Myths and misconceptions in the management of sepsis

Mervyn Singer
BLOOMSBURY INSTITUTE OF INTENSIVE CARE MEDICINE
UNIVERSITY COLLEGE LONDON, UK
DISCUSSION POINTS ..

• Guidelines should be slavishly followed
• One size fits all
• Every hour of antibiotic delay kills
• How long should a course of antibiotics last?
• Sepsis mortality is improving
• Why do people die of sepsis?
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- Patients do **NOT** necessarily follow the rule book
- **MUST** tailor therapy to the individual
- Guidelines should **NOT** be used as rigid protocols/rules of stone
- Clinical expertise is **VITAL**
INDIVIDUALS VERSUS POPULATIONS

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- Guidelines should NOT be used as rigid protocols/rules of stone
- Clinical expertise is VITAL

.. not my words, but David Sackett’s
Evidence based medicine: what it is and what it isn’t

It’s about integrating individual clinical expertise and the best external evidence

Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough. Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient.
Evidence based medicine is not “cookbook” medicine. Because it requires a bottom up approach that integrates the best external evidence with individual clinical expertise and patients’ choice, it cannot result in slavish, cookbook approaches to individual patient care. External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision.
QUALITY - OR LACK - OF EVIDENCE

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**QUALITY - OR LACK - OF EVIDENCE**

- Overall evidence base for sepsis is - sadly - rather weak
- Only a few awarded ‘high’ quality (but generally ‘do nots’ rather than ‘do’s’)
**DOGMA SHOULDN’T RULE ...**

- Need decent evidence to confirm need to change
- For example, Rivers showed EGDT was beneficial in 2001 .. but why?
Dogma shouldn’t rule...

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**Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock**

Emanuel Rivers, M.D., M.P.H., Bryant Nguyen, M.D., Suzanne Havstad, M.A., Julie Ressler, B.S., Alexandnia Muzzin, B.S., Bernhard Knoblich, M.D., Edward Peterson, Ph.D., and Michael Tomlanovich, M.D., for the Early Goal-Directed Therapy Collaborative Group

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A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators®

A  Cumulative In-Hospital Mortality to 60 Days

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Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZCS Clinical Trials Group

A Cumulative In-Hospital Mortality to 60 Days

Probability of Survival


Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc.,
David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D.,
Rah Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D.,
Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, O.M.,
and Kathryn M. Rowan, Ph.D., for the ProMISE Trial Investigators*.

Goal-Directed Resuscitation for Patients with Early Septic Shock

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Adjusted hazard ratio, 0.94 (0.79−1.11), P=0.46


TAKE-HOME MESSAGE

- Identify patient early
- Treat promptly and appropriately
- .. but the specific Rivers’ protocol doesn’t seem to offer any overall added benefit
LOWEST COMMON DENOMINATOR?

Standardised mortality ratio

good performing hospitals

not-so-good performing hospitals
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BUT....

Guidelines are often taken too literally by:

• clinical zealots
• institutions
• governments
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.. with financial penalties or ‘name-and-shame’ for non-compliance
TAKE-HOME MESSAGE

• Use guidelines/protocols as an aide memoire

• .. but not rules of stone

• Don’t be afraid to deviate .. but be able to justify why
Discussion Points...

- Guidelines should be slavishly followed
- One size fits all
- Every hour of antibiotic delay kills
- How long should a course of antibiotics last?
- Sepsis mortality is improving
- Why do people die of sepsis?
THE INTERVENTION .. OR TARGETED ENDPOINT .. MUST BE RATIONAL FOR EVERYONE
High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gerdaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guillon, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonneller, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien Du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D. for the SEPSISPAM Investigators

High versus Low Blood-Pressure Target in Patients with Septic Shock

The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mm Hg during initial resuscitation of patients with septic shock. However, whether this blood-pressure target is more or less effective than a higher target is unknown.

In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.
METHODS
In a multicenter trial of children with septic shock to understand the optimal duration for achieving an arterial pressure of 85 mm Hg (or higher) or a central venous pressure of 8 mm Hg (or higher), the primary outcome was death of any cause within 30 days. The primary end point was death within 30 days of randomization.
SO WHY TARGET A POPULATION, AND NOT AN INDIVIDUAL!!!!!!
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<td>Renal-replacement therapy from day 1 to day 7</td>
<td>139 (35.8)</td>
<td>130 (33.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>Serious adverse events — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>69 (17.8)</td>
<td>74 (19.1)</td>
<td>0.64</td>
</tr>
<tr>
<td>Acute myocardial infarction‡</td>
<td>2 (0.5)</td>
<td>7 (1.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (2.8)</td>
<td>26 (6.7)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

