Practical

Septic shock resuscitation
Important steps in sepsis resuscitation

- Early recognition
- Early resuscitation
- Early goal achievement
- Early antibiotics
- Effective source control
- Optimal organ support
- Effective after shock care
why

The story of sepsis

Local infection .... Local inflammation .... Controlled...

If uncontrolled ... ... dissemination .... Generalized inflammation

...vascular effects ..... Perfusion defect .... end organ effects

...shock ...... ischemic effect ... immune defect ... coag.defect ...... MODS ...... death
Basic pathophysiology

Initiating Stimuli
- Exotoxins
- C5a
- LPS-LBP

CD14 → sTNFr

IL-2
- TNF-α
- IL-6
- IL-1β
- IL-1ra

IL-1ra

Paracrine effects
- Local Vascular Endothelium
- I-CAM

Systemic Effects
- IL-8
- TNF-α
- IL-1β
- IFN-γ
- IL-10
- TGF-β
- Shedding L-selectin
- CD11b/CD18

Nitric Oxide

I-CAM

Systemic Vascular Endothelium

Organs
The shock cascade

Fig. 1. The shock “cascade.”

Strategy 1 Early recognition of sepsis

Patient setting

- Fever, no other symptoms
- Fever, with symptoms and/or signs
- Afebrile, with sepsis signs
- Shock
- etc

- ทำอย่างไรจึงจะวินิจฉัยได้แต่ต้น
  - Vital signs
  - Early warning scores eg. EWS, MEWS, SOS scores
  - Quick SOFA or SOFA
Former definition of **Sepsis**

**ACCP/SCCM consensus conference 1992**

### Various stages of disease
- Bacteremia
- Systemic inflammatory response syndrome
- Sepsis syndrome
- Septic shock: early and refractory

### Systemic Inflammatory Response Syndrome
- Widespread inflammatory response to variety of severe clinical insults.
- Recognized by the presence of two or more of the followings:
  - Temp > 38°C or < 36°C
  - HR > 90/min
  - RR > 20/min or PaCO2 < 32mmHg
  - WBC > 12,000,000/ cu.mm. Or < 4000/cu.mm.
# SOFA score

## Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score<sup>a</sup>

<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>
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<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt;/FiO&lt;sub&gt;2&lt;/sub&gt;, mm Hg (kPa)</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>
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<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
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<tr>
<td>Platelets, ×10&lt;sup&gt;3&lt;/sup&gt;/µL</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>
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<tr>
<td>Bilirubin, mg/dL (µmol/L)</td>
<td>&lt;1.2 (20)</td>
<td>1.2-1.9 (20-32)</td>
<td>2.0-5.9 (33-101)</td>
<td>6.0-11.9 (102-204)</td>
<td>&gt;12.0 (204)</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>
<td></td>
<td>Dopamine &lt;5 or dobutamine (any dose)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MAP &lt;70 mm Hg</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<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&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
<td></td>
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<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Creatinine, mg/dL (µmol/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 (300-440)</td>
<td>&gt;5.0 (440)</td>
<td></td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td></td>
<td></td>
<td>&lt;500</td>
<td>&lt;200</td>
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</tbody>
</table>

Abbreviations: FiO<sub>2</sub>, fraction of inspired oxygen; MAP, mean arterial pressure; PaO<sub>2</sub>, partial pressure of oxygen.  
<sup>a</sup> Adapted from Vincent et al.<sup>27</sup>  
<sup>b</sup> Catecholamine doses are given as µg/kg/min for at least 1 hour.  
<sup>c</sup> Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.
**Patient with suspected infection**

qSOFA ≥2? (see A)  
- No → Sepsis still suspected?  
  - No → Monitor clinical condition; reevaluate for possible sepsis if clinically indicated  
  - Yes → Assess for evidence of organ dysfunction

Assess for evidence of organ dysfunction

- Yes → SOFA ≥2? (see B)  
  - No → Monitor clinically and reevaluate for sepsis if clinically indicated  
  - Yes → Sepsis

**Despite adequate fluid resuscitation, 1. vasopressors required to maintain MAP ≥65 mm Hg AND 2. serum lactate level >2 mmol/L?**

- Yes → Septic shock  
- No → Monitor clinically and reevaluate for sepsis if clinically indicated

**qSOFA Variables**
- Respiratory rate
- Mental status
- Systolic blood pressure

**SOFA Variables**
- $\text{PaO}_2/\text{FiO}_2$ ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count
Influence of Systemic Inflammatory Response syndrome and Sepsis on Outcome of Critically Ill infected Patients

Cumulative incidences of death of patients with infection (from date of infection to hospital discharge) according to sepsis stage: blue line for infection, red line for sepsis, green line for severe sepsis, black line for septic shock.

