressor.[48-50] When norepinephrine fails to achieve the MAP target, epinephrine added to and potentially substituted for norepinephrine may be needed to maintain adequate blood pressure.[51,52] Alternatively, vasopressin up to 0.03 units/minute can be added to norepinephrine with the intent of either raising MAP or decreasing norepinephrine dosage.[53] Low dose vasopressin is not recommended as the single initial vasopressor therapy and is not recommended to be used at doses higher than 0.03–0.04 units/minute unless used for salvage therapy (failure of other vasopressors to achieve adequate MAP). Dopamine as an alternative vasopressor agent to norepinephrine is in general discouraged but may be used in highly selected patients groups (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia).[49] Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low and difficult to maintain with vasopressor, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target. Low-dose dopamine should not be used for renal protection.[54] All patients requiring vasopressor therapy should have an arterial catheter placed as soon as practical if resources are available.

During initial resuscitation dobutamine may be used to increase oxygen delivery in the presence of ongoing signs of hypoperfusion (such as lactic acidosis), despite achieving adequate intravascular volume and adequate MAP in patients with $ScvO_2$ <70%. Following initial resuscitation of patients with sepsis induced hypoperfusion, where tissue hypoperfusion persists, a trail of dobutamine infusion up to 20 μg/kg/min may be administered singularly or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP.

Steroid therapy

Intravenous corticosteroids are not recommended in the treatment of adult septic shock if adequate fluid resuscitation and vasopressor therapy is able to restore hemodynamic stability.[55-59] In case this goal is not achieved, intravenous hydrocortisone alone at a dose of 200 mg per day (50 mg q6h IV or 50 mg IV followed by 24 h continuous infusion to minimize swings in glucose) for up to 7 d is suggested.[60,61] It is not necessary to use the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone. Instead, bedside clinical assessment as described above should be used. In patients treated with hydrocortisone for septic shock tapering should be performed when vasopressors are no longer required and steroids may be delivered for up to 7 d.[62] Steroids should not be administered for the treatment of sepsis in the absence of shock.

Other supportive therapy of severe sepsis

Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic heart disease, red blood cell transfusion should occur only when hemoglobin concentration decreases to <7.0 g/dL.[63] The anemia of severe sepsis should not be treated with erythropoietin unless another indication exists.[64,65] Fresh frozen plasma should not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures.[66,67] Antithrombin is not indicated to treat severe sepsis.[68,69] In patients with severe sepsis, and without significant risk of bleeding or with planned invasive procedures or active bleeding, transfusion threshold for platelets is <10 000/mm^3.[70] Platelets should be transfused when <20 000/mm^3 if the patient has a significant risk of bleeding and platelet counts ≥50 000/mm^3 should be maintained in the presence of active bleeding or if surgery or invasive procedures are needed. Immunoglobulins are not recommended in adult patients with severe sepsis or septic shock.[71] Possibly exceptions include toxic shock syndrome or severe life threatening H1N1 ARDS. There is no current data that would support the use of intravenous selenium for the treatment of severe sepsis.

In the patient with sepsis induced acute respiratory distress syndrome (ARDS), ARDSnet lung protective strategy is recommended to include targeting 6 mL/kg predicted body weight (PBW) tidal volume and a plateau pressure ≤30 cm H_2O.[72] When a tidal volume of 6 mL/kg/PBW results in plateau pressure >30 cm H_2O then tidal volume is decreased to as low as 4 mL/kg in 0.5 ml/kg/PBW increments in order to achieve a <30 cm H_2O plateau pressure target. Plateau pressures higher than 30 cm H_2O may be allowed in patients with increased chest wall or abdominal elastance (morbid obesity or anasarca). A level of positive end-expiratory pressure (PEEP) should be applied to avoid alveolar collapse at end expiration (atelectotrauma).[73] Strategy based on higher rather than lower levels of PEEP is suggested for patients with sepsis-induced moderate or severe ARDS.[74-77] Recruitment maneuvers are suggested in sepsis patients with ARDS induced severe refractory hypoxemia.[78,79] Prone positioning is suggested to be used in sepsis-induced ARDS patients with a PaO_2/FiO_2 ratio ≤100 mmHg in facilities that have experience with such practices.[80,81]

A conservative rather than a liberal fluid strategy is recommended for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion.[82] Utilizing a CVP target of <4 mmHg is equally effective as using a pulmonary artery catheter to target a pulmonary artery occlusive pressure of <8 mmHg. In the absence of bronchospasm, β 2-agonists should not be used in patients with sepsis- induced ARDS.[83] Neuromuscular blocking agents (NMBAs) should be avoided in the septic patient without ARDS;[84,85] however, a short course of NMBA is suggested (for not greater than 48 h) in the patient with early sepsis induced ARDS and a PaO_2/FiO_2 <150 mmHg.[86]

When two consecutive glucose levels >180 mg/dL are encountered a continuous infusion of insulin should be instituted, targeting an upper blood glucose ≤180 mg/dL.[87] Hypoglycemia should be avoided.[88] Blood glucose values should be monitored every 1–2 h until glucose values and insulin infusion rates are stable and then every 4 h thereafter.[88] Glucose levels obtained with point-of-care testing of capillary blood should be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values.[89-91]

Continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure.[92-96] The use of continuous renal replacement therapies to facilitate management of fluid balance in hemodynamically unstable septic patients is an acceptable approach. Sodium bicarbonate given to septic patients with tissue hypoperfusion and a pH ≥7.15 should not be expected to improve hemodynamics or decrease vasopressor requirement when compared with equimolar quantities of crystalloid.[97,98]

Deep vein thrombosis and stress ulcer prophylaxis are both recommended in the patient with severe sepsis.[99-105] Deep vein thrombosis prophylaxis should be given with either daily low-molecular weight heparin (LMWH) or unfractionated heparin (UFH) thrice daily. If creatinine clearance is <30 mL/min and LMWH is given, either dalteparin or another form of LMWH with a low degree of renal metabolism or unfractionated heparin should be used. Severely septic patients with a contraindication to heparin use (e.g., clinically significant thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage), should receive mechanical prophylactic treatment such as graduated compression stockings or intermittent compression devices, unless contraindicated. It is suggested that patients with severe sepsis receive both pharmacologic therapy and intermittent pneumatic compression devices when there are no contraindications to the use of either therapies in patients with severe sepsis. Stress ulcer prophylaxis is strongly recommended with either an H2 blocker or a proton pump inhibitor. Proton pump inhibitors have a weak preference over H2 blockers.[106,107] In the absence of risk factors, no stress ulcer prophylaxis should be given.

Within 48 h after a diagnosis of severe sepsis/septic shock administer oral or enteral feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose.[108-111] Low dose feeding beginning with 500 calories per day (intravenous glucose plus enteral feeding) advanced as tolerated, is recommended over initial mandatory full caloric feeding (addition of TPN to achieve) in the first week. There is no indication for specific immunomodulating supplementation in patients with severe sepsis.[112-114]

In patients with severe sepsis and septic shock, it is important to discuss goals of care and prognosis with patients and families.[115-117] As appropriate, the goals of care, including any end of life care planning or the use of palliative care principles should be accomplished. Although goals of care should be addressed as early as feasible, this should occur no later than 72 h following ICU admission.

See **Tables S1–3** for concise summations of SSC guidelines recommendations.

Sepsis performance improvement programs[118-120]

Guidelines have little immediate impact on bedside behavior in the management of disease processes. Guidelines, however, serve as a resource document for creation of treatment protocols that when coupled with audit and feedback as part of a formal hospital based performance improvement initiative can change bedside practice. Bundles represent a number of treatment goals to be achieved in a disease process over a set time period and function as measurable quality indicators. When chart audit scores performance on bundle goals, and is followed by feedback to the treating clinicians (audit and feedback) bedside behavior is likely to change in line with guideline recommendations.

Sepsis bundles are created to act as a cohesive unit to ensure all steps of care are consistently delivered.[121-124] The Surviving Sepsis Campaign and the Institute for Healthcare Improvement collaborated to apply the sepsis guidelines of 2004 to assemble two sepsis bundles, the 6-h resuscitation and 24-h management bundles. Following the creation of the 2012 guidelines, the bundles were revised, creating a 3-h and a 6-h bundle (**Fig. 1**). A free standardized database, provided by the Surviving Sepsis Campaign, allows hospitals to enter de-identified patient data and track sepsis bundle performance and outcomes. Participating hospitals are urged to transmit their Health Insurance Portability and Accountability Act (HIPAA) compliant data to a central repository at the Society of Critical Care Medicine for aggregate analysis. Queries of data and graphical display of bundle indicator performance can be retrieved locally using the electronic database. Patients are identified for entry into the database based on a standardized screening tool (**Fig. 2**). Steps to implement a sepsis protocol are shown in **Table 3**.

