ONCE UPON A TIME

THE GOOD PEOPLE OF SEPSIS-LAND GOT TOGETHER..
We were given a 6 hour bundle and a 24 hour bundle ... .. and were told this was the one true way
SURVIVING SEPSIS RECOMMENDATIONS

6 hour bundle
- measure lactate
- take blood cultures
- early antibiotics
- EGDT

24 hour bundle
- activated protein C
- corticosteroids
- glycaemic control
- avoid high plateau pressures
EARLY ANTIBIOTICS SAVES LIVES..

Thanks to PENICILLIN
...He Will Come Home!

From Ordinary Mold—
the Greatest Healing Agent of This War!
D. Antimicrobial Therapy

1. The administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis should be the goal.

presence of septic shock or administration of effective therapy, increase in mortality in a number of studies (15, 68, 70–72). Overall, the preponderance of data support giving antibiotics as soon as possible in patients with severe sepsis with or without septic shock (15, 68, 70–77).

Future trials should endeavor to provide an evidence base in this regard.
Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program

Ricard Ferrer, MD, PhD; Ignacio Martin-Loeches, MD, PhD; Gary Phillips, MAS; Tiffany M. Osborn, MD, MPH; Sean Townsend, MD; R. Phillip Dellinger, MD, FCCP, FCCM; Antonio Artigas, MD, PhD; Christa Schorr, RN, MSN; Mitchell M. Levy, MD, FCCP, FCCM

Figure 2. Predicted hospital mortality and the associated 95% CIs for time to first antibiotic administration. The results are adjusted by the sepsis severity score (SSS), ICU admission source (emergency department [ED], ward, vs ICU), and geographic region (Europe, United States, and South America).
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**TABLE 1. Patient Characteristics by Timing in Hours to the First Antibiotic**

<table>
<thead>
<tr>
<th>Patient Characteristic, ( n ) (%)</th>
<th>0.0–1.0</th>
<th>1.0–2.0</th>
<th>2.0–3.0</th>
<th>3.0–4.0</th>
<th>4.0–5.0</th>
<th>5.0–6.0</th>
<th>&gt; 6.0</th>
<th>( p^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location where sepsis identified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>3,028 (64.0)</td>
<td>3,716 (80.9)</td>
<td>2,424 (80.3)</td>
<td>1,322 (76.2)</td>
<td>727 (70.1)</td>
<td>417 (65.2)</td>
<td>1,294 (57.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ED mortality</td>
<td>797 (26.3)</td>
<td>935 (25.2)</td>
<td>629 (26.0)</td>
<td>352 (26.6)</td>
<td>209 (28.8)</td>
<td>132 (31.7)</td>
<td>404 (31.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ward</td>
<td>1,198 (25.3)</td>
<td>680 (14.8)</td>
<td>469 (15.5)</td>
<td>326 (18.8)</td>
<td>244 (23.5)</td>
<td>177 (27.7)</td>
<td>689 (30.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ward mortality</td>
<td>481 (40.2)</td>
<td>274 (40.3)</td>
<td>195 (41.6)</td>
<td>131 (40.8)</td>
<td>94 (38.5)</td>
<td>83 (46.9)</td>
<td>332 (48.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICU</td>
<td>502 (10.6)</td>
<td>199 (4.3)</td>
<td>127 (4.2)</td>
<td>86 (5.0)</td>
<td>66 (6.4)</td>
<td>46 (7.2)</td>
<td>253 (11.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>234 (46.6)</td>
<td>83 (41.7)</td>
<td>39 (30.7)</td>
<td>34 (39.5)</td>
<td>34 (51.5)</td>
<td>19 (41.3)</td>
<td>149 (58.9)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Crit Care Med 2014; 42:1749–1755*
Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program

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Mortality (%)

Time to antibiotic (hr)

- ED
- Ward
- ICU
The 558 patients who received effective antimicrobial therapy before onset of hypotension (and were therefore not included in the primary analysis) and the 2,154 who received such therapy after onset of hypotension were comparable except for a higher proportion of patients requiring source control (44.8% vs. 37.9% of the total respectively). Survival in this subgroup was slightly higher than the overall group at 52.2%.

