Management of Severe Sepsis and Septic Shock

The approach below is based largely on the Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis (Crit Care Med 2004;32:858-71) and guidelines for early goal-directed therapy (NEJM 2001), but contains many differences as practiced by the LSUHSC Critical Care Service. Note, however, patient variability mandates that physician judgment be used when employing these guidelines.

Recognition of Severe Sepsis

Systemic Inflammatory Response Syndrome (SIRS) is a systemic syndrome recognized by the presence of at least 3 of the following clinical criteria in the appropriate setting:

- Tachycardia
- Tachypnea (or requirement for mechanical ventilation)
- Hyperthermia or hypothermia
- Leukocytosis or leukopenia

Biochemical markers of inflammation include C-reactive protein, which correlates with elevations in interleukin-6 as a marker of inflammation, and D-dimer, which correlated with activation of coagulation in sepsis and inflammation.

Sepsis is identified when SIRS is due to known or suspected infection. 30-35% of patients with sepsis are culture negative.

Severe sepsis is identified when sepsis is associated with one or more organ failures (respiratory, cardiovascular, renal, coagulation, hepatic, CNS). Common sites of infection in severe sepsis include pulmonary, abdominal, urinary tract, and bacteremias, although any site can lead to severe sepsis. If hypotension (SBP < 90) is present and unresponsive to fluid loading, the term septic shock is used.

Monitoring of Severe Sepsis

Patient monitoring in severe sepsis is implemented during resuscitation, and should not delay initiation of resuscitation. However, hemodynamic monitoring provides for appropriate goals for directed therapy, and should be completed as soon as feasible.

Hemodynamic monitoring includes right atrial pressure monitoring (with SraO2) at a minimum, and should include pulmonary artery monitoring (with EDVI, CI and SvO2) for septic shock. These measurements should be continuous.

Regional perfusion monitoring includes sublingual tonometry and/or gastric tonometry every 8 hours initially.

Metabolic monitoring includes serial measurements of serum lactate, glucose, electrolytes, ionized calcium every 8 hours initially. C-reactive protein is measured daily.

Coagulation monitoring includes INR, aPTT, D-dimer, and fibrinogen every 8 hours initially.

Fluid monitoring includes total protein (to estimate plasma oncotic pressure) and albumin at least daily.
**Initial Resuscitation**

Initial resuscitation of patients with septic shock or elevated serum lactate must be rapid, or mortality can increase by 30%. The following should be achieved within 4 hours of the onset of septic shock:

**Fluid resuscitation** is initiated to achieve a right atrial pressure of 8 to 12 mm Hg (if a right atrial catheter is in place) or an end-diastolic volume index of 120-140 ml/M² (if a pulmonary artery catheter is in place).

**Vasoactive drugs** are then used to achieve a mean arterial pressure of 65 to 70 mm Hg.

**Inotropic agents** are used to achieve a physiologically appropriate cardiac output (about 1.5 times normal) if myocardial function is depressed, and/or a right atrial or mixed venous oxygen saturation of at least 70%.

**Urine output** should be at least 0.5 and preferably at least 1 ml/kg/hr.

**Fluid Therapy**

Fluid challenges in patients with perfusion deficits are given rapidly (1000 ml over 30 min for crystalloid, or 500 ml over 30 min for colloid). Initial fluid choice is **balanced isotonic crystalloid** (e.g. Normosol or Plasmalyte) up to a limit of 2 to 3 liters. If the response to this initial fluid loading is insufficient or transient, then **colloid** (e.g. 5% albumin) is used to complete the goal. Patients with marked hypo-oncotic states (total protein < 5.2) should receive concentrated albumin, but only after volume expansion is complete or near complete.

**Antibiotic Therapy**

Antibiotics are initiated within 1 hour of recognition of severe sepsis. **Monotherapy** with carbapenems is usually sufficient in non-neutropenic patients, with consideration for vancomycin for resistant Gram positive organisms. Neutropenic patients should receive **combination therapy**. Antibiotic therapy should consider the incidence and susceptibility patterns within the hospital.

