

Septic Shock: Improving Patient Outcomes

Introduction

The mortality of septic shock in most medical facilities remains unacceptably high. Similar to an acute myocardial ischemic attack and an acute brain attack, the speed and appropriateness of therapy administered in the initial hours after the syndrome develops are likely to influence outcome.

A group of international critical care and infectious disease experts in the diagnosis and management of infection and sepsis and representing 11 organizations (including the Society of Critical Care Medicine), collaborated on the development of guidelines for use by the bedside clinician to improve outcomes in severe sepsis and septic shock. These guidelines are directly reflected in the *Septic Shock Order Set*.

Although the *Septic Shock Order Set* is written primarily for the patient in the intensive care unit setting, multiple orders are appropriate for the pre-ICU setting and should be initiated as early as personnel and material resources permit. These particular orders are gray-highlighted on the order set.

Sepsis & Septic Shock: A Brief Review

Definitions

Sepsis is a systemic inflammatory response to infection. If the systemic inflammatory response is *not* caused by an infection (i.e. pancreatitis, ischemia or trauma), it is referred to as SIRS, or systemic inflammatory response syndrome. Two or more of the following are present in sepsis (and SIRS):

- Temperature > 38 OR <36 degrees Celsius
- Heart rate > 90 bpm
- Respiratory rate > 20 breaths/minute OR PaCO₂ < 32 mm Hg
- White blood cell count > 12,000/mm³ OR < 4,000/mm³ OR > 10% immature (band) forms

If a patient has accompanying organ dysfunction, hypoperfusion or hypotension, (s)he is in *severe* sepsis. Severe sepsis may be manifested as altered mental status, hypotension, lactic acidosis and/or oliguria. If the hypotension does not respond to adequate fluid resuscitation, the patient is in septic shock. It is sometimes initially difficult to distinguish severe sepsis from septic shock. Septic shock carries a mortality rate of 40 - 60%.

Etiology

Gram-negative organisms account for most adult cases of septic shock. In the hospitalized patient, the most common gram-negative organisms are E. Coli, Klebsiella, Enterobacter and Pseudomonas aeruginosa.

Gram-positive organisms are becoming increasingly associated with sepsis due to the use of intravenous catheters and invasive devices. The most common gram-positive organisms seen are the Staphylococcus and Streptococcus species as well as Pneumococcus and Enterococcus faecalis.

Viruses, protozoa, parasites, fungi (i.e. Candida albicans) and anaerobic organisms (i.e. Clostridium, Bacteroides fragilis) are also known to be associated with sepsis.

The most common sites of origin are:

- Urinary tract (i.e. upper)
- Gastrointestinal tract (i.e. peritonitis)
- Respiratory tract (i.e. pneumonia)
- Skin and wounds (i.e. cellulitis)

Predisposing Factors

Predisposing factors for developing sepsis and septic shock include:

- Extremes of age (very old and very young)
- Granulocytopenia (reduced number of neutrophils, eosinophils and basophils)
- Prior antibiotic therapy
- Severe burn injury, recent trauma, recent surgery and/or invasive procedures
- Functional asplenia (no spleen)
- Immunosuppression
- Malnutrition and total parenteral nutrition
- Alcohol and drugs of abuse
- Prolonged ICU stay, *especially* endotracheal intubation > 48 hours and ventilator-associated pneumonia

Pathophysiology

In short, there is among other things, an overproduction of cytokines. Cytokines, also known as lymphokines, interleukins or chemokines, are released from cells of the immune system and their function is to signal other cells. They are small secreted proteins that mediate and regulate immunity, inflammation, and hematopoiesis. Cytokines and other mediators activated by bacteria released from the immune system are responsible for the sequelae of sepsis/septic shock:

- Systemic vasodilation with decreased afterload and hypotension
- Increased capillary permeability with decreased preload, third spacing and interstitial edema
- Decreased tissue oxygenation extraction
- Platelet aggregation, fibrin deposits and activation of the clotting cascade, leading to microcirculatory coagulation and tissue hypoxia
- Multiple organ dysfunction

Objectives

1. Provide a brief review of sepsis and septic shock, including definitions, etiology, predisposing factors and pathophysiology.
2. Summarize key learning points in the initial management of septic shock.
3. Familiarize clinicians with the standardized *Septic Shock Order Set*.

For additional information, contact the Clinical Nurse Specialist or Nurse Manager.

