Some Hot Topics in the ICU

2013

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Disclosure

I have no actual or potential conflict of interest in relation to this program/presentation.


More monitoring or more treatment → no benefit or even worse outcome?
Sepsis Guidelines
Do they work?

Challenges to early- and late-goal directed therapy in sepsis

Multicenter Implementation of a Severe Sepsis and Septic Shock Treatment Bundle
- Does the sepsis bundle really work?
  - Compliance with bundle increased 4.9% to 73.4%
  - Mortality fell 21.2% to 8.7% (12.2% for shock)
  - Mortality fell even in patients who did not get all bundle elements.
  - Cause and Effect?


Highlights of Surviving Sepsis—2013 Update
- Broad-spectrum antimicrobials therapy within 1 h of recognition of septic shock
- Infection source control with attention to balance of risks and benefits of chosen method within 12 h of diagnosis

* Only guidelines with supportive evidence?
Highlights of Surviving Sepsis—2013 Update

- Initial fluid resuscitation with crystalloid
- Initial fluid challenge in patients with tissue hypoperfusion and suspicion of hypovolemia to minimum of 30 mL/kg of crystalloids
- Consideration of addition of albumin in patients who continue to require substantial amounts of crystalloid to maintain adequate MAP
- Avoid hetastarch

* Does the type of crystalloid matter?

No more hetastarch

798 severe sepsis randomized to fluid resuscitation with 6% HES 130/0.42 or Ringer’s acetate at a dose of up to 33 ml/kg IBW/day.

Significantly higher mortality and more patients reached end point (death or dialysis dependent at 90 days) for hydroxyethylstarch compared to Ringer’s acetate resuscitation.


Highlights of Surviving Sepsis—2013 Update

- Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L).

- Goals during the first 6 hrs of resuscitation:
  a) Central venous pressure 8–12 mm Hg

What’s the evidence for CVP?
CVP and Volume Status or Responsiveness

Meta-analysis of 24 studies with 803 patients demonstrated a very poor relationship between CVP and blood volume...

Plus, CVP and ΔCVP did not predict response to a fluid challenge.

"CVP should not be used to make clinical decisions regarding fluid management."


"Later" Goal-Directed Therapy

CVP reflects fluid balance (some) at 12 hours, but does not correlate on Day 4 (fluid in last 24 hours).


"Later" Goal-Directed Therapy

- 778 patients with septic shock on NE divided into fluid balance quartiles in multicenter, randomized trial of Vasopressin in Septic Shock (VASST)
- Fluid balance at 12 hours (enrollment) and 4 days compared to CVP and 28-day mortality.

Patients divided by fluid balance quartiles showed significantly different 28-day mortality.

Best survival in those with least positive fluid balance at 12 hours or on Day 4.


“Later” Goal-Directed Therapy

Liberal fluids early?
Conservative fluids late?

Highlights of Surviving Sepsis—2013 Update

- Norepinephrine is first-choice vasopressor to maintain MAP >65 mmHg
- When an additional agent is needed? Epinephrine
- Vasopressin (0.03 U/min) added to NE to raise MAP to target or to decrease NE dose (should not be initial vasopressor)
- Dopamine not recommended except in selected circumstances.

But, I always used dopamine as a resident!
The end of dopamine?

- 5 observational and 6 randomized trials of 2,768 patients (1,474 NE; 1,294 DA)

- In 2 trials, arrhythmias more frequent with DA than with NE (RR, 2.34; CI, 1.46–3.77; p<.001).

Crit Care Med 2012; 40:725–730

The end of dopamine?

- In 4 observational studies, dopamine associated with increased risk of death (RR, 1.23; CI, 1.05–1.43; p < .01).

- In 6 randomized trials, dopamine associated with increased risk of death (RR, 1.12; CI, 1.01–1.20; p = .035).

Crit Care Med 2012; 40:725–730

Highlights of Surviving Sepsis—2013 Update

- Dobutamine infusion administered or added to vasopressor in the presence of:
  - (a) myocardial dysfunction (elevated filling pressures and low cardiac output), or
  - (b) ongoing signs of hypoperfusion despite achieving adequate intravascular volume and adequate MAP.
**Prognostic value of troponins in sepsis: a meta-analysis**

- 13 studies, 1,227 patients. Elevated troponin in 61% associated with all-cause mortality (RR 1.91)
- In 4 studies with 791 patients, elevated troponin associated with an increased risk of death (OR 1.92; CI 1.35–2.74).

