ICU Case Presentation

Treatment of Septic Shock

Leah Jackson, BScPhm
Pharmacy Resident
April 17, 2007
Learning Objectives

At the end of the presentation, the audience will be able to:

- Describe the meaning of sepsis, SIRS, and septic shock
- Explain the basic pathophysiology of sepsis and how it presents
- List the interventions available to treat sepsis (toolkit)
- Understand the basis for the preprinted ICU order set (adjuvant therapy for sepsis) and access 3 landmark studies for further information if desired
Mr. C, 77 yo ♂

**PMH**
- HTN (20+ years)
- CAD → 1998, 2005
- CHF (grade 2/3 ventricle)
- A fib (pacemaker 2002)
- AVR, MVR 1997 (mechanical)
- AAA
- PVD (bilateral bypasses 2004)
- TIA
- ESRD (peritoneal dialysis)
- BPH
- Hypothyroidism
- DM type 2 (recent dx; diet-controlled)

**Home medications**
- Metoprolol 50mg BID
- Amiodarone 200mg daily
- Digoxin 0.125mg daily
- Atorvastatin 10mg daily
- Warfarin
- Ferrous fumarate 300mg daily
- Darbepoetin 50mcg q 2 wk
- Ca carbonate 625mg am and 1250mg noon
- Replavite daily
- Levothyroxine 0.1mg daily
- ?metolazone, ?ASA
Mar 21: adm. for tPA treatment of ischemic leg
Mar 22: adm. to CCU → UA/NSTEMI
Mar 25: PCI → stent to LAD
Mar 28: R leg above-knee amputation
Apr 1: adm. to ICU: BP 68/40, CXR changes
  - sepsis vs cardiac source
  - Rx pip-tazo for possible HAP
Apr 5: stabilized → SDU
Apr 8: readm. to ICU with likely sepsis
What is Sepsis?

◆ Systemic inflammatory response to infection

◆ SIRS criteria:
  - T > 38°C or <36°C
  - HR > 90 bpm
  - RR > 20 breaths/min or PaCO₂ < 32 mmHg
  - WBC > 12 or <4 or >10% immature neutrophils

Resources:
1. 2007 UHN Guidelines for Antimicrobial Use (pg 221-2)
Pathophysiology

- Pathogenic organisms (endo/exotoxins, cell wall components)
- Host response → release of TNF, interleukins, nitric oxide; complement activation
- Increased endothelial permeability (↓ SVR, vasodilation)
- Neutrophil activation
Manifestations and complications

- **SIRS**
  - $T > 38^\circ \text{C}$ or $< 36^\circ \text{C}$
  - $HR > 90 \, \text{bpm}$
  - $RR > 20 \, \text{breaths/min or PaCO}_2 < 32 \, \text{mmHg}$
  - $WBC > 12$ or $< 4$ or $> 10\%$ immature neutrophils
- **↑ blood glucose**
- **↓ platelets, ↑ INR → DIC**
Manifestations and complications

- ↓ BP, ↓ perfusion → shock (BP = SVR x CO)
  - altered mental status
  - global tissue hypoxia (↑ lactate)
  - low central venous oxygen saturation (ie/ <70%)
  - organ dysfunction (“severe” sepsis)
  - oliguria (u/o < 0.5 mL/kg/hr), ↑ Scr, ↑ BUN
  - acute respiratory distress syndrome
  - shock liver (↑ transaminases, ↓ albumin, ↑ INR)
  - ischemic bowel

- 40% mortality rate
Shock

Shock: an acute, generalized state of inadequate perfusion of critical organs that can produce pathophysiologic consequences, including death


Septic shock
- sepsis with SBP <90 mmHg (hypotension)
- vasodilation (BP = SVR x CO); “warm”

Hypovolemic shock and cardiogenic shock
- ↓ CO; “cool”
How did Mr. C present?

