Severe Sepsis and Septic Shock: Bringing Best Practice to the Bedside

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Disclosures

NONE
Sepsis: Epidemiology

~ 1-3 million cases per year

~15-30% mortality

Increased incidence and mortality with age and co-morbidity

2/3 occur in hospitalized patients

Incidence increasing in the North America

• Gaieski et.al., CCM 2013;41:1167-1174
Systemic Inflammatory Response Syndrome (SIRS)

A complex systemic response which includes two or more of the following manifestations:

- fever or hypothermia (>38°C or < 36°C)
- tachycardia (> 90 beats/min)
- tachypnea (> 20 breaths/min)
- WBC count of > 12,000 or <4,000 cells/mm³ or > 10% immature neutrophils
Sepsis
Confirmed or suspected infection, plus
> 2 SIRS criteria

Severe Sepsis
Sepsis
> 1 organ dysfunction
Septic Shock

Sepsis with hypotension (SBP < 90 mm Hg or a reduction of > 40 mm Hg from baseline) despite adequate fluid resuscitation along with perfusion abnormalities:

• lactic acidosis
• oliguria
• altered mental status
Sepsis: A Complex Disease

This Venn diagram provides a conceptual framework to view the relationships between various components of sepsis.

The inflammatory changes of sepsis are tightly linked to disturbed hemostasis.

Accuracy of Procalcitonin for Sepsis Diagnosis in Critically Ill Patients: Systematic Review and Meta-analysis

Systematic review of 18 studies evaluating the diagnostic accuracy of procalcitonin in sepsis diagnosis in critically ill patients

Sensitivity and specificity was 71%

Conclusion: Procalcitonin cannot reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients.

Lancet Infect Dis 2007;7:210-17
Sepsis: Etiology

~ 1/2 culture positive cases are gram negative organisms

~ 1/2 gram positive organisms

2 - 5% fungi or mixed infections

Mycobacteria, rickettsiae, viruses and protozoans may cause sepsis

1/3 of cases culture negative
Sepsis: A Network of Cascading Events

- INFECTION
- PROINFLAMMATORY MEDIATORS
- ANTI-INFLAMMATORY MEDIATORS
- INFLAMMATION
  - Activated Protein C
  - Protein C
  - TF
- COAGULATION
  - TAF-1
  - T-PA
  - PAI-1
- ENDOTHelial INJURY
- FIBRINOLYSIS
Sepsis: Current Treatment

Removal of source of infection

Antimicrobials

Fluid resuscitation

Hemodynamic support

General supportive care

? Attack inflammatory response
Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock

Retrospective cohort design

2,731 adult patients with septic shock

Administration of effective abx for isolated or suspected pathogen was associated with 80% survival

Each hour delay associated with 8% reduction in survival

Only 50% of septic shock patients received abx with 6 hours of hypotension

• Kumar et al, CCM 34:1589-1596, 2006
Septic Shock: Hemodynamic Therapy

Adequate volume resuscitation (colloids vs crystalloid)
- CVP 8-12 (12-16 if intubated)

Pressors to goal MAP ≥ 65
- Norepinephrine 1st line
- Epinephrine 2nd line
- Phenylephrine if tachyarrhythmias
- Dopamine if bradyarrhythmias
- Vasopressin in refractory hypotension
What is the “Best” Fluid: Crystalloids vs Colloids?

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Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

Prospective study of 1500 patients

Compared chloride rich (ie NS), vs chloride poor (ie LR, Plasmalyte)

Chloride rich fluids associated with significantly higher serum creatinine

Risk of RRT 10% vs 6%

- JAMA, 2012, 308:1566-1572
Quotables

“You have to swell to get well”

Don Smith, MD circa 1994
Norepinephrine or Dopamine for the Treatment of Hyperdynamic Septic Shock?

