Antibiotic delays in severe sepsis: do they begin in the ambulance

Christopher W. Seymour, MD MSc
Assistant Professor of Critical Care Medicine
Core Faculty Member, CRISMA Center
University of Pittsburgh School of Medicine
Disclosures

• Research funding:
  – NIH / NIGMS K23 award
  – Surgical Infection Society

• Consulting fees from Beckman Coulter on sepsis biomarkers

• No tobacco relationships

• Member: Surviving Sepsis Campaign, 2014 Sepsis Definitions Task Force
Caveats

• I am not a paramedic or emergency medical services clinician, and I do not work in an emergency department

• I’m currently involved in a Canadian trial of prehospital antibiotics

• I’m an optimist
Objectives

- Briefly address equipoise about timing of antibiotics in sepsis
- Explore the tension of when the clock starts
- Delays that begin in the ambulance
- Do these delays “matter”? 
When does the clock start for antibiotics?


- **ED**
- Time of presentation
- **Ward**
- Time of meeting all criteria
- **3 hr**
- **6 hr**
- Guideline recommended care

NATIONAL QUALITY FORUM

Measure Information - Composite
Ways to measure the clock start

• Fixed time point
  • Good if this corresponds to onset of abnormal physiology
  • Objective, easy to measure
  • Which one to chose?

• Symptom onset
  • More likely to provide true information about treatment
Figure 2. Physiology early after CLP: heart rate and core temperature

A

Heart Rate (bpm)

6 hours: 476-709 bpm  12 hours: 225-680 bpm

B

Temperature (celsius)

6 hours: 29.3-36.6 C  12 hours: 22.2-36.0 C

Time after CLP (minutes)
The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis*

Sarah A. Sterling, MD; W. Ryan Miller, MD; Jason Pryor, MD; Michael A. Puskarich, MD; Alan E. Jones, MD

• Fixed time point
  OR = 1.16 (0.92, 1.46)

• Variable time point related to symptomatology
  OR = 1.46 (0.89, 2.40)
Equipoise remains

• Does giving prompt antibiotics actually improve outcomes?

• Should we use onset of symptoms vs. fixed time point for time zero?

• If the latter, what fixed time point is “right”? 
Is ED arrival the proper fixed time point?

- **Prehospital care**
- **Time of first medical contact**
- **Time of presentation**
- **ED**
- **VERY EARLY**
- **EARLY**
- **3 hr**
EMS commonly encounter sepsis

All sepsis

Community sepsis AND transport by EMS

Seymour et al., 2012, AJRCCM
How do we operationalize EMS delays?

Field-triaged to a PCI center

Symptom onset → EMS call → Arrival at PCI center → Primary PCI

Patient delay | Transportation delay | Door-to-balloon delay

- Prehospital system delay
- System delay
- Treatment delay

JAMA, 2010
How do we operationalize EMS delays in sepsis?

Are system delays in antibiotic administration associated with outcome?

First medical contact
9-1-1 notification
ED arrival
Cohort in southwestern PA

Adults, ground EMS transports from 21 agencies to 9 UPMC hospitals
N = 58,934

Excluded

No community infection
N = 48,411
No organ dysfunction
N = 7,686
Duplicate encounters
N = 154

Community severe sepsis
N = 2,683
How long are delays?

Median medical contact delay 4.2 hrs [IQR: 2.8, 8.1 hrs]
How do we analyze delays?

- **Indication bias**
  - Sicker patients get antibiotics sooner

- **Missing data**
  - Sicker patients more likely to have EMS variables recorded

- **Discharge bias**
  - More ill patients off loaded by hospitals to LTAC and SNF (where they die)

- **Multivariable logistic regression**
- **Outcome:** in-hospital mortality
- **Clustering** by hospital, 10 imputed datasets
- **A priori confounders** during prehospital care
## Primary model and sensitivity analyses

<table>
<thead>
<tr>
<th>Primary analysis</th>
<th>No.</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adjustment</td>
<td>2,682</td>
<td>1.01 (0.99, 1.04)</td>
</tr>
<tr>
<td>Partial adjustment</td>
<td>2,682</td>
<td>1.01 (0.99, 1.04)</td>
</tr>
<tr>
<td>Full adjustment</td>
<td>2,682</td>
<td>1.03 (1.00, 1.05)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative criteria or subpopulation</th>
<th>No.</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumed infection</td>
<td>2,102</td>
<td>1.03 (1.00, 1.06)</td>
</tr>
<tr>
<td>SOFA &gt;=3 points</td>
<td>1,782</td>
<td>1.03 (1.00, 1.05)</td>
</tr>
<tr>
<td>SSC criteria</td>
<td>4,625</td>
<td>1.02 (1.00, 1.05)</td>
</tr>
<tr>
<td>Abnormal prehospital physiology</td>
<td>1,354</td>
<td>1.04 (1.02, 1.06)</td>
</tr>
</tbody>
</table>

Odds ratio for hospital mortality

- Later antibiotics better
- Later antibiotics worse
Risk of death may change with medical contact delay
Limitations

• Organ failures and severity defined primary using SOFA on arrival

• Too few numbers to analyze only patients with prehospital shock

• "Appropriate" ness of antibiotics difficult to assess using observational data

• Generalizability to EMS systems outside of southwestern Pennsylvania and US
Why medical contact delay?

- Captures yet unrecognized period to time where the system of care for severe sepsis could be improved
- Association with in-hospital mortality among EMS patients with severe sepsis
- Objective
- Continues to emphasize the potential importance of the prehospital phase in sepsis care
The future of prehospital sepsis

- Lactate measurement
  - Observational data, no RCT

- Prehospital fluid
  - Uncommon, observational data
  - No RCT
  - Unclear standard of care (<500mL)

- Antibiotics
  - Small experience in AUS/UK
  - 1 Dutch trial ongoing

PITSTOP trial (Canada)
Pre-ProCESS trial (US)
Visit us at
www.ccm.pitt.edu/crisma