

## Management of Sepsis and Septic Shock in Adults

### About the Guideline

- The sepsis guidelines reflect best practices and recommendations for the treatment of sepsis and septic shock in adults.
- The updated guidelines are especially important now as seriously ill patients with COVID-19 are vulnerable to sepsis.
- In this update, there is an increased emphasis on improving the care of patients after they are discharged from the intensive care unit (ICU).
- This update also represents greater geographic and gender diversity than previous versions.

### Key Clinical Considerations

Become familiar with the recommendations and best-practice statements provided in this guideline, especially if you work in an acute care setting.

### Screening and Early Treatment

#### Screening

- A performance improvement program, including screening for acutely ill, high-risk patients, and standard treatments, should be used.
- The quick Sequential Organ Failure Score (qSOFA), systemic inflammatory response syndrome (SIRS) criteria, National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS) should not be used as single screening tools.
- Blood lactate should be measured for patients with suspected sepsis.

#### Initial Resuscitation

- **BEST PRACTICE STATEMENT:** Sepsis and septic shock are medical emergencies; treatment should begin immediately.
- Administration of at least 30 mL/kg of IV crystalloid is suggested within the first 3 hours.
- Dynamic parameters (passive leg raising combined with cardiac output [CO] measurement, fluid challenges against stroke volume [SV], systolic pressure or pulse pressure, and increases of SV in response to changes in intrathoracic pressure) should guide fluid administration beyond the initial resuscitation, rather than physical examination or static parameters alone.
- In patients with elevated lactate, guide resuscitation to decrease serum lactate level.
- Use capillary refill time to guide resuscitation as an adjunct to other measures of perfusion, such as temperature of the extremities and skin mottling.
- For adults with septic shock on vasopressors, the recommended initial target mean arterial pressure (MAP) is 65 mm Hg.
- For improved outcomes, patient satisfaction, patient safety, patient flow, and staff morale, it is suggested that patients who require ICU admission be admitted to the ICU within 6 hours.

### Infection

- **BEST PRACTICE STATEMENT:** Continuous reassessment of alternative, non-infectious diagnoses is recommended, along with discontinuation of antimicrobials if an alternative cause is demonstrated or strongly suspected.
- Administration of antimicrobials should begin immediately, ideally within one hour of sepsis or septic shock recognition, for patients with a high likelihood of sepsis or possible septic shock.
- For patients with possible sepsis but without shock, rapid assessment of an infectious versus non-infectious cause of acute illness is recommended (within 3 hours, when possible).
  - This includes:
    - History
    - Clinical examination
    - Tests for infectious and non-infectious causes
    - Immediate treatment of acute conditions that mimic sepsis
  - If concern for infection persists, administration of antimicrobials within 3 hours from when sepsis was first recognized is suggested.
  - For patients with low likelihood of infection, deferring antimicrobials and close monitoring is suggested.
- The biomarker procalcitonin should not be used in addition to clinical evaluation to guide starting an antimicrobial.
- **BEST PRACTICE STATEMENT:** For patients with sepsis or septic shock at high risk of methicillin-resistant *Staphylococcus aureus* (MRSA), use of empiric antimicrobials with MRSA coverage is recommended.
  - Risk factors for MRSA
    - History of MRSA infection or colonization
    - Recent IV antibiotics
    - History of recurrent skin infections or chronic wounds
    - Presence of invasive devices
    - Hemodialysis
    - Recent hospital admissions
    - Severity of illness
  - For those at low risk of MRSA, use of empiric antimicrobials with MRSA coverage is not suggested.
- For patients with sepsis or septic shock who are at high risk for multidrug resistant (MDR) organisms, use of 2 antimicrobials with gram-negative coverage is suggested over one gram-negative agent.
  - Risk factors for MDR organisms
    - Proven infection or colonization with antibiotic-resistant organisms within the preceding year
    - Local prevalence of antibiotic-resistant organisms
    - Hospital-acquired or healthcare-associated infection (as opposed to community-acquired)
    - Broad spectrum antibiotic use in the preceding 90 days
    - Hospitalization abroad within the preceding 90 days
  - For patients at low risk for MDR organisms, use of 2 antimicrobials with gram-negative coverage is not suggested.