Achieving performance improvement goals requires ongoing data collection and feedback. Protocols can be successful in changing bedside behavior only with the application of education and commitment of physician, nursing, and other health care professional champions from key areas of the hospital (ICU, ED, and hospital floors). Success of severe sepsis performance improvement programs require, not only champions but also multidisciplinary commitment from physicians, nurses, pharmacy, respiratory, and administration. Programs must be multispecialty as well, and include medicine, surgery, emergency medicine, and others. Establishing support from key ICU, ED, and floor leaders is crucial. Interdepartmental communication and collaboration facilitate seamless steps in the continuum of care, and give the best chance of success. And ultimately behavior is changed with audit and feedback.

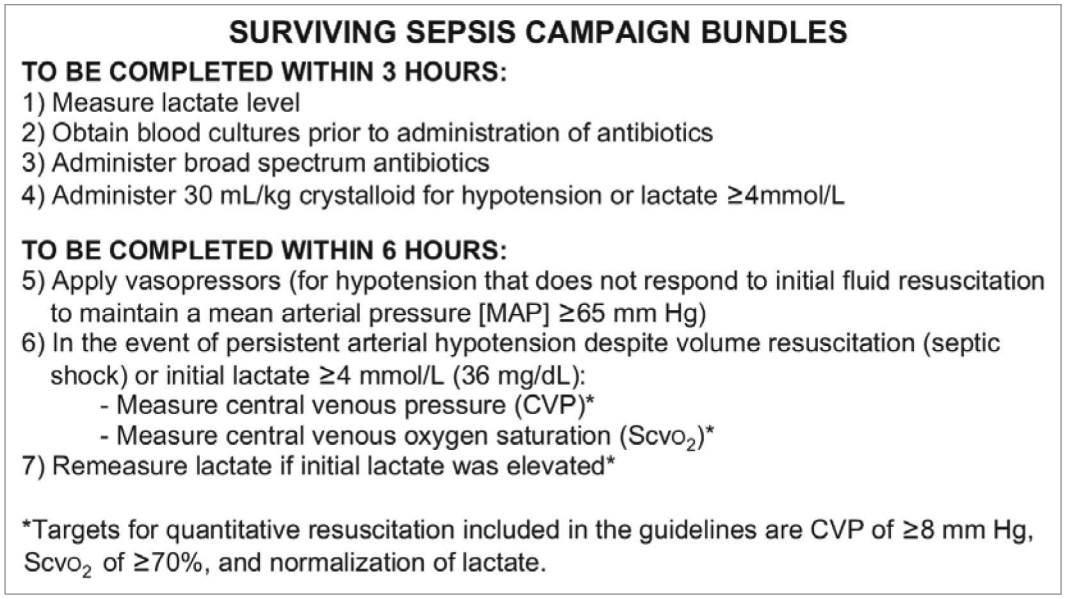

Figure 1. Surviving sepsis campaign bundles. Used with permission from reference 6.

Programs typically start with a hospital-wide education initiative, centered around early identification and familiarity with the treatment protocol that will be applied once the patient is identified. Educational sessions are conducted by members of the sepsis performance improvement leadership team. Education may be provided through departmental conferences, staff meetings, and unit-based in-services. Baseline data may or may not be collected prior to initiation of the formal performance improvement initiative. Data collection typically occurs Monday through Friday morning with a review of patients admitted to the ICU service over the last 24 h, applying the screening tool to ascertain if the patient qualifies for entry into the severe sepsis database. Performance is assessed periodically, typically quarterly through query of the database. The SSC software allows performance to be plotted and displayed over time with tables and linear or bar graphs. This display functions as the feedback tool. Evaluation of process change requires consistent data collection, measurement of indicators and feedback in order to facilitate performance improvement. Ongoing educational sessions to reinforce early identification and treatment steps continue in line with the protocol are needed. When roadblocks are encountered in process improvement a plan, do, study, act process (PDSA cycle) is employed to study the reasons for failure and to implement changes to improve process performance. This process includes initiation of a plan of action, studying results and when problems are identified, altering the plan to solve the problem. Since performance is being judged based on the time to accomplish the indicator, it is necessary to have a time zero (T0) representing when the clock starts ticking for scoring indicator compliance in treatment of severe sepsis. For ED admissions T0 is triage time. For patients presenting with severe sepsis in units other than the ED, T0 is the time that the chart reveals variables allowing the identification of the patient as having severe sepsis.

Conclusion

Only with early diagnosis and expedited treatment based on evidence based medicine can sepsis morbidity and mortality be decreased. Sepsis guidelines create a base to allow change in healthcare practitioner behavior, but lead to only modest slow change in bedside behavior. Change comes when institutions initiate a formal performance improvement program with a formal treatment protocol, education on early identification of severe sepsis patients, followed by audit of performance and periodic feedback to the healthcare professionals taking care of these patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Supplemental Materials

Supplemental materials may be found here:
www.landesbioscience.com/journals/virulence/article/27409

Evaluation for Severe Sepsis Screening Tool

Instructions: **Use this optional tool to screen patients for severe sepsis in the emergency department, on the medical/surgical floors, or in the ICU.**

1. Is the patient's history suggestive of a new infection?

- ☐ Pneumonia, empyema
- ☐ Urinary tract infection
- ☐ Acute abdominal infection
- ☐ Meningitis
- ☐ Skin/soft tissue infection
- ☐ Bone/joint infection
- ☐ Wound infection
- ☐ Blood stream catheter infection
- ☐ Endocarditis
- ☐ Implantable device infection
- ☐ Other infection _____

___ Yes ___No

2. Are any two of following signs & symptoms of infection both present and new to the patient? Note: laboratory values may have been obtained for inpatients but may not be available for outpatients.

- ☐ Hyperthermia > 38.3 °C (101.0 °F)
- ☐ Hypothermia < 36 °C (96.8 °F)
- ☐ Altered mental status
- ☐ Tachycardia > 90 bpm
- ☐ Tachypnea > 20 bpm
- ☐ Leukocytosis (WBC count >12 000 µL–1)
- ☐ Leukopenia (WBC count < 4000 µL–1)
- ☐ Hyperglycemia (plasma glucose >140 mg/dL) or 7.7 mmol/L in the absence of diabetes

___ Yes ___No

If the answer is yes, to both questions 1 and 2, *suspicion of infection* is present:

- ✓ Obtain: **lactic acid**, **blood cultures**, CBC with differential, basic chemistry labs, bilirubin.
- ✓ At the physician's discretion obtain: UA, chest x-ray, amylase, lipase, ABG, CRP, CT scan.

3. Are any of the following organ dysfunction criteria present at a site remote from the site of the infection that are NOT considered to be chronic conditions? Note: in the case of bilateral pulmonary infiltrates the remote site stipulation is waived.

- ☐ SBP < 90 mmHg or MAP <65 mmHg
- ☐ SBP decrease > 40 mm Hg from baseline
- ☐ Creatinine > 2.0 mg/dl (176.8 mmol/L) or urine output < 0.5 ml/kg/h for 2 h
- ☐ Bilirubin > 2 mg/dl (34.2 mmol/L)
- ☐ Platelet count < 100 000 µL
- ☐ Lactate > 2 mmol/L (18.0 mg/dl)
- ☐ Coagulopathy (INR >1.5 or aPTT >60 secs)
- ☐ 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

___ Yes ___No

If *suspicion of infection* is present AND *organ dysfunction* is present, the patient meets the criteria for SEVERE SEPSIS and should be entered into the severe sepsis protocol.

Date: ____/____/____ (circle: dd/mm/yy or mm/dd/yy) **Time: ____: ____ (24 h. clock)**

Version 7.2.13

Figure 2. Evaluation for severe sepsis screening tool. Online at http://www.survivingsepsis.org/SiteCollectionDocuments/ScreeningTool.pdf.

Table 3. Steps to implementing a sepsis protocol

• Obtain administrative support
• Evaluate inter-departmental interactions
• Develop and relay a firm understanding of the goals
• Establish a formal interactive relationship with the emergency department and the critical care unit
• Collaborate with the general/internal medicine team
• Identify champions/unit protocol leaders
• Provide a unit/hospital system wide education campaign

Used with permission from reference 126.

