WHAT IS SEPSIS?
IN THE BEGINNING THERE WAS “SEPSIS-1”

**ACCP/SCCM Consensus Conference**

**Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis**

*The ACCP/SCCM Consensus Conference Committee:*

- Roger C. Bone, M.D., F.C.C.P., Chairman
- Robert A. Balk, M.D., F.C.C.P.
- Frank B. Cerra, M.D.
- R. Phillip Dellinger, M.D., F.C.C.P.

- Alan M. Rein, M.D., F.C.C.P.
- William A. Knaus, M.D.
- Roland M. H. Schein, M.D.
- William J. Sibbald, M.D., F.C.C.P.

*Ches 1992; 101:1644-55*

**Sepsis** = the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or PaCO₂ <32 mm Hg; and white blood cell count >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms.

**Severe sepsis** = sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

**Septic shock** = sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
2001 SCCM Conference

Mitchell M. Levy
Derek Angus, M
Jean-Louis Vincent

SEPSIS-2 recognised problems with SEPSIS-1... but lacked evidence to support change.

Table 1. Diagnostic criteria for sepsis

| Infection, documented or suspected, and some of the following:
| General variables |
| Fever (core temperature >38.3°C) |
| Hypothermia (core temperature <36°C) |
| Heart rate >90 min⁻¹ or >2 SD above the normal value for age |
| Tachypnea |
| Altered mental status |
| Significant edema or positive fluid balance (>20 mL/kg over 24 hrs) |
| Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes |

Inflammatory variables

| Leukocytosis (WBC count >12,000 µL⁻¹) |
| Leukopenia (WBC count <4000 µL⁻¹) |
| Normal WBC count with >10% immature forms |
| Plasma C reactive protein >2.0 in above the normal value |
| Plasma procalcitonin >2.0 above the normal value |

Hemodynamic variables

| Arterial hypotension* (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg in adults |
| or <2 SD below normal for age |
| 80/60 >70% |
| Cardiac index >3.5 L/min 1.7M |

Organ dysfunction variables

| Arterial Hypoxemia (PaO₂/FIO₂ <300) |
| Acute oliguria (urine output <0.5 mL/kg/h or <45 mmol/L for at least 2 hrs) |
| Creatinine increase >0.5 mg/dL |
| Coagulation abnormalities (INR >1.5 or aPTT >60 sec) |
| Ileus (absent bowel sounds) |
| Thrombocytopenia (platelet count <100,000 µL⁻¹) |
| Hyperbilirubinemia (plasma total bilirubin >4 mg/dL, or 71 mmol/L) |

Tissue perfusion variables

| Hyperlactatemia (>1 mmol/L) |
| Decreased capillary refill or mottling |

Conclusion of experts and guidelines and four symptoms of evidence exist of evidence diagnosing sepsis.
RECOGNISED ISSUES WITH THE OLD DEFINITIONS..

1-in-8 ICU patients with sepsis-related MOF

50% of inpatients

Not very life-threatening!
Sepsis = the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or PaCO₂ <32 mm Hg; and white blood cell count >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms.

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‘OLD’ SEPTIC SHOCK

VARIABLY DEFINED —>
4-FOLD VARIATION IN MORTALITY
10-FOLD VARIATION IN INCIDENCE

n = 44 observational studies

.. AND THERE ARE BROADER ISSUES

- Sepsis is a syndrome with no perfect diagnostic test
- .. but the science has moved on considerably since 2001
- Sepsis is much, much more than systemic inflammation
- Patients don’t die of infection *per se*, but from the consequent organ dysfunction
- Organ dysfunction relates to an abnormal host response
- A small minority of people with infection develop ‘bad’ infection
- How many people who die from sepsis are/should be salvageable?
A DEFINITION —> .. WHAT SOMETHING ‘IS’, .. THE ‘ESSENCE’ OF SOMETHING ..

CLINICAL CRITERIA OPERATIONALIZE THE DEFINITION .. AND OFFER CONSISTENCY SO WE ALL TALK THE SAME LANGUAGE
SEPSIS-3
Special Communication | Caring for the Critically Ill Patient

February 23, 2016

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP\textsuperscript{1}; Clifford S. Deutschman, MD, MS\textsuperscript{2}; Christopher Warren Seymour, MD, MSc\textsuperscript{3}; \textit{et al}

850,000 patients (predominantly from US) who had cultures taken and antibiotics started

~90% from Emergency Department or Ward
SEPSIS-3 PROVIDES ...

