Management of Severe Sepsis

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Overview of sepsis

- Major cause of morbidity and mortality\(^1–^3\)
- Uncontrolled systemic response to infection\(^4,^5\)
- Can rapidly escalate to severe sepsis causing acute organ dysfunction and ultimately death\(^3,^6\)
- Affects healthy people or people with pre-existing illnesses at any age\(^7,^8\)

A nonspecific clinical response including more than one of the following:

- Temperature $>38^\circ C$ or $<36^\circ C$
- Heart rate $>90$ beats/min
- Respiratory rate $>20$/min or $\text{PaCO}_2 < 32$mmHg
- White blood cell count $>12,000$/mcL or $<4,000$/mcL

As well as infection, SIRS can also be caused by trauma, burns, pancreatitis and other insults

**SIRS**: systemic inflammatory response syndrome
The disease continuum: sepsis

- Infection
- SIRS
- Sepsis
- Severe sepsis
- Death

SIRS with a confirmed or suspected infectious process

SIRS: systemic inflammatory response syndrome
The disease continuum: severe sepsis

- **SIRS**: Systemic inflammatory response syndrome

- **Severe sepsis**: Sepsis with signs of at least one acute organ dysfunction
  - Renal
  - Respiratory
  - Hepatic
  - Haematological
  - Central nervous system
  - Unexplained metabolic acidosis
  - Cardiovascular

- **Septic shock**: Severe sepsis with hypotension refractory to adequate volume resuscitation

SIRS: Systemic inflammatory response syndrome
Host response to infection

Progression to sepsis and severe sepsis

1–4

Loss of homeostasis

Organ dysfunction

Death

Homeostasis

- Pro-inflammatory
- Coagulation

- Anti-inflammatory
- Fibrinolysis
Loss of homeostasis in sepsis

Endothelial dysfunction

- Anti-inflammatory
- Fibrinolysis
- Pro-inflammatory
- Coagulation

Loss of homeostasis

Diagnosing and managing the patient with sepsis

- Patient history
- Examination
- Investigations
  - Routine
  - Specific

SIRS / sepsis

Rapid assessment and initial resuscitation

A B C D E approach

Early therapy
- Organ support (respiratory, cardiovascular)
- Specific (antibiotics, source control)
- Other (steroids, APC, glycaemic control)
Management of sepsis: ABCDE algorithm and monitoring

- Airway!
- Breathing!
- Circulation!
Monitoring of the critically ill patient

- Critically ill patients should not be left unattended.
- All critically ill patients should be moved to a level 2 or 3 area (as appropriate) as soon as practicable.
- Monitoring should include:
  - continuous ECG
  - blood pressure (non-invasive until invasive established)
  - oxygen saturations (pulse oximeter)
  - central venous pressure monitoring
- Do not delay treatment for placement of invasive lines.
Further management

Is the patient improving?

YES

Further investigations?
Make a management plan

NO

Call for help?
Re-assess ABCDE
Surviving Sepsis Campaign (SSC)
Guidelines for Management of Severe Sepsis and Septic Shock


Crit Care Med 2004;32:858–73
Intensive Care Med 2004;30:536–55
Treatment bundles

- Defined as a ‘group of interventions related to a disease that when instituted together give better outcomes than when done individually’

- Severe sepsis/septic shock bundles:
  - Resuscitation Bundle (6 hours)
  - Management Bundle (24 hours)

Resuscitation Bundle
To be accomplished as soon as possible and scored over first 6 hours

- Serum lactate measured
- Blood cultures obtained prior to antibiotic administration
- Broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED admissions
- In the event of hypotension (SBP <90mmHg, MAP <70mmHg) and/or lactate >4mmol/L
  - deliver an initial minimum of 20mL/kg of crystalloid (or colloid equivalent)
  - apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP ≥65mmHg
In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4mmol/L
  - Achieve CVP ≥8mmHg
  - Achieve ScvO₂ >70%*

*Achieving mixed venous saturation (SvO₂) of 65% is an acceptable alternative

CVP: central venous pressure, ScvO₂: central venous oxygen saturation
Management Bundle
To be accomplished as soon as possible and scored over first 24 hours

- Low-dose steroids administered for septic shock in accordance with a standard ICU policy
- Drotrecogin alfa (activated) administered in accordance with a standard ICU policy
- Glucose control maintained ≥ lower limit of normal, but <150mg/dL (8.3mmol/L)
- Inspiratory plateau pressures maintained <30cm H₂O for mechanically ventilated patients
## SSC grading system