The First Six Hours: Resuscitation

Resuscitation = cultures + antibiotics + early goal-directed therapy

The resuscitation of a patient in septic shock should begin as soon as it is recognized and *should not be delayed pending intensive care unit admission*.

Blood cultures should be obtained and the first antibiotics administered within three hours of Emergency Department (ED) admission and within one hour of non-ED admission.

Early goal-directed therapy (EGDT) has been shown to improve survival for emergency department patients presenting with septic shock and reduce the 28-day mortality.

EGDT includes:

- Central venous pressure (CVP) 8 - 12 mm Hg
- Mean arterial pressure (MAP) \geq 65 mm Hg
- Urine output \geq 0.5 ml/kg/hour
- Central venous (superior vena cava) saturation (ScvO₂) \geq 70% or mixed venous oxygen saturation (SvO₂) \geq 65%

The First 24 Hours: Management

Management = steroids + Xigris + glucose control + protective ventilation

Assess patient for appropriateness of administration of low dose steroids and recombinant human activated protein C (Xigris) therapy.

Maintain blood glucose <150 mg/dl (use existing hospital blood glucose protocol).

Maintain median inspiratory plateau pressure < 30 cm H₂O for mechanically ventilated patients.

Septic Shock Order Set: A Closer Look at Each Order Entry

Note: The gray-highlighted orders correlate with those that may be initiated in the pre-ICU setting.

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| <p>1. Appropriate candidates for the Septic Shock Protocol are patients with:</p> <ul style="list-style-type: none">a) documented or strong suspicion for infection <p>and</p> <ul style="list-style-type: none">b) three or more of the Systemic Inflammatory Response Syndrome (SIRS) Criteria <p>and</p> <ul style="list-style-type: none">c) SBP less than 90 or MAP less than 65 or Serum Lactate greater than 4 mmol/L <p>Serum lactate level greater than 4.0 with an anion gap in the presence of above is also strongly indicative of sepsis</p> <p>SIRS criteria defined as:</p> <ul style="list-style-type: none">• Core temperature of greater than 38° C (100.4 °F) or less than 36 °C (96.8 °F)• Heart rate of greater than 90 beats/minute except in patients with a medical condition known to increase the heart rate or those receiving treatment that would prevent tachycardia• Respiratory rate greater than 20 breaths/minute or a P_aCO₂ less than 32mm Hg or the use of mechanical ventilation for an acute respiratory process• White-cell count of greater than 12,000/mm³ or less than 4,000/mm³ or a differential showing greater than 10 percent immature neutrophils |
| <p>2. STAT CBC with Diff, BMP with iCa+ AND serum lactate</p> |

Serum lactate is a clinically useful global marker of tissue perfusion. It is a measure of the amount of lactic acid in the blood (normally 4.5 – 19.8 mg/dl or 0.5 – 2.2 mmol/L). Poor tissue perfusion triggers anaerobic metabolism within muscle tissue and results in a build-up of lactic acid in the bloodstream. *An elevated serum lactate level identifies tissue hypoperfusion in patients at risk who are not hypotensive or oliguric.*

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| <p>3. STAT portable CXR re: r/o pneumonia</p> |
| <p>4. Obtain two sets of peripheral blood cultures</p> |

Collaborate with the physician on obtaining blood cultures through a pre-existing intravascular device (i.e. central line). Ideally, at least one blood culture should be drawn through *each* lumen of each intravascular access device (unless inserted < 48 hours).

If a blood culture drawn through an intravascular access device is positive more than two hours earlier, the intravascular access device may be the likely source of infection. Intravascular access devices are believed to be the most likely source of nosocomial bloodstream infections. In cases where the cause of the infection is not known, the physician may elect to remove and replace the intravascular access device.

Volume of blood collected may be important. Be sure to consult an appropriate resource to determine minimal acceptable volume for each blood culture.

Blood cultures are frequently negative in cases of septic shock. The decision to

continue, narrow or discontinue antibiotics is then based on clinical judgment and other culture results.

5. Send urine sample for urinalysis, culture and sensitivity

Collaborate with the physician on obtaining cultures from other potential sites of infection, including but not limited to cerebrospinal fluid and wounds.

6. Obtain sputum cultures and gram stain if appropriate

7. If MAP less than 65 give 20 ml/kg Normal Saline over 30 minutes

Establishing vascular access and initiating aggressive fluid resuscitation is the first priority in septic shock.

