

Advocate Christ Hospital Medical Center

Evidence Based Guidelines:

Treatment of Severe Sepsis and Septic Shock

Definitions:

Systemic Inflammatory Response Syndrome (SIRS)

The systemic inflammatory response to a wide variety of severe clinical insults, manifested by two or more of the following conditions:

1. Temperature $\geq 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
2. Heart rate > 90 beats/minute
3. Respiratory rate >20 breaths/minute or $\text{PaCO}_2 < 32$ mmHg
4. White blood cell count $> 12,000/\mu\text{L}$ or $<4,000/\mu\text{L}$, or $>10\%$ immature (band) forms

Sepsis

The systemic inflammatory response to a documented infection. The clinical manifestations would include two or more of the SIRS criteria as a result of a documented infection.

Severe Sepsis/SIRS

Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Sepsis/SIRS-Induced Hypotension

Systolic blood pressure <90 mmHg or a reduction of ≥ 40 mmHg from baseline in the absence of other causes for hypotension.

Septic Shock/ SIRS Shock

Sepsis/SIRS induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction, yet they would still be considered to have septic/SIRS shock.

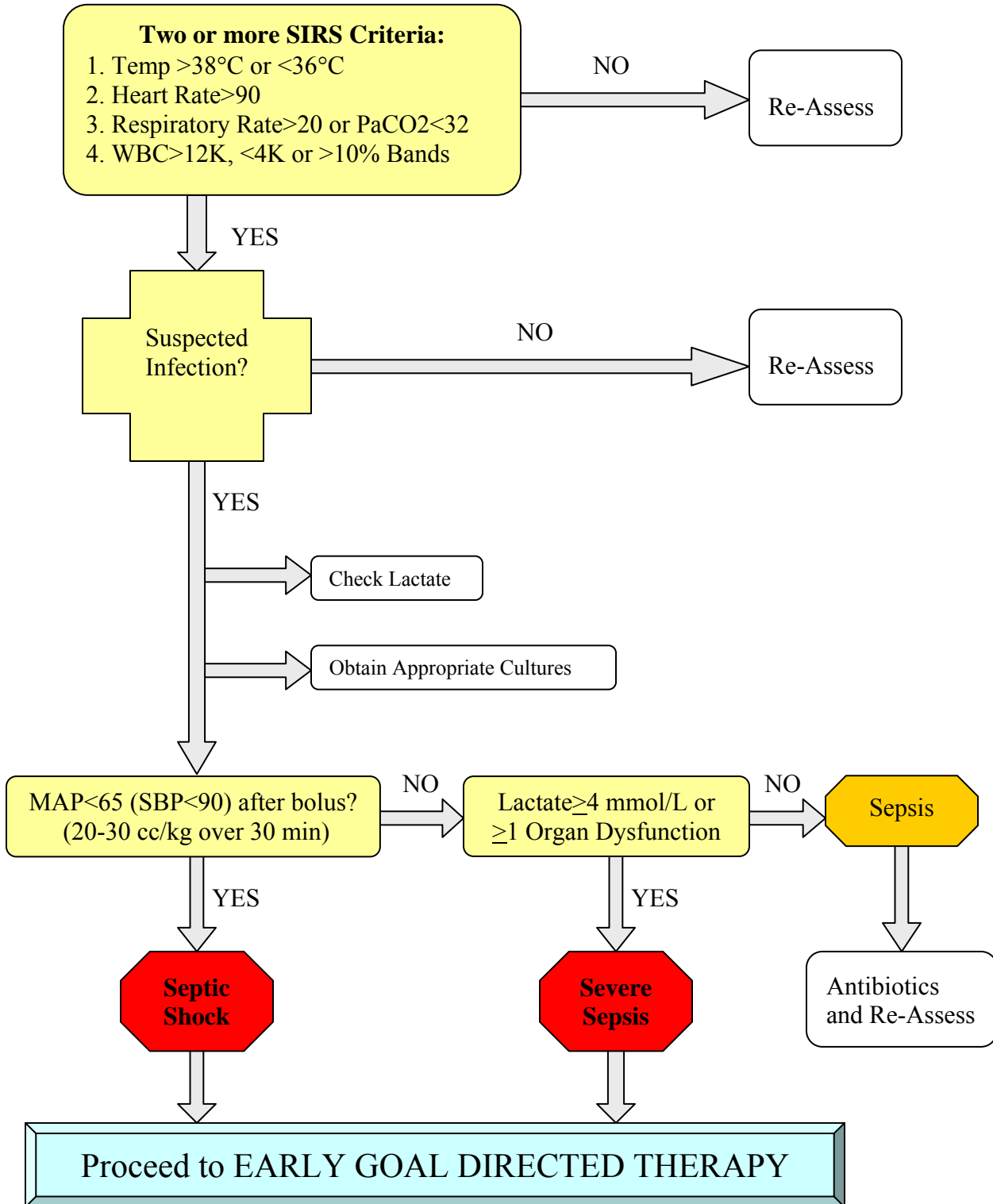
Multiple Organ Dysfunction Syndrome

Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Reference:

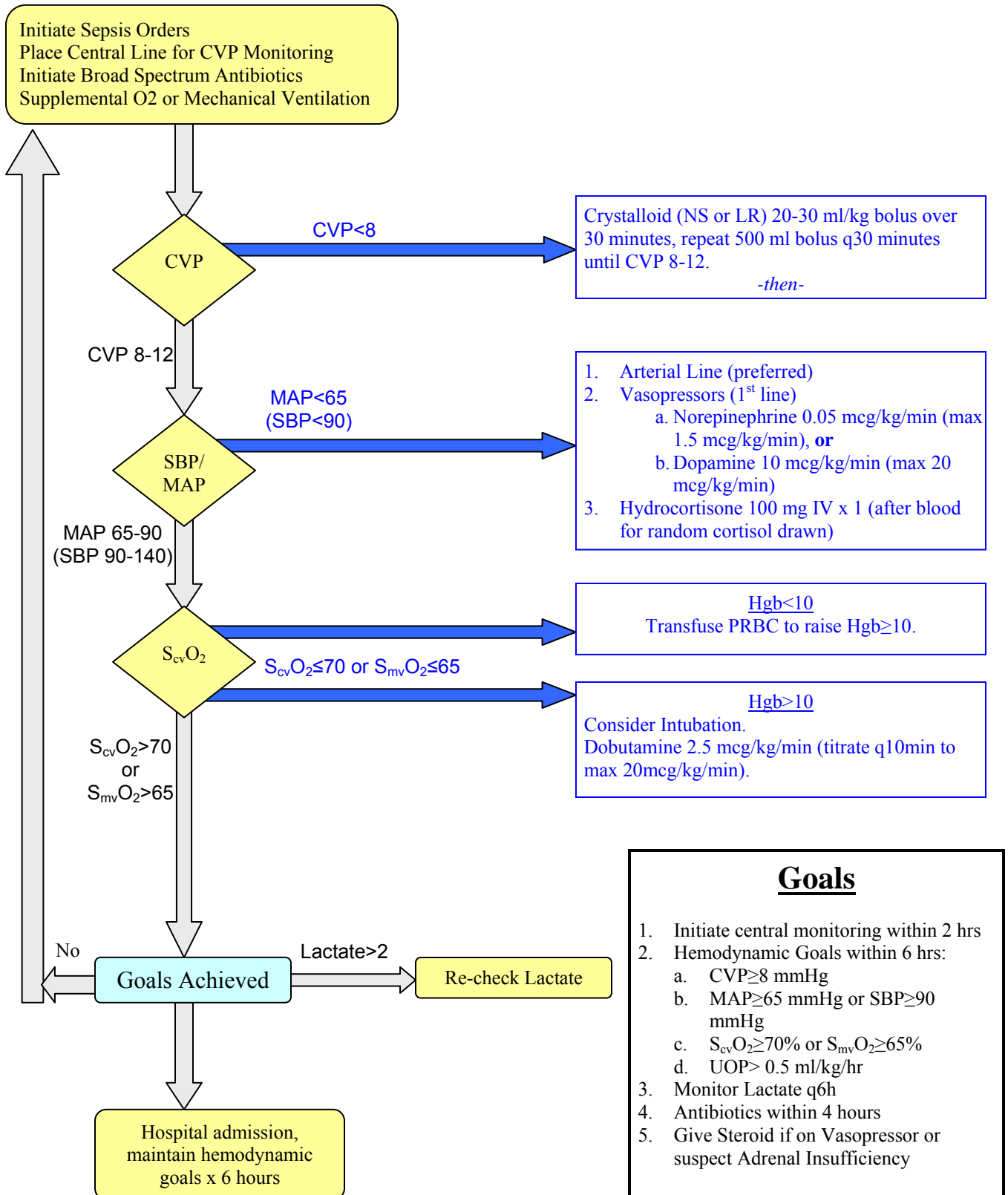
Bone RC, Balk RA, Cerra FB, et al. ACCP/SCCM Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644-55.

