What’s New in Sepsis?

Judith Hellman, M.D.
Associate Professor
UCSF Department of Anesthesia
Division of Critical Care Medicine
Outline

• Review recent epidemiology
• Discuss recent and ongoing clinical trials
• Describe knowledge of basic mechanisms as it relates to the clinical trials
• Review some promising preclinical studies
Epidemiology
## Epidemiology: Mortality of Sepsis

Table B. Deaths and death rates for 2007 and age-adjusted death rates and percent changes in age-adjusted rates from 2006 to 2007 for the 15 leading causes of death: United States, final 2006 and preliminary 2007

[Data are based on a continuous file of records received from the states. Rates are per 100,000 population; age-adjusted rates per 100,000 U.S. standard population based on the year 2000 standard; see "Technical Notes." For explanation of asterisks (*) preceding cause-of-death codes, see "Technical Notes." Figures for 2007 are based on weighted data rounded to the nearest individual, so categories may not add to totals]

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>...</td>
<td>All causes</td>
<td>2,424,059</td>
<td>803.7</td>
<td>760.3</td>
<td>776.5</td>
<td>-2.1</td>
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<td>1</td>
<td>Diseases of heart (H00-H09, I10-I13, I20-I51)</td>
<td>615,651</td>
<td>204.1</td>
<td>190.7</td>
<td>200.2</td>
<td>-4.7</td>
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<td>2</td>
<td>Malignant neoplasms (C00-C37)</td>
<td>560,187</td>
<td>185.7</td>
<td>177.5</td>
<td>180.7</td>
<td>-1.8</td>
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<td>3</td>
<td>Cerebrovascular diseases (I60-I69)</td>
<td>133,900</td>
<td>44.4</td>
<td>41.6</td>
<td>43.8</td>
<td>-4.6</td>
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<td>4</td>
<td>Chronic lower respiratory diseases (J40-J47)</td>
<td>128,311</td>
<td>42.9</td>
<td>41.2</td>
<td>40.5</td>
<td>-1.7</td>
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<td>5</td>
<td>Accidents (unintentional injuries), (V01-X59, Y85-Y86)</td>
<td>117,075</td>
<td>38.5</td>
<td>37.6</td>
<td>39.5</td>
<td>-5.0</td>
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<tr>
<td>6</td>
<td>Alzheimer's disease (G30)</td>
<td>74,844</td>
<td>24.8</td>
<td>22.6</td>
<td>22.6</td>
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<td>7</td>
<td>Diabetes mellitus (E10-E14)</td>
<td>70,805</td>
<td>23.5</td>
<td>22.4</td>
<td>23.3</td>
<td>-3.9</td>
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<td>8</td>
<td>Influenza and pneumonia (J09-J18)</td>
<td>52,847</td>
<td>17.5</td>
<td>16.3</td>
<td>17.8</td>
<td>-8.4</td>
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<td>9</td>
<td>Nephritis, nephrotic syndrome and nephrosis (N00-N07, N17-N19, N25-N27)</td>
<td>46,095</td>
<td>15.3</td>
<td>14.4</td>
<td>14.5</td>
<td>-0.7</td>
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<tr>
<td>10</td>
<td>Septicemia (A40-A41)</td>
<td>34,851</td>
<td>11.6</td>
<td>11.0</td>
<td>11.0</td>
<td>0.0</td>
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<tr>
<td>11</td>
<td>Intentional self-harm (suicide) [J01-J06, X60-X84, Y87.0]</td>
<td>33,185</td>
<td>11.0</td>
<td>10.8</td>
<td>10.9</td>
<td>-0.9</td>
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<td>12</td>
<td>Chronic liver disease and cirrhosis (K70-K73-K74)</td>
<td>28,504</td>
<td>9.5</td>
<td>8.9</td>
<td>8.8</td>
<td>1.1</td>
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<td>13</td>
<td>Essential hypertension and hypertensive renal disease ([I10-I15, I16])</td>
<td>23,769</td>
<td>7.9</td>
<td>7.3</td>
<td>7.5</td>
<td>-2.7</td>
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<tr>
<td>14</td>
<td>Parkinson's disease ([G20-G21])</td>
<td>20,156</td>
<td>6.7</td>
<td>6.4</td>
<td>6.3</td>
<td>1.6</td>
</tr>
<tr>
<td>15</td>
<td>Assault (homicide) [J01-J02, X66-X67, Y97.1]</td>
<td>17,620</td>
<td>5.8</td>
<td>5.8</td>
<td>6.2</td>
<td>-6.5</td>
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<td></td>
<td>All other causes (residual)</td>
<td>465,089</td>
<td>154.2</td>
<td>...</td>
<td>...</td>
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</tr>
</tbody>
</table>

