Critical Care Medicine Update for Non-Intensivists 2015

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In accordance with the guidelines of the Florida Medical Association/Accreditation Council for Continuing Medical Education, I acknowledge that I have no Conflict of interest to disclose that will affect my ability to present an unbiased presentation.

The planning committee for this activity has also indicated that they have no conflict of interest to disclose which influenced their ability to plan an unbiased presentation.
Areas of Focus

• Sepsis
  • Impact and key points of “Surviving Sepsis Guidelines”
  • “Sniffer” mechanisms

• Controversies in Fluids

• ARDS
  • New definition
  • Prevention & ventilation

• Nutritional support in critical illness

• Cognitive Outcomes

• Future Challenges
Intensive care in the USA

• 5 million people are cared for ICU in US annually
• 55,000 critically ill patients daily
• 26.9 % of hospital stays involve ICU stay
  • 47.5 % of aggregate hospital cost
    • HCUP AHRQ December 2014
ICU beds per capita exceeds most countries

<table>
<thead>
<tr>
<th>Country</th>
<th>ICU Beds per 100,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>24.6</td>
</tr>
<tr>
<td>Belgium</td>
<td>21.9</td>
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<tr>
<td>Croatia</td>
<td>20.3</td>
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<tr>
<td>U.S.</td>
<td>20</td>
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<tr>
<td>Canada</td>
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<tr>
<td>France</td>
<td>9.3</td>
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<tr>
<td>South Africa</td>
<td>8.9</td>
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<td>Sweden</td>
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<td>Netherlands</td>
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<td>Spain</td>
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<td>New Zealand</td>
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<td>Trinidad and Tobago</td>
<td>2.1</td>
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<tr>
<td>Sri Lanka</td>
<td>1.6</td>
</tr>
</tbody>
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67,357 ICU beds
ICU Utilization is Expected to Increase

% Hospital Beds Dedicated to ICU Projected

The Impact of Sepsis

- From 2007-2009, over 2,047,038 patients with sepsis related illness
  - 52.4% ED
  - 35% Hospital wards
- Number 1 cause of death in non-coronary ICUs
  - Mortality 20-50%
  - STEMI 3-5%
  - Ischemic CVA 1-2%
- Attributable cost for sepsis/severe sepsis $14-18 billion annually
Surviving Sepsis Guidelines: 2012

International effort to reduce mortality of patients with severe sepsis and septic shock worldwide

Joint collaboration between Society of Critical Care Medicine and European Society of Intensive Care Medicine

Initial work began in 2002

Third edition

- Critical Care Medicine, February 2013 [www.survivingsepsis.org](http://www.survivingsepsis.org)
The Continuum of the Syndrome

Systemic inflammatory response syndrome (SIRS)
- ≥2 of following:
  - Temperature >38°C or <36°C
  - Heart rate >90 bpm
  - Respiratory rate >20 or PaCO₂ < 32 mmHg
  - WBC >12,000/mm³, <4,000/mm³, or >10% bands

Sepsis
- SIRS and documented or suspected infection

Severe sepsis
- Sepsis-induced hypotension, tissue hypoperfusion, or organ dysfunction
- Lactic acidosis, SBP <90 mmHg or SBP drop of 40 mmHg from baseline

Septic shock
- Severe sepsis with hypotension despite adequate fluid resuscitation
Non-Infectious Insults Can Causes Systemic Inflammatory Response
Surviving Sepsis: Timely Bundled Care

TO BE COMPLETED WITHIN 3 HOURS:
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
Early Antibiotics: Time Matters!

Each 1 hour delay in effective antimicrobials was associated with a mean decease in survival of 7.6%

Kumar, Crit Care Med 2006;34:1589-96
Surviving Sepsis: Timely Bundled Care

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg.
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (Scvo₂)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Scvo₂ of ≥70%, and normalization of lactate.
Key Components of Sepsis Care

• Early recognition and intervention
  • Value of hospital and EMR systems

• Quantifiable, objective resuscitation goals
  • Crystalloid fluid to obtain increase urine output (0.5 cc/hr/kg)
  • Goal MAP 65 mm Hg

• Early use of broad spectrum antibiotics

• Vigorous search for infections that may require invasive therapy

• Steroids (hydrocortisone 200 mg/day) for persistent vasopressor dependent shock despite adequate fluid resuscitation
What has been “debunked”