TAKE-HOME MESSAGE
**TITRATE**

- Titrate to the individual e.g. what BP suits them? MAP 55-60 or 75-80?
**TAKE-HOME MESSAGE**

- Titrate to the individual e.g. what BP suits them? MAP 55-60 or 75-80?
- Titrate to a goal
  - if a patient needs fluid (if hypovolaemia -> hypoperfusion), give fluid
  - if not hypovolaemic and hypoperfused, don’t give fluid
• Titrate to the individual e.g. what BP suits them? MAP 55-60 or 75-80?
• Titrate to a goal
  • if a patient needs fluid (if hypovolaemia -> hypoperfusion), give fluid
  • if not hypovolaemic and hypoperfused, don’t give fluid
• Avoid excess - too much fluid, too much oxygen, too much catecholamine …
DISCUSSION POINTS ..

• Guidelines should be slavishly followed

• One size fits all

• Every hour of antibiotic delay kills

• How long should a course of antibiotics last?

• Sepsis mortality is improving

• Why do people die of sepsis?
INTERESTING FACTS - 1

Guitar Sales

Ugly guys with good looking girls
Interesting Facts - 1

- Multiple papers - including EVERY prospective study I’m aware of - do NOT show a correlation between a short-term delay in administering antibiotics and mortality
INTERESTING FACTS - 2
Interesting Facts - 2

- Studies claiming ‘every hour counts’ are all based on retrospective analyses of databases collected for other reasons (usually administrative), but lacking vital data e.g. antibiotic sensitivities.
• Studies claiming ‘every hour counts’ are all based on **retrospective** analyses of databases collected for other reasons (usually administrative), but **lacking vital data** e.g. antibiotic sensitivities

• .. and use complex **adjustments** to find a mortality difference
INTERESTING FACTS - 2

• Studies claiming ‘every hour counts’ are all based on retrospective analyses of databases collected for other reasons (usually administrative), but lacking vital data e.g. antibiotic sensitivities

• .. and use complex adjustments to find a mortality difference

• .. and often incorporate very delayed treatment (>6h) into the analysis
Studies claiming ‘every hour counts’ are all based on retrospective analyses of databases collected for other reasons (usually administrative), but lacking vital data e.g. antibiotic sensitivities.

- .. and use complex adjustments to find a mortality difference
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- .. and often lack biological plausibility
Studies claiming ‘every hour counts’ are all based on retrospective analyses of databases collected for other reasons (usually administrative), but lacking vital data e.g. antibiotic sensitivities.

- .. and use complex adjustments to find a mortality difference.
- .. and often incorporate very delayed treatment (>6h) into the analysis.
- .. and often lack biological plausibility.
- .. and cannot explain why there was a delay in treatment in some
Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock.

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

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Documented infections were present in 77.9% of cases. The remaining 22.1% of cases represented suspected infections without either a plausible bacterial pathogen isolated or definitive radiologic, surgical, autopsy, or biopsy evidence of infection.
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%.
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**Cumulative effective antimicrobial initiation**

- Survival fraction
- Fraction of total patients

![Graph showing time following hypotension (hours)](image)
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(Crit Care Med 2014; 42:1749–1755)

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], general medical/other [MED/OTH], or special care unit [SCU]), sex, and age.
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infection source
(pneumonia, urinary tract infection, abdominal, etc.), various organ failures, hypotension (resolved and unresolved), mechanical ventilation, and other clinical characteristics (T. Osborn et al, unpublished observation, 2013).

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Mortality (%)

<table>
<thead>
<tr>
<th>Time to antibiotic (hr)</th>
<th>0-1</th>
<th>1-2</th>
<th>2-3</th>
<th>3-4</th>
<th>4-5</th>
<th>5-6</th>
<th>&gt;6</th>
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<tbody>
<tr>
<td>Mortality (%)</td>
<td>60</td>
<td>45</td>
<td>30</td>
<td>15</td>
<td>0</td>
<td></td>
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Mortality (%) vs Time to antibiotic (hr)

- ED
- Ward
- ICU

Mortality (%)

<table>
<thead>
<tr>
<th>Time to antibiotic (hr)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>20</td>
</tr>
<tr>
<td>1-2</td>
<td>30</td>
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<td>2-3</td>
<td>35</td>
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<tr>
<td>3-4</td>
<td>40</td>
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<tr>
<td>4-5</td>
<td>45</td>
</tr>
<tr>
<td>5-6</td>
<td>50</td>
</tr>
<tr>
<td>&gt;6</td>
<td>55</td>
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Mortality (%)

Time to antibiotic (hr)

0-1 1-2 2-3 3-4 4-5 5-6 >6
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Mortality (%) vs. Time to antibiotic (hr)

Mortality (%)