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# Data from Intensive Care Med 2013; 39:1181–1189

<table>
<thead>
<tr>
<th>Studies</th>
<th>OR (95% CI)</th>
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<tr>
<td>Bruce 2008</td>
<td>2.40 (1.08–5.38)</td>
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<tr>
<td>Joos 2008</td>
<td>4.35 (1.71–10.93)</td>
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<tr>
<td>John 2009</td>
<td>2.05 (1.13–3.74)</td>
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<tr>
<td>John 2010</td>
<td>2.01 (1.13–3.54)</td>
</tr>
<tr>
<td>Total</td>
<td>2.00 (1.13–3.54)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: χ² = 6.35, P = 0.04.
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**Highlights of Surviving Sepsis—2013 Update**

- Avoid IV hydrocortisone in septic shock if fluid resuscitation and vasopressors restore hemodynamic stability
- Hemoglobin target of 7–9 g/dL in absence of tissue hypoperfusion, ischemic CAD, or acute hemorrhage
- Protocolized glucose management—insulin when 2 consecutive glucose >180 mg/dL, targeting an upper glucose at 180 mg/dL.

**It’s not you, it’s me**

ICU relationships, but not what you think.
“Can we still be friends?”

- 56% of 2100 vascular, neuro-, and CT surgeons responded to a questionnaire.
- 43% *sometimes* or *always* experienced conflicts about postoperative goals of care with intensivists.


Conflicts with intensivists occurred 2.5x more for surgeons with *less* time in practice.

Conflicts with intensivists about goals of postoperative care *40% lower* in “open” ICUs.


Say that again?

Why you might not have to remember the definition of ALI
Acute Respiratory Distress Syndrome
The Berlin Definition

Mild, moderate, severe ARDS related to increased mortality and increased duration of MV.
Compared with AECC definition, Berlin Definition had better predictive validity for mortality.
HFOV goes away

- Randomly assigned adults with ARDS to HFOV or usual care.
- \( P_{a}O_2/FiO_2 \leq 200 \) and expected ventilation \( \geq 2 \) days.
- \(< 7 \) days on ventilator, hospitals experienced with HFOV, all in UK.
- Algorithms for HFOV, compared to ARDSNet PCV, low VT, PEEP.


- No difference in 30-day all-cause mortality between groups.
- After adjustment for APACHE II, \( P_{a}O_2/FiO_2 \), study center, gender: OR for survival in conventional group 1.03 (NS)
- HFOV not recommended for routine care.


HFOV goes away

- Randomly assigned adults with new onset ARDS to HFOV or low VT, high PEEP.
- \( P_{a}O_2/FiO_2 \leq 200, \; FiO_2 > 0.5, \; ARDS < 72 \) hours.
- Protocol for HFOV: mean 30 cm H2O, low HFOV VT using highest \( f \) to give pH > 7.25.
- 6 ml/kg VCV or PSV, low VT, high PEEP (e.g. \( FiO_2 \) 0.4, PEEP 10-18)

• In hospital mortality 47% HFOV vs. 35%, independent of baseline physiology. HFOV received more sedation, NM blockers, vasoactive drugs.

• Higher PEEP strategy beneficial? HFOV high mean airway pressure harmful?

How many nurses does it take to turn a patient prone?

Highlights of Surviving Sepsis—2013 Update

- Recruitment maneuvers in sepsis patients with severe refractory hypoxemia due to ARDS (2C)

- Prone positioning in sepsis-induced ARDS patients with a PaO2/FiO2 ratio <100 mm Hg in facilities that have experience with such practices
Will prone positioning ever go away?

- 466 severe ARDS randomized at <36 hr to prone sessions at least 16 hr or left in supine.
- Severe ARDS: PaO2/FIO2 < 150 mm Hg; FIO2 > 0.6; PEEP>5 cm H2O
- France, Spain; BMI 28-29

28-day mortality 16% prone and 33% in supine (P<0.001), HR 0.39.

Complications not different between groups, except for cardiac arrests, higher in supine group.

And he weighs how much?

- 26 ARDS patients with BMI 38 ± 5 kg/m2 matched to non-obese (25 ± 5 kg/m2) patients with ARDS.
- Median (25th-75th %ile) prone duration 9 h (6-11 h) in obese patients vs. 8 h (7-12 h) in non-obese patients (P = .28).
- ICU has experience with prone positioning.
And he weighs how much?

PaO2/FIO2 increased more in obese (118 ± 43 to 222 ± 84 mm Hg) than in non-obese patients (from 113 ± 43 to 174 ± 80 mm Hg; P = .03).

80% of obese had >20% increase in PaO2/FIO2 vs. 62% of non-obese.

No difference in complications. Obese patients had lower mortality?

Prone positioning is way too hard. I’ll just add more PEEP.