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Epidemiology of severe sepsis

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Severe sepsis is a leading cause of death in the United States and the most common cause of death among critically ill patients in non-coronary intensive care units (ICU). Respiratory tract infections, particularly pneumonia, are the most common site of infection, and associated with the highest mortality. The type of organism causing severe sepsis is an important determinant of outcome, and gram-positive organisms as a cause of sepsis have increased in frequency over time and are now more common than gram-negative infections.

Recent studies suggest that acute infections worsen preexisting chronic diseases or result in new chronic diseases, leading to poor long-term outcomes in acute illness survivors. People of older age, male gender, black race, and preexisting chronic health conditions are particularly prone to develop severe sepsis; hence prevention strategies should be targeted at these vulnerable populations in future studies.

Sepsis and severe sepsis (sepsis accompanied by acute organ dysfunction) are leading causes of death in the United States and the most common cause of death among critically ill patients in non-coronary intensive care units (ICU).[1] Recent data suggest the annual cost of hospital care for patients with septicemia is $14 billion in United States.[2] Therefore, sepsis and severe sepsis are important public health problems. This article focuses on the epidemiology of severe sepsis and discusses common etiologies, risk factors, and long-term outcomes. The information provided is focused primarily on developed countries, and the epidemiology of severe sepsis in resource-limited countries may differ substantially.

Definitions

In 1991, the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference proposed a broad framework to define systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis (**Table 1**).[3] This syndrome was envisioned as a continuum of worsening inflammation, starting with SIRS, and evolving from sepsis to severe sepsis and septic shock. The criteria for SIRS were based on temperature, heart rate, respiratory rate, and white blood cell count. At least 2 of these 4 criteria had to be met to define SIRS. Although SIRS often occurs in the setting of infection, noninfectious conditions, such as burns, acute pancreatitis, and trauma, can lead to SIRS. Sepsis was defined as the presence of the SIRS criteria and presumed or proven infection. Severe sepsis was defined as sepsis accompanied by acute organ dysfunction.

Although the 1991 Consensus Conference laid the framework to define sepsis, it had important limitations. The "2 out of 4" criteria for SIRS were arbitrary and not specific to sepsis alone. The criteria did not include biochemical markers, such as C-reactive protein, procalcitonin (PCT), or interleukin (IL)-6, which are often elevated in sepsis.

A 2001 Consensus Conference by the Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society was convened to modify these definitions.[4] The criteria for sepsis were revised to include infection and presence of any of the diagnostic criteria shown in **Table 2**. These criteria were based on clinical and laboratory parameters. The conference participants acknowledged that there was no single parameter or a set of clinical or laboratory parameters that are adequately sensitive or specific to diagnose sepsis. Severe sepsis criteria remained unchanged and it was defined as sepsis with an organ dysfunction. Although there are several criteria to define organ dysfunction during sepsis, the use of the Sepsis-related Organ Failure (SOFA) score by Vincent and colleagues[5] was recommended to define organ dysfunction during sepsis. A more explicit definition for septic shock was also proposed. Septic shock was defined as persistent hypotension with systolic blood pressure <90 mmHg or mean arterial blood pressure <70 mmHg, despite adequate fluid resuscitation.

Epidemiological studies of administrative data sets often rely on imprecise definitions such as ICD-9CM codes for "septicemia" and "bacteremia" along with separate codes for organ dysfunction,[6] which may underreport the diagnosis of sepsis.[7] Diagnosis of severe sepsis can be made more sensitive by combining codes for various infections (e.g., pneumonia) and acute organ system dysfunctions.[1]

Epidemiology

Incidence and mortality

In the United States, the incidence of severe sepsis is estimated to be 300 cases per 100 000 population.[1] Approximately half of these cases occur outside the ICU. A fourth of patients who develop severe sepsis will die during their hospitalization. Septic shock is associated with the highest mortality, approaching 50%.

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Table 1. Criteria for SIRS, sepsis, severe sepsis, and septic shock based on the 1991 ACCP/SCCM Consensus Conference

Term	Criteria
SIRS*	2 out of the 4 following criteria:
	Temperature >38 °C or <36 °C
	Heart rate >90/min
	Hyperventilation evidenced by respiratory rate >20/min or arterial CO_2 lower than 32 mmHg
	White blood cell count >12 000 cells/μL or lower than 4000 cells/μL
Sepsis	SIRS criteria with presumed or proven infection
Severe sepsis	Sepsis with organ dysfunction
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation

Note: *SIRS, systemic inflammatory response syndrome.

Table 2. Criteria for sepsis based on 2001 SCCM/ACCP/ATS/ESCIM/SIS Consensus Conference

Term	Criteria
Sepsis	Documented (or suspected) infection with any one of the following clinical or laboratory criteria
General parameters	Fever, hypothermia, tachycardia, tachypnea, altered mental status, arterial hypotension, decreased urine output, significant peripheral edema, or positive fluid balance
Inflammatory parameters	Leukocytosis, leukopenia, hyperglycemia, increased C-reactive protein, procalcitonin, or creatinine, coagulation abnormalities, increased cardiac output, reduced mixed venous oxygen saturation
Hemodynamic parameters	Hypotension, elevated mixed venous oxygen saturation, elevated cardiac index
Organ dysfunction parameters	Arterial hypoxemia, acute oliguria, increase in creatinine level, elevated international normalized ratio or activated partial thromboplastin time, ileus, thrombocytopenia, hyperbilirubinemia
Tissue perfusion parameters	Hyperlactatemia, decreased capillary refill, or mottling

The cumulative burden of organ failure is the strongest predictor of death, both in terms of the number of organs failing and the degree of organ dysfunction.

In 2003, Martin and colleagues found an increase in septicemia incidence and septicemia-related deaths over the past 2 decades in United States.[6,8] This trend is expected to continue due to aging of the population, increasing burden of chronic health conditions, and increased use of immunosuppressive therapy, transplantation, chemotherapy, and invasive procedures. National estimates of severe sepsis incidence are often based on use of administrative data sets. Changes in coding practices, particularly increased coding of organ dysfunction, may overestimate the rate of increase.[9]

Over the past 2 decades, the case-fatality has declined due to advances in supportive care for the critically ill.[10] For example, since implementation of bundled care processes (e.g., Surviving Sepsis Campaign) and low tidal volume ventilation in patients with acute respiratory distress syndrome (ARDS), mortality among critically ill patients with severe sepsis has decreased over the past decade.[11-15]

Point prevalence studies in the ICU are the simplest approach to describing the epidemiology of sepsis. For example, 32.8% of 895 patients in 254 Mexican ICUs had sepsis on a single day in 1995.[16] Extrapolation of such data to population estimates assumes all patients with sepsis will be in an ICU. Even in the most advanced health care systems this is unlikely to be the case.[1] Prevalence studies have other limitations. For example, the prevalence may increase if illness duration increases with better survival, even if incidence falls. Data from point prevalence studies have been used to estimate population incidence,[17] but without information on illness duration, these figures are difficult to interpret.

Prospective cohort studies in which incidence is directly observed are potentially more accurate. A cohort study of sufficient duration may also overcome problems of seasonal variation. However, cohort studies limited to ICU patients may underestimate the incidence. Extrapolating ICU incidence to population incidence remains flawed because not all patients with sepsis are treated in an ICU. A discussion of the epidemiology of sepsis is therefore really one of "treated sepsis".[18] The threshold of eligibility for treatment almost certainly differs by time and country, with different cultural approaches to end-of-life care, different availability of acute hospital and ICU beds, varying levels of universal health insurance, and other cultural and economic factors.[19] For example, in Spain in 2003 only 32% of patients with severe sepsis were admitted to the ICU[20] compared with 51.1% in the United States.[1] Furthermore, an unrepresentative sample of ICUs may bias the result. Most countries have only quantified the epidemiology of sepsis in their intensive care populations and the estimates would be influenced by the availability of ICU beds in each country. It has been postulated that the high ICU incidence of sepsis in countries such as the UK (27.1%) and Brazil (27.3%) reflects a scarcity of ICU beds, as only the sickest patients can be admitted.[18] There are 8.6 ICU beds per 100 000 population in the UK compared with 38.4 and 30.5 per 100 000 in France and the United States,[21] where the mean ICU frequency of sepsis is 12.4% and 12.6%, respectively.

