



Management of Severe Sepsis

Monty Mythen

*Smiths Medical Professor of
Anaesthesia and Critical Care,
University College London*

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}

1. Edbrooke DL, et al. Crit Care Med 1999;29:1760–7.

2. Wenzel RP, et al. Clin Infect Dis 1996;22:407–13.

3. Rangel-Frausto M, et al. JAMA 1995;273:117–23

4. Mesters R, et al. Thromb Haemost 1996;75:902–7.

5. Wheeler A, Bernard G. N Engl J Med 1999;340:207–14.

6. Opal S, Cohen J. Crit Care Med 1999;27:1608–16.

7. Sands K, et al. JAMA 1997;278:234–40.

8. Intensive Care National Audit & Research Centre Case Mix Programme Database, 2005.

The disease continuum: SIRS



Infection

SIRS

Sepsis

Severe
sepsis

Death

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

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

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

The disease continuum: sepsis



The disease continuum: severe sepsis



Infection

SIRS

Sepsis

Severe
sepsis

Death

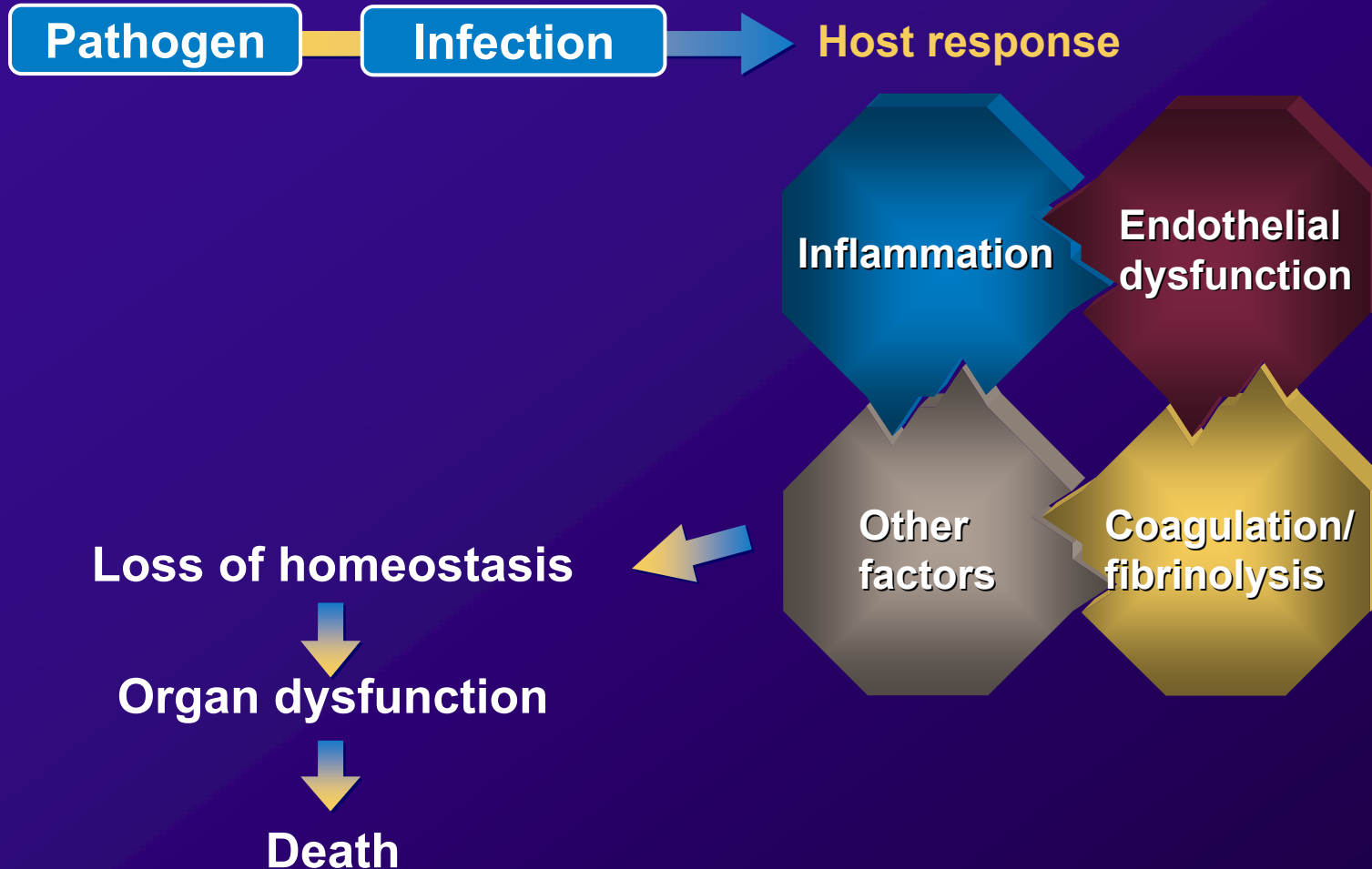
Sepsis with signs of at least one acute organ dysfunction

