Sepsis: Update

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Syllabus

Prevalence of High Profile Dzs

Mortality of High Profile Diseases

Sepsis: Consistently high mortality rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>Mortality Rate (%)</th>
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<tbody>
<tr>
<td>Brun-Buisson, 1995</td>
<td>Severe sepsis</td>
<td>55%–60% (1052)</td>
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<tr>
<td>Abraham, 1997</td>
<td>Septic shock</td>
<td>42% (62)</td>
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<tr>
<td>Matas, 1998</td>
<td>Severe or shock</td>
<td>38% (1359)</td>
</tr>
<tr>
<td>Friedman, 1986</td>
<td>Septic shock</td>
<td>49.7% (10,684)</td>
</tr>
<tr>
<td>Panacek, 2004**</td>
<td>Severe or shock</td>
<td>47.8% (2,834)</td>
</tr>
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<td>Now; 2013-2014</td>
<td>Severe or shock</td>
<td>15–30% (several studies)</td>
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*Prospective survey 26 sk mortality; randomized placebo-controlled trial, 20-day mortality. 
**Outcome of patients using a 32-center hospital database. 
†Change of 20% in 30 and 60 days.

Sepsis therapy questions

• Diagnosing & understanding the pathology
• Therapy: overview
• Therapy: investigational
• Therapy: back to the basics
• Therapy: EGDT…all or part
• Tx: Steroids? Transfusions? Inotropes?
• CMS reporting measures

Looking for sepsis
Screening and risk stratification
The Sepsis Continuum (defined)

<table>
<thead>
<tr>
<th>SIRS</th>
<th>Sepsis</th>
<th>Severe Sepsis</th>
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<td>SIRS due to infection</td>
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SIRS clinical criteria

≥ 2 of the following:
- T > 38°C or < 36°C
- HR > 90
- RR > 20
- WBC abnormality
  - > 12,000 or < 4,000 (or > 10% Bands)

Bone Chest 101: 1644, 1992

SIRS ≠ Sepsis

Horeczko, Green, Panacek. Epidemiology of SIRS in ED. WestJEM. 2014
- NHAMCS dataset analysis 2007-10 (103,701 pts)
- Frequency of SIRS in the ED = 17.8%
  - = ~ 16.6 million adult ED visits with SIRS per year.
- Infection accounted for only 26% of SIRS patients.
  - Traumatic causes of SIRS comprised 10% of presentations
  - other traditional categories of SIRS were rare
- Conclusions: SIRS is very common in ER
  - Vast majority are not sepsis
  - SIRS screens best if modified by clinician judgment

SIRS does not always → SIRS*

Efforts to identify serologic markers to Dx sepsis and risk stratify pts
- Like a panel of LFTs for infection
- CRP, PCT, IL-6, TNF, others
- No panel yet validated
- Lactate most useful so far

Serum lactate as a predictor of mortality in patients with infection.
- 1187 adult patients admitted for infectious process with serum lactate tested in ED
- Stratified lactate into 3 categories
  - 0-2.0 mmol/L (normal)
  - 2.4 mmol/L (mild elevation)
  - ≥ 4.0 mmol/L (marked elevation)
But lactate is ~ non-specific and affected by multiple factors

- Post seizures
- Underlying liver disease
- Type A and Type B lactic acidosis
- Metformin decreases prognostic utility
  

Therapy of sepsis

Standard care

Investigative options

The SEPSIS cascade and therapy options

- Local infection  ➔  Antibiotics
- Source control
- Local inflammation  ➔  non-specific anti-inflammatory
- Systemic inflammation  ➔  Immunomodulation Tx
- Shock  ➔  Pressors, steroids
- Multiple organ failure  ➔  Supportive ICU care
- Death (or recovery)

Decades of Negative Sepsis Trials targeting sepsis cascade mediators

<table>
<thead>
<tr>
<th>Prostaglandins</th>
<th>Ibuprofen</th>
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<tr>
<td>Endotoxin</td>
<td>HA-1A, E5, removal by dialysis</td>
</tr>
<tr>
<td>Interferon - gamma</td>
<td>Interferon - gamma</td>
</tr>
<tr>
<td>GCSF</td>
<td>Filgrastim</td>
</tr>
<tr>
<td>Free Radicals</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Deltibant</td>
</tr>
<tr>
<td>Endorphins</td>
<td>Naloxone</td>
</tr>
<tr>
<td>Microcirculation</td>
<td>Pentoxyfilline</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>L-NMMA</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>Antithrombin III inhibitor</td>
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Only 1 FDA approved biotech agent for the treatment of sepsis

Approved in 2001

Recombinant Activated Protein C

“Drotecrogin alpha” (Xigris)

Approval withdrawn 2013
Does the use of appropriate antibiotics impact sepsis outcome?

