Severe Sepsis and Septic Shock—Recent Concepts

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Definitions

Systemic inflammatory response syndrome (SIRS): SIRS refers to the consequences of a dysregulated host inflammatory response. It is clinically recognized by the presence of two or more of the following:
- Temperature >38.5°C or <35°C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or PaCO2 <32 mmHg
- WBC >12,000 cells/mm³ or <4000 cells/mm³, or >10 percent immature (band) forms

All these criteria need not be present always. SIRS can result from a variety of conditions, such as infection, autoimmune disorders, pancreatitis, MI, vasculitis, thromboembolism, burns, or surgery.

Sepsis: in sepsis, the clinical signs that define SIRS are present and are due to either a culture-proven infection or an infection identified by visual inspection.

When sepsis is associated with dysfunction of organs distant from the site of infection, the patient has severe sepsis. Severe sepsis exists if there is sepsis plus at least one of the following signs of organ hypo perfusion or dysfunction:
- Areas of mottled skin capillary refilling requires three seconds or longer
- Urine output <0.5 mL/kg for at least one hour, or renal replacement therapy
- Lactate >2 mmol/L
- Abrupt change in mental status
- Platelet count <100,000 platelets/mL./DIC.
- Acute lung injury or acute respiratory distress syndrome. Cardiac dysfunction, as defined by echocardiography.

Septic shock: Septic shock exists if there is severe sepsis plus one or both of the following: Systemic mean blood pressure is <60 mmHg (or <80 mmHg if the patient has baseline hypertension for at least 1 h) despite adequate fluid resuscitation. (adequate fluid resuscitation is defined as infusion of 20 to 30 mL/kg of starch, infusion of 40 to 60 mL/kg of saline solution, or a measured pulmonary capillary wedge pressure (PCWP) of 12 to 20 mmHg) or maintaining the systemic mean blood pressure >60 mmHg (or >80 mmHg if the patient has baseline hypertension) requires dopamine >5 mcg/kg per min, nor epinephrine <0.25 mcg/kg per min, or epinephrine <0.25 mcg/kg per min despite adequate fluid resuscitation.

Refractory septic shock: Refractory septic shock exists if maintaining the systemic mean blood pressure >60 mmHg (or >80 mmHg if the patient has baseline hypertension) requires dopamine >15 mcg/kg per min, nor epinephrine >0.25 mcg/kg per min, or epinephrine >0.25 mcg/kg per min despite adequate fluid resuscitation.

Aetiology

Microbial invasion of the blood stream is not essential for the development of severe sepsis. Local inflammation can also elicit distant organ dysfunction. Blood cultures are positive in only in 20%-40% of cases of severe sepsis and 40%-70% of cases of septic shock. The risk of developing severe sepsis was strongly related to the site of primary infection: bacteraemia arising from a pulmonary or abdominal source was eightfold more likely to be associated with severe sepsis than was bacteremic urinary tract infection.
Pathogenesis

Innate immunity achieves our primary host defence by recognizing invading microorganisms through pathogen-associated molecular patterns (PAMPs) and by reacting to tissue damage signals called damage-associated molecular patterns (DAMPs)\(^1\). Pathogen-associated molecular patterns include lipopolysaccharides in gram-negative bacteria and peptidoglycan in gram-positive bacteria. A host protein (LPS-binding protein or LBP) binds lipid A and transfers the LPS to CD14 on the surfaces of monocytes, macrophages, and neutrophils. LPS then is passed to MD-2, which interacts with Toll-like receptor (TLR) 4 to form a molecular complex that transduces the LPS recognition signal to the interior of the cell. Intracellular NOD1 and NOD2 proteins, which recognize discrete fragments of bacterial peptidoglycan. Receptor binding results in activation of intracellular signalling pathways that lead to a variety of responses, including increased transcription of inflammatory cytokines, up-regulation of adhesion-molecule expression, stimulation of humoral and cell-mediated immune responses, and activation of vascular endothelial cells. Another pathogenesis is by super antigen-producing Staphylococcus aureus or Streptococcus pyogenes.