- Use of “renal dose” dopamine
- Cosotropyn stimulation test to identify those who would benefit from steroid supplementation
- Tight glucose control
  - Target $\leq 180$ mg/dl as upper limit
- Heavy sedation and paralysis
Temporal Changes in Severe Sepsis* Mortality

101,000 patients

* Severe sepsis with or without shock
Impact of Campaign

Levy MM. Crit Care Med 2015;43:3-12
Early Goal-Directed Therapy (EGDT)

Protocol for sepsis management

Single-center trial showing mortality with EGDT < standard therapy (30.5% vs. 46.5%)
The Value of EGDT...Or Not

<table>
<thead>
<tr>
<th>n/Site</th>
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<tbody>
<tr>
<td>ProCESS ¹</td>
<td>1241 (USA)</td>
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<tr>
<td>ARISE ²</td>
<td>1600 (AUS)</td>
</tr>
<tr>
<td>ProMISE ³</td>
<td>1251 (UK)</td>
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</tbody>
</table>

¹ NEJM 2014;370:1638-93 ² NEJM 2014;371:1496-1506 ³ NEJM 2015;
The Value of EGDT…Or Not

• “Usual care” now closely mimics EGDT
  • Temporal changes in mortality
  • 18-29% in these 3 trial
  • Rivers EGDT 30.5% (treatment) v. 46.5% (control)

• Usual care arm of each trial used ScVO2 monitoring minimally

• More interventions in EGDT arm

• Early recognition, prompt antibiotics and frequent re-assessments likely most beneficial
Institutional Measures to Identify Sepsis

• Predicated on importance of timely recognition and intervention

• Variety of approaches
  • Manual screens
  • Automated EMR “sniffers”

• Need institutional support for first line personnel initiating therapy
  • Importance of adherence to provider’s scope of practice
SEPSIS INDUCED HYPOPREFUSION?
(Clinical picture of severe sepsis plus one or both of the following criteria)
1. hypotension AFTER initial fluid bolus (30 ml/kg)
OR
2. Lactate greater than or equal to 4 mEq/L with any BP

For Lactate 2-2.9
NO

Initiate General Care Severe Sepsis Bundle on back and complete interventions

YES

Activate CODE SEPSIS

Initiate transfer to ICU

For Lactate 3.3-9 or initial hypotension that responded to the 30 ml/kg fluid bolus, initiate transfer to IMC

Meanwhile, continue crystalloid resuscitation of 250-1000ml boluses if hypotensive after the initial bolus – per physician order

Initiate the Septic Shock Clinical Pathway on back and complete interventions
Take Home Points: Sepsis

• Mortality from sepsis remains significant but is decreasing
• Early recognition and intervention is critical
  • Institutional processes to facilitate early recognition are helpful
• Although the necessity of “Early Goal Directed Therapy (EGDT)” has been questioned, protocolized management likely has benefit
• The need for early recognition and intervention must be balanced with awareness of alternative diagnosis
Fluid Management Controversies

• Safety concerns with NSS
• Crystalloid v. colloid
• Role of PRBCs
Sepsis: Fluid Resuscitation

Crystalloid, normally saline, is primary choice
- Initial: 30 ml/kg = 2.1 L for 70 kg
  - Subsequent boluses to defined endpoint
- Endpoints:
  - Normal mixed venous oxygen saturation 65-70%
  - Normal lactate
  - Urine output > 0.5 ml/kg/hr
  - MAP > 65 mm Hg

Weak indication for albumin (Grade 2B)

Avoid hetastarch with high molecular weight (> 200 kD)
Potential Dangers of Saline

• Saline administration
  • Hypertonic relative to blood
  • Often causes hyperchloremic metabolic acidosis

• Does it cause renal injury?