Time to antibiotic (hr)

- ED
- Ward
- ICU
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Mortality (%)

Time to antibiotic (hr)

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ED  Ward  ICU
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Mortality (%) vs Time to antibiotic (hr)

- ED
- Ward
- ICU

Graph showing mortality (%) over time to antibiotic (hr) with distinct bars for ED, Ward, and ICU categories.
Quality Improvement Initiative for Severe Sepsis and Septic Shock Reduces 90-Day Mortality: A 7.5-Year Observational Study*

Christian S. Scheer, MD; Christian Fuchs, MD; Sven-Olaf Kuhn, MD; Marcus Vollmer, MSM; Sebastian Rehberg, MD, PhD; Sigrun Friescke, MD; Peter Abel, MD; Veronika Balau, MD; Christoph Bandt, PhD; Konrad Meissner, MD, PhD; Klaus Hahnenkamp, MD, PhD; Matthias Gründling, MD

<table>
<thead>
<tr>
<th>Full Model</th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures before antibiotic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.626 (0.57–0.68)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Calculated antibiotic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not adequate</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>0.616 (0.52–0.80)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to antibiotic therapy, hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>1–6</td>
<td>1.125 (0.92–1.37)</td>
<td>0.242</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>1.215 (0.96–1.54)</td>
<td>0.104</td>
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*(Crit Care Med 2017; 45:241–252)*
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- 1373 ICU patients between 2006-13 coded as septic/septic shock
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- 1373 ICU patients between 2006-13 coded as septic/septic shock
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis


BACKGROUND

In 2013, New York began requiring hospitals to follow protocols for the early identification and treatment of sepsis. However, there is controversy about whether more rapid treatment of sepsis improves outcomes in patients.

METHODS

We studied data from patients with sepsis and septic shock that were reported to the New York State Department of Health from April 1, 2014, to June 30, 2016. Patients had a sepsis protocol initiated within 6 hours after arrival in the emergency department and had all items in a 3-hour bundle of care for patients with sepsis (i.e., blood cultures, broad-spectrum antibiotic agents, and lactate measurement) completed within 12 hours. Multilevel models were used to assess the associations between the time until completion of the 3-hour bundle and risk-adjusted mortality. We also examined the times to the administration of antibiotics and to the completion of an initial bolus of intravenous fluid.

Among patients who had the 3-hour bundle completed within 12 hours, a longer time to the completion of the bundle was associated with higher risk-adjusted in-hospital mortality (odds ratio, 1.04 per hour; 95% confidence interval [CI], 1.02 to 1.05; P<0.001), as was a longer time to the administration of antibiotics (odds ratio, 1.04 per hour; 95% CI, 1.03 to 1.06; P<0.001) but not a longer time to the completion of a bolus of intravenous fluids (odds ratio, 1.01 per hour; 95% CI, 0.99 to 1.02; P=0.21).
Among patients who had the 3-hour bundle completed within 12 hours, a longer time to the completion of the bundle was associated with higher risk-adjusted in-hospital mortality (odds ratio, 1.04 per hour; 95% confidence interval [CI], 1.02 to 1.05; \( P<0.001 \)), as was a longer time to the administration of antibiotics (odds ratio, 1.04 per hour; 95% CI, 1.03 to 1.06; \( P<0.001 \)) but not a longer time to the completion of a bolus of intravenous fluids (odds ratio, 1.01 per hour; 95% CI, 0.99 to 1.02; \( P=0.21 \)).
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## Time to Treatment and Mortality during Mandated Emergency Care for Sepsis


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<th>P Value*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Yes (N = 40,696)</td>
<td>No (N = 8635)</td>
</tr>
<tr>
<td>Positive blood cultures — no. (%)</td>
<td>14,574 (29.5)</td>
<td>12,322 (30.3)</td>
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<td>3943 (45.7)</td>
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<tr>
<td>Teaching facility — no. (%)</td>
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<td>7,739 (19.0)</td>
<td>7300 (84.5)</td>
</tr>
<tr>
<td>In-hospital death — no. (%)</td>
<td>11,251 (22.8)</td>
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* P values were calculated using chi-square or Fisher's exact test as appropriate.
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## Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus F. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 49,331)</th>
<th>3-Hr Bundle Completed in 3 Hr</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-Hr Bundle Completed in 3 Hr</td>
<td>No (N = 8635)</td>
<td></td>
</tr>
<tr>
<td>Positive blood cultures — no. (%)</td>
<td>14,574 (29.5)</td>
<td>12,322 (30.3)</td>
<td>2252 (26.1)</td>
</tr>
<tr>
<td>Septic shock — no. (%)</td>
<td>22,316 (45.3)</td>
<td>18,393 (45.7)</td>
<td>3943 (45.7)</td>
</tr>
<tr>
<td>Teaching facility — no. (%)</td>
<td>40,257 (81.5)</td>
<td>7,739 (19.0)</td>
<td>7300 (84.5)</td>
</tr>
<tr>
<td>In-hospital death — no. (%)</td>
<td>11,251 (22.8)</td>
<td>9,213 (22.6)</td>
<td>2038 (23.5)</td>
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*Note: P values are calculated using appropriate statistical tests.
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*P-values are calculated using chi-square tests.*