... Category not applicable.

1Rank based on number of deaths.

2For unintentional injuries, suicides, and homicides, preliminary and final data may differ significantly because of the truncated nature of the preliminary file.

3New code J06 (influenza due to identified avian influenza virus) was added to the category in 2007.

NOTES: Data are subject to sampling and random variation. For information regarding the calculation of standard errors and further discussion of the variability of the data, see "Technical Notes."
Epidemiology: Postoperative Sepsis


- Followed trends in rates of post-op sepsis following elective major surgery between 1997-2006
- Used the Nationwide Inpatient Sample
- Evaluated 2 million elective admissions
- ICU LOS > 3 days
- Endpoints – severe sepsis, sepsis-related mortality, excess hospital costs
**Epidemiology: Postoperative Sepsis**

Anesthesiology 2010;112(4):917

- **Incidence of Sepsis**
  - Increased from 0.7 to 1.3% \((P < 0.001)\)

- **Incidence of Severe Sepsis**
  - Increased from 0.3 to 0.9% \((p < 0.001)\)

- **Sepsis-related mortality**
  - Decreased from 44.4% to 34% \((p < 0.001)\)

- **Excess hospital costs**
  - 1997 - $119,337 ± 144,705
  - 2006 - $157,882 ± 162,999
Recently Reported Clinical Trials

• Bundled therapies for sepsis
  – Crit Care Med. 2010;38(2):367-74

• Steroids + insulin in septic shock
  – JAMA. 2010;303(4):341-8

• Renal replacement therapy
  – NEJM 2008;359:7-20

• GM-CSF to reverse sepsis-associated immunosuppression
  – Am J Respir Crit Care Med. 2009;180(7):640-8

• Eritoran – TLR4 antagonist
  – Crit Care Med. 2010 Jan;38(1):72
Bundled Therapies for Sepsis


• Goal – Use sepsis bundles to change clinical behavior

• Participating centers – ICUs, ERs and wards of hospitals in the US, Europe, and South America

• Bundles of guidelines to be implemented within 6 hours (“resuscitation bundle”) and 24 hours (“management bundle”)

• Endpoints followed for ~ 3 years
  • Primary – Compliance with bundle targets
  • Secondary – Hospital mortality
Results: Bundled Therapies

Crit Care Med. 2010;38(2):367-74

- Enrolled 15,022 subjects in 30 centers
- Compliance with regimen increased from 10.9% to 31.3% over the study period (Jan05-Mar08)
  - Compliance with most facets of regimen increased
  - Compliance with inspiratory plateau pressures did not increase, but this was high at baseline
- Mortality
  - Decreased from 37 to 30.8% over the study period
  - Adjusted odds ratio for mortality got better the longer the site was in the “Campaign”
Results: Bundled Therapies (cont’d)

Crit Care Med. 2010;38(2):367-74

• Factors associated with improved mortality
  • Broad spectrum antibiotics (p < 0.0001)
  • Obtaining blood cultures before antibiotics (p < 0.0001)
  • Controlling blood glucose (p < 0.0001)
  • Drotrecogin alfa in first 24 hours if shock was associated with sepsis
  • Achieving plateau pressure control (p < 0.0001)

• Factors not associated with improved mortality
  • Measuring lactate
  • Low dose steroids
  • Goal CVP ≥ 8
  • Goal Scvo₂ ≥ 70%
Bundled Therapies: Other Studies and Concerns

