“Sepsis and septic shock”

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Disclosures

No conflicts of interest

Dellinger R.P., Critical Care Medicine 2013

Severe Sepsis and Septic Shock
Derek C. Angus, M.D., M.P.H., and Tom van der Poll, M.D., Ph.D.

Angus D.C., NEJM 2013

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Singer M., JAMA 2016
Surviving Sepsis Campaign Responds to Sepsis-3
The SSC offers clarification on the implications of the new definition statements and guidance for hospitals and practitioners.

New Recommendations Aim to Redefine Definition and Enhance Diagnosis of Sepsis, Septic Shock
The recommendations are published in the February 2016 issue of JAMA and were recently highlighted for clinicians and media at the SCCM 46th Critical Care Congress in Orlando, Florida.

New Self-Directed Sepsis Performance Improvement Course is Now Available
Improve your strategies for the recognition and treatment of sepsis with the Self-Directed Sepsis Performance Improvement course.
68 y.o. woman

Two-day history of chills, high fever, cough and shortness of breath.

PMH
T2DM; HTN; COPD

Admission to ED
Patient appears ill, is coughing, restless and sleepy, but rousable.

BP 70/40 mmHg
HR 120/min (regular)
RR 34/min
T 40.2 °C

ABG: 7.21/25/55/16
Lactate: 4.3 mmol/L
37 y.o. man

15-days hospital stay for severe mucositis secondary to chemotherapy for non-Hodgkin HIV-related lymphoma.

CCRT called for hypotension

After 2.5 L RL:
BP 70/40 mmHg
HR 120/min
RR 34/min

Mottled skin
Two not uncommon cases...

Sepsis?
KEY CONCEPTS OF SEPSIS

- Sepsis is a syndrome shaped by pathogen factors and host factors with characteristics that evolve over time.
- What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.

**PATHOGEN FACTORS**

**HOST FACTORS**

(sex, race and other genetic determinants, age, comorbidities, environment)
SIRS

SEPSIS

SEVERE SEPSIS

SEPTIC SHOCK

Sepsis + organ dysfunction or tissue hypoperfusion

Sepsis-induced hypotension persisting despite adequate fluid resuscitation
Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

Kirsi-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M., D. Jamie Cooper, M.D., Ph.D., and Rinaldo Bellomo, M.D., Ph.D.

Kaukonen K.M., NEJM 2015
Even a modest degree of organ dysfunction when infection is first suspected is associated with an in-hospital mortality in excess of 10%.

Singer M., JAMA 2016
Neurologic
Respiratory
Hepatic/GI
Renal
Coagulation
Cardiovascular
<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>
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<td></td>
</tr>
<tr>
<td>PaO₃/FiO₂, mm Hg (kPa)</td>
<td></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>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, ×10⁹/μL</td>
<td></td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
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<tr>
<td>Bilirubin, mg/dL (μmol/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>
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<tr>
<td>MAP ≥70 mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dopamine &lt;5 or dobutamine (any dose)⁰</td>
<td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1⁰</td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td></td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL (μmol/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>
<td></td>
<td>&lt;500</td>
<td>&lt;200</td>
</tr>
</tbody>
</table>

Abbreviations: FiO₂, fraction of inspired oxygen; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen.

⁰ Catecholamine doses are given as μg/kg/min for at least 1 hour.

² Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score⁴

Adapted from Vincent et al.²⁷

Vincent J.L., ICM 1996
Singer M., JAMA 2016
NEW DEFINITIONS

• Sepsis is defined as **life-threatening organ dysfunction caused by a dysregulated host response to infection.**
• Organ dysfunction can be identified as an acute change in total **SOFA score ≥ 2 points consequent to the infection.**
• The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
• SOFA score ≥ 2 —> Mortality risk ~ 10% in general hospital population with suspected infection.
SEPSIS
SOFA score \( \geq 2 \) points
Hospital mortality \( \sim 10\% \)

SEVERE SEPSIS

SEPTIC SHOCK

- Persisting hypotension requiring vasopressors to maintain MAP \( \geq 65\text{mmHg} \)
- Serum lactate level \( > 2 \text{mmol/L (18mg/dL)} \) despite adequate volume resuscitation.

Hospital mortality is in excess of 40%.
THE IMPORTANCE OF SCREENING

<table>
<thead>
<tr>
<th>Box 4. qSOFA (Quick SOFA) Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate ≥22/min</td>
</tr>
<tr>
<td>Altered mentation</td>
</tr>
<tr>
<td>Systolic blood pressure ≤100 mm Hg</td>
</tr>
</tbody>
</table>
qSOFA Diagnostic Characteristics

Review

Annals of Internal Medicine

Prognostic Accuracy of the Quick Sequential Organ Failure Assessment for Mortality in Patients With Suspected Infection
A Systematic Review and Meta-analysis
Shannon M. Fernando, MD, MSc; Alexandre Tran, MD; Monica Taljaard, PhD; Wei Cheng, PhD; Bram Rochwerger, MD, MSc; Andrew J.E. Seely, MD, PhD; and Jeffrey J. Perry, MD, MSc

- Included 38 studies (n=385,333 patients)
- Looked to summarize prognostic accuracy of qSOFA as compared to SIRS for predicting mortality in those with suspected infection

SIRS better for screening?