*(N Engl J Med 2017;376:2235-44.)*
### Table: Risk-Adjusted Odds Ratios of In-Hospital Death in the Primary Model and Prespecified Subgroups

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<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Bacteremia</td>
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<td></td>
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<tr>
<td>Gram positive</td>
<td>7,175</td>
<td>1.01 (0.98–1.05)</td>
</tr>
<tr>
<td>Gram negative</td>
<td>6,431</td>
<td>1.05 (1.01–1.09)</td>
</tr>
<tr>
<td>Other</td>
<td>965</td>
<td>1.15 (1.07–1.24)</td>
</tr>
<tr>
<td>None</td>
<td>34,757</td>
<td>1.03 (1.02–1.05)</td>
</tr>
</tbody>
</table>

**Figure 2.** Risk-Adjusted Odds Ratios of In-Hospital Death in the Primary Model and Prespecified Subgroups. Shown are odds ratios, with 95% confidence intervals, for in-hospital death for each hour that it took to complete the 3-hour bundle.
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis


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Figure 2. Risk-Adjusted Odds Ratios of In-Hospital Death in the Primary Model and Prespecified Subgroups.
Shown are odds ratios, with 95% confidence intervals, for in-hospital death for each hour that it took to complete the 3-hour bundle.

... and no data on antibiotic sensitivities, adequacy of dosing, source control, etc..

Figure 2. Risk-Adjusted Odds Ratios of In-Hospital Death in the Primary Model and Prespecified Subgroups. Shown are odds ratios, with 95% confidence intervals, for in-hospital death for each hour that it took to complete the 3-hour bundle.
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

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B Administration of Antibiotics

C Initial Bolus of Intravenous Fluids

In Hospital Mortality (%)

Time to Administration of Antibiotics (hr)

Time to Completion of Bolus (hr)

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis
Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D.,
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Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

.. yet 45% of patients (early and late treated) had ‘septic shock’!!
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

B Administration of Antibiotics

- Crude
- Risk adjusted

In-Hospital Mortality (%) vs. Time to Administration of Antibiotics (hr)

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

B  Administration of Antibiotics

In-Hospital Mortality (%) vs. Time to Administration of Antibiotics (hr)

Crude vs. Risk adjusted
B Administration of Antibiotics

- Crude
- Risk adjusted

In-Hospital Mortality (%) vs. Time to Administration of Antibiotics (hr)

- 82.5% of pts
- 2% of pts

B Administration of Antibiotics

- Crude
- Risk adjusted

Time to Administration of Antibiotics (hr)

In-Hospital Mortality (%)

- 82.5% of pts
- 22.6% †
- 23.6% †
- 2% of pts

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

B Administration of Antibiotics

- In-Hospital Mortality (%)
- Time to Administration of Antibiotics (hr)

- 82.5% of pts
- 15.5% of pts
- 2% of pts

Crude
Risk adjusted

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

B Administration of Antibiotics

- Crude
- Risk adjusted

In-Hospital Mortality (%) vs Time to Administration of Antibiotics (hr)

- 82.5% of pts
- 15.5% of pts
- 2% of pts
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

B Administration of Antibiotics

- Crude
- Risk adjusted

In-Hospital Mortality (%) vs. Time to Administration of Antibiotics (hr)

- 82.5% of pts
- 15.5% of pts
- 2% of pts

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

**B Administration of Antibiotics**

- **Crude**
- **Risk adjusted**

**In-Hospital Mortality (%)**

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Crude Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5%</td>
</tr>
<tr>
<td>1</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>25%</td>
</tr>
<tr>
<td>5</td>
<td>30%</td>
</tr>
<tr>
<td>6</td>
<td>35%</td>
</tr>
</tbody>
</table>

- 82.5% of pts
- 15.5% of pts
- 2% of pts

PROSPECTIVE STUDIES SHOW NO DIFFERENCE
Prospective studies show no difference

- Often designed to specifically look at impact of antibiotics on outcomes
- None show an ‘each-hour-delay-kills’ signal

