Sepsis overview

Dr. Tsang Hin Hung
MBBS FHKCP FRCP
- Epidemiology
- Sepsis, severe sepsis, septic shock
- Pathophysiology of sepsis
- Recent researches and advances
- From bench to bedside
- Sepsis bundle
Severe sepsis in US

Today

>750,000 cases of severe sepsis/year in the US*

Future

Incidence projected to increase by 1.5% per year

Comparable Global Epidemiology

- 95 cases per 100,000
  - 2 week surveillance
  - 206 French ICUs
- 95 cases per 100,000
  - 3 month survey
  - 23 Australian/New Zealand ICUs
- 51 cases per 100,000
  - England, Wales and Northern Ireland.
Comparison With Other Major Diseases

Incidence of Severe Sepsis

Mortality of Severe Sepsis

Cases/100,000

Deaths/Year

AIDS* Colon Cancer§ Breast Cancer§ CHF† Severe Sepsis‡

AIDS* Breast Cancer§ AMI† Severe Sepsis‡

What is Sepsis?

- Systemic inflammatory response syndrome
- Infection
Definition of sepsis

Sepsis is considered present if infection is highly suspected or proven and two or more of the following systemic inflammatory response syndrome (SIRS) criteria are met:

- **Heart rate** > 90 beats per minute (tachycardia)
- **Body temperature** < 36 °C (96.8 °F) or > 38 °C (100.4 °F) (hypothermia or fever)
- **Respiratory rate** > 20 breaths per minute or, on blood gas, a PaCO2 less than 32 mm Hg (4.3 kPa) (tachypnoea or hypocapnoea due to hyperventilation)
- **White blood cell count** < 4000 cells/mm³ or > 12000 cells/mm³ or greater than 10% band forms (immature white blood cells).
Definition of sepsis

- **Sepsis** is a serious medical condition characterized by a whole-body inflammatory state (called a systemic inflammatory response syndrome or SIRS) caused by infection.

- Severe sepsis: sepsis + acute organ dysfunction (organ hypoperfusion)

- Septic shock: sepsis + refractory arterial hypotension (SBP <90mmHg)
Septic shock

Severe sepsis

Sepsis

Mortality
Sepsis – a systemic disease!!
<table>
<thead>
<tr>
<th>Cytokines types</th>
<th>Individual cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphokines</td>
<td>MAF (macrophage activating factor), MMIF (macrophage migration inhibition factor),</td>
</tr>
<tr>
<td></td>
<td>MCF (macrophage chemotactic factor), LMIF (monocyte migration inhibition factor),</td>
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<tr>
<td></td>
<td>HIF-α (histamine releasing factor), TF (transfer factor)</td>
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<tr>
<td>Interleukins</td>
<td>IL-1, IL-2, ..., IL-15</td>
</tr>
<tr>
<td>Tumour necrosis factors</td>
<td>TNF-α (endothelin), TNF-β (lymphotoxin)</td>
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<tr>
<td>Interferons</td>
<td>IFN-α, IFN-β, IFN-γ, IFN-ω, IF-γ</td>
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<tr>
<td>Colony stimulating factors</td>
<td>G-CSF (granulocyte colony stimulating factor), GM-CSF (granulocyte-macrophage CSF),</td>
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<td>M-CSF (macrophage CSF), multi-CSF (IL-3)</td>
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<tr>
<td>Polypeptide growth factors</td>
<td>aFGF (acidic fibroblast growth factor), bFGF (basic fibroblast growth factor), EGf</td>
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<tr>
<td></td>
<td>(epidermal growth factor), NGF (nerve growth factor), PDGF (platelet-derived growth</td>
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<tr>
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<td>factor), VEGF (vascular endothelial growth factor)</td>
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<td>Transforming growth factors</td>
<td>TGF-α, TGF-β</td>
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<td>α-Chemokines</td>
<td>IL-8, NAP-2 (neutrophil activating protein 2), PF-4 (platelet factor 4),</td>
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<td>βTG (β-thromboglobulin)</td>
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<td>β-Chemokines</td>
<td>MCP-1 (monocyte chemotactic protein 1), MCF-2, MIP-1α, MIP-1β,</td>
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<td>(macrophage inflammatory protein 1/β), RANTES</td>
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<tr>
<td>Stress proteins</td>
<td>HSPs (heat shock proteins), GRPs (glucose-regulated proteins), ubiquitin, superoxide</td>
</tr>
<tr>
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<td>dismutase (Mn)</td>
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</table>