- SIRS
  - Pooled sensitivity – 88.1% (95% CI 82.3-92.1)
  - Pooled specificity – 25.8% (95% CI 17.1-36.9)

- qSOFA
  - Pooled sensitivity – 60.8% (95% CI 51.4-69.4)
  - Pooled specificity – 72.0% (95% CI 63.4-79.2)
KEY CONCEPTS OF SEPSIS

Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection.

Unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.

Singer M., JAMA 2016
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.

Singer M., JAMA 2016
Major cause of morbidity and mortality worldwide

- 2% of all hospitalizations in developed countries (sepsis)
- > 750,000 cases of severe sepsis in the US annually
- > 400,000 cases of septic shock
- 215,000 deaths annually in the US

- 11th leading cause of death overall in the US
- Leading cause of death in non-coronary ICU
- Severe sepsis accounting for 6-30% of all admissions to ICUs

Angus D.C., NEJM 2013
Angus DC, Crit Care Med 2001
Sands KE, JAMA 1997
Murphy SL, National Vital Statistics Reports 1998
A CANADIAN PERSPECTIVE

30,000 admissions with sepsis
- 31% Mortality

↓

12,000 admissions with severe sepsis
- 45% mortality

Canadian Institute for Health Information, In Focus: A National Look at Sepsis (Ottawa, Ont.: CIHI, 2009)
Sepsis is the **primary cause of death from infection**, especially if not recognized and treated promptly. Its recognition mandates urgent attention.
A substantial incidence increase

Incidences projected to increase by 1.5% per year

Martin G. NEJM 2003
A decreasing mortality...

Martin G. NEJM 2003

Kaukonen K., JAMA 2014
EPIDEMIOLOGY

28-day mortality (n = 1680 pts)
Ranieri M., NEJM 2012

28-day mortality (n = 1795 pts)
Caironi, NEJM 2014

28-day mortality (n = 776 pts)
Asfar, NEJM 2014

90-day mortality (n = 1600 pts)
ARISE Investigators, NEJM 2014

90-day mortality (n = 1260 pts)
ProMISE Investigators, NEJM 2015

26.4% 24.2%
Xigris Placebo

27.0% 20.3% 13.5% 6.8% 0.0%
28-day mortality (n = 1680 pts)
Ranieri M., NEJM 2012

31.8% 32.0%
Albumin Cristalloids

27.0% 20.3% 13.5% 6.8% 0.0%
28-day mortality (n = 1795 pts)
Caironi, NEJM 2014

34.0% 36.6%
Low MAP High MAP

27.0% 20.3% 13.5% 6.8% 0.0%
28-day mortality (n = 776 pts)
Asfar, NEJM 2014

18.6% 18.8%
EGDT Usual Care

27.0% 20.3% 13.5% 6.8% 0.0%
90-day mortality (n = 1600 pts)
ARISE Investigators, NEJM 2014

21.0% 18.2% 18.9%
EGDT Protocol-based ST Usual Care

27.0% 20.3% 13.5% 6.8% 0.0%
60-day mortality (n = 1341)
The ProCESS Investigators, NEJM 2014

29.5% 29.2%
EGDT Usual Care

27.0% 20.3% 13.5% 6.8% 0.0%
90-day mortality (n = 1260 pts)
ProMISE Investigators, NEJM 2015
### Table 3. Distribution of Septic Shock Cohorts and Crude Mortality From Surviving Sepsis Campaign Database (n = 18 840 patients)

<table>
<thead>
<tr>
<th>Cohorts #</th>
<th>Lactate Category, mmol/L</th>
<th>No. (% of total) [n = 18 840]</th>
<th>Acute Hospital Mortality, No. (%) [95% CI]</th>
<th>( \chi^2 ) Test for Trend</th>
<th>Mortality Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (hypotensive after fluids and vasopressor therapy and serum lactate levels &gt; 2 mmol/L)</td>
<td>&gt;2 to ≤3</td>
<td>2453 (13.0)</td>
<td>818 (33.3) [31.5-35.3]</td>
<td>&lt;.001</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;3 to ≤4</td>
<td>1716 (9.1)</td>
<td>621 (36.2) [33.9-38.5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>4351 (23.1)</td>
<td>2163 (49.7) [48.2-51.2]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>8520 (45.2)</td>
<td>3602 (42.3) [41.2-43.3]</td>
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<td></td>
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</tr>
<tr>
<td>Group 2 (hypotensive after fluids and vasopressor therapy and serum lactate levels ≤2 mmol/L)</td>
<td>≤2</td>
<td>3985 (21.2)</td>
<td>1198 (30.1) [28.6-31.5]</td>
<td>NA</td>
<td>0.57 (0.52-0.62)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Group 3 (hypotensive after fluids and no vasopressors and serum lactate levels &gt; 2 mmol/L)</td>
<td>&gt;2 to ≤3</td>
<td>69 (0.4)</td>
<td>15 (21.7) [12.7-33.3]</td>
<td>.04</td>
<td>0.65 (0.47-0.90)</td>
<td>.009</td>
</tr>
<tr>
<td></td>
<td>&gt;3 to ≤4</td>
<td>57 (0.3)</td>
<td>14 (24.6) [14.1-37.8]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>97 (0.5)</td>
<td>35 (36.1) [26.6-46.5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>223 (1.2)</td>
<td>64 (28.7) [22.9-35.1]</td>
<td></td>
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<tr>
<td>Group 4 (serum lactate levels &gt; 2 mmol/L and no hypotension after fluids and no vasopressors)</td>
<td>&gt;2 to ≤3</td>
<td>860 (4.6)</td>
<td>179 (20.8) [18.1-23.7]</td>
<td>&lt;.001</td>
<td>0.71 (0.62-0.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>&gt;3 to ≤4</td>
<td>550 (2.9)</td>
<td>105 (19.1) [15.9-22.6]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>1856 (9.9)</td>
<td>555 (29.9) [27.8-32.0]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>3266 (17.3)</td>
<td>839 (25.7) [24.2-27.2]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 5 (serum lactate levels between 2-4 mmol/L and no hypotension before fluids and no vasopressors)</td>
<td>&gt;2 to ≤3</td>
<td>1624 (8.6)</td>
<td>489 (30.1) [27.9-32.4]</td>
<td>NA</td>
<td>0.77 (0.66-0.90)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>&gt;3 to ≤4</td>
<td>1072 (5.7)</td>
<td>313 (29.2) [26.5-32.0]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>790</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>All</td>
<td>2696 (14.3)</td>
<td>802 (29.7) [28.0-31.5]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 6 (hypotensive after fluids and no vasopressors and serum lactate ≤2 mmol/L)</td>
<td>≤2</td>
<td>150 (0.8)</td>
<td>28 (18.7) [12.8-25.8]</td>
<td>NA</td>
<td>0.32 (0.20-0.51)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; OR, odds ratio.