- Puskarich, CCM 2011 septic shock (ED)
- Hranjec, Lancet Infect Dis 2012 sepsis/septic shock (ICU)
- Kaasch, Infection 2013 S aureus bacteraemia (Ward/ICU)
- Bloos, Crit Care 2014 sepsis/septic shock (ICU)
- De Groot, Crit Care 2015 ED sepsis/septic shock (ED)
- Fitzpatrick, Clin Microbiol Infect 2016 Gm -tive bacteraemia (Ward)
- Alan, Lancet Respir Dis 2018 sepsis (pre-hospital ED)
• **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))
Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

Nadia Alom, Fruck Uskam, Patricia M. Stassen, Pieter Mel van Exder, Peter M van de Ven, Harm E. Haak, Fris Holleman, Arthur van Zanten, Hien van Leeuwen-Nguyen, Victor Bon, Bart A. M. Duineveld, Rishi S. Naman Pandey, Mark H. H. Kramer, Prabath W B. Nainayakkara, on behalf of the PHANTASi Trial Investigators and the CRCA (Onderzoeks Consortium Acute Geneeskrunde) Research Consortium the Netherlands

Lancet Respir Med 2018; 6: 40–50
• 2672 patients randomised to receive pre-hospital antibiotics (ceftriaxone 2g) from paramedics on suspicion of sepsis OR start antibiotics in ED
• Mean 96 minute difference in time to administration of antibiotics
Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

<table>
<thead>
<tr>
<th></th>
<th>Usual care group (n=1137)</th>
<th>Intervention group (n=1535)</th>
<th>Relative risk (95% CI)</th>
<th>Risk difference (%), 95% CI</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>28 day mortality</td>
<td>93 (8%)</td>
<td>120 (8%)</td>
<td>0.915 (0.74 to 1.24)</td>
<td>-0.37 (-2.5 to 1.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>90 day mortality</td>
<td>134 (12%)</td>
<td>178 (12%)</td>
<td>0.98 (0.80 to 1.21)</td>
<td>-0.20 (-2.7 to 2.3)</td>
<td>0.87</td>
</tr>
<tr>
<td>Median TTA in the ED (min)</td>
<td>70 (36–128)</td>
<td>70 (36–128)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTA in the ED (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–60</td>
<td>410 (42%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61–120</td>
<td>254 (26%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>121–180</td>
<td>125 (13%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>181–240</td>
<td>78 (8%)</td>
<td>78 (8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;240</td>
<td>56 (6%)</td>
<td>56 (6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>50 (5%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antibiotics in the ED</td>
<td>164 (14%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>admission</td>
<td>98 (9%)</td>
<td>155 (10%)</td>
<td>1.17 (0.92 to 1.49)</td>
<td>1.5 (-0.73 to 3.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>28 day re-admission</td>
<td>119 (10%)</td>
<td>102 (7%)</td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Median length of stay (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>3 (2–8)</td>
<td>4 (2–10)</td>
<td></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Hospital</td>
<td>6 (3–9)</td>
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Lancet Respir Med 2018; 6: 40–50
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Lancet Respir Med 2018; 6: 40-50
Antibiotics for Sepsis: Does Each Hour Really Count, or Is It Incestuous Amplification?

Mervyn Singer

Incestuous amplification—the (extreme) reinforcement of ideas and/or beliefs that occurs when like-minded people communicate with each other (1).
TAKE-HOME MESSAGE
TAKE-HOME MESSAGE

• Every second doesn’t count .. but reasonable/rational to treat sepsis and septic shock promptly
• Rather than simply throwing antibiotics at the patient, apply some thought, seek advice, and think source control
DISCUSSION POINTS ..

- Guidelines should be slavishly followed
- One size fits all
- Every hour of antibiotic delay kills
- How long should a course of antibiotics last?
- Sepsis mortality is improving
- Why do people die of sepsis?
Duration of Antimicrobial Treatment for Bacteremia in Canadian Critically Ill Patients

Nick Daneman, MD; Asgar H. Kishu, MBBS; Wei Xiong, MSc; Sean M. Bagshaw, MD; Peter Dodek, MD; Richard Hall, MD; Anand Kumar, MD; Francois Lamontagne, MD; Francois Lauzier, MD; John Marshall, MD; Claudio M. Martin, MD; Lauralyn McIntyre, MD; John Muscedere, MD; Steve Reynolds, MD; Henry T. Stelfox, MD; Deborah J. Cook, MD; Robert A. Fowler, MD; on behalf of the Canadian Critical Care Trials Group

Crit Care Med 2016;44:256–264
Figure 2. Impact of excluding early deaths on the association of treatment duration and survival among propensity-matched patients receiving shorter versus longer duration antimicrobial treatment.
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If shorter course treatment is noninferior within a study sufficiently powered to exclude clinically important outcome differences, there could be large-scale reductions in antimicrobial use and complications for critically ill patients.
Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults
A Randomized Trial

Jean Chastre, MD
Michel Wolff, MD
Jean-Yves Fagon, MD
Sylvie Chevret, MD
Franck Thomas, MD
Delphine Wermert, MD
Eva Clementi, MD
Jesus Gonzalez, MD
Dominique Jusserand, MD
Pierre Asfar, MD

Context  The optimal duration of antimicrobial treatment for ventilator-associated pneumonia (VAP) is unknown. Shortening the length of treatment may help to contain the emergence of multiresistant bacteria in the intensive care unit (ICU).