- A new definition .. and more precise clinical criteria to describe sepsis

**definition**

life-threatening organ dysfunction due to a dysregulated host response to infection

**clinical criteria**

![Sepsis Clinical Criteria Diagram]
SOFA SCORE ... LOOK FOR CHANGE IN BASELINE ≥ 2

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P_{aO_2}/FIO_2 ), mm Hg (kPa)</td>
<td></td>
<td>≥400 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
<td>&lt;100 (13.3) with respiratory support</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Platelets, ( \times 10^3/\mu L )</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
<td></td>
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<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bilirubin, mg/dL (umol/L)</td>
<td>&lt;1.2 (20)</td>
<td>1.2-1.9 (20-37)</td>
<td>2.0-5.0 (44-101)</td>
<td>6.0-11.9 (102-204)</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MAP ≥ 70 mm Hg</td>
<td></td>
<td></td>
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<tr>
<td>MAP &lt; 70 mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dopamine &lt;5 or dobutamine (any dose)²</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1</td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL (umol/L)</td>
<td>&lt;1.2 (110)</td>
<td>1.2-1.9 (110-170)</td>
<td>2.0-3.4 (171-299)</td>
<td>3.5-4.9 (300-410)</td>
<td>&gt;5.0 (410)</td>
<td></td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;500</td>
<td>&lt;200</td>
</tr>
</tbody>
</table>
SOFA SCORE

- It's not perfect
- .. but long established and well-validated relationship to mortality risk
- Uses variables routinely measured in any unwell patient in developed world and in many LMICs
- Assume baseline SOFA = 0 in previously healthy people
- Big data analysis showed >10% risk of death if change in SOFA ≥2
- SOFA is an epidemiology/research tool .. not intended as a triage tool
WE TREAT THE PATIENT IN FRONT OF US..

- hypotensive
- hypoxaemic
- hypercarbic
- tachycardic
- oliguric
- hyperlactataemic/acidotic
- decreased GCS
- ....

AND WE DON’T STOP TO CALCULATE APACHE, SAPS, AKI SCORES... OR SOFA
Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit

CONCLUSIONS AND RELEVANCE  Among adults with suspected infection admitted to an ICU, an increase in SOFA score of 2 or more had greater prognostic accuracy for in-hospital mortality than SIRS criteria or the qSOFA score.
SEPSIS-3 PROVIDES...

- A new definition .. and more precise clinical criteria to describe septic shock definition
circulatory, cellular, and metabolic abnormalities associated with greater risk of mortality than sepsis alone

clinical criteria

SEPTIC SHOCK

SEPSIS + VASOPRESSORS TO MAINTAIN MAP 265 mmHg
AND
SERUM LACTATE LEVEL >2 mmol/l

IN THE ABSENCE OF HYPOVOLEMIA
SURVIVING SEPSIS CAMPAIGN (SSC) REGISTRY

- 28,150 infected patients with $\geq 2$ SIRS criteria + $\geq 1$ organ dysfunction after fluid resuscitation

- Hospital mortality
  - 42.3% in patients having both hypotension + hyperlactataemia (>2)
  - 25.7% with hyperlactataemia alone
  - 30.1% with fluid-resistant hypotension alone
  - 25.0% with organ dysfunction but lactate $\leq 2$ and MAP $\geq 65$
THE PROPAGANDA: SEPSIS IS A MAJOR KILLER ...
SEPSIS KILLS 44,000 PEOPLE EVERY YEAR IN THE UK
EVERY 3.5 SECONDS SOMEONE DIES FROM SEPSIS
PLACING ‘INFECTION’ AND ‘SEPSIS’ INTO PERSPECTIVE

- 34 million antibiotic prescriptions by English GPs in 2015
- 1.3 million hospital patient episodes with a sepsis/infection discharge code in England p.a.
- .. with 32,300 in-hospital deaths = 2.5% mortality rate
- BUT only 36,000 cases of sepsis had an ICU admission, of whom 11,000 died
DO PATIENTS DIE ‘FROM’ OR ‘WITH’ SEPSIS?

HOW MANY WARRANTED LIFE-PROLONGING THERAPY ± ICU ADMISSION???