# Conversion factor: To convert serum lactate values to mg/dL, divide by 0.11.
# Mean arterial pressure less than 65 mm Hg was used to define hypotension.
# “After fluids” was defined using the field “Crysaloids” coded as a binary term within the Surviving Sepsis Campaign database.

+ Using \( \chi^2 \) tests, trends in mortality across serum lactate categories within groups (>2 to ≤3 mmol/L; >3 to ≤4 mmol/L; and >4 mmol/L) were assessed.
+ \( \chi^2 \) test for trend could only be performed if there were 3 or more serum lactate categories.
+ Excluded from full case analysis.

## Site of infection

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infections</td>
<td>40-60%</td>
</tr>
<tr>
<td>Intra-abdominal infections</td>
<td>10-25%</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>10-20%</td>
</tr>
<tr>
<td>Blood stream infections</td>
<td>10-20%</td>
</tr>
<tr>
<td>Skin/Soft tissue/wound infections</td>
<td>5-14%</td>
</tr>
<tr>
<td>Device related infections</td>
<td>5-15%</td>
</tr>
<tr>
<td>Others/Unknown sources</td>
<td>10-18%</td>
</tr>
<tr>
<td>CNS</td>
<td>3-10%</td>
</tr>
</tbody>
</table>

*Vincent J.L., JAMA 2009*
*Vincent J.L., Crit Care Med 2006*
*Angus D.C., Crit Care Med 2001*
*Lagu T., Crit Care Med 2012*
*Abraham E., JAMA 2003*
*Opal S.M., Clin Infect Dis 2003*
EPIDEMIOLOGY

No. of Cases of Sepsis

- Gram-negative bacteria
- Gram-positive bacteria
- Fungi

Martin G. NEJM 2003
### Positive microbiological culture results

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative organisms</td>
<td>62%</td>
</tr>
<tr>
<td>Gram-positive organisms</td>
<td>47%</td>
</tr>
<tr>
<td>Fungi</td>
<td>19%</td>
</tr>
</tbody>
</table>

Vincent J.L., JAMA 2009
Sepsis is an emergency – there is a golden hour!

- Trauma
- Acute Myocardial Infarction
- Stroke
- Cardiac Arrest
- Severe Sepsis

Daniels R., Global Sepsis Alliance
Two not uncommon cases...

What are the most important interventions to be completed in the early phase?
Same patient... different phases

3-6 hours

Recognition

Resuscitation

ICU management

Hospital stay

Recovery/Post-ICU syndrome

Pre and post-discharge
Step 1
Screening and Management of Infection

Step 2
Screening for Organ Dysfunction and Management of Sepsis (formerly called Severe Sepsis)

Step 3
Identification and Management of Initial Hypotension

Initial Management Bundle
(< 3 & < 6 hrs)

ICU Management Bundle

Dellinger R.P., Critical Care Medicine 2013
Initial Management Bundle - Pathophysiological Rationale

The Problem

Sepsis-induced tissue hypoperfusion

Infection

Resuscitation and hemodynamic support
- Restore hemodynamic stability and tissue perfusion
- Institute appropriate physiologic support to prevent further tissue injury

Antimicrobial therapy
Diagnosis
Source control

Initial Management Bundle (< 3 & < 6 hrs)
Surviving Sepsis Campaign

Updated Bundles in Response to New Evidence
Physiology First!
Hypovolemia
- Venodilation
- Capillary leak *Loss of endothelial barrier function*
- Insensible losses
- Reduced fluid intake

Arteriolar dilation

Sepsis-induced tissue hypoperfusion

Ventricular dysfunction
- Septic cardiomyopathy
- Stress-induced cardiomyopathy

Microcirculatory dysfunction
- Microvascular thrombosis
- Altered vasomotor tone (shunting)
“A rude unhinging of the machinery of life”
Samuel Gross, late 1800s

