Surviving Sepsis

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NHS Institute Safer Care Faculty
Chair: United Kingdom Sepsis Trust & Pre-hospital Working Group
ICC Birmingham, March 2010
### Severe Sepsis or Septic shock

<table>
<thead>
<tr>
<th>ICNARC data 6 months to 01/06</th>
<th>Admissions</th>
<th>Total 21,025</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU mortality n (%)</td>
<td>Total 6,534 (31.1%)</td>
<td></td>
</tr>
<tr>
<td>Hospital mortality n (%)</td>
<td>Total 8,372 (39.8%)</td>
<td></td>
</tr>
</tbody>
</table>

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A U.K. Perspective

Annual UK mortality (2003), thousands

Lung\textsuperscript{1} Colon\textsuperscript{2} Breast\textsuperscript{3} Sepsis\textsuperscript{4}
cancers

\textsuperscript{1,2,3} www.statistics.gov.uk,
\textsuperscript{4} Intensive Care National Audit Research Centre (2006)

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Surviving Sepsis Campaign:
International guidelines for management of severe sepsis and septic shock: 2008
Sepsis Resuscitation Bundle
(To be started immediately and completed within 6 hours)

Serum lactate measured

Blood cultures obtained prior to antibiotic administration

From the time of presentation, broad-spectrum antibiotics to be given within 1 hour

Control infective source

In the event of hypotension and/or lactate >4 mmol/L (36 mg/dl):

    Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent)
    Give vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) ≥ 65 mm Hg.

In the event of persistent arterial hypotension despite volume resuscitation (septic shock) and/or initial lactate >4 mmol/l (36 mg/dl):

    Achieve central venous pressure (CVP) of ≥8 mm Hg
    Achieve central venous oxygen saturation (ScvO₂) ≥70%
**Sepsis Resuscitation Bundle**
*(To be started immediately and completed within 6 hours)*

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The Sepsis Six

1. Give high-flow oxygen via non-rebreath bag
2. Take blood cultures and consider source control
3. Give IV antibiotics according to local protocol
4. Start IV fluid resuscitation Hartmann’s or equivalent
5. Check lactate
6. Monitor hourly urine output consider catheterisation

within one hour

..plus Critical Care support to complete EGDT
SSC guidelines:

*Diagnosis, antimicrobials, control*
It’s not all about the infection!
Septic shock: the golden hours

- Shock threshold
- Organ injury
- Inflammatory response
- Toxic load
- Microbial load

Acknowledgement to Anand Kumar
SSC- diagnosis

• Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration (1C)

• Obtain two or more BCs
  One or more percutaneously
  One from each vascular access device in place > 48 hrs
  Other sites as clinically indicated

• Perform imaging studies promptly to confirm and sample any source of infection, if safe to do so (1C)
SSC- diagnosis

Obtain two or more BCs
One or more percutaneously

Citation: Weinstein MP et al. Rev Infect Dis 1983

n = 500
Retrospective
99% sensitivity if 2 samples cultured

More recent work not cited, e.g:

Mayo Clinic 2005
n = 37,568
2 cultures 80%, 3 cultures 96%, 4 cultures 100%
SSC- diagnosis

One from each vascular access device in place > 48 hrs

Citation: Blot F et al J Clin Microbiol 1998

No mention of DTP

91% specific, 94% sensitive for CRBSI (long-term)

No mention of gram stain AOLC test
SSC- antibiotics (1)

• Begin IV antibiotics as early as possible, and always within the first hour of recognising severe sepsis (1D) and septic shock. (1B)

• Broad-spectrum: one or more agents active against likely bacterial/ fungal pathogens and with good penetration into presumed source. (1B)

• Reassess antimicrobial regimen daily to optimise efficacy, prevent resistance, avoid toxicity & minimise costs. (1C)

• Consider combination therapy in Pseudomonas infections. (2D)
Begin IV antibiotics as early as possible, and always within the first hour of recognising severe sepsis (1D) and septic shock. (1B)