7.6% decrease in survival per hour of delay following hypotension (hours)
studies heavily criticized

• weak methodologies
• multiple limitations
Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol

Michael A. Puskarich, MD; Stephen Trzeciak, MD; Nathan I. Shapiro, MD; Ryan C. Arnold, MD; James M. Horton, MD; Jonathan R. Studnek, PhD; Jeffrey A. Kline, MD; Alan E. Jones, MD; on behalf of the Emergency Medicine Shock Research Network (EMSHOCKNET)

Crit Care Med 2011; 39:2066–2071

- 291 prospective admissions to 3 ERs

Conclusion: In this large, prospective study of emergency department patients with septic shock, we found no increase in mortality with each hour delay to administration of antibiotics after triage. However, delay in antibiotics until after shock recognition was associated with increased mortality.

- 2.4-fold increased risk of hospital mortality if initial antibiotic started after shock recognition

- ... but is this a function of underlying illness severity?
Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol

Michael A. Puskarich, MD; Stephen Trzeciak, MD; Nathan I. Shapiro, MD; Ryan C. Arnold, MD; James M. Horton, MD; Jonathan R. Sturinek, PhD; Jeffrey A. Kline, MD; Alan F. Jones, MD;
Delay in the administration of appropriate antimicrobial therapy in *Staphylococcus aureus* bloodstream infection: a prospective multicenter hospital-based cohort study

A. J. Kaasch · S. Rieg · J. Kuetscher · H.-R. Brodt · T. Widmann · M. Herrmann · C. Meyer · T. Welte · P. Kern · U. Haars · S. Reuter · I. Hübner · R. Strauss · B. Sinha · F. M. Brunkhorst · M. Hellmich · G. Fätkenheuer · W. V. Kern · H. Seifert · The preSABATO study group*

In conclusion, within the limitations of this and previous studies, a delay in AAT may not influence survival as strongly as widely perceived.

- Early AAT \( (n=126) \)
  - Crude 90-day mortality: 34.9%

- Delayed AAT \( (n=12) \)
  - Crude 90-day mortality: 28.6%

Infection (2013) 41:979–985
Several research reports have been published detailing specific measures that hospitals have undertaken to ensure an early diagnosis and the effect on patient-oriented outcomes such as mortality and length of stay (6–8). However, subsequent reports have detailed increasing rates of misdiagnosis and antibiotic overuse for non-CAP conditions (9–13).
Results: Eight studies were identified. All were Grade C or D and of “Adequate” quality: two studies supported TFAD by showing improved outcomes (improved survival in one study and no survival difference but shorter hospital length-of-stay in the second) in CAP patients after the implementation of TFAD; one neutral article reported no difference in survival with improved TFAD timing; five studies opposed TFAD either by showing increases in antibiotic overuse in non-CAP patients, or suggesting that TFAD measurement would promote antibiotic misuse.
3. What are the key findings?

The strength of evidence is variable on whether the measurement of TFAD in CAP improves outcomes, however, recent studies show that implementing this core measure may lead to antibiotic overuse. The AAEM does not support continued measurement of TFAD for CAP in US EDs.

4. How is patient care impacted?

If the Joint Commission and the Centers for Medicare & Medicaid Services stopped using measurement of TFAD in CAP as a core measure, this may reduce antibiotic overuse in US EDs, but this would require further study.
ED bedside point-of-care lactate in patients with suspected sepsis is associated with reduced time to iv fluids and mortality

Adam J. Singer, MD *, Maria Taylor, RN, Debra LeBlanc, RN, Justin Williams, BA, Henry C. Thode Jr., PhD

Department of Emergency Medicine, Stony Brook University, Stony Brook, NY

Objective: Early recognition and treatment of sepsis improves outcomes. We determined the effects of bedside point-of-care (POC) lactate measurement on test turnaround time, time to administration of IV fluids and antibiotics, mortality, and ICU admissions in adult ED patients with suspected sepsis. We hypothesized that bedside lactate POC testing would reduce time to IV fluids and antibiotics.