- 77 y.o. male, in hospital x 2.5wks; DM, ESRD (PD), hypothyroidism, ++CV conditions

- April 8:
  - **CNS** – ↓ LOC
  - **Resp** – new infiltrates on CXR, purulent sputum (?aspiration pneumonia), RR 26
  - **CVS** – HR 120, BP 75/50, ScvO₂ 49%
How did Mr. C present?

**GI** – abdomen distended (ischemic bowel vs intra-abdominal infection)

**GU** – anuric (as usual); PD Δ’d to CVVHD

**ID** – T 36.4°, WBC 27.8; cultures sent (blood x 2, sputum, PD dialysate, IV catheter tip)

**Abnormal labs** – lactate 7.4, pH 7.23, AST 400, ALT 270, INR 1.85
Consistent with septic shock?

- **Source of infection** (lungs, possibly abdomen)
- **SIRS criteria (3/4)**
  - T > 38°C or < 36°C (36.4)
  - HR > 90 bpm (120)
  - RR > 20 breaths/min (26)
  - WBC > 12, < 4, or > 10% (WBC 27.8)
- **BP ↓ (75/50 mmHg)**
- **altered mental status**
- ↑ lactate (7.4), ↓ pH (7.23)
- ↓ ScvO₂ (49%)
- ↑ liver transaminases and INR (400, 270, 1.85)
- ?ischemic bowel
Clinical question

- How do we treat a patient with septic shock?
Therapeutic alternatives: Sepsis toolkit

1. Appropriate antibiotics
2. Insulin
3. Early goal-directed therapy → fluids, blood, vasoactive agents, inotropes
4. Steroids
5. Activated protein C
Appropriate antibiotics

- Sepsis is an infectious process → treat the source
- High mortality, esp. due to sudden circulatory collapse → start promptly (ie/ <24 hours)\textsuperscript{1,2}
- Empiric tx based on site of (suspected) infection; adjust ASAP when C & S reported
Appropriate antibiotics

New Nosocomial Pneumonia guidelines in UHN antimicrobial handbook (pages 127-131)

- Nosocomial bugs: enteric GNB, S. aureus, S. pneumoniae, H. influenzae

- ICU/VAP bugs: resistant GNB → pseudomonas, ESBL producing E.coli and Klebsiella, bugs with inducible chromosomal beta-lactamases; legionella

*Q: how would you empirically treat Mr. C?
Insulin – in brief

- In sepsis, blood glucose can increase (↑).
- Tight glucose control has been studied in various populations, showing some benefits (cardiac sx pts and various mixed populations).
- Insulin nomograms used in ICU.
- Sugar study ongoing!
Sepsis toolkit

- Appropriate antibiotics
- Insulin
- Early goal-directed therapy → fluids, blood, vasoactive agents, inotropes
- Steroids
- Activated protein C
Early goal-directed therapy in the treatment of severe sepsis and septic shock
Rivers et al. NEJM 2001;345:1368-77.

- Sepsis: peripheral vasodilation, intravascular volume depletion, myocardial depression, and increased metabolism
  - $O_2$ demand > delivery, tissue hypoxia, shock; can lead to multiorgan failure and death

- Resuscitation needed; past studies of “hemodynamic optimization” enrolled patients up to 72hrs after adm. to ICU (neutral)
Early goal-directed therapy
Rivers et al. NEJM 2001;345:1368-77.

- Standard hemodynamic assessment (physical findings, VS, central venous pressure, urinary output) fails to detect persistent global tissue hypoxia

