Sepsis: A clinical overview and an update on early goal directed therapy

David T. Huang, MD, MPH

Associate Professor
Critical Care Medicine
Emergency Medicine
Clinical and Translational Science
School of Medicine
University of Pittsburgh
Outline – 35 minutes

Clinical overview
- What is sepsis?
- What is the epidemiology?
- What’s it look like?

EGDT
- Background
- ProCESS
  - Design, update, “sibling” trials

Conclusions
What is sepsis?

“the culmination of complex interactions between the infecting microorganism and the host immune, inflammatory, and coagulation responses”

Russell, JA. NEJM 2006
Not just a “cytokine storm”!

- GenIMS (Genetic + Inflammatory Markers of Sepsis)
- NIGMS/NIH R01 y2001-2005
- Inception cohort study of patients presenting to ED with community-acquired pneumonia
  - N = 2,320 at 28 hospitals clustered in 4 states

Specific aim # 2:
- To investigate the relationships [between....] inflammatory mediator response, and clinical course and outcome
HMGB-1 persistently elevated in ~ ALL CAP pts

Cytokines

- Levels are varied, persistent, + clinically overlap

Kellum et al. Arch Int Med 2007

- IL-6
- TNF
- IL-10
Blocking inflammation doesn’t work

بذل دعمًا فعالًا

أو على الأقل تدفق دفعًا 1 مسار معنوي لا يعمل

أطول تاريخ من الفشل في التجارب

- 2000 - E5 (نفازونتسيك أنبيبي حيوان)
- 2003 - OPTIMIST (مسار على سرير بائس انباور)
- 2011 - ACCESS (TLR-4 مثبط)

- أيضًا في 2011، جائزة نوبل في الطب منحها على TLR-4 مستقبلات
Pathophysiology – the bottom line

- Incredibly complex

- No one knows entire story

- Sepsis still
  - Mysterious
  - Frustrating
  - Very bad

Incredibly complex
No one knows entire story
Sepsis still
- Mysterious
- Frustrating
- Very bad
Epidemiology

- **Who gets it? And dies from it?**
  - Elderly, comorbidities

- **Where does it occur?**
  - ½ outside the ICU

- **When does it occur?**
  - First few days of hospitalization
Incidence by Age

Angus et al, CCM 2001
Mortality by Age
What everyone quotes

- **Common**
  - 750K severe sepsis cases/year

- **Expensive**
  - $17 billion/year

- **Deadly**
  - 1 in 3 die
  - As many deaths/year as myocardial infarction
Epidemiology nuances that matter

“Treated incidence”
3147 pts, 198 ICUs, 24 European countries

Sepsis – common, lethal, and highly variable across countries

Mortality, %

Y = 0.51 x - 0.11

R² = 0.80
“Treated incidence” effect?

Less ICU beds <-> higher ICU sepsis incidence and mortality

## Sepsis outside the ICU

**Sepsis not exclusively an ICU disease**

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>Condition</strong></td>
<td>Sepsis syndrome</td>
<td>Severe sepsis</td>
<td>Severe sepsis</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>8 U.S. academic centers</td>
<td>U.S. hospital discharge data (nat’l projection)</td>
<td>3 Spanish academic centers</td>
</tr>
<tr>
<td>% that did NOT receive ICU care</td>
<td>41%</td>
<td>48.9%*</td>
<td>68%</td>
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(*31.6%, if incl. IMU + CCU)
Sepsis epidemiology - ED

Only 2 national U.S. studies
# Sepsis epidemiology - ED

<table>
<thead>
<tr>
<th></th>
<th>Wang 2007</th>
<th>Strehlow 2006</th>
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<tbody>
<tr>
<td>Primary aim</td>
<td>Severe sepsis</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Data source</td>
<td>ED visit national sample</td>
<td>ED visit national sample</td>
</tr>
<tr>
<td>Strategy</td>
<td>ICD-9-CM codes</td>
<td>ICD-9-CM codes</td>
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<tr>
<td>Case definition</td>
<td>1. Infection OR abnormal Temp +</td>
<td>“Sepsis” (septicemia)</td>
</tr>
<tr>
<td></td>
<td>2. organ dysfunction OR hypotension</td>
<td></td>
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<tr>
<td>Estimate</td>
<td>571,000 cases/year (suspected cases)</td>
<td>282,000 cases/year (23,000 severe sepsis)</td>
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Sepsis epidemiology - ED