- Bundled therapies have been criticized
  - Unclear value of the different facets (e.g.: Hct goals in EGDT)
  - Some therapies in bundles may not be appropriate for a given patient (e.g.: APC after CVA)

Recent Trials: Steroids + Insulin


• Hypotheses
  • Primary – Normalization of BS improves outcome in adult sepsis
  • Secondary – Fludrocortisone, in addition to hydrocortisone improves outcome

• Multicenter randomized, open label trial in patients on corticosteroids

• Inclusion – Septic shock, MODS (SOFA ≥ 8), pressor req’t, receiving hydrocortisone (HC) for septic shock
Steroids + Insulin (Cont’d)

• Groups (all groups received hydrocortisone)
  • Intensive insulin therapy (Glucose 80-110, n = 126)
  • Conventional glucose control (n = 138)
  • Intensive insulin therapy + Fludrocortisone (n = 129)
  • Conventional glucose control + Fludrocortisone (n = 116)

• Outcomes
  Primary – In-hospital mortality
  Secondary – 28-, 90-, 180-d mortality; pressor-free days;
  vent-free days; time to SOFA < 8; ICU and Hospital LOS;
time to SOFA < 8; ICU and Hospital LOS;
superinfection; weakness; PTSD
Results: Steroids + Insulin


- Blood sugar lower in intensive insulin group
- No significant differences in primary outcome between any groups
- No significant differences in most secondary outcomes
- Complications
  - More hypoglycemia in IV insulin groups (p = 0.003)
  - Fludrocortisone – Higher superinfection rate (p = 0.02)
- Interesting other aspects
  - Mortality ~ 45-50%
  - Gram-negative bacteria isolated ~ 41%
  - Medical patients represented 85-90% study pop’n
  - Cosyntropin non-responders ~ 66-68%
Renal Replacement Therapy in Critically Ill Patients (2008)

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury. NEJM 2008;359:7-20

• Critically-ill patients with AKI and ≥ 1 non-kidney organ failure or sepsis

• High intensity versus standard RRT

• Endpoints
  • 1° – All cause mortality by day 60
  • 2° – In-hospital mortality, renal recovery, etc
Results: RRT in Critically Ill Patients

NEJM 2008; 359:7-20

• 1124 subjects enrolled
  • AKI due to sepsis in 54.9%
  • Incidence of sepsis 63%
• No difference in survival or other major secondary endpoints
• Hypophosphatemia more common in high intensity group

• Conclusion: “In critically ill patients with acute kidney injury, treatment with higher-intensity continuous renal-replacement therapy did not reduce mortality at 90 days”
Targeting Sepsis Mediators

Basic Science of Sepsis
Pathophysiology of Sepsis

- Interactions between cells of host cells and microbes →
  - Upregulation of inflammation
  - Complex coagulation disturbances
  - Vascular leak
  - Apoptosis
- Innate immune pathways are central to this interaction
- A state of immunosuppression may also occur
Recent Trials: GM-CSF

GM-CSF to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. AJRCCM 2009;180(7):640-8

- Objective – Reverse immunosuppression in sepsis
- Design – Small multicenter randomized trial, treated with SQ GM-CSF vs placebo
- Endpoints
  - Primary – mHLA-DR expression (marker for immunocompetence)
  - Secondary – Time on ventilator, APACHE, SOFA, and TISS scores, ICU and Hospital LOS, inflammatory markers
Results: GM-CSF
AJRCCM 2009;180(7):640-8

• Entered 38 subjects entered; 37 completed study
• Sepsis due to Gram-negative, Gram-positive, and fungal infections
• Primary endpoint - mHLA-DR expression increased to baseline levels in GM-CSF subjects (p < 0.0001)
• Secondary endpoints
  – Mortality – Not significantly different
  – Inflammatory mediators mostly not different – except TNF which was increased in GM-CSF group (p = 0.02)
  – Inflammatory cells – Increased PMN, monocytes, T-cells, not B cells or NK cells
  – Clinical Parameters
    • Shorter time of mechanical ventilation (p = 0.037)
Toll-Like Receptors