- "Golden hours" before serious illness may elapse early on

- 1° efficacy outcome: in-hospital mortality
# Results: primary outcome

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>STANDARD THERAPY (N=133)</th>
<th>EARLY GOAL-DIRECTED THERAPY (N=130)</th>
<th>RELATIVE RISK (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>59 (46.5)</td>
<td>38 (30.5)</td>
<td>0.58 (0.38–0.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>Patients with severe sepsis</td>
<td>19 (30.0)</td>
<td>9 (14.9)</td>
<td>0.46 (0.21–1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Patients with septic shock</td>
<td>40 (56.8)</td>
<td>29 (42.3)</td>
<td>0.60 (0.36–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with sepsis syndrome</td>
<td>44 (45.4)</td>
<td>35 (35.1)</td>
<td>0.66 (0.42–1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>28-Day mortality†</td>
<td>61 (49.2)</td>
<td>40 (33.3)</td>
<td>0.58 (0.39–0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>60-Day mortality†</td>
<td>70 (56.9)</td>
<td>50 (44.3)</td>
<td>0.67 (0.46–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Causes of in-hospital death‡</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sudden cardiovascular collapse</td>
<td>25/119 (21.0)</td>
<td>12/117 (10.3)</td>
<td>—</td>
<td>0.02</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>26/119 (21.8)</td>
<td>19/117 (16.2)</td>
<td>—</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.
†Percentages were calculated by the Kaplan–Meier product-limit method.
‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.
Rivers conclusions

- Early, aggressive resuscitation is very important.

- Practically speaking, we may not always have access to all parameters measured (they were equipped in ER for early goal-directed therapy).
### Inotropes and vasoactive drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common dose</th>
<th>Common use</th>
</tr>
</thead>
</table>
| **Dopamine**    | <3 ug/kg/min (DA)  
3 - 10 ug/kg/min (DA, β₁)  
>10 ug/kg/min (β₁,α₁) | - inotrope, vasopressor  
- low doses not proven to prevent/treat renal failure |
| **Norepinephrine** | 2 - 20 ug/min (β₁,α₁) | - primarily used as a vasopressor (inotropic effects) |
| “LEVOPHED”      | 0.5 - 9 ug/kg/min (α₁) | - vasopressor  
- often used if arrhythmias with DA or NE |
| **Epinephrine** | -start at 0.01 ug/kg/min (β₁, β₂ → α₁) | - refractory sepsis (splanchnic circulation)  
- powerful vasopressor, inotrope |
| **Dobutamine**  | 2 - 20 ug/kg/min (β₁, β₂) | - inotrope, vasodilator  
- improves CO; may need combo |
| **Vasopressin** | 0.01 - 0.04 units/min (V1 receptors) | - vasopressor; natural hormone deficient in septic shock |
Sepsis toolkit

- Appropriate antibiotics
- Insulin
- Early goal-directed therapy → fluids, blood, vasoactive agents, inotropes
  - Steroids
  - Activated protein C
Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock

Annane et al. JAMA 2002;288:862-71

- Sepsis is an inflammatory process
  - high doses/short courses not favourable

- Observation: severe sepsis may be associated with relative adrenal insufficiency
  - replacement therapy proposed to treat septic shock
Annane et al.

1° objective:
- to assess whether low doses of corticosteroids improve 28-day survival in patients with septic shock and relative adrenal insufficiency
Methods
Annane et al.

- Very sick patients: site of infection, hyper or hypothermia, HR > 90, SBP < 90 mmHg, oliguria, lactate > 2, mech. ventilation

- Corticotropin stimulation test: blood immediately before, 30 & 60 min post
  - Take highest cortisol level as response
  - Increase of at least 250 nmol/L = responder
Methods
Annane et al.

干预措施:
- Hydrocortisone 50mg IV q6h x 7 days
- Fludrocortisone 50ug NG daily x 7 days

注释：类固醇等效性（CPS）

<table>
<thead>
<tr>
<th></th>
<th>抗炎药物剂量</th>
<th>钠钙类固醇等效性</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20mg</td>
<td>2</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5mg</td>
<td>1</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>10mg</td>
<td>125</td>
</tr>
</tbody>
</table>
### Results