Key points

- Case definition!
- Defining sepsis in ED particularly challenging
- ED sepsis is common
Day 1 is most common day of death (1997 Medicare data)

Kaplan et al. AJRCCM 2002
Day of onset of sepsis-related organ failure in CAP

- Highest frequency is first hospital day (GenIMS)
Timing of ARDS development

Gajic et al. AJRCCM 2011
What’s sepsis look like?

All about the case definition!
What’s sepsis look like?

All about the case definition!
2001 International Sepsis Definitions Conference

1992 definitions left essentially unchanged
- Sepsis = infection + systemic inflammation
- Severe sepsis = sepsis + organ dysfunction
- Septic shock = sepsis + hypotension

Broader definition of “systemic inflammation”
- “looks septic”
- “facilitating a bedside diagnosis should have primacy over research entry criteria”
- So not just SIRS
  - Temperature
  - Heart rate
  - WBC, bands
  - Respiratory rate, pCO2

Levy et al. Crit Care Med 2003
Nonspecific signs and symptoms

Table 1. Diagnostic criteria for sepsis

<table>
<thead>
<tr>
<th>Infection, documented or suspected, and some of the following:</th>
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<tbody>
<tr>
<td>General variables</td>
</tr>
<tr>
<td>Fever (core temperature &gt;38.3°C)</td>
</tr>
<tr>
<td>Hypothermia (core temperature &lt;36°C)</td>
</tr>
<tr>
<td>Heart rate &gt;90 min⁻¹ or &gt;2 SD above the normal value for age</td>
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<tr>
<td>Tachypnea</td>
</tr>
<tr>
<td>Altered mental status</td>
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<tr>
<td>Significant edema or positive fluid balance (&gt;20 mL/kg over 24 hrs)</td>
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<tr>
<td>Hyperglycemia (plasma glucose &gt;120 mg/dL or 7.7 mmol/L) in the absence of diabetes</td>
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<thead>
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<th>Inflammatory variables</th>
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<tbody>
<tr>
<td>Leukocytosis (WBC count &gt;12,000 µL⁻¹)</td>
</tr>
<tr>
<td>Leukopenia (WBC count &lt;4000 µL⁻¹)</td>
</tr>
<tr>
<td>Normal WBC count with &gt;10% immature forms</td>
</tr>
<tr>
<td>Plasma C-reactive protein &gt;2 SD above the normal value</td>
</tr>
<tr>
<td>Plasma procalcitonin &gt;2 SD above the normal value</td>
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<th>Hemodynamic variables</th>
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<tr>
<td>Arterial hypotension⁶ (SBP &lt;90 mm Hg, MAP &lt;70, or an SBP decrease &gt;40 mm Hg in adults or &lt;2 SD below normal for age)</td>
</tr>
<tr>
<td>Svo₂ &gt;70%⁶</td>
</tr>
<tr>
<td>Cardiac index &gt;3.5 L min⁻¹ M⁻²</td>
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<th>Organ dysfunction variables</th>
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<tr>
<td>Arterial hypoxemia (Pao₂/Fio₂ &lt;300)</td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt;0.5 mL  kg⁻¹ hr⁻¹ or 45 mmol/L for at least 2 hrs)</td>
</tr>
<tr>
<td>Creatinine increase &gt;0.5 mg/dL</td>
</tr>
<tr>
<td>Coagulation abnormalities (INR &gt;1.5 or aPTT &gt;60 secs)</td>
</tr>
<tr>
<td>Impaired bowel sounds</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt;100,000 µL⁻¹)</td>
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<tr>
<td>Hyperbilirubinemia (plasma total bilirubin &gt;4 mg/dL or 70 mmol/L)</td>
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<th>Tissue perfusion variables</th>
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<tr>
<td>Hyperlactatemia (&gt;1 mmol/L)</td>
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<tr>
<td>Decreased capillary refill or mottling</td>
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WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; Svo₂, mixed venous oxygen saturation; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

*Infection defined as a pathologic process induced by a microorganism; Svo₂ sat >70% is normal in children (normally, 75–80%), and CI 3.5–5.5 is normal in children; therefore, NEITHER should be used as signs of sepsis in newborns or children; diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5 or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.
Biomarkers?

