The STOP Sepsis Bundle Toolkit

Strategies to Timely Obviate the Progression of Sepsis

Department of Emergency Medicine
Division of Pulmonary and Critical Care Medicine
Department of Anesthesiology and Surgical Intensive Care
Department of Quality Resource Management
Loma Linda University Medical Center

for the STOP Sepsis Working Group

Version 9.3
September 2006

www.llu.edu/llumc/emergency/patientcare

Table of Contents

INTRODUCTION

What is a bundle?

A bundle is a group of interventions related to a disease that when performed together result in better outcome than when individually done. It increases the use of evidence-based science in clinical practice and provides a mechanism to enforce teamwork. A bundle is not guidelines, but a method to implement the guidelines. In creating a bundle, several rules have to be met: 1) the components of the bundle are solid and accepted into clinical practice, 2) the components must be completed in the same space and time interval, 3) the completion of each component can be answered by a "Yes" or "No", 4) the delivery of the whole bundle can be answered by a "Yes" or "No", and 5) the function of the bundle or the disease process it targets needs to be frequently occurring[1].

What is the STOP Sepsis Bundle?

The STOP Sepsis Bundle is an implementation of an early sepsis treatment model specific to the emergency department at Loma Linda University. It focuses on the first 6 hours of care after severe sepsis or septic shock is recognized. While it was designed for the emergency department setting, the bundle can be applied in any location where care is being given to patients with severe sepsis or septic shock; e.g. the medical ward, the recovery room, or the intensive care unit. It has additionally evolved to incorporate care in the intensive care unit, beyond the first 6 hours of disease presentation.

What is the evidence and support for the STOP Sepsis Bundle?

The Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock[2] serve as framework for the bundle. The advances in therapy behind the bundle are early goal-directed therapy (EGDT)[3], corticosteroids[4], and activated protein C[5]. Most important in the first 6 hours of therapy for severe sepsis or septic shock is the implementation of EGDT as originally presented by Rivers et al[3]. The STOP Sepsis Bundle was not conceived to replace or modify EGDT, but is presented as an adaptation of the original EGDT research, and with the hope of making EGDT as widely implemented as possible. This suggested bundle is a practical application of the sepsis bundles provided by the Institute for Health Care Improvement[1] to the clinical environment at our institution. It also takes into consideration quality indicators being considered as sepsis core measures. Completion of the entire 6-hour bundle at our institution was associated with an 18.7% absolute decreased in mortality.

Disclaimer

The content of this toolkit is a clinical template and will change with time. The clinician should use judgment for individual patient encounters. We would appreciate any feedback or suggestions to improve on the quality of the toolkit.

H. Bryant Nguyen, MD, MS
hbnguyen@llu.edu
for the STOP Sepsis Working Group

1. Sepsis Bundle. http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis (April 2006).
2. Dellinger RP, Carlet JM, Masur H, Gerlach H, al. e. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004; 32:858-72.
3. 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; 345:1368-77.
4. 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.
5. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344:699-709.

The STOP Sepsis Bundle

Loma Linda University

Two or more of the following:
1) Temp > 38.3C(100.9F) or < 36.0C(96.8F)
2) Heart Rate > 90
3) Resp Rate > 20 or $PaCO_2$ < 32 mmHg
4) WBC > 12K, < 4K or > 10% Bands

Suspected Infection — NO → Re-Assess; YES → Obtain Appropriate Cultures; Check Lactate

NO → Re-Assess

SBP < 90 after Bolus — NO → Lactate ≥ 4 mmol/L or Multi-Organ Dysfunction — NO → Lactate > 2 mmol/L or Organ Dysfunction — NO → Sepsis → Antibiotics & IVF Re-Assess

YES → Septic Shock

YES → Severe Sepsis High Risk

YES → Severe Sepsis Low Risk → Antibiotics & IVF Re-check Lactate

Early Goal-Directed Therapy

Initiate Sepsis Orders → Central Line Placement for $CVP/ScvO_2$ Monitoring

Initiate Broad Spectrum Antibiotics → Supplemental Oxygen OR Mechanical Ventilation with Lung Protective Strategies

CVP
- CVP < 8 → 1. NS 500 mL Bolus until CVP 8-12, then Continue at 150 mL/hr; 2. Consider Adding Colloid if CVP < 4
- CVP > 15 and SBP > 160 (MAP > 110) → Nitroglycerin 10-60 mcg/min until CVP < 12 or SBP < 140 (MAP < 90)
- CVP 8-12

SBP/MAP
- SBP < 90 (MAP < 65) → 1. Arterial Line Placement (preferred); 2. Norepinephrine 2-20 mcg/min; 3. Dopamine 5-20 mcg/kg/min; 4. Phenylephrine 40-200 mcg/min (if HR > 120); 5. Vasopressin 0.01-0.04 U/min (if on another Vasopressor); 6. Epinephrine 2-10 mcg/min; 7. Dexamethasone 2 mg IV q 6 hrs OR Hydrocortisone 50 mg IV q 6 hrs after CST (if on Vasopressor or Adrenal Insufficiency)
- SBP > 160 (MAP > 110) → 1. Nitroglycerin 10-60 mcg/min; 2. Hydralazine 10-40 mg IV
- SBP 90-140 (MAP 65-90)

$ScvO_2$
- $ScvO_2$ < 70 → **Hgb**
  - Hgb < 10 → Transfuse PRBC
  - Hgb ≥ 10 → 1. Arterial Line Placement (preferred); 2. Dobutamine 2.5-20 mcg/kg/min (if HR < 100 and SBP > 100); 3. Dopamine 5-10 mcg/kg/min
- $ScvO_2$ ≥ 70

Intubation and Mechanical Ventilation with Lung Protective Strategies

Heart Rate
- HR > 120 → Consider Digoxin 0.25 –0.5 mg IV
- HR ≤ 120

Goals Achieved
- Lactate > 2 → Re-check Lactate
- YES

APACHE II ≥ 25
- YES → Consider Drotrecogin alfa activated 24 mcg/kg/hr x 96 hr
- NO → Supplemental Oxygen OR Mechanical Ventilation with Lung Protective Strategies

6-Hour STOP Sepsis Bundle Goals for Severe Sepsis or Septic Shock

- Initiate $CVP/ScvO_2$ Monitoring within 2 hours
- Give Broad Spectrum Antibiotics within 4 hours
- Achieve Hemodynamic Goals within 6 hours
  - CVP ≥ 8 mmHg
  - MAP ≥ 65 mmHg / SBP ≥ 90 mmHg
  - $ScvO_2$ ≥ 70%
- Monitor for Decreasing Lactate
- Give Steroid if on Vasopressor or suspect Adrenal Insufficiency

Strategies to Obviate the Progression of Sepsis
Loma Linda University

Sepsis has recently received renewed interest, beginning with a revised international definition. Therapies that significantly decrease sepsis mortality include: early and appropriate antibiotics, early goal-directed therapy, corticosteroid, recombinant human activated protein C, lung protective strategies, and tight glucose control.

These advances have resulted in a management guidelines from the international Surviving Sepsis Campaign. In implementing the new guidelines, the Institute for Healthcare Improvement recommends the development of sepsis change bundles. These bundles include a group of interventions that must be given to patients with severe sepsis as they present and are admitted to the hospital. These efforts are endorsed by 11 international medical societies with the goal of decreasing sepsis mortality by 25 percent.

Levy MM, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International sepsis definitions conference. Crit Care Med 2003;31:1250-1256.

Dellinger RP, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858-73.

