

INTRODUCTION

Sepsis is a clinical syndrome characterized by systemic inflammation due to infection. There is a continuum of severity ranging from sepsis to septic shock. Over 1,665,000 cases of sepsis occur in the United States each year, with a mortality rate up to 50 percent. Even with optimal treatment, mortality due to septic shock is approximately 40 percent and can exceed 50 percent in the sickest patients.

Currently sepsis is diagnosed by clinical identification of an infection in a patient who meets the clinical criteria for systemic inflammatory response syndrome (SIRS). According to the international consensus definition published in 1991 (and reviewed in 2001) SIRS is defined by the presence of 2 or more criteria from a collection of clinical signs and laboratory investigations as follows:

- Temperature $>38.3^{\circ}\text{C}$ (101°F) or $<36.0^{\circ}\text{C}$ (96.8°F)
- Tachycardia >90 bpm
- Tachypnoea >20 breaths/minute or $\text{PaCO}_2 <4.3$ kPa (32 mmHg)
- Hyperglycaemia (blood glucose >7.7 mmol/L [>140 mg/dL]) in the absence of diabetes mellitus
- Acutely altered mental status
- Leukocytosis (WBC count $>12 \times 10^9/\text{L}$ [12,000/microlitre])
- Leukopenia (WBC count $<4 \times 10^9/\text{L}$ [4000/microlitre])
- Normal WBC count with $>10\%$ immature forms.

The international consensus definitions have been updated in 2016 (Sepsis-3), and the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) criteria and 'quick' (q)SOFA criteria have been proposed to replace the SIRS criteria.

The SOFA score is calculated based on the assessment of the following systems in the ICU setting:

- Respiratory ($\text{PaO}_2/\text{FiO}_2$ ratio)
- Neurological (as assessed by the Glasgow coma scale)
- Cardiovascular (mean arterial pressure [MAP] or administration of vasopressors)
- Coagulation (platelet count)
- Renal (creatinine level and urine output)

- Hepatic (bilirubin level).

At present, the SIRS criteria remain the current standard for identifying sepsis.

In the 1991/2001 international consensus definitions, severe sepsis is defined as sepsis that leads to dysfunction of 1 or more organ systems, and includes the subset septic shock. Organ dysfunction variables are:

- Arterial hypoxaemia ($\text{PaO}_2/\text{FiO}_2$ ratio <300) with new pulmonary infiltrates
- A new or increased oxygen requirement to maintain $\text{SpO}_2 >90\%$
- Acute oliguria (urine output <0.5 mL/kg/hour for at least 2 hours)
- Serum creatinine >176.8 micromol/L (2.0 mg/dL)
- Coagulation abnormalities (INR >1.5 or aPTT >60 seconds)
- Thrombocytopenia (platelets $<100 \times 10^9/\text{L}$ [100,000/microlitre])
- Hyperbilirubinaemia (total bilirubin >68.42 micromol/L [4 mg/dL])
- Arterial hypotension (systolic BP <90 mmHg, mean BP <65 mmHg, or reduction in systolic BP >40 mmHg from baseline)
- Serum lactate >2 mmol/L (>18 mg/dL).

In the 1991/2001 international consensus definitions, septic shock is defined as:

- Arterial hypotension (systolic BP <90 mmHg, mean BP <65 mmHg, or reduction in systolic BP >40 mmHg from baseline) persisting for at least 1 hour, despite adequate fluid resuscitation, or
- Serum lactate >4 mmol/L (>36 mg/dL) after adequate fluid resuscitation.

The use of vasopressor agents to correct hypotension does not exclude shock.

According to the 2016 international consensus definitions, septic shock is defined as sepsis with the following:

- Persistent hypotension requiring vasopressors to maintain mean MAP ≥ 65 mmHg, and
- Serum lactate >2 mmol/L (>18 mg/dL) despite adequate volume resuscitation.

The 2016 international consensus definitions state that

this group is associated with hospital mortality rates greater than 40%.