- Cytokines
- soluble (glyco)proteins
- nonimmunoglobulin in nature
- released by living cells of the host
- act nonenzymatically in picomolar to nanomolar concentrations
- through specific receptors to regulate host cell function.
<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Cell source</th>
<th>Target</th>
<th>Actions</th>
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<tbody>
<tr>
<td></td>
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<td>Lymphocytes</td>
<td>Enhances responses</td>
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<td>Endothelial cell</td>
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<td></td>
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<td>CNS</td>
<td>Activates</td>
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<td>Liver</td>
<td>Fever, sickness behavior</td>
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<td>Synthesis and release of acute-phase proteins</td>
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<tr>
<td>IL-1</td>
<td>Macrophage</td>
<td>Liver</td>
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<td>Dendritic cell</td>
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<td>IL-6</td>
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<td>Endothelium: Th2 cell</td>
<td>Synthesis and release of acute-phase proteins</td>
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<tr>
<td>TNF-alpha</td>
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<td>Endothelial cell</td>
<td>Proliferation</td>
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<td></td>
<td>Dendritic cell</td>
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<td></td>
<td>Th1 cell</td>
<td>Neutrophil</td>
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<td>Hypothalamus</td>
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<td>IL-10</td>
<td>Macrophage</td>
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<td>Inhibits IL-12 production</td>
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<td>Th2</td>
<td>Dendritic cell</td>
<td>Inhibits pro-inflammatory cytokine synthesis</td>
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<td>II-12</td>
<td>Macrophage</td>
<td>CD4+T helper cell</td>
<td>Th1 differentiation</td>
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<td>IFN-gamma synthesis</td>
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<tr>
<td>IL-2</td>
<td>T cell</td>
<td>T cell</td>
<td>Proliferation</td>
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<td>NK Cell</td>
<td>Activation and proliferation</td>
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<td>B cell</td>
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<td>IL-4</td>
<td>Th2 cell</td>
<td>T cell</td>
<td>Proliferation</td>
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<td>Mast cell</td>
<td>NK Cell</td>
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<td>B cell</td>
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<tr>
<td>IFN-gamma</td>
<td>Th1 cell</td>
<td>T cell</td>
<td>Th1 cell development/proliferation</td>
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<td>Cytotoxic T cell</td>
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<td>Isotype switch to IgE</td>
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<td>NK cell</td>
<td>B cell</td>
<td>Inhibit IFN-gamma activation</td>
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<td></td>
<td></td>
<td>Macrophage</td>
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<td></td>
<td>Th1 cell development</td>
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<td>Isotype switch to IgG</td>
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<td>Activation</td>
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Cytokine storm
Cardiovascular changes in septic shock.
<table>
<thead>
<tr>
<th>Search History</th>
<th>(2 searches)</th>
<th>(Click to close)</th>
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</thead>
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<td>sepsis.mp. [mp=title, original title, abstract, name of substance word, subject heading word]</td>
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<td>limit 1 to (english language and yr=&quot;2004 - 2008&quot;)</td>
</tr>
</tbody>
</table>

Remove Selected    | Combine selections with: And Or

Save Search History
Fluid Therapy

- Fluid resuscitation
- Colloids or crystalloids?