24-Hour STOP Sepsis Bundle Goals for Severe Sepsis or Septic Shock

- **Initiate steroids for catecholamine resistance/adrenal insufficiency**
- **Initiate drotrecogin alfa activated if APACHE II ≥25**
- **Maintain blood glucose control < 150 mg/dL**
- **Achieve plateau pressure ≤30 cmH_20 if mech ventilation**
- **Reassess antimicrobial therapy**
- **Maintain sedation/analgesia for ventilator synchrony & comfort**
- **Initiate stress ulcer and DVT prophylaxis**
- **Nutrition within 24 hours of admission**
- **Titrate off vasopressors while maintaining:**
  - **CVP ≥ 8 mmHg**
  - **MAP ≥ 65 mmHg / SBP ≥ 90 mmHg**
  - **SvO_2/$ScvO_2$ ≥ 70% on FiO_2 ≤ 0.5**

Continue 6-hour goals while achieving 24-hour goals

Adrenal Insufficiency
- On pressor → **Start/Continue dexamethasone** → **ACTH Stimulation**
  - Δ Cortisol > 9 mcg/dL → **Discontinue Steroid Therapy**
  - Δ Cortisol ≤ 9 mcg/dl → **Change dexamethasone to hydrocortisone and fludrocortisone, continue for 7 days**
- Off pressor → **No steroid or discontinue steroid**

Activated Protein C
- APACHE II ≥ 25 → **Drotrecogin alfa activated 24 mcg/kg/hr x 96 hrs**
  Discontinue if serious bleeding (>2 Units PRBC in 48 hrs)
- APACHE II < 25 → **Reassess q 24 hrs**

Blood Glucose Control
- Glucose ≥ 150 mg/dL → **ICU Insulin Infusion Guidelines to target glucose < 150 mg/dL**

pPlat ≤ 30 cm H_2O → **Refer to Lung Protective Strategy protocol**
Decrease tidal volume to 4-8 mL/kg
Maintain pH ≥7.20

Antimicrobial Therapy → **Reassess antimicrobial therapy q 12 hrs based on culture & sensitivity results**

Sedation/ Analgesia → **Titrate to Modified Ramsey Sedation Scale & Pain Scale**

Stress Ulcer/ DVT Prophylaxis
- → **H_2 Blocker / PPI**
- → **Heparin SQ / SCD**

Nutrition → **Nutrition consult within 24 hrs of admission**

24 hr goals achieved?
- Yes → **Attempt to wean off ventilator**
  Titrate vasopressor
  PT/OT
  Follow-up on cultures and imaging studies
- No → **After 96 hours, reassess patient for continued aggressive support**

Diagnostic criteria for sepsis

Infection, documented or suspected, and some of the following:

General variables
- Fever (core temperature >38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90/min or
  - >2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance
  - (>20 mL/kg over 24 hrs)
- Hyperglycemia
  - plasma glucose >120 mg/dL
  - in the absence of diabetes

Inflammatory variables
- Leukocytosis (WBC count >12,000/μL)
- Leukopenia (WBC count <4000/μL)
- Normal WBC count with >10% bands
- Plasma C-reactive protein >2 SD above normal
- Plasma procalcitonin >2 SD above normal

Hemodynamic variables
- Arterial hypotension
  - SBP <90 mm Hg
  - MAP <70 mm Hg or
  - SBP decrease >40 mm Hg in adults
- $ScvO_2$/SvO_2 >85% or <65%
- Cardiac index > 3.5 L/min/m^2

Organ dysfunction variables
- Arterial hypoxemia (PaO_2/FIO_2 <300)
- Acute oliguria (urine output <0.5 mL/kg/hr)
- Creatinine increase >0.5 mg/dL
- Coagulation abnl (INR >1.5 or aPTT >60 secs)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000/μL)
- Hyperbilirubinemia (total bilirubin > 4 mg/dL)

Tissue perfusion variables
- Hyperlactatemia (>2 mmol/L)
- Decreased capillary refill or mottling

A CLINICAL OUTLINE FOR THE CARE OF PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK

for the STOP Sepsis Bundle - Strategies to Timely Obviate the Progression of Sepsis

Version 9.3

SEPSIS DEFINITIONS:

Note: These definitions are used by the STOP Sepsis Working Group and are adaptation of the formal definitions. Refer to bibliography for formal definitions.[1, 2]

Infection: A microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms. An infection can be recognized as:

1. Presence of white cells in a normally sterile body fluid **OR**
2. Positive culture (urine, blood, sputum) **OR**
3. Perforated viscous **OR**
4. Radiographic evidence of pneumonia in association with the production of purulent sputum

Signs of Inflammation: A systemic response to inflammation and is manifested by two or more of the following:

1. Temperature > 38.3°C/100.9F or < 36°C/96.8F
2. Heart rate > 90 beats/min (sinus rhythm)
3. Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg
4. WBC > 12,000 cells/mm^3, < 4000 cells/mm^3, or > 10% bands

Sepsis: The systemic response to an infection, and can be recognized by the presence of suspected or confirmed infection AND the systemic inflammatory response.

Severe Sepsis: Sepsis associated with more than one acute organ dysfunction or hypoperfusion. Hypoperfusion may include, but are not limited to lactic acidosis (or lactate > 2 mmol/L), oliguria, or an acute alteration in mental status. Organ dysfunction can be defined as: respiratory failure, acute renal failure, acute liver failure, coagulopathy, or thrombocytopenia. Laboratories that will suggest organ dysfunction include:

1. PaO_2(mmHg)/FiO_2 < 300
2. Creatinine > 2.0 OR Creatinine Increase > 0.5 mg/dL
3. INR > 1.5
4. PTT > 60 s
5. Platelets < 100,000/uL
6. Total bilirubin > 4 mg/dL

Septic Shock: Sepsis with hypotension, despite adequate fluid resuscitation of 20 ml/kg crystalloid, 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 who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured. *Cryptic* septic shock is sepsis with severe lactic acidosis (lactate ≥ 4 mmol/L) irrespective of blood pressure, and is considered to be equivalent to traditional septic shock (sepsis with hypotension).

Hypotension: A systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure < 65 mmHg or a reduction in SBP of > 40 mmHg from baseline in the absence of other causes for hypotension.

PATIENTS WHO WILL BENEFIT FROM EARLY GOAL-DIRECTED THERAPY[3]:

1. Two or more signs of inflammation
   AND
2. Suspected or confirmed infection
   AND
3. Systolic blood pressure < 90 mmHg after a 20 ml/kg fluid bolus OR
   Lactate ≥ 4 mmol/L

Exclusion criteria (used in the trial):[3] age < 18 yrs, pregnancy, stroke, acute coronary syndrome, acute pulmonary edema, status asthmaticus, active GI hemorrhage, seizure, drug overdose, burn, trauma, emergent surgery, uncured cancer, immunosuppression, do-not-resuscitate order.

LABORATORY DATA OBTAINED WITHIN ONE HOUR AFTER PHYSICIAN EVALUATION:

1. Baseline
   a. CBC with differential, comprehensive metabolic panel, PT/PTT, D-Dimer, Troponin I, urine analysis, type & screen
   b. CXR, ECG
   c. Urine culture, blood culture, sputum culture and sensitivities
2. Baseline and every 3 hours
   a. $ScvO_2$ (central venous blood gas if using intermittent measurements)
   b. Lactate (grey-top tube on ice)

HEMODYNAMIC MONITORING WITHIN 2 HOURS AFTER PHYSICIAN EVALUATION:

1. Cardiac monitoring
2. Pulse oximetry
3. Central venous pressure (CVP) monitoring with intermittent $ScvO_2$ measurements[4]
   a. Central venous catheterization via internal jugular or subclavian vein method
4. OR (Preferred) Continuous central venous oxygen saturation ($ScvO_2$) monitoring[5]
   a. $ScvO_2$ catheterization via internal jugular or subclavian vein method
5. Intra-arterial catheterization (preferred)

TREATMENT PROTOCOL (TO BE COMPLETED WITHIN 6 HOURS AND UNTIL ICU ADMISSION):[3, 4]

1. Initiate mechanical ventilation when indicated
   a. Maintain low tidal volume to achieve peak inspiratory plateau pressure ≤ 30 cm H_2O
2. Give appropriate antimicrobial agent(s) within 4 hours
3. Central venous pressure (CVP) - Preload
   a. CVP < 8 mmHg
      i. 500 mL bolus of normal saline every 30 minutes until CVP reaches 8-12 mmHg, then continue at 150 mL/hr
      ii. Consider lactate ringer instead of normal saline if hyperchloremic acidosis is present
      iii. Consider adding colloid to crystalloid if CVP < 4 mmHg[6]
   b. CVP > 15 mmHg and MAP > 110 (or SBP > 160) mmHg
      i. Initiate nitroglycerin 10-60 mcg/min until CVP < 12 mmHg or MAP < 90 (or SBP < 140) mmHg[7, 8]
4. Mean arterial pressure (MAP) - Afterload
   a. MAP < 65 (or SBP < 90) mmHg after 2 liters of crystalloid
      i. Initiate vasopressors in the order below until MAP > 65 (or SBP > 90) mmHg[4, 9]
         1. Norepinephrine 2-20 mcg/min (first line therapy in severe sepsis)