Some of these problems are overcome using administrative databases that record data from an entire population or correctly weighted samples thereof. Such an approach relies on accurate coding of disease by personnel entering data for another purpose, usually reimbursement. Problems of case definition are particularly important when using administrative databases. For example, Gaieski et al. demonstrated an up to 3.5-fold difference in the incidence and mortality of severe sepsis depending on the method of database abstraction used.[22]

Etiology and Site of Infection

Etiology

Gram-positive organisms as a cause of sepsis have increased in frequency over time and are now almost as common as

Table 3. Types of organisms in culture-positive infected patients and associated risk of hospital mortality (modified from reference 32)

	Frequency (%)	OR (95% CI)
Gram-positive	46.8	
Staphylococcus aureus	20.5	0.8 (0.6–1.1)
MRSA	10.2	1.3 (0.9–1.8)
Enterococcus	10.9	1.6 (1.1–2.3)
S. epidermidis	10.8	0.9 (0.7–1.1)
S. pneumoniae	4.1	0.8 (0.5–1.4)
Other	6.4	0.9 (0.7–1.2)
Gram-negative	62.2	
Pseudomonas species	19.9	1.4 (1.2–1.6)
Escherichia coli	16.0	0.9 (0.7–1.1)
Klebsiella species	12.7	1.0 (0.8–1.2)
Acinetobacter species	8.8	1.5 (1.2–2.0)
Enterobacter	7.0	1.2 (0.9–1.6)
Other	17.0	0.9 (0.7–1.3)
Anaerobes	4.5	0.9 (0.7–1.3)
Other bacteria	1.5	1.1 (0.6–2.0)
Fungi		
Candida	17.0	1.1 (0.9–1.3)
Aspergillus	1.4	1.7 (1.0–3.1)
Other	1.0	1.9 (1.0–3.8)
Parasites	0.7	1.3 (0.5–3.3)
Other organisms	3.9	0.9 (0.6–1.3)

OR, odds ratio; CI, confidence interval; MRSA, methicillin-resistant *S. aureus*

gram-negative infections,[6,23-25] likely due to greater use of invasive procedures and the increasing proportion of hospital-acquired infection.[26] More frequent use of broad-spectrum antibiotics in increasingly sick patients who remain in the ICU for longer periods of time has likely resulted in an increased bacterial resistance over time.[27,28] Antibiotic resistance is problematic, prolonging length of stay and duration of mechanical ventilation, although the effect on mortality is uncertain.[29-31] International variations in the implementation of the two main strategies to control resistance (the more rational use of antibiotics and the prevention of cross-infection between patients) may explain different rates in different countries.[28]

The type of organism causing severe sepsis is an important determinant of outcome. Although most recent studies have suggested an increasing incidence of gram-positive organisms, the latest European Prevalence of Infection in Intensive Care (EPIC II) study reported more gram-negative organisms (62.2% vs. 46.8%).[32] Patterns of infecting organisms were similar to those in previous studies, with predominant organisms being *Staphylococcus aureus* (20.5%), *Pseudomonas* species (19.9%), *Enterobacteriacae* (mainly *E. coli*, 16.0%), and fungi (19%). *Acinetobacter* was involved in 9% of all infections, with significant variation of infection rates across different regions (3.7% in North America vs. 19.2% in Asia). The only organisms associated with hospital mortality in multivariable logistic regression analysis were *Enterococcus*, *Pseudomonas*, and *Acinetobacter* species.[32] The microbiologic results of the EPIC II are summarized in **Table 3**.

Table 4. Common sites of infection in patients with severe sepsis by sex and associated crude mortality rates (based on Mayr et al.)[37]

Site of infection	Frequency (%)		Mortality (%)	
	Male	Female	Male	Female
Respiratory	41.8	35.8	22.0	22.0
Bacteremia, site unspecified	21.0	20.0	33.5	34.9
Genitourinary	10.3	18.0	8.6	7.8
Abdominal	8.6	8.1	9.8	10.6
Device-related	1.2	1.0	9.5	9.5
Wound/soft tissue	9.0	7.5	9.4	11.7
Central nervous system	0.7	0.5	17.3	17.5
Endocarditis	0.9	0.5	23.8	28.1
Other/unspecified	6.7	8.6	7.6	6.5

A large metaanalysis of 510 studies reported that gram-negative bacteremia was associated with a higher mortality compared with gram-positive bactermia.[33] The most common bloodstream infections were due to coagulase-negative *Staphylococcus* and *E. coli*, but these were associated with a relatively low mortality (20% and 19%, respectively) compared with *Candida* (43%) and *Acinetobacter* (40%) species. Gram-positive pneumonia due to *Staphylococcus aureus* had a higher mortality (41%) than that due to the most common gram-positive (*Streptococcus pneumoniae*, 13%), but the gram-negative bacillus *Pseudomonas aeruginosa*, had the highest mortality of all (77%). This study demonstrated the interaction of organism and site of infection in determining mortality, and called for this to be incorporated into the risk stratification of clinical trials. However, approximately a third of patients with severe sepsis never have positive blood cultures.[34] Before ascribing causative risk to a particular organism, it is also necessary to take into account the confounding effect of the context in which the organism most commonly develops. For example, the association of *Acinetobacter* with high mortality probably reflects the tendency of *Acinetobacter* to develop as a nosocomial infection after a prolonged ICU course in patients with many comorbidities. These factors, rather than the organism's virulence, may explain the high associated mortality.

Site of infection

Respiratory tract infections, particularly pneumonia, are the most common site of infection, and associated with the highest mortality.[35] However, the relative importance of pneumonia has decreased over time.[26] Men and alcoholics are particularly prone to developing pneumonia,[36] while genitourinary infections are more common among women.[1,35] Other common sources of infection include abdominal, skin, and soft tissue, device-related, central nervous system, and endocarditis.[1,37] Common sites of infection in severe sepsis patients are summarized in **Table 4**.

Risk Factors

Risk factors for severe sepsis can broadly be divided into risk factors for infection and, contingent upon developing infection, risk factors for organ dysfunction. Most of the risk factors of severe sepsis described in this paragraph relate to the infection risk, as risk factors that predispose someone with an infection to developing acute organ dysfunction are less well understood.[37]

For example, age, male gender, black race, and increased burden of chronic health conditions are important risk factors for severe sepsis. Moreover, a recent study reported an inverse relationship between socioeconomic status and the risk of blood stream infection.[38] The incidence of severe sepsis increases disproportionately in older adults, and more than half of severe sepsis cases occur in adults over 65 y of age.[37] More than half of patients who develop severe sepsis also have at least one chronic health condition. Severe sepsis is more likely to occur in individuals with chronic obstructive pulmonary disease, cancer, chronic renal and liver disease, and diabetes. Other risk factors include residence in long-term care facilities, malnutrition, and use of immunosuppressive medications and prosthetic devices. Finally, abnormalities in the immune response to infection, as described below, increase risk of infection and severe sepsis. These abnormalities may be secondary to chronic diseases or age (i.e., immunosenesence).

Despite improved understanding of clinical risk factors influencing susceptibility and outcomes of sepsis, why some subjects develop severe sepsis and succumb to the infection while others do not, remains unclear. Thus genetic factors have been examined to explain variability in susceptibility and outcomes of infection. A study by Sorensen and colleagues[39] suggests that genetic factors may be more important in outcomes of infectious diseases compared with cardiovascular disease. In this study, adopted children whose biological parents died due to infectious causes had a 5.8-fold increased risk of dying due to infections. In comparison, the increased risk of death due to cardiovascular causes was 4.5-fold if their biological parents died of cardiovascular causes. Because sepsis is common and often fatal, the pattern of inheritance is unlikely to be Mendelian, where phenotypic differences are attributed to a single gene. Multiple genes may interact with pathogens (environmental factors) and influence susceptibility, response and outcome of sepsis. Some of the candidate genes that have shown promising results in preliminary studies include tumor necrosis factor (TNF), plasminogen activator inhibitor (PAI)-1, Toll-like receptor (TLR)-1 and TLR-4, and the Mal functional variant required for downstream signaling of TLR-2 and TLR-4.[40-42] A single center study in Belgium reported an association of MASP2 and NOD2/TLR4 genotypes with susceptibility to bacteremia and in-hospital mortality, respectively.[43]

The relative contribution of clinical and genetic factors to susceptibility and outcomes of severe sepsis remains unclear. Genetic factors may play an important role in younger individuals but could be less important in older adults where chronic diseases may play a more important role. Furthermore, common variants may have a smaller attributable risk, while certain rare variants may lead to a higher attributable risk. Recent advances in technology using genome-wide scans, where up to 1 million polymorphisms can be assayed in a single individual will allow identification of novel genetic variants.

