Management of Intra-operative Sepsis

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Physician Lead, UCSF Sepsis Bundle Compliance and Mortality Reduction

Intra-operative Management of Sepsis

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Agenda

• Epidemiology
• Definitions
• Treatment
  – Definitive
  – End-organ support
Epidemiology

• Observational cohort study
• 847 non-federal hospitals in seven states
• 192,980 patients
• Patients with documented infection and acute organ dysfunction by ICD-9

Angus et al, Crit Care Med, 2001

Epidemiology

• 750,000 cases per year
• 3 cases per 1000 population
• 51% received intensive care
• 17% received mechanical ventilation
• Overall mortality 28%, increasing with age
• $ 22,100 per case
• $ 16.7 billion nationally
• Estimated 1.5% increase annually

Angus et al, Crit Care Med, 2001
Compared to other major diseases

Incidence of Severe Sepsis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence (Cases/100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>50</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>200</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>250</td>
</tr>
<tr>
<td>CHF</td>
<td>300</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>500</td>
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</tbody>
</table>

Figure Legend:
Frequency of admission and mortality rates due to severe sepsis, 2000-2007. Bars represent SEM.
Death rate over time

Source of Sepsis

- Blood: 36%
- Skin: 20%
- Abdomen: 7%
- Urinary tract: 5%
- Other: 13%
Agenda

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- Definitions
- Treatment
  - Definitive
  - End-organ support

What is Sepsis??

- A variable condition that affects each of us differently and is initiated by a known or suspected infectious insult.
Sepsis Definitions

- SIRS
- Sepsis
- Severe Sepsis
- Septic Shock

Sepsis: ACCP/SCCM Definitions

- SIRS
  - T > 38.3°C or < 36°C
  - HR > 90 beats/min
  - Tachypnea
  - WBC > 12K or < 4K

- Sepsis
  - SIRS plus confirmed or suspected infection

- Severe Sepsis
  - SEPSIS plus evidence of at least one alteration in organ perfusion

- Septic Shock
  - SEVERE SEPSIS plus hypotension (Systolic blood pressure < 90 or Mean Arterial Blood Pressure < 65) OR Lactate > 4
Severe Sepsis Definition

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)

- Sepsis-induced hypotension
- Lactate above upper limits laboratory normal
- Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
- Acute lung injury with PaO₂/FIO₂ < 250 in the absence of pneumonia as infection source
- Acute lung injury with PaO₂/FIO₂ < 200 in the presence of pneumonia as infection source
- Creatinine > 2.0 mg/dL (170.8 µmol/L)
- Bilirubin > 2 mg/dL (34.2 µmol/L)
- Platelet count < 100,000 µL
- Coagulopathy (international normalized ratio ≥ 1.5)


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San Francisco Definition

- Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection.
Inflammatory Response

Excessive systemic inflammatory response

Immunodepression

Early mortality

Late mortality

Coagulation Regulation

• Normal response to injury is a contained explosion of thrombin generation
• TNF and IL-1 activate coagulation pathway
• Endothelium acts like a fire extinguisher
  – Antithrombin
  – Thrombomodulin/Protein C
  – Act to neutralize thrombin and prevent conversion of fibrinogen to fibrin
Loss of Homeostasis in Sepsis

- Proinflammatory mediators
- Endothelial injury
- Tissue factor expression
- Thrombin production

Pathophysiology of Sepsis

- Increased PAI-1
- Reduced Protein C

Sepsis

- Coagulation
- Fibrinolysis
- Inflammation

Endothelial Injury

Organ Failure

Death
Agenda

• Epidemiology
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  – Definitive
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Definitive Treatment

• Antibiotics
• Source Control
Management of Severe Sepsis and Septic Shock


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Figure 1. Surviving Sepsis Campaign Care Bundles.
Management of Severe Sepsis and Septic Shock

• Antibiotics should be administered within 60 minutes from the time of recognition.

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

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Figure 1. Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hrs) following first documentation of septic shock-associated hypotension. Black bars represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The gray bars represent the cumulative fraction of patients having received effective antimicrobials at any given time point.

Figure 2. Mortality risk (expressed as adjusted odds ratio of death) with increasing delays in initiation of effective antimicrobial therapy. Bars represent 95% confidence interval. An increased risk of death is already present by the second hour after hypotension onset (compared with the first hour after hypotension). The risk of death continues to climb, though, to >36 hrs after hypotension onset.
End-organ support (by improving tissue perfusion)...

Management of Severe Sepsis and Septic Shock

**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 ≥4mmol/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 (SvO₂)*
7) Remeasure lactate if initial lactate was elevated

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, SvO₂ of ≥70%, and normalization of lactate.

Figure 1. Surviving Sepsis Campaign Care Bundles.
Management of Severe Sepsis and Septic Shock

• Normalization of lactate as a resuscitation goal is suggested
  – Use of rate of lactate clearance is mentioned, but not endorsed as a sole target

Management of Severe Sepsis and Septic Shock

• Fluid Therapy
  – Crystalloids are first choice for the overwhelming majority of patients
  – Albumin can be used to reduce volume from crystalloids
  – Hydroxyethyl starches should not be used
Management of Severe Sepsis and Septic Shock

- Fluid Therapy
  - WATCH OUT!!!!!
  - Too much fluid is bad and not enough is bad...

H. Vasopressors
1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of ≥60 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (U/G).
5. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (U/G).
6. 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) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) 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 (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (U/G).

I. Inotropic Therapy
1. A trial of dobutamine infusion up to 20 micrograms/kg/min 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 (grade 1C).
Management of Severe Sepsis and Septic Shock

- Corticosteroids
  - For refractory hypotension despite fluids and vasopressors/inotropes
  - Do not perform ACTH stimulation test
- Glucose
  - Target level to less than 180 mg/dL

Things more specific to the OR...

- Avoid etomidate
  - Inhibits adrenal mitochondrial hydroxylase activity
  - Decreases steroidogenesis
- Pre-treatment with alpha/beta-agonist before induction
Things more specific to the OR...

• NMDA
  – Increase in initial dose
    • Increase in volume of distribution
    • Increase in alpha-1 acid glycoprotein
  – Prolonged recovery from renal and liver dysfunction

Things more specific to the OR...

• Lung Injury
  – All patients at risk
  – Low-tidal volume (6cc/kg IBW)
  – Plateau pressure < 30 cm H₂O
  – Permissive hypercapnia
  – Minimize FIO₂
Things more specific to the OR...

- **Glucose homeostasis**
  - Hyperglycemia very common, but can have hypoglycemia

- **Kidney and Liver dysfunction**

- **Coagulation abnormalities**
  - Disseminated Intravascular Coagulation (DIC)

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Things more specific to the OR...

- **METABOLIC ACIDOSIS**
  - Treat the underlying cause
  - Sodium Bicarbonate
    - Better tolerated as continuous infusion rather than intermittent bolus dosing
    - Acidemia is better for oxygen unloading from hemoglobin (left-shift of HGB-Oxygen dissociation curve)
    - Can worsen intra-cellular acidosis leading to worsening of organ dysfunction
Conclusions

• We will all have patients that will develop severe sepsis while in the OR or will already have severe sepsis/septic shock and is in the need for source control
• Definitive treatment for severe sepsis/septic shock involves rapid appropriate antibiotic administration and source control

Conclusions

• Etomidate should not be used as a first-line agent for induction
• Drugs may take longer to work and last longer than expected
• Acidemia is not necessarily bad
QUESTIONS??