Perioperative Management of Sepsis: A Paradigm Shift

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29th March 2017
Outline of Presentation

- Definition of Sepsis
- Overview of Pathophysiology
- Initial resuscitation of patients with sepsis undergoing surgical intervention
- Surviving Sepsis Campaing Guideline
- Perioperative Issues
- Conclusion
The Impact of Sepsis

- Sepsis and septic shock are *major healthcare problem*

- Accounts for as much as 2 5% of intensive care unit (ICU) bed utilization

- Common in elderly, immunocompromised and critically ill patients

- Mortality from septic shock remain high (30-50%)
The Impact on Our OR/ICU?

- Generalized Peritonitis
  - Bowel perforation
  - Bowel obstruction
- Wound Infections
- ICU – CAP, HAP, VAP
Definitions

The Third International Consensus Definitions (Sepsis-3)

**Sepsis**
Life-threatening *organ dysfunction* caused by a *dysregulated* host response to infection

**Organ Dysfunction**
Increase in the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score of 2 points or more

**Septic Shock**
Vasopressor requirement to maintain a MAP of $\geq 65$ mmHg and serum lactate $>2$ mmol/L (18mg/dL) in the absence of hypovolemia

Mervyn et al, SEPSIS-3 : *JAMA. 2016;315(8):801-810*
## Sequential [Sepsis-Related] Organ Failure Assessment Score

<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>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(P_{a}O_2/FIO_2, \text{ mm Hg (kPa)})</td>
<td></td>
<td>(\geq 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>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, (\times 10^3/\mu L)</td>
<td></td>
<td>(\geq 150)</td>
<td>(&lt; 150)</td>
<td>(&lt; 100)</td>
<td>(&lt; 50)</td>
<td>(20)</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL ((\mu mol/L))</td>
<td></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>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (\geq 70\ \text{mm Hg})</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MAP (&lt; 70\ \text{mm Hg})</td>
<td></td>
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</tr>
<tr>
<td>Dopamine (&lt; 5) or dobutamine (any dose)]</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dopamine (5.1-15) or epinephrine (&lt; 0.1) or norepinephrine (\leq 0.1)]</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine (&gt; 15) or epinephrine (&gt; 0.1) or norepinephrine (&gt; 0.1)]</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score[^c]</td>
<td></td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>6</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL ((\mu mol/L))</td>
<td></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>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

The Process of Sepsis Definitions by Task Force

Systemic Inflammatory Response Syndrome (SIRS): Two or more of the following:
- Temperature > 38°C or < 36°C
- Heart rate > 90 beats per minute
- Tachypnoea (respiratory rate > 20 breaths.min⁻¹) or hyperventilation (PaCO₂ < 4.25kPa)
- White blood count > 12 x 10⁹.L⁻¹, or < 4 x 10⁹.L⁻¹

Sepsis: Two or more SIRS criteria in response to infection.

Severe sepsis: Sepsis associated with hypotension or organ dysfunction or organ hypoperfusion (e.g. oliguria, altered mental status, lactic acidosis).

Septic shock: Sepsis-induced hypotension (systolic blood pressure < 90mmHg or a reduction ≥ 40mmHg from baseline) despite adequate fluid resuscitation along with signs of hypoperfusion.

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### 2001

<table>
<thead>
<tr>
<th>General signs and symptoms</th>
<th>Hemodynamic alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigor - Fever (sometimes hypothermia)</td>
<td>Arterial hypotension</td>
</tr>
<tr>
<td>Tachypnea / Respiratory alkalosis</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Positive fluid balance - edema</td>
<td>Increased cardiac output / wide PP / low SVR / high SvO2</td>
</tr>
<tr>
<td>General hematologic/inflammatory reaction</td>
<td>Altered skin perfusion</td>
</tr>
<tr>
<td>Increased (sometimes decreased) WBC</td>
<td>Decreased urine output</td>
</tr>
<tr>
<td>Increased CRP, IL-6 &amp; procalcitonin concentration</td>
<td>Hyperlactatemia - Increased base deficit</td>
</tr>
<tr>
<td>Signs of organ dysfunction</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Hypoxemia (ALI)</td>
<td>Thrombocytopenia, DIC</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>Alteration in liver tests (hyperbilirubinemia)</td>
</tr>
<tr>
<td>Alteration in renal function</td>
<td>Intolerance to feeding (altered GI motility)</td>
</tr>
</tbody>
</table>

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Why SOFA score ???