Environmental risk factors

Severe sepsis is more common in colder months, both in the UK (35% higher in winter than in summer)[44] and US (17.7% higher in fall than in summer).[45] The case fatality rate for sepsis is also higher in winter, despite similar severity of illness. Respiratory infections have the greatest seasonal change, with their highest incidence in colder months, whereas genitourinary infections are significantly more frequent in summer. This seasonal variation relates to climate and is reflected by the regional differences within the US: incidence variation is highest in the northeast and lowest in the south. Recent studies have also explored the relationship of light exposure and critical illness. Consistent with the winter immunoenhancement theory, a shorter exposure to sunlight (i.e., photoperiod) in the month before critical illness was associated with a reduced risk of death in a single center observational cohort study.[46] However, once patients were in the ICU their exposure to natural light was almost negligible and hence future studies are warranted whether manipulating light exposure, before or during ICU admission, can enhance survival.

Special Populations

As mentioned above, increased burden of chronic health conditions are important risk factors for severe sepsis. Many comorbidities such as diabetes and chronic renal failure influence susceptibility to and outcome from severe sepsis.[37] However, some patient populations deserve special mentioning.

Malignancy

Cancer is one of the most common co-morbidities among patients with severe sepsis.[47] Analysis of a subgroup of patients with cancer in the 1979–2001 National Hospital Discharge Survey found cancer of all types increased the risk of developing sepsis almost 10-fold. Malignancy increased the risk of sepsis more than any other comorbidity, and the source of infection was related to the type of cancer; for example lung cancer patients were particularly likely to develop pneumonia. Sepsis contributed to 30% of all hospitalized cancer deaths. Cancer increased the case fatality rate of sepsis by 55%. However this is declining with time (cancer associated sepsis case fatality rates fell from 44.7% in 1979 to 23.8% in 2001), perhaps due to safer chemotherapy, or maybe just in parallel to the overall improvement in sepsis treatment. While the risk of developing severe sepsis was 8.7 times higher in hematological malignancy compared with solid tumors, the in-hospital mortality from severe sepsis was similar in each group.

Obesity

Obesity is a fast growing epidemic worldwide and is associated with other morbid conditions including diabetes, cardiovascular and respiratory diseases as well as cancer.[48] The effects of obesity on severe sepsis susceptibility and outcomes are not well described, but there is accumulating evidence that obese patients are more susceptible to infections and more likely to develop

serious complications of common infections.[49] Recently, Arabi et al. reported similar outcomes for obese and normal weight patients with septic shock in an international multi-center study after adjusting for baseline characteristics and treatment interventions.[50] Interestingly, obese patients received less fluid resuscitation and lower doses of antimicrobial agents adjusted for body weight compared with normal weight patients. The intricacies of caring for morbidly obese critically ill patients have been nicely summarized by El-Solh.[51]

Human immunodeficiency virus (HIV)

The epidemiology of sepsis in patients with HIV is changing significantly with advancements in highly active antiretroviral therapy (HAART) and *Pneumocystis jirovecii* prophylaxis. Over the past decade, the proportion of HIV-positive patients admitted to the ICU has steadily increased, as has their overall survival.[52] Compared with the pre-HAART era, most HIV-positive patients who are hospitalized or admitted to the intensive care unit die of non-AIDS-related illness, the most common being sepsis.[53-55]

Data from a recent single center study in the United States found approximately 13.7% HIV-positive patients among all ICU admissions, with an overall in-hospital mortality of 42%.[54] Among HIV-positive patients, 194 acute infections were identified, of which the majority were nosocomial or healthcare-associated (57.7%). The remainder were AIDS-related (28.4%) or community-acquired (13.9%). Similar to the "general" population, sepsis in AIDS patients is increasingly due to multi-resistant organisms.[56]

Children

The subject of pediatric sepsis is discussed in detail in this special issue on sepsis (see contribution by Randolph and McMulloh).

Analysis of a large administrative database using hospital discharge data from 7 US states recently reported an 81% increase in pediatric sepsis cases between 1995 and 2005, corresponding with an increased prevalence from 0.56 to 0.89 per 1000 pediatric population.[57] This increase was largely driven by a disproportionate increase in severe sepsis in neonates, particularly those with very low birth weight (9.7 vs. 4.5 per 1000 births). Of cases where a site of infections was identified, respiratory (48.9%) and primary bacteremia (18.1%) were the two most common.

Out-of-hospital severe sepsis

The emphasis on early recognition and aggressive treatment of sepsis was illustrated by the "early goal directed therapy" study, which showed that early aggressive resuscitation measures significantly improved mortality.[58] As a consequence, early fluid resuscitation, vasopressor support and blood transfusion to improve hemodynamics have been incorporated into treatment recommendations. Nevertheless, a recent multicenter cohort study showed that out-of-hospital interventions including fluid resuscitation, monitoring, and serial vital signs occurred in less than half of subjects.[59] Hence, there is a need to address the role of out-of-hospital interventions in improving clinical outcomes in severe sepsis and recognition strategies for severe sepsis before hospital arrival, as the limited data available suggest that only a third of patients with severe sepsis who are transported to the hospital with emergency medicine services (EMS) receive out-of-hospital fluid resuscitation.[60]

Sex and race

Women appear to be at lower risk of developing sepsis than men.[1,61] Whether the greater male risk of developing severe sepsis reflects an increased risk of developing infection or of progressing to severe sepsis is not known, as are the underlying mechanisms of these disparities. A combination of differences in chronic disease burden, particularly subclinical disease, social and environmental factors, and genetic predisposition causing differences in the host immune response to infection likely contribute to the observed differences. For example, healthy female volunteers showed a more pronounced pro-inflammatory response after endotoxin infusion compared with healthy men.[62] In addition, men tend to be treated more aggressively and undergo more invasive procedures,[63] whereas women more frequently have a "do not resuscitate" order written.[64] Another paper in this special issue by Angele et al. explores the role of estrogens and androgens that may account for the gender differences in sepsis outcomes.

Epidemiological studies consistently report a higher incidence of severe sepsis among black compared to white patients.[65,66] The higher severe sepsis rate is due to both a higher infection rate in black patients and a higher risk of developing acute organ dysfunction.[37] These results are independent of sex, robust across different sources and etiologies of infections, and persist after adjusting for poverty level and hospital effect. The underlying mechanisms of racial disparities in infection and severe sepsis are poorly understood. Similar to gender differences, a combination of differences in chronic disease burden, social and environmental factors, and the immune response to infection likely contribute to the observed differences in infection and severe sepsis-related hospitalization rates. A higher prevalence of chronic kidney disease and diabetes among black patients hospitalized for infection may partly explain higher infection-related hospitalization rates among black patients. Furthermore, the differences in co-morbidities did not explain higher risk of organ dysfunction among those hospitalized for infection. Differences in host immune response may partly explain these differences,[67,68] and recent studies suggesting polymorphisms in key proteins involved in the host response to infection suggest an increased susceptibility to severe infections and septic shock among people of African descent.[41,42] In addition, the majority of black patients receive care for common infections, such as community-acquired pneumonia, at hospitals that provide overall poorer quality of care regardless of race. Thus, policy interventions directed at hospitals that provide care to large number of black patients seem most promising to reduce racial disparities for CAP and severe sepsis.[69]

Long-Term Outcomes

The traditional focus of care in patients with infectious disease has been to reduce short-term mortality and clinical trials have used 28-d or 90-d mortality as an endpoint. However, recent studies suggest that infection may worsen long-term outcomes.[70-73] While it is commonly perceived that serious infections occur in

older subjects with chronic health conditions and that these conditions contribute to higher mortality even after recovery from acute illness, several studies show that higher long-term mortality is independent of baseline functional and health status.[74]

Adverse long-term outcomes are not limited to increased mortality risk. For example, elderly survivors of severe sepsis are up to three times as likely to develop persistent cognitive and functional impairments compared with elderly controls not hospitalized for sepsis.[75] Acute infections may worsen pre-existing chronic diseases or new chronic diseases may emerge. The relationship between acute infection and chronic illness may be bidirectional. Whereas the increased burden of chronic health conditions increase the risk of infection and sepsis, survivors of infection may develop a higher burden of chronic disease. For example, individuals with renal disease are at higher risk for serious infection. The episode of serious infection can lead to renal failure and eventually lead to chronic dialysis. Similarly, it has been shown that infection with influenza is associated with increased risk of cardiovascular disease. These examples underscore the complex relationship between infection and underlying chronic disease, where co-morbid conditions are both a risk factor and are modified by the infectious event. The worsening of chronic illness following infection is in turn a risk factor for subsequent acute illness, thereby initiating a spiral of events that can ultimately lead to death.