32 patients with hyperdynamic septic shock randomized to receive dopamine (2.5-25 mcg/kg/min) or NE (0.5 - 5.0 mcg/min)

Goal to achieve at 6 hours (1) SVR > 1,100 dynes and/or MAP > 80 mm Hg (2) CI > 4.0 L/min/m² (3) DO₂ > 550 ml/min/m² (4) VO₂ > 150 ml/min/m²

Dopamine 5/16 achieved goal, NE 15/16 reached goal

10/11 Dopamine patients who failed, met goal when NE started

NE more reliable at reversing septic shock hemodynamics

• Martin et al, CHEST 1993;103:1826-31
Comparison of Dopamine and Norepinephrine in the Treatment of Shock
19 patients with vasodilatory septic shock

Administered 0.04 U/min continuous infusion AVP

BP increased from 92/52 to 146/66 (p<.001)

SVR increased from 644 to 1187 dynes (p<.001)

Mean vasopressin level 3.1 pg/mL vs 22.7 in patients with cardiogenic shock

Vasopressin levels normalized with infusion

- Landry et al 1997;95:1122-1125
Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

778 patients on minimum of 5 mcg/min NE were randomized to receive low dose vasopressin (0.01 to 0.03 units/min) or NE 5-15 mcg/min

Mortality rates 35% vs 39% (non-significant)

- NEJM 2008;358:877-887.
Oxygen Consumption/Delivery

\[ \text{VO}_2 = \text{CO} \times (\text{CaO}_2 - \text{CvO}_2) \]

\[ \text{DO}_2 = \text{CO} \times (\text{CaO}_2) \]

\[ \text{CaO}_2 = \{\text{O}_2 \text{ sat} \times \text{Hg (gm/dL)} \times 1.34 \text{ ml O}_2/\text{gm Hg}\} + \text{PaO}_2 (0.003 \text{ ml O}_2/\text{mm Hg}) \]
A Trial of Goal-Oriented Hemodynamic Therapy in Critically Ill Patients

Randomly assigned 756 critically ill patients to control, cardiac-index group and oxygen-saturation group

Mortality rates were 48.4%, 48.6% and 52.1% respectively

Number of organ dysfunctions and ICU length of stay were similar

Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

Assigned 263 patients with severe sepsis or septic shock to six hours of conventional or goal directed therapy

Standard: CVP 8-12, MAP ≥ 65, U/O ≥ 0.5 ml/hr

Goal directed: Standard + SVO2 ≥ 70% using blood trx to Hct ≥ 30 and dobutamine

In-hospital mortality 30.5% (Goal directed) vs. 46.5% standard therapy (p=0.009)

Over first 72 hours goal directed therapy group had lower lactate levels, higher pH and lower APACHE II scores
  • Rivers et al, NEJM 2001
Patients Treated with EGT Received More Fluids, RBCs and Dobutamine

The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: A meta-analysis *

Jones, Alan; Brown, Michael; MD, MSc; Trzeciak, Stephen; MD, MPH; Shapiro, Nathan; MD, MPH; Garrett, John; Heffner, Alan; Kline, Jeffrey

Critical Care Medicine. 36(10):2734-2739, October 2008. DOI: 10.1097/CCM.0b013e318186f839
Crit Care Med 2013;41:580-637

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (Scvo₂)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Scvo₂ of ≥70%, and normalization of lactate.
The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis


DOI: 10.1097/CCM.0b013e3181cb0cdc
A Randomized Trial of protocol-Based Care for Early Septic Shock

31 emergency rooms in academic centers randomly assigned
1341 patients with septic shock to:
  • Protocol based EGDT (Group 1)
  • Protocol based standard therapy (Group 2)
  • Usual care (Group 3)

By 60 day mortality
  • 21% Group 1
  • 18% Group 2
  • 19% group 3

Conclusion: Protocol based resuscitation showed no difference in outcome
  • The ProCESS investigators, New Engl J Med 2014
Surviving Sepsis Campaign Responds

3 hour bundle done in most
• All patients received greater than 2 L IVF prior to randomization
• 75% received antibiotics prior to randomization
• Usual care group mortality 19% vs 45% in River’s study
• Did not address severe sepsis without septic shock

6 hour bundle
• Companion paper supports MAP 65
• Current paper does not assess serial lactates
• Majority of all patient’s had central lines

Continues to recommend all elements of the sepsis bundle
General Supportive Care

Protective ventilatory strategies (low tidal volume ventilation)

Electrolytes, glucose (goal less than 180)

Renal dysfunction

Nutritional support

GI/DVT prophylaxis
Mean Serum TNF Levels in Survivors and Non-survivors of Septic Shock

Non-Survivors
n = 17

Survivors
n = 34

*p < 0.05

Pooled SE:

TNF (pg/ml)

0 12 24 48

Time (hours)