- PEEP can recruit lung, but it can also lead to “tidal hyperinflation” (beyond steep part of PV curve)
- Prone position might recruit without hyperinflation

24 ARDS patients
- CT breath-hold at 5, 15, 45 cm H2O while supine and prone
- PEEP 15 → 45 decreased non-aerated tissue, increased tidal hyperinflation
- PP further decreased non-aerated tissue, reduced tidal hyperinflation
Prone positioning is way too hard. I’ll just add more PEEP.

- … prone positioning enhances the effects of high PEEP on lung recruitment and cyclic recruitment/de-recruitment, whereas it prevents the effects of high PEEP on tidal hyperinflation.
- … lung recruitability, assessed by CT at high airway pressures, does not predict lung recruitment induced by prone positioning.

Am J Respir Crit Care Med 2013; 188:440–8

Highlights of Surviving Sepsis—2013 Update

- Low tidal volume and limitation of inspiratory plateau pressure for ARDS
- Application of at least a minimal amount of positive end-expiratory pressure (PEEP) in ARDS
- Higher rather than lower level of PEEP for patients with sepsis-induced moderate or severe ARDS.

Pplat: What does it mean?

- In ARDS, 6 ml/kg ideal weight associated with better outcome.
- But, second limit of Pplat ≤30 cm H2O, too.
- Who has Pplat > 30 cm H2O after low VT?
1,398 patients in several ARDSNet studies
21% had high Pplat on day 1, defined as:
A. VT set < 5.5 ml/kg or
B. Pplat ≥ 30 cm H2O for
VT 5.5-6.5.

Crit Care Med 2013;41:756-64

Non-White race, very high BMI,
and severity of lung injury are
independently associated with
elevated plateau pressure.

Neuromuscular blockers in early
ARDS

- Multicenter, double-blind trial
- 340 patients with severe ARDS within 48
  hours randomize for 48 hours to
cisatracurium (178 patients) or placebo
(162 patients).
- Severe ARDS = PaO2/FiO2) <150, PEEP
  ≥5 cm H2O.
- Outcome:  adjusted 90-day mortality


Neuromuscular blockers in early
ARDS

- HR for 90 day
  mortality in
cisatracurium
  group 0.68 (p =
0.04), after
  adjustment for
  baseline
PaO2/FiO2, Pplat,
  and SAPSII.
- Relevant to APRV
  and spontaneous
  breathing?

"I’m not an intensivist, but I play one in the ICU.”

"Dressed to …..”

- Three medical ICUs in Calgary showed 337 family members pictures of ICU physicians with cross-section of gender, age, dress, grooming, race, tattoos, piercings, etc.

I'll look it up…

PEEP in ARDS

Setting PEEP

- ICUs at BI Deaconess.
- Supine, head of bed elevated 30 deg.
- Esophageal balloon 40 cm from incisors.
- Heavily sedated or paralyzed.
- Only predicted weights reported.


Setting PEEP

- Patients randomized:
  - PEEP set for transpulmonary pressure of 0-10 cm H2O at end expiration.
  - PEEP set by protocol 5-24 cm H2O.
  - VT 6 ml/kg predicted body weight, FiO2 by protocol
  - Goals: PaO2 55-120 or SpO2 88-98%, pH 7.30-7.45, and PaCO2 40-60 mm Hg.

Treatment group: PEEP lowered in only 3 but PEEP raised by more than 5 cm H2O in 18/30. (i.e. many needed more PEEP to reach transpulmonary pressure target.)

Control group: PEEP lowered or not changed in 30/31.

"Thus, the key difference ... appears to be that measurement of esophageal pressure identifies patients who derive benefit from higher levels of PEEP than would ordinarily be used."

These patients are on "PEEP" but mean trans-pulmonary pressures are negative.
Setting PEEP

Note that (at least) 3 studies have suggested that a global "high PEEP" strategy does not lead to improved outcome...
Highlights of Surviving Sepsis—2013 Update

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High vs Low PEEP

- Main analysis: hospital mortality in 3 studies comparing high vs low PEEP with same tidal volume in both groups.
  - Brower NEJM 2004; Meade JAMA 2008; Mercat JAMA 2008

Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD009098

- No significant differences in mortality between two groups, RR 0.90, 95% CI 0.81 to 1.01
- Risk of barotrauma (RR 0.97, 95% CI 0.66 to 1.42).
- Oxygenation improved in high-PEEP group, although heterogeneity.
High vs Low PEEP

• "...the use of high levels of PEEP does not reduce mortality before hospital discharge, although...a trend towards a mortality benefit in the higher-PEEP group.