Favors Crystalloids  
Favors Colloids
The Saline versus Albumin Fluid Evaluation (SAFE) Study investigators

- 3497 patients were assigned to receive albumin and 3500 to receive saline

- Primary outcome: 28-day mortality
Kaplan-Meier Estimates of the Probability of Survival. P=0.96 for the comparison between patients assigned to receive albumin and those assigned to receive saline.
# Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Albumin Group</th>
<th>Saline Group</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>726/3473</td>
<td>729/3460</td>
<td>0.99 (0.91–1.09)</td>
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<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81/596</td>
<td>59/590</td>
<td>1.36 (0.99–1.86)</td>
</tr>
<tr>
<td>No</td>
<td>641/2831</td>
<td>666/2830</td>
<td>0.96 (0.88–1.06)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>185/603</td>
<td>217/615</td>
<td>0.87 (0.74–1.02)</td>
</tr>
<tr>
<td>ARDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24/61</td>
<td>28/66</td>
<td>0.93 (0.61–1.41)</td>
</tr>
<tr>
<td>No</td>
<td>697/3365</td>
<td>697/3354</td>
<td>1.00 (0.91–1.09)</td>
</tr>
</tbody>
</table>

**Annotations:**
- **Severe sepsis** circle indicates a significant difference between albumin and saline groups.
- **ARDS** circle indicates no significant difference.
Which vasopressors?

- Noradrenaline is better than dopamine or adrenaline?
- Vasopressin is better?
Low dose dopamine for renal protection?
Surviving sepsis campaign 2008

Vasopressors
- Maintain MAP ≥ 65 mm Hg (1C)
- **Norepinephrine** and dopamine centrally administered are the initial vasopressors of choice (1C)
  - Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C). Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone
  - Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).
- **Do not use low-dose dopamine for renal protection (1A)**
- In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)

Inotropic therapy
- Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output (1C)
- Do not increase cardiac index to predetermined supranormal levels (1B)
Use of steroid in sepsis
Effect of treatment with low doses hydrocortisone and fludrocortisone on mortality in patients with septic shock

Annane et al, JAMA 2002
Hydrocortisone Therapy for Patients with Septic Shock  CORTICUS  NEJM 2008
Activated protein C
Results: 28-Day All-Cause Mortality

Primary analysis results

2-sided p-value: 0.005
Adjusted relative risk reduction: 19.4%
Increase in odds of survival: 38.1%

Mortality (%)

Placebo (n=840) - 30.8%
Drotrecogin alfa (activated) (n=850) - 24.7%

6.1% absolute reduction in mortality

Mortality and APACHE II Quartile

*Numbers above bars indicate total deaths

Adapted from Figure 2, page S90, with permission from Bernard GR. Drotrecogin alfa (activated) (recombinant human activated protein C) for the treatment of severe sepsis. Crit Care Med 2003; 31[Suppl.]:S85-S90
Mortality and Numbers of Organs Failing

Adapted from Figure 4, page S91, with permission from Bernard GR. Drotrecogin alfa (activated) (recombinant human activated protein C) for the treatment of severe sepsis. Crit Care Med 2003;31[Suppl.]:S85-S90
Recombinant Human Activated Protein C (rhAPC)

- **High risk of death**
  - APACHE II ≥ 25
  - Sepsis-induced multiple organ failure
  - Septic shock
  - Sepsis induced ARDS

- **No absolute contraindications**

- **Weigh relative contraindications**
6 Hour Resuscitation
Golden hours for sepsis resuscitation

- Early Identification
- Early Antibiotics and Cultures
- Early Goal Directed Therapy
The Importance of Early Goal-Directed Therapy for Sepsis Induced Hypoperfusion


NNT to prevent 1 event (death) = 6-8

- Standard therapy
- EGDT

Mortality (%)

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

NNT to prevent 1 event (death) = 6-8

Do not delay resuscitation pending ICU admission
Intensive insulin therapy
At 12 months, intensive insulin therapy reduced mortality by 3.4% (P<0.04)

