Prehospital \textit{treatment} of sepsis

Christopher W. Seymour, MD MSc

The CRISMA Center
Assistant Professor of Critical Care Medicine & Emergency Medicine
University of Pittsburgh School of Medicine
Disclosures

• Received funding from:
  NIH NIGMS, SCCM, AHA, MedicOne, SIS

• Consulting fees from Beckman Coulter, Edwards Inc.

• Member, Surviving Sepsis Campaign, ATS representative

• Member, 2016 Third International Sepsis Definitions Task Force
Caveats

• I am not an EMS clinician

• Involved in prehospital sepsis treatment trial (CIHR, PI: Scales, PITSTOP) planning to enroll in 2018

• Intensivist at UPMC-Mercy in Pittsburgh, PA
Objectives

• What did we discuss last lecture
  • Definitions, criteria

• What are the main tenets of sepsis treatment

• What can we do NOW during prehospital care

• What will we do in the FUTURE

• Questions
Sepsis is everywhere.

2 million US cases each year

5 percent of US healthcare spending

Singer et al., JAMA, 2016
Sepsis defined

- Infection
- Organ dysfunction
- Life threatening
- Dysregulated host response
Clinical criteria for sepsis

- Infection plus 2 or more SOFA points above baseline

Prompt to consider sepsis outside the ICU

- Infection plus 2 or more qSOFA points
Finding sepsis in prehospital care

Organ dysfunction

qSOFA, PreSEP

Shock index, SOFA

Infection

Fever

Clinical acumen

No infection

No organ dysfunction
Conclusions – last time

• Sepsis is an enormous public health problem

• New sepsis definitions released in 2016

• Clinical suspicion for infection remains a challenge

• New tools such as qSOFA may be prompts but are not adequately sensitive

• New and old biomarkers – good for research – not yet ready for prime time
So now what?

I’ve found a septic patient, what can we do...
Primary elements of management

(after recognition and risk stratification)

- Identification and control of sepsis source
- Timely administration of antibiotics
- Hemodynamic support for shock with appropriate monitoring
- Explicit use of serum lactate
- Fluid bolus therapy
Source control

All those physical measures used to control a focus of invasive infection and to restore the optimal function of the affected area.

John Marshall

- Drainage of closed space infection, liquid
- Debridement or physical removal of infected tissue/device
- Abdomen, chest, skin, soft tissue
Source control,

99 Medical – surgical ICUs
3,663 patients severe sepsis, septic shock
2011 – 2013

OR for source control: 0.81 (95%CI: 0.65, 0.99, p=0.04)
E. Source Control

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).

2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).

3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess) (UG).

4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).
Timely administration of antibiotics

Clinical practice guidelines and CMS

1. We recommend the administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock (strong recommendation; moderate quality of evidence).
Mice with CLP polymicrobial sepsis and physiologic deterioration, test early vs late antibiotic administration

- Measure 24 hr biomarkers
- Survival

Example of preclinical data

Example of preclinical data, \textsuperscript{2}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{graph.png}
\caption{Survival rates over time for different antibiotic treatment conditions.}
\end{figure}

\textsuperscript{2} Lewis et al. \textit{unpublished data}
Meta analysis → not so fast

- No benefit from antibiotics administered with 3 hours of ED arrival

- Unintended consequences?
  - Adverse effects
  - Burden on clinical team
  - Over-use, resistance

- No randomized clinical trial

Sterling et al., Crit Care Med, 2015
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Time to antibiotics administered in New York State

Odds ratio for in-hospital mortality = 1.04 [1.03 – 1.06]
Risk of death

B Administration of Antibiotics

In-Hospital Mortality (%)

Crude
Risk adjusted

Time to Administration of Antibiotics (hr)

*Predictive margins from average of independent variables
# Recommendations

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Severe Sepsis</th>
<th>Septic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surviving Sepsis Campaign, 2012 *</td>
<td>1 hr of recognition</td>
<td>1 hr of recognition</td>
</tr>
<tr>
<td>CMS SEP1 bundle</td>
<td>3 hr of recognition</td>
<td>3 hr of recognition</td>
</tr>
</tbody>
</table>