SOFA score of 2 or greater identified a 2- to 25-fold increased risk of dying compared with patients with a SOFA score less than 2.

SOFA score is not intended to be used as a tool for patient management but as a means to **clinically characterize** a septic patient.

**SIRS Criteria**

The task force wishes to stress that SIRS criteria may still remain useful for the **identification of infection**.
Overview of Pathophysiology

Endotoxin (LPS)

LBP on CD 14
Macrophage, Endothelial

Intracellular Signal Transduction via TLR

Complex Endothelial-Leucocyte Interaction

Increased TF and PAI
Procoagulant
Microvascular occlusion

O$_2$ radical, Cytokine, Complement, Lipid mediators
Capillary Leak, Vasodilatation
CVS instability

Proinflammatory Vs Anti-inflammatory
Dysregulated Immune Response

MODF
Early recognition and treatment of sepsis is important.

Not all septic patients have self-evident septic focus

Initial assessment followed by secondary assessment

a. State of IV Volume status

b. The need and Adequacy of resuscitation

c. Severity of Organs dysfuctions

d. Presence of Comorbid conditions
Early haemodynamic optimization can reduce mortality

Adequate resuscitations
Early IV Antibiotics
Source Control

Reduce Mortality and Morbidity

Initial Assessment and Management

A brief history taking with limited examination (eSOFA)

Airway

- Recovery position, oro/ or nasopharyngeal airway
- Appropriate Oxygen therapy
- Early intubation

Breathing

- Signs of respiratory failure
- Head up position
- Assisted by Ambu bag/Waters to and fro
- NIV Vs Intubation and Mechanical Ventilation

Circulation

- Rapid assessment (HR, BP, Capillary refill etc)
- Fluid resuscitation – 20-30 ml/kg

Circulation

Surviving Sepsis Campaign Guidelines
Early Goal Directed Therapy (EGDT)

Fluid Resuscitation

How much?

Types

How Fast?

When to stop?
**How Much ???**

At least 30 ml/kg

**How Fast ???**

Within first 3 hours

<table>
<thead>
<tr>
<th>Study</th>
<th>Events, OR (95% CI)</th>
<th>EGDT</th>
<th>control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISE Investigators (2014)</td>
<td>0.98 (0.76, 1.26)</td>
<td>147/792</td>
<td>150/796</td>
<td>30.71</td>
</tr>
<tr>
<td>ProMISe Investigators (2015)</td>
<td>1.02 (0.80, 1.30)</td>
<td>184/623</td>
<td>181/620</td>
<td>32.23</td>
</tr>
<tr>
<td>Overall (I-squared = 56.7%, p = 0.055)</td>
<td>1.01 (0.88, 1.16)</td>
<td>495/2134</td>
<td>582/2601</td>
<td>100.00</td>
</tr>
</tbody>
</table>
**Fluid of Choices ?????**

### Crystalloids Vs Colloids

Crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement

### Balanced Salt Solution Vs 0.9% Normal Saline

Either is acceptable

Close monitoring of serum Cl\(^-\) to avoid hyperchloraemic metabolic acidosis
Suggest using Albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement.

A trend toward reduced 90-day mortality was observed in severe sepsis patients resuscitated with albumin compared with crystalloid and saline.
Role of Synthetic Colloids

Recommend **Against** using Hydroxyethyl Starches (HES) for intravascular volume replacement.