Oxygen Supply

Oxygen Demand
- Tissue requirements
- Tissue ability to extract the oxygen available
Sepsis-induced tissue hypoperfusion

\[ \text{DO}_2 = \text{CO} \times \text{CaO}_2 \]

- **Oxygen Delivery**
- **Cardiac Output**
- **Arterial Oxygen Content**

**Cardiac Output (CO)**

\[ \text{CO} = \text{SV} \times \text{HR} \]

- **Preload**
- **Afterload**
- **Contractility**

**Arterial Oxygen Content (CaO₂)**

\[ \text{CaO}_2 = 1.34 \times \text{Hgb} \times \text{SaO}_2/100 + 0.003 \times \text{PaO}_2 \]
A standardized approach to critically ill patients
Emergency Management of the Critically Ill Patient
Resuscitation and hemodynamic support

Airway
Breathing
Circulation
Disability
Endpoints of Resuscitation
Physiology First!

+ 

Standardized approach to critically ill patients

= 

Physiologic standardized/protocolized approach to septic patients
A time-sensitive emergency... managed with a protocolized, quantitative approach
Early protocol-driven resuscitation, targeting optimization of global hemodynamic parameters has been associated with the largest mortality benefit to date in sepsis.

Levy MM, Intensive Care Med 2010
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

NEJM, March 2014

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

NEJM, March 2015

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

NEJM, October 2014
The ProCESS Investigators, NEJM 2014

ARISE Investigators, NEJM 2014

ProMISe Investigators, NEJM 2015
Airway Breathing

Rivers, NEJM 2001

The ProCESS Investigators, NEJM 2014
Optimize preload

The ProCESS Investigators, NEJM 2014
Adequate afterload

Rivers, NEJM 2001

The ProCESS Investigators, NEJM 2014
### TO BE COMPLETED WITHIN 3 HRS OF TIME OF PRESENTATION

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

### TO BE COMPLETED WITHIN 6 HRS OF TIME OF PRESENTATION

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain MAP ≥ 65 mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mmHg) or if initial lactate was ≥ 2 mmol/L, re-assess volume status and tissue perfusion
7. Re-measure lactate if initial lactate elevated
<table>
<thead>
<tr>
<th>TO BE COMPLETED WITHIN 3 HRS OF TIME OF PRESENTATION</th>
<th>TO BE COMPLETED WITHIN 6 HRS OF TIME OF PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Measure lactate level</td>
<td>5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain MAP ≥ 65 mmHg</td>
</tr>
<tr>
<td>2. Obtain blood cultures prior to administration of antibiotics</td>
<td>6. In the event of persistent hypotension after initial fluid administration (MAP &lt; 65 mmHg) or if initial lactate was ≥ 4 mmol/L, re-assess volume status and tissue perfusion</td>
</tr>
<tr>
<td>3. Administer broad spectrum antibiotics</td>
<td></td>
</tr>
<tr>
<td>4. Administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L</td>
<td>7. Re-measure lactate if initial lactate elevated</td>
</tr>
</tbody>
</table>
Resuscitation and hemodynamic support - Assess for adequate perfusion

<table>
<thead>
<tr>
<th>Severe sepsis (initial presentation)</th>
<th>Prevalence (%)</th>
<th>Hospital Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension and Lactate &gt; 4 mmol/L</td>
<td>16.6</td>
<td>46.1</td>
</tr>
<tr>
<td>Hypotension</td>
<td>49.5</td>
<td>36.7</td>
</tr>
<tr>
<td>Lactate &gt; 4 mmol/L</td>
<td>5.4</td>
<td>29.9</td>
</tr>
</tbody>
</table>

Levy M., Intensive Care Medicine 2013
Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy
A Randomized Clinical Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lactate Clearance Group (n = 150)</th>
<th>Scvo₂ Group (n = 150)</th>
<th>Proportion Difference (95% Confidence Interval)</th>
<th>( P ) Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality, No. (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 (17)</td>
<td>34 (23)</td>
<td>6 (~3 to 15)</td>
<td>( P ) Value&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intent to treat</td>
<td>25 (17)</td>
<td>33 (22)</td>
<td>5 (~3 to 14)</td>
<td>( P ) Value&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Per protocol</td>
<td>25 (17)</td>
<td>33 (22)</td>
<td>5 (~3 to 14)</td>
<td>( P ) Value&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Length of stay, mean (SD), d ICU</td>
<td>5.9 (8.46)</td>
<td>5.6 (7.39)</td>
<td>.75</td>
<td>( P ) Value&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Length of stay, mean (SD), d Hospital</td>
<td>11.4 (10.89)</td>
<td>12.1 (11.68)</td>
<td>.60</td>
<td>( P ) Value&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hospital complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator-free days, mean (SD)</td>
<td>9.3 (10.31)</td>
<td>9.9 (11.09)</td>
<td>.67</td>
<td>( P ) Value&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Multiple organ failure, No. (%)</td>
<td>37 (25)</td>
<td>33 (22)</td>
<td>.68</td>
<td>( P ) Value&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Care withdrawn, No. (%)</td>
<td>14 (9)</td>
<td>23 (15)</td>
<td>.15</td>
<td>( P ) Value&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; Scvo₂, central venous oxygen saturation.
<sup>a</sup>Primary study end point.
<sup>b</sup>Continuous data are compared using an unpaired t test; categorical variables, using the \( \chi^2 \) test.