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

Patients may be allowed to die from/with sepsis due to the severity of their underlying comorbidity - terminal cancer, end-stage heart/kidney/lung disease, severe stroke, severe dementia …
‘SUSPICION OF SEPSIS’ ADMISSIONS IN ENGLAND 2011-17

‘SUSPICION OF SEPSIS’ MORTALITY 2011-17

8% OF DEATHS

77.5% OF DEATHS
Dementia? Stroke? Other severe disability?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 49,331)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at admission — yr</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>73</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>60–83</td>
</tr>
<tr>
<td>Coexisting condition — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
<td>5,738 (11.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10,092 (20.5)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>5,207 (10.6)</td>
</tr>
<tr>
<td>Admission source — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>33,464 (67.8)</td>
</tr>
<tr>
<td>Skilled nursing facility</td>
<td>13,233 (26.8)</td>
</tr>
<tr>
<td>Other‡</td>
<td>2,634 (5.3)</td>
</tr>
</tbody>
</table>
SEPSIS OUTCOMES HAVE IMPROVED DRAMATICALLY ...?
Conclusions: An increasing number of admissions for severe sepsis combined with declining mortality rates contribute to more individuals surviving to hospital discharge.
Conclusions: An increasing number of admissions for severe sepsis combined with declining mortality rates contribute to more individuals surviving to hospital discharge.
The latest estimated figures for sepsis suggest 44,000 people a year are dying in the UK from the condition and the Scottish government quotes a figure of 3,500, as a proportion of this mortality.

Its official statistician, the ISD, said problems with "coding" of sepsis deaths meant it was "currently difficult for us to define and accurately report on a complete picture".

A call for a national campaign to raise awareness of sepsis has been rejected by the Scottish government, BBC Scotland can reveal.

Campaigners described the decision as "absurd" and "complacent" and said ministers were putting lives at risk.
Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

<table>
<thead>
<tr>
<th>Year of ICU Admission</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td>2000</td>
<td>949</td>
</tr>
<tr>
<td>2001</td>
<td>1271</td>
</tr>
<tr>
<td>2002</td>
<td>1455</td>
</tr>
<tr>
<td>2003</td>
<td>1573</td>
</tr>
<tr>
<td>2004</td>
<td>1841</td>
</tr>
<tr>
<td>2005</td>
<td>1833</td>
</tr>
<tr>
<td>2006</td>
<td>1961</td>
</tr>
<tr>
<td>2007</td>
<td>2090</td>
</tr>
<tr>
<td>2008</td>
<td>2106</td>
</tr>
<tr>
<td>2009</td>
<td>2264</td>
</tr>
<tr>
<td>2010</td>
<td>2386</td>
</tr>
<tr>
<td>2011</td>
<td>2418</td>
</tr>
<tr>
<td>2012</td>
<td>2300</td>
</tr>
</tbody>
</table>

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).
PATIENT MANAGEMENT
Well-intentioned exercise to raise standards by offering a standardized, evidence-based approach to Rx

But the evidence base remains poor, and the strength of most of the recommendations is weak

Multiple bundles of care have been touted ... but subsequently found wanting in prospective RCTs

Today’s dogma = tomorrow’s chip paper
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 Hawstad, M.A., Julie Ressler, B.S., Allxandria Muzzin, B.S., Blainard Knoblich, M.D., Edward Plinston, Ph.D., and Michail Tomlanovich, M.D., for the Early Goal-Directed Therapy Collaborative Group

- Single-centre, open study
- March 1997 - March 2000
- ER in inner-city Detroit
- n = 263
- Half got EGDT for 6 h
- Thereafter standard care on ICU/ward

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Therapy (N = 133)</th>
<th>Early Goal-Directed Therapy (N = 130)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In hospital mortality†</td>
<td>59 (46.5)</td>
<td>38 (30.5)</td>
<td>0.58 (0.38 - 0.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>All patients</td>
<td>19 (30.0)</td>
<td>9 (14.9)</td>
<td>0.46 (0.21 - 1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Patients with severe sepsis</td>
<td>40 (56.8)</td>
<td>29 (42.3)</td>
<td>0.60 (0.36 - 0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with septic shock</td>
<td>44 (45.4)</td>
<td>35 (35.1)</td>
<td>0.66 (0.42 - 1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>Patients with sepsis syndrome</td>
<td>61 (49.2)</td>
<td>40 (33.3)</td>
<td>0.58 (0.39 - 0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>28 Day mortality†</td>
<td>70 (56.9)</td>
<td>50 (44.3)</td>
<td>0.67 (0.46 - 0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>60-Day mortality†</td>
<td>61 (49.2)</td>
<td>40 (33.3)</td>
<td>0.58 (0.39 - 0.87)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*NEngl J Med 2001;345:1368-77.*
Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*
NICE (OR NOT-SO-NICE) GUIDELINES