Annane et al.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Steroids</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonresponders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>115</td>
<td>114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day mortality</td>
<td>73 (63)</td>
<td>60 (53)</td>
<td>0.54 (0.31-0.97)</td>
<td>.04</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>81 (70)</td>
<td>66 (58)</td>
<td>0.50 (0.28-0.89)</td>
<td>.02</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>83 (72)</td>
<td>70 (61)</td>
<td>0.53 (0.29-0.96)</td>
<td>.04</td>
</tr>
<tr>
<td>1-Year mortality</td>
<td>88 (77)</td>
<td>77 (68)</td>
<td>0.57 (0.31-1.04)</td>
<td>.07</td>
</tr>
<tr>
<td><strong>Responders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>34</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-Day mortality</td>
<td>18 (53)</td>
<td>22 (61)</td>
<td>0.97 (0.32-2.99)</td>
<td>.96</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>20 (59)</td>
<td>24 (67)</td>
<td>0.99 (0.31-3.16)</td>
<td>.99</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>20 (59)</td>
<td>25 (69)</td>
<td>1.20 (0.38-3.76)</td>
<td>.75</td>
</tr>
<tr>
<td>1-Year mortality</td>
<td>24 (71)</td>
<td>25 (69)</td>
<td>0.70 (0.20-2.40)</td>
<td>.57</td>
</tr>
<tr>
<td><strong>All Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>149</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-Day mortality</td>
<td>91 (61)</td>
<td>82 (55)</td>
<td>0.65 (0.39-1.07)</td>
<td>.09</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>101 (68)</td>
<td>90 (60)</td>
<td>0.61 (0.37-1.02)</td>
<td>.06</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>103 (69)</td>
<td>95 (63)</td>
<td>0.67 (0.40-1.12)</td>
<td>.12</td>
</tr>
<tr>
<td>1-Year mortality</td>
<td>112 (75)</td>
<td>102 (68)</td>
<td>0.62 (0.36-1.05)</td>
<td>.08</td>
</tr>
</tbody>
</table>
Sepsis toolkit

- Appropriate antibiotics
- Insulin
- Early goal-directed therapy → fluids, blood, vasoactive agents, inotropes
- Steroids
  - Activated protein C (Xigris®)
Severe sepsis (=sepsis with acute organ dysfunction) results from generalized inflammatory and procoagulant response to infection.

Inflammatory and procoagulant host responses are closely related:

- Cytokines can activate coagulation and inhibit fibrinolysis
- Thrombin can stimulate inflammatory pathways
Activated protein C (APC) has antithrombotic, antiinflammatory and profibrinolytic properties

1° Outcome: death from any cause 28 days after the initiation of the infusion
Intervention

- Inclusion: source of infection, 3/4 SIRS criteria, and dysfunction of ≥ 1 organ or system within 24 hours of study enrollment

- IV drotrecogin alfa (APC) 24ug/kg/hr x 96h or placebo

- Protocol did not standardize approach to abx, fluids pressors, ventilatory support
## Results

### Table 4. Analysis of the Rates and Risks of Death from Any Cause at 28 Days.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PLACEBO GROUP</th>
<th>DROTRECOCIN ALFA ACTIVATED GROUP</th>
<th>P VALUE†</th>
<th>RELATIVE RISK OF DEATH (95% CI‡)</th>
<th>ABSOLUTE REDUCTION IN RISK (95% CI§)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treated patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonstratified analysis</td>
<td>259/840 (30.8)</td>
<td>210/850 (24.7)</td>
<td>0.005</td>
<td>0.80 (0.69 to 0.94)</td>
<td>6.1 (1.9 to 10.4)</td>
</tr>
<tr>
<td>Stratified analysis¶</td>
<td></td>
<td></td>
<td>0.005</td>
<td>0.81 (0.70 to 0.93)</td>
<td>6.2 (1.6 to 10.8)</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>215/670 (32.1)</td>
<td>182/709 (25.7)</td>
<td>0.009</td>
<td>0.80 (0.68 to 0.95)</td>
<td>6.4 (1.6 to 11.2)</td>
</tr>
<tr>
<td>No</td>
<td>28/105 (26.7)</td>
<td>14/90 (15.6)</td>
<td>0.06</td>
<td>0.58 (0.33 to 1.04)</td>
<td>11.1 (−0.4 to 22.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>16/65 (24.6)</td>
<td>14/51 (27.5)</td>
<td>0.73</td>
<td>1.12 (0.60 to 2.07)</td>
<td>−2.8 (−19.0 to 13.4)</td>
</tr>
<tr>
<td><strong>Randomized patients¶¶</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonstratified analysis</td>
<td>268/857 (31.3)</td>
<td>216/871 (24.8)</td>
<td>0.003</td>
<td>0.79 (0.68 to 0.92)</td>
<td>6.5 (2.2 to 10.7)</td>
</tr>
</tbody>
</table>
Conclusions and issues

