Sepsis Update 2019

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The Facts

- Sepsis is diagnosed in over one million patients each year in the United States
- Sepsis treatment resulted in an estimated $27 billion or 5.2 percent of the total cost for all hospitalizations
- Most expensive condition treated in the year 2011/12/13/14/15/16/17/18
- Mortality rate of 28-50%

-National Center for Health Statistics Data Brief No. 62 June 2011
-CDC 2016
“Except on few occasions, the patient appears to die from the body's response to infection rather than from it.”

Sir William Osler – 1904
The Evolution of Modern Medicine
Fig. 1. Pathophysiology of septic shock.

IL-interleukin, IL-1ra-interleukin 1 receptor antagonist, LP-lipopolysaccharide, NO-nitric oxide, ROS-reactive oxygen species, TNF-a-tumor necrosis factor-alpha.
OLD Terminology:

Sepsis: Systemic manifestations of infection

Severe sepsis: Sepsis with organ dysfunction, hypoperfusion, or hypotension

Septic shock: Sepsis with arterial hypotension, despite fluid resuscitation, with organ dysfunction
Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis

- Altered Consciousness
- Confusion
- Psychosis

- Tachypnea
  - $\text{PaO}_2 < 70 \text{ mm Hg}$
  - $\text{SaO}_2 < 90\%$
  - $\text{PaO}_2/\text{FiO}_2 \leq 300$

- Jaundice
  - $\uparrow$ Enzymes
  - $\downarrow$ Albumin
  - $\uparrow$ PT

- Tachycardia
- Hypotension
- Altered CVP
- Altered PAOP

- Oliguria
- Anuria
  - $\uparrow$ Creatinine

- $\downarrow$ Platelets
  - $\uparrow$ PT/APTT
  - $\downarrow$ Protein C
  - $\uparrow$ D-dimer

Figure 1. The Systemic Inflammatory Response Syndrome (SIRS).

Two or more of the following:

- Temperature >38° C or <36° C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or PaCO₂ <32 torr
- WBC >12,000 cell/mm³, <4,000 cells/mm³, or >10% immature (band) forms

Bone, et al. 1992
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH
Definition Changes in 2016

• A task force of 19 leaders in the field of sepsis was convened by SCCM and the European Society of Intensive Care Medicine (ESICM)

• Sepsis
  • A life-threatening organ dysfunction caused by a dysregulated host response to infection

• The new diagnostic tool for sepsis: quickSOFA (qSOFA), 2 of 3 indicators below:
  • An alteration in mental status
  • A decrease in systolic blood pressure of less than 100 mm Hg
  • A respiration rate greater than 22 breaths/min

Definition Changes in 2016

• Septic Shock:

• A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

• Persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg
  • Blood lactate >2 mmol/L despite adequate volume resuscitation

Infection

Sepsis
Mortality ≥ 10%

Septic shock
Mortality ≥ 40%
<table>
<thead>
<tr>
<th></th>
<th>OLD</th>
<th>NEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPSIS</td>
<td>suspected infection + SIRS</td>
<td>suspected infection + 2 ≥ qSOFA or rise in SOFA score by ≥ 2</td>
</tr>
<tr>
<td>SEVERE SEPSIS</td>
<td>sepsis + hypotension, hypoxia, elevated lactate or other lab markers of end organ dysfunction</td>
<td>(category removed)</td>
</tr>
<tr>
<td>SEPTIC SHOCK</td>
<td>sepsis + hypotension after adequate fluid resuscitation</td>
<td>sepsis + vasopressors + lactate &gt; 2</td>
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</tbody>
</table>
LOOK For: Quick SOFA score - Sepsis-related Organ Failure Assessment

Score >2 = mortality of 10%
Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock

Patient with suspected infection

qSOFA ≥2? (see A)

- Yes: Assess for evidence of organ dysfunction
  - SOFA ≥2? (see B)
    - 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 clinical condition; reevaluate for possible sepsis if clinically indicated
    - No: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated

- No: Sepsis still suspected?
  - Yes: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated

A. qSOFA Variables
   - Respiratory rate
   - Mental status
   - Systolic blood pressure

B. SOFA Variables
   - PaO₂/FiO₂ 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

The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.
2018 Sepsis Treatment Guidelines

The Surviving Sepsis Campaign Bundle: 2018 Update

Mitchell M. Levy, MD, MCCM¹; Laura E. Evans, MD, MSc, FCCM²; Andrew Rhodes, MBBS, FRCA, FRCP, FFICM, MD (res)³
**HOUR-1 BUNDLE: INITIAL RESUSCITATION FOR SEPSIS AND SEPTIC SHOCK:**

1) Measure lactate level.*
2) Obtain blood cultures before administering antibiotics.
3) Administer broad-spectrum antibiotics.
4) Begin rapid administration of 30mL/kg crystalloid for hypotension or lactate ≥4 mmol/L.
5) Apply vasopressors if hypotensive during or after fluid resuscitation to maintain a mean arterial pressure ≥ 65 mm Hg.