CHEST 103:565-575, 1993
Limiting the Sepsis Response

- Endotoxin blockade
- Anti-TNF
- Anti-IL-1
- Anti-PAF
- Corticosteroids
- Anti-oxidants
- Coagulation system interference
- NO interference
- Hemofiltration
"Say ... what's a mountain goat doing way up here in a cloud bank?"
Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock

300 patients with septic shock, unresponsive to IVF and low dose pressors as well as organ dysfunction

All underwent co-syntropin stim test

Hydrocortisone 50 mg iv q 6h and fludrocortisone 50 ug daily or placebos x 7days

28 day survival distribution in patients with relative adrenal insufficiency

• Annane et al JAMA 288:862-871,2002
Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock: Results

229 nonresponders and 70 responders to the cosyntropin

Nonresponders:
• 73 (63%) deaths in placebo group; 60 (53%) deaths in treatment group (p=0.02)
• Vasopressor therapy withdrawn within 28 days in 46 (40%) in the placebo group and in 65 (57%) in the treatment group (p=0.001)

Responders: No significant difference

Adverse event rates similar
Corticosteroid Therapy of Septic Shock (CORTICUS)

Included all patients in septic shock no matter how they responded to pressors

Faster resolution of septic shock in those that received steroids

ACTH response did not predict responders

No mortality benefit

Steroids in Sepsis: Conclusions

Altered HPA axis function common in septic shock

Candidates for steroid replacement are those hypotensive (SBP<90) despite 1 hour of pressors

Replacement of steroids in such patients is associated with improved survival

No routine ACTH tests or steroids in most sepsis patients
Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis

1690 randomized patients with severe sepsis

Drotecogin alfa (activated) vs placebo

Both groups received general supportive care

Mortality rate 30.8% in placebo group, 24.7% in treatment group at 28 days (p<0.01)

Serious bleeding 3.5% treatment group vs 2.0% placebo (p=0.06)

- Bernard et al NEJM 2001;344:699-709
APC Follow Up Trials

ADDRESS (2005): Low disease severity
• 28-day mortality 18.5% APC vs 17.0% placebo (NS)
• Severe bleeding 3.9% APC vs 2.2% placebo (p= 0.01)

XPRESS (2007): Adjunctive heparin
• 28-day mortality 28.3% heparin vs 31.9% placebo
• Severe bleeding 5.2% heparin vs 3.9 % placebo (p=0.16)

ENHANCE (2005) (open label APC)
• Mortality 25.3%
• Severe bleeding 6.5%
1696 patients with vasopressor-dependent septic shock were randomly assigned to receive rhAPC or placebo [61].

Preliminary analyses done by the maker of the drug indicated that rhAPC did not improve 28-day mortality (26.4 versus 24.2 percent for placebo, RR 1.09, 95% CI 0.92-1.28)

“C’mom, c’mom—it’s either one or the other.”
Sepsis: Care Improvement

Early identification of severe sepsis and septic shock

Early goal directed therapy

- Culture before antibiotics
- Serial blood lactates
- IVF to predetermined goals
- Pressors to predetermined MAP
- Targeting improved oxygen delivery
“It’s time we face reality, my friends. … We’re not exactly rocket scientists.”
Patient requires Culturing

Suspected Sepsis Order panel used

Lactate >=4

Notify Team
Activate RRT

Lactate >=2

Q 4 hours x3 Then per order

Notify team/RRT of:
↑HR, ↑RR, ↓SBP
Mental Status ∆

Lactate < 2

Per order

Notify team/RRT of:
↑HR, ↑RR, ↓SBP
Mental Status ∆

Proposed Elements:
- Blood Culture x2
- U/A C&S
- Sputum GS/C&S
- STAT LACTATE

Consider:
- CBC/diff
- Chem 14

↑HR, ↑RR, ↓SBP
Mental Status ∆
URMC – Adult Non-Invasive Sepsis Resuscitation Protocol

For use with Adult* patients where goals of care are curative

Patient has 2 or more of the following criteria:
- Temp <36 or >38
- RR >20
- HR>90
- WBC <4 or > 12 or > 10% bands
- Acute Mental Status Change

Does not meet sepsis criteria, continue supportive care

Patient has known or suspected infection?