Objective  To determine whether 8 days is as effective as 15 days of antibiotic treatment of patients with microbiologically proven VAP.

Design, Setting, and Participants  Prospective, randomized, double-blind (until day 8) clinical trial conducted in 51 French ICUs. A total of 401 patients diagnosed as having developed VAP by quantitative culture results of bronchoscopic specimens and who had received initial appropriate empirical antimicrobial therapy were enrolled between May 1999 and June 2002.

Intervention  A total of 197 patients were randomly assigned to receive 8 days and 204 to receive 15 days of therapy with an antibiotic regimen selected by the treating physician.
Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults
A Randomized Trial

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**Context**  The optimal duration of antimicrobial treatment for ventilator-associated pneumonia (VAP) is unknown. Shortening the length of treatment may help to contain the emergence of multiresistant bacteria in the intensive care unit (ICU).

**Objective**  To determine whether 8 days is as effective as 15 days of antibiotic treatment of patients with microbiologically proven VAP.

**Design**, **Setting**, **Intervention**  A double-blind, day 8 vs day 15 randomized placebo-controlled clinical trial of patients having developed VAP between May 1999 and the end of 2004 who had received inotropes at presentation. A total of 204 patients were randomized.

**Figure 2. Kaplan-Meier Estimates of the Probability of Survival**

Probability of survival is for the 60 days after ventilator-assisted pneumonia onset as a function of the duration of antibiotic administration.
Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults
A Randomized Trial

Jean Chastre, MD
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Objective  To determine whether 8 days is as effective as 15 days of antibiotic treatment of patients with microbiologically proven VAP.

Design, Setting, day 8) clinical trial of having developed a patient who had received between May 1999 a
Intervention  A hospital 204 to receive 15 or a physician.

Notably, among patients who developed recurrent pulmonary infections, multiresistant pathogens emerged significantly less frequently in those who had received 8 days of antibiotics (42.1% vs 62.3% of recurrent infections; P = .04).

Figure 2. Kaplan-Meier Estimates of the Probability of Survival

<table>
<thead>
<tr>
<th>Days After Bronchoscopy</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic Regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-Day Antibiotic Regimen</td>
<td>197</td>
<td>187</td>
<td>172</td>
<td>158</td>
<td>151</td>
<td>148</td>
<td>147</td>
</tr>
<tr>
<td>15-Day Antibiotic Regimen</td>
<td>204</td>
<td>194</td>
<td>179</td>
<td>167</td>
<td>157</td>
<td>151</td>
<td>147</td>
</tr>
</tbody>
</table>

Survival is for the 60 days after ventilator-assisted pneumonia onset as a function of the duration administration.
Early Antibiotic Discontinuation in Patients With Clinically Suspected Ventilator-Associated Pneumonia and Negative Quantitative Bronchoscopy Cultures*

Kirthana Raman, PharmD1-3; Michael D. Naior, PharmD, BCPS (AQ-ID)1-2; David P. Nicolau, PharmD, FCCP, FIDSA5-8; Jaber Aslanzadeh PhD, D(ABMM)9; Michelle Nadeau, PharmD2; Joseph I. Kuti, PharmD4

<table>
<thead>
<tr>
<th></th>
<th>Early Discontinuation (n = 40)</th>
<th>Late Discontinuation (n = 49)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of antibiotics</td>
<td>4 (3, 4)</td>
<td>9 (6, 14)</td>
<td>&lt;0.001</td>
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**Conclusions:** In this severely ill population with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoalveolar lavage cultures, early discontinuation of antibiotics did not affect mortality and was associated with a lower frequency of MDR superinfections.
Bacteraemia incidence, causative organisms and resistance patterns, antibiotic strategies and outcomes in a single university hospital ICU: continuing improvement between 2000 and 2013

Vincenzo De Santis¹, Mihaela Gresaiu¹, Alberto Corona², A. Peter R. Wilson³ and Mervyn Singer¹*
Bacteraemia incidence, causative organisms and resistance patterns, antibiotic strategies and outcomes in a single university hospital ICU: continuing improvement between 2000 and 2013