<table>
<thead>
<tr>
<th></th>
<th>Conventional Treatment (n = 783)</th>
<th>Intensive Insulin Treatment (n = 765)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of ICU for patients with &gt;5 days' ICU stay</td>
<td>15</td>
<td>12</td>
<td>.003</td>
</tr>
<tr>
<td>Vent days for patients with &gt;5 days' ICU stay</td>
<td>12</td>
<td>10</td>
<td>.006</td>
</tr>
<tr>
<td>Dialysis (CVVH)</td>
<td>64 (8.2%)</td>
<td>37 (4.8%)</td>
<td>.007</td>
</tr>
<tr>
<td>Transfusions</td>
<td>2 (0.025%)</td>
<td>1 (0.013%)</td>
<td>.001</td>
</tr>
<tr>
<td>ICU sepsis</td>
<td>61 (7.8%)</td>
<td>32 (4.2%)</td>
<td>.003</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>107 (13.7%)</td>
<td>45 (5.9%)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; CVVH, continuous veno-venous hemofiltration.
'Median.
'n (%).
Intensive insulin therapy in medical ICU

van den Berghe G, NEJM 2006
Multiple organ failure in sepsis

- Acute respiratory distress syndrome – ARDS
- Circulatory failure
- Acute renal failure – ARF
- Liver derrangement
- Coagulopathy
- Encephalopathy
ARDS – Acute respiratory distress syndrome
Mechanical Ventilation of Sepsis-Induced ALI/ARDS
ARDSnnet Mechanical Ventilation Protocol
Results: Mortality

Renal failure in sepsis

- Renal replacement therapy
- Blood purification
Transfusion Strategy in the Critically Ill

Other supportive therapies in sepsis

- DVT prophylaxis
- Stress ulcer prophylaxis
- Sedation and weaning from ventilator
Tight glycemic control?
Which vasopressors?
Steroid?
APC?
Colloid?
Blood transfusion?
From Bench to Bedside
Surviving Sepsis Campaign

A global program to:

- Evidence based guideline
- Implementation and education
- Reduce mortality rates
- Improve standards of care

Sepsis Bundle Approach
6 - hour Severe Sepsis/Septic Shock Bundle

- **Early Detection:**
  - Obtain serum lactate level.

- **Early Blood Cx/Antibiotics:**
  - within 3 hours of presentation.

- **Early EGDT:**
  - Hypotension (SBP < 90, MAP < 65) or lactate > 4 mmol/L:
    - initial fluid bolus 20-40 ml of crystalloid (or colloid equivalent) per kg of body weight.

- **Vasopressors:**
  - Hypotension not responding to fluid
  - Titrate to MAP > 65 mmHg.

- **Septic shock or lactate > 4 mmol/L:**
  - CVP and ScvO₂ measured.
  - CVP maintained >8 mmHg.
  - MAP maintain > 65 mmHg.

- **ScvO₂<70% with CVP > 8 mmHg, MAP > 65 mmHg:**
  - PRBCs if hematocrit < 30%.
  - Inotropes.
24 - hour Severe Sepsis and Septic Shock Bundle

- **Glucose control:**
  - maintained on average <150 mg/dL (8.3 mmol/L)

- **Drotrecogin alfa (activated):**
  - administered in high risk patients and without contraindication

- **Steroids:**
  - for septic shock requiring continued use of vasopressors for equal to or greater than 6 hours.

- **Lung protective strategy:**
  - Maintain plateau pressures ≤ 30 cm H₂O, tidal volume 6-8ml/kg and optimal PEEP
Thank you
Mechanical Ventilation of Sepsis-Induced ALI/ARDS

- Reduce tidal volume over 1–2 hrs to 6 ml/kg predicted body weight
- Maintain inspiratory plateau pressure < 30 cm H₂O
Mechanical Ventilation of Sepsis-Induced ALI/ARDS

- **Minimum PEEP**
  - Prevent end expiratory lung collapse

- **Setting PEEP**
  - FIO2 requirement
  - Thoracopulmonary compliance