- Once the causative agent is known, use of double gram-negative coverage is not suggested.
- For patients with sepsis or septic shock who are at high risk for fungal infection, antifungal therapy is suggested.
  - For patients with sepsis or septic shock who are at low risk for fungal infection, antifungal therapy is not suggested.
- There is no recommendation on the use of antiviral agents; specific clinical guidelines for viral illnesses, including influenza and SARS CoV-2, should be consulted.
- For patients with sepsis or septic shock, prolonged infusion of beta-lactams for maintenance (after an initial bolus) is recommended over conventional bolus infusion.
- **BEST PRACTICE STATEMENT:** Optimizing dosing strategies of antimicrobials based on pharmacokinetics and pharmacodynamics of specific drugs is recommended.
- **BEST PRACTICE STATEMENT:** Rapidly identifying or excluding specific anatomical diagnosis of infection that requires emergent source control and intervening as soon as possible is recommended.
  - Examples of source control
    - Abscess drainage
    - Debridement of infected necrotic tissue
    - Removal of potentially infected device
    - Control of ongoing microbial contamination, such as intra-abdominal abscess or an infected implanted device
  - Selection of source control method must weigh risks and benefits, patient preference, clinician expertise, availability, potential delays, and probability of success.
- **BEST PRACTICE STATEMENT:** Prompt removal of intravascular devices that are a potential source of sepsis or septic shock is recommended after alternative vascular access has been established.
- Daily assessment for de-escalation of antimicrobials is suggested.
  - Once the pathogen and susceptibilities are known, stopping an antimicrobial that is no longer necessary, or changing the antimicrobial to narrow the spectrum is encouraged.
- For those with an initial diagnosis of sepsis or septic shock and adequate source control, the shortest course of antimicrobial therapy is suggested.
  - For patients with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is not clear, it is suggested to use procalcitonin and clinical evaluation to determine discontinuation of antimicrobials.

### Hemodynamic Management

- Crystalloids are recommended as first-line for fluid resuscitation.
  - Balanced crystalloids are suggested instead of normal saline solution.
  - Albumin is suggested in patients who received large volumes of crystalloids over using crystalloids alone.
  - Use of starches is not recommended.
  - Use of gelatin is not suggested.
- For patients with septic shock, norepinephrine is recommended as the first-line agent over other vasopressors.

- If norepinephrine isn't available, epinephrine or dopamine can be used, with special attention to patients at risk for arrhythmias.
- For patients on norepinephrine with inadequate MAP, the addition of vasopressin is suggested (usually when norepinephrine dose is 0.25-0.5 µg/kg/min.)
- For patients on norepinephrine and vasopressin with inadequate MAP, the addition of epinephrine is suggested.
- Use of terlipressin is not suggested.
- For patients with septic shock and cardiac dysfunction who have persistent hypoperfusion despite adequate volume and blood pressure, the addition of dobutamine to norepinephrine, or use of epinephrine alone, is suggested.
  - In the absence of improvement in hypoperfusion or in the presence of adverse events, the use of dobutamine or epinephrine should be discontinued.
  - The use of levosimendan is not suggested for these patients.
- When possible, invasive monitoring of arterial blood pressure is suggested over noninvasive monitoring.
  - Arterial catheters should be removed as soon as continuous monitoring is no longer required.
- Administration of vasopressors peripherally is suggested (only for a short time [less than 6 hours] and in a vein in or proximal to the antecubital fossa) rather than delaying administration until central access is available.
- After initial fluid bolus, there is insufficient evidence for a recommendation on fluid strategy in the first 24 hours for patients with continued signs of hypoperfusion and volume depletion. Administration should be guided by perfusion parameters and not only by hemodynamic response.

## Ventilation

- Patients with sepsis-induced hypoxemic respiratory failure
  - There is insufficient evidence for a recommendation on using conservative oxygen targets.
  - The use of high flow nasal oxygen is suggested over noninvasive ventilation.
  - There is insufficient evidence for a recommendation on using noninvasive ventilation in comparison to invasive ventilation.
- Patients with sepsis-induced acute respiratory distress syndrome (ARDS)
  - The use of a low tidal volume strategy (6 mL/kg) over a high tidal volume strategy (greater than 10 mL/kg) is recommended.
    - The precise tidal volume requires adjustment for plateau pressure, positive end-expiratory pressure (PEEP), thoracoabdominal compliance, and the patient's breathing effort.
    - Those with profound metabolic acidosis, high minute ventilation, or short stature may also require adjustment of tidal volume.
  - An upper limit goal of 30 cm H<sub>2</sub>O for plateau pressure is recommended.
  - A higher PEEP strategy is recommended.
- For patients with sepsis-induced respiratory failure without ARDS, the use of a low tidal volume strategy is suggested.

- Patients with sepsis-induced moderate-severe ARDS
  - Traditional recruitment maneuvers are suggested, however using incremental PEEP titration is not recommended.
  - Prone ventilation for more than 12 hours daily is recommended.
  - Use of intermittent neuromuscular blocking agent (NMBA) boluses is suggested over continuous infusion.
  - Venovenous (VV) extracorporeal membrane oxygenation (ECMO) is suggested when conventional mechanical ventilation fails.