Methods: We compared 80 ED patients with suspected sepsis and a lactate level of 2 mmol/L or greater before and 80 similar measurements after introduction of POC lactate measurements.

Introduction of POC lactate was associated with significant reductions in test turnaround time (34 [26-55] vs. 122 [82-149] minutes; P < 0.001), time to IV fluids (55 [34-83] vs. 71 [42-110] minutes; P = 0.03), mortality (6% vs. 19%; P = 0.02), and ICU admissions (33% vs. 51%, P = 0.02), but not time to IV antibiotics (89 [54-156] vs. 88 [60-177] minutes; P = 0.35).

814 patients, 66% received appropriate empiric therapy

- those getting ‘right’ a/b -> increased 30 day mortality (HR 1.52 [95% CI 0.99-2.34])

- longer time to appropriate Rx was protective for mortality (HR 0.79; [95% CI 0.60-1.03]) ...

- .... except among the healthiest quartile (HR 1.44; [95% CI 0.66-3.15])

PLoS 2010 5: e11432
99 (40%) of 247 patients with ICU-acquired infections (all sites) died in the aggressive treatment group compared with 50 (21%) of 237 in the conservative period (p<0.0001).

Aggressive treatment generated an adjusted OR of death of 2.5 (95% CI 1.5–4.0) when individual infections were studied.
Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study

Tjasa Hranjec, Laura H Rosenberger, Brian Swenson, Rosemarie Metzger, Tanya R Fioh, Arrani D Politano, Lin M Roccio, Kimberley A Popovsky, Robert G Sawyer

<table>
<thead>
<tr>
<th></th>
<th>Aggressive</th>
<th>Conservative</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections associated with MAP &lt;60 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>95</td>
<td>110</td>
<td>0.077</td>
</tr>
<tr>
<td>APACHE II score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>22.0 (6.9)</td>
<td>22.4 (6.4)</td>
<td>0.71</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>21 (17–29)</td>
<td>22 (17–27)</td>
<td>0.79</td>
</tr>
<tr>
<td>Time from blood culture to initiation of treatment (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.2 (14.0)</td>
<td>31.8 (37.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4 (3–12.5)</td>
<td>20 (8–39)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure.

Table 8: Distribution of mean arterial pressures and descriptive statistics and outcomes for infections treated with MAP less than 60 mm Hg.

<table>
<thead>
<tr>
<th>Duration of antimicrobial treatment (days)</th>
<th>Aggressive (n=247)</th>
<th>Conservative (n=237)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>17.7 (28.1)</td>
<td>12.5 (10.7)</td>
<td>&lt;0.008</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>11 (7-8)</td>
<td>10 (7-14)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Table 4: Time to start of treatment and appropriateness of antibiotic therapy

Not all patients had blood cultures drawn or had fever (temperature ≥38.5°C). Antibiotics were generally switched to appropriate coverage 3 days after cultures were sent when sensitivities returned. *Data for appropriate initial therapy were available from 214 patients in the aggressive group, and 231 in the conservative group.
• prospective observational study in 3 Dutch EDs
• hospitalized ED patients requiring iv antibiotics
• stratified by illness severity (low, intermediate, high)
• time to antibiotics <1 hour vs 1-3 hours vs >3 hours
• 1168 patients enrolled - overall mortality 10%
• 85% received antibiotics within 3 hours, 95% within 6 hours
No association between time to a/b and surviving days outside hospital or mortality

In low illness severity group, delayed (>3h) antibiotics associated with more surviving days outside hospital (HR 1.46 (95%CI 1.05-202)
Conclusion: Using the available pooled data, we found no significant mortality benefit of administering antibiotics within 3 hours of emergency department triage or within 1 hour of shock recognition in severe sepsis and septic shock. These results suggest that currently recommended timing metrics as measures of quality of care are not supported by the available evidence.
SUMMARY

• don’t change your current practice ..
• .. yet bear in mind that today’s truth may not be borne out over time
• give Abx in reasonable timeframe
• don’t start antibiotics if not needed
• do stop antibiotics if not needed
• better diagnostics may help!