Early Recognition



Exclusion: Age <18 yrs, Acute Coronary Syndrome, Acute Pulmonary Edema, Trauma.

Early Goal Directed Therapy (0-6 hours)



Rivers E, Nguyen B, Havstad S, et al. Early goal directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368-1377

Early goal directed therapy (EGDT) could significantly decrease in-hospital mortality in patients with severe sepsis. The goal is to identify early global tissue hypoxia to ensure that delivery dependent factors are maximized early in the course of the septic process. Results of a randomized study showed that EGDT reduced the absolute and relative risk of in-hospital mortality by 16% and 39%, respectively (p=0.009). Twenty-eight day and 60 day mortality rates were also significantly reduced in the EGDT group. Despite initial aggressive therapy, patients in the EGDT arm received overall less fluid volume, less blood transfusion, less vasopressor support, and achieved a 3.8 day decrease in hospitalization.

Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004 September; 32(9):1928-1948

When an appropriate fluid challenge fails to restore adequate blood pressure and organ perfusion, therapy with vasopressor agents should be started. Early transient pressor use may be warranted to treat life-threatening hypotension while fluid challenge is in progress. An arterial catheter should be placed as soon as practical

Norepinephrine or dopamine are recommended as first line vasopressors to correct hypotension in septic shock. Recent studies suggest that norepinephrine can increase oxygen utilization and delivery in the septic population. Phenylephrine may be considered when a patient remains hypotensive despite fluid resuscitation, and there is a concern that adrenergic agents may precipitate a tachyarrhythmia.

Vasopressin infusion (0.01-0.04 unit/min) may be considered in patients on high dose vasopressors with refractory shock. Splanchnic blood flow may be decreased.

In patients with low cardiac output despite fluid resuscitation, dobutamine may be used to increase cardiac output (25-50%). In severe sepsis, dobutamine can increase oxygen delivery and consumption. Dobutamine therapy should be considered in patients with an inappropriately low CI despite adequate or increased filling pressure and blood pressure.

Correction of acidosis with sodium bicarbonate for the purpose of improving hemodynamics or reducing vasopressor requirements is not recommended.

Goals for first two hours after criteria are met

1. Peripheral IV, Monitor, O₂, Pulse Oximetry
2. Central venous access, Subclavian or Internal Jugular Veins are preferred sites.
3. Monitoring (hourly)
 - a. Vitals
 - b. S_vO₂
 - c. CVP
 - d. S_pO₂
4. Obtain Sepsis Labs
 - a. ABG
 - b. CBC with differential (at 6, 12, and 24 hours)
 - c. CMP with Magnesium
 - d. PT/PTT/INR
 - e. Type and Cross
 - f. Lactate (PRN within first 6 hours, at 6, 12, and 24 hours)
 - g. Random Cortisol
 - h. Troponin I
5. Microbiology
 - a. Quantitative blood culture x 2 sites, one from a peripheral stick and the other from IV site (if present).
 - b. Urinalysis with culture and sensitivity
 - c. Other (as indicated):
 - i. CSF
 - ii. Tissue
 - iii. Sputum/Mini BAL
6. Obtain control of easily accessed sources of ongoing microbial contamination (i.e. abscess, central line, urinary catheter, decubitus ulcer, Necrotizing fasciitis, peripheral IV line)
7. CXR
8. ECG