### **Additional Therapies**

- For patients with septic shock and an ongoing need for vasopressor support, the use of IV corticosteroids is suggested.
  - Hydrocortisone 200 mg/day as 50 mg IV every 6 hours or by continuous infusion is the typical agent and dose.
  - It is suggested that this is started when norepinephrine or epinephrine is greater than or equal to 0.25 mcg/kg/min for at least 4 hours after initiation to maintain the target MAP.
- The use of polymyxin B hemoperfusion is not suggested; there is insufficient evidence to make a recommendation on other blood purification techniques.
- The use of a restrictive transfusion strategy is recommended.
  - The typical hemoglobin concentration transfusion trigger is 70 g/L (7g/dL).
  - A patient's overall clinical status and extenuating circumstances (i.e., acute myocardial ischemia, severe hypoxemia, acute hemorrhage) should be considered.
- The use of IV immunoglobulins is not suggested.
- For patients with risk factors for gastrointestinal bleeding (coagulopathy, shock, chronic liver disease), stress ulcer prophylaxis is suggested.
- Pharmacologic venous thromboembolism (VTE) prophylaxis is recommended unless contraindicated.
  - Low molecular weight heparin is recommended over unfractionated heparin.
  - Mechanical VTE prophylaxis in addition to pharmacologic prophylaxis is not suggested over pharmacologic prophylaxis alone.
  - If pharmacologic prophylaxis is contraindicated, patients may benefit from mechanical VTE prophylaxis, however no data exists.
- In patients with acute kidney injury (AKI) who require renal replacement therapy, the suggestion is for either continuous or intermittent therapy.
  - For patients with AKI and no definitive indication for renal replacement therapy, the suggestion is against using renal replacement therapy.
- Starting insulin therapy at a glucose level of greater than or equal to 180 mg/dL is recommended.
  - The typical target blood glucose range is 144-180 mg/dL.
- The use of IV vitamin C is not suggested.
- For patients with septic shock and hypoperfusion-induced lactic acidemia, the use of sodium bicarbonate is not suggested.

- For adults with septic shock, severe metabolic acidemia (pH less than or equal to 7.2), and AKI, the use of sodium bicarbonate is suggested.
- For patients who can be fed enterally, initiation of enteral nutrition within 72 hours is suggested.

### Long-Term Outcomes and Goals of Care

- **BEST PRACTICE STATEMENT:** Discussing goals of care and prognosis with patients and families is recommended.
  - The suggestion is to start addressing goals of care within 72 hours.
  - No recommendation can be made as to specific criteria to initiate the discussion.
- **BEST PRACTICE STATEMENT:** Integrating palliative care principles into the treatment plan is recommended, when appropriate, to address patient and family symptoms and suffering. This may include palliative care consultation, based on clinician judgement.
  - Routine formal palliative care consultation is not suggested.
- Referral to peer support groups for survivors and families is suggested.
- A handoff process is suggested at transitions of care. There is insufficient evidence to recommend any specific handoff tool.
- **BEST PRACTICE STATEMENT:** Screening for economic and social support (including housing, nutrition, financial, and spiritual support), along with appropriate referrals, is recommended.
- Provision of written and verbal sepsis education prior to discharge and at follow-up is suggested.
- **BEST PRACTICE STATEMENT:** The opportunity for patients and families to participate in shared decision making in post-ICU and discharge planning is recommended.
- A critical care transition program is suggested upon transfer to the floor.
- **BEST PRACTICE STATEMENT:** Reconciling medications is recommended at both ICU and hospital discharge.
- **BEST PRACTICE STATEMENT:** It is recommended that the written and verbal discharge summary include key information from hospitalization, including:
  - Information about the ICU stay
  - Sepsis and related diagnoses
  - Treatments
  - Information on post-ICU/post-sepsis syndrome
- **BEST PRACTICE STATEMENT:** Discharge plans including follow-up with clinicians to support and manage new and long-term sequelae is recommended.
  - There is insufficient evidence to recommend early versus routine post-hospital follow-up.
- There is insufficient evidence to recommend early cognitive therapy for survivors.
- **BEST PRACTICE STATEMENT:** Assessment and follow-up for physical, cognitive, and emotional problems is recommended after hospital discharge.
  - Referral to a post-critical illness follow-up program is suggested.
  - For survivors who received mechanical ventilation for more than 48 hours or who had an ICU stay longer than 72 hours, referral to a post-hospital rehabilitation program is suggested.

**Reference:**

Evans, L., Rhodes, A., Alhazzani, W., Antonelli, M., Coopersmith, C. M., French, C., Machado, F. R., McIntyre, L., Ostermann, M., Prescott, H. C., Schorr, C., Simpson, S., Wiersinga, W. J., Alshamsi, F., Angus, D. C., Arabi, Y., Azevedo, L., Beale, R., Beilman, G., Belley-Cote, E., ... Levy, M. (2021). Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive care medicine*, 1–67. Advance online publication. <https://doi.org/10.1007/s00134-021-06506-y>