Clinical Manifestations

Hyperventilation is often an early sign of the septic response some patients with sepsis are normo- or hypothermic; the absence of fever is most common in neonates, in elderly patients, and in persons with uraemia or alcoholism. Sepsis-induced hypotension usually results from a generalized maldistribution of blood flow and blood volume, from hypovolemia that is due, to diffuse capillary leakage of intravascular fluid, insensible fluid losses, vomiting or diarrhea, and polyuria. During early septic shock, systemic vascular resistance is usually elevated and cardiac output may be low. After fluid repletion, cardiac output typically increases and systemic vascular resistance falls. Normal or increased cardiac output and decreased systemic vascular resistance distinguish septic shock from cardiogenic, extra cardiac obstructive, and hypovolaemic shock. Other processes that can produce this combination include anaphylaxis, beriberi, cirrhosis, and overdoses of nitroprusside or narcotics. The clinical manifestations of severe sepsis can involve almost all organs.

Investigations

Abnormalities that occur early in septic shock include leucocytosis with left shift, (leucopenia may develop) thrombocytopenia, and proteinuria. The neutrophils may contain toxic granulations, Dohle bodies, or cytoplasmic vacuoles. Active haemolysis suggests clostridial bacteraemia, malaria, drug reaction or DIC. As the sepsis progresses thrombocytopenia worsens, with prolongation of thrombin time, decreased fibrinogen, and the presence of D-dimers suggesting DIC. Azotemia and hyperbilirubinemia and rise in transaminases occur. Hyperglycaemia is common in diabetics with sepsis. Sepsis may precipitate DKA. Serum albumin level declines as sepsis continues. X-ray chest may be normal or show evidence of underlying pneumonia, volume overload, or ARDS. Other investigations include CT chest, ECG, and Echo.

Blood Culture Definitive etiologic diagnosis requires isolation of the microorganism from blood or a local site of infection. At least two blood samples (10 mL each) should be obtained (from different venipuncture sites) for culture. In 20% to 30% of cases, a causative organism is not identified, which may be due to prior administration of antibiotics, the presence of slow growing or fastidious organisms or absence of microbial invasion of the blood stream, fact that an inflammatory state is not always due to infection Gram staining and culture of fluid from the primary site of infection. With severe sepsis microorganisms are sometimes visible on buffy coat smears of peripheral blood.

Many biomarkers have been evaluated for use in sepsis primarily as prognostic markers in sepsis\(^3\). Relatively few have been used for diagnosis. None has sufficient specificity or sensitivity to be routinely employed in clinical practice. Procalcitonin and CRP have been most widely used, but even these have limited ability to distinguish sepsis from other inflammatory conditions or to predict outcome. The most useful biomarker for routine clinical use
seems to be PCT due to its high specificity for bacterial and fungal infections and its adequately sized diagnostic window due to a half-life of approximately 20-24 h. The plasma concentration of soluble TREM-1 (triggering receptor expressed on myeloid cells), a member of the immunoglobulin super family that is specifically up regulated in the presence of bacterial products, is increased in patients with sepsis.

**Management of septic shock**

The Surviving Sepsis Campaign represents an international collaboration of healthcare experts; the campaign is committed to the reduction of the mortality from severe sepsis worldwide. In March 2004, recommendations drawn from research, clinical trials and expert opinion were collated and published as the ‘Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock’ 4. These were subsequently revised in 2008 BUNDLING OF THERAPIES From the Surviving Sepsis Guidelines, the Institute for Healthcare Improvement recommended the development of sepsis “bundles” for initial resuscitation (six hours) and management (24 hours) as performance improvement tools. These bundles when implemented as a whole provide better outcomes than when performed individually. The criteria to initiate the bundle include all three of these items 6.

1. Two or more of the following
   a. Temperature >38.38°C or <36.08°C
   b. Heart rate >90 beats/min
   c. Respiratory rate >20 breaths/min
   d. White blood cell count >12,000 or <4,000/ mm3, or >10% bandemia
2. A suspected infection determined by the physician.
3. Systolic blood pressure <90 mm Hg after 20 mL/kg fluid bolus or lactate level >4 mmol/L.