- Disappointing and heavily criticized (by Royal Colleges etc.)
- Evidence base over-extrapolated and often mis-interpreted
- Far too complex
- Minimal uptake as considered non-implementable in routine practice
Evolving sepsis definitions and their impact on Acute Medical Units

Thompson A, Stevens M, Collin I & Wennike N.

Methods: Data on 212 admissions was collected, on time of admission and review, and number of patients with sepsis by each diagnostic criteria calculated.

Results: The NICE criteria identified 69% of admissions as requiring review within one hour, compared to 6% with qSOFA and 18% with previous sepsis definitions. The mean time to review was 1hr 18min, and only 50% of patients meeting the NiCE criteria were reviewed within one hour.
SO WHAT SHOULD WE DO?

- New (more sensible) guidance hopefully emerging soon from NHS England
ASK YOURSELF...

- Does this patient with suspected infection warrant antibiotic treatment?
- Does this patient with suspected infection likely have organ dysfunction (i.e. sepsis)?
- Is the unwell patient in front of me possibly septic?

- 15-30% of patients initially diagnosed as ‘septic’ have a non-infectious condition
**QUICK SOFA:**

- qSOFA - a suggested rapid bedside tool in Sepsis-3 for risk-stratifying patients likely to have sepsis

n.b. qSOFA is **not** part of the sepsis definitions

qSOFA was never intended to be a screening tool

strong recommendation to prospectively validate qSOFA in multiple healthcare settings
The UK National Early Warning Score (NEWS) must be superior to SOFA as it measures a further 4 criteria.

<table>
<thead>
<tr>
<th>Physiological Parameters</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration Rate</td>
<td>≤ 8</td>
<td>9 - 11</td>
<td>12 - 20</td>
<td>21 - 24</td>
<td>≥ 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen Saturations</td>
<td>≤ 91</td>
<td>92 - 93</td>
<td>94 - 95</td>
<td>96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Supplemental Oxygen</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>≤ 35.0</td>
<td>35.1 - 36.0</td>
<td>36.1 - 38.0</td>
<td>38.1 - 39.0</td>
<td>≥ 39.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>≤ 90</td>
<td>91 - 100</td>
<td>101 - 110</td>
<td>111 - 219</td>
<td>≥ 220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>≤ 40</td>
<td>41 - 50</td>
<td>51 - 90</td>
<td>91 - 110</td>
<td>111 - 130</td>
<td>≥ 131</td>
<td></td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>A</td>
<td>V, P, or U</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Dr called at NEWS ≥ 5

- Plans to roll out NEWS as uniform national score across hospital wards, EDs, community (GPs), nursing homes and ambulance crews.
INFECTION MANAGEMENT

- Antibiotics
- Source control - pus is poorly treated by antibiotics alone
- Remove likely infected lines ... + metalwork etc..
EVERY HOUR OF ANTIBIOTIC DELAY KILLS

.. AN EXERCISE IN BIOLOGICAL IMPLAUSIBILITY

• 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 (!!)
• Many studies also fail to show an outcome difference between appropriate and inappropriate antibiotics (!!)

• ?? under-dosing issues
• ?? discordance between in vivo and in vitro sensitivities
• ?? inadequate source control
• ?? other - ?attributable impact of Abx
• It is reasonable to treat sepsis promptly
• .. and, ideally, choose the right antibiotic
• But does every second count?
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; \( P = 0.21 \)).
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Getersen, M.D., Hallie C. Prescott, M.D., Marcus E. 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>Yes (N = 40,696)</td>
<td>No (N = 8635)</td>
<td></td>
</tr>
<tr>
<td>Positive blood cultures — no. (%)</td>
<td>14,574 (29.5)</td>
<td>12,392 (30.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septic shock — no. (%)</td>
<td>22,336 (45.3)</td>
<td>18,393 (45.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Teaching facility — no. (%)</td>
<td>40,257 (81.5)</td>
<td>7,759 (19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital death — no. (%)</td>
<td>11,251 (22.8)</td>
<td>9,213 (22.6)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