INITIAL EVALUATION

As for all acutely ill patients, initial evaluation should follow the ABCDE format, to include assessment of the airway, respiratory, and circulatory sufficiency, and conscious level (Glasgow Coma Scale or AVPU [Alert, responds to Voice, responds to Pain, Unresponsive]). Attention should be paid to seeking other signs of organ dysfunction (jaundice, purpura fulminans, cyanosis), and signs of circulatory insufficiency including oliguria, mottling of the skin, and prolonged capillary refill times. Oxygen saturation, respiratory rate, heart rate, BP, temperature, and accurate hourly fluid balance (including urine output) should be monitored. It is important to seek clinical evidence for the source of infection. This will aid diagnosis and provide vital information as to the patient's risk factors for sepsis. Risk factors strongly associated with sepsis include: underlying malignancy, age >65 years, pregnancy, haemodialysis, history of alcoholism and diabetes mellitus.

INVESTIGATIONS

Initial investigations cover 4 purposes:

1. Investigations to identify causative organisms: Identification of pathogens permits early broadening of spectrum in patients whose initial antimicrobial cover is inadequate, and narrowing of spectrum in those with sensitive organisms. Blood cultures should be taken immediately and preferably before antibiotics are started, provided their sampling will not delay administration of antibiotics. Ideally, at least one set should be taken percutaneously, and one set from any vascular access device that has been in situ for more than 24 hours. Other cultures (e.g. sputum, stool, and urine) should be taken as clinically indicated. Imaging studies performed promptly to confirm a potential source of infection. If no localizing signs are present, examination and culture of all potential sites of infection including wounds, catheters, prosthetic implants, epidural sites, and pleural or peritoneal fluid, as indicated by the clinical presentation and history, is required. If meningitis is suspected, a lumbar puncture (LP) for CSF microscopy and culture should be performed. If an enclosed collection such as an abscess or empyema is suspected, it is recommended that this be drained and cultured early in the course of the illness (within 6 hours following identification). Intubated patients in whom there is a suspicion of pneumonia should have tracheal aspirates, broncho-alveolar lavage, or protected brush specimens taken.
2. Evaluation for organ dysfunction: This demands baseline assessment of liver function tests, an CBC, coagulation profile, serum creatinine, and blood urea. Serum electrolytes and glucose are frequently deranged, and should be measured at baseline

and regularly until the patient improves. Elevated serum lactate highlights tissue hypoperfusion, and is most reliably assessed using an arterial blood gas (ABG) sample. Markers of inflammation including CRP and procalcitonin, are of use in determining clinical progress and response to therapy. The combination of procalcitonin, TREM-1 and CD64 expression appears to be superior to the use of any of these markers alone.

3. Investigations to identify the source of the infection: The source of infection may be immediately evident; for example, with classical signs and symptoms of pneumonia (purulent sputum, dyspnoea, tachypnoea, cyanosis) or peritonism (abdominal pain, guarding, distension, tenderness, absent bowel sounds). However, in many patients the origin must be actively sought. Diagnostic studies may identify a source of infection that requires removal of a foreign body or drainage to maximise the likelihood of a satisfactory response to therapy. Chest x-rays and ultrasound scans can be performed at the bedside. In patients at risk of, or with symptoms compatible with, bacterial endocarditis, a transthoracic or transoesophageal echocardiogram is useful.
4. To prognosticate and in selection of an appropriate level of care: Certain investigations carry prognostic value and can help determine the need for critical care. Lactate measurement is a useful assessment of perfusion once a diagnosis of sepsis has been established. High lactate carries adverse prognostic value if elevated to >2 mmol/L (>18 mg/dL), and still worse outcomes are associated with levels >4 mmol/L (>36 mg/dL). Studies with trauma patients have evaluated lactate levels against Acute Physiology and Chronic Health Evaluation (APACHE) scores and lactate clearance rates and found lactate levels to be inferior. However, an APACHE score takes 24 hours to calculate. An alternative measure is serum procalcitonin levels. Some experts recommend the use of shock index (heart rate divided by systolic BP) as a predictor of requirement for critical care, with one group finding an index of >0.9 to be predictive. More recently, non-invasive impedance echocardiography has been shown, if a cardiac index of <2 is identified, to predict poor outcome.

MANAGEMENT

Initial Resuscitation

Protocolized, quantitative resuscitation of patients with sepsis induced tissue hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L) (grade 1C). Goals during the first 6 hrs of resuscitation (Early Goal Directed Therapy):

- a. Central venous pressure (CVP) 8–12 mm Hg,
- b. Mean arterial pressure (MAP) ≥ 65 mm Hg,

- c. Urine output ≥ 0.5 mL/kg/hr,
- d. Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively.

In patients with elevated lactate levels, targeting resuscitation to normalize lactate (grade 2C).

Antimicrobial Therapy

Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.