- No “troponin” of sepsis
- No “gold standard” for infection/sepsis

**Procalcitonin**
- Promising, but not proven
- Most trials from Switzerland/Europe
  - Design features not feasible in U.S.

**Lactate**
- Not specific for sepsis
- But sensitive for occult critical illness
- #1 clinically useful biomarker
Conclusions - Sepsis

- Sepsis is complex, not well understood
- Age, comorbidities at highest risk
- Common, expensive, deadly

**Occurs**
- In first 1-3 days
- ½ outside the ICU

**Protean manifestations**
- Lactate for occult cases
Systemic hypoperfusion (global tissue hypoxia) is a cardinal, yet often cryptic, feature of severe sepsis and septic shock.

In sepsis, global tissue hypoxia results from:
- Inflammatory cascade leading to cardiovascular insufficiency
- Increased metabolic demands
- Decreased oxygen delivery
  - Hypovolemia, vasodilation, myocardial depression
- Increased oxygen extraction
- Mitochondria defects and / or cytopathic hypoxia

EGDT may provide early recognition and resolution of global tissue hypoxia:
- Rivers thus focused on Emergency Department
  - Past negative, even harmful, ICU studies (Hayes,Gattinoni)
Early Goal-Directed Therapy

Supplemental oxygen ± endotracheal intubation and mechanical ventilation

SIRS + Infection + (SBP < 90 mmHg after bolus OR LA ≥ 4 mmol/L)

Central venous and arterial catheterization

Sedation and/or paralysis (if intubated)

CVP

MAP

ScvO₂

Goals achieved

Hospital admission

<8 mm Hg

≥65 and ≤90 mm Hg

≥70% and ≤90 mm Hg

≥70% and ≤90 mm Hg

<70%

≥70%

<65 mm Hg

>90 mm Hg

<70%

≥70%

Vasoactive agents

Transfusion of red cells to hematocrit ≥30%

Inotrope agents

Crystalloid

Colloid

No

Yes

Hospital admission
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

❖ Single center study
❖ N=263

❖ Protocolized EGDT vs. control

❖ 16% absolute mortality reduction
❖ 30% vs. 46%
EGDT in the First Six Hours

Control: 3.5L IV fluids
EGDT: 5.0L IV fluids

Percent

Control - EGDT

PRBC: 19 - 64
Vasopressor: 30 - 27
Inotrope: 1 - 14
Meeting ScvO2 Goal: 60 - 95
Concerns

- **High control arm mortality (46%)**
  - Subsequent studies 20-25% mortality

- **Low initial ScvO2 (49%)**
  - Subsequent studies >65-70% ScvO2 (Nguyen 2007, Jones 2010)

- **What ‘is’ the intervention, exactly?**
  - The suite of physiology-based instructions and therapies?
  - Presence of dedicated sepsis team?

- **Are the catheter, blood, and inotropes necessary?**
  - Nguyen 2007 – 11% transfusion
  - Jones 2010 – 3% transfusion
Treatment of low Hb / ScvO2

- Do nothing else.
- Transfuse PRBCs for Hb > 10 g/dl
- Increase norepi; no need to assess CO
- Add inotrope; no need to assess CO
- Place CO monitor and Rx as indicated
- Clinical examination and act as indicated

Reade, Huang et al Emerg Med J 2010
Post-Rivers

Endorsement in Surviving Sepsis Campaign
- 2008: GRADE 1C recommendation

But, adoption slow overall
- Logistical burden to initiate change
- Knowledge transfer
- Resource concerns
  - Huang et al CCM 2007, Cardblom et al CCM 2008

Many single center reports of benefit
- ‘Before-and-after’ designs

4 subsequent RCTs
- 100 – 300 subjects
- Only 1 ED-based
Protocolized Care of Early Septic Shock