With venodilation and continuous capillary leak, most septic shock patients will require ongoing fluid resuscitation within the first 24 hours. Typically during this time, input is greater than output and the I/O ratio is of no value in judging fluid resuscitation needs.

8. Distal port CVL to CVP monitor; if ScvO₂ catheter prepare for continuous monitoring

SvO₂, sampled from the pulmonary artery via a special catheter, is a reliable indicator of global tissue oxygenation. ScvO₂, sampled from a central vein via a centrally inserted catheter, provides a reasonable representation of SvO₂ without the need for a pulmonary artery catheter.

Antimicrobial agents:

NOTE: Vancomycin is automatic until culture reports are back unless allergic

9. Vancomycin 1 gram IV piggyback every 12 hours
(pharmacy consult to assist with subsequent dosing based upon levels)

10. Please choose one from section a, +/- one from section b;

a) Piperacillin/Tazobactam (preferred agent) 3.375 gm IV piggyback every 6 hours

Cefepime 2gm IV piggyback every 8 hours

Aztreonam (for PCN allergy) 2 gm IV piggyback every 8 hours

Imipenem/Cilistatin 500 mg IV piggyback every 6 hours (if recent antimicrobial exposure)

Other: _____

b) Gentamicin 7 mg/kg IV piggyback every 24 hours (pharmacy consult to assist with dosing and levels)

Ciprofloxacin 400 mg IV piggyback every 8 hours

Intravenous antibiotic therapy should be started within the first hour of recognition of

septic shock, *after the appropriate cultures have been obtained*. If there is difficulty in obtaining cultures (i.e. sputum), notify the physician who will then determine if antibiotics are to be started with the final culture(s) pending.

The initial empiric antimicrobial regimen should be broad enough to cover all likely pathogens as there is little margin for error in critically ill patients. There is ample evidence that failure to initiate appropriate therapy promptly has adverse consequences on outcome.

Patients with severe sepsis or septic shock warrant broad-spectrum therapy until the causative organism and its antibiotic susceptibilities are identified. All patients should receive a full loading dose of each antimicrobial. However, the pharmacist may need to be consulted for those with abnormal renal or hepatic function and those who have abnormal volumes of distribution due to aggressive fluid resuscitation.

**Septic Shock Order Set
Page 1 of 3 (continued)**

11. Admit patient to ICU

**Septic Shock Order Set
Page 2 of 3**

*****DO NOT USE OUTSIDE OF CRITICAL CARE*****
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12. Evaluation for drotrecogin alpha (Xigris) (see drotrecogin alpha order set)

Xigris is FDA-approved for increasing survival in high-risk adult patients with severe sepsis. The exact mechanism by which it does this is unknown. Xigris is a recombinant version of human Activated Protein C (anti-inflammatory protein), which modulates microvascular function by decreasing inflammation and coagulation and increasing fibrinolysis.

Xigris is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (as determined by APACHE II guidelines). Xigris is *not* indicated in adult patients with severe sepsis and *lower* risk of death.

Xigris can only be administered in an ICU but may be used in the emergency department setting when lack of an ICU bed may delay transfer.

13. Evaluation for other active sepsis protocols – page research coordinator at pager: 475-8204

14. If the patient is on vasopressors, draw a random cortisol level stat; if the random cortisol is less than 25mcg/mL, give corticosteroids

If patient is not on vasopressors, draw a baseline random cortisol level, give cosyntropin 250 mcg IV push and then repeat random cortisol levels 30 and 60 min post cosyntropin. If the difference between baseline and maximum is less than 9, give steroids

- Hydrocortisone 50 mg IV Push every 6 hours [OR]
- Dexamethasone 4 mg IV Push every 8 hours
- Fludrocortisone 100 mcg Feeding tube daily

The patient may require *low dose* corticosteroids because of the risk of sepsis-induced adrenal suppression and the resulting inability to produce adequate amounts of cortisol in response to stress.

Corticosteroid administration may help to restore the vasopressor response to norepinephrine.