Goals for therapy within six hours after criteria met

1. Antibiotics within **four hours**
2. Achieve hemodynamic goals

Initial Antibiotic Recommendations for Severe Sepsis 2005*

| Source | Primary Regimen | Alternative Regimen (penicillin allergy) |
|--|---|--|
| Intra-abdominal | Community: Ampicillin/Sulbactam 1.5 gram IV (3 gram if > 80 kg) Traumatic/Nosocomial: Piperacillin/tazobactam 3.375 gram IV | Community/Traumatic/Nosocomial: Ciprofloxacin 400 mg IV, plus Metronidazole 500 mg IV |
| Pneumonia | Community Acquired: Ceftriaxone 1 gram IV, plus Clarithromycin 500 mg Po or Erythromycin 500 mg IV if NPO Nursing Home Acquired/Nosocomial: Piperacillin/tazobactam 3.375 gram IV, plus Clarithromycin 500 mg po or Erythromycin 500 mg IV if NPO | Community Acquired: Moxifloxacin 400 mg IV Nursing Home Acquired/Nosocomial: Ciprofloxacin 400 mg IV, plus Clindamycin 600 mg IV |
| Skin- Necrotizing | Community Acquired: Clindamycin 600 mg IV Plus Nafcillin 3 gram IV Immunocompromised/diabetic: Piperacillin/tazobactam 3.375 gram IV | Community Acquired: Clindamycin 600 mg IV, plus Vancomycin 1 gram IV Immunocompromised/diabetic: Clindamycin 600 mg IV, plus Ciprofloxacin 400 mg |
| Skin- Diabetic Foot | Ampicillin/Sulbactam 1.5 gram IV (3 gram if > 80 kg) | Clindamycin 600 mg IV, plus Ciprofloxacin 400 mg |
| Urine | Piperacillin/tazobactam 3.375 gram IV | Gentamicin 7 mg/kg IV |
| Bacterial Meningitis | Ceftriaxone 2 gram IV, plus Ampicillin 3 gram IV, plus Vancomycin 1.5 gram IV Dexamethasone 10 mg IV 15 minutes prior to Antibiotic** | Ceftriaxone 2 gram IV, plus Vancomycin 1.5 gram IV Dexamethasone 10 mg IV 15 minutes prior to antibiotic** |
| Neutropenic Fever With Septic Shock | Imipenem/cilastatin 500 mg IV, or Cefepime 2 gram IV, plus Vancomycin 15 mg/kg | Amikacin 20 mg/kg IV, plus Aztreonam 2 gram IV, plus Vancomycin 15 mg/kg |
| Catheter Related | Vancomycin 15 mg/kg IV | Vancomycin 15 mg/kg IV |
| Unknown Origin | Piperacillin/tazobactam 3.375 gram IV | Ciprofloxacin 400 mg IV, plus Clindamycin 600 mg IV |

* Recommendations based upon ACMC 2004 antibiogram and most likely pathogen for the given infection. Please refer to the institutional antibiogram for more information.

** de Gans J, van de Beek D et al: Dexamethasone in adults with bacterial meningitis.

N Engl J Med 2002; 347(20); 1549-1556. Use Dexamethasone 10 mg IV Q6h x 4 days in lieu of hydrocortisone.

Recommended cultures prior to antibiotic administration:

Quantitative blood culture x 2 from different sites, one from a peripheral stick and the other from IV site (if present).

Urinalysis with culture and sensitivity

Other cultures as clinically dictated

Sputum/ Mini BAL

Tissue

CSF

Sepsis Specific Interventions

Source Control

Jimenez MF, Marshall JC. Source control in the management of sepsis. *Intens Care Med* 2001;32:858-73.

Every patient presenting with severe sepsis should be evaluated for the presence of a focus of infection amenable to source control measures: Drainage of an abscess or local focus of infection, debridement of infected necrotic tissue, removal of an infected device, definitive control of a source of ongoing microbial contamination

When a focus of infection amenable to source control measures has been identified as the cause for severe sepsis or septic shock, source control measures should be instituted as soon as possible after initial resuscitation. Intravascular access devices that are potentially the source of infection should be promptly removed after adequate alternative vascular access is established.

Steroid Replacement

Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.

Intravenous corticosteroids (hydrocortisone 100 mg q8h for 7 days) are recommended in patients with septic shock who, despite adequate fluid replacement, require vasopressor therapy to maintain adequate blood pressure. Doses of corticosteroids > 300 mg hydrocortisone equivalent daily should not be used in severe sepsis or septic shock. In the absence of shock, corticosteroids should not be administered for the treatment of sepsis. There is no contraindication to continuing maintenance therapy or using stress doses if the patient's history is consistent with chronic use.

Potential mechanisms of action:

- Correction of relative adrenal insufficiency
- Inhibition of the synthesis of iNOS
- Improved hemodynamics secondary to restoration of sensitivity of catecholamine receptors
- Decreased transcription of inflammatory cytokines and increased synthesis and release of the receptor antagonist of IL-1

Random cortisol levels and ACTH stimulation tests may be helpful in determining patient benefit from steroid therapy, though not required. Consideration can be made to discontinue corticosteroid therapy in patients in which a random cortisol level (if drawn) is > 25, and the patient is not requiring vasopressor support.

