Update Critical Care Medicine 2011

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When it’s new?
When it’s “proven”?
When it’s “disproven”?
When it’s time to reconsider?

WHEN IS MEDICAL INFO WORTH TALKING ABOUT?
When Is a Given Medical Treatment “Proven”? 

- When there is biological plausibility
  - Relevant lab, pre-clinical development
- When there is sufficient evidence of a meaningful clinical response to the treatment
  - Conduct of high quality clinical trials
Time Frame is Not Short Term

• Therapies may take years to establish
• Once unsuccessful therapies may become successful due to technical innovation
  – e.g. current PCI for acute coronary disease vs. initial reports of angioplasty
• Many therapies are
  – Best guesses based on incomplete information
  – Subject to therapeutic fashions
  – Most recently published/in media = most attention
Issues of Study Design Directly Effect What We “Know”...
<table>
<thead>
<tr>
<th><strong>Desirable Clinical Endpoint</strong></th>
<th><strong>Surrogate Endpoint</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Septic Shock study: Alive at some relevant time interval</td>
<td>• Septic Shock study: Time to shock reversal</td>
</tr>
<tr>
<td>• ARDS study: Home, off a ventilator</td>
<td>• ARDS study: Oxygenation</td>
</tr>
<tr>
<td>• CPR study: Good neurological function</td>
<td>• CPR study: Return of Spontaneous Circulation</td>
</tr>
</tbody>
</table>
How Hard Are You Looking?

≈How Many Subjects In Study
Sample Size: The Art of the Possible

**Ideally**
- Smaller predicted effects requiring larger sample sizes
- Estimate a biologically plausible effect size
- Or “Minimally Clinically Important Difference”

**Real World**
- Larger “predicted” effects permit smaller sample sizes
- Cost
- Time
- Likelihood of accrual
Suppose some clinical outcome occurs 35% of the time....

# Subjects Required To “See” Various Differences

<table>
<thead>
<tr>
<th>Difference</th>
<th>Subjects Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5% Drop</td>
<td>11390</td>
</tr>
<tr>
<td>5% Drop</td>
<td>2834</td>
</tr>
<tr>
<td>7.5% Drop</td>
<td>1250</td>
</tr>
<tr>
<td>10% Drop</td>
<td>698</td>
</tr>
<tr>
<td>15% Drop</td>
<td>302</td>
</tr>
</tbody>
</table>
Major Journal Publication of Critical Care Randomized Controlled Treatment Trials: “Planned” vs. Actual Differences Between Groups

If no bias between expected and observed differences expect = above/below blue line

Most differences smaller than expected

Significant tended to have negative effect of treatment

Smaller than planned
For but positive treatment effects
The Point Being...

• A number of treatments may actually have been helpful but are lost because too few subjects are enrolled
  – For treatments remaining accessible, clinical judgment is required.
  – Novel therapeutic agents typically disappear.
  – Ethical issues for those participating/designing trials
  – Resource allocation issues
We’re Always Looking For “Breakthroughs”
But really, in any given year, we see

- “Settling” of old issues as enough evidence accumulates
  - Which vasopressor?
- Need to recalibrate treatments, behaviors because of unexpected results
  - “tight” glucose control
  - Development of “guidelines”
- Rejection of some new approaches
  - TLR4 blocker
- Cause for optimism in new ideas, not yet subjected to full scrutiny
  - Endotoxin binding filters
  - Talactoferrin
“Settling” old business...
Which Pressor? Probably Norepinephrine

• In fluid resuscitated septic shock:
  – Higher response rate, more rapid response in crossover study
  – Less splanchnic or renal ischemia than dopamine, epinephrine
  – Less lactic acidosis than epinephrine
  – Now “no difference” study noerepi/dobutamine vs. epinephrine
    • Small study
    • NE/Dobutamine : Epi :: 34% mortality: 40% mortality (28 days)
  – Less tachycardia than dopamine
Norepinephrine vs. Epinephrine: 280 Shock Patients

No difference in % or time to reach MAP goal

Myburgh et al Intensive Care Med, 2008
Norepinephrine vs. Epinephrine: Outcomes

• No difference in survival
• Increased drop out in NE group for lactic acidosis + tachycardia
Dopamine vs. Norepinephrine for Shock

• 1679 Patients:
  – ICU
  – Shock
  • After fluids: MAP < 70 or SBP < 100
  • Hypoperfusion
    – Oliguria
    – AMS
    – Mottled skin
    – Lactate

■ Treatment to target BP or open label if still in shock:
  ■ Dopamine:
    ■ 2-20 mcg/kg/min
  ■ Norepinephrine:
    ■ 0.02-0.19 mcg/kg/min

Dopamine vs. Norepinephrine for Shock: Etiology of Shock

Dopamine vs. Norepinephrine for Shock: Outcome

Dopamine vs. Norepinephrine for Shock: Outcome

<table>
<thead>
<tr>
<th>Period</th>
<th>% Mortality</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dopa</td>
<td>Norepi</td>
</tr>
<tr>
<td>ICU</td>
<td>50.2</td>
<td>45.9</td>
</tr>
<tr>
<td>Hospital</td>
<td>59.4</td>
<td>56.6</td>
</tr>
<tr>
<td>28 Days</td>
<td>52.5</td>
<td>48.5</td>
</tr>
<tr>
<td>6 Months</td>
<td>63.8</td>
<td>62.9</td>
</tr>
<tr>
<td>12 Months</td>
<td>65.9</td>
<td>63.0</td>
</tr>
</tbody>
</table>

## Dopamine vs. Norepinephrine for Shock: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Dopamine</th>
<th>Norepinephrine</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days w/o Vasopressors</td>
<td>11</td>
<td>12.5</td>
<td>Y (0.01)</td>
</tr>
<tr>
<td>Days w/o Ventilator</td>
<td>8.5</td>
<td>9.5</td>
<td>N (0.13)</td>
</tr>
<tr>
<td>Days w/o Renal Support</td>
<td>