* Strong recommendation, moderate quality of evidence

https://www.acep.org/content.aspx?id=104615
Hemodynamic support
(vasopressors for shock)

- SOAP II trial
- 1,044 septic shock
- More arrhythmias in dopamine vs. norepinephrine

Hemodynamic support, 2

- Not specified in CMS SEP1 bundle

- Appropriate for patients with septic shock (defined?) who are not responsive to initial fluid challenge

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed Risk</th>
<th>Corresponding Risk</th>
<th>Relative Effect (95% CI)</th>
<th>No. of Participants (Studies)</th>
<th>Quality of the Evidence (GRADE) Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term mortality</td>
<td>530 per 1000</td>
<td>482 per 1000 (440 to 524)</td>
<td>RR 0.91 (0.83 to 0.99)</td>
<td>2043 (6 studies)</td>
<td>@@@@ moderate&lt;sup&gt;Ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serious adverse events — Supraventricular arrhythmias</td>
<td>229 per 1000</td>
<td>82 per 1000 (34 to 195)</td>
<td>RR 0.47 (0.38 to 0.58)</td>
<td>1931 (2 studies)</td>
<td>@@@@ moderate&lt;sup&gt;Ac&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serious adverse events — Ventricular arrhythmias</td>
<td>39 per 1000</td>
<td>15 per 1000 (8 to 27)</td>
<td>RR 0.35 (0.19 to 0.66)</td>
<td>1931 (2 studies)</td>
<td>@@@@ moderate&lt;sup&gt;Ac&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
### Recommendations

<table>
<thead>
<tr>
<th>Vasopressor choice</th>
<th>Role</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>Primary</td>
<td>Moderate</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Secondary</td>
<td>Low</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Adjunct, norepi sparing</td>
<td>Moderate</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Primary if bradycardia</td>
<td>Low</td>
</tr>
</tbody>
</table>

Serum lactate measurement

- Prognostic marker for low organ / tissue perfusion
- Robust association in more than > 100 cohorts
- Not a diagnostic marker
- Unclear role in management protocols

Seymour et al. JAMA, 2016
Serum lactate measurement,

**Sepsis CMS Core Measure (SEP-1)**

- Measure within 3 hrs
- Repeat within 6 hrs

Measures every 2 hrs during guided resuscitation protocol

49% reduction in odds of death

*Early Lactate-Guided Therapy in Intensive Care Unit Patients: A Multicenter, Open-Label, Randomized Controlled Trial*

Tim C. Jansen¹, Jasper van Bommel¹, F. Jeanette Schoonderbeek¹, Steven J. Slootwijk Vissers¹, Johan M. van der Klooster¹, Alex P. Lima¹, Sten P. Willemsen³, and Jan Bakker¹, for the LACTATE study group*
# Recommendations

<table>
<thead>
<tr>
<th>Lactate measurement</th>
<th>Purpose</th>
<th>Timing</th>
<th>Recommended by..</th>
</tr>
</thead>
<tbody>
<tr>
<td>First measurement</td>
<td>Help determine if shock present or not</td>
<td>Triage or immediate at sepsis recognition</td>
<td>SSC – dx criteria SEP1, mandated</td>
</tr>
<tr>
<td>Repeat measure</td>
<td>Response to initial resuscitation</td>
<td>Minimum- 2 hrs Max – 6 hrs</td>
<td>SSC, low quality SEP1, mandated RCTs, improve mortality</td>
</tr>
</tbody>
</table>
Reassessment after a change

- Turn the dial
- Check the water temp
- Intervene on sepsis
- Check on the patient
- Check on the patient
# Reassessment after a change

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommendation</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS SEP1 bundle</td>
<td>Assessment of volume status, tissue perfusion</td>
<td>“Best practice”</td>
</tr>
</tbody>
</table>

## Focused physical exam must include:
- Vital signs
- Cardiopulmonary exam
- Capillary refill
- Peripheral pulse evaluation
- Skin exam