**Elements of the Resuscitation Bundle**

1. Serum lactate Lactate, or lactic acid, is the product of anaerobic metabolism of glucose by the tissues. This process is less efficient than aerobic metabolism in terms of ATP production per unit of substrate. There is good evidence that lactate carries prognostic value. Patients with a lactate measurement in excess of 4 mmol/l had a mortality of around 40%, compared with under 15% for patients with a lactate of <2 mmol/l 7. Lactate is particularly useful measured serially, 0, 6, 12 hours then daily until <2mmol/L, to guide response to resuscitation and fluid therapy.

2. Blood cultures obtained prior to antibiotic administration

   Two or more blood cultures are recommended, one drawn percutaneously and one through each vascular access device if it has been in for longer than 48 hours. The rationale behind this is that, if the culture from the access device is positive earlier than that for the percutaneous sample, the device may well be the source of infection 8. Similarly, if the same organism is isolated from more than one culture, the chance that this is the organism responsible for the sepsis is elevated. Consideration should be given to sampling of other bio fluids- cerebrospinal fluid, sputum, urine, synovial fluid, pleural fluid etc- where clinical signs point to a source of infection.

3. Antibiotic administration

   The SSC Bundle stipulates that antibiotics should be given within 1 hour. A large retrospective study showed that, in patients with septic shock, to delay administration of antibiotic was associated with an increase in mortality of 7.6% for each hour’s delay 9. Antibiotics should be administered according to local pathogen profiles, taking into account knowledge of local resistance patterns and organisms. One or more broad spectrum antibiotic should be administered in the first instance, with review and probable change to a narrower spectrum once the causative organism has been isolated. The duration of antibiotic therapy is somewhat controversial; however, current recommendations
are to continue therapy for 7 to 10 days. Longer courses of therapy may be appropriate in patients who have a slow clinical response, undrainerable focus of infection, or immunologic deficiencies, such as neutropenia. In most cases of severe sepsis or septic shock, antimicrobial cultures are negative and thus the decision to continue, taper, or stop antibiotic therapy must be made on the basis of clinical information.

4. Fluid Therapies: What fluid to give

The two most commonly used crystalloid solutions are 0.9% sodium chloride solution and Ringer’s lactate. Under ideal conditions, about 25% of the infused amount remains in the intravascular space while the rest is distributed to the extra vascular space. Clinically, 100 to 200 mL of intravascular volume expansion can be expected after the infusion of 1 L of isotonic crystalloids. Accumulating data support the view that the use of large volumes of normal saline, but not Ringer’s lactate solution, promotes the development of hyperchloremic metabolic acidosis.

Colloids are higher-molecular-weight solutions that increase plasma oncotic pressure. There are many different colloidal solutions available including: a) plasma protein fraction; b) albumin; c) gelatins; d) dextrans; and e) hydroxyethyl starch. Albumin is a naturally occurring plasma protein The 5% solution contains 12.5 g of albumin diluted in 250 mL of normal saline and has a colloid osmotic pressure of 18 to 20 mm Hg. After 1 L of 5% albumin has been infused, plasma volume expansion ranges from 500 to 1000 ml. The Saline versus Albumin Fluid Evaluation (SAFE) study compared fluid resuscitation with albumin or saline on mortality and found similar 28-day mortalities and secondary outcomes in each arm.

Patients with septic shock can be successfully resuscitated with either crystalloid or colloids. Crystalloid solutions will require 2 to 4 times more volume than colloids and may require slightly longer periods to achieve desired hemodynamic end points. Due to their higher molecular weight, colloids stay in the intravascular space significantly longer than crystalloids with an intravascular half-life for albumin of 16 h versus 30–60 min for normal saline and Ringer lactate. Colloid solutions are much more expensive than crystalloid solutions.