Citation: Kumar A et al. Crit Care Med 2006: 34(6)

Retrospective, 15 years, 14 sites
n = 2,154
median 6 h, 50% administered in 6h
Only 5% first 30 minutes- survival 87%
12% first hour- survival 84%
SSC- antibiotics (1)

Broad-spectrum: one or more agents active against likely bacterial/ fungal pathogens and with good penetration into presumed source (1B)

Citation: Ibrahim et al. Chest 2000;118:146–155

BSI, n = 492
59.1% HAI
29.9% inadequate, 8.3% fungal

![Bar chart showing mortality comparison between appropriate and inappropriate initial antibiotic choices with a p-value of <0.001.](chart.png)
Consider combination therapy in Pseudomonas infections (2D)

Citation: Garnacho-Montero et al. *Crit Care Med* 2007; 25

n=183
Initial combination Rx reduced risk inadequate cover
No outcome difference combination vs. mono

NNIS (US) 25% fluoroquinolone resistant
Safdar N et al. *Lancet Infect Dis* 2004; 4

Meta-analysis of 6 RCTs

Summary Risk Ratio 0.50 (0.32-0.79) in favour of combination

Strong *trend* in support in retrospective SGA of Paul meta-analysis
SSC- antibiotics (2)

- Consider combination empiric therapy in neutropenic patients. (2D)

- Combination therapy no more than 3-5 days and de-escalation following susceptibilities. (2D)

- Duration of therapy typically limited to 7–10 days; longer if response slow, undraining foci of infection, or immunologic deficiencies. (1D)

- Stop antimicrobial therapy if cause is found to be non-infectious (1D)
Consider combination empiric therapy in neutropenic patients. (2D)

Combination therapy no more than 3-5 days and de-escalation following susceptibilities. (2D)

Citations incl: Cochrane Syst Rev 2006 Jan 25;(1)

\[ n = 7586 \ (68 \ RCT) \]
\[ \beta\text{-lactam alone or } \beta\text{-lactam + aminoglycoside} \]
No all-cause mortality difference: RR 0.87(0.75-1.02)
Similar results with vancomycin Paul et al JAC 2005
## Combination or mono- HAP?

<table>
<thead>
<tr>
<th>Author</th>
<th>Drugs</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangi</td>
<td>Cefoloperazone vs Ceftaz/ Gent</td>
<td>87 vs 72</td>
<td>Monotherapy cheaper</td>
</tr>
<tr>
<td>Cometta</td>
<td>Imipenem vs Imipen/ Netil</td>
<td>80 vs 86</td>
<td>6 nephrotoxicitiy with combo</td>
</tr>
<tr>
<td>Rubinstein</td>
<td>Ceftazidine vs Ceftriax/ Tobra</td>
<td>85 vs 77</td>
<td>9 nephrotoxicity with combo</td>
</tr>
<tr>
<td>Seiger</td>
<td>Meropenem vs Ceftriax/ Tobra</td>
<td>80 vs 72</td>
<td>Monotherapy superior</td>
</tr>
<tr>
<td>Alvarez-Lerma</td>
<td>Meropenem vs Ceftaz/ Amikacin</td>
<td>88 vs 85</td>
<td>Monotherapy superior for VAP</td>
</tr>
<tr>
<td>Heyland</td>
<td>Meropenem vs. Mero/ Cipro</td>
<td>80 vs 82</td>
<td>No difference</td>
</tr>
</tbody>
</table>
Antibiotics- summary

Adequacy of initial spectrum the key
Reduce microbial and toxic load

Possible role for combination therapy
Pseudomonas, neutropenia, septic shock

Hit hard and hit fast

.... BUT....
Who’s gonna develop shock?

We often don’t know the source, let alone the bug....

AND the biggest ‘but’ of all:
Severe Sepsis Screening Tool

Are any 2 of the following SIRS criteria present and new to your patient?

