Objectives

- Review the etiology/epidemiology/costs of Sepsis
- Discuss the definition and diagnosis of Sepsis
- Describe interventions that should occur within the first hour of patient presentation that can change outcomes
  - Choice of agent to facilitate rapid sequence intubation
  - Adequate fluid resuscitation
  - Pressor or Inotrope support

Introduction

- Major cause of morbidity and mortality worldwide.
  - Leading cause of death in noncoronary ICU.
  - 11th leading cause of death overall.
- More than 750,000 cases of severe sepsis in US annually.
- In the US, more than 500 patients die of severe sepsis daily.
Sepsis: Definitions

Systemic Inflammatory Response Syndrome (SIRS)
Two or more of the following:
- Temperature of >38°C or <36°C
- Heart rate of >90
- Respiratory rate of >20
- WBC count >12 x 10^9/L or <4 x 10^9/L or 10% immature forms (bands)

Sepsis
SIRS plus a culture-documented infection

Severe Sepsis
Sepsis plus organ dysfunction, hypotension, or hypoperfusion
(including but not limited to lactic acidosis, oliguria, or acute mental status changes)

Septic Shock
Hypotension (despite fluid resuscitation) plus hypoperfusion

Relationship Between Sepsis and SIRS

Severe Sepsis is deadly

Mortality

Sands, et al
Zeni, et al
Angus, et al
Severe Sepsis is Common

Severe Sepsis is increasing in Incidence

Severe Sepsis is a Significant Healthcare Burden

- Sepsis consumes significant healthcare resources.
- In a study of Patients who contract nosocomial infections, develop sepsis and survive:
  - ICU stay prolonged an additional 8 days.
  - Additional costs incurred were $40,890/patient.
- Estimated annual healthcare costs due to severe sepsis in U.S. exceed $16 billion.
Comparison With Other Major Diseases

Incidence of Severe Sepsis

Mortality of Severe Sepsis

Surviving Sepsis Campaign

A global program to:

- Reduce mortality rates
- Improve standards of care
- Secure adequate funding

An Important Message for EMS

- TIMING OF INTERVENTIONS IS CRITICAL!!
- Numerous studies suggest that the longer delay between appropriate therapy the higher the mortality in severe sepsis
- EMS personnel actions in the field can positively impact septic patients farther downstream
  - Such an impact may be more difficult for EMS personnel to realize
Agents for Rapid Sequence Intubation: What to Use in Septic Shock?

Induction Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Duration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td>0.3 mg/kg IV</td>
<td>3-10 minutes</td>
<td>May aid in lowering ICP; may lower BP</td>
</tr>
<tr>
<td>Versed</td>
<td>0.2-0.3 mg/kg IV</td>
<td></td>
<td>May aid in lowering BP</td>
</tr>
</tbody>
</table>

Etomidate

- Hypnotic without analgesic properties
- Minimal effect on cardiac and respiratory systems
- Onset 30-60 seconds
- Duration 3-10 minutes
- If used in RSI, consider Versed or Fentanyl for amnesic properties
- Not used routinely outside of the OR or RSI due to adrenal suppression
**Versed (Midazolam)**

- Benzodiazepine used to relieve tension, or to impair memory for endotracheal intubation
- Use with caution in patients who are known to have alcohol, narcotics or CNS depressants on board
- Can cause respiratory depression or arrest
- Can cause hypotension

**Neuromuscular Blocking Agents**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>Adult 1-1.5mg/kg IVP</td>
<td></td>
</tr>
<tr>
<td>Pedi 1-2mg/kg IVP</td>
<td>May cause ICP. Traumatic head injury patients who already display signs of increasing BP, or patients displaying signs or symptoms of CVA, should be considered candidates for Norcuron.</td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.1mg/kg IVP</td>
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<tr>
<td></td>
<td>Used to maintain paralysis</td>
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</tbody>
</table>

**Succinylcholine (Anectine)**

- Depolarizing neuromuscular blockade
- Onset 30-60 seconds
- Duration 4-10 minutes
- Onset and duration will be longer in IM administration
- Consider the use of Lidocaine in the presence of TBI
- DOES NOT AFFECT MEMORY, must concurrently use an sedative before consideration of a paralytic
Etomidate: Recap of its properties

- Why we use it:
  - Duration: 3-5 minutes (predictable)
  - Easy to dose: 30-fold difference effective: lethal dose
  - No histamine release
  - Hemodynamic stability (α-agonist effect)

BUT

- Inhibition of 11 β-hydroxylase - adrenal suppression

Relative (Functional) Adrenal Insufficiency

- Reported in many critically ill patients
- Subnormal adrenal corticosteroid production
- Hypoadrenal state without clearly defined defects in HPA axis
- Difficult to define based on serum cortisol concentrations:
  - Although cortisol level may be normal, it may remain inadequate for the patient's metabolic demands
- Rapid improvement on Hydrocortisone therapy