How much fluid to give: According to one study repeated boluses of crystalloid (isotonic sodium chloride solution or lactated Ringer’s injection), 500 to 1,000 mL intravenously over 5 to 10 minutes are given until mean arterial pressure and tissue perfusion are adequate (about 4 to 8 L total over 24 hours for the typical patient) Boluses of 250 mL might be appropriate for patients who are elderly or who have heart disease or suspected pulmonary edema. Fluid is administered as bolus, rather than a continuous infusion, because this allows more rapid restoration of circulating volume and minimizes the duration of inadequate organ perfusion. The goal is to increase mean arterial pressure to 65 to 75 mm Hg and improve organ perfusion within 1 hour of the onset of hypotension. In hypoperfused patients, a minimum volume of 20 ml/kg is recommended as an initial bolus. Patients with shock will frequently require volumes of up to 60 ml/kg in resuscitation. Patients often continue to require large volumes of fluid in the 24 to 72 hours after the initial phase. The major complications of fluid resuscitation are pulmonary and systemic edema. The FACTT trial and subsequent studies differentiate adequate initial fluid resuscitation from conservative late fluid management. Whereas appropriate fluid resuscitation based on the resuscitation or ebb phase leads to improved outcomes, liberal and late fluid resuscitation is a negative contributor to outcome.

4. Early Goal-Directed Therapy: The remainder of the Resuscitation Bundle falls under the umbrella of Early Goal-Directed Therapy (EGDT).
Completion of early goal-directed therapy (EGDT) in the emergency department (ED), which was shown to be associated with a 16% absolute decrease in mortality. EGDT as discussed by Rivers et al., in which 263 patients presenting to an Emergency Department with severe sepsis or septic shock were randomly assigned to receive either EGDT or standard therapy during the first 6 hours of their care. In hospital mortality for the EGDT group was 30.5%, as compared with 46.5% for the control group. Previous researchers have explored this approach with treatment being started on the intensive care unit after the development of organ failure. The aim of Rivers’ approach was uniquely different because he initiated resuscitation and treatment early, before the onset of organ failure on the logic that early intervention may help prevent a catastrophic and irreversible decline.

Oxygen supply and delivery Oxygen supply (also known as oxygen delivery, DO2) is the amount of oxygen delivered to the whole body from the lungs. Oxygen delivery can be thought of as: DO2 = CO x Hb x SaO2. The resuscitation strategy in the Rivers study enhances oxygen delivery (DO2) to the tissues by optimising cardiac output (CO). This is achieved by improving cardiac preload, after load and contractility.

The first goal: CVP > 8mmHg

Patients with sepsis that continue to be hypotensive (or have a high lactate in excess of 4 mmol/l) despite an initial bolus of 20 ml/kg crystalloid have septic shock. They should have a central venous catheter inserted. Their central venous pressure (CVP) should be measured and resuscitation should be commenced with fluid boluses of 500-1500ml every 30 minutes to achieve and maintain a CVP greater than 8 mmHg. Fluid boluses should be repeated as required. This can be thought of as the first goal or first resuscitation end point.

Second goal: MAP at or above 65 mmHg.

If the CVP is greater than 8 mmHg (the patient is adequately ‘filled’); but the MAP (mean arterial blood pressure) is less than 65 mmHg or systolic less than 90 mmHg, a vasoressor should be started to maintain a MAP of at least 65 mmHg in these circumstances. The aim of this intervention, in the presence of adequate intravascular resuscitation, is to ensure adequate perfusion to the organs. This can be thought of as the second goal or second resuscitation end point, aiming to keep the MAP at above 65 mmHg.

Vasoactive drugs

Vasoactive drug therapy is used to manipulate the relative distribution of blood flow and restore tissue perfusion. These agents are classically subdivided into two separate class types: vasoressors and Inotropes. Vasoressors modulate vasoconstriction and thereby increase blood pressure, whereas Inotropes increase cardiac performance and thereby improve CO.

The proper selection of one or more agents greatly depends on a basic understanding of the physiologic mechanisms driving a particular shock state. The main categories of adrenergic receptors relevant to vasoactive therapy are the a1-, a2-, b1-, and b2-adrenergic receptors, and the dopamine receptors. Alpha-adrenergic receptors stimulation exerts a primary effect on smooth muscle with resultant constriction. Stimulation of postsynaptic a2 receptors causes vasodilatation by endothelial nitric oxide production. Beta-adrenergic receptor agonism produces increases in heart rate and contractility, leading to improved cardiac performance and output. Beta2 receptor stimulation causes relaxation of smooth muscle. Dopaminergic receptors -through dopamine receptors, dopamine increases CO by improving myocardial contractility and at certain doses increasing heart rate. In the kidney, dopamine acts by D1 and D2 receptors to stimulate diuresis and naturesis.