Vincenza De Santis¹, Mihaela Gresoiu¹, Alberto Corona², A. Peter R. Wilson³ and Mervyn Singer¹*

- 6 month audit in University hospital medical-surgical ICU
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• 113 bacteraemia episodes in 87 patients
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Very low incidence of antimicrobial resistance or fungaemia
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Short-course monotherapy (4-5 days) used in 65.7%

Low rates of bacteraemia breakthrough/relapse

Very low incidence of antimicrobial resistance or fungaemia

Less ICU-acquired MRSA, MDR Gram -tives, VRE and fluconazole-resistant candidaemia c/f similar audit in 2000
MDR fluconazole-resistant methicillin-resistant VRE

- 2000
- S. aureus
- CoNS
- Streptococcus pneumoniae
- Enterococcus
- Other Gram-positive
- E. coli
- Klebsiella
- Pseudomonas
- Enterobacter
- Other Gram-negative
- Candida spp.

- 2012-13
- S. aureus
- CoNS
- Enterococcus
- Other Gram-positive
- E. coli
- Klebsiella
- Pseudomonas
- Enterobacter
- Other Gram-negative
- Candida spp.

- Community acquired
- Ward acquired
- ICU acquired

fluconazole-resistant, methicillin-resistant, VRE, MDR
MDR fluconazole-resistant methicillin-resistant VRE no fluconazole-resistance
MDR fluconazole-resistant methicillin-resistant VRE no fluconazole-resistance 1 VRE Community acquired Ward acquired ICU acquired no fluconazole-resistance
MDR fluconazole-resistant methicillin-resistant VRE no fluconazole-resistance
1 VRE no MRSA no fluconazole-resistance
Community acquired Ward acquired ICU acquired
Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection


METHODS

We randomly assigned 518 patients with complicated intraabdominal infection and adequate source control to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy (control group), or to receive a fixed course of antibiotics (experimental group) for 4±1 calendar days. The primary outcome was a composite of surgical-site infection, recurrent intraabdominal infection, or death within 30 days after the index source-control procedure, according to treatment group.
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RESULTS

The median duration of antibiotic therapy was 4.0 days (interquartile range, 4.0 to 5.0) in the experimental group, as compared with 8.0 days (interquartile range, 5.0 to 10.0) in the control group.

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection


4 vs 8 days

DISCUSSION POINTS ..

- Guidelines should be slavishly followed
- One size fits all
- Every hour of antibiotic delay kills
- How long should a course of antibiotics last?
- Sepsis mortality is improving
- Why do people die of sepsis?

Cagan Kumar, MD; Nilay Kumar, MD, MPH; Amit Taneja, MD; Thomas Kaleekal, MD; Sergey Tarima, PhD; Emily McClure, MPH; Edgar Jimenez, MD; Anand Mohan, MD; Hani Ahmed Khan, MD; Jeff Whittle, MD, Elizabeth Jacobs, MD, FCCP; and Rahul Nanchal, MD, FCCP; from the Milwaukee Initiative in Critical Care Outcomes Research (MICCOR) Group of Investigators
Conclusions: An increasing number of admissions for severe sepsis combined with declining mortality rates contribute to more individuals surviving to hospital discharge.
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Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014

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[A] Adjusted sepsis incidence

[B] Adjusted in-hospital sepsis mortality or discharge to hospice

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A. Adjusted sepsis incidence

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence, %</th>
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<tbody>
<tr>
<td>2009</td>
<td>2.0</td>
</tr>
<tr>
<td>2010</td>
<td>3.0</td>
</tr>
<tr>
<td>2011</td>
<td>4.0</td>
</tr>
<tr>
<td>2012</td>
<td>5.0</td>
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<td>2013</td>
<td>6.0</td>
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</table>

B. Annual total hospitalizations, No.

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Hospitalizations, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>696807</td>
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<tr>
<td>2010</td>
<td>737695</td>
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<tr>
<td>2012</td>
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<td>2013</td>
<td>24853637</td>
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<tr>
<td>2014</td>
<td>2354056</td>
</tr>
</tbody>
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C. Adjusted in-hospital sepsis mortality or discharge to hospice.