Incidence of Relative Adrenal Insufficiency

[Graph showing incidence of relative adrenal insufficiency in septic shock and other ICU patients]

CORTICUS Study

- Multicenter, double-blind, RCT
- 52 ICUs, March 2002 – Nov 2005 (3.5 yrs)
- Pts > 18 yrs with sepsis and onset of shock within the previous 72h (SBP < 90 despite fluids or need for vasopressors for ≥ 1 hour)
- Hydrocortisone or Placebo:
  - 50 mg IV q 6h x 5 days
  - 50 mg IV q 12h on days 6 to 8
  - 50 mg IV q 24h on days 9 to 11 then stopped


28 day mortality: all patients

<table>
<thead>
<tr>
<th>survival</th>
<th>day</th>
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<tbody>
<tr>
<td>1.00</td>
<td>0</td>
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<tr>
<td>0.75</td>
<td>5</td>
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<td>0.50</td>
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<td>0.25</td>
<td>15</td>
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<tr>
<td>0.00</td>
<td>20</td>
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p value for log rank test: 0.813

Time to shock reversal: responders

<table>
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<tr>
<th>septic shock</th>
<th>day</th>
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<tr>
<td>1.00</td>
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p value for log rank test: <0.001
Etomidate in Sepsis

- Prospective observational study to identify risk factors for RAI in ICU patients.
- N=62, ICU patients on ventilator: 33% septic, 24% cardiogenic shock, 18% neurologic etiology
- Etomidate was the single most important factor associated with RAI 24h after intubation (OR=12.2)


Etomidate in Septic Shock

- N=655 patients in 12 French EMS system with 65 participating ICUs.
- Analyzed 469 patients in an a priori defined modified intention to treat analysis.
- Double blind RCT - randomized patients to Etomidate or Ketamine for RSI.
- Median of 7h post induction:
- Median cortisol: 16(E) vs 25mcg/dL(K), p<0.001

Relative Adrenal Insufficiency

Early Goal Directed Therapy

- What early hemodynamic maneuvers can improve outcome in sepsis?
- RCT in Severe sepsis/shock receiving protocolized care vs. standard care
  - N=263, mortality difference: 46.5 vs. 30.5% (p=0.009)
  - 13 hospitals N=1298, ARR 20%, NNT =5

SAFE Study

- In a randomized, controlled trial conducted in 16 ICUs in Australia and New Zealand 6997 patients were randomized to receive either saline or 4% albumin for fluid resuscitation
- The albumin group received less fluid volume, but required more transfusion in the first 48h

NEJM 2004;350:2247
Primary Endpoint was 28 day mortality

SAFE STUDY
There were also no differences in duration of mechanical ventilation or ICU stay, development of single or multiple organ failure or duration of hospitalization.

Relative Risk of Death from Any Cause among All the Patients and among the Patients in the Six Predefined Subgroups
Just Fluids Can Make The Difference

- Retrospective, Before/After study
- Outcomes after initiation of standardized sepsis bundle
- In protocol rapid assessment and large amounts of saline (20ml/kg TBW) were given ASAP
- Outcomes assessed based on interventions made

What Pressors for Septic Shock?

- Several non-randomized studies and one small prospective randomized study of dopamine vs norepinephrine for septic shock suggest that survival may be improved with the use of norepinephrine.

Pressor/Inotrope Review

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Norepinephrine vs Dopamine+/- Epinephrine in Septic Shock

Claude, Critical Care Med 2000;28:2758
Norepinephrine Vs Dopamine in Sepsis
- Largest RCT to look at two pressors in septic shock
- n = 1679, patients received either dopamine or norepinephrine as first-line vasopressor therapy to restore and maintain blood pressure followed by open label pressors
- Outcomes included 28-day mortality, time in ICU and others


Results

![Graph showing mortality and arrhythmic events]

* = 0.03

Vasopressin?
- Vasopressin is emerging as a valuable addition to therapy for septic shock in patients with catecholamine refractory hypotension
- Not a replacement for norepinephrine or dopamine as a first-line agent
- Consider in refractory shock despite high-dose conventional vasopressors
- If used, administer at 0.01-0.04 units/minute in adults

**Bottom Line**

Sepsis is still a leading killer of Americans

What EMS personnel can do:

1. Consider other induction agents for intubation besides etomidate
2. FLUIDS, FLUIDS, FLUIDS (20 ml/kg TOTAL BODY WEIGHT)
3. Norepi is preferred to dopamine for the first vasopressor used