2. Dopamine 5-20 mcg/kg/min
3. Phenylephrine 40-200 mcg/min (preferred if HR > 120 bpm)
4. Vasopressin 0.01-0.04 U/min[10-12] (if on another vasopressor)
5. Epinephrine 2-10 mcg/min (may increase lactate)

ii. Consider adrenal insufficiency if vasopressor dependent[13]
1. Perform cosyntropin stimulation test (CST)
a. Measure baseline cortisol level
b. Administer ACTH (Cosyntropin/Cortrosyn) 250 mcg IV
c. Measure cortisol level at 30 min and 60 min after given ACTH
i. Change in cortisol $\leq$ 9 ug/dl suggests relative adrenal insufficiency[14]
2. Give Hydrocortisone 50 mg IV (OR dexamethasone 2 mg IV if not performing CST) q 6 hrs
3. Give Fludrocortisone 50 mcg PQ qd

b. MAP > 110 (or SBP > 160) mmHg[7, 8]
i. Initiate nitroglycerin 10-60 mcg/min until MAP < 90 (or SBP < 140) mmHg
ii. Consider hydralazine 10-40 mg IV

5. Central venous oxygen saturation ($ScvO_2$)[3, 5] – Contractility and oxygen content
a. $ScvO_2$ < 70% after above therapy and Hb < 10 g/dL
i. Transfuse packed red blood cells
b. $ScvO_2$ < 70% after above therapy and Hb $\geq$ 10 g/dL
i. Dobutamine 2.5–20 mcg/kg/min titrated until $ScvO_2 \geq$ 70% OR MAP < 70 (or SBP < 100) mmHg OR heart rate > 100 bpm
1. Caution with starting Dobutamine when MAP < 70 (or SBP < 100 mmHg) OR heart rate > 100 bpm

ii. Dopamine 5-10 mcg/kg/min
c. Consider intubation and mechanical ventilation to decrease respiratory muscle oxygen consumption
i. Maintain low tidal volume to achieve peak inspiratory plateau pressure $\leq$ 30 cm H_2O

6. Heart rate:
a. Heart rate > 120 bpm
i. Consider digoxin 0.25-0.5 mg IV (possible benefit as inotrope and in controlling heart rate in sepsis with underlying cardiomyopathy)[15]

7. Obtain intensive care consult for admission after above goals are met
8. Go back to each step above until patient is transferred to intensive care unit

THERAPEUTIC GOALS TO BE ACHIEVED <u>WITHIN 24 HOURS</u>, AND MAINTAINED AFTER ICU ADMISSION[4, 9, 16-18]:

1. Mechanical ventilation if indicated, with low tidal volume to maintain peak inspiratory plateau pressure $\leq$ 30 cm H_2O
a. Decreases absolute mortality by 9 percent[19]
2. Hemodynamic monitoring established (within 2 hours)
3. Appropriate broad-spectrum antibiotics administered
a. Given within 4 hours decreases length of stay by 2 days, and decreases absolute mortality by 24 percent[20-23]
b. Every hour delay in antibiotic increases the odds-ratio for mortality and decreases the chance for survival by 7.6%[24]
4. Early goal directed therapy goals
a. Achieved within 6 hours decreases absolute mortality by 16 percent[3]
b. Central venous pressure 8-12 mmHg
b. Mean arterial pressure 65 to 90 OR systolic blood pressure 90 to 140 mmHg
c. Central venous oxygen saturation ($ScvO_2$) $\geq$ 70%

    d. Urine output > 0.5 ml/kg/hr
6. Decreased lactic acidosis
    a. Lactate ≥ 4 mmol/L in non-hypotensive patients has 96% specificity of predicting mortality[25]
    b. Lactate ≥ 4 mmol/L in the ED was associated with 28.4% in-hospital mortality, and 22.4% mortality within 3 days[26]
    c. Lactate normalized to < 2 mmol/L within 24 hours decreases absolute mortality by 25 percent[27, 28]
    d. Lactate clearance (or decrease) of ≥ 10% after 6 hours of resuscitation in the emergency department is associated with improved outcome[29]
7. Administer steroid if on chronic steroid, vasopressor dependent, or suspect adrenal insufficiency
    a. Decreases absolute mortality by 10 percent[13]
8. Consider drotrecogin alfa activated/Xigris (recombinant human activated protein C)
    a. Decreases absolute mortality by 13 percent in patients with APACHE II score ≥ 25[30]
    b. ENHANCE Study suggests that Xigris given on day 1 compared to day 2 (or after) is associated with a lower mortality[31]
    c. No benefit and FDA warning for use in patients with single organ dysfunction and recent surgery within 30 days (ADDRESS Trial)[32]
9. Consider insulin if required to maintain glucose 80-110 mg/dl
    a. Decreases absolute mortality by 3.4 percent at 12 months in surgical intensive care patients[33]
    b. Decreases morbidity (renal failure, mechanical ventilation, length of stay) but not mortality in medical intensive care patients[34]

REFERENCES:

1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20:864-74.
2. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003; 29:530-8.
3. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345:1368-77.
4. Hollenberg SM, Ahrens TS, Annane D, Astiz ME, Chalfin DB, Dasta JF, Heard SO, Martin C, Napolitano LM, Susla GM, Totaro R, Vincent JL, Zanotti-Cavazzoni S. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med 2004; 32:1928-48.
5. Rivers EP, Ander DS, Powell D. Central venous oxygen saturation monitoring in the critically ill patient. Curr Opin Crit Care 2001; 7:204-11.
6. Groeneveld AB. Albumin and artificial colloids in fluid management: where does the clinical evidence of their utility stand? Crit Care 2000; 4 Suppl 2:S16-20.
7. Cerra FB, Hassett J, Siegel JH. Vasodilator therapy in clinical sepsis with low output syndrome. J Surg Res 1978; 25:180-3.
8. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF. Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 2002; 360:1395-6.
9. Dellinger RP. Cardiovascular management of septic shock. Crit Care Med 2003; 31:946-55.
10. Holmes CL, Patel BM, Russell JA, Walley KR. Physiology of vasopressin relevant to management of septic shock. Chest 2001; 120:989-1002.
11. Klinzing S, Simon M, Reinhart K, Bredle DL, Meier-Hellmann A. High-dose vasopressin is not superior to norepinephrine in septic shock. Crit Care Med 2003; 31:2646-50.
12. Landry DW, Levin HR, Gallant EM, Ashton RC, Jr., Seo S, D'Alessandro D, Oz MC, Oliver JA. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997; 95:1122-5.

13. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. Jama 2002; 288:862-71.
14. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. Jama 2000; 283:1038-45.
15. Nasraway SA, Rackow EC, Astiz ME, Karras G, Weil MH. Inotropic response to digoxin and dopamine in patients with severe sepsis, cardiac failure, and systemic hypoperfusion. Chest 1989; 95:612-5.
16. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003; 348:138-50.
17. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004; 32:858-73.
18. Nguyen HB, Rivers EP, Abrahamian FM, Moran GJ, Abraham E, Trzeciak S, Huang DT, Osborn T, Stevens D, Talan DA. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. Ann Emerg Med 2006; 48:28-54.
19. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301-8.
20. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999; 115:462-74.
21. Leone M, Bourgoin A, Cambon S, Dubuc M, Albanese J, Martin C. Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. Crit Care Med 2003; 31:462-7.
22. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003; 31:2742-51.
23. Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. Arch Intern Med 2002; 162:682-8.
24. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006; 34:1589-96.
25. Aduen J, Bernstein WK, Khastgir T, Miller J, Kerzner R, Bhatiani A, Lustgarten J, Bassin AS, Davison L, Chernow B. The use and clinical importance of a substrate-specific electrode for rapid determination of blood lactate concentrations. JAMA 1994; 272:1678-85.
26. Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, Weiss JW. Serum lactate as a predictor of mortality in emergency department patients with infection. Ann Emerg Med 2005; 45:524-8.
27. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. J Trauma 1993; 35:584-8; discussion 588-9.
28. Vincent JL, Dufaye P, Berre J, Leeman M, Degaute JP, Kahn RJ. Serial lactate determinations during circulatory shock. Crit Care Med 1983; 11:449-51.
29. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004; 32:1637-42.
30. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ, Jr. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344:699-709.
31. Vincent JL, Bernard GR, Beale R, Doig C, Putensen C, Dhainaut JF, Artigas A, Fumagalli R, Macias W, Wright T, Wong K, Sundin DP, Turlo MA, Janes J. Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: Further evidence for survival and safety and implications for early treatment. Crit Care Med 2005; 33:2266-2277.