Strategy 2  *Early resuscitation*

**เป้าหมายในการรักษา**

- Mean arterial pressure > 65 mmHg
- Urine output > 0.5 ml/kg/hr
- Reversal of tissue hypoxia
- Within 6 hours

**• Fluid replacement**

**• Vasopressors if blood pressure (BP) goal is not reached**

**• Check and normalize tissue perfusion after BP goal**
Fluid replacement

- **Fluid Bolus**
  - Initial fluid loading ... 30 ml/kg or more
  - Isotonic crystalloids (0.9%NaCl, LRS or other balanced salt solution are recommended)

- **Fluid challenge**
  - if BP goal is not reached
  - CVP or other volume responsive tests
  - Used as check point (ie. CVP 8-12 mmHg)

- **Fluid maintenance**
  - After the goal is reached
### Four Phases in the Treatment of Shock

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salvage</strong></td>
<td>Aggressive restoration of blood pressures</td>
</tr>
<tr>
<td><strong>Optimization</strong></td>
<td>Provide adequate oxygen delivery. Optimize CO, ScvO₂ and lactate</td>
</tr>
<tr>
<td><strong>Stabilization</strong></td>
<td>Provide organ support</td>
</tr>
<tr>
<td><strong>De-escalation</strong></td>
<td>Vasopressor weaning. Achieve a negative balance</td>
</tr>
</tbody>
</table>


*Fig 2 Patients’ volume status at different stages of resuscitation. Reproduced with permission from ADQI (www.ADQI.org).*
What fluid?

- Isotonic crystalloids
  - NSS
  - LRS or acetate
  - Balance salt solution
- Albumin
- Synthetic colloids
- Others

Fluid Challenge

When intravascular volume status is uncertain

- Static (pressure parameters)
  - CVP, PAOP

- Dynamic (functional)
  parameters derived from heart lung interaction:
  - PPV, SPV
  - IVC
  - EEO

- PLR

- Cardiac output
  - Invasive
    - Thermodilution
  - Less invasive
    - Indicator dilution
    - Pulse contour
  - Impedance
  - Doppler
  - Echo
If the BP target is not reached after adequate fluid replacement.

แนวทางการรักษา
• Fluid replacement
• Vasopressors if blood pressure (BP) goal is not reached
• Check and normalize tissue perfusion after BP goal

เป้าหมายในการรักษา
• Mean arterial pressure > 65 mmHg
• Urine output > 0.5 ml/kg/hr
• Reversal of tissue hypoxia
• Within 6 hours

• Norepinephrine
  – 0.1-2µg/kg/min
  – First line agent

• Dopamine
  – If NE contraindicated
  – Arrhythmia, common complication

• Adrenaline
  – If no response from the above agents
Can vasopressors be given earlier?
Early norepinephrine administration vs. standard treatment during severe sepsis/septic shock resuscitation: a randomized control trial

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Siriraj Hospital, Mahidol University Bangkok 10700 THAILAND

ESICM 2017, September 26
## Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Early Norepinephrine (N = 155)</th>
<th>Standard Norepinephrine (N = 155)</th>
<th>Relative Risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved target MAP + tissue perfusion goal within 6 hours – no (%)</td>
<td>118 (76.1)</td>
<td>75 (48.4)</td>
<td>1.76 (1.42-2.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 28 days – no (%)</td>
<td>22 (14.2)</td>
<td>33 (21.3)</td>
<td>0.77 (0.54-1.08)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hospital mortality – no (%)</td>
<td>33 (21.3)</td>
<td>37 (23.9)</td>
<td>0.93 (0.70-1.22)</td>
<td>0.59</td>
</tr>
<tr>
<td>Time from initial treatment to achieve target MAP and tissue perfusion goal – hr:min</td>
<td>5:52±5:17</td>
<td>7:22±4:35</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>
Detection and reversal of tissue hypoxia