- Renal
- Respiratory
- Hepatic
- Haematological
- Central nervous system
- Unexplained metabolic acidosis
- Cardiovascular

Septic shock
Severe sepsis
with hypotension
refractory to
adequate volume
resuscitation

Host response to infection

Progression to sepsis and severe sepsis¹⁻⁴



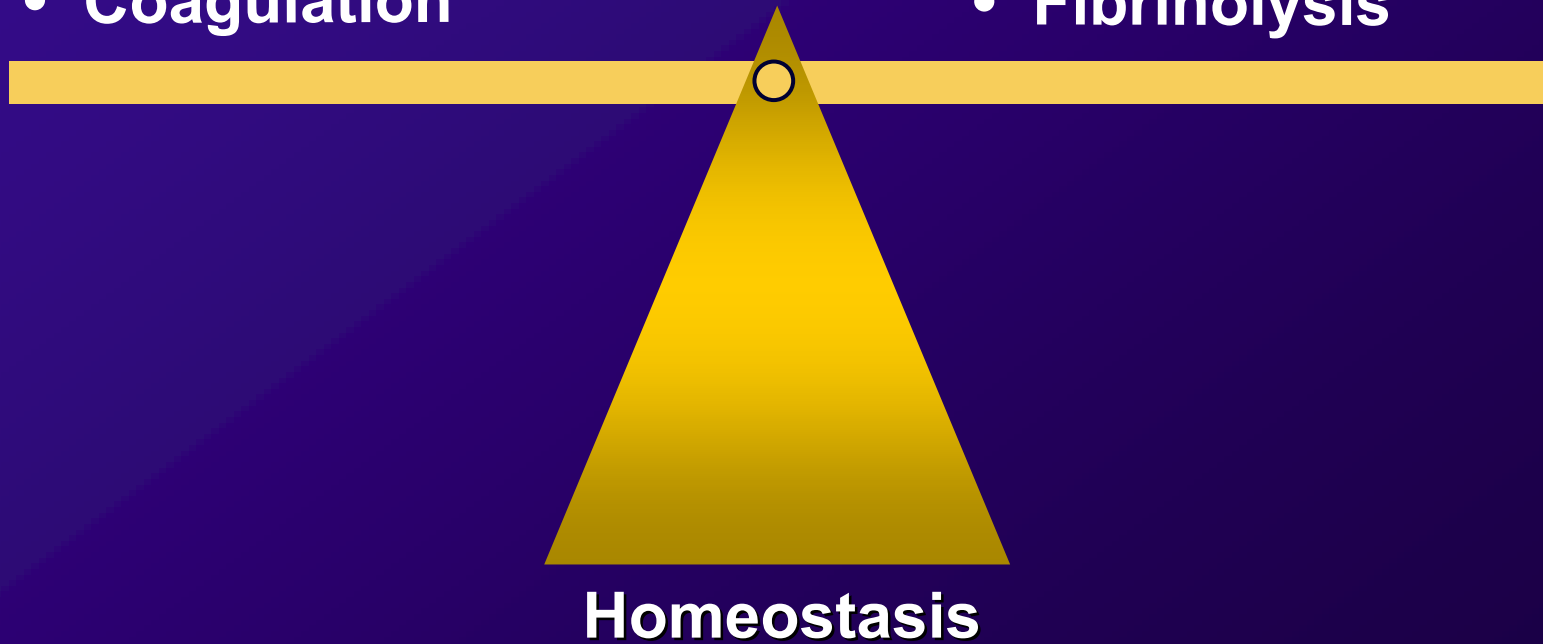
1. McGill S, et al. *World J Surg* 1998;22:171–8.
2. Hooper W, et al. *J Immunol* 1998;161:2567–73.
3. Singer M, Brealey D. *Biochem Soc Symp* 1999;66:149–66.
4. Kidokoro A, et al. *Shock* 1996;5:223–8.