Vasopressin receptors Vasopressin is a peptide hormone whose primary role is to regulate the body’s
retention of water. It also raises blood pressure by inducing moderate vasoconstriction through its stimulation of V1 receptors.

Common complications associated with vasopressors and inotropic agents include dysrhythmias, myocardial ischemia and hypoperfusion. With all of these factors in mind, the choice of agent should be selective and titrated to the minimal effective dose to achieve target end points.

**Epinephrine** At doses of 2 to 10 µg/min, epinephrine’s beta 1 receptor stimulation predominates. At doses above 10 µg/min, alpha receptor stimulation results in generalized vasoconstriction and an increased MAP mediated through an increased SVR. Continuous IV infusion. Usual rate: 1 to 4 ug/min.

**Phenylephrine** has pure alpha activity and results in veno and arteriolar vasoconstriction. It causes an increase in systolic, diastolic, and MAP and can lead to reflex bradycardia. It may be clinically useful as a second-tier agent for the support of hyperdynamic vasodilatory shock in sepsis. IV infusion: initial rate: 100 to 180mcg/min. Usual maintenance rate: 40-60 mcg/min. Calculation of drip rate (40 mg/250ml of diluent) (ml/hr) = (mg/min) x 375.

**Nor epinephrine** acts on both a- and b-adrenergic receptors producing potent vasoconstriction and a less pronounced increase in CO. In low doses (2 µg/min), nor epinephrine stimulates b-adrenergic receptors. In usual clinical doses (>3 µg/min), nor epinephrine stimulates alpha receptors promoting vasoconstriction. Nor epinephrine dosage is stated in terms of nor epinephrine base and intravenous formulation is nor epinephrine bitartrate. Nor epinephrine bitartrate 2 mg = Nor epinephrine base 1 mg. usual range: 8-30 mcg/minute. Range used in clinical trials: 0.01-3 mcg/kg/minute. Calculation of drip rate 8 mg/250 ml (ml/hr) = mcg/min x 1.875. Supplied as Injection: 1 mg/ml - 4 ml

Consensus guidelines and expert recommendations suggest that either dopamine or nor epinephrine may be used as a first-choice vasopressor in patients with shock. There was no significant between-group difference in the rate of death at 28 days. However, there were more arrhythmic events among the neither patients treated with dopamine than among those treated with nor epinephrine. A subgroup analysis showed that dopamine, as compared with nor epinephrine, was associated with an increased rate of death at 28 days among the patients with cardiogenic shock but not among the patients with septic shock or hypovolaemic shock. The exact cause of the increased mortality cannot be determined, but the early difference in the rate of death suggests that the higher heart rate with dopamine may have contributed to the occurrence of ischemic events. Whatever the mechanism may be, these data strongly challenge the current American College of Cardiology–American Heart Association guidelines, which recommend dopamine as the first-choice agent to increase arterial pressure among patients who have hypotension as a result of an acute myocardial infarction.

**Dopamine** stimulates á- and â-adrenergic receptors and may be converted to nor epinephrine. At low infusion rates (0.5–2µg/kg/min) dopamine stimulates D1 receptors resulting in selective vasodilatation of the renal, splanchnic, cerebral, and coronary vasculature. Even at low doses, some beta stimulation occurs, which may increase MAP and CO. At rates from 2 to 5 µg/kg/min, dopamine stimulates nor epinephrine release and has mixed receptor activity. Infusions of 5 to 10 µg/kg/min stimulate á 1 receptors increasing stroke volume, heart rate, and CO. At doses greater than 10 µg / kg/min, dopamine activates both á 1 and â adrenergic receptors. With escalating doses (>10 µg/kg/min), alpha effects predominate causing vasoconstriction in most vascular beds. Severely ill patient: initially 5 mcg/kg/min, increase by 5 to 10 mcg/kg/min (q10 to 30 min) up to max of 50 mcg/kg/min.