Jones A.E., JAMA 2010
**Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock**

The ANDROMEDA-SHOCK Randomized Clinical Trial

<table>
<thead>
<tr>
<th>Outcome (CRT vs Lactate)</th>
<th>Relative Measure (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 day Mortality</td>
<td>HR 0.75 (0.55-1.02)</td>
</tr>
<tr>
<td>Amount of fluid in 1\textsuperscript{st} 8hrs</td>
<td>408ml less (110 less to 705 less)</td>
</tr>
</tbody>
</table>

**TO BE COMPLETED WITHIN 3 HRS OF TIME OF PRESENTATION**

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

**TO BE COMPLETED WITHIN 6 HRS OF TIME OF PRESENTATION**

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain MAP ≥ 65 mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mmHg) or if initial lactate was ≥ 2 mmol/L, re-assess volume status and tissue perfusion
7. Re-measure lactate if initial lactate elevated
Fluid resuscitation in severe sepsis/septic shock

Which fluid?

How much?

How fast?
FLUIDS ARE DRUGS!
Resuscitation and hemodynamic support - Optimize preload

Which fluid?

**Crystalloids**
- 0.9% sodium chloride
- Lactated Ringer’s Solution

**Colloids**
- 6% HES 130/0.4
- Albumin
Resuscitation and hemodynamic support - Optimize preload

The 2012 papers...

Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study

Bertrand Guidet, Olivier Martinet, Thierry Boullain, François Philippart, Jean François Xavier Forceville, Marc Feissel, Michel Hasselmann, Alexandra Heininger, and Hugo Vi

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D., Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D., and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*
Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation: A Systematic Review and Meta-analysis

HES associated with
- increased mortality (RR, 1.09; 95% CI, 1.02 to 1.17; n. 10 290 patients)
- increased renal failure (RR, 1.27; 95% CI, 1.09 to 1.47; n. 8725 patients)
- increased use of RRT (RR, 1.32; 95% CI, 1.15 to 1.50; 9258 patients).
Resuscitation and hemodynamic support - Optimize preload

Which fluid?

**Crystalloids**
- 0.9% sodium chloride
- Lactated Ringer’s Solution

**Colloids**
- NO HES!!!
- Albumin
Resuscitation and hemodynamic support - Optimize preload

Caironi, NEJM 2014
Which fluid?

**Crystalloids**
- 0.9% sodium chloride
- Lactated Ringer’s Solution

**Colloids**
- **NO HES**
- ...maybe!

?selected patients?
Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

Table 2. Composition of Trial Fluids\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>0.9% Saline</th>
<th>Hartmann</th>
<th>4% Gelatin</th>
<th>Plasma-Lyte 148</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>150</td>
<td>129</td>
<td>154</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>Potassium</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Chloride</td>
<td>150</td>
<td>109</td>
<td>120</td>
<td>98</td>
<td>128</td>
</tr>
<tr>
<td>Calcium</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Lactate</td>
<td>0</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acetate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Gluconate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Octanoate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6.4</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All concentrations in mmol/L.

Yunos N.M., JAMA 2012
### Table 2. Crystalloids Received in the Emergency Department According to Assigned Treatment Group. 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Balanced Crystalloids (N = 6708)</th>
<th>Saline (N = 6639)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total crystalloid volume</td>
<td>1608±1095</td>
<td>1597±1105</td>
</tr>
<tr>
<td>Mean — ml</td>
<td>1089 (1000–2000)</td>
<td>1071 (1000–2000)</td>
</tr>
<tr>
<td>Median (IQR) — ml</td>
<td>2207 (32.9)</td>
<td>2150 (32.4)</td>
</tr>
<tr>
<td>≥2000 ml — no. (%)</td>
<td>1000 (1000–2000)</td>
<td>0</td>
</tr>
<tr>
<td>Median volume of balanced crystalloids (IQR) — ml</td>
<td>0</td>
<td>1000 (1000–2000)</td>
</tr>
<tr>
<td>Percentage of crystalloid volume consistent with assigned group — no. (%)</td>
<td>5620 (83.8)</td>
<td>6160 (92.8)</td>
</tr>
</tbody>
</table>

| 100%: per-protocol population                 | 514 (7.7)                       | 270 (4.1)         |
| 51–99%                                        | 254 (3.8)                       | 131 (2.0)         |
| 1–50%                                         | 320 (4.8)                       | 78 (1.2)          |

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.
Balanced Crystalloids versus Saline in Noncritically Ill Adults

Wesley H. Self, M.D., M.P.H., Matthew W. Semler, M.D.,
Jonathan P. Wanderer, M.D., Li Wang, M.S., Daniel W. Byrne, M.S.,
Sean P. Collins, M.D., Corey M. Slovis, M.D., Christopher J. Lindsell, Ph.D.,
Jesse M. Ehrenfeld, M.D., M.P.H., Edward D. Siew, M.D.,
Andrew D. Shaw, M.B., Gordon R. Bernard, M.D.,
and Todd W. Rice, M.D., for the SALT-ED Investigators*