*Remeasure lactate if initial lactate elevated (> 2 mmol/L).
Surviving Sepsis Campaign

1. *Act quickly upon sepsis & septic shock recognition
2. Minimize time to treatment - sepsis & septic shock are medical emergencies
3. Monitor closely for response to interventions
4. Communicate sepsis status in hand-offs

*All elements of the Hour-1 bundle may or may not be completed in the first hour after sepsis recognition

survivingsepsis.org
Screening

• Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C)
• Hospital based performance improvement efforts in severe sepsis
• Role of the Sepsis Team
Goals

• First 6 hrs of resuscitation:
  – a) Central venous pressure 8–12 mm Hg
  – b) Mean arterial pressure (MAP) ≥ 65 mmHg?
  – c) Urine output ≥ 0.5 mL/kg/hr
  – d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C)

• In patients with elevated lactate levels targeting resuscitation to normalize lactate
Antibiotics

• Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock
• Antimicrobial regimen should be reassessed daily for potential de-escalation (grade 1B)
• Empiric combination therapy should not be administered for more than 3–5 days. (grade 2B)
• Duration of therapy typically 7–10 days (grade 2C)
• Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C)
Source control

• When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg. percutaneous rather than surgical drainage of an abscess)

• If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established
Resuscitation

• Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B)
• Avoid Hetastarch or Hespan compounds (grade 1B)
• Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C)
• Initial fluid challenge in patients with sepsis induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids. More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C)
• Fluid challenge technique be applied where in fluid administration is continued as long as there is hemodynamic improvement
Vasopressors

- Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg
- Norepinephrine as the first choice vasopressor (grade 1B)
- All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available

Catecholamine Sparing Strategies
Vasopressors

• First isolated ~ 1900
• Catecholamines
  • Norepinephrine
  • Epinephrine
  • Dopamine
• Non-catecholamines
  • Phenylephrine
  • Vasopressin/terlipressin
  • Angiotensin II (AT2)
Adverse Effects of Catecholamines

- Arrhythmias
- Ischemia
- Increased myocardial O2 demand
- Hyperglycemia
- Decreased cardiac output
- Inflammation
- Immunosuppression
- Increased mortality??
Corticosteroids

- Indicated with persistent hemodynamic instability
- Hydrocortisone 50mg IV every 6 hours. OR Hydrocortisone 100mg IV every 8 hours
- DO NOT use the ACTH stimulation test (grade 2B)
- In treated patients hydrocortisone, taper when vasopressors are no longer required
- Corticosteroids not be administered for the treatment of sepsis in the absence of shock
- Multiple studies have shown decreased time on vasopressors. No mortality benefit
- Complications associated with steroids
Vasopressin

• VASST Trial
• Evaluated vasopressin (AVP) versus norepinephrine (NE) effect on 28 day mortality in septic shock
  • Multicenter, randomized, double-blind; N = 778
  • Stratified by baseline NE dose
  • No difference in primary outcome (35.4% vs. 39.3%) 28- day Mortality
  • Secondary outcomes: No difference in 90 day mortality, any organ dysfunction subgroup, or LOS
  • No difference in adverse effects

• Conclusions – AVP significantly decreased NE doses at day 4 (p < 0.001) – AVP MAY improve mortality in patients with less severe shock
Angiotensigen → Renin → Angiotensin I → Converting enzyme → Angiotensin II → Aldosterone
- Stimulation of aldosterone secretion
- Increased water and sodium retention → Increased Preload
- Constriction of vascular smooth muscle → Increased Afterload
GIAPREZA™
(angiotensin II)
Injection for Intravenous Infusion

RENIN ANGIOTENSIN-ALDOSTERONE

CATECHOLAMINES¹: SYMPATHETIC NERVOUS

VASOPRESSIN: ARGinine-VASOPRESSIN
ATHOS-3

• Phase III trial evaluating AT2 for severe vasodilatory shock
  • Randomized, double-blind, multicenter, placebo controlled; May 2015-January 2017
  • N = 321
  • Purpose: to determine effectiveness of AT2 for vasodilatory shock resistant to high-dose vasopressors
  • Primary Outcome: MAP response 3 hours after start of infusion
### ATHOS-3 Results

| Outcome                              | AT2  
|                                      | $N=163$ (%) | Placebo  
<table>
<thead>
<tr>
<th></th>
<th>$N=158$ (%)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>MAP response at hour 3</td>
<td>114* (70)</td>
<td>37 (23)</td>
</tr>
<tr>
<td>Mean change in SOFA score</td>
<td>1.05±5.5</td>
<td>1.04±5.34</td>
</tr>
<tr>
<td>7-day all cause mortality</td>
<td>47 (29)</td>
<td>55 (35)</td>
</tr>
<tr>
<td>28-day all cause mortality</td>
<td>75 (46)</td>
<td>85 (54)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>99 (61)</td>
<td>106 (67)</td>
</tr>
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</table>