**BMJ**

*BMJ* 2013;346:f839 doi: 10.1136/bmj.f839 (Published 15 February 2013)

**Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis**

Nicolai Haase *physician*¹, Anders Perner *professor*¹, Louise Inkeri Hennings *physician*¹, Martin Siegemund *professor*², Bo Lauridsen *physician*¹, Mik Wetterslev *medical student*¹, Jørn Wetterslev *chief physician*³

**HES 130/0.38-0.45 increased the use of RRT, RBC transfusion and resulted in more serious adverse events**
Role of Synthetic Colloids (Gelatins)

Gelatin use in critically ill adult patients did not increase mortality or acute kidney injury compared to albumin or crystalloid.

SSC suggest using **Crystalloids over Gelatins** when resuscitating patients with sepsis or septic shock.
What are GOALS for EGDT???

2012

- MAP > 65 mmHg
- Urine Output > 0.5 ml/kg/hr
- Capillary Refill < 2 sec
- CVP 8-12 mmHg
- ScvO₂ > 70%
- Serum Lactate < 4 mmol/L

Dynamic over static variables

CVP and ScvO₂: Not reliable and fail to show improve outcome

MAP 65 Vs 85 mmHg: No difference outcome

Serum lactate guided resuscitation: Significant reduction in mortality
Norepinephrine as the first-choice vasopressor

Adding Epinephrine (20-50 mcg/min)/Vasopressin (upto 0.03 U/min)

Dopamine only in selected cases (risk of arrhythmia)

Dobutamine for hypoperfusion with fluid & vasopressor agents

Phenylepherine : Still controversial !!!
Dose of Norepinephrine

The mean dose of norepinephrine ranges from 0.2 to 1.3 mcg/kg/min with a maximum dosage of 3.3 mcg/kg/min.

When to consider adding another vasopressor?

Potential benefit in the population requiring ≥ 15 μg/min of norepinephrine
Corticosteroids

Against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability

When to Start and How much??

- Only if Adequate fluid therapy and vasopressor fail to achieve target MAP
- IV hydrocortisone at a dose of 200 mg per day
- Use continuous flow
RBC transfusion only when hemoglobin concentration decreases to < 7.0 g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage

Against the use of erythropoietin for treatment of anaemia associated with sepsis

A Randomized Trial of Protocol-Based Care for Early Septic Shock
Against the use of fresh frozen plasma to correct clotting abnormalities in the absence of bleeding or planned invasive procedures.

Prophylactic platelet transfusion when counts are < 10,000/mm³ (10 × 10⁹/L) in the absence of apparent bleeding and when counts are < 20,000/mm³ (20 × 10⁹/L) if the patient has a significant risk of bleeding.

Higher platelet counts (≥ 50,000/mm³ [50 × 10⁹/L]) are advised for active bleeding, surgery, or invasive procedures.

### SSC Guidelines Against

<table>
<thead>
<tr>
<th>Use of IV immunoglobulins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of blood purification techniques (CPFA, Hemoadsorption etc)</td>
</tr>
<tr>
<td>Use of Antithrombin</td>
</tr>
<tr>
<td>No recommendation regarding the use of thrombomodulin or heparin</td>
</tr>
</tbody>
</table>
Blood Culture

Appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy

Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic)
Antibiotic Therapy

Administration of IV antimicrobials should be initiated **as soon as possible** after recognition and within one hour.

Empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens.

**Daily Assessment**

Antibiotic **de-escalation** should be done within first few days depending on clinical improvements and/or evidence of infection resolution.
Antibiotic Therapy

Antimicrobial treatment duration of 7 to 10 days is adequate for most serious infections.

Longer Duration: Only for poor clinical resolution.