Dexamethasone 4 mg IV x 1 may be used in lieu of hydrocortisone if an ACTH stimulation test is to be performed.

Recombinant activated protein C (Xigris)

Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699-709.

Activated protein C (APC) is a vitamin K dependant protein that appears to help maintain endothelial cell function. APC inhibits clotting factors Va and VIIIa, and inhibits the release/accelerates the removal of PAI-1 in order to limit coagulation and restore endogenous fibrinolysis. The PROWESS trial produced a 19.4% relative (6.1 % absolute) risk reduction in mortality for patients receiving APC in a randomized fashion versus placebo. Greater benefits were achieved in the most severely ill patients. There was a trend toward more significant bleeding in the APC group. APC is administered as a continuous infusion of 24 mcg/kg/hr for 96 hours.

Criteria for use of APC are as follows:

Please confirm the following (all must apply):

- The patient is at high risk of death.
- DNR status has been addressed, and all necessary life support measures will be used if needed. (i.e., patient is not DNR)
- Exclusive of sepsis, there is a reasonable expectation of survival.
- If infection is suspected, it is being treated appropriately.
- A Critical Care Attending Physician is officially seeing the patient.

The patient has three of four systemic inflammatory response syndrome (SIRS) criteria (see above in definitions section).

The patient has at least two of the following sepsis-induced organ failures below present for less than 48 hours (see following table for more details):

- MAP < 70 or SBP < 90 despite fluid resuscitation or need for vasopressor support
- Urine output < 0.5 ml/kg/hr despite adequate fluid resuscitation, >50% increase in SCr
- PaO₂ / FiO₂ ratio < 250, or need for mechanical ventilation
- Platelets < 80,000 or 50% decline over previous three days
- Unexplained metabolic acidosis pH ≤ 7.3 or BE ≥ -5 with lactate >1.5 times normal
- Liver enzyme elevations > 2x the upper limit of normal

Contraindications*:

- Active bleeding at any site
- Recent surgery or trauma with uncertain hemostasis
- Recent gastrointestinal bleeding (within 6 weeks)
- Closed head injury, intracranial or spinal surgery, or stroke within the past 3 months
- Intracranial mass lesion, AVM, or aneurysm
- Recent or planned epidural catheter

*-Risk/benefit should be assessed in patients with platelets<30K, INR>3, recent use of thrombolytics (3 days) or GP IIb/IIIa inhibitors (7 days), full dose anticoagulation (heparin, LMWH, ASA, warfarin), cirrhosis with portal hypertension, patients with known bleeding disorders, during pregnancy, recent surgery, and 1 or no organ failure.

Infusion will be initiated within 12 hours of order receipt once the above criteria are confirmed and required baseline laboratory values obtained.

Clinical and Lab Tools to Identify Organ Dysfunction

| Organ System | Clinical | Laboratory/Monitoring |
|------------------|--|--|
| Respiratory | Tachypnea Orthopnea Cyanosis Mechanical ventilation with or without PEEP | PaO ₂ < 70 mmHg SaO ₂ < 90% PaO ₂ /FIO ₂ ≤ 300 |
| Renal | Oliguria Anuria Renal replacement therapy | Elevated creatinine |
| Hepatic | Jaundice | Hyperbilirubinemia Increased AST, ALT Increased LDH Increased alkaline phosphatase Hypoalbuminemia Increased PT/INR |
| Cardiovascular | Tachycardia Hypotension Arrhythmia HR:MAP ratio Cardiac arrest Hemodynamic support | Altered CVP/PAOP |
| Hematological | Bleeding Thrombotic episodes | Thrombocytopenia Altered WBC Increased PT or apt Decreased protein C Increased fibrin split products, D-dimer |
| Gastrointestinal | GI bleeding or perforation Ileus Intestinal ischemia or infarction Acalculous cholecystitis Acute pancreatitis Intolerance of enteral nutrition | Decreased pHi |
| Neurological | Altered consciousness Impaired mentation Confusion Psychosis Delirium | Decreased GCS CAM-ICU |
| Endocrine | Weight loss | Hyperglycemia Decreased cortisol Hypertriglyceridemia Hypoalbuminemia |
| Immune | Pyrexia Nosocomial infection | Leukocytosis Abnormalities of T-cell subsets Impaired leukocyte function |

Balk RA. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. *Crit Care Clin* 2000;16:337-52.