OR any two of the following:
- Central venous pressure
- Central venous oxygen
- Bedside cardiovascular ultrasound
- Passive leg raise or fluid challenge
Intravenous fluids

• Ubiquitous intervention in acute medicine
  • Drug like any other from pharmacy

• Millions of unit administered to patients each day
  • Hypovolemic shock
  • Dehydration
  • Many others
"The very remarkable effects of this remedy require to be witnessed to be believed. Shortly after the commencement of the injection the pulse, which was not perceptible, gradually returns; the eyes, which were sunk and turned upwards, are suddenly brought forward, and the patient looks round as if in health, the natural heat of the body is gradually restored, the tongue and breath, which were in some cases at the temperature of 79 and 80, rise to 88 and 90, and soon become natural, the laborious respiration and oppression of weight of the chest are relieved ... the whole countenance assumes a natural healthy appearance”
Physiology of fluid resuscitation

- Altered membrane permeability in critically ill patients
  - Endothelial glycocalx loses integrity
  - Increased interstitial edema
  - Particularly in surgical trauma and sepsis
Comparison of early vs. 2 hour delayed fluids

No difference in heart rate or temperature trajectory
Comparison of early vs. 2 hour delayed fluids,

No significant difference in pH, base excess, or lactate with earlier fluids

Lewis et al., under review, 2017
Comparison of early vs. 2 hour delayed fluids, 3

No significant difference in survival
Risk of death, 2

C Initial Bolus of Intravenous Fluids

- Crude
- Risk adjusted

*Predictive margins from average of independent variables
Recent national policies reinforce fluids

- **Centers for Medicare and Medicaid bundle for sepsis (SEP1)**
  - All severe sepsis or septic shock patients must receive a fluid bolus of 30cc/kg of crystalloid fluids
  - Hospitals must report all cases, compliance with fluid bolus completion

- **Controversial**
  - No exclusions for ESRD
  - No exclusions for CHF
What for prehospital?
**Advanced notification**

- Modeled after STEMI and stroke alert systems
- Mostly small before / after studies testing activation of sepsis teams
- No large cluster RCT
- Proposed to speed process measures at the hospital
  - Source control
  - Antibiotic administration
  - Hospital fluids
What about destination for sepsis?
Direct treatment with fluids

- Prehospital fluids
- No RCTs yet
- Observational studies in large cohorts

<table>
<thead>
<tr>
<th>Model</th>
<th>+ Catheter, no fluid OR (95%CI)</th>
<th>+ Catheter, + fluid OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.27 (0.71, 2.27)</td>
<td>2.05 (1.71, 2.46)</td>
</tr>
<tr>
<td>Partial adjustment: demographics &amp; prehospital physiology *</td>
<td>0.98 (0.52, 1.86)</td>
<td>1.27 (0.98, 1.62)</td>
</tr>
<tr>
<td>Full adjustment **</td>
<td>0.31 (0.17, 0.57)</td>
<td>0.45 (0.23, 0.89)</td>
</tr>
</tbody>
</table>

**Sensitivity analyses:**
- Prehospital hypotension (SBP <=110mmHg): 0.40 (0.08, 2.07) 0.26 (0.08, 0.85)
- Advanced life support only: 0.24 (0.14, 0.38) 0.31 (0.15, 0.66)
What can we do?
Other treatments?

- ED antibiotics
- Prehospital antibiotics
Prehospital antibiotics

• Recommended blood cultures before treatment

• Appropriate vs. aggressively timed
  • Which drug(s)?
  • What dose?

• Who is the right population to target?

• Are we allowed to do this?

Better preclinical and clinical data required
Demonstration project in EMS

* 356 Blood cultures collected from 433 patients
* Patient demographics included 55.3% male and mean age of 65
* Most common admitting diagnosis was Sepsis 202/356 (56.7%)
Randomized trial in Europe

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

So now what? Take home…

• Awareness and recognition is most important

• Consider advanced notification, don’t be shy

• Follow existing protocols for fluids (shock)

• No role for antibiotics (for now)

European, Canadian, and US trials either funded or under review to generate a larger evidence base
Questions