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[Graphs showing adjusted sepsis incidence and adjusted in-hospital sepsis mortality or discharge to hospice with data points and trend lines.]
Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Kirsi Maija Kaukonen, MD, PhD, EDIC; Michael Bailey, PhD; Satoshi Suzuki, MD; David Pilcher, FCICM; Rinaldo Bellomo, MD, PhD

<table>
<thead>
<tr>
<th>Year of ICU Admission</th>
<th>No. of Events</th>
<th>Sepsis</th>
<th>No Sepsis</th>
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<tbody>
<tr>
<td>2000</td>
<td></td>
<td>949</td>
<td>4807</td>
</tr>
<tr>
<td>2001</td>
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<td>1271</td>
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<td>1573</td>
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<td>2004</td>
<td></td>
<td>1841</td>
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<td>2005</td>
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<td>1833</td>
<td>7825</td>
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<td>2006</td>
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<td>2090</td>
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<td>2418</td>
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</tr>
<tr>
<td>2012</td>
<td></td>
<td>2300</td>
<td>8010</td>
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</tbody>
</table>

Adjusted Odds Ratio (95% CI)

JAMA. 2014;311(13):1308-1316
Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Kirsia Maja Kaukonen, MD, PhD, EDIC; Michael Bailey, PhD; Satoshi Suzuki, MD; David Pilcher, FCICM; Rinaldo Bellomo, MD, PhD

When considered as a continuous variable, there was no difference between patients with severe sepsis or septic shock and other patients in the database for the decline in mortality over time (odds ratio [OR], 0.94 [95% CI, 0.94-0.95] vs 0.94 [95% CI, 0.94-0.94]; P = .37).

JAMA. 2014;311(13):1308-1316
Discussion Points..

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- One size fits all
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- How long should a course of antibiotics last?
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- Why do people die of sepsis?
SEPSIS KILLS 44,000 PEOPLE EVERY YEAR IN THE UK
EVERY 3.5 SECONDS SOMEONE DIES FROM SEPSIS
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EVERY
3.5
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MAINTAINING A SENSE OF PROPORTION...
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- 34 million antibiotic prescriptions by English GPs in 2015-6
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- 1.3 million hospital patient episodes with a sepsis/infection code in England p.a.
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- .. with 32,300 in-hospital deaths = 2.5% mortality rate
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- 34 million antibiotic prescriptions by English GPs in 2015-6
- 1.3 million hospital patient episodes with a sepsis/infection code in England p.a.
- .. with 32,300 in-hospital deaths = 2.5% mortality rate
- BUT … only 11,000 cases of sepsis had an ICU admission
DO ALL SEPTIC PATIENTS WARRANT LIFE-PROLONGING TREATMENT???
DO ALL SEPTIC PATIENTS WARRANT LIFE-PROLONGING TREATMENT???

“Pneumonia is the old man’s friend” - Sir William Osler

Patients may be allowed to die from sepsis due to the severity of their underlying comorbidity - terminal cancer, severe stroke, end-stage chronic organ failure, severe dementia …
‘SUSPICION OF SEPSIS’ HOSPITAL ADMISSIONS IN ENGLAND 2011-17

Age

N

0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90+
'SUSPICION OF SEPSIS' HOSPITAL ADMISSIONS IN ENGLAND 2011-17

Mortality (%)

' S U S P I C I O N O F S E P S I S ' M O R T A L I T Y  2 0 1 1 - 1 7

Age

N

800000

600000

400000

200000

0

0-4

5-9

10-14

20-24

25-29

30-34

35-39

40-44

45-49

50-54

55-59

60-64

65-69

70-74

75-79

80-84

85-89

90+

Age

456

115

113

208

396

603

933

1812

3196

5165

8359

14708

24767

35270

55626

82544

95925

98039

0-4

5-9

10-14

15-19

20-24

25-29

30-34

35-39

40-44

45-49

50-54

55-59

60-64

65-69

70-74

75-79

80-84

85-89

90+
‘SUSPICION OF SEPSIS’ HOSPITAL ADMISSIONS IN ENGLAND 2011-17

‘SUSPICION OF SEPSIS’ MORTALITY 2011-17

77.5% OF DEATHS
### Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 49,331)</th>
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<tbody>
<tr>
<td><strong>Age at admission — yr</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>73</td>
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<tr>
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<td>60–83</td>
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<td><strong>Coexisting condition — no. (%)</strong></td>
<td></td>
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<tr>
<td>Chronic respiratory failure</td>
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<tr>
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<td>Home</td>
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- Dementia?
- Stroke?
- Other severe disability?
# Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

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Stroke?  
Other severe disability?
CONCLUSION
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- Apply physiology to patient management
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- Apply physiology to patient management
- Personalization not rigid protocolization
CONCLUSION

• Apply physiology to patient management

• Personalization not rigid protocolization

• Challenge dogma based on weak/contrived evidence
CONCLUSION

• Apply physiology to patient management

• Personalization not rigid protocolization

• Challenge dogma based on weak/contrived evidence

• Sepsis only constitutes a small proportion of infection … but should be identified and acted upon promptly .. but with some thought applied
CONCLUSION

- Apply physiology to patient management.
- Personalization not rigid protocol.
- Challenge dogma based on what is known.
- Sepsis only constitutes a small percentage.
  - Identified and acted upon promptly.
- 