Resuscitating the Septic Shock Patient

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Harborview Medical Center
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Disclosures

• I have no relevant financial relationships with a commercial interest.
• I do think timely recognition, rapid treatment and escalation of care in sepsis saves lives.

Objectives

• Define Sepsis-3 compared to prior taxonomy
• Discuss the importance of antibiotic timing
• Describe the benefit & harm of volume resuscitation
• Choose best vasopressor based on physical exam
• Decide when a patient is resuscitated from septic shock

Outline Links

• Define Sepsis-3
• Sepsis Clinical Presentation & Mimics
• Tenets & Controversies
  – Antimicrobials
  – Volume Resuscitation
  – Vasopressors
  – Corticosteroids
• Metabolic Resuscitation
• Resuscitation Endpoints

SEPSIS-3 DEFINITION
Sepsis 3

life-threatening organ dysfunction dysregulated host response infection

Singer et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016

Septic Shock

- Sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg
- Serum lactate level >2 mmol/L
- Despite adequate volume resuscitation

Shankar-Hari et al., JAMA, 2016

CLINICAL PRESENTATION SEPSIS MIMICS

Multiple Scores

SIRS
- RR > 20 bpm
- T: >38˚C or <36˚C
- HR >90 bpm
- WBC >12,000, WBC <4,000, or >10% bands
- 2/4 for Sepsis-1

qSOFA (non-ICU)
- RR > 22 bpm
- GCS ≤13
- SBP <100
- 0-3 points
- 2+ for Sepsis-3

qSOFA (ICU)
- GCS
- PaO2/FiO2
- Platelets
- Bilirubin
- MAP or Pressors
- Creatinine
- 0-24 points
- 2+ for Sepsis-3

In-hospital mortality >10%

Seymour et al. JAMA 2016

Lactate vs. Hypotension

Vasopressor

Isolated Hypotension Sepsis-3 Shock

Hemodynamic Normal Isolated Elevated Lactate

Endogenous Epinephrine

Lactate vs. Hypotension

Lactate & Mortality

Predicted Hospital Mortality

<table>
<thead>
<tr>
<th>Lactate</th>
<th>qSOFA = 0</th>
<th>qSOFA = 1</th>
<th>qSOFA = 2</th>
<th>qSOFA = 3</th>
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</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>1%</td>
<td>3%</td>
<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td>2 - 4</td>
<td>2%</td>
<td>5%</td>
<td>7%</td>
<td>19%</td>
</tr>
<tr>
<td>≥4</td>
<td>7%</td>
<td>10%</td>
<td>23%</td>
<td>43%</td>
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</table>

Seymour et al. JAMA 2016

2019-10-10 - Carlbom 2019 ACP Septic Shock version 3 - October 25, 2019
Data Integration

Infection?
- Hypo & Hyper-thermia
- Rigors, Night sweats
- Organ-system specific
- Pneumonia
- Pyelonephritis
- Meningitis

Physio Stress?
- Tachypnea
- Tachycardia
- Shock Index (HR / SBP > 0.8)
- ▶ Lactate
- ▶ WBC, Plt
- ▼ ▼ Glucose

Organ Failure?
- "Warm" Shock
  - Hypotension
  - ▼ Diastolic Bp
  - Wide pulse pressure
- "Cold" Shock
  - Hypotension
  - Motting
  - ▼ Capillary refill
  - Narrow pulse pressure

Sepsis Mimics

<table>
<thead>
<tr>
<th>Infection</th>
<th>Tox</th>
<th>Gl</th>
<th>Endocrine</th>
<th>Misc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td>ASA Poisoning</td>
<td>Mesenteric Ischemia</td>
<td>Adrenal Crisis</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Influenza</td>
<td>Beta/Cal+ Blocker</td>
<td>Obstruction</td>
<td>Thyroid Storm</td>
<td>Macrophage Activation</td>
</tr>
<tr>
<td>Tick-Borne Disease</td>
<td>Carbon Monoxide</td>
<td>Pancreatitis</td>
<td>DKA</td>
<td>Aspiration Pneumonitis</td>
</tr>
<tr>
<td>Fungal</td>
<td>Metformin</td>
<td>Hepatic Failure</td>
<td></td>
<td>Dermatologic (DRESS)</td>
</tr>
<tr>
<td>PJP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

"Warm" Shock Hypotension
Diastolic Bp
Wide pulse pressure

"Cold" Shock Hypotension
Motting
Capillary refill
Narrow pulse pressure

Infection? Physio Stress? Organ Failure?

ANTIBIOTICS SOURCE CONTROL

Abx Delay: 1990's

Abx Delay: 2013-2017

- Non-trauma adult ED pts. with clinical sepsis admitted to four hospitals 2013 - 2017
- 10,811 pts: Median door-to-antibiotic time was 166 minutes & 1-year mortality 19%

Abx Delay: 2013-2017

- Each additional hour from ED arrival to antibiotic initiation:
  - 10% (5 -14%) increased odds of 1-year mort.
  - Similar for inpatient-, 30-day and 90-day mort
- 1yr mortality higher when door-to-antibiotic times were >3 hours versus ≤3 hours
  - OR 1.27 (1.13-1.43)

Abx Delay: 2013-2017

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Abx Delay: 2013-2017

- 1yr mortality higher when door-to-antibiotic times were >3 hours versus ≤3 hours
  - OR 1.27 (1.13-1.43)
Antibiotics before Cultures?