Glycemic Control/Nutrition

Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-67

Following initial stabilization of patients with severe sepsis, maintain blood glucose <150 mg/dL using the existing Critical Care Insulin Infusion Protocol. Studies supporting the role of glycemic control have used continuous infusion of insulin and glucose. Glucose should be monitored hourly during the initiation of continuous insulin therapy, then on a regular basis once the blood glucose concentration has been stabilized.

A randomized, controlled study of 1548 patients, intensive glucose control (80-110 mg/dL) in the treatment arm produced significantly decreased morbidity and mortality. Additional benefit included reductions in bloodstream infections, acute renal failure requiring CRRT, and number of blood transfusions. It is unclear at this time whether the benefit is from maintaining normoglycemia or from the metabolic effects of insulin. Recommendations from the American College of Endocrinology state that all ICU patients achieve near normoglycemia (blood glucose < 110 mg/dL).

In patients with severe sepsis, a strategy of glycemic control should include a nutrition protocol with the preferential use of the enteral route. Caloric goals in critically ill patients should be in the range of 20-25 kcal/kg/day (total calories) in order to not exacerbate hyperglycemia.

Stress Ulcer Prophylaxis

Stress ulcer prophylaxis should be given to all patients with severe sepsis. H₂ receptor inhibitors (famotidine 20 mg q12h) are the preferred agents. Proton pump inhibitors (pantoprazole, lansoprazole) have not been assessed in a direct comparison with H₂ receptor antagonists and, therefore, their relative efficacy is unknown.

Risk factors for bleeding include mechanical ventilation for >48 hours, coagulopathy, head injury, organ transplant, burns, a past history of peptic ulcer disease, and organ dysfunction (particularly renal failure). Enteral nutrition decreases the risk.

Deep Vein Thrombosis (DVT) Prophylaxis

Severe sepsis patients should receive DVT prophylaxis with either low molecular weight heparin (enoxaparin 40 mg daily or 30 mg BID) or low dose unfractionated heparin (5000 units q8 hours). For those patients with a contraindication for heparin, a mechanical prophylaxis device (SCD, TED hose) is recommended. In very high-risk patients such as those with severe sepsis and history of DVT, a combination of pharmacologic and mechanical measures is recommended.

Transfusion Requirements in Critically Ill Patients

Once tissue hypoperfusion has been resolved and in the absence of extenuating circumstances, such as significant coronary artery disease, acute hemorrhage, or lactic acidosis, red blood cell transfusion should occur only when hemoglobin decreases to < 7.0 g/dL to a target hemoglobin of 7-9 mg/dL.

Recombinant Erythropoietin in Critically Ill Patients

Erythropoietin is not recommended as a specific treatment of anemia associated with severe sepsis, but may be used when septic patients have other accepted reasons for administration such as renal failure.

Platelet Administration

Platelets should be administered when counts are < 5,000/mm³ regardless of apparent bleeding. Platelet transfusion may be considered when counts are 5,000-30,000/mm³ and there is a significant risk of bleeding. Higher platelet counts may be required for surgery or invasive procedures.

Sedation and Analgesia

The continuous sedation protocol should be used when sedation of critically ill mechanically ventilated patients is required. The protocol includes the use of a sedation goal, measured by a standardized subjective sedation scale (MAAS), and orders for routine pain assessment and analgesic administration. Either intermittent bolus or continuous infusion sedation may be used. Daily interruption or lightening of the sedation with awakening and re-titration is recommended.

Disclaimer:

These guidelines were developed to assist health professionals at Advocate Christ Medical Center in providing care for the patient presenting with severe sepsis or septic shock. The guidelines are not intended to be a “standard of care” that typically connotes legal responsibilities related to the patient’s care. Similarly, the guidelines are not intended to be comprehensive documents concerning the topic, but rather are intended to provide a systematic, consistent approach to treatment. Deviations from the guidelines may be appropriate and necessary in patient specific situations.

While the guidelines reflect the medical literature at the time of distribution, periodic revisions will be necessary as new developments occur. Therefore, the clinician should not rely solely on these guidelines for decisions regarding patient care. The clinician is advised to confirm the doses cited in these guidelines with other available sources.