Balanced Crystalloids versus Saline in Critically Ill Adults

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Avinash B. Kumar, M.D., Christopher G. Hughes, M.D.,
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Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D.,
Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D.,
and Todd W. Rice, M.D., for the SMART Investigators
and the Pragmatic Critical Care Research Group∗

A Sodium

B Chloride

A Chloride Concentration

B Bicarbonate Concentration

No. of Patients with Measurement
Balanced crystalloids
Saline

No. of Patients with Measurement
Balanced crystalloids
Saline

0 24 48 72
0 24 48 72
0 24 48 72
0 24 48 72
0 24 48 72
0 24 48 72
0 24 48 72
0 24 48 72
0 24 48 72
0 24 48 72
0 24 48 72
0 24 48 72
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and Todd W. Rice, M.D., for the SALT-ED Investigators*

Table 3. Clinical Outcomes According to Assigned Treatment Group in the Intention-to-Treat Analysis.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Balanced Crystalloids (N = 6780)</th>
<th>Saline (N = 6639)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median hospital-free days to day 28 (IQR)</td>
<td>25 (22–26)</td>
<td>25 (22–26)</td>
<td>0.98 (0.92–1.04)</td>
<td>0.41</td>
</tr>
<tr>
<td>Major adverse kidney event within 30 days — no. (%)</td>
<td>315 (4.7)</td>
<td>370 (5.6)</td>
<td>0.82 (0.70–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td>94 (1.4)</td>
<td>102 (1.5)</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>New renal-replacement therapy — no./total no. (%)</td>
<td>18/6582 (0.3)</td>
<td>31/6530 (0.5)</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Final serum creatinine ≥200% of baseline — no./total no. (%)</td>
<td>253/6582 (3.8)</td>
<td>293/6530 (4.5)</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Stage 2 or higher acute kidney injury — no./total no. (%)</td>
<td>528/6582 (8.0)</td>
<td>560/6530 (8.6)</td>
<td>0.91 (0.80–1.03)</td>
<td>0.14</td>
</tr>
<tr>
<td>In-hospital death — no. (%)</td>
<td>95 (1.4)</td>
<td>105 (1.6)</td>
<td>0.88 (0.66–1.16)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H.,
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and Todd W. Rice, M.D., for the SMART Investigators
and the Pragmatic Critical Care Research Group*
LESSON N. 5

Which fluid?

Crystalloids

- 0.9% sodium chloride
- Lactated Ringer’s Solution

Cautious use

Colloids

- 6% HES 130/0.4
- Albumin

NO HES...maybe!

?selected patients?
BLOOD TRANSFUSION?
Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Jan Werner, M.D., Ph.D., Anne B. Guttormsen, M.D., Ph.D., Sari Karlsson, M.D., Ph.D., Pär I. Johansson, M.D., Ph.D., Anders Åneman, M.D., Ph.D., Marianne L. Yang, M.D., Robert Widing, M.D., Lars Nebrich, M.D., Helle L. Nibro, M.D., Ph.D., Bodil S. Rasmussen, M.D., Ph.D., Johnny R.M. Lauridsen, M.D., Jane S. Nielsen, M.D., Anders Oldner, M.D., Ph.D., Ville Pettila, M.D., Ph.D., Maria B. Cronhjort, M.D., Lasse H. Andersen, M.D., Ulf G. Pedersen M.D., Nanna Reiter, M.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Lene Russell, M.D., Klaus J. Thornberg, M.D., Peter B. Hjortrup, M.D., Rasmus G. Müller, M.D., Morten H. Möller, M.D., Ph.D., Morten Steensen, M.D., Inga Tjäder, M.D., Ph.D., Kristina Kilsand, R.N., Suzanne Odeberg-Werner, M.D., Ph.D., Brit Sjøbø, R.N., Helle Bundgaard, M.D., Ph.D., Maria A. Thyø, M.D., David Lodahl, M.D., Rikke Mærkedahl, M.D., Carsten Albeck, M.D., Dorte Illum, M.D., Mary Kruse, M.D., Per Winkel, M.D., D.M.Sci., and Anders Perner, M.D., Ph.D., for the TRISS Trial Group* and the Scandinavian Critical Care Trials Group
Resuscitation and hemodynamic support - Optimize preload

How much?
When to stop?
Reassessment of volume status and tissue perfusion with:

- Either **repeat focused exam** (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings

- Or **2 of the following**:
  - measure CVP
  - measure ScvO2
  - bedside cardiovascular ultrasound
  - dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge
Cumulative Fluid Balance as a Predictor of Mortality in Septic Shock

Table 7. Multivariate, forward stepwise logistic regression analysis in sepsis patients (n = 1177), with intensive care unit mortality as the dependent factor

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS II score&lt;sup&gt;a&lt;/sup&gt; (per point increase)</td>
<td>1.0 (1.0–1.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cumulative fluid balance&lt;sup&gt;b&lt;/sup&gt; (per liter increase)</td>
<td>1.1 (1.0–1.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.0 (1.0–1.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Initial SOFA score (per point increase)</td>
<td>1.1 (1.0–1.1)</td>
<td>.002</td>
</tr>
<tr>
<td>Blood stream infection</td>
<td>1.7 (1.2–2.4)</td>
<td>.004</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2.4 (1.3–4.5)</td>
<td>.008</td>
</tr>
<tr>
<td><em>Pseudomonas</em> infection</td>
<td>1.6 (1.1–2.4)</td>
<td>.017</td>
</tr>
<tr>
<td>Medical admission</td>
<td>1.4 (1.0–1.8)</td>
<td>.049</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.4 (1.0–1.8)</td>
<td>.044</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

<sup>a</sup>At admission; <sup>b</sup>within the first 72 hrs of onset of sepsis.
CVP as a surrogate of fluid responsiveness/fluid status?
Resuscitation and hemodynamic support - Optimize preload

Preload assessment ≠ Preload-dependence assessment

Cardiac output

Ventricular preload

normal heart

preload-dependence

preload-independence

failing heart
Two not uncommon cases...