Recommend **against** sustained systemic antimicrobial prophylaxis in patients with **severe inflammatory states of noninfectious origin** (e.g., severe pancreatitis, burn injury).
Against the use of sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥ 7.15
Sepsis Bundles

**WITHIN 3 HOURS**
1. Measure *lactate* level
2. Obtain *blood cultures*
3. I.V broad spectrum *antibiotics*
4. I.V 30ml/kg *crystalloid* for hypotension or lactate ≥4mmol/L

**WITHIN 6 HOURS**
1. Apply *vasopressors* (MAP ≥65mmHg)
2. *Re-assess* volume status and tissue perfusion
3. *Re-measure lactate*

Initial Assessment and Resuscitation should be followed by Secondary Assessment
Preoperative Assessment

Detailed History & Examination + Airway Assessment

**Investigations**
- Full blood count /BUN/ Creatinine/Electrolyte/Coagulation profile/Blood Glucose
- CXR /EKG
- Imaging studies – May be helpful for decision of source control procedure

**Diagnosis and the clinical course** ➔ **Timing and Degree of Surgery**

!!! Immediate goal !!!
Aequate source control with the least physiological embarrassment
Communication with Surgical Team is critically important
Preoperative Preparation

- Optimize patient using SSC guidelines (Bundles)
  - Heamodynamic stability
  - Correction of coagulopathy
  - Aspiration prophylaxis
  - Blood glucose control (≤ 180 mg%)

- Prepare for Post-operative plan (ICU or HDU)

- Explain the possible risks and outcome after anesthesia and surgery with patients and family
Choice of Anesthetic Technique

Severity of Sepsis (esp CVS stability)

Nature and extent of surgical procedure

Expertise of anesthesiologist on specific technique

Neuraxial Anesthesia
- Relative contraindication
- Exaggerated physiological response
- Coagulopathy
- Epidural abscess, epidural haematoma

General Anesthesia
- CVS instability
- Need for RSI
- Easily desaturate
- Can provide high FiO2
- Lungs protective ventilation

Peripheral nerve block
- Can avoid systemic effects of IV or inhalational agents
- CVS stability
- Pharmacokinetic of LA on acidic environment
# Intraoperative Management

## Before Induction
- Emergency medications/ anesthetic machine/ airway and resuscitation equipment
- Prepare for i.v lines (16 – 14 G)

## Monitoring
- EKG, SpO2, NIBP, EtCO2, Temperature, Urine Output
- Other monitoring (IBP, CVP, ScVO2, lactate, CO monitoring, TEE only if available)

## Induction
- RSI is the usual technique of choice
- Preoxygenation with 100% O₂
- *Step-wise* process, *Small* doses of i.v agents, *Titrated* to clinical response
- The CARE how anesthetic agents are administered
# Choosing an Induction Agent

<table>
<thead>
<tr>
<th><strong>Etomidate</strong> (0.2 to 0.3 mg/kg)</th>
<th><strong>Midazolam</strong> (0.1-0.3 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Rapid onset and short DOA</td>
<td>▪ Rapid onset, short DOA</td>
</tr>
<tr>
<td>▪ CVS stability</td>
<td>▪ Directly relax laryngeal muscle</td>
</tr>
<tr>
<td>▪ Issue of Adrenal insufficiency</td>
<td>▪ Decrease in BP (approx 10%)</td>
</tr>
<tr>
<td>▪ Current literature doesn’t support absolute mortality effect</td>
<td>▪ Reflex increase in HR</td>
</tr>
<tr>
<td></td>
<td>▪ Cardiac index is well maintained</td>
</tr>
</tbody>
</table>

**Ketamine**
- I.V 1-2 mg/kg
- Rapid onset and short DOA
- Increase in HR, BP, SVR
- Increase in myocardial O₂ demand
- Maintain airway reflexes and increase secretion
- Useful for septic shock
Choosing an Induction Agent

**Propofol (1.5 – 2 mg/kg)**
- Rapid onset, short DOA
- Inhibit airway reflexes
- Reduce BP, SVR (30% from base line)
- Impaired baroreceptor reflex
- Inhibitory effect on Neutrophil
- Do not affect by renal dysfunction