15. Implement the following ICU protocols:

- **Sepsis mechanical ventilation/weaning protocol** – respiratory therapy consult
- **Intensive insulin order set** (see ICU intensive insulin order set)
- **ICU Electrolyte Protocols**
(Potassium, Magnesium, Phosphorous, Calcium) (See ICU Electrolyte Order Sets)
- **Clinical Nutrition Consult**

16. Implement ICU Sedation Protocol

Sedation goal (circle one): -3 -2 -1 0

Choose one each for pain and sedation management

(see ICU Sedation Order Set for dosages and titration)

Pain Management

- Fentanyl (for hemodynamically unstable patients)
- Morphine

Anxiety/Agitation

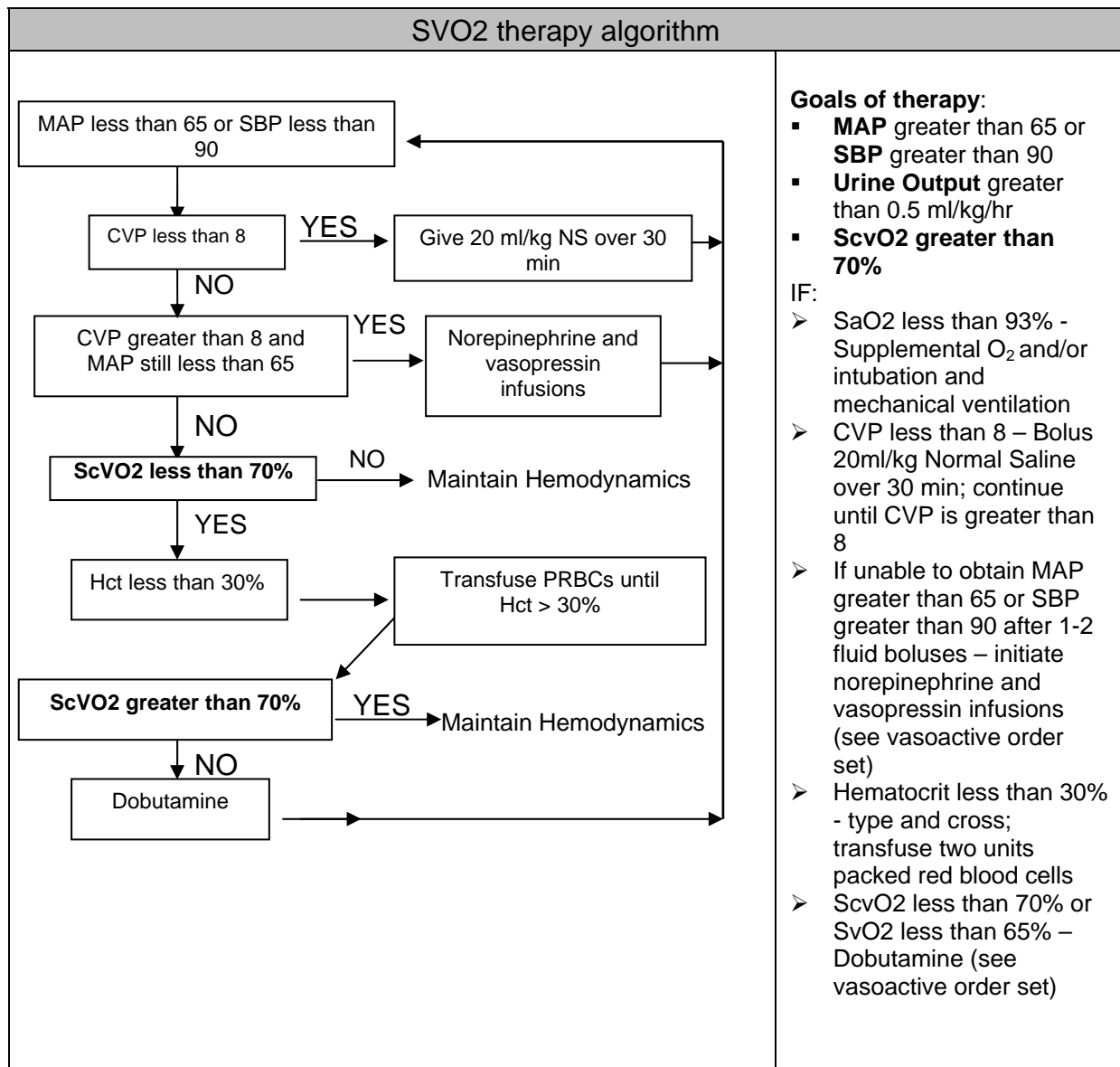
- Midazolam (**Versed**) (for most intubated patients)
- Lorazepam (**Ativan**) (for patients requiring long term sedation greater than 7 days)
- Propofol (**Diprivan**) (for patients with **acute asthma, COPD, head injury, or multiple organ failure**)

