Early Antibiotics for Sepsis and Septic Shock: A Gold Standard

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Surviving Sepsis Bundle 2012

Severe Sepsis 3-Hour Resuscitation Bundle

- administer broad spectrum antimicrobials (1 hr)
- lactate level
- blood cultures prior to administration of antimicrobials
- 30 ml/kg crystalloid for hypotension or lactate ≥4 mmol/l
The Gold Standard for Evidence in Medical Science

- RCT?
  - Generalizability
  - Reproducibility!
    - Glycemic control
    - Physiologic corticosteroid therapy
    - Activated protein C (drotrecogin-alfa)
    - Goal-directed resuscitation
The Gold Standard for Evidence in Biological Science

- Biologic rationale...a reasonable hypothesis
- Reproducibility across a wide range of study designs including observational studies; in the case of early antimicrobials
  - Experimental animal studies
  - Direct observational human data
  - Indirect but related observational data
  - Bundle analysis
Speed is Life

• The speed of clearance of the microbial pathogen is the critical determinant of outcome in septic shock (and other conditions where there is a time-dependent risk of irreversible and irreplaceable organ failure)
Sepsis and Septic Shock: An Intensivist’s Immunologic View

Antimicrobials

Infection

CARS

Antiinflammatory (endogenous)

Organ Injury

RECOVERY

Time

van der Poll T, van Deventer SJH. Infect Dis Clin N Am
An Injury Paradigm of Septic Shock: The Golden Hours
A Kumar, Virulence 2014;5:80–97

- Microbial load
- Inflammatory response
- Toxic burden
- Cellular dysfunction/tissue injury

TIME

Shock Threshold

DEATH
An Injury Paradigm of Sepsis and Septic Shock

Microbial load
Inflammatory response
Toxic burden
Cellular dysfunction/tissue injury

TIME
earlier antimicrobial therapy
Shock Threshold

A Kumar, Virulence 2014;5:80–97
**E. coli** murine peritonitis/septic shock mortality vs time of antibiotic initiation

Kumar et al, JID 2006
Mean Arterial Pressure in Murine Septic Shock

Kumar et al, JID 2006
Cumulative Initiation of Effective Antimicrobial Therapy and Survival in Septic Shock

fraction of total patients

survival fraction

cumulative antibiotic initiation

time from hypotension onset (hrs)

Mortality Risk with Increasing Delays in Initiation of Effective Antimicrobial Therapy

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Odds Ratio of Death (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1.99</td>
<td>1 (1-10)</td>
</tr>
<tr>
<td>2-2.99</td>
<td>10 (1-100)</td>
</tr>
<tr>
<td>3-3.99</td>
<td>100 (1-1000)</td>
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<tr>
<td>4-4.99</td>
<td>1000 (1-10000)</td>
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<td>5-5.99</td>
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<td>6-8.99</td>
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<td>9-11.99</td>
<td>1000000 (1-10000000)</td>
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<td>12-23.99</td>
<td>10000000 (1-100000000)</td>
</tr>
<tr>
<td>24-35.99</td>
<td>100000000 (1-1000000000)</td>
</tr>
<tr>
<td>&gt; 36</td>
<td></td>
</tr>
</tbody>
</table>
Time to Antimicrobial: Severe Sepsis

### Benefit of Early versus Late Antibiotics

#### Odds Ratio of Survival (95% CI)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miner</td>
<td>2001</td>
<td>171</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Larche</td>
<td>2002</td>
<td>88</td>
<td>Bact/pneumonia*</td>
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<tr>
<td>Houck</td>
<td>2004</td>
<td>13,771</td>
<td>Pneumonia</td>
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<tr>
<td>Proulx</td>
<td>2005</td>
<td>118</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Meehan</td>
<td>1997</td>
<td>14,069</td>
<td>Pneumonia</td>
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<tr>
<td>Gacouin</td>
<td>2002</td>
<td>213</td>
<td>Legionella</td>
</tr>
<tr>
<td>Iregui</td>
<td>2006</td>
<td>107</td>
<td>VAP</td>
</tr>
<tr>
<td>Lodise</td>
<td>2003</td>
<td>167</td>
<td>S. aureus</td>
</tr>
<tr>
<td>Kang</td>
<td>2003</td>
<td>123</td>
<td>P. aeruginosa</td>
</tr>
</tbody>
</table>

* courtesy, C Natanson

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*Harm vs Benefit* Odds Ratio of Survival (95% CI)
Impact of Appropriateness of Initial Antimicrobial Therapy on Survival from Septic Shock

Kumar et al, Chest 2009; 136:1237–1248
Meta-analysis: IAA in severe infection

Paul AAC
2010;54: 4851–4863
CAP Septic Shock: Finnsepsis

![Cumulative survival graph](image)

Antibiotic < 3h

Log Rank $P < 0.001$

Antibiotic > 3h

Days alive

Impact of Bundle Elements on Mortality of Septic Shock

- 0-1 hr: Hazard Ratio 1, p value .008
- 1-3 hr: Hazard Ratio 1, p value .127
- 3-6 hr: Hazard Ratio 1, p value .419
- prev AbRx: Hazard Ratio .383
- fluid challenge: Hazard Ratio 1, p value .966
- low dose steroid: Hazard Ratio 1, p value .688
- aPC: Hazard Ratio 1, p value .004

Ferrer et al, AJRCCM 2009;180:861-6
Studies of Severe Sepsis Bundles Survival

**Author/Yr**
- Rivers ‘01
- Trzeciak '06
- Kortgen '06
- Shapiro '06
- Micek '06
- Nguyen '07
- Jones '07
- El Solh ‘08

**Overall Odds Ratio of Survival (95% CI)**
- **Favors Control**
  - 0.01
  - 0.1
  - 1
  - 10
  - 100
- **Favors Bundle**

**Heterogeneity**
- $I^2 = 0\%$, $p = 0.97$

*p < 0.0001*
Studies of Severe Sepsis Bundles (what changes?): Hours to Antibiotics

Author/Yr
Rivers '01
Trzeciak '06
Kortgen '06
Shapiro '06
Micek '06
Nguyen '07
Jones '07
El Solh ‘08

Weighted Mean Difference (± 95% CI)

Favors Control  Favors Bundle

Heterogeneity
$\chi^2 = 0\%, \ p = 0.89$

$p < 0.0001$

Studies of Severe Sepsis Bundles Resuscitation Components (what changes?)

Author / Year
- Rivers '01
- Trzeciak '06
- Kortgen '06
- Shapiro '06
- Micek '06
- Nguyen '07
- Jones '07
- El Solh '08

Crystalloid Usage (L)

- I^2 = 89%
- p < 0.0001

Vasopressor Usage

- I^2 = 84%
- p < 0.0001

Inotropes

- I^2 = 0%
- p = 0.57

RBC

- I^2 = 89%
- p < 0.0001

Time to Antimicrobial in Sepsis/Septic Shock: Sterling Meta-analysis

the “purgamentum init, exit purgamentum” problem
Requirements for an appropriate time to antimicrobial study

1. Plausible biologic rationale
2. Index to appropriate antimicrobial
   – Systematic bias to null
3. Index to an appropriate clinical start-point
   – Physiologic parameter vs administrative
   – Inclusion of patients with unclear start-point (systematic bias to null)
Time to Antimicrobial: Severe Sepsis

Kumar et al. July 2003 Septic Shock data set
Early Antimicrobials in Sepsis and Septic Shock: The Gold Standard