Homeostasis

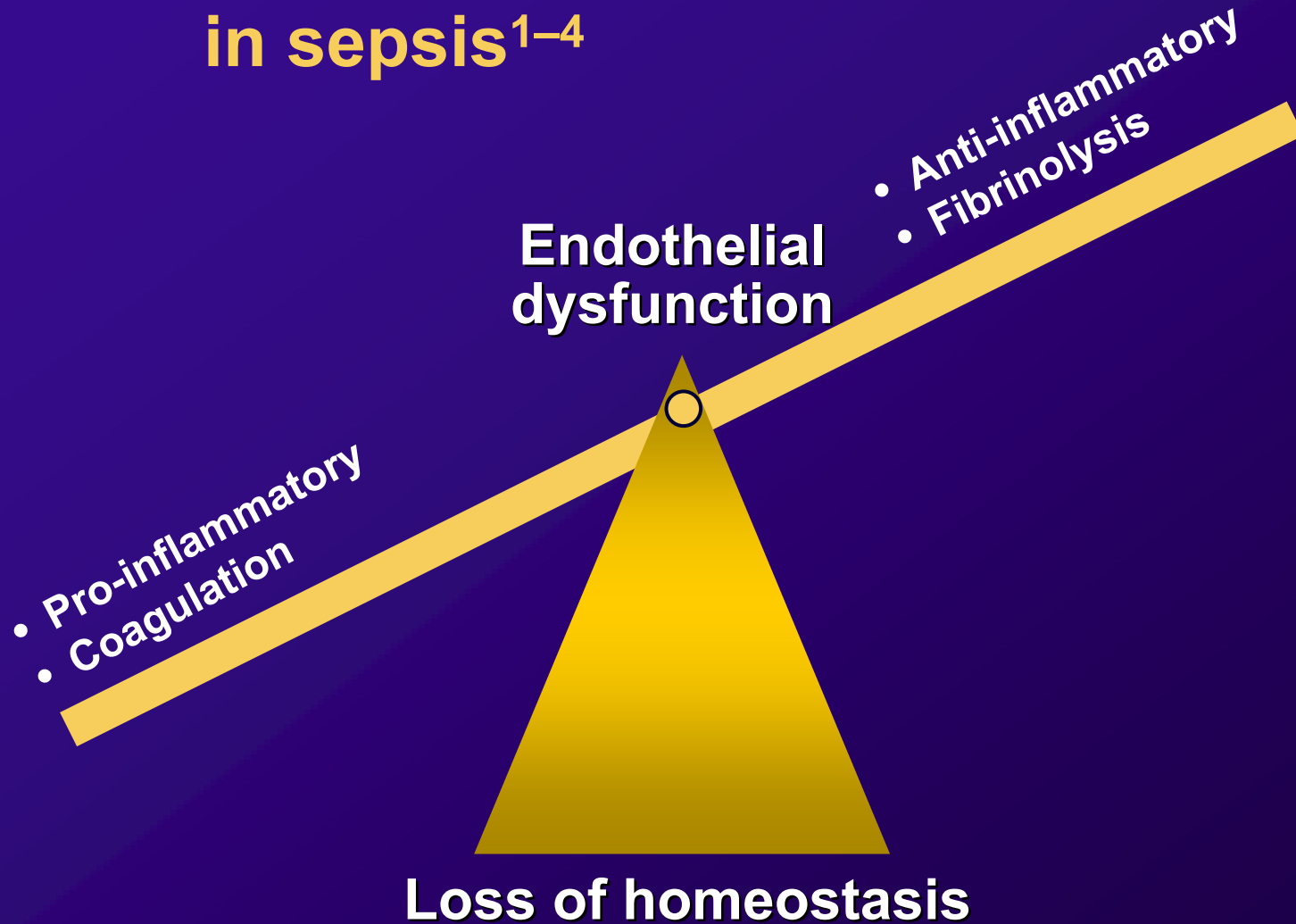


- Pro-inflammatory
- Coagulation

- Anti-inflammatory
- Fibrinolysis

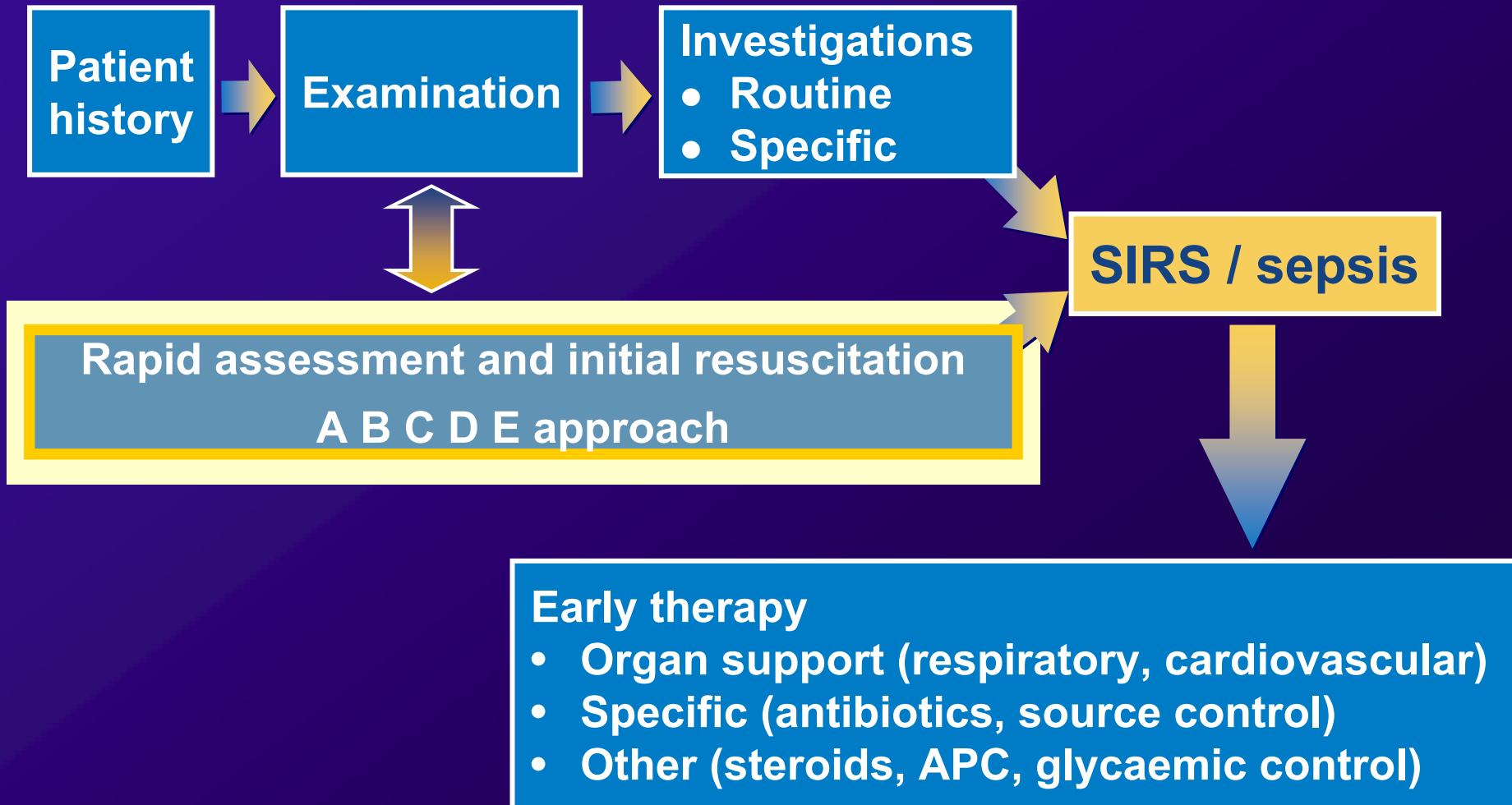


Loss of homeostasis in sepsis¹⁻⁴



1. Kidokoro A, et al. Shock 1996;5:223-8.
2. Carvalho A, Freeman NJ. J Crit Illness 1994;9:51-75.
3. Vervloet M, et al. Semin Thromb Hemost 1998;24:33-44.
4. Bone RC. JAMA 1996;276:565-6.

Diagnosing and managing the patient with sepsis



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



**Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J,
Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G,
Zimmerman JL, Vincent JL, Levy MM and the
SSC Management Guidelines Committee**

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 \geq 65mmHg**

Resuscitation Bundle

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



- In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate $>4\text{mmol/L}$
 - Achieve CVP $\geq 8\text{mmHg}$
 - Achieve ScvO₂ $>70\%$ *

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

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 \geq lower limit of normal, but $<150\text{mg/dL}$ (8.3mmol/L)**
- **Inspiratory plateau pressures maintained $<30\text{cm H}_2\text{O}$ for mechanically ventilated patients**