- 325 pts. septic shock
- BCx obtained prior & w/in 120min after initiation of antibiotics
- BCx after empirical Abx reduces sensitivity by ~50%

Cheng et al., Annals IM 2019

Risk-Based

At present, guidelines and quality improvement rigidly dichotomize
But, benefit of earlier abx varies, and diagnostic uncertainty is common.

How sick?

Current, time to antibiotics is similar across illness severity.

90d Mortality

ARISE 2014

EGDT: 18.6%
Usual: 18.8%

ProCESS 2014

EGDT: 31.9%
Protocol: 30.8%
Usual: 33.7%

ProMISe 2015

EGDT: 29.5%
Usual: 29.2%

Non-
=> significant p-values.

ProCESS Investigators. NEJM 2014
ARISE Investigators & ANZICS CCTG. NEJM 2014
ProMISe Trial Investigators. NEJM 2015

Volume Resuscitation

- Mortality if crystalloid initiation within:
  ≤ 30 minutes 17.8%
  31–120 minutes 18.7%
  >120 minutes 24.5%

- Compared with more than 120 minutes:
  ≤ 30 minutes OR 0.76 (CI, 0.64–0.90; p = 0.002)
  31–120 minutes OR 0.76 (CI, 0.62–0.92; p = 0.004)

- Mortality odds increased by 1.09/hour to initiation
  (CI, 1.03–1.16; p = 0.002)

Leisman et al., CCM, 2017

Volume if crystalloid initiation within:

Early antibiotics and fluids

Non-
=> significant p-values.

Usual Care: not using ScvO₂ or CVP

Volume Resuscitation
“30by3”

- 1,032 pts., 49% “30by3”
- Men, elders, ESRD, HF, “volume overload” less likely to get volume

RCT of Fluid in Septic Shock

- Two randomized trials demonstrated increased adverse outcomes with aggressive volume resuscitation

Restrictive IV Fluid

- 109 patients with septic shock randomly assigned:
  - ≤ 60mL/kg of IV fluid usual care
  - Restrictive group 47.1 mL/kg
  - Usual care 61.1 mL/kg
- 30 day mortality similar
- No differences in new organ failure, hospital or ICU length of stay, or serious adverse events

CLOVERS: RCT

- Just over 1000 (of 2200 planned) patients enrolled
- No major adverse safety events
- Passed first interim analysis by DSMB separation between the groups total fluid volume in the first 24h
- Outcomes blinded

Volume Tolerant?

<table>
<thead>
<tr>
<th>Large Volume</th>
<th>Moderate Volume</th>
<th>No Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-50 mL/kg (3-4 liters)</td>
<td>30 mL/kg (2-3 liters)</td>
<td>Little or no resuscitative volume</td>
</tr>
<tr>
<td>Give first 20mL/kg quickly</td>
<td>Give first 20mL/kg quickly</td>
<td></td>
</tr>
<tr>
<td>Give remainder slowly (300mL/h IV)</td>
<td>Give remainder slowly (300mL/h IV)</td>
<td></td>
</tr>
</tbody>
</table>

VASOPRESSORS

- SBP < 100
- MAP < 65
- 1L IVF

Fluids if NorEpi > 20mcg/kg
- Vasopressor
- Liberal Fluid
- Vasopressor Overload >5L

Safe et al., Annu Emerg Med (2018)
Isoproterenol

• Improve renal function

Low-dose vasopressin may avoid hyperchloremic acidosis

AT-2 depleted in lung & renal injury

Novel vasopressor

Peripherally Vasopressors

- 734 patients mean age 72 yrs.
- NorEpi, Dopa, Phenyl via peripheral IV
- Duration 49 ± 22 hours
- Extravasation occurred in 19 patients (2%), tx w/ local phentolamine & NTG paste
- 13% receiving vasoactive medication through peripheral IV eventually required central access

Vasoactives

Dobutamine

Isoproterenol

Epinephrine

Norepinephrine

Phenylephrine

Vasopressin

Vasopressin

Mitriline

PDE-I

Renoresuscitation

- Avoid ACEI, NSAIDS
- Avoid hyperchloremic acidosis
- Norepinephrine improves renal perfusion
- Low-dose vasopressin may improve renal function

Vasopressin

- Background: 4 RCTs show vaso levels low, repletion improves renal function
- VASST (adding vaso to NE) overall negative, but improved survival in low-dose NE group
- But not used much:
  - 17.2% received vasopressin
  - 6.1% alone
  - 93.9% in combination with other vaso

Angiotensin-2

- Novel vasoressor
- AT-2 depleted in lung & renal injury
- Raises MAP, non-significant trend to improved survival

Angiotensin-2

- More study needed
- Promising survival benefit in responders to AT-2 treatment
- 36.3% absolute reduction in death
Multi-modal Vasopressors