Mechanisms underlying increased long-term mortality and morbidity remain unclear. Unresolved immune response during recovery may worsen long-term outcomes. For example, higher circulating levels of inflammatory and coagulation markers were observed at hospital discharge when patients appeared to have clinically recovered from infection and increased subsequent mortality.[76]

Conclusion

Sepsis and severe sepsis are leading causes of death in the United States and the most common cause of death among critically ill patients in non-coronary intensive care units. Recent studies also suggest that acute infections worsen pre-existing chronic diseases or result in new chronic diseases, hence leading to poor long-term outcomes in acute illness survivors. People of older age, male gender, black race, and preexisting chronic health conditions are particularly prone to develop severe sepsis, hence prevention strategies should be targeted at these vulnerable populations. The epidemiology of severe sepsis in developing countries may differ significantly from developed countries, which warrants greater attention in future studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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The current understanding of sepsis and research priorities for the future

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Keywords: sepsis, septic shock, innate immunity, bacterial toxins, endotoxin, host–pathogen interactions, clinical trials

This special issue of *Virulence* is entirely devoted to the topic of sepsis and septic shock. Septic shock continues to pose formidable challenges for emergency room physicians, critical care specialists, surgeons, and infectious disease clinicians alike in caring for these critically ill patients. Early recognition of sepsis and improved therapies to manage the multi-organ dysfunction that frequently follows sepsis pathophysiology remain major unmet medical needs. The interplay between virulence factors of the pathogen and the antimicrobial defenses of the host are critical determinants of outcome in sepsis and septic shock.[1] This issue of *Virulence* will specifically focus on both the pathogen-related factors and the host defense mechanisms that lead to septic shock and contribute to its resolution or fatal outcome. We have assembled a stellar group of international experts in the field of sepsis research and compiled their ideas and collective wisdom in this special issue. We hope to provide a detailed review of the state of the art and science of septic shock research as it currently exists, extending from the molecular level to the population level.

This issue begins with a description of current secular trends into the epidemiology of sepsis and septic shock worldwide. The paper by Mayr, Yende, and Angus[2] provides an overview of the clinical parameters and consequences of sepsis across different populations of "at risk" patients worldwide. The complex interactions between pre-existing, chronic diseases, and host response capabilities against invasive microbial pathogens are considered in this epidemiologic review. The impact of gender and sex sterol effects on the host response in sepsis is reviewed by Angele and colleagues.[3] Females throughout the mammalian class are less susceptible to infection and death from infection compared with their male counterparts. This appears to be true in humans as well and insights into the explanation for these gender differences might provide some new therapeutic approaches to sepsis.

The history behind the current classification of sepsis and the systemic inflammatory response is provided by Robert Balk,[4] a long standing colleague and frequent co-author of Roger Bone. John Marshall provides an alternative way of looking at, and better characterizing, the acute systemic inflammatory process in sepsis using the PIRO model (predisposition, insult/infection, response, organ dysfunction) that he helped to develop.[5] The terminology of sepsis and our lack of ability to specifically identify important subgroups within a large and heterogeneous group of patients defined by term "sepsis" remain imprecise and an area of much-needed additional research.[6]

Our current understanding about the interaction between pathogen and host immune defenses is considered in a series of three manuscripts in this issue of *Virulence*. The first paper is by Drs Wiersinga, Leopold, Cranendonk, and van der Poll.[7] The host immune response and the pattern recognition receptors that orchestrate the host response to infection are reviewed in detail in this paper. An in-depth discussion of the relative importance of the hyper-inflammatory process vs. the prolonged, sepsis-induced, immunosuppressive phase is provided by Drs Boomer, Green, and Hotchkiss.[8] The weight of evidence now supports the view that the immune-suppressive phase is the predominant immunologic response in most patients with sepsis.[9] This changes the paradigm for treatment interventions when trying to establish immune reconstitution in septic patients. The next paper by Giamarellos and Christaki focuses on those special virulence characteristics possessed by bacterial pathogens that can evade host defenses and disseminate into the systemic circulation of the host.[10]

The fundamental role of mitochondrial dysfunction in sepsis is expertly reviewed by Mervyn Singer.[11] Cellular energetics and the loss of mitochondrial function play a major role in the pathophysiology of sepsis at the cellular and tissue level. Insights into new treatment strategies are being illustrated through the investigation of mitochondrial function and dysfunction during sepsis. The critically important, underlying pathophysiology of the microcirculatory dysfunction of sepsis is reviewed in detail by Drs DeBacker, Cortes, Donadello, and Vincent.[12] Ultimately, the presence or absence of reacquisition of adequate tissue perfusion to vital organs largely determines the outcome in septic shock and remains a major target for improved therapeutic interventions.

The role of specific pathogens and related host responses directed against these pathogens are considered in a series of papers in this issue of *Virulence*. Anand Kumar presents compelling evidence of an alternative way of looking at sepsis focused on pathogen load and the need to bring the microbial burden to a rapid resolution is essential in treating septic shock.[13] The unique role of meningococcal disease and its complex interactions with various components of the complement system is considered by Lewis and Ram.[14] A similarly distinct and highly specialized host response to group A streptococci in the

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pathogenesis of toxic shock syndrome is detailed by Reglinski and Sriskandan.[15] The immunology of superantigens and the myriad of exotoxins produced by group A streptococci are reviewed in this paper. Finally, the complex interactions between influenza and bacterial pathogens in severe sepsis are described by Florescu and Kalil.[16] Although many viral pathogens predispose to secondary bacterial infections, influenza is likely the most common and potentially most lethal virus that contributes to bacterial sepsis.

The lack of success with translating discoveries in the animal laboratory to successful treatments for patients in the intensive care unit with sepsis is a stark reminder of how inadequate our animal models are when it comes to understanding sepsis. The various issues related to animal models of sepsis are considered in an objective and critical manner by Mitchell Fink.[17] Recent evidence of the poor to completely absent predictive correlations between the genomics of mice and humans following systemic infection bespeaks of the need to improve our preclinical models in septic shock.[18]

The critical need for improved biomarkers for the rapid diagnosis of sepsis is detailed by Bloos and Reinhart.[19] Our current inability to detect important subpopulations within the septic patient population by clinical criteria alone is evidenced by the simple lack of value of SIRS criteria to distinguish between hyperinflammatory or hypoinflammatory host responses in sepsis.[1,9] Efforts to develop better biomarkers to assist the clinician in the rapid and accurate diagnosis of sepsis are considered in this review.

Special populations with unique yet overlapping characteristics are considered in a series of papers in this issue. The first manuscript relates to the problem of invasive candidiasis in the critically ill patient. Drs Delaloye and Calandra discuss the current diagnostic algorithms available to make a rapid diagnosis of candidiasis in the ICU patient.[20] This is a major challenge from both a clinical and laboratory perspective. The poor outcomes associated with delayed or inadequate treatment for disseminated candidiasis is a stark reminder of the importance of making this diagnosis with skill and alacrity. Improvements in molecular diagnostic methods and treatment strategies are now underway in the management of candidiasis in the ICU.

The unique characteristics of sepsis in neonates (expertly reviewed by Shah and Padbury[21]) and the post-neonatal, pediatric sepsis patients are highlighted by Randolph and McCulloh.[22] These special patient populations require individualized treatment that may differ substantially from the management of adult sepsis. A brief review of the new surviving sepsis campaign guidelines for the treatment of adult sepsis is provided by Schorr, Zanotti, and Dellinger.[23] The 2012 guidelines are practical, informative, and quite helpful in organizing the appropriate treatment approach to a septic patient.[24] Optimal fluid management and glucose control is described in detail in the following article by Simon Finfer.[25]

The final section of this sepsis issue relates to complexities of treatment of systemic infections in an age of progressively increasing, antibiotic resistance. The emerging issues of extreme drug resistance in gram-negative bacteria are discussed in a timely review by Pop-Vicas.[26] We are running out of antimicrobial agents to treat common gram-negative infections and the future looks rather bleak with respect to the development of new chemotherapeutic agents. Because of this shortcoming, therapies other than antimicrobial chemotherapy are now under consideration. One option is to approach the intrinsic virulence of the organism based upon the toxins produced by the invasive bacterial pathogen. The current status of the role of bacterial toxins in sepsis pathogenesis is discussed by Dr Ramachandran.[27]

One of the most attractive targets for management of septic shock from an immunologic perspective is vaccines or immunotherapy directed against bacterial endotoxin. This topic is discussed at length by Alan Cross in his paper on anti-endotoxin vaccines.[28] The last manuscript in this issue rekindles an old idea that is making a distinct comeback as a potential therapeutic option. Instead of using chemotherapy, the idea of using phage therapy with a specific bacteriophage or phages against specific bacterial pathogens is witnessing a rebirth in interest by clinical investigators. The promise and problems of phage therapy as an alternative to antibiotics is discussed by Xavier Wittebole.[29] Some combination of non-antibiotic therapy with standard antibiotic strategies might become a common management approach for septic shock therapy in the future.