**Obs:**
- Temperature >38.3 or <36 °C
- Respiratory rate >20 min⁻¹
- Heart rate >90 bpm
- Acutely altered mental state

**Bloods:**
- White cells <4x10⁹/l or >12x10⁹/l
- Glucose >7.7mmol/l (if patient is not diabetic)

If yes, patient has SIRS
Is this likely to be due to an infection?

For example:

- Cough/ sputum/ chest pain
- Dysuria
- Abdo pain/ diarrhoea/ distension
- Headache with neck stiffness
- Line infection
- Cellulitis/wound infection/septic arthritis
- Endocarditis

If yes, patient has SEPSIS
Start SEPSIS SIX
Senior staff: check for SEVERE SEPSIS

BP
Syst < 90 / Mean < 65
(after initial fluid challenge)

Lactate
> 4 mmol/l

Urine output
< 0.5 ml/kg/hr for 2 hrs

INR
> 1.5

aPTT
> 60 s

Bilirubin
> 34 µmol/l

O₂
Needed to keep SpO₂ > 90%

Platelets
< 100 x 10⁹/l

Creatinine
> 177 µmol/l or UO < 0.5 ml/kg/hr

Severe Sepsis: Ensure Outreach and Senior Doctor attend NOW!
SSC- source control

• A specific anatomical source of infection amenable to urgent drainage be sought and diagnosed or excluded as soon as possible (1C) and within 6 hours following presentation (1D)

• If infected peripancreatic necrosis is identified, source control is best delayed until adequate demarcation has occurred (2B)

• The intervention associated with the least insult should be employed (1D)

• When VADs are a potential source, they should be promptly removed (1C)
The remainder of the Bundle:

**EGDT**
The Importance of Early Goal-Directed Therapy for Sepsis Induced Hypoperfusion


<table>
<thead>
<tr>
<th></th>
<th>Standard therapy</th>
<th>EGDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT to prevent 1 event (death)</td>
<td>6-8</td>
<td></td>
</tr>
<tr>
<td>ARR 16%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Early delivery of EGDT could be associated with favourable lifetime cost effectiveness projections*


*Prospective interventional evaluation of continuous EGDT ED to ICU. 9% ARR, 33% RRR*
3 arms, n=650 each

- Rivers’
- ‘Simple’ protocol- no transfusion, OGD
- Standard care

Subprojects

- Efficacy
- Mechanisms
- Cost
Open label RCT

Rivers’ vs standard care

118 of 1800 recruited across 21 sites

90 day mortality
ProMISE

UK

Protocolised management in septic shock

Design/ prospective centre recruitment
Evidence emerging
Sepsis Nurse Practitioners

NIHR grant
1.0 WTE for 1 year

Duties:
- Prospective observational study
- Education
- Clinical lead
- Data capture and reporting
Compliance at Good Hope Hospital (%)
## Mortality by Sepsis Six

<table>
<thead>
<tr>
<th></th>
<th>Cohort size</th>
<th>Mortality %</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>567</td>
<td>34.7</td>
<td></td>
</tr>
</tbody>
</table>

**‘Sepsis Six’**: Oxygen therapy  
Blood culture  
Antibiotic administration  
Fluid challenges  
Lactate and haemoglobin measurement  
Urine output monitoring…. *within one hour*

Resuscitation Bundle: SSC, within 6 hours following recognition

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### Mortality by Sepsis Six

<table>
<thead>
<tr>
<th>Cohort size (%)</th>
<th>Mortality %</th>
<th>RRR % (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis Six ✓</td>
<td>Pending publication: data withheld</td>
<td>Risk reduction &gt; 40%</td>
</tr>
</tbody>
</table>
## Mortality by SSC

### Resuscitation Bundle

<table>
<thead>
<tr>
<th>Cohort size</th>
<th>Mortality %</th>
<th>RRR % (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>Pending publication: data withheld</td>
</tr>
</tbody>
</table>

- **Resusc.bundle**: Risk reduction > 70%

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# Mortality by antibiotics

<table>
<thead>
<tr>
<th>Cohort size</th>
<th>Mortality %</th>
<th>RRR % (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>Pending publication: data withheld</td>
<td>Risk reduction &gt; 35%</td>
</tr>
<tr>
<td>Delayed Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics within 1 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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# Mortality by fluid challenges

<table>
<thead>
<tr>
<th>Cohort size</th>
<th>Mortality %</th>
<th>RRR % (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Pending publication: data withheld</td>
<td>Risk reduction &gt; 40%</td>
</tr>
<tr>
<td>No fluids in 1h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluids in 1h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Mortality by fluids and antibiotics

<table>
<thead>
<tr>
<th></th>
<th>Cohort size</th>
<th>Mortality %</th>
<th>RRR % (NNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Pending publication: data withheld</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither fluids nor antibiotics in 1hr</td>
<td></td>
<td>Risk reduction &gt; 40%</td>
<td></td>
</tr>
<tr>
<td>Antibiotics after BC and fluids</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Perspective

<table>
<thead>
<tr>
<th></th>
<th>Severe Sepsis</th>
<th>Acute coronary syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. cases per 100,000 per annum</strong></td>
<td>127</td>
<td>200</td>
</tr>
<tr>
<td><strong>NNT ‘basic’ care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis Six (our data)</td>
<td>6.4</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>β-blockade</td>
<td>42</td>
<td>β-blockade</td>
</tr>
<tr>
<td>Aspirin</td>
<td>26</td>
<td>Aspirin</td>
</tr>
<tr>
<td><strong>NNT invasive care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGDT (Rivers)</td>
<td>6.3</td>
<td>Thrombolysis</td>
</tr>
<tr>
<td>Resusc Bundle (SSC)</td>
<td>18.5</td>
<td>PCI over thrombolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33</td>
</tr>
</tbody>
</table>
15,022 patients, 165 sites

Compliance up from 11 to 31% (in 2 years)

ARR 6.2%

RRR 16.8%

P < 0.001
## SSC Results: Critical Care Medicine 2010; 38(2): 1-8

<table>
<thead>
<tr>
<th>Bundle target</th>
<th>OR (95% CI) for mortality</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>0.86 (0.79-0.93)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Blood cultures</td>
<td>0.76 (0.70-0.83)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Glycaemic control</td>
<td>0.67 (0.63-0.71)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
What next?
Medical Malpractice - delay in treatment resulting in death


Question
On 10/10 my husband was given an antibiotic at his dialysis treatment for a suspected infection. On 10/12 about an hour into his dialysis treatment he requested to be taken to the hospital. When I got to the hospital he was on oxygen. He was very cold and it was hard to understand his speech. They did blood work and took urine to culture. Then they told me he was going to the ICU because he had a Sepsis infection. Once there they did his history and then brought in the machines to finish his dialysis. When I asked them when he would be getting antibiotics they said it would be after his dialysis treatment. So it took about 4 hours from the start till he received antibiotics. On 10/13 at about 3am he had a heart attack and went into cardiac arrest. They brought him back but he was on a ventilator. Later that day I was told that the chance for recovery was about 10%. The doctor said that the heart had too much damage and he would probably not wake up from the coma. On 10/14 I had him taken off the ventilator and he died. Everything I have read about sepsis says that antibiotics need to be started as soon as sepsis is suspected not confirmed. It said that survival rate decreases 6 to 10% with every hour that passes and if antibiotics aren’t started within the first couple of hours that the chances of survival are slim. My husband already had a compromised immune system due to the renal failure. I believe that the doctor was wrong in fi

Get the answer below
As at 1\textsuperscript{st} March:

- 491 trials registered
- 51 phase II actively recruiting
- 52 phase III actively recruiting
Global Sepsis Alliance

U.K Pre-hospital Sepsis Working Group

U.K Sepsis Trust

NPSA
Recognition

Biomarker ‘blueprint’

Procalcitonin, CRP, IL-6, Adrenomedullin, Soluble adhesion molecules, lipoprotein binding molecule

Genetic predisposition/ risk stratification

GenOSept in progress (ESICM)
Standardised genotyping- TNFα receptor, TLR 4
<table>
<thead>
<tr>
<th>Pathway</th>
<th>Target</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host-pathogen interaction</td>
<td>LPS</td>
<td>Anti-endotoxin</td>
</tr>
<tr>
<td></td>
<td>Toll receptors</td>
<td>TLR antagonists- TAK-242</td>
</tr>
<tr>
<td></td>
<td>Neutrophil</td>
<td>G-CSF</td>
</tr>
<tr>
<td></td>
<td>Cell adhesion</td>
<td>Leukocyte-endothelial interactions</td>
</tr>
<tr>
<td>Inflammatory cascade</td>
<td>TNF alpha</td>
<td>Anti TNF</td>
</tr>
<tr>
<td></td>
<td>IL1 beta</td>
<td>IL1-ra</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>IL-6 antagonist</td>
</tr>
<tr>
<td></td>
<td>Prostaglandins, leukotrienes</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High dose steroids</td>
</tr>
<tr>
<td></td>
<td>Platelet activating factor</td>
<td>PAF acetyl hydrolase</td>
</tr>
<tr>
<td></td>
<td>Isoprenoid intermediates</td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td>High-Mobility Group B1 Protein</td>
<td>Ethyl pyruvate</td>
</tr>
<tr>
<td></td>
<td>Oxidants</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Microcirculation</td>
<td>Microcirculatory dysfunction</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitrates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dobutamine</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Protein C</td>
<td>Activated protein C</td>
</tr>
<tr>
<td></td>
<td>Protein S</td>
<td>Protein S</td>
</tr>
<tr>
<td></td>
<td>Antithrombin III</td>
<td>Antithrombin III</td>
</tr>
<tr>
<td></td>
<td>Tissue factor</td>
<td>Tissue factor antagonist</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>White cell apoptosis</td>
<td>Anticaspases</td>
</tr>
<tr>
<td></td>
<td>Epithelial cells</td>
<td>Anticaspases</td>
</tr>
</tbody>
</table>

Potential sites for targeted therapies

With permission from Daniels R, Perkins G. NHS Evidence Library, October 2009
Summary

Sepsis is the world’s second biggest killer

The SSC has generated guidelines, discussion and multi centre trials

Guidelines and evidence are incomplete

Data suggests improved outcomes

SCCM/ACCP consensus definitions are imperfect and will be improved upon

We’ll have more robust bundles soon...
To Survive Sepsis...

Organisational awareness
Individual awareness
Empowered personnel
Immediate
  Sampling
  Antibiotics
  Fluids
  Sepsis Six?

In non-responders
  CVC and vasopressors
  EGDT?
## The choices

<table>
<thead>
<tr>
<th></th>
<th>Inaction</th>
<th>SSC evangelist</th>
<th>We’ll do our own thing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rationale</strong></td>
<td>I’ll wait for evidence</td>
<td>International guidance</td>
<td>Local excellence</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td>Robust medicine, lack of harm</td>
<td>Supported by many and by much evidence, doing something</td>
<td>More likely to lead to innovation</td>
</tr>
<tr>
<td><strong>Concerns</strong></td>
<td>Patients denied treatment</td>
<td>Patients treated inappropriately and ? harmed</td>
<td>Good practice may not be disseminated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reproducibility</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>39.8%. That’s ok.</td>
<td>Strive toward 30%</td>
<td>May be lower than 30%, may not be</td>
</tr>
</tbody>
</table>
Statement of interests

Within the last 24 months, I have received travel expenses to deliver one European lecture and have been sponsored to attend one European international meeting by Eli Lilly and Co. I have received no honoraria or other personal remuneration.