• Prospective, sequential, single institution pilot study

• Chloride restrictive v. chloride liberal
  • Restrictive
    • Lactated solution or plasma-lyte

• $N = 776$ (liberal)
• $N = 773$ (restrictive)

Nor’azim MY. JAMA 2012; 308(15):1566-1572
• Results
  ◦ Limiting use of normal saline
    • Less acute kidney injury and reduced need for dialysis in hospital
    • No difference in length of stay or mortality
    • No difference in need for dialysis after hospital discharge

• Current take home
  ◦ Uncertain
  ◦ Have a reason for giving saline
    ◦ Defined endpoint
  ◦ Probably should consider alternative fluid if large volume required

Nor’azim MY. JAMA 2012; 308(15):1566-1572
Crystalloid v. Colloid

SAFE Trial
- 7,000 ICU patients needing fluid resuscitation (not all sepsis)
- No mortality difference between NSS or 4% albumin

Meta-Analysis
- 17 studies/1977 patients with sepsis
- Albumin associated with lower mortality (OR 0.82, 0.67-1.0, p = .047)
  - Delaney Crit Care Med 2011; 39(2):386

CRISTAL
- 2900 ICU patients with hypovolemia from any cause
- Colloids (albumin or HES) v. crystalloid (NS or LR)
- No difference in 28 day mortality
  - Annane D JAMA 2013;310(17): 1809
Where does Blood Transfusion Fit?

Surviving Sepsis Campaign

Once tissue hypoperfusion resolves, transfuse < 7.0 g/dL, Goal 7.0-9.0 g/dL
Lower v. Higher Hemoglobin threshold for Transfusion in Septic Shock

Background
- TRICC Trial- Canadian Critical Care Trials Group
- ICU patients not actively bleeding, transfuse at < 7 gm/dl v. Maintain 7-9 gm/dl
- Similar mortality in both groups
- Lower mortality in restrictive group among “less sick” and younger

Study question
- Relative benefit and harm from transfusions in septic shock

Design
- Randomized those with Hgb < 9 gm/dl to transfusion trigger of 7 v. 9 throughout ICU stay

Lower v. Higher Hemoglobin threshold for Transfusion in Septic Shock: Outcomes

Fewer patients received transfusion (66% v. 99%) and less blood transfused in conservative group
  ◦ About 1,500 fewer units transfused

No difference in mortality @ 90 days
  ◦ 43% v. 45%

The Lungs Like it Dry...

FACCT Trial

- 1000 patients with ARDS, not in shock
- “Dry” patients had fewer days on ventilator WITHOUT increase need for dialysis
  - No difference in mortality

Take Home

• Provide fluids liberally in shock BUT with a defined endpoint
• Use NSS initially
• Consider lactated ringers solution is high volume
• Albumin for selected cases
• Probably should avoid heta-starch
• Hgb 7 gm/dl as transfusion trigger
• Once shock is reversed; keep dry
New Berlin Definition of ARDS

• Respiratory failure not fully explained by cardiogenic pulmonary edema
  • Assessment for cardiac dysfunction if no risk factors for ARDS
• Occurring within one week of clinical insult or new/worsening respiratory symptoms
• Bilateral opacities not fully explained by effusions, collapse, or nodules
• $\text{PaO}_2/\text{FiO}_2 \leq 300$ with PEEP $\geq 5$ cm
  • 200 - $\leq 300$ mild
  • 100 - $\leq 200$ moderate
  • $< 100$ - severe

Ranieri VM. JAMA 2012;307(23):2526
Some Success with ARDS
Prone Positioning in ARDS (PROSEVA)

- Prone positioning had been repeatedly shown to improve oxygenation but not mortality
- 474 patients with severe ARDS
  - PaO₂/fiO₂ < 150
- Proned * 16 hrs day up to 28 days
- Mortality @ 28 days
  - 38/237 (16%)
  - 75/229 (33%)
- No difference in 90 days mortality

New Eng J Med. 2013
• Commercially available beds to facilitate but can be done manually
• Important to provide appropriate padding to face and head
• Adverse effects comparable in PROSEVA study
• But experienced centers
The Importance of Prevention in ARDS

Low tidal volume ventilation (6 cc/kg IBW) reduces mortality in established ARDS

Prevention

- 332 ICU patients without ARDS-Use of VT > 6 cc/kg IBW associated with development (OR 1.3 for every 1 cc > 6)
  - Gajic O. Int Care Med 2005;31(7):922

- Cardiac surgery (n = 3434) Prolonged ventilation and ICU LOS in highest TV group postoperatively (although average was > 10 cc/kg)
  - Lellouche F. Anesthesiology 2012;116(5):1072

- 400 patients undergoing abdominal surgery – lower pulmonary or nonpulmonary complications in low Vt + PEEP group
  - Futier E. Ne Eng J Med 2013;369:428
### Other Measures That May Prevent ARDS