SSC grading system



Grade Grading of recommendation

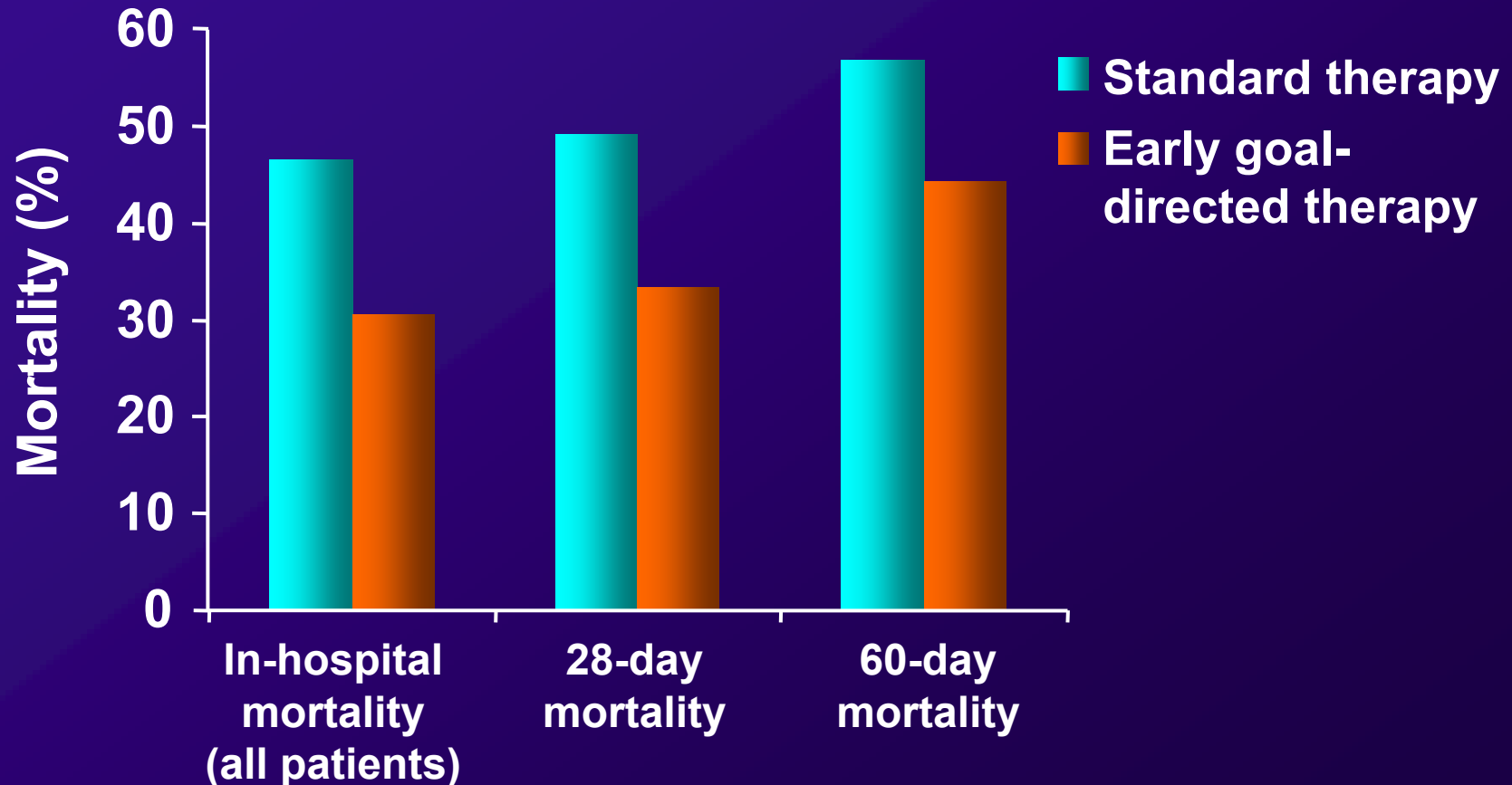
A	Supported by at least two level I investigations
B	Supported by one level I investigation
C	Supported by level II investigations only
D	Supported by at least one level III investigation
E	Supported by level IV or V evidence

Grading of evidence

I	Large, randomised trials with clear-cut results; low risk of false-positive (alpha) error or false-negative (beta) error
II	Small, randomised trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error
III	Non-randomised, contemporaneous controls
IV	Non-randomised, historical controls and expert opinion
V	Case series, uncontrolled studies and expert opinion

Initial resuscitation: early goal-directed therapy

NNT to prevent 1 event (death) = 6–8



Initial resuscitation



- **In the presence of sepsis-induced hypoperfusion**
 - **hypotension**
 - **lactic acidosis**

Initial resuscitation: goals during first 6 hours

- Central venous pressure 8–12mmHg
- Mean arterial pressure ≥ 65 mmHg
- Urine output ≥ 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 $20\mu\text{g/kg/min}$

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 ≥ 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

Inotropic 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

Yu, et al. Crit Care Med 1993;21:830–8.

Hayes, et al. N Engl J Med 1994;330:1717–22.

Gattinoni, et al. N Engl J Med 1995;333:1025–32.

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 $<150\text{mg/dL}$ (8.3mmol/L) – **YES!**
- Inspiratory plateau pressures maintained $<30\text{cm H}_2\text{O}$ 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