**Thiopentone (3-5mg/kg)**
- Rapid onset
- Short DOA
- Decrease SVR, Increase HR
- Direct Myocardial depression
- Immunosuppressive action
- Inhibition of granulocyte recruitment and phagocytosis

Role of Opioids

- Can enable to reduce dose of I.V agents.
- Can avoid decrease in SVR
- DOA may be increased by impaired hepatic and renal function
- Fentanyl/Alfentanil/Remifentanil: NO MORPHINE
- Bradycardia (Most are already tachycardiac)

Muscle Relaxants

- DN MBA can be used for RSI (hyperkalaemia)
- For maintenance, cis-atracurium or atracurium has organ independent metabolism.
- Vecuronium is devoid of CVS insults (biliary and renal metabolism)
**Perioperative Issues**

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Blood Components</th>
<th>Others</th>
</tr>
</thead>
</table>
| • Continue EGDT  
• Accessed by by CVP, Capillary refill, *Urine Output* etc.  
• Global O2 Delivery : Serum lactate -2 mmol/L and ScvO2 >70% | • Keep Hb% 7-9 g/dl  
• FFP and Platelet concentrate depending on amount of blood loss and presence of coagulopathy | • Keep Normothermia  
• Blood glucose level < 180 mg/dL  
• Proper Timing of I.V Antibiotic |
## Mechanical Ventilation

<table>
<thead>
<tr>
<th>Target</th>
<th>SpO2 &gt;90% with pH &gt;7.2 (permissive hypercapnia: PaCO2 &lt; 10 kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO2</td>
<td>Adjusted with target SpO2 (usually within 0.5-0.6)</td>
</tr>
<tr>
<td>Tidal Volume</td>
<td>6-8 ml/kg</td>
</tr>
<tr>
<td>Plateau pressures</td>
<td>30cmH₂O</td>
</tr>
<tr>
<td>Other</td>
<td>Recruitment manoeuvres</td>
</tr>
<tr>
<td>PC-IRV</td>
<td>Failed oxygenation with lungs protective ventilation strategy</td>
</tr>
</tbody>
</table>
**Postoperative Management**

- The *Rate of blood loss* should be minimal
- Decision to extubate depend on
  - Severity of Sepsis (Hemodynamic Instability)
  - Presence of comorbid diseases
  - Extensiveness of surgical procedures
- Monitoring should be continued at PACU / Pain Control
- Safe transfer of the patient to the ICU/HDU is essential
- A focused hand-over report is helpful for the ICU colleagues
- **Pre-resuscitation measurements** should be used to calculate the ICU APACHE score
Conclusion

A major healthcare issue with a high mortality

Definitions has been changed recently

Fluid resuscitation with vasopressors to optimize CVS parameter is critically important

Timely intervention to complete sepsis bundles can improve outcome
Conclusion

I.V Antibiotic should be started ASAP & Continued intraoperatively if required

Decision for source control with appropriate surgical intervention always depend on sincere communication between surgical and anaesthesia teams

If intubation is decided in ER, always consider appropriate anaesthetic agents depending on pharmacodynamic/kinetics in relation to sepsis
Application of Fluid Resuscitation in Adult Septic Shock

Sepsis-induced hypotension or lactate ≥ 4 mmol/L
(Based on SSC bundle and CMS threshold)

- No high flow oxygen and No ESRD on dialysis or CHF
  - Rapid infusion of 30 ml/kg crystalloid

- Pneumonia or ALI with high flow oxygen requirements
  - Not intubated/mechanically ventilated
  - Consider intubation/mechanical ventilation to facilitate 30 ml/kg crystalloid infusion
  - If Yes: Rapid infusion of 30 ml/kg crystalloid
  - If no: Total of 30 ml/kg with frequent reassessment of oxygenation

- Intubated/mechanically ventilated
  - Total of 30 ml/kg crystalloid with frequent reassessment of oxygenation

- ESRD on hemodialysis or CHF
  - Total of 30 ml/kg crystalloid with frequent reassessment of oxygenation
Thank You for Attention