*79/114 (69%) were “super-responders”

## Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>AT2 (N=163)</th>
<th>Placebo (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>142</td>
<td>145</td>
</tr>
<tr>
<td>Any leading to discontinuation</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral ischemia</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Delirium</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Acidosis</td>
<td>9</td>
<td>1</td>
</tr>
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</table>

## Subgroup Analyses

<table>
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<tr>
<th>Population</th>
<th>N</th>
<th>Day 28 Mortality (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(AT2 = 163; placebo = 158)</td>
<td>(AT2 vs. placebo)</td>
<td>(AT2 vs. placebo)</td>
</tr>
<tr>
<td>“Super-responders”</td>
<td>79 vs. 84 N/A (placebo)</td>
<td>32.9 vs. 58.6</td>
<td>53.9</td>
</tr>
<tr>
<td>APACHE II &gt; 30</td>
<td>58 vs. 65</td>
<td>51.8 vs. 70.8</td>
<td></td>
</tr>
<tr>
<td>AKI on RRT</td>
<td>45 vs. 60</td>
<td>53 vs. 30</td>
<td></td>
</tr>
<tr>
<td>MAP &lt; 65</td>
<td>52 vs. 50</td>
<td>54.2 vs. 70.4</td>
<td></td>
</tr>
<tr>
<td>ARDS*</td>
<td>122 vs. 121</td>
<td>48 vs. 57</td>
<td></td>
</tr>
<tr>
<td>AT1/AT2 &gt; 1.63**</td>
<td>68 vs. 72</td>
<td>HR 0.64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(AT2 = 142; placebo = 139)</td>
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*Defined by baseline PaO2/FiO2 < 300
**Signifies relatively low AT2 state

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ADMINISTERING GIAPREZA™ (angiotensin II) injection for intravenous infusion

Visit www.giapreza.com

Recommended starting dose of GIAPREZA is 20 ng/kg/min, which is equivalent to 0.02 mcg/kg/min via continuous intravenous infusion

 Dosage is measured in NANOGRAMS (ng)

 Monitor blood pressure closely after GIAPREZA initiation

The median response time was approximately 5 minutes

 The median dose of GIAPREZA was 10 ng/kg/min at 30 minutes

Titrate GIAPREZA to effect in each patient

 Titrate up every 5 minutes by increments of up to 15 ng/kg/min

 Once the underlying shock has sufficiently improved, down-titrate every 5 to 15 minutes in increments of up to 15 ng/kg/min based on blood pressure

 - Half-life of GIAPREZA is less than 1 minute

 During the first 3 hours, the maximum dose should not exceed 80 ng/kg/min. Maintenance dose should not exceed 40 ng/kg/min
Angiotensin II

• Good
  • Effective vasopressor
  • Catecholamine-sparing
  • May provide benefit in certain populations

• Bad
  • Very limited published data in septic shock
  • Concerning ADEs

• Ugly
  • $1800 per vial
The resuscitation challenge
The Sepsis Trilogy

ProCESS  ARISE  ProMISe

Protocolized Care for Early Septic Shock (ProCESS) – 31 ED’s in US

Australasian Resuscitation in Sepsis Evaluation (ARISE) – 51 ED’s in Australia, New Zealand, Finland, Hong Kong, Ireland

The Protocolised Management in Sepsis (ProMISe) Trial – 56 ED’s in the UK
ProMise, ProCess and ARISE Trials

• Key points
  – Fluid administration similar in both control and experimental groups
  – Vasopressor use similar in both groups
  – Antibiotics administered similarly in both groups
  – Lactates obtained in both groups
  – Mortality rates (<20%) is not as common outside centers with well designed sepsis recognition/management programs

• Problems – Antibiotics and fluids given in both control and experimental groups within 3 hours
Take away Points

• **IF** Patients are
  • identified early
  • Receive antibiotics EARLY
  • receive IVF EARLY

• **THEN** ScvO2 and CVP monitoring does not seem to add a benefit

• **BUT** EGDT with ScvO2 not really tested since resuscitation had already occurred
Types of Fluids

• Is normal saline normal?
• Lactated Ringers vs normal saline – are they comparable?
Setting Goals

• Discuss goals of care and prognosis with patients and families (grade 1B)
  – Sepsis has a high mortality rate. Families should understand and recognize that determining what the patient’s wishes are may help dictate the aggressiveness of therapy

• Incorporate goals of care into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (grade 1B)

• Address goals of care as early as feasible, but no later than within 72 hours of ICU admission (grade 2C)
Questions?
Thank You!