• Moreover...we cannot recommend the routine use of high levels of PEEP in patients with ARDS because no agreement has been reached...as to which patients should receive that specific intervention and how those high PEEP levels should be applied."

Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD009098

6 ml/kg

6 ml/kg...6 ml/kg...6 ml/kg

A low VT protective strategy in non ARDS?

• Meta-analysis 20 studies, 2822 subjects; mostly surgical

JAMA 2012;308:1651-1659
Low VT Patients vs. High VT

- Lung injury: RR 0.33, NNT 11
- Mortality: RR 0.64, NNT 23
- Pulmonary infections: RR 0.45, NNT 26

Mean hospital LOS, days: 6.91 (low VT) vs 8.87 (higher VT)

A Trial of Intraoperative Low-Tidal-Volume Ventilation in Abdominal Surgery

- Randomized 400 adults at intermediate to high risk of pulmonary complications after major abdominal surgery.
- VT 10-15 ml/kg, no PEEP, no recruitment vs. VT 6-8 ml/kg, PEEP 6-8 cm H2O, q30 min recruitment (30 cm H2O x 30 s).

Lung-protective: Less pneumonia, MV or NIPPV for acute respiratory failure, severe sepsis/shock, death.

At 7 days, 10 vs. 34 had acute respiratory failure.

Hospital LOS shorter with protective strategy.

* non-standardized fluids, criteria for NIPPV

Change happens…

- 18,302 patients on mechanical ventilation
- 927 units in 40 countries

- Crude ICU mortality 31% in 1998 vs. 28% in 2010 (OR 0.87)
- Adjusted ICU mortality. OR 0.78 (95% CI 0.67-0.92) adjusted for baseline and management variables.

Am J Respir Crit Care Med 2013; 188:220-30

Change happens…

- Did lower VT or higher PEEP contribute to improvement in outcome?

Am J Respir Crit Care Med 2013; 188:220-30

Nutritional Support

Is it lunch time YET?
Early trophic feeding

- 508 ARDS given “trophic” feeds (mean 400 kcal/day, 25% goal) vs. 492 full-feeding (1300 kcal/day, 80% goal) for first 6 days.
- Trophic did not increase ventilator-free days or reduce 60-day mortality.
- No differences in infectious complications.
- Full-feeding experienced more vomiting; elevated gastric residual.
- Mean glucose and hourly insulin higher in full-feeding.

JAMA 2012;307:795-803

Early trophic feeding

- Conclusion:
  In ALI, compared with full enteral feeding, initial trophic enteral feeding for up to 6 days did not improve VFD, 60-day mortality, or infectious complications but was associated with less GI intolerance.

Alternate conclusion…?
Trophic feeding is not inferior to full-ental feeding and was associated with less GI intolerance.

JAMA 2012;307:795-803

Early trophic feeding

- 525 trophic or full-feeding (6 days) compared at 6 and 12 months.
- Initial trophic vs full feeding did not affect mean SF-36 physical function at 12 months, survival to 12 months (65% v 63%, P=0.63).

BMJ 2013;346:f1532
My patient can’t take enteral nutrition

- 1372 patients “unable to receive enteral feeding” randomized to standard care (n = 686) or early PN (686).
- Standard care: 29.2% initially EN, 27.3% PN, 40.8% not fed.
- Mean time to EN or PN in standard care 2.8 days. Early PN commenced mean 44 minutes after enrollment.
- Intent-to-treat: No difference in 60-day mortality, but fewer ventilator days, no difference in ICU/hospital days.

Can I give enteral feeding with vasopressors?

- 1174 patients required MV > 2 days and treated with vasopressor agents.
- Retrospective: 2 groups: early enteral nutrition (n = 707, <48 hours start of MV) vs 467 late enteral nutrition group (>48 hours).
- ICU and hospital mortality lower in early enteral nutrition than in the late enteral: 22.5% vs 28.3%; P = .03; and 34.0% vs 44.0%; P < .001, respectively.

Am J Crit Care 2010;19:261-268

Can I give enteral feeding with vasopressors?

- Propensity analysis, matching patients for entry variables by propensity for enteral nutrition.

Am J Crit Care 2010;19:261-268
Can I give enteral feeding with vasopressors?

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Interim Analysis</th>
<th>Final Analysis</th>
<th>p</th>
<th>Odds ratio</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Vasopressors</td>
<td>Yes</td>
<td>No</td>
<td>0.03</td>
<td>0.36-0.91</td>
<td></td>
</tr>
</tbody>
</table>

Odds of hospital mortality 0.36 for those >1 pressors; only 0.70 for 1 pressor.