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Cases and Controls After Removing 2001–2002 (n = 308 pairs)</th>
<th>Cases and Controls After Adjusting for Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Any adverse events</td>
<td>4.7 (3.0–7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inadequate empiric antimicrobial</td>
<td>2.5 (1.3–4.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Aspiration</td>
<td>34.0 (4.7–248.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RBCs&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.4 (1.2–1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fresh frozen plasma&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.4 (1.2–1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.9 (1.6–5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tidal volume-predicted body weight&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.3 (0.82–2.2)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Ahmed A. Crit Care Med 2014; 42:31
ARDS: What doesn’t appear to work

High frequency oscillating ventilation
- OSCAR (UK) n= 795
  - 40% mortality in both groups

- OSCILLATE (USA & Canada) n= 548
  - Greater mortality in HFOV group (47% v. 35%)
  - Stopped early due to futility

Statins
- Rosuvastatin (40 mg daily) * 21 days (n = 412) v. placebo (n = 391)
  - No difference in
    - Favorable functional status @ 6 months
    - Mortality @ 6 months
    - Ventilator free days

Young D. New Eng J Med 2013;
Ferguson N New Eng J Med 2013;
New Eng J Med 2014;
Take Home Points: ARDS

• Mortality appears to be improving
• Prone positioning associated with reduced mortality in severe ARDS
• Lung protective strategies appear to prevent ARDS; high frequency oscillating ventilation not supported by literature
• Other measures that may prevent ARDS in those at risk include appropriate antibiotic therapy, avoidance of aspiration, and transfusions
Recent Advances in ICU Nutrition: EDEN

- 1,000 patients with ALI/ARDS
- Randomized to trophic feeds (20 cal/hr) v. full feeding (80 cal/hr) * 6 days
  - Full calories after day 6
- More calories received in full calorie group
- No difference in ventilator free days, infection or 60 day mortality

Rice TE JAMA 2012;
Recent Advances in ICU Nutrition: OMEGA

- 272 patients with ALI/ARDS
- Randomized to omega -3 fatty acids + antioxidants or placebo
- Stopped early due to futility

Rice TE JAMA 2012;
Recent Advances in ICU Nutrition: Early PN Trial

• 1,327 patients who could not tolerate enteral feeds in first 2 days of ICU
• Randomized to TPN or “standard” care
  • Standard care included both no feeding (41%) and delayed enteral or parenteral nutrition
• Insulin to maintain glucose < 180 mg/dl
• TPN group achieved nutritional goals earlier and received more calories
• No difference in mortality or infections or function at 60 days
• TPN associated with one less day of intubation

Doig GS. JAMA 2013; 309(20):2130-2138
ICU Nutrition: Summary

- No compelling evidence for omega 3 or antioxidant therapy
- Imperative to control glucose if using TPN
- Current recommendations:
  - Enteral route preferred
  - Timing of initiation unclear
    - Probably first 24-48 hrs unless significant vasopressor requirements
  - Elevate head of bed to minimize aspiration
  - Don’t hold for gastric residual volume < 250 ml (or 500 ml)
Long Term Cognitive Impairment after Critical Illness

• Purpose:
  • Characterize and quantify cognitive impairment in survivors of critical illness
  • Identify associations between
    • Development and duration of delirium and outcomes
    • Sedative & analgesic use and delirium

• Design: Prospective observational study n= 821
• Age 61 (51-71); APACHE 25 (19-31)
• 68% MICU
• 74 % delirium
  • Duration (d) 4 (2-7)

Pandharipande PP, NEJM 2013;369:1306-16
Cognitive Impairment Persists after Critical Illness

Pandharipande PP, NEJM 2013;369:1306-16
Future Challenges in Critical Care

• Gain better understanding of components of care that impact outcome
• Disseminate and implement successful interventions
• Develop systems to continue improvements after ICU stay
• Begin to move towards personalized medicine
• Finally...
  • Knowing when to say when when knowing is impossible
Futile Care in ICU

36 intensivists assessed 1136 patients

8.6% probably futile treatment

11% (n= 123) futile treatment
  ◦ Age 67 (17-99); LOS 15 (1-111)

Outcome of those receiving futile care
  ◦ 84/123 died during hospitalization
  ◦ 20/123 died with 6 months
  ◦ 3/123 discharged home/hospice
  ◦ None of the remaining 16 achieved any level of independence

Cost
  ◦ $2.6 million
  ◦ (3.5%) of total cost of 1136 patients studied

Thank you!!

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