17. Stress Ulcer Prophylaxis <input type="checkbox"/> Famotidine (Pepcid) 20 mg IV piggyback every 12 hours <input type="checkbox"/> Lansoprazole (Prevacid) 30 mg per feeding tube daily (for patients with thrombocytopenia) <input type="checkbox"/> Other: _____
18. Venous Thrombosis Prophylaxis <input type="checkbox"/> Sequential Compression Devices <input type="checkbox"/> Enoxaparin (Lovenox) 40 mg subcutaneous daily – (avoid in renal dysfunction) <input type="checkbox"/> Heparin 5000 units Subcutaneous every 8 hours
19. <input type="checkbox"/> Docusate 100mg per feeding tube twice a day

*****DO NOT USE OUTSIDE OF CRITICAL CARE*****
20. Vasoactive Medications: (see vasoactive order set for dosage and titration) <input type="checkbox"/> Norepinephrine (drug of choice for septic shock) and Vasopressin (non titrated) (adjunct drug of choice for septic shock) <input type="checkbox"/> Dopamine <input type="checkbox"/> Phenylephrine <input type="checkbox"/> Dobutamine
If Multiple Medications are Ordered: Start with _____ and add _____ if goal not obtained
Cardiovascular Goals: Titrate appropriate medication to keep <input type="checkbox"/> Mean Arterial Pressure OR <input type="checkbox"/> Systolic Blood Pressure greater than _____ mmHg <input type="checkbox"/> Heart Rate greater than _____ per minute <input type="checkbox"/> Cardiac Index greater than _____ liter per minute
Call MD if: Cardiovascular goals not met. OR heart rate less than or equal to _____ OR greater than or equal to _____

Below a certain MAP, autoregulation in various vascular beds may be lost. Perfusion then becomes linearly dependent on pressure. Patients may require vasopressor therapy to achieve a minimal perfusion pressure and maintain adequate flow. Norepinephrine is the preferred first agent.

It has been demonstrated that vasopressin levels are elevated early in septic shock, but with continued shock, decrease to a normal range. However, the normal expectation with hypotension is the vasopressin level would remain high. The significance of this finding is unknown. This is why vasopressin, a direct vasoconstrictor without inotropic or chronotropic effects, is administered concurrently with norepinephrine. It may raise blood pressure in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors. Use with caution in cardiac dysfunction.



Selected References

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Name: _____ Unit: _____ Date: _____

True/False

1. _____ It is generally recommended to wait until the patient is admitted to the ICU before implementing the *Septic Shock Order Set*.
2. _____ Blood cultures should be obtained and the first antibiotics administered within three hours of Emergency Department (ED) admission and within one hour of non-ED admission.
3. _____ An elevated serum lactate level identifies tissue hypoperfusion in patients at risk who are not hypotensive or oliguric.
4. _____ Blood cultures are frequently negative in cases of septic shock.
5. _____ ScvO₂ provides a reasonable representation of SvO₂ without the need for a pulmonary artery catheter.

Multiple Choice

6. Severe sepsis may be manifested as:
 - a. Altered mental status
 - b. Lactic acidosis
 - c. Oliguria
 - d. All of the above
7. Early goal-directed therapy includes all of the following *except*:
 - a. Central venous pressure \geq 8 mm Hg
 - b. Mean arterial pressure \geq 90 mm Hg
 - c. Urine output \geq 0.5 ml/kg/hour
 - d. Central venous (ScvO₂) saturation (ScvO₂) \geq 70% OR mixed venous (SvO₂) saturation \geq 65%
8. What is the number one priority in treating septic shock?
 - a. Establish vascular access and begin aggressive fluid resuscitation
 - b. Obtain blood cultures and administer antibiotic(s)
 - c. Start norepinephrine infusion
 - d. Give steroids STAT
9. Which of the following statements regarding blood cultures and antibiotics is *false*?
 - a. Begin with broad-spectrum antibiotics until the causative organism and its antibiotic susceptibilities are identified.
 - b. Failure to promptly initiate appropriate antibiotic therapy has adverse consequences on outcome.
 - c. Gram-positive organisms (i.e. *Staph*, *Strep*) account for most adult cases of septic shock.
 - d. Antibiotic(s) should be started after the appropriate cultures have been obtained
10. Which of the following is the preferred first agent in septic shock?
 - a. Dopamine
 - b. Dobutamine
 - c. Norepinephrine
 - d. Vasopressin