32. Abraham E, Laterre PF, Garg R, Levy H, Talwar D, Trzaskoma BL, Francois B, Guy JS, Bruckmann M, Rea-Neto A, Rossaint R, Perrotin D, Sablotzki A, Arkins N, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med 2005; 353:1332-41.
33. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001; 345:1359-67.
34. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. N Engl J Med 2006; 354:449-61.

Clinical Pathway (v9.3)

Case Type: **Severe Sepsis or Septic Shock** Target ICU LOS: 7 days

DESIRED OUTCOME	1. Early identification of severe sepsis and septic shock 2. Early hemodynamic monitoring 3. Early intervention of severe sepsis and septic shock 4. Prevent the progression of multi organ failure and increase chances of survival
DAY	**0-6 hours**
LOCATION	**ED/ PACU/ ICU**
Assessments	Primary Assessment (nurse Triage): Assign treatment category based on assessment, vital signs every hour Secondary Assessment: vital signs every hour, pain control, physician evaluation, determine sepsis category (sepsis, severe sepsis, or septic shock)
Tests	CBC w/ diff, comprehensive metabolic panel, PT, PTT, D-Dimer, Troponin I, urine analysis, Lactate, type and screen CXR, ECG Appropriate cultures and sensitivities prior to antibiotics
Activity	Bedrest
Treatments	Cardiac monitoring, Pulse oximetry Supplemental Oxygen or Mechanical Ventilation Central Line Placement for CVP/$ScvO_2$ Monitoring Arterial Line Placement if needed Early antibiotics and Source control Hemodynamic optimization (early goal-directed therapy) Monitor input and output
Medications	Broad-spectrum IV antibiotics Crystalloid, colloid, PRBC Norepinephrine, Dopamine, Phenylephrine, Vasopressin, Epinephrine, Dobutamine Dexamethasone, Hydrocortisone
Nutrition	NPO
Teaching	Review treatment plan with patient/family.
Consults	Intensive care consult, surgical consult if needed
Goals prior to ICU admission	1. CVP/$ScvO_2$ monitoring within 2 hours 2. Broad spectrum antibiotics within 4 hours 3. Optimal hemodynamics: CVP $\geq$ 8 mmHg, MAP $\geq$ 65 mmHg (or SBP $\geq$ 90 mmHg), $ScvO_2$ $\geq$ 70% within 6 hours 4. Resolution of tissue hypoperfusion (decreasing lactate) 5. Initiate corticosteroid if on vasopressor or suspect adrenal insufficiency

Clinical Pathway (v9.3)

Case Type: **Severe Sepsis or Septic Shock** Target ICU LOS: 7 days

DESIRED OUTCOME	1. Titrate vasopressor while maintaining optimal hemodynamics and resolving tissue hypoperfusion 2. Assess and initiate optimal therapies for severe sepsis and septic shock 3. Prevent complications of severe sepsis and septic shock
DAY	**Admission Day 1**
LOCATION	**ICU**
Assessments	Continuous cardiac monitoring, hemodynamic monitoring, CVP/$ScvO_2$ every hour, VS every hour, input/output every hour
Tests	CBC w/ diff, comprehensive metabolic panel, PT, PTT, D-Dimer, Troponin I, Lactate ABG, VBG (for $ScvO_2$ monitor calibration) APACHE II calculation Cosyntropin stimulation test CXR, ECG Imaging studies if needed
Activity	Bedrest
Treatments	Mechanical Ventilation if indicated with Lung Protective Strategies CVP/$ScvO_2$ or pulmonary artery catheter (SvO_2) for hemodynamic monitoring Hemodynamic optimization Antibiotics and source control Corticosteroid Recombinant human activated protein C FAST HUG (Feeding, Analgesia, Sedation, Thromboembolic prevention, Head of bed elevation, stress Ulcer prophylaxis, Glucose control)
Medications	Appropriate IV antibiotics Crystalloid, colloid, PRBC Norepinephrine, Dopamine, Phenylephrine, Vasopressin, Epinephrine, Dobutamine Hydrocortisone and fludrocortisone if on vasopressor and adrenal insufficiency Drotrecogin alfa activated Insulin infusion Opiate, Sedative H_2-blocker, Proton pump inhibitor, Heparin
Nutrition	Nutrition consult within 24 hours of admission
Teaching	Review treatment plan with patient/family.
Consults	Nutrition, Subspecialties
Goals at 24-hour after ICU admission	1. Optimal hemodynamics CVP $\geq$ 8 mmHg, MAP $\geq$ 65 mmHg (or SBP $\geq$ 90 mmHg), $ScvO_2$ (or SvO_2) $\geq$ 70% while titrating vasopressors 2. Corticosteroid if on vasopressor and adrenal insufficiency 3. Drotrecogin alfa activated if APACHE II $\geq$ 25 4. Glucose < 150 mg/dL 5. Plateau pressure $\leq$ 30 cmH_2O if mechanical ventilation 6. Sedation/analgesia for patient comfort (using Ramsay Sedation Scale) 7. Antimicrobial appropriateness 8. Stress ulcer and DVT prophylaxis 9. Early nutrition

Clinical Pathway (v9.3)

Case Type: **Severe Sepsis or Septic Shock** Target ICU LOS: 7 days

DESIRED OUTCOME	1. Titrate vasopressor while maintaining optimal hemodynamics and resolving tissue hypoperfusion 2. Assess and initiate optimal therapies for severe sepsis and septic shock 3. Prevent complications of severe sepsis and septic shock 4. Weaning from mechanical ventilator 5. Decrease ICU length of stay and in-hospital mortality
DAY	**Day 2 until Day 7 (ICU Discharge)**
LOCATION	**ICU**
Assessments	Continuous cardiac monitoring, hemodynamic monitoring, CVP/$ScvO_2$ every hour, VS every hour, input/output every hour Assess risks for bleeding, DVT, nosocomial infection
Tests	CBC w/ diff, comprehensive metabolic panel, Lactate ABG, VBG (for $ScvO_2$ monitor calibration) CXR, ECG Imaging studies if needed
Activity	Bedrest
Treatments	Mechanical Ventilation if indicated with Lung Protective Strategies CVP/$ScvO_2$ or pulmonary artery catheter (SvO_2) for hemodynamic monitoring Hemodynamic optimization Antibiotics and source control Corticosteroid Recombinant human activated protein C (discontinued if bleeding) FAST HUG (Feeding, Analgesia, Sedation, Thromboembolic prevention, Head of bed elevation, stress Ulcer prophylaxis, Glucose control)
Medications	Appropriate IV antibiotics Crystalloid, colloid, PRBC Norepinephrine, Dopamine, Phenylephrine, Vasopressin, Epinephrine, Dobutamine Hydrocortisone and fludrocortisone (total of 7 days) Drotrecogin alfa activated (total infusion of 96 hours) Insulin infusion Opiate, Sedative H_2-blocker, Proton pump inhibitor, Heparin
Nutrition	Enteral versus parenteral feeding
Teaching	Review treatment plan with patient/family. Reassess patient for continued aggressive support.
Consults	Physical Therapy, Occupational Therapy, Case Manager, Subspecialties
Goals on each day after ICU admission	1. Optimal hemodynamics CVP $\geq$ 8 mmHg, MAP $\geq$ 65 mmHg (or SBP $\geq$ 90 mmHg), $ScvO_2$ (or SvO_2) $\geq$ 70% while titrating vasopressors 2. Discontinue corticosteroid if not adrenal insuffiency (responder to cosyntropin stimulation test) 3. Assess for bleeding if on drotrecogin alfa activated 4. Glucose < 150 mg/dL 5. Plateau pressure $\leq$ 30 cmH_2O if mechanical ventilation, weaning off ventilator as appropriate 6. Sedation/analgesia for patient comfort (using Ramsay Sedation Scale) 7. Antimicrobial appropriateness 8. Stress ulcer and DVT prophylaxis 9. Nutrition 10. ICU discharge planning

Adult Severe Sepsis Orders (version 9.3)

√	
√	**Attending Physician:**
	Diagnosis: □ **Severe Sepsis** □ **Septic Shock**
	Condition: Critical Code Status: □ Full □ DNR