- Treatment with APC reduces mortality in patients with severe sepsis and may be associated with risk of bleeding.

- Adverse events: serious bleeding higher in APC group; only during infusion period and primarily if predisposed (GI ulcer, plt <30).

- Optimal duration not known (? incomplete resolution of procoagulant state after 96 hrs).
Summary

- All 3 studies (early goal-directed therapy, steroid replacement, and APC) showed a MORTALITY benefit
Interventions for Mr. C - abx

- Apr 8: continued on pip-tazo (began Apr 1)
  - added vanco briefly (?line infection)

- Apr 9: ischemic bowel → OR
  - 1m small bowel resected
  - jejunostomy and mucus stoma created
  - added fluconazole
Interventions for Mr. C - abx

- **Apr 10**: “GNB” in sputum
  - Δ’d pip-tazo to meropenem

- **Apr 11**: *Klebsiella pneumoniae*
  - R: amp, cefazolin, cefuroxime, pip-tazo
  - S: ceftriaxone, cipro, gent, Septra, meropenem (called lab)

- **Did not narrow spectrum with new abdo process**
HAP/VAP Guidelines

For your reference:

- UHN Antibiotic Handbook 2007
Mr. C – Glycemic Control

- ICU insulin nomogram
Mr. C – goal-directed therapy

- Fluid resuscitation, norepinephrine, transfusions; ultimately intubated
- Complicated by OR
- CVP 11, MAP 59, SaO₂ 94%, ScvO₂ 49%
- General monitoring of NE: hypertension, arrhythmias, ischemic injury (ie/ extremities, gut)
Mr. C – steroids

- Cosyntropin stimulation test April 8
- Began hydrocortisone 50mg IV q6h
  - Stim test results later reported (cortisol levels):
    - 1209h: 1507 nmol/L
    - 1250h: 1813 nmol/L
    - 1330h: 2010 nmol/L
  - **Responder or not? What to do with hydrocortisone?**
- No fludrocortisone
Steroid monitoring

- **Short-term tx:**
  - Psychosis
  - ↑ Blood sugar
  - Hypokalemia
  - Sodium and fluid retention; HTN, CHF
  - ↑ WBC
  - Gastric irritation, ulceration
  - ...
Mr. C – APC

- Inclusion criteria likely met April 8:
  - Serious infection managed with supportive care
  - Commitment to aggressive tx by team/family
  - 3 or more SIRS criteria
  - New onset (<48h) sepsis-induced organ dysfunction of at least 2 organs (CV, acidosis)
  - No absolute contraindications

- April 9 to OR (CI if concern for active major bleeding)

- Relative CI’s
  - Need for therapeutic anticoagulation (on heparin for valves)
Outcome

- Slow improvements until April 12, then:
  - bowel → stomas dusky, Ø BS, Ø output, foul smelling
  - became hypothermic (T 34.9°C)
  - WBC ↑ 17.7
  - lactate ↑ 3.7, pH 7.33
  - platelet drop (186 → 94), INR ↑ 1.30
  - CVP 1, ScvO₂ 54%
  - levophed ↑ 20ug/min to maintain BP

- Withdrawal of care April 13
References