MacArthur, Panacek, Albertson, Marshall. CID. 2004

- Post-hoc analysis of a large sepsis RCT
- Compared patients receiving antibiotics that covered the offending organism at the time of study entry vs. not
- Overall, 91% of patients received appropriate Abx
- Absolute mortality rate 10% lower in the appropriate Rx group (33% vs 43%)

Duration of hypotension before Abx is a determinant of survival in sepsis


- Retro cohort study, 2184 adults, 14 ICUs
  - Tx with Abx after onset of sepsis shock
  - Examined survival by timing of initial Abx
- Results:
  - Median time to effective Abx = 6 hours
    - Interquartile range 2-15 hrs
  - Best survival when Abx within 1 hr of ↓ BP
  - Each hr of delay ↓ survival by 7.6%

Changed approach to antibiotic selection

1980s - 1990s
- Start narrow, ordered by inpt physician
- Culture and revise, broaden as needed
- Reason: Cost control. ID gatekeepers

2000s
- Start broad, early
- Culture early, later narrow if able, based on sensitivities
- EBM: ↓ hospital LOS, better outcomes

Sepsis & Abx: Take-home points

- Early & broad spectrum
  - Culture early
  - Generally multiple antibiotics, not single-drug therapy for suspected sepsis
- Give initial dose ASAP
  - In the ED, if presenting there
Does adequate infection source control impact sepsis mortality?

Marshall, Johnson, Panacek, Albertson. CCM, 2001

- Post-hoc analysis of large sepsis RCT
- Compared patients receiving appropriate and timely infection source control (of the sepsis cause) vs. not
  - This could be surgical or other interventions
- Results: Absolute mortality 9% lower in the appropriate Tx group

Sepsis and source control: Take home points

- Early, effective drainage of focused infections is as important as other therapies
- Early surgical consultation, or other interventions (when relevant)

Steroids for the treatment of septic shock

- ? a non-specific modulator of the inflammatory response
- Studies of high dose therapy showed no benefit and possibly an adverse effect NEJM. 1986
  - e.g. 30mg/kg of solumedrol IV

Landmark low dose steroid Tx study


- Stress dose steroid RCT in septic shock pts (requiring pressors)
- 50 mg of HC IV q 6 hr and 50 mg of FC p.o. Q D, for 7 days (started within 8 hours of Dx) vs. placebo
- 299 total pts (229 ACTH non-responders)
- Absolute mortality reduction of 15% (65 VS 50%) in the treated group

Steroids in sepsis: Controversies

- Most later studies of low dose steroids in sepsis have been negative
  - e.g. CORTICUS study, 2007
- Initial HC Tx in the ER can interfere with subsequent adrenal testing
  - Cortisol levels, Cortosyn stimulation test

Recent review: “In our view, refraining from all steroid use, administering only to the most ill, or giving it to a wider group of pts with septic shock, all remain rational courses of action”
  - Lamontagne. Annals IM. 2008 (JC4-6)

Vasopressor therapy in sepsis

Choice of pressors
Choice of pressors for the treatment of septic shock: Norepinephrine wins


- RCT: dopamine vs. norepinephrine in septic pts with shock despite adequate volume resuscitation and moderate doses of dopamine +/- dobutamine
- Mortality:
  - Dopamine as the pressor: 40%
  - Norepinephrine: 28%

**Take home points**

- By 2012, multiple concordant studies.
- Dopamine should no longer be the first choice pressor for septic shock
  - And maybe not for much else either

**Pressor take home points**

For septic shock:
- Avoid dopamine
- Levophed = first line pressor
- Vasopressin = next best choice
  - ?epinephrine as second line option
- Tx target = MAP 65-70

**2001: A landmark article on resuscitative support in the ER treatment of sepsis!**

Early Goal Directed Therapy
“EGDT”