I would like to thank each of the authors for their thoughtful contributions and in particular I would extend my sincere gratitude to the members of the International Sepsis Forum for their contributions to this special issue of *Virulence*.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Gram-positive and gram-negative bacterial toxins in sepsis

A brief review

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Keywords: sepsis, LPS, superantigens, TLR4, TNFα, cytokine storm

Bacterial sepsis is a major cause of fatality worldwide. Sepsis is a multi-step process that involves an uncontrolled inflammatory response by the host cells that may result in multi organ failure and death. Both gram-negative and gram-positive bacteria play a major role in causing sepsis. These bacteria produce a range of virulence factors that enable them to escape the immune defenses and disseminate to remote organs, and toxins that interact with host cells via specific receptors on the cell surface and trigger a dysregulated immune response. Over the past decade, our understanding of toxins has markedly improved, allowing for new therapeutic strategies to be developed. This review summarizes some of these toxins and their role in sepsis.

Introduction

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) in the presence of suspected or proven infection.[1] It is the second most common cause of death in non-coronary intensive care units (ICU) and the tenth overall cause of death in high income countries.[2,3] The incidence of sepsis in the past two decades has annually increased by 9%, to reach 240 per 100 000 people in the USA by 2013.[4,5]

Initially it was thought that the major organisms that caused bacterial sepsis were gram-negative bacteria.[6] However, over the past 25 y it has been shown that gram-positive bacteria are the most common cause of sepsis.[7] Some of the most frequently isolated bacteria in sepsis are *Staphylococcus aureus* (*S. aureus*), *Streptococcus pyogenes* (*S. pyogenes*), *Klebsiella* spp., *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa* (*P. aureginosa*).[8]

In order to cause disease, pathogens have to employ an array of factors known as virulence factors that protect them from the host innate immune system and enable them to cross mucosal barriers, disseminate, and replicate in distant organs.[9,10] Importantly, each stage of infection involves the expression of different virulence factors depending on the stage of infection. Some of the most important bacterial virulence factors are toxins. These toxins include endotoxin or lipopolysaccharide (LPS) that is present in the outer membrane of the gram-negative bacterium and several other secreted exotoxins and enterotoxins in other bacteria. Bacterial toxins are mainly divided into three types based on their mode of action. Type I toxins disrupt host cells without the need to enter the cells. These include superantigens (SAgs) produced by *S. aureus* and *S. pyogenes*.[11] Type II toxins, such as hemolysins and phospholipases destroy host cell membranes to invade and interrupt host defense processes within the cell.[12] Type III toxins, also known as A/B toxins due to their binary structure; disrupt host cell defenses to allow dissemination to remote organs. The B component of these toxins binds to the host cell surface, while the A component possess the enzymatic activity to damage the cell.[12] Several lethal toxins including Shiga toxin, cholera toxin, and anthrax lethal toxin belong to the Type III toxin family.

The host innate immune cells recognize several of the bacterial virulence factors via unique receptors called pattern-recognition receptors (PRRs).[13] PRRs recognize conserved motifs on the pathogen surface to initiate an innate immune response. Over the last decade with major research in the field of toxins and their interaction with host cells and PRRs, there has been a wealth of knowledge in understanding sepsis. This review aims to briefly focus on our current knowledge of some important toxins and their functions.

Endotoxins

Endotoxins are the glycolipid, LPS macromolecules that make up about 75% of the outer membrane of gram-negative bacteria that are capable of causing lethal shock.[14,15] The structure of LPS generally consists of a hydrophobic lipid A domain, an oligosaccharide core, and the outermost O-antigen polysaccharide.[16] Lipid A is a di-glucosamine-based lipid that serves as a hydrophobic anchor of LPS to the microbial membrane. *E. coli* is known to harbor approximately 10^6 lipid A residues on the surface.[17,18] Lipid A is a highly diverse molecule and the diversity is manifested in part in the number of fatty-acid side chains and the presence of terminal phosphate residues. Lipid A of *E. coli* that is hexa-acylated with side chains of 12–14 carbons has enhanced stimulatory effect of human cells compared with lipid A where the length of the side chains or the charge has been altered.[19-21] The lipid A of some human pathogens like *Francisella* spp., *Yersinia pestis*, and

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Helicobacter pylori contain typically only 4 or 5 acyl chains of 16–18 carbons in length and are poorly recognized by human LPS receptor known as Toll-like receptor 4 (TLR4).[22-24]

Lipid A is the single region of LPS that is recognized by the innate immune system. Picomolar concentrations of lipid A are sufficient to trigger a macrophage to produce proinflammatory cytokines like TNF-α and IL1β.[25-27] To trigger an innate immune response, the lipid A portion of LPS alone is sufficient, yet the adaptive immune response during infection is usually directed toward the O-antigen.[28] The key pattern recognition receptor for LPS recognition is Toll-like receptor 4 (TLR4).[29] LPS in circulation is solubilized by LPS-binding protein (LBP) in the serum.[30] The endotoxin is then transferred to an extrinsic glycosylphosphatidylinositol-anchored membrane protein on leukocytes called CD14.[31] CD14 can also be present in the soluble form. CD14 transfers LPS to MD2, which then binds to TLR4 to form the TLR4-MD2 receptor complex and triggers LPS recognition.[31] Soluble MD2 non-covalently associates with TLR4, however it binds to LPS directly even in the absence of TLR4.[32-34] Once the LPS-MD2-TLR4 complex forms, the entire complex dimerizes[35] and recruits cytoplasmic adaptor molecules, through the interaction with Toll-interleukin-1 receptor (TIR) domains.[36]

When TLR4 is activated upon its recognition of LPS, it signals through either a MyD88 (myeloid differentiation primary response gene 88)-dependent or a MyD88-independent pathway. The MyD88-dependent pathway induces the activation of NFκB and mitogen-activated protein kinase genes leading to the release of proinflammatory cytokines, whereas the MyD88 independent pathway (also known as the TRIF pathway-Toll-interleukin-1 receptor domain-containing, adaptor-inducing interferon β) activates the Type-1 interferon-inducible genes followed by NFκB production.[37]

The lipid A component of LPS is sufficient to cause endothelial cell injury by promoting the expression of tissue factor and proinflammatory cytokines, leading to apoptosis of these cells.[38-40] In a blood stream infection, presence of lipid A can lead to endotoxin shock. In murine TLR4, an 82-amino acids long hypervariable region is responsible for recognition of lipid A.[27] The structure-length and the number of acyl chains are critically important in human TLR4 signaling.

Several gram-negative bacteria have developed ways to modify lipid A structure depending on the environment and host cells leading to greater resistance to host cationic antimicrobial peptides (CAMPs) and altering TLR4 recognition.[41] CAMPs are a group of peptides produced by eukaryotes that are an important component of the innate immune responses against pathogens. Due to their cationic nature, CAMPs disrupt bacterial surface by inserting into the anionic cell wall and phospholipid membrane, thereby killing the pathogen.[42] Studies report that an extremely low concentration of CAMPs is sufficient to modify lipid A.[43] Modifications of lipid A are regulated by a two component system that is an environmental sensor-kinase regulator called PhoP-PhoQ in several gram-negative bacteria including *S.* Typhimurium. This two component system promotes the resistance of *S.* Typhimurium to CAMPs and also enables the pathogen to survive within human and murine macrophages.[41] PhoP–PhoQ regulated lipid A modifications involves the deacylation of several fatty acids and also the addition of palmitate, aminoarabinose, and phosphoethanolamine to the lipid A structure. Compared with non-regulated lipid A, PhoP–PhoQ regulated lipid A modifications leads them to be less recognized and stimulatory to the TLR4 complex, a phenomenon that could lead to the persistence of infection.[43,44] Acylation of lipid A is regulated by three enzymes, PagP, PagL, and LpxO in *Salmonella*, which catalyze the acylation, deacylation, and hydroxylation of lipid A respectively.[45-48] PagP enables the addition of C_{16}:0 fatty acid by transferring the fatty acids from the inner membrane portion of lipid A to the outer membrane region of the molecule.[45] PagL causes deacylation of the lipid A structure and decreases the recognition of lipid A when the pathogen colonizes host cells.[44] Both PagP and PagL modify the recognition of lipid A by the TLR4 complex. Addition of aminoarabinose decreases the negative charge of lipid A, making it more resistant to CAMPs.[49] Similarly, clinical isolates of *P. aeruginosa* that colonize the airways of cystic fibrosis patients synthesize unique lipid A molecules with an highly modified aminoarabinose and fatty-acid chains has been identified.[50]