Antibiotic therapy is reassessed upon determination culture results and sensitivities within 48 to 72 hours. Taper therapy as much as possible to the causative organism. Stop antimicrobials within 72 hours if no infectious source is found.

**Source Control**

Evaluate the patient for an identifiable focus of infection, and initiate source control as soon as identified. Abscess drainage can be performed percutaneously in most instances of an accessible and localized process. Inadequate drainage or non-localized sources should undergo consideration of surgical drainage. Devitalized tissue should be debrided.

In most instances, sepsis associated with vascular devices requires removal of the device, and replacement at a separate site. Tunneled devices without external drainage may receive consideration for sterilization via antibiotic therapy. Suspected but unconfirmed infection of vascular devices may be exchanged over a guidewire and cultured. A positive semi-quantitative culture demands replacement at a new site.

**Vasopressor Therapy**

Vasopressor therapy is indicated when the following conditions are met:
Hypotension (MAP < 60-65)
Completed fluid resuscitation (target RAP/EDVI reached)
Normal or elevated cardiac index (e.g. low SVRI), or lack of peripheral vasoconstriction on physical exam

Do not use vasopressors in vasoconstrictive or low cardiac output states (without inotropes or without monitoring), or in volume depleted patients.

The vasopressor of choice is norepinephrine. Initial dose is 0.1-0.2 mcg/kg/min, up to 1 mcg/kg/min. Doses above 1 mcg/kg/min should initiate re-evaluation for contributing conditions. Do not exceed 5 mcg/kg/min. Do not use epinephrine or neosynephrine unless concomitant inotropes are used. Dopamine is generally not considered, and low-dose dopamine is not used.

The use of vasopressors will raise pressure, but may depress cardiac output. Thus, hemodynamic monitoring should be used if moderate to higher doses of norepinephrine are required. The need for further fluid administration or inotropic agents can be identified.

Inotropic Therapy

Dobutamine is used for patients with low cardiac index (or a decrease in cardiac index with vasopressors) following targeted fluid resuscitation. Dobutamine is titrated to achieve a normal to physiologic cardiac output (up to 1.5 times normal, e.g. 4.5 L/min). Do not titrate to supraphysiologic cardiac index.

Endocrinologic Therapy

Consider hydrocortisone 50mg Q6H for 7 to 10 days in patients with hyperdynamic vasopressor-dependent shock despite adequate fluid resuscitation, which may help improve hemodynamic response to catecholamines. Consider fludrocortisone 0.1 mg enterally daily.

Patients with low-dose vasopressor requirements may undergo an ACTH stimulation test, and steroids withheld if an adequate response is noted.

Consider vasopressin 0.0005 to 0.001 u/kg/min to patients with vasopressor dependence as a physiologic replacement for vasopressin deficiency in severe sepsis. Do not titrate to blood pressure.

Recombinant Activated Protein C (rhAPC)

Patients with septic shock requiring vasopressors or patients with 3 or more sepsis-related organ failures should receive rhAPC if no absolute contraindications exist. Patients with relative contraindications should have risk/benefit evaluated before proceeding. Patients who do not meet the above requirements, but their APACHE II score is > 24, should receive therapy.

Extracorporeal Support

Theoretically, blood “purification” removes numerous circulating cytokines and other substances thought to mediate sepsis. The systems currently in are continuous renal replacement therapies (CRRT), mainly high-volume hemofiltration, and plasma therapies.

Therapeutic plasma exchange is initiated in severe sepsis using the following criteria:
Severe vasopressor-dependent septic shock
Elevated lactate level (> 5 mM/L) that persists 12-24 hours despite therapy

Exchanges are provided daily up to 3 - 4 days. Exchanges are single plasma volume, calculated according to wt(kg)*70*(1-hct), and should be at least 35-40 ml/kg. Replacement is usually half albumin and half FFP, with the albumin given for the first part of the exchange, followed by the FFP. In severe coagulopathy, FFP alone may be used.