Calculation of drip rate (ml/hr) 400mg/250 ml: wt(kg) x mcg/min x 0.0375. The renal protective
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mechanisms of dopamine have been questioned and “reno-protection” has largely been rejected 17.

Either nor epinephrine or dopamine is recommended as a first-line agent for the treatment of septic shock by the Surviving Sepsis Campaign 5.

Dobutamine is a synthetic catecholamine that is viewed primarily as an inotropic agent. It is predominantly a 1 agonist with only weak a- and a 2 effects. The selective a 1 activity of Dobutamine primarily increases the inotropic effect because of increased stroke volume and heart rate with a variable effect on blood pressure. Dobutamine’s typical therapeutic doses range from 2.5 to 10 µg/kg/min. Dobutamine might be used to augment inotropic activity and improve perfusion in septic shock patients with global myocardial dysfunction. Dosage Adult (usual): 2.5 to 20 mcg/kg/minute. Maximum: 40 mcg/kg/min. Titrate to desired response. Usual doses to increase cardiac output are 2.5 to 15 mcg/kg/minute IV. Drip rate (500mg/250 ml) ml/hr = wt (kg) x (mcg/min) x 0.03. Tolerance may be seen after 48-72 hrs, presumably due to down-regulation of beta receptors. This may necessitate an increase in dose. Onset of action within 2 min and maximal effect associated with a given infusion rate occurs approximately 10 min after starting the infusion.

Vasopressin is an endogenous hormone with vasoconstrictive effects whose relative deficiency has been tried to refractory hypotension in vasodilatory shock. There is support for using a low-dose continuous infusion (0.01–0.03 U/min) in conjunction with other agents to treat refractory vasodilatory shock 18. Surviving Sepsis Campaign recommends it not be used as a first-line agent. When a vasopressor infusion is started, doses should be carefully titrated to restore MAP, without impairing stroke volume. Should the stroke volume become impaired, the dose of vasopressor should be lowered, or the use of Dobutamine considered. One Cochrane review 19 evaluated the data supporting the selection of one Vasoactive drug over another. They were unable “to determine whether a particular vasopressor is superior to other agents in the treatment of shock states”.

The third goal: ScvO2 > 70%

Central venous oxygen saturation (ScvO2). If the ScvO2 is low then interventions which may help include increasing the oxygen content of the blood and increasing cardiac output. Oxygen content may be improved through the administration of high-flow oxygen or consideration to the provision of ventilation. Additionally, if the patient is anaemic, transfusion may improve oxygen carrying capacity. The first recommendation in the event of a low ScvO2 is thus to transfuse the patient to achieve a hematocrit of >30% (approximating to a haemoglobin concentration of >10g/dl). In the TRICC trial 20 euvolemic critically ill patients were randomized to restricted target haemoglobin of greater than 7 g/dL or greater than 10 g/dL and were transfused to maintain these targets. Overall mortality was similar between the two groups; however, younger patients who had lower APACHE II scores had overall lower mortality rates with the restricted target when compared with the liberal haemoglobin target. If the patient is not anaemic, or if a repeat ScvO2 after transfusion remains low, the next strategy to redress the imbalance between oxygen delivery and demand is to increase the cardiac output to improve oxygen delivery. To enhance cardiac output, an inotropic infusion of Dobutamine is started.

The Surviving Sepsis Campaign Management Bundle: The Management Bundle consists of a set of 4 tasks to be completed within 24 hours of the onset of severe sepsis

1. Low-dose steroids

Earlier studies showed that steroids administered at physiological dosage to patients with shock resistant to fluid resuscitation, and requiring the administration of vasopressors, are of benefit 21,22. The European CORTICUS study 23 did not support
these conclusions. According to this study hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. However, there were more episodes of super infection, including new sepsis and septic shock. The new guidelines stipulate that steroids be considered in patients with shock unresponsive to fluids and vasopressors according to local policy. ACTH stimulation testing does not appear to predict steroid-responsiveness and is not recommended.