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

![Time to Treatment and Mortality during Mandated Emergency Care for Sepsis](image)

**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.
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).
% MORTALITY OF PATIENTS ADMITTED TO HOSPITAL WITH ‘SUSPICION OF SEPSIS’
(TRUSTS IN N & NE LONDON, ESSEX AND HERTS)

% mortality


UCLH
UNINTENDED CONSEQUENCES

THAT'S ODD... MY NECK SUDDENLY FEELS BETTER...

EARLY ACUPUNCTURE
# Results of antibiotic consumption to Mar-17

<table>
<thead>
<tr>
<th>Drug (DDD/1000 adm inc daycase) Rx-Info</th>
<th>ED 2015-6</th>
<th>ED 2016-7</th>
<th>Acute Trust 2015-6</th>
<th>Acute Trusts 2016-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IV AB</td>
<td>110.7</td>
<td>134 (+21%)</td>
<td>907.6</td>
<td>325 (+1.7%)</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>7.2</td>
<td>7.5 (+4.2%)</td>
<td>35.1</td>
<td>77.8 (-8.6%)</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>13.4</td>
<td>14.4 (+7.5%)</td>
<td>112.8</td>
<td>102.6 (-9.0%)</td>
</tr>
</tbody>
</table>
Association of Adverse Events With Antibiotic Use in Hospitalized Patients

Pranita D. Tamra, MD, MHS; Edina Avdic, PharmD, MBA; David X. Li, BS; Kathryn Dzintars, PharmD; Sara E. Cosgrove, MD, MS

We found that 20% of hospitalized patients receiving at least 24 hours of antibiotic therapy developed an antibiotic-associated ADE. Moreover, 20% of ADEs were attributable to antibiotics prescribed for conditions for which antibiotics were not indicated.
n=28150 ICU patients
Lactate Measurements in Sepsis-Induced Tissue Hypoperfusion: Results From the Surviving Sepsis Campaign Database

n=28150 ICU patients

FLUID MANAGEMENT (1)

- Most septic patients need some fluids … but not too much!
- SSC guidelines recommend “at least 30 ml/kg within first 3 hours” (strong recommendation, low quality of evidence)
- However, evidence suggests too much fluid is injurious
- So more (physio)logical to give repeated 200-250 ml challenges, assessing intravascular volume status after each bolus
- Lactate = marker of stress .. of which hypovolaemia is but one cause
- Rapid normalisation of lactate associated with better prognosis
FLUID MANAGEMENT (2)

- What fluid? Currently synthetic colloids are out of favour (though this relates to many litres of fluid) - importantly, no evidence of benefit
- Balanced (e.g. Hartmann’s) or unbalanced (e.g. n-saline) solution.
  - no clear evidence to show difference (watch plasma chloride level)
- Albumin - mixed evidence base
VASOACTIVE DRUGS

- Catecholamines recommended as 1st line
- .. though increasing evidence of an association with harm
- Groundswell for ’decatecholaminization’ - use lowest possible dose
**VASOACTIVE DRUGS**

- Catecholamines recommended as 1st line
- .. though increasing evidence of an association with harm
- Groundswell for ‘decatecholaminization’ - use lowest possible dose
- Target an adequate BP for that patient (NO magic number)
- Target adequate organs perfusion
OTHER

- No proven magic bullet
- Steroid controversy still rages … maybe useful in sicker patients??
- No alternative pressor shown to be superior to catecholamines
- Novel strategies being tested - beta-blockers, nivolumab …. 
CURRENT MANAGEMENT
(SINGER DOGMA)

- identify early
- resuscitate promptly … but don’t overdo it
- antibiotics are additive
  .. but does every hour count?
  .. 3 hour window adequate for most cases (but shouldn’t unnecessarily delay)
  .. not a panacea
  .. stop EARLY (4-5 days for most infections)
- early source control
- target reasonable BP for that patient .. and titrate to response
- minimize use of catecholamines (as generally evil)
- minimize use of sedatives (as generally evil)
SOLDIERS EAT BABIES

THAT'S A FACT

Think of the children. Join Team Demoman TODAY, and make those monsters PAY.