**Early goal-directed therapy in the Tx of severe sepsis and septic shock**

*Rivers, et al. NEJM. 2001;345:1368*

- RCT in severe sepsis pts in the ED for 6 hrs
  - BP shock, lactate shock or organ failure pts
- “standard” vs aggressive protocol (EGDT)
  - Targets for CVP, mixed venous O₂, MAP, UO and Hct
- Results: In-hospital mortality much lower in the “Goal-directed” group: 30% vs 46%
  - -> less resource utilization during hospitalization
What did EGDT teach us?
Several lessons for EM and CCM
1. “cryptic” shock exists is sepsis
   • Identified with elevated serum lactate levels
2. Resuscitation in sepsis needs other/better end points than HR, BP, pH
3. Physicians under fluid-resuscitate sepsis
   • Giving 1.5-2 liters too little IVF initially
4. The early initial period of care (1-6 hrs) makes a major difference in outcomes
   • Perhaps more than any other factor

2003-12: Several “Before and after” type studies endorsed the value of EGDT

.... And in 2014, two large multicenter RCTs were published that tried to prospectively study EGDT Tx:

**ProCESS and ARISE**

“ProCESS” Study
(Protocolized care of early severe sepsis).
Yealy, Angus, et al. NEJM 2014

• 20 center NIH study, 1341 patients
• Goal: Externally validate EGDT in the ED
  • 3 arm RCT → EGDT, Protocolized ICF, vs usual care
• Results: no significant difference in any arm
  • 60 day mortality: EGDT 21%, PSC 18%, Usual 19%
• No significant differences in:
  - 1-year mortality
  - the need for organ support.

Goal-Directed Resuscitation for Patients with Early Septic Shock. ARISE study

• 51 centers, 1600 pts, RCT EGDT vs usual care
• Results: no difference in mortality:
  - 18.6 vs 18.8%
• EGDT pts received more of:
  - IVF in 6 hrs (1964 ml vs. 1713ml)
  - vasopressor infusions (66.6% vs. 57.8%)
  - red-cell transfusions (13.6% vs. 7.0%)
  - dobutamine (15.4% vs. 2.6%)

Common ProCESS/ARISE interpretation:

**EGDT doesn’t work.**
Original study was wrong.

*Is that ....True?*

ProCESS & ARISE Lessons

What they did find:
• Overall sepsis mortality rates are dropping
• Early recognition is important
• Std care has evolved. Early aggressive IVF is routine
• Transfusions, CVP monitoring, and dobutamine do not have proven additional value

What they did not find:
• Delays in recognition, resuscitation, care are OK
• Initial EGDT study results were erroneous
• CVP, dobutamine and transfusion have no role
Sepsis care has evolved significantly since the EGDT study was performed

- Earlier recognition
- Liberal lactate ordering
- Early liberal fluid resuscitation

CMS core measures

Sepsis bundles

CMS sepsis related metrics

- Started October 1, 2015
- Compliance with sepsis “bundles” for pts with Severe Sepsis & Septic Shock
  - All hospital pts, not just ED
  - 3 hour and 6 hour bundles
- Will be publically reported data
- Eventually will affect hospital payments

CMS sepsis required bundles

- 3 hour bundle:
  - Measure lactate
  - BCs and antibiotics (acceptable Abx)
  - 30ml/Kg IVF if in shock
- 6 hour bundle:
  - Repeat lactate if initial is elevated
  - If in shock:
    - Vasopressors
    - Recheck volume status and tissue perfusion assessment

CMS sepsis controversies

- Non-EBM based definitions of “Severe Sepsis” and Septic Shock
- Failure to recognize pre-existing organ dysfunctions as not sepsis related
- Restrictive acceptable initial antibiotic regimens for sepsis treatment
- Expect changes from CMS...

To summarize..
Conclusions: Sepsis for 2015

• Early recognition of SIRS, sepsis
  – SIRS screening alerts, Liberal use of lactates
• Early broad spectrum antibiotics
  – Blood cultures, then first dose in the ER
  – generally more than one antibiotic
• Early infection source control
• Aggressive volume resuscitation in most pts → 2-3 liters quickly
  – More as needed

Sepsis EM conclusions (2)

• If shock, despite volume resuscitation → start norepinephrine as the pressor of choice
  – If norepi doesn’t work, add vasopressin
  – Target = MAP 65-70
• ? Stress replacement doses of steroids in selected patients with refractory septic shock (i.e. requiring pressors)
• Selective use of CVC → pts with ongoing shock and unclear CVP status

Sepsis EM conclusions (3)

Other considerations:
• Selective use of transfusions
• Selective use of inotropes

And ……
• Beware of the CMS performance metrics
  – The basic 3 and 6 hour bundles will continue
  – Definitions and details will change

The end