NIH-funded program-project (P50)
- Subproject #1: Clinical efficacy
- Subproject #2: Mechanism of action
- Subproject #3: Cost, cost-effectiveness, and logistics

Primary questions
- Is team-based protocolized resuscitation with timed instructions superior to ‘usual’ care?
- If so, does the addition of ScvO2 monitoring with titration of blood and inotropes to optimize ScvO2 further improve survival?
Clinical efficacy

- **Primary endpoint**
  - Hospital mortality (prior to discharge or 60 days, whichever comes first)

- **Secondary endpoints**
  - Long-term survival
  - Organ failure

- **Powered to find 6-7% mortality reduction**
  - Assumes ~25% control mortality

- **3 arms**
  - ‘Usual care’
  - Sepsis team delivering the Rivers EGDT protocol
  - Sepsis team delivering Protocolized Standard Care (PSC)
Considerations

- **3 vs. 2 arms**
  - Incremental benefits of the Rivers protocol per se

- **Protocolized Standard Care (PSC) arm**
  - Clinicians
    - Is there a simpler approach than EGDT?
  - NIH
    - What is usual care?
    - *Considering Usual Medical Care in Clinical Trial Design: Scientific and Ethical Issues. Bethesda, MD, Nov. 2005*
  - Created a structured, alternative approach that:
    - Provides 6h of team-based, protocolized care
    - Uses only common ED equipment and treatments
    - Does **not** routinely mandate central lines, inotropes, blood
    - Is based on current optimal practice, literature review, Site PI feedback, international survey
    - Serves as a structured control arm
Considerations

- **Randomizing by patient, not site**
  - Risk by patient is contamination
    - Reduces treatment benefit
    - Counteract with sample size
  - Risk by site is uneven baseline variables
    - Potential fatal flaw

- **Using a sepsis team**
  - Standardized identification, training, and QA of team
    - Can be ED or ICU based (or hybrid model)
    - Easier to describe, reproduce, and disseminate
  - Minimize drift between usual care and intervention arms
ProCESS Update

- Expanded to ~30 sites with additional NIH ARRA funding
- 1230 subjects enrolled as of October 2012
  - 1st interim analysis completed
Generalizability

- Measure of effect dependent on control arm

- Therefore, differences in current usual care between regions and countries will threaten generalizability

- We know there are differences in usual care

- Conduct ‘ProCESS’ in different countries
  - But, unlike NICE-SUGAR, multiple studies
    - Stand-alone
    - Be combined post-hoc, based on pre-hoc plan
ARISE (Australasia)

- ANZICS, funded by Australian MRC
- EGDT vs. usual care
- Primary aim: all-cause 90 day mortality
- 46 sites
- Enrolled 838 subjects (Jan 2012)
- ARISE and ProCESS enrolling at near-identical rates per site
  - Common intervention
  - Common procedures
ProMISe (UK)

- ICNARC/ICS, funded by UK MRC
- EGDT vs. usual care

Two primary aims:
- 90 day mortality
- Cost per QALY at 1 year

- 47 sites
- Enrolled 262 subjects (Jan 2012)
Plans to understand generalizability

- 3 national studies

- Joint, prospectively-defined, patient-level meta-analysis
  - PRISM
    - Reade et al Intensive Care Med 2010

- Oversight and coordination
  - Common Rivers intervention arm
    - Standardized training and implementation
  - Common inclusion criteria
    - Early severe sepsis in the ED; randomize within 2h
  - Common data collection variables

- Joint trial methodology paper (CONSORT)

- Advantages
  - Each study informs locally of likely benefit
  - Power to find overall smaller but still meaningful effects
  - Power to explore subgroups of patients
Conclusions - EGDT

- EGDT has highlighted and can potentially revolutionize initial sepsis management
  - Few question “earlier is better”

- But concerns remain…
  - Generalizability
  - Complexity

- Background context is a dominating factor
  - Very different from ‘placebo’
  - Precludes traditional ‘multinational’ approach

- Attempt multiple national clinical trials
  - Coordinated aspects to facilitate prospective meta-analysis