LPS induces inflammatory cells to express a number of proinflammatory cytokines including IL-8, IL-6, IL-1β, IL-1, IL-12, and IFNγ;[51,52] however, TNFα seems to be of critical importance during endotoxic shock[53-55] and causes tissue damage.[56] In some clinical studies and animal models of sepsis, anti-TNF antibodies have shown to help in the treatment of septic shock.[57] Mice lacking the TNF receptor have an attenuated response to endotoxins.[58,59] During LPS-induced shock, TNFα, in addition to inducing anti-inflammatory cytokines such as IL-10 and IL-4,[60] also triggers the expression of proinflammatory cytokines, IL-1, IL-6, and IL-8 among others.[61] Apart from cytokine induction, TNFα also induces nitric oxide synthase (iNOS) and cyclooxygenase (COX-2) that catalyze the production of nitric oxide (NO) and prostaglandin E2 (PGE2).[62,63] Both NO and PGE2 are vasodilators that may cause the reduction in the migration of neutrophils to the site of infection by inhibiting the endothelium–leukocyte binding.[62-64] LPS in combination with TNFα induces apoptosis of the endothelium layer in several tissues including intestine, lungs, and thymus.[65] Several strategies to ameliorate endotoxin shock have been tested in both preclinical and in clinical trials. Despite the compelling evidence that LPS is a major factor in the pathophysiology of septic shock, recent trial targeting lipid-A portion of LPS with a drug called eritoran was unable to improve outcome in a large phase 3 clinical trial.[66]

Superantigens

Superantigens (SAg) are one of the most potent toxins produced by bacteria, namely, *S. aureus* and *S. pyogenes*. They are non-glycosylated proteins that have a relatively low molecular weight.[67] SAgs produced by *S. aureus* include staphylococcal enterotoxins SE (A–E) and toxic shock syndrome toxin-1 (TSST-1), while the toxins produced by *S. pyogenes* include streptococcus pyrogenic exotoxin A and C (SPEA and SPEC)[68,69] and the streptococcal mitogenic exotoxin Z (SMEZ).[67] These toxins are

capable of producing a massive cellular immune response that could lead to a fatal toxic shock.[70] Unlike conventional antigens that are processed by antigen presenting cells and presented to T cells through the MHC-II molecules, SAgs bind directly to the outer leaflet of MHC-II molecules[71-73] specific domains of the variable portion of β-chain (Vβ) of the T-cell receptor.[70,74-77] This allows for bypassing the processing by antigen presenting cells and stimulates most T cells. In addition to binding to MHC-II and the Vβ-chain, it has been recently shown that SAgs also engage a third receptor, CD28, which is a costimulatory molecule on T cells.[78-81] SAg bind directly at the homodimer interface of CD28 to cause toxicity by inducting a cytokine storm.[81] Unlike conventional antigens that normally activate <0.01% of T cells, SAgs activate >20% of T cells by binding to the MHC-II and T-cell receptor directly.[82-84] This leads to a massive induction of proinflammatory T-helper 1 (Th1) cytokines including tumor necrosis factor (TNF), interferon γ (IFN γ), and interleukin-2 (IL-2).[82,83,85,86] Further details on superantigens can be found in the paper by Reglinski and Sriskandan in this issue of *Virulence*.[87]

P. aeruginosa and Exotoxin A

In ICUs *P. aeruginosa*, a gram-negative bacterium is among the top five organisms causing pulmonary, urinary tract, soft-tissue, and bloodstream infections.[88] *P. aeruginosa* express several virulence factors such as flagella, pili, and LPS that play an important role in their pathogenesis. However, the toxins of *P. aeruginosa* are some of the most potent factors these organisms express and secrete.[89] Apart from the toxins they secrete, *P. aeruginosa* also inject one set of toxins directly into host cells through a macromolecular syringe called Type III secretion system.[90]

On the basis of weight, exotoxin A of this organism is the most toxic compound it produces.[91] Exotoxin A is part of an enzyme family called mono-ADP-ribosyltransferase.[91] The toxin affects the protein synthesis in host cells by catalyzing the ADP ribosylation of eukaryotic elongation factor 2, much like the mechanism of diphtheria toxin.[91] It is released by *P. aeruginosa* as a proenzyme that is toxic to animals and cultured cells but has very low enzymatic activity.[92] This toxin undergoes partial proteolysis by the serine endoprotease called furin, and then enters host cells through receptor mediated endocytosis. Exotoxin A is internalized into clatherin coated vesicles and moves into the endosomes.[93] The LD50 of exotoxin A was shown to be 0.2 μg in a 20 g mouse by the intraperitoneal route of administration. Between 80% and 90% of all clinical isolates of *P. aeruginosa* have demonstrated exotoxin A production in vitro.[94,95] It is presumed to escape into the cytosol through a translocation event. Studies have demonstrated that domain Ia of exotoxin A is the primary region of the toxin involved in cellular binding. In vivo studies with mice injected with purified exotoxin A lacking the Ia domain showed attenuation of toxicity compared with mice injected with native exotoxin A.[91] Administration of IVIG that are enriched in neutralizing antibodies to exotoxin A, however, led to no clinical improvement in patients with established *Pseudomonas* bacteremia.

Bacillus anthracis and Toxins

Bacillus anthracis (*B. anthracis*), the causative agent of the disease anthrax is a gram-positive bacteria that is able to survive in the environment in the spore form.[96] The disease is generally contracted mainly through three routes, namely, cutaneous, gastrointestinal, and the inhalation routes.[97-99] In spite of appropriate therapy, all the three routes of infection can lead to fatal disease as a result of sepsis and shock-like symptoms.[100] The inhalation route generally leads to the highest fatality and is a serious bioterrorism threat today.[101] The toxins of *B. anthracis* play a vital role in the pathogenesis of the disease. The toxins are made up of three secreted proteins working in binary combinations, namely protective antigen (PA), lethal factor (LF), and edema factor (EF).[102,103] The PA combines with EF to form the edema toxin (ET) and with LF to form the lethal toxin (LT).[104]

LF, a 90-kD zinc protease consisting of 4-folding domains,[105] is known to recognize six out of the seven mitogen-activated protein kinases, 1–4, 6, and 7. These are bound by domains II and III and cleaved at the N-terminus by domain IV.[106-108] The cleavage, results in the possible disruption of downstream signaling, mainly the inactivation of ERK1/2 (extracellular-signal-regulated-kinases), p38, and SAPK (stress-activated protein kinases)/JNK (Jun N-terminal kinases) pathways that are important for the activation of immune responses.[109] LT induces apoptosis in different cell types including Human umbilical vein endothelial cells by disrupting the ERK, p38, and JNK/SAPK pathways, with the ERK pathway being of upmost importance.[110] LT affects the translocation of tight junction proteins and alters the cytoskeleton reorganization by reducing levels of F-actin and blocking localization of vascular endothelial cadherin.[111] In human endothelial cells that are TNF-induced, LT amplifies expression of vascular cell adhesion molecule-1 that results in vasculitis and barrier disruption of cells.[112-114] Lymphocytic processes like T-cells activation, proliferation, and cytokine production are shown to be suppressed by both LT and ET.[115-117] The mechanism of T-cell suppression is the direct effect of LT cleaving MAPKKs, whereas ET suppresses T-cell processes by elevating the level of cAMP activity.[118] Both LT and ET prevent chemotaxis of T cells and macrophages by reducing the activation of MAPK to different chemokines.[119] While EF plays a greater role in disrupting the neutrophil migration and cytokine production, LF is directly lethal to macrophages and prevents dendritic cell maturation.[120,121] These deleterious effects of LF and EF on the immune cells impair phagocytosis of inhaled spores and vegetative forms of *B. anthracis*, allowing them to be transported to lymph nodes. A hemorrhagic and septic medistinitis develops accompanied by high-grade bacteremia, septic shock, and death. The toxic nature of both LT and ET results in bacterial dissemination to remote organs resulting in widespread tissue necrosis and death. A number of therapeutic strategies have been developed in an attempt to block the effects of anthrax toxins and improve outcomes.[122]

Conclusion

Treatment of sepsis still remains a serious concern and challenge in hospitals. Bacterial toxins from both gram-positive and gram-negative bacteria allow the pathogen to modulate host defenses through their interaction with cells enabling the bacteria to escape the innate immune system to remote organs. The type of toxin plays a major role in the outcome of disease. Over the last decade our understanding of the mechanisms by which these toxins modulate host defense has tremendously improved. This could enable a more efficient way of targeting the toxins and better clinical outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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