- a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B)
- b. Antimicrobial regimen should be reassessed daily for potential de-escalation (grade 1B).
Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics (grade 2C).
- c. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B).
- d. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B)

Duration of therapy is typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus*; some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C).

Source Control

A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C). If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).

Infection Prevention

Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia (grade 2B).

HEMODYNAMIC SUPPORT AND ADJUNCTIVE THERAPY

Fluid Therapy of Severe Sepsis

Crystalloids should be used as the initial fluid of choice in

the resuscitation of severe sepsis and septic shock (grade 1B)..Albumin should be added to fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C). Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).

Vasopressors

Vasopressor therapy is initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C). Norepinephrine is used as the first choice vasopressor (grade 1B). Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B). Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG). Dopamine is used as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C). 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 or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C). Low dose dopamine should not be used for renal protection (grade 1A). All patients requiring vasopressors have an arterial catheter placed as a trial of dobutamine infusion up to 20 micrograms/kg/min be administered 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 (grade 1C).

Corticosteroids

Intravenous hydrocortisone should not be used to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. In case this is not achievable, intravenous hydrocortisone should be used at a dose of 200 mg per day (grade 2C). In treated patients hydrocortisone should be tapered when vasopressors are no longer required (grade 2D). Corticosteroids should not be administered for the treatment of sepsis in the absence of shock (grade 1D).

OTHER SUPPORTIVE THERAPY OF SEVERE SEPSIS

Blood Product Administration

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 be done only when hemoglobin concentration decreases to <7.0 g/dl to target a hemoglobin concentration of 7.0–9.0 g/dL in adults (grade 1B). Erythropoietin should not be used as a specific treatment of anemia associated with severe sepsis (grade 1B). Fresh frozen plasma should not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D). In patients with severe sepsis, administer platelets prophylactically when counts are < 20,000/mm³ (20 × 10⁹/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥50,000/mm³ [50 × 10⁹/L]) are advised for active bleeding, surgery, or invasive procedures (grade 2D).

Mechanical Ventilation of Sepsis-Induced ARDS

Tidal volume of 6 mL/kg predicted body weight should be kept in patients with sepsis-induced ARDS (grade 1A) vs. 12 mL/kg. Positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end expiration (atelectotrauma) (grade 1B). Prone positioning should be used in sepsis-induced ARDS patients with a PaO₂/FiO₂ ratio ≤ 100 mm Hg in facilities that have experience with such practices (grade 2B). A weaning protocol should be in place and mechanically ventilated patients with severe sepsis should undergo spontaneous breathing trials regularly. If the spontaneous breathing trial is successful, consideration should be given for extubation (grade 1A). A conservative rather than liberal fluid strategy should be used for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (grade 1C). In the absence of specific indications such as bronchospasm, beta 2-agonists should not be used for treatment of sepsis-induced ARDS (grade 1B).

Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

Continuous or intermittent sedation should be minimized in mechanically ventilated sepsis patients, targeting specific titration endpoints (grade 1B). Neuromuscular blocking agents (NMBAs) should be avoided if possible in the septic patient without ARDS due to the risk of prolonged neuromuscular blockade following discontinuation (grade 1C).

Glucose Control

Insulin dosing should be commenced when 2 consecutive blood glucose levels are >180 mg/dL. This protocolized approach should target a blood glucose of 140–180 mg/dL. Blood glucose values should be monitored every 1–2 hrs until glucose values and insulin infusion rates are stable and then every 4 hrs thereafter (grade 1C).

Renal Replacement Therapy

Continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure (grade 2B).

Bicarbonate Therapy

Sodium bicarbonate therapy should not be used for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥7.15 (grade 2B).

Deep Vein Thrombosis Prophylaxis

Patients with severe sepsis should receive daily pharmacoprophylaxis against venous thromboembolism (VTE) (grade 1B). Septic patients who have a contraindication for heparin use should receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices (grade 2C), unless contraindicated. When the risk decreases, start with pharmacoprophylaxis (grade 2C).

Stress Ulcer Prophylaxis

Stress ulcer prophylaxis using H₂ blocker or proton pump inhibitor be given to patients with severe sepsis/septic shock who have bleeding risk factors (grade 1B).

Nutrition

Oral or enteral (if necessary) feedings, should be administered rather than either complete fasting or provision of only intravenous glucose within the first 48 hours after a diagnosis of severe sepsis/septic shock (grade 2C).

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