	Routine Nursing Orders
	Cardiac Monitoring & Continuous Pulse Oximetry
	Supplement oxygen to keep O_2 sat > 92%
	Vitals q 1 hr with Progress Note Documentation by Nurse or MD
	Monitor input and output q 1 hr
	Activity: Bed Rest
	Diet: NPO
	IV Saline lock with flush of Normal Saline 3 mL q 12 hours
	Calibrate & Initiate Central Venous Pressure and $ScvO_2$ Monitoring after line placement verified by MD
	Mechanical ventilator: Mode__, Freq__, V_T__, FiO_2__, PEEP__, mPaw__, I:E__, PS__, $PEEP_H$__, $PEEP_L$__, $HIGH_T$__, Seconds Amplitude__, %I-time__
	Alert MD if Central Venous Pressure is < 8 mmHg or > 15 mmHg
	Alert MD if Systolic Blood Pressure < 90 mmHg or > 160 mmHg (Mean Arterial Pressure < 65 mmHg or > 90 mmHg)
	Alert MD if $ScvO_2$ < 70%
	Alert MD if Hemoglobin (or Hemacue) < 10 g/dL
	Alert MD if Lactate > 2 mmol/L
	Alert MD if O_2 saturation < 88% or peak-inspiratory plateau pressure > 30 cm H_2O (on mechanical ventilation)

	Diagnostics
	Blood culture & sensitivity, urine culture & sensitivity, sputum culture & sensitivity, urinalysis, CBC with differential, comprehensive metabolic panel, PT/PTT/INR, D-Dimer, Trop I
	Lactate level (drawn in grey tube on ice) now and repeat in 6 hours
	Venous blood gas from central line & arterial blood gas
	Cosyntropin stimulation test: Obtain cortisol level, administer ACTH 250 mcg IV, then obtain cortisol at 30 and 60 min
	Measure peak-inspiratory plateau pressure every 4 hours
	Glucose level every 4 hours
	12-lead ECG
	Chest X-ray - Reason:
	Ultrasound – Location and Reason:
	CT scan - Location and Reason:

	Medications (Date and time must be entered for each order)		
	Physician Signature	**Date and Time**	**ALLERGIES: Weight (kg):**
			Intravenous fluids - NS 500 mL IV bolus until Central Venous Pressure 8 to 12 mmHg, then continue NS to run at 150 mL/hour
			Antibiotics - See Parenteral Antibiotics Order Form
			Tylenol 1 gm PO q 4 hr PRN Temperature > 38.3 ^oC
			Heparin 5,000 units SQ q 12 hr
			Famotidine 20 mg IV q 12 hr
			Midazolam 100 mg/NS 100 mL at 1-10 mg/hr, titrate to sedation scale
			Morphine 100 mg/NS 100 mL at 1-10 mg/hr, titrate to pain relief
			Vasopressors - (SBP = Systolic Blood Pressure)
			Norepinephrine 8 mg/D_5W 250 mL at 2-20 mcg/min, titrate to SBP > 90 mmHg
			Dopamine 800 mg/D_5W 250 mL at 5-20 mcg/kg/min, titrate to SBP > 90 mmHg
			Phenylephrine 10 mg/NS 250 mL at 40-200 mcg/min, titrate to SBP > 90 mmHg
			Vasopressin 20 units/NS 100 mL at 0.01-0.04 units/min, titrate to SBP > 90 mmHg
			Epinephrine 1 mg/NS 250 mL at 2-10 mcg/min, titrate to SBP > 90 mmHg
			Dobutamine 500 mg/NS 250 mL at 2.5-20 mcg/kg/min, titrate to $ScvO_2$ > 70%, maintaining SBP > 90 mmHg and Heart Rate < 140 per min
			Nitroglycerin 100 mg/D_5W 250 mL at 10-60 mcg/min, titrate to SBP < 140 mmHg
			Type & Cross 2 units
			Transfuse ___ unit PRBC
			Hydrocortisone 50 mg IV q 6 hr, and **Fludrocortisone** 50 mcg PO qd
			Xigris (Drotrecogin alfa activated) 24 mcg/kg/hr for 96 hr **- See Institutional Guidelines**
			Regular Insulin 100 units/NS 100 mL titrate to keep glucose < 150 mg/dL

MEDICATION ORDER FORM (Version 9.3)
Xigris (Drotrecogin alfa activated) for Adult Patients with Severe Sepsis or Septic Shock

INDICATIONS (Circle "Yes" or "No" for each of the following below):

NOTE: Patient must have all three indications to receive Xigris (drotrecogin alfa activated)

1. Yes / No - **Patient has high risk for mortality due to severe sepsis or septic shock defined as:**
   a. (2) and (3) below **AND**
   b. Cardiovascular dysfunction: Arterial systolic blood pressure < 90 mmHg or the mean arterial pressure < 70 mmHg despite adequate fluid resuscitation, requiring the use of vasopressor **AND**
   c. APACHE II Score ≥ 25 or the presence of two or more organ dysfunction
2. Yes / No - **Patient has known or suspected infection defined as:**
   a. Presence of white cells in a normally sterile body fluid **OR**
   b. Positive culture (urine, blood, sputum) **OR**
   c. Perforated viscous **OR**
   d. Radiographic evidence of pneumonia in association with the production of purulent sputum
3. Yes / No - **Patient has three or more signs of inflammation defined as:**
   a. Temperature > 38.3^{O}C (100.9F) or < 36.0^{O}C (96.8F)
   b. Heart Rate > 90 beats per minute
   c. Respiratory > 20 breaths per minute or $PaCO_2$ < 32 mmHg
   d. WBC > 12,000/mm^3 or < 4,000/mm^3 or > 10% bands

CONTRAINDICATIONS and WARNINGS (Circle "Yes" or "No"):

NOTE: Patient **MUST NOT** receive Xigris (drotrecogin alfa activated) if one or more of the absolute contraindications exist

Absolute Contraindications	Warnings
Yes / No – Active internal bleeding	Yes / No – Concurrent therapeutic dosing of heparin to treat an active thrombotic or embolic event
Yes / No – Recent hemorrhagic stroke within 3 months	Yes / No – Platelet count < 30,000 x 10^6/L, even if the platelet count is increased after transfusions
Yes / No – Recent intracranial, intraspinal surgery, or severe head trauma within 2 months	Yes / No – Prothrombin time-INR > 3.0
Yes / No – Trauma with an increased risk of life-threatening bleeding	Yes / No – Recent gastrointestinal bleeding within 6 weeks
Yes / No – Presence of an epidural catheter	Yes / No – Recent administration of thrombolytic therapy within 3 days
Yes / No – Intracranial neoplasm or mass lesion or evidence of cerebral herniation	Yes / No – Recent administration of oral anticoagulants or glycoprotein IIb/IIIa inhibitors within 7 days
Yes / No – Known hypersensitivity to drotrecogin alfa (activated) or any component of this product	Yes / No – Recent administration of aspirin > 650 mg per day or other platelet inhibitors within 7 days
	Yes / No – Recent ischemic stroke within 3 months
	Yes / No – Intracranial arteriovenous malformation or aneurysm
	Yes / No – Known bleeding diathesis
	Yes / No – Chronic severe hepatic disease
	Yes / No – Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location
	Yes / No – Single organ dysfunction and recent surgery less than 30 days

Allergies: _____ **Patient Weight = _____ kg** **APACHE II Score: _____**

Patient Weight Range (kg)	Dosing: Check [√] dose that applies to patient's weight
27-43	[ ] Xigris 10 mg in NS 100 mL to run at 8 mL/hour for 8 bags total
44-60	[ ] Xigris 15 mg in NS 150 mL to run at 13 mL/hour for 8 bags total
61-78	[ ] Xigris 20 mg in NS 200 mL to run at 17 ml/hour for 8 bags total
79-95	[ ] Xigris 25 mg in NS 250 mL to run at 21 ml/hour for 8 bags total
96-113	[ ] Xigris 30 mg in NS 300 mL to run at 25 ml/hour for 8 bags total
114-130	[ ] Xigris 35 mg in NS 350 mL to run at 29 ml/hour for 8 bags total
131-135	[ ] Xigris 40 mg in NS 400 mL to run at 33 ml/hour for 8 bags total
Attending Physician Signature:	**Date and Time:**