- Lung & Renal Injury
- NorEpi complications
- Low EF%
- Inapprop. normal lactate

Vaso
- Warm Shock
- Renal Injury

AT-2

Epi

NorEpi

Balanced 'pressor

Vasopressor Timing

- RCT ~300 septic shock patients
- Shock resolution @ 6h
  - Early NorEpi 76.1%
  - Usual Care 48.4%
- 28d mortality was not different
  - Early NorEpi 15.5%
  - Usual Care 21.9%

CORTICOSTEROIDS

- XS vasoconstriction
  - Mottling, cold
- XS inotropy
  - Tachy >140, LVEF ↑

Dobutamine
Epinephrine
Norepinephrine
Phenylephrine

CORTICOSTEROIDS

Adrenal 2018

- Randomized placebo controlled trial, stratified according to participating site & medical vs surgical admission
- 69 medical-surgical ICUs in Australia, UK, New Zealand, Saudi Arabia, and Denmark: March 2013 – April 2017
- Adult patients with septic shock requiring vasopressors and mechanical ventilation:
  2 of 4 SIRS criteria
  Mechanical ventilation, including non-invasive ventilation
  Vasopressors/inotropes for 4 hours to maintain systolic BP >90mmHg, or MAP >60mmHg
- Exclusion criteria:
  - Met all inclusion criteria >24 hours prior
  - Clinicians expects to prescribe systemic corticosteroids
  - Treated with etomidate or amphotericin B
  - Cerebral malaria or strongloides infection
  - Death deemed inevitable or imminent

Adrenal: No Difference

- Medical vs. surgical admission;
  - (nor)epinephrine <15 vs. ≥15μg/min;
  - pulmonary sepsis vs. non-pulmonary; male vs. female; APACHE II <25 vs. ≥25; duration of shock

- Mortality by region
  - Australia: 25.1% vs. 27.6%
  - UK: 35.3% vs. 31.7%

Venkatesh et al., N Engl J Med 2018
• Multicenter RCT, 2-by-2 factorial design: hydrocortisone-plus-fludrocortisone therapy activated protein C combination of the three drugs placebos
• After APC withdrawn, trial continued with a two-group parallel design
• 1241 patients in 34 French ICUs: Intensive care patients with indisputable or probable septic shock for less than 24h SOFA score of 3 or 4 for at least 2 organs and at least 6 hours in duration Vasopressor therapy for at least 6 hours to maintain SBP ≥90mmHg or MAP ≥65mmHg

After APC withdrawn, trial continued with a two-group parallel design placebos combination of the three drugs activated protein C hydrocortisone-plus-fludrocortisone therapy Multicenter RCT, 2-by-2 factorial design: RR 0.87 (0.76-1.0) P=0.02 by log-rank test

My Opinion
• May be mortality benefit
• Acceptable increase in adverse effects
• Extubation & resolution of shock (removal of CVC) are patient-centered outcomes
• I use steroids for other diseases w/o mortality benefit (COPD)

Thiamine Supplementation

Complete group (n = 88) Thiamine deficient group (n = 28)

metabolic resuscitation

Cochrane

RR 0.87 (0.76-1.0)
Vitamin C: Case Series

- Historical Control Study

- Vit C 1.5 grams IV q6h
- Thiamine 200 mg IV q12h
- Hydrocortisone 50 mg IV q6h

- 4 days duration of therapy (or ICU d/c if <4 days)

VitC & Acute Lung Injury

- 167 pts. w/ sepsis and ARDS present for less than 24h
- Vit C 50mg/kg IV q6h vs Placebo
- No significant differences between the vit C and placebo:
  - SOFA score @ 96h
  - C-reactive protein
  - Thrombomodulin levels

VitC & Acute Lung Injury

- Secondary Outcome
  - Day 28 Mortality
  - 46.3% in the placebo group
  - 29.8% in the vitamin C group (16.5% absolute reduction)
  - Concerns about multiple comparisons

Vitamin C Trials

- 9 RCTs completed
- 21 RCTs enrolling

RESUSCITATION ENDPOINTS
Some Options

- MAP >65, maybe higher
- HR 90-110
- UOP? Less helpful (AKI)
- Lactate rising lactate = re-assessment
- Skin Exam

Best MAP?

- MAP 80 - 85
- MAP 65 - 70

Mottling

- 259 pts. septic shock observed in Brazil, 14-day mortality 37%

Guiding Principles

- Unless there is a source of ongoing fluid loss, ongoing fluid resuscitation is unlikely to help
- Resuscitative endpoints may be most useful for titrating vasopressors and inotropes
- Failure to meet resuscitative endpoints should prompt overall re-evaluation:
  - Correct etiology of shock?
  - Antibiotic selection correct?
  - Source control?
“Strike hard, strike fast, no remorse”

- Josh Farkas, MD

SUMMARY

Antibiotics

Source Control

Fluid

(NorEpi / Epi) + Vaso + Ang-II

Metabolic Resus: HC, vit C, thiamine

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Save The Date:
June 15-16, 2020

PACIFIC NORTHWEST
SEPSIS CONFERENCE