Am J Crit Care 2010;19:261-268

How about those other patients in the ICU?

- Randomized, double-blind, placebo controlled, non-inferiority trial; 311 patients.
- 40 mg prednisone daily for 5 vs 14 days
- Non-inferiority ≤ 15% absolute increase in exacerbations over 180 days.
- All received antibiotics, tiotropium, long-acting beta-agonists.

JAMA. 2013;309(21):2223-2231
Short-term vs conventional steroids in COPD exacerbation

Estimates of re-exacerbation rates 37.2% for short-term vs. 38.4% for conventional.
Mean cumulative prednisone 793 mg vs. 379 mg. No difference in hyperglycemia or hypertension.

Transfusion strategy for acute UGI bleeding

- NEJM 1999: Restrictive transfusion—no difference in outcome and trend of fewer complications in ICU. Excluded UGI bleeding.
- 461 UGIB randomized to transfusion for Hbg < 7 g/dL (target 7-9) vs. 460 to Hbg < 9 g/dL (target 9-11).
- Excluded exsanguinating bleeding, ACS, stroke, PAD, recent surgery, LGIB.

Transfusion strategy for acute UGI bleeding

50% peptic ulcer
2%-24% varices
5%-7% in-hospital bleeding
49% vs. 86% received at least one RBC transfusion
Mean/patient 1.5 ± 2.3 vs. 3.7 ± 3.8 units

Survival at 6 weeks higher in restrictive than in liberal group (95% vs. 91%, P = 0.02). Better in peptic ulcer, cirrhosis with Child A-B, but not Child C.

Sedation vacations?

- In 2000, NEJM study showed benefits of daily interruption of sedation
- Canadian CCTG randomized 430 ventilated adults to protocolized sedation + daily interruption 2008-11.
Sedation vacations?

- Median time to extubation, ICU and hospital LOS, unintended extubations did not differ.
- Daily interruption associated with higher daily doses of midalozam and fentanyl.
- Nurse workload higher with interruption.

Did protocolized sedation (using validated scales) reduce the need for "sedation vacations"?

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BNP and Weaning?

- Randomized 304 patients to BNP-driven or physician-driven fluid management during weaning (computerized weaning protocol)
- BNP group: if BNP > 200 pg/ml—decrease baseline fluids, TPN; no saline; furosemide 10-30 mg/3 hrs to target urine output.

Am J Respir Crit Care Med 2012; 186:1256
BNP and Weaning?

- BNP group, furosemide, acetazolamide given more often, resulting in more negative fluid balance during weaning.
- Time to extubation shorter with BNP strategy (58.6 vs. 42.4 h).
- BNP strategy increased ventilator-free days but not LOS or mortality.
- Effect on weaning time strongest in patients with LV systolic dysfunction.

Do you use procalcitonin?

- 132 patients met criteria for severe sepsis or septic shock.
- 25% of patients with PCT <0.5 ng/ml had positive blood cultures.

<table>
<thead>
<tr>
<th>Procalcitonin at presentation</th>
<th>Blood cultures (n)</th>
<th>Total (n)</th>
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<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
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<tr>
<td>&lt;0.5 ng/ml</td>
<td>24</td>
<td>9</td>
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<tr>
<td>0.5 to 2.0 ng/ml</td>
<td>16</td>
<td>5</td>
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<td>2.0 to 10 ng/ml</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>≥10 ng/ml</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>36</td>
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干预措施 = 建议在 PCT 有显著下降（PCT 的高峰水平的80%以下）或降至0.5 ng/ml 以下时停用抗生素。

假设 = PCT 导向疗法与标准治疗方案相比非劣于或优于，并实现了减少抗生素使用的目的。

1600 名患者随机分配至试验组与对照组。
Do you use procalcitonin?

- In adult ICU patients, PCT-guided discontinuation of antibiotics reduced antibiotic duration by 2.05 days without increased morbidity or mortality.
- PCT-guided intensification of antibiotics in adult ICU patients increased antibiotic usage and morbidity.

J Hosp Med August 2013

Early tracheostomy?

- In UK, 909 adults estimated to need >7 days of MV randomized to:
  - tracheostomy at <4 days
  - later (if needed)

JAMA 2013;309:2121-2129
ALI/ARDS: Who gets it?

- 160 infected patients with 2 SIRS criteria + refractory hypotension or persistent lactate
- 44% developed ALI, 90% within first 12 hours (90% met ARDS criteria).

Crit Care Med 2008; 36:1518–1522

ALI/ARDS: Who gets it?

Can ARDS be limited in high risk patients?
Treatment delay, transfusions.