**Hemofiltration** utilizes convective clearance to move fluid across a dialysate membrane with relatively large pore size. This movement of fluid across the membranes taking with it small to large molecules. This system utilizes the adjustment of convective movement to determine the degree of clearance and the size of solutes cleared. Continuous renal replacement therapy is used when one or more of the following are present:

- Acute renal failure of sepsis
- Inability to achieve or maintain an appropriate extracellular volume using diuretics or fluid restriction. Therapy is started before excess accumulation occurs.
- Severe, vasopressor-dependent septic shock. High-volume hemofiltration is initiated following therapeutic plasma exchange.

The hemofiltration dose should be at least 35-40 ml/kg/hour. Replacement is with bicarbonate-based solutions (Normocarb), in which K and Ca are added. If dialysis is employed in combination, bicarbonate-based solutions are used (Prismasate).

**Blood Product Administration**

**Red blood cells** are limited to the following circumstances:

- Volume- and vasopressor/inotrope-resuscitated patients with an SvO2 or SraO2 < 65% (to achieve a target SvO2 > 65%). In the absence of these measurements, evaluate for excessive cardiovascular work and the presence of lactic acidosis).
- Coronary artery disease with recent angina or coronary syndrome (to achieve a target of 12 g/dl).
- Acute ongoing hemorrhage in the face of anemia (hgb < 9).

Administer **erythropoietin** 600 u/kg SQ weekly (40,000 units for typical adults) for hgb < 11. Administer **FFP** only for clinical bleeding or need to undergo an invasive procedure. Administer **platelets** for counts < 10,000, or < 30,000 and there is risk of bleeding. For invasive procedures (surgery or access of a non-compressible vessel), a platelet count > 50,000 is usually desirable.

**Metabolic and Nutritional Therapy**

Maintain **blood glucose** 80 to 120 through the use of appropriate caloric support and **insulin** infusion following initial stabilization.

Do not administer sodium bicarbonate for metabolic (anion-gap) acidosis, such as lactic acidosis if the pH is > 7.15. For a lower pH, consider a trial of 50 to 100 mEq NaHCO3 by slow infusion, with evaluation for improvement in hemodynamics. For non-anion gap acidosis (hyperchloremic), consider correction with **sodium bicarbonate** to achieve a base excess > -
5 mEq/L, and avoidance of hyperchloremic intravenous solutions.

Initiate enteral nutrition following stabilization. If gastric tonometry is used, delay nutritional support until significant intracellular acidosis is improved. Continuous gastric or post-pyloric feeding is preferred, with appropriate precautions for over distension, including the use of promotility agents (erythromycin) if needed. Parenteral nutrition should be avoided unless there is an absolute contraindication to enteral feeding (e.g. mechanical obstruction).

Do not replace calcium unless ionized calcium is < 0.9 mMol/L. Replace with calcium chloride to achieve a level in the range 0.9 to 1.1.

**Sedation**

Target sedation to predetermined sedation score. Use minimal sedation necessary. Combination regimens may be better. Benzodiazepines in low to moderate doses in intermittent dosing is useful. Low-dose narcotics are also helpful. If these regimens are insufficient, consider addition of dexmetetomidine.

Agitation requires treatment with antipsychotic agents (Geodon or Haldol). Titration to higher doses of benzodiazepines or narcotics is not recommended, and can compound the agitation/delirium.

In long-term sedation, transition to shorter acting agents is recommended prior to attempts at extubation.

**Stress Ulcer Prophylaxis**

Provide stress ulcer prophylaxis in all patients. Use proton pump inhibitors enterally if absorption is good, otherwise intravenously. H2 antagonists are second line choice.

**Deep Venous Thrombosis Prophylaxis**

Provide DVT prophylaxis with low-molecular weight heparin or low-dose unfractionated heparin in the absence of significant bleeding risk. Combine mechanical intermittent compression with pharmacologic prophylaxis in all but low-risk patients.