APACHE II Score Calculation

1. Temperature (^oC / F)	Points	6. Arterial pH	Points	11. White Blood Count (per mm^3)	Points
≥ 41°C / ≥ 105.8F	4	≥ 7.70	4	≥ 40	4
39-40.9 / 102.1-105.7	3	7.60-7.69	3	20-39.9	2
38.5-38.9 / 101.3-102	1	7.50-7.59	1	15-19.9	1
36-38.4 / 96.8-101.2	0	7.33-7.49	0	3-14.9	0
34-35.9 / 93.1-96.7	1	7.25-7.32	2	1-2.9	2
32-33.9 / 89.5-93	2	7.15-7.24	3	< 1	4
30-31.9 / 85.9-89.4	3	< 7.15	4	12. Glasgow Coma Scale (GCS)	
≤ 29.9 / ≤ 85.8	4	7. Serum Sodium (mmol/L)		Eyes Opening	
2. MAP = [(2 * DBP) + SBP] / 3 (mm Hg)		≥ 180	4	Spontaneous	4
≥ 160	4	160-179	3	To voice	3
130-159	3	155-159	2	To pain	2
110-129	2	150-154	1	Absent	1
70-109	0	130-149	0	Verbal Response	
50-69	2	120-129	2	Converses / Oriented	5
≤ 49	4	111-119	3	Converses / Disoriented	4
3. Heart Rate (beats per min)		≤ 110	4	Inappropriate	3
≥ 180	4	8. Serum Potassium (mmol/L)		Incomprehensible	2
140-179	3	≥ 7	4	Absent	1
110-139	2	6-6.9	3	Motor Response	
70-109	0	5.5-5.9	1	Obeys commands	6
55-69	2	3.5-5.4	0	Localizes pain	5
40-54	3	3-3.4	1	Withdraws from pain	4
≤ 39	4	2.5-2.9	2	Decorticate (flexion) rigidity	3
4. Respiratory Rate (breaths per min)		< 2.5	4	Decerebrate (extension) rigidity	2
≥ 50	4	9. Serum Creatinine (mg/dL)		Absent	1
35-49	3	≥ 3.5 & acute renal failure	8	GCS Score =	
25-34	1	2.0-3.4 & acute renal failure	6	GCS Points = 15 – GCS Score =	
12-24	0	1.5-1.9 & acute renal failure	4	**APS Points (Sum of 12 points above) =**	
10-11	1	≥ 3.5 & chronic renal failure	4	**Age Points**	
6-9	2	2.0-3.4 & chronic renal failure	3	≥ 75	6
≤ 5	4	1.5-1.9 & chronic renal failure	2	65-74	5
5. Oxygenation		0.6-1.4	0	55-64	3
a. A-a gradient if FiO_2 ≥ 0.5		< 0.6	2	45-54	2
≥ 500	4	10. Hematocrit (%)		≤ 44	0
350-499	3	≥ 60	4	**Chronic Health Points***	
200-349	2	50-59.9	2	Yes, Non-operative	5
< 200	0	46-49.9	1	Yes, Emergency post-operative	5
b. PaO_2 if FiO_2 < 0.5		30-45.9	0	Yes, Elective post-operative	2
> 70	0	20-29.9	2	No	0
61-70	1	< 20	4	**APACHE II Score =** APS Points + Age Points + Chronic Health Points	
55-60	3				
< 55	4				

NOTE: Points are determined from the worst physiologic variables in the first 24 hours after patient presentation.

***Chronic Health:**

Organ insufficiency or immunocompromised state must have been evident prior to this hospital admission and conform to the following criteria:
LIVER: Biopsy-proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.
CARDIOVASCULAR: New York Heart Association Class IV
RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction; i.e. unable to climb stairs or perform household duties, or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mm Hg), or respiratory dependency.
RENAL: Receiving chronic dialysis.
IMMUNOCOMPROMISED: Patient has received therapy that suppresses resistance to infection; e.g. immunosuppression, chemotherapy, radiation, long-term or recent high-dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection; e.g. leukemia, lymphoma, AIDS.

STOP SEPSIS BUNDLE EMERGENCY DEPARTMENT / 6-HOUR CHECKLIST (Version 9.3)

CRITERIA FOR INITIATING BUNDLE

1) Two or more signs of inflammation:
   a) Temperature >38.3°C (100.9F) or <36°C (96.8F)
   b) Heart rate >90 beats/min
   c) Respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg
   d) WBC > 12,000 cells/mm^3, <4000 cells/mm^3, or >10% bands

2) Suspected or confirmed infection

3) Systolic blood pressure < 90 mmHg after fluid bolus **(septic shock)** OR
   Lactate ≥ 4 mmol/L **(high risk severe sepsis / cryptic shock)** OR
   Evidence of > 1 organ dysfunction **(severe sepsis)**

LABORATORIES AND PROCEDURES (within 2 hours after meeting bundle criteria)

1) Peripheral IV, cardiac monitor, oxygen, pulse oximetry

2) Obtain **Sepsis panel** (Blood culture, sputum culture, urine culture, sensitivities, urine analysis, CBC w/differential, comprehensive metabolic panel, PT/PTT, D-Dimer, Troponin I, Lactate)

3) Calibrate and initiate **CVP and $ScvO_2$ monitoring** after CXR verification of line placement

4) Obtain central venous blood gas from central line

5) Repeat **lactate** at 6 hours after 1st draw

THERAPY (within 6 hours after meeting bundle criteria)

1) Broad Spectrum Antibiotics within 4 hours

2) Normal saline 500 mL bolus until CVP 8-12 mmHg, then continue at 150 ml/hr

3) Intervention is required if:
   a) Pulse Ox < 93% (Consider intubation and mechanical ventilation)
   b) Peak inspiratory plateau pressure > 30 cm H_2O (Consider decreasing tidal volume)
   c) Lactate > 2 mmol/L (Repeat lactate in 6 hours)
   d) CVP > 15 mmHg (Consider nitroglycerin if SBP > 160 mmHg or MAP > 110 mmHg)
   e) SBP < 90 mmHg (MAP < 65 mmHg) after 2 Liters IVF (Consider vasopressor)
   f) SBP > 160 mmHg (MAP > 110 mmHg) (Consider afterload reducer)
   g) $ScvO_2$ < 70% (Consider transfusion for hemoglobin < 10 g/dL and/or dobutamine)

4) Target hemodynamic goals by 6 hours and maintained until ICU transfer:
   a) CVP ≥ 8 mmHg
   b) MAP ≥ 65 mmHg / SBP ≥ 90 mmHg
   c) $ScvO_2$ ≥ 70%

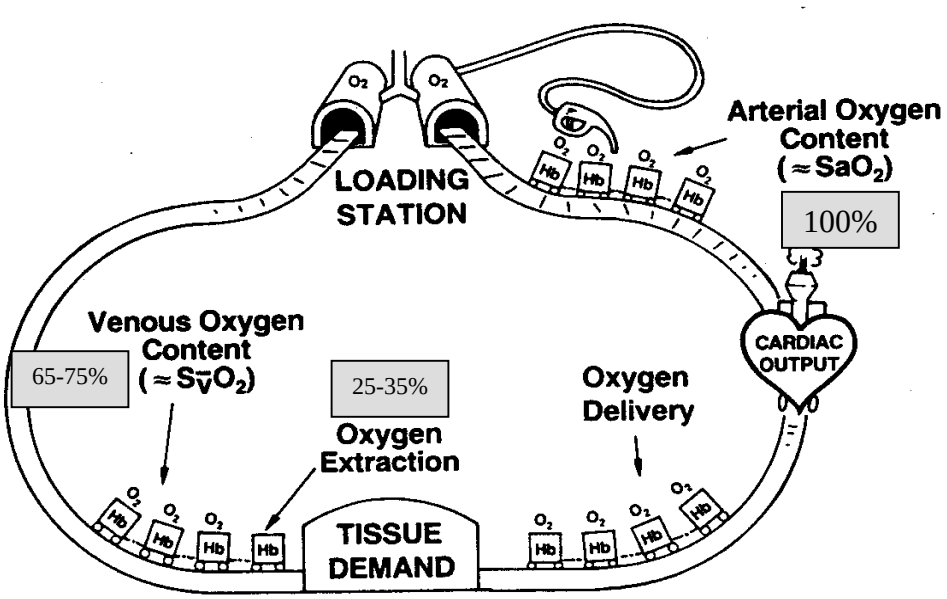
5) If patient is on vasopressor and/or APACHE II score ≥ 25, consider:
   a) Corticosteroid and perform Cosyntropin Stimulation Test
   b) Recombinant human Activated Protein C (Drotrecogin alfa activated)

$SvO_2/ScvO_2$ Made Ridiculously Simple – v9.3

For the STOP Sepsis Bundle - Strategies to Obviate the Progression of Sepsis

What is SvO_2?