30 ml/kg RL

More fluids?
Two not uncommon cases...

30 ml/kg RL

More fluids?
A word of caution
Respiratory variations of inferior vena cava diameter to predict fluid responsiveness in spontaneously breathing patients with acute circulatory failure: need for a cautious use

Laurent Muller, Xavier Bobbia, Mehdi Toumi, Guillaume Louart, Nicolas Molinari, Benoit Ragonnet, Hervé Quintard, Marc Leone, Lana Zoric, Jean Yves Lefrant and the AzuRea group
### To Be Completed Within 3 Hrs of Time of Presentation

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 ml/kg crystalloid for hypotension or lactate $\geq 4$ mmol/L

### To Be Completed Within 6 Hrs of Time of Presentation

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain MAP $\geq 65$ mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP $< 65$ mmHg) or if initial lactate was $\geq 4$ mmol/L, re-assess volume status and tissue perfusion
7. Re-measure lactate if initial lactate elevated
Vasopressors in severe sepsis/septic shock

Which vasopressor?

When to start?
Resuscitation and hemodynamic support - Adequate afterload

- Isoproterenol
- Dobutamine
- Dopamine
- Epinephrine
- Norepinephrine
- Phenylephrine

Diagram showing different adrenergic agonists and their effects on pressure.

Hollenberg S.M., AJRCCM 2011
Norepinephrine as the first choice vasopressor

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed Risk</th>
<th>Corresponding Risk</th>
<th>Relative Effect (95% CI)</th>
<th>No. of Participants (Studies)</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term mortality</td>
<td>530 per 1000</td>
<td>Study population (440 to 524)</td>
<td>RR 0.91 (0.83 to 0.99)</td>
<td>2043 (6 studies)</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events—Supraventricular arrhythmias</td>
<td>229 per 1000</td>
<td>Study population (34 to 195)</td>
<td>RR 0.47 (0.38 to 0.58)</td>
<td>1931 (2 studies)</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events—Ventricular arrhythmias</td>
<td>39 per 1000</td>
<td>Study population (8 to 27)</td>
<td>RR 0.35 (0.19 to 0.66)</td>
<td>1931 (2 studies)</td>
<td>moderate</td>
<td></td>
</tr>
</tbody>
</table>

*Dellinger R.P., Critical Care Medicine 2013*
• Adequate fluid resuscitation should ideally be achieved before vasopressors and inotropes are used.

• However, using vasopressors early as an emergency measure in patients with severe shock is frequently necessary.

_Dellinger R.P., Critical Care Medicine 2013_
Norepinephrine as the first choice vasopressor... that’s all?

- Vasopressin (up to 0.04 U/min) can be added to NE with the intent of raising MAP to target or decreasing NE dosage (UG)
- Low-dose vasopressin not recommended as the single initial vasopressor
- Vasopressin doses higher than 0.03-0.04 U/min should only be reserved for salvage therapy (UG)

_Dellinger R.P., Critical Care Medicine 2013_
Vasopressin may decrease Afib?

Original Investigation
May 8, 2018

Association of Vasopressin Plus Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock
A Systematic Review and Meta-analysis

William F. McIntyre, MD1; Kevin J. Um, BA1; Waleed Alhazzani, MD, MSc1; Alexandra P. Lengyel1; Ludmila Hajjar, MD2; Anthony C. Gordon, MD3,4; François Lamontagne, MD, MSc5; Jeff S. Healey, MD, MSc1; Richard P. Whitlock, MD, PhD1; Emilie P. Belley-Côté, MD, MSc1

Author Affiliations | Article Information

The guidelines

“We recommend that vasopressor therapy initially target a MAP of 65 mmHg (grade 1C)”

An individualized MAP target?

Dellinger R.P., Critical Care Medicine 2013
High versus Low Blood-Pressure Target in Patients with Septic Shock

No. at Risk
- Low target: 379, 256, 233, 225
- High target: 375, 249, 227, 219

Asfar, NEJM 2014
Resuscitation and hemodynamic support - Role of steroids

Adjacent Glucocorticoid Therapy in Patients with Septic Shock


Hydrocortisone plus Fludrocortisone for Adults with Septic Shock


No at Risk
Hydrocortisone 1832 1591 1481 1418 1388 1374 1356 1348 1328 1321
Placebo 1826 1546 1433 1376 1354 1337 1330 1322 1312 1300

Days since Randomization

Probability of Survival

No at Risk
Hydrocortisone + Fludrocortisone 614 405 372 353
Fludrocortisone 627 381 333 319
Placebo 627 381 333 319
Adjunctive Glucocorticoid Therapy in Patients with Septic Shock


Hydrocortisone plus Fludrocortisone for Adults with Septic Shock


Graphs showing the resolution of shock and days since randomization for patients treated with hydrocortisone or placebo.
### Benefit??