Adequacy of tissue perfusion

- Urine < 0.5 ml/kg/hr
- Low ScvO₂ < 70%
- Lactate > 2 mmol/l, or lactate clearance > 10%

If perfusion goal is not reached

- Check afterload/ intense vasoconstriction
- Correct anemia
- Dobutamine, in those with low cardiac output
- Correct metabolic acidosis
Strategy 3,4 *Early goal achievement*

*Early antibiotics*

Hemodynamic restoration within 6 hours

- Macrocirculation
- *mocrocirculation*

Antibiotics within 1 hour
Therapeutic goal achievements and their association with patients' outcomes during severe sepsis and septic shock resuscitation

Milestone achievements during guideline implementation and their association with patients’ mortality were reported.

These milestones include:

1. mean arterial $\geq 65$ mmHg
2. urine output $\geq 0.5$ ml/kg/hour
3. superior vena cava $O_2$ saturation $\geq 70\%$ or serum lactate clearance $\geq 10\%$.

## Main results

<table>
<thead>
<tr>
<th>Outcomes/goal achievement</th>
<th>No goal (n = 25)</th>
<th>Blood pressure (n = 31)</th>
<th>Blood pressure and urine output (n = 75)</th>
<th>Blood pressure and urine output and lactate (n = 23)</th>
<th>Urine output (n= 21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 days mortality (%)</td>
<td>44</td>
<td>35.5</td>
<td>16</td>
<td>8.7</td>
<td>23.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Hospital mortality (%)</td>
<td>48</td>
<td>41.9</td>
<td>18.7</td>
<td>8.7</td>
<td>28.6</td>
<td>0.003</td>
</tr>
<tr>
<td>ICU LOS 48 pts (days)</td>
<td>16.2±13.9</td>
<td>20.1±25.0</td>
<td>5.7±4.7</td>
<td>5.8±5.0</td>
<td>61.5±58.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>24.5±21.9</td>
<td>31.0±30.0</td>
<td>19.0±16.5</td>
<td>23.5±30.7</td>
<td>28.6±22.1</td>
<td>0.34</td>
</tr>
</tbody>
</table>
The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock.

The temporal patterns of inflammatory mediators were serially examined over the first 72 hrs of hospitalization after early hemodynamic optimization strategies of EGDT trial.

Delayed initiation of antimicrobial therapy increases mortality.

Strategy 5  Effective source control


We recommend that a specific anatomic diagnosis of infection requiring emergent source control should be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention should be implemented as soon as medically and logistically practical after the diagnosis is made (BPS).

Crit Care Med 2017; 45:486–552
Ease of removal of colonized devices

- Urinary catheter
- Intravascular catheter
- Endotracheal tube
- Peritoneal dialysis catheter
- Prosthetic joint; orthopedic hardware
- Vascular graft
- Prosthetic heart valve
- Left ventricular assist device
Strategy 6 *Optimal organ support*

- Organ failure in sepsis and shock
  - Hemodynamics
  - Respiration
  - Renal
  - Coagulation system
  - GI
  - Metabolic
  - Immune
  - Etc.
Strategy 6 Effective after shock care

- Patients’ condition after shock
  - Source controlled??
  - High risks hemodynamics
    - Adequate/ inadequate volume
    - Continued leakage
    - Myocardial blood supply
  - Organ failure/ recovery
  - Anergy
    - High risk of HAI or reactivation of silent infection
Key success factors
in sepsis resuscitation

• Early recognition
• Early resuscitation
• Early goal achievement
• Early antibiotics
• Effective source control
• Optimal organ support
• Effective after shock care
Hemodynamic management
Good restoration of hemodynamic (MAP ≥ 65 mmHg) and adequate organ perfusion.

Give IV fluid
- NSS 500-1,000 ml in ½ hour (lower rate in aging or cardiac patients)
- Follow up BP and JVP (CVP if possible)

Acceptable BP

Evaluate intravascular volume (CVP, PCWP)

Adequate volume

Dopamine/NE
Adrenaline in persistent hypotension

Fluid challenge
- If Hct < 30%, PRC is indicated
- Acidosis or low SvO₂ trial dobutamine

Adequate perfusion

Goal achieved
Frequent assessment

Evaluate organ perfusion
- Urine ≥ 0.5 ml/kg/hr
- Arterial blood pH ≥ 7.30

Guideline
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