- Notify provider for orders
- Obtain Blood Cultures**
- Broad spectrum antibiotics after cultures**
- STAT Lactate**

Source Control
- Infected Catheter
- Operative Intervention
- Drainable pus

Supplemental Oxygen to maintain SpO2 >92%

Identify reasons for SIRS criteria
- Consider VS q4hrs x3

SBP <90 or Lactate ≥ 4***

- Continue supportive care
- Monitor s/sx of hypoperfusion
  - Acute mental status change
  - ↓ urinary output
  - Cool/clammy skin
  - Delayed capillary refill
  - Cyanosis
- Recheck lactate in 2-4 hours
- If lactate ↑ or SBP <90 restart protocol

***Lactate ≥ 2 and <4
- Consider VS q2hrs x2 then q4 x3

Rapid Response Team Consult - Admitted Patients

Crystalloid Bolus – 30mL/kg**
(bolus as rapidly as possible)

SBP <90
Lactate ≥ 4 ***or <20% lactate clearance

Review goals of care with patient/family.
Goals of care remain curative?

- Continue rapid fluid resuscitation
- Goal: MAP >65, Normal Serum Lactate
(Most pts with severe sepsis/septic shock require ≥ 5L in the first 6 hrs)
- Obtain consent and establish central venous access

ICU Consult - All Patients

Crystalloid Bolus – 30mL/kg**
(bolus as rapidly as possible)

Initiate Septic Shock Management Protocol

* - refer to attached guidelines
** - provider order required

Guidelines are intended to be flexible. They serve as reference points or recommendations, not rigid criteria. Guidelines should be followed in most cases, but there is an understanding that, depending on the patient, the setting, the circumstances, or other factors, guidelines can and should be tailored to fit individual needs.
### URMC – Adult Septic Shock Management Protocol

For use with adult patients where goals of care are curative

**Ensure Sepsis Resuscitation Protocol Initiated**

Consider the following therapies for continued management of septic shock

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<tr>
<th>CVP &lt; 8 (CVP &lt; 12 if intubated)</th>
<th>MAP &lt; 65</th>
<th>ScvO₂ &lt; 70 (only after CVP &amp; MAP goals met)</th>
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<tr>
<td>NS 500mL boluses q 30 min until goal</td>
<td>Initiate Vasopressor (see below)</td>
<td>Consider PRBC transfusion for HCT &lt; 30</td>
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<tr>
<td>Maintenance IVF once target CVP met ≥ 8 (≥ 12 if intubated)</td>
<td>Titrate to MAP ≥ 65</td>
<td>Consider Dobutamine 2.5-20 mcg/kg/min (see below)</td>
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<tr>
<td>Recheck CVP after each bolus until goal and then in 4 hours</td>
<td>Obtain ScvO₂ (central versus oxygen saturation)</td>
<td>Recheck ScvO₂ q 2 hours until ≥ 70 and then in 4 hours</td>
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Check lactate q 2 hours until > 20% lactate clearance and then in 4 hours

**Goal – normalization of lactate**

### Vasopressors:

1. Norepinephrine as the first choice vasopressor. (usual range 1-80 mcg/min)
2. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure. (usual range 0.01-1 mcg/kg/min)
3. Vasopressin can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage in the setting of refractory hypotension. (usual range 0.01-0.04 units/min)
4. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia). (usual range 1-20 mcg/kg/min)
5. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target. (usual range 20-200 mcg/min)

### Inotropic Therapy:

1. A trial of dobutamine infusion may be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP. (usual range 2.5-20 mcg/kg/min)

* - refer to attached guidelines

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Sepsis: Prognosis

Severe sepsis carries mortality over 30%

Prognosis influenced by the presence of shock, nature of underlying disease, and the organisms causing sepsis

Negative prognostic host factors include immune dysfunction and reduced cardiorespiratory reserve
Sepsis: Conclusions

Sepsis represents a complex host reaction to severe infection involving coagulation and inflammation

MUST remove source of infection (drainage/abx)

MUST use early, effective antibiotics

Early, aggressive volume resuscitation (with pressors as needed) to predetermined goals is beneficial in patients with severe sepsis and septic shock

Check lactate!

Sepsis bundles are best way to assure best practice!

Corticosteroids in pressor unresponsive septic patients may be associated with reduced mortality

Like in MI and CVA, in Sepsis time is tissue! There is a golden treatment period in the first 6 hours...This requires a team effort!
Medicine of the Highest Order