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>GRADE certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.93 (95% CI 0.84-1.03)</td>
<td>Low</td>
</tr>
<tr>
<td>Shock reversal at 1 week</td>
<td>1.26 (95% CI 1.12-1.42)</td>
<td>High</td>
</tr>
<tr>
<td>SOFA score at 1 week</td>
<td>-1.39 (95% CI -1.88 to -0.89)</td>
<td>High</td>
</tr>
</tbody>
</table>

Crit Care Med. 2018 Sep;46(9):1411-1420
### Is there Harm?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pooled Relative Risk</th>
<th>GRADE certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatremia</td>
<td>1.64 (95% CI 1.32-2.03)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1.16 (95% CI 1.08-1.24)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Neuromuscular Weakness</td>
<td>1.21 (95% CI 1.01-1.45)</td>
<td>Low</td>
</tr>
</tbody>
</table>
People with sepsis
SOFA score of at least 2

**Population**

- **Recommendation applies to:**
  - Adults and children
  - Any infectious source
  - Patients with and without shock
  - Intra-abdominal infections
  - Pneumonia

- **Recommendation does not apply to:**
  - Patients with pre-existing adrenal insufficiency
  - Anaphylactic
  - Cardiogenic
  - Hypovolaemic
  - Non-infectious causes of shock
  - Neonates
  - Pregnant women

*BMJ* 2018;362:k3284
Resuscitation and hemodynamic support - Role of steroids

We suggest corticosteroid therapy rather than no corticosteroid therapy. Either option is reasonable.

Comparison of benefits and harms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Favours corticosteroids</th>
<th>No important difference</th>
<th>Favours no corticosteroids</th>
<th>Events per 1000 people</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>236</td>
<td>18 fewer</td>
<td>254</td>
<td></td>
<td>★★★★ Low</td>
</tr>
<tr>
<td>Neuromuscular weakness</td>
<td>303</td>
<td>53 fewer</td>
<td>250</td>
<td></td>
<td>★★★★ Low</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td>★★★★ None</td>
</tr>
<tr>
<td>Stroke</td>
<td>10</td>
<td>No important difference</td>
<td>5</td>
<td></td>
<td>★★★★ Very low</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>27</td>
<td>No important difference</td>
<td>30</td>
<td></td>
<td>★★★★ Very low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean number of days</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of ICU stay</td>
<td>12.4</td>
<td>0.7 fewer</td>
<td>13.1</td>
<td>★★★★ Moderate</td>
<td></td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>31.3</td>
<td>0.7 fewer</td>
<td>32.0</td>
<td>★★★★ Moderate</td>
<td></td>
</tr>
</tbody>
</table>

BMJ 2018;362:k3284
## TO BE COMPLETED WITHIN 3 HRS OF TIME OF PRESENTATION

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

## TO BE COMPLETED WITHIN 6 HRS OF TIME OF PRESENTATION

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain MAP ≥ 65 mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mmHg) or if initial lactate was ≥ 4 mmol/L, re-assess volume status and tissue perfusion
7. Re-measure lactate if initial lactate elevated
Initial Management Bundle - Infection Issues

Infection

- Diagnosis
- Antimicrobial Therapy
- Source Control
**Infection**

**DIAGNOSIS**
- Is my patient infected?
- What is the site from which the infection is arising?
- What is/are the infecting pathogen(s)?

**ANTIMICROBIAL THERAPY**
- Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobials
- Imaging studies performed promptly

**SOURCE CONTROL**
Infection

DIAGNOSIS

ANTIMICROBIAL THERAPY

SOURCE CONTROL

Kumar A., Crit Care Med 2006
Infection

DIAGNOSIS

ANTIMICROBIAL THERAPY

SOURCE CONTROL

Every hour in delay of appropriate ABX

7.6% lower survival

Kumar A., Crit Care Med 2006
Antibiotics prescribed in EDs only in 61% (95% CI, 57–65) of explicit sepsis visits.

Crit Care Med 2013
“Hectic fever, at its inception, is difficult to recognize but easy to treat; left unattended it becomes easy to recognize and difficult to treat”

Niccoló Machiavelli, The Prince (1513)
Critical Care Medicine as Preventive Medicine

Window for Early Treatment & Prevention

Morning Rounds

911 | Emergency Room
--- | ---
Operating room | Recovery room
Hospital ward | Rapid response team

ICU

Gajic O., CCCF 2012
Seymour C., JAMA 2015
“The ProCESS trial identifies early recognition of sepsis, early administration of antibiotics, early adequate volume resuscitation, and clinical assessment of the adequacy of circulation as the elements we should focus on to save lives.”
The five most important things to know

What you absolutely need to know to be proficient in basic goal-directed trans-thoracic echocardiography:

**CONTENTS** [hide]

1. ***KNOW YOUR LIMITS***
2. Echo views
3. Eye-ball assessment of LV function
4. Diagnosis of pericardial and pleural effusion
5. Assessment of volume status

***KNOW YOUR LIMITS***

... and call for help!
Thank you!
Grazie!

alberto.goffi@gmail.com