• Innate immune receptors
  • Pattern recognition receptors (PRRs)
• Mobilize early defenses against infections
• Present on multiple cell types – Leukocytes, endothelial cells, cardiomyocytes, airway epithelial cells
• TLRs are important in sepsis
• TLR4 is being targeted for sepsis therapies
TLRs and Agonists

TLR2 - Lipoproteins, LTA, Zymosan

- Triacylated Lipoproteins
- Diacylated Lipoproteins
- Zymosan
- TLR2/6
- TLR2/Dectin-1
- LPS (Endotoxin)
- Flagellin
- TLR4
- TLR5

Endosome

- dsRNA
- Imidazoquinolines
- ssRNA
- CpG DNA
- TLR3
- TLR7
- TLR8
- TLR9

Cytoplasmic Membrane
Eritoran: TLR4 Antagonist

• Background
  • TLR4 is the receptor for endotoxin
  • MD2 - Adapter protein that interacts with LPS and TLR4 and is also required for activation

• Eritoran
  • Synthetic TLR4 antagonist
  • Competitively inhibits LPS binding to MD2 thereby interfering with MD2/TLR4/LPS complex formation and downstream signaling
  • Protective in animal models
Eritoran: Phase 2 Trial in Severe Sepsis
Crit Care Med. 2010 Jan;38(1):72

- Objectives
  - Assess safety and efficacy of eritoran tetrasodium
  - Establish therapeutic dose
- Randomized, double-blind, phase II trial
- Included 300 adults with severe bacterial or fungal sepsis
- Treated for 6 days with placebo vs 2 different doses of eritoran
- Endpoints
  - 28 day mortality
  - Laboratory parameters (CBC, coags, serum chemistries, IL-6, endotoxin, eritoran levels)
**Results Eritoran Phase 2 Trial**

- All cause 28-d mortality not significantly different
- Prespecified subgroup analyses showed trend towards lower mortality in patients with high APACHE II scores treated with eritoran (NS)

**Figure 3:**
Crit Care Med. 2010 Jan;38(1):72
Eritoran: Phase 3 Trial in Progress
Activated Protein C

• Activated protein C
  – Anticoagulant
  – Effects on inflammation

• PROWESS
  – Recombinant APC (Xigris) treatment reduced mortality in patients with severe sepsis/high APACHE

• Use is still limited
  – Expensive
  – Concerns regarding safety and efficacy
Activated Protein C (cont’d)

• European Medicines Agency
  – Approved Xigris with req’t of yearly review by agency
  – Discussion with EU have indicated need to more clearly define appropriate Xigris candidates

• Large multicenter Phase III trial underway in Europe in patients with severe sepsis at high risk of dying
Preclinical Studies

• **Apoptosis inhibition (IL-7, IL-15)**
  - IL-7 and IL-15, both inhibitors of apoptosis improve survival in sepsis models.
    - IL-7 promotes T cell viability, trafficking, and functionality and improves survival in sepsis. J Immunol. 2010;184(7):3768-79

• **Nervous system**
  - Pre-op administration of central sympatholytic reduced mortality (clonidine: p = 0.015; dexmedetomidine: p = 0.029) and decreased inflammatory mediator production in CLP model in mice.

• **Extracellular histones**
  - Antibodies to histones protect in CLP model of sepsis
Other Areas of Interest & Inquiry

- Using biomarkers as tools for diagnosis and prognostication, and to monitor resuscitation
  - Procalcitonin
  - Central venous $O_2$ sats, Lactate
    Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial JAMA. 2010;303:739

- Targets and therapies
  - Melatonin
  - Leptin
    J Neurosci. 2010 Apr 28;30(17):6036-47; CNS leptin action modulates immune response and survival in sepsis

- Misc - Omega 3, Statins

- Extracorporeal removal of toxins and host mediators (Japan)
What’s in the Future in Sepsis?

• Thoughts based on recently published data
  • Available data does not support continued use of fludrocortisone
  • Bundled therapies that present goals and targets seem to be associated with better outcomes
  • Still need to understand much more about the basic science of sepsis

• Stay tuned for results of large trials
  • Eritoran (TLR4 antagonist)
  • Drotrecogin alfa
  • ProCESS - Protocolized Care for Early Septic Shock
Thank You!