2. Activated Protein C

Activated protein C is a potent anticoagulant and profibrinolytic enzyme capable of inactivating clotting cofactors Va and VIIIa and plasminogen-activator inhibitor. Reduced levels of protein C in patients with sepsis have been correlated with an increase in the risk of death. These observations led to the hypothesis that the administration of activated protein C might be beneficial in patients with sepsis. PROWESS study was a large randomised controlled trial that demonstrated a significant reduction in mortality (6.1% absolute reduction) in patients with an APACHE II score of >25. A second RCT ADDRESS trial evaluated the role of DrotAA therapy in patients with severe sepsis, associated with either single-organ failure or an APACHE II score below 25. The study was stopped, after enrolling 2640 patients, because there was no indication of a positive effect. Results from the forthcoming PROWESS-Shock study will hopefully provide more clarification. The 2008 guidelines downgraded the recommendation for DrotAA therapy. However, severe sepsis and response to Protein C are time-sensitive. It would be illogical to wait and watch a patient deteriorate to an arbitrary defined physiology score before commencing potentially life-saving treatment. The dose of DrotAA, as in the PROWESS protocol, should be 24 ìg per kilogram of body weight per hour, administered as a continuous infusion over a period of 96 hours, within 24 hours after the onset of severe sepsis. The main side effect is bleeding. The overall cost of treatment with DrotAA is approximately 3-4 lakhs.

3. Tight glycaemia control

The initial recommendation to control blood glucose arose from work by van den Berghe et al who recommended that intensive insulin therapy to maintain blood glucose at or below 110 mg per decilitre reduces morbidity and mortality among critically ill patients in the surgical intensive care unit. On repeating the trial in a medical patient population, the same investigators found no outcome benefit in terms of mortality. NICE-SUGAR trial and the multi-centre German VISEP study showed no benefit in mortality. The COIITSS Study concluded that compared with conventional insulin therapy, intensive insulin therapy did not improve in-hospital mortality among patients who were treated with hydrocortisone for septic shock. The addition of oral fludrocortisone did not result in a statistically significant improvement in in-hospital mortality.

4. Protective ventilation

It has been known for some time that ventilator-associated lung injury (VALI), is exacerbated by barotrauma (excessive airway pressures) and cyclical volutrauma (cycling from large to small lung volumes). Tidal volumes during mechanical ventilation of 6ml per kg body weight were associated with better outcomes than tidal volumes of 12ml/kg. Other studies have shown benefits in limiting plateau airway pressures. The recommendation within the Management Bundle is to limit plateau airway pressures to <30cmH20.

Other issues in management

The Eritoran Sepsis Study evaluated safety and tolerability of two dose regimens of eritoran tetrasodium, a synthetic Toll-like receptor 4 antagonist, and explored whether it decreases 28-
day mortality rate in subjects with severe sepsis. Intravenous eritoran tetrasodium (total dose of either 45 mg or 105 mg) or placebo administered every 12 hrs for 6 days. Eritoran tetrasodium treatment appears well tolerated. The observed trend toward a lower mortality rate at the 105-mg dose, in subjects with severe sepsis and high predicted risk of mortality, should be further investigated.

Platelet transfusions are given when platelets when counts < 5000/mL. Platelet counts > 50,000/mL are frequently required for invasive procedures or surgery. Similarly, fresh frozen plasma should be administered in the presence of active bleeding or before surgical or invasive procedures if there is elevated PT, aPTT or INR. Early nutrition has been demonstrated to improve wound healing, host immune function, nitrogen balance, and preserve intestinal mucosal integrity. DVT prophylaxis with either low-dose unfractionated heparin or low molecular weight heparin. Stress ulcer prophylaxis using a proton pump inhibitor or H2 antagonists prevent upper gastrointestinal bleeding.

Prognosis

Approximately 20–35% of patients with severe sepsis and 40–60% of patients with septic shock die within 30 days. Others die within the ensuing 6 months. Late deaths often result from poorly controlled infection, immunosuppression, complications of intensive care, failure of multiple organs, or the patient’s underlying disease. Clinical characteristics that relate to the severity of sepsis include an abnormal host response to infection, the site and type of infection, the timing and type of antimicrobial therapy, and the development of shock. Failure to develop a febrile response and the presence of leucopenia are characteristic of severe disease, and probably represent anomalies in the host’s inflammatory response.

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