1. Venous oxygen saturation (SvO_2) reflects a balance between oxygen delivery (DO_2) and oxygen consumption (VO_2).



2. DO_2 comprises of cardiac output and arterial oxygen content:
    a. $DO_2 = CO \times [(1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)]$
    b. DO_2 results in 100% oxygen delivered to the tissue.
    c. The tissue will consume (VO_2) with an oxygen extraction ratio of 25-35%.
    d. The remainder in the venous side (or venous oxygen content) is 65-75%.
3. When DO_2 and VO_2 are balanced, the optimal venous oxygen content will be reflected by a mixed venous oxygen saturation (SvO_2) of 65-75% .
4. SvO_2 is traditionally measured in the pulmonary artery via a pulmonary artery catheter (Swan-Ganz catheter).
5. SvO_2 has diagnostic, prognostic, and therapeutic value in the care of critically ill patients with acute myocardial infarction, severe heart failure, cardiogenic shock, traumatic and hemorrhagic shock, septic shock, and general medical and surgical intensive care.[1]

What is $ScvO_2$ and Why use $ScvO_2$?

1. The central venous oxygen saturation ($ScvO_2$) reflects central venous oxygen content, excluding the venous oxygen delivered from the coronary sinus (from the heart).
2. $ScvO_2$ can be measured in the superior vena cava or right atrium.
3. $ScvO_2$ has been shown to correlate well with SvO_2.[2-8]
4. An accepted normal SvO_2 > 65%.
5. An accepted normal $ScvO_2$ > 70%, which is about 7% higher than SvO_2, since $ScvO_2$ does not mix with the de-saturated venous blood of the coronary sinus.[3]
6. $ScvO_2$ can be measured via a central venous blood gas or a central venous catheter with oximetry technology.
7. $ScvO_2$ measured via a central venous catheter with oximetry technology allows for continuous $ScvO_2$ monitoring; i.e. analogous to continuous arterial pulse oximetry (SaO_2) monitoring.[1, 9]
    a. Continuous $ScvO_2$ allows for monitoring dynamic changes in $ScvO_2$ in response to treatments.
    b. Continuous $ScvO_2$ monitoring via a central venous catheter is practical and more easily performed than continuous SvO_2 monitoring via the pulmonary artery catheter.
8. The addition of continuous $ScvO_2$ monitoring in a protocolized approach to resuscitation of severe sepsis and septic shock has been shown to significantly improve outcome.[10]

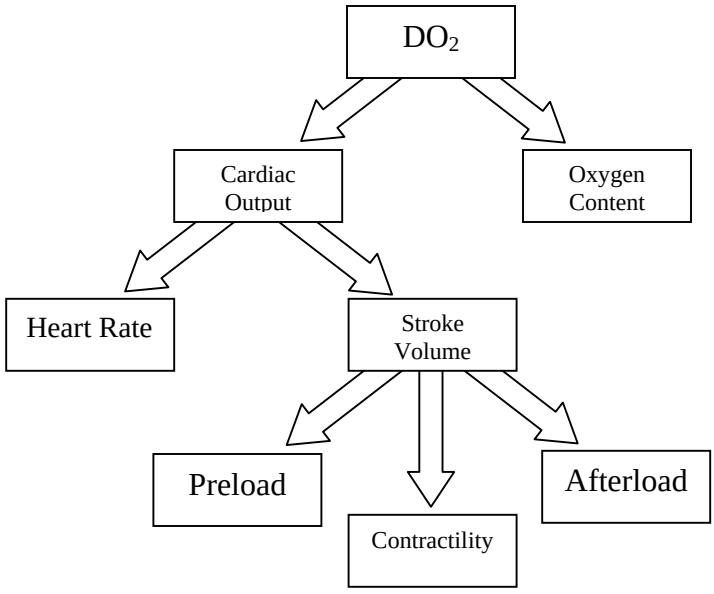
What do abnormalities in $ScvO_2$ mean?

1. Troubleshooting an abnormal $ScvO_2$ requires understanding of the causes of abnormal DO_2 and VO_2.[11]
    a. For example, a low DO_2 in the presence of normal VO_2 will result in less oxygen delivered to the venous circulation; therefore, a low $ScvO_2$.
    b. A critically ill patient will have various combinations of DO_2 and VO_2.
        i. For example, sepsis patients can have a hypodynamic low DO_2 state resulting in low $ScvO_2$; or a hyperdynamic high DO_2 state combined with a low VO_2 state from cellular mitochondria defect, resulting in high $ScvO_2$.

Low $ScvO_2$ (<< 70%)		High $ScvO_2$ (>> 70%)	
Low DO_2	High VO_2	High DO_2	Low VO_2
Hypoxia, Suctioning (low SaO_2)	Exercise	Hyperoxia (high FiO_2)	Hypothermia
Anemia, Hemorrhage (low Hb)	Pain	Erythrocytosis (high Hb)	Anesthesia, Pharmacologic paralysis
Cardiac dysfunction, Hypovolemia, Shock, Arrhythmia (low CO)	Hyperthemia, Shivering, Seizure	Hyperdynamic state (high CO)	Arterio-venous shunting, Mitochondria defect, Terminal shock

How do we treat an abnormal $ScvO_2$?

1. Low $ScvO_2$ – usually results from low DO_2, a scenario that is treatable by optimizing DO_2. Figure below illustrates the components of DO_2. DO_2 is increased to normal range by increasing these various components. Note that normalizing DO_2 is not the same as increasing DO_2 to supranormal values.[12-14]



   a. Optimizing Preload – increase central venous pressure (or pulmonary capillary wedge pressure) by increasing end-diastolic volume with fluid resuscitation.
   b. Optimizing Afterload – increase mean arterial pressure (or systemic vascular resistance) with vasopressor agents. Sometimes a vasodilator may be necessary to decrease afterload in order to optimize DO_2.[15]
   c. Optimizing Oxygen content – $(1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)$
      i. Increase PaO_2/SaO_2 with oxygen supplementation; e.g. mechanical ventilation.
      ii. Increase hemoglobin with transfusion.
   d. Optimizing Contractility – increase with inotrope agent; e.g. dobutamine.[16, 17]
   e. Oxygen content and contractility should be targetted when $ScvO_2$ is persistently low after preload and afterload have been optimized.
      i. For example, transfusion and/or inotrope should be considered when CVP > 12 mmHg, MAP > 90, and $ScvO_2$ < 70%. Simply giving a fluid bolus when $ScvO_2$ < 70% in this scenario may not be appropriate.
2. High $ScvO_2$ – resulting from high DO_2, or low VO_2.
   a. Usually it is difficult to treat a high $ScvO_2$, except to optimize the current therapies: maintaining optimal preload, afterload, contractility and oxygen content.
      i. For example, prognosis is poor when a patient is on multiple vasopressors with significant lactic acidosis, and $ScvO_2$ > 90%.[18, 19]

What other references do we have about SvO_2/$ScvO_2$ or organ hypoperfusion in sepsis:

1. Rivers EP, Ander DS, Powell D. Central venous oxygen saturation monitoring in the critically ill patient. Curr Opin Crit Care 2001; 7:204-11.
2. Reinhart K, Kersting T, Fohring U, Schafer M. Can central-venous replace mixed-venous oxygen saturation measurements during anesthesia? Adv Exp Med Biol 1986; 200:67-72.
3. Reinhart K, Kuhn HJ, Hartog C, Bredle DL. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. Intensive Care Med 2004; 30:1572-8.
4. Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM. Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. Chest 1989; 95:1216-21.
5. Schou H, Perez de Sa V, Larsson A. Central and mixed venous blood oxygen correlate well during acute normovolemic hemodilution in anesthetized pigs. Acta Anaesthesiol Scand 1998; 42:172-7.
6. Lee J, Wright F, Barber R, Stanley L. Central venous oxygen saturation in shock: a study in man. Anesthesiology 1972; 36:472-8.
7. Scheinman MM, Brown MA, Rapaport E. Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. Circulation 1969; 40:165-72.
8. Berridge JC. Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation. Br J Anaesth 1992; 69:409-10.
9. Rady M, Rivers EP, McGeorge F. Continuous central venous oximetry for the evaluation and treatment of acute cardiac failure in the emergency department. Int J Int Care 1995; 1.
10. 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; 345:1368-77.
11. Ander D, Rivers EP, McGerorge F, Rady MY. Continous central venous oxygen saturation monitoring as an adjunct in the treatment of cardiac arrest and shock: principles and practice. Clinical Intensive Care 1994; 5:232-240.
12. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988; 94:1176-86.
13. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. N Engl J Med 1995; 333:1025-32.
14. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994; 330:1717-22.
15. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF. Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 2002; 360:1395-6.
16. Qiu HB, Yang Y, Zhou SX, Liu SH, Zheng RQ. Prognostic value of dobutamine stress test in patients with septic shock. Acta Pharmacol Sin 2001; 22:71-5.
17. Rhodes A, Lamb FJ, Malagon I, Newman PJ, Grounds RM, Bennett ED. A prospective study of the use of a dobutamine stress test to identify outcome in patients with sepsis, severe sepsis, or septic shock. Crit Care Med 1999; 27:2361-6.
18. Fink MP. Bench-to-bedside review: Cytopathic hypoxia. Crit Care 2002; 6:491-9.
19. Fink MP. Cytopathic hypoxia. A concept to explain organ dysfunction in sepsis. Minerva Anestesiol 2000; 66:337-42.

The STOP Sepsis Bundle **Quality Measurement Tool** Version 9.3 Loma Linda University Copyright ©2006	Date of Admission: Time of ED / ICU Arrival: Patient Name: MRN: Age: Sex:

[ ] **Signs of Inflammation:** Manifested by two or more of the following conditions: [ ] Temperature >38.3°C or <36°C (value=) [ ] Heart rate >90 beats/min (value=) [ ] Respiratory rate >20 breaths/min or (value=) $PaCO_2$ <32 mmHg (value=) [ ] WBC > 12,000 cells/mm^3, <4000 cells/mm^3, or >10% bands (value=)	**CRITERIA FOR SEVERE SEPSIS BUNDLE:** 1. [ ] Two or more Signs of Inflammation AND 2. [ ] Suspected infection OR positive cultures AND 3. [ ] SBP < 90 mmHg after fluid bolus OR Lactate ≥ 4 mmol/L OR mechanical ventilation OR vasopressor dependent OR evidence of ≥ 2 acute organ dysfunction*
[ ] **Sepsis:** Signs of inflammation & suspected infection+	**PATIENT MET ALL THREE CRITERIA: Y / N**
[ ] **Severe Sepsis:** Sepsis associated with ≥ 2 organ dysfunction, or hypoperfusion (lactate > 2 mmol/L)	Date & Time meeting Criteria:
[ ] **Septic Shock:** Sepsis with hypotension (BP < 90/60), despite a fluid bolus of 20 mL/kg	Location meeting Criteria: ED / Ward / PACU / ICU

+Infection may represent meningitis, pneumonia, uti, cellulitis, line infection, abdominal infection, etc…

*Organ dysfunction = resp failure, acute renal failure, acute liver failure, coagulopathy, or thrombocytopenia

1) **Early recognition of high risk patient – Lactate measured**	LA:	Y / N

Within 2±1 hours of meeting Bundle Criteria	**Time**	**Completed by 2 hrs**
2) **Initiate hemodynamic monitoring** □ Triple lumen catheter □ Pulmonary artery catheter (Swan-Ganz) □ CVP monitoring □ $ScvO_2$ monitoring □ SvO_2 monitoring		Y / N

Within 4±1 hours of meeting Bundle Criteria	**Time**	**Completed by 4 hrs**
3) **Cultures obtained prior to antibiotic administration**		Y / N
4) **Give broad spectrum antibiotic(s)**		Y / N

After 6±1 hours of meeting Bundle Criteria and/or at ICU adm		**Time**	**Completed after 6 hrs**
5-7) **Achieve and maintain hemodynamic goals (all three goals below)**			Y / N
□ CVP ≥ 8 mmHg	Y / N		
□ MAP ≥ 65 mmHg or SBP ≥ 90 mmHg	Y / N		
□ $ScvO_2$ (or SvO_2) ≥ 70%	Y / N		

After 24±2 hours of meeting Bundle Criteria and/or ICU adm		**Completed after 24 hrs**
8a) **Cosyntropin Stimulation Test Performed**	ΔCortisol:	Y / N
8b) **Corticosteroid if on Vasopressor and/or ΔCortisol ≤ 9 mcg/dL**		Y / N
9) **Drotrecogin Alfa (activated) Eligibility Assessed** **APACHE II Score computed**	APACHE II:	Y / N
10) **Drotrecogin Alfa (activated) Indicated and Administered (within 48hrs) if APACHE II ≥ 25 and/or Vasopressor Dependent**		Y / N
11) **Achieve and maintain median glucose level < 150 mg/dL** Glucose (0hr)____ (2hr)____ (4hr)____ (6hr)____ (8hr)____ (10hr)____(12hr)____ Glucose (14hr)____ (16hr)____ (18hr)____ (20hr)____ (22hr)____ (24hr)____		Y / N
12) **Achieve and maintain median plateau pressure ≤ 30 cm H_20 if mechanical ventilation** Pplat (0hr)____ (4hr)____ (8hr)____ (12hr)____ (16hr)____ (20hr)____(24hr)____		Y / N

Rx in first 24 hours: IVF _____ mL, Vasopressor (Y / N), Inotrope (Y / N), Transfusion (Y / N), Mech Vent (Y / N)

STOP Sepsis Bundle Quality Achieved (All Quality Indicators Met): Y / N

[ ] Bundle Quality was NOT targeted because of patient advanced directive or clinician judgment (noted in the chart)

TOTAL LENGTH OF STAY IN THE EMERGENCY DEPARTMENT (if applicable) _____ (hrs)
TOTAL DAYS OF MECHANICAL VENTILATION (if applicable) _____ (days)
TOTAL LENGTH OF STAY IN THE ICU _____ (days)
TOTAL LENGTH OF HOSPITAL STAY _____ (days)
IN-HOSPITAL MORTALITY Died / Lived

STOP Sepsis Bundle Quality Indicators (v9.3)

Loma Linda University

Denominator: Number of patients (monthly) meeting criteria for septic shock or severe sepsis with lactate $\geq$ 4 mmol/L.

Process Measures (Numerator): Percentage of patients having each of the following *process measures* completed within the first 48 hours of meeting criteria for septic shock or severe sepsis with lactate $\geq$ 4 mmol/L.

LLU-SS-1 – Lactate measured

LLU-SS-2 – CVP/$ScvO_2$ monitoring within 2 hours

LLU-SS-3 – Cultures obtained prior to antibiotics

LLU-SS-4 – Antibiotics within 4 hours

LLU-SS-5 – CVP $\geq$ 8 mmHg within 6 hours

LLU-SS-6 – MAP $\geq$ 65 mmHg or SBP $\geq$ 90 mmHg within 6 hours

LLU-SS-7 – $ScvO_2$ (or SvO_2) $\geq$ 70% within 6 hours

LLU-SS-8 – Corticosteroid if vasopressor dependent and/or adrenal insufficiency

LLU-SS-9 – Assess for drotrecogin alfa activated (APACHE II calculated) within 24 hours

LLU-SS-10 – Drotrecogin alfa activated within 48 hours if indicated

LLU-SS-11 – Median glucose maintained < 150 mg/dL

LLU-SS-12 – Median plateau pressure maintained $\leq$ 30 cmH_20 if on mech ventilation

Outcome measures (for all patients in the denominator):

LLU-SS-13 – Mechanical ventilator days

LLU-SS-14 – ICU length of stay

LLU-SS-15 – In-hospital mortality

Note: These indicators are measurable at our institution, and are adapted from ongoing efforts by the Surviving Sepsis Campaign / Institute for Healthcare Improvement (Adv Sepsis 2005;4(3):108-111), Volunteer Hospitals of America Transforming the ICU (TICU) Project, JCAHO, and the STOP Sepsis Quality Improvement Project (LLUMC).