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grading of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Supported by at least two level I investigations</td>
</tr>
<tr>
<td>B</td>
<td>Supported by one level I investigation</td>
</tr>
<tr>
<td>C</td>
<td>Supported by level II investigations only</td>
</tr>
<tr>
<td>D</td>
<td>Supported by at least one level III investigation</td>
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<tr>
<td>E</td>
<td>Supported by level IV or V evidence</td>
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</tbody>
</table>

### Grading of evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Large, randomised trials with clear-cut results; low risk of false-positive (alpha) error of false-negative (beta) error</td>
</tr>
<tr>
<td>II</td>
<td>Small, randomised trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error</td>
</tr>
<tr>
<td>III</td>
<td>Non-randomised, contemporaneous controls</td>
</tr>
<tr>
<td>IV</td>
<td>Non-randomised, historical controls and expert opinion</td>
</tr>
<tr>
<td>V</td>
<td>Case series, uncontrolled studies and expert opinion</td>
</tr>
</tbody>
</table>
Initial resuscitation: early goal-directed therapy

NNT to prevent 1 event (death) = 6–8

- In-hospital mortality (all patients)
- 28-day mortality
- 60-day mortality

Mortality (%)

Standard therapy
Early goal-directed therapy

Figure adapted from Rivers E, et al.
Initial resuscitation

- In the presence of sepsis-induced hypoperfusion
  - hypotension
  - lactic acidosis
Central venous pressure 8–12 mmHg

Mean arterial pressure $\geq 65$ mmHg

Urine output $\geq 0.5$ mL/kg/h

Central venous (superior vena cava) or mixed venous oxygen saturation $\geq 70\%$

Central venous or mixed venous oxygen saturation $< 70\%$ after CVP of 8–12 mmHg

Treatment options:
- packed red blood cells to haematocrit 30%
- dobutamine to maximum $20 \mu$g/kg/min

Grade B
Fluid therapy

- Fluid resuscitation may consist of natural or artificial colloids or crystalloids  
  Grade C

- Fluid challenge over 30 minutes
  - 500–1000mL crystalloid
  - Or 300–500mL colloid

- Repeat based on response and tolerance  
  Grade E
Diagnosis

- Appropriate cultures
- Minimum two blood cultures
  - One percutaneous
  - One from each vascular access that has been in situ for \( \geq 48 \) hours

Grade D
Antibiotic therapy

- Begin intravenous antibiotics within first hour of recognition of severe sepsis
  Grade E

- One or more drugs active against likely bacterial or fungal pathogens
- Consider micro-organism susceptibility patterns in the community and hospital
  Grade D

- Re-assess antimicrobial regimen at 48–72 hours
  - microbiologic and clinical data
  - narrow-spectrum antibiotics
  - non-infectious cause identified
  - prevent resistance, reduce toxicity, reduce costs
  Grade E
Vasopressors

- Either norepinephrine or dopamine administered through a central catheter is the initial vasopressor of choice
  - failure of fluid resuscitation
  - during fluid resuscitation
  Grade D

- Do not use low-dose dopamine for renal protection
  Grade B

- Vasopressin
  - not a replacement for norepinephrine or dopamine as a first-line agent
  - consider in refractory shock despite high-dose conventional vasopressors
  - if used, administer at 0.01–0.04 units/minute in adults
  Grade E

Inotropc therapy

- Consider dobutamine in patients with evidence of low cardiac output despite fluid resuscitation
- Continue to titrate vasopressor to mean arterial pressure of 65mmHg or greater

Grade E

- Do not increase cardiac index to achieve an arbitrarily predefined elevated level of oxygen delivery

Grade A

What do we do at UCL Hospitals?

- Low-dose steroids administered for septic shock in accordance with a standard ICU policy – NO!
- Drotrecogin alfa (activated) administered in accordance with a standard ICU policy – YES/NO
- Glucose control maintained $\geq$ lower limit of normal, but <150mg/dL (8.3mmol/L) – YES!
- Inspiratory plateau pressures maintained <30cm H$_2$O for mechanically ventilated patients – YES!
Evidence-based critical care at UCL Hospitals?

- Transfusion trigger – Hb 6.0g/dl
- Stress ulcer prophylaxis – H2 antagonist
- Elevated head of bed
- DVT prophylaxis – Low MW Heparin
- Early enteral nutrition – naso-gastric
- Early tracheostomy?
- Minimal sedation
- Reduce total body water
Consideration for limitation of support

- Advance care planning, including communication of likely outcomes and realistic goals of treatment, should be discussed with patients and families. Decisions for less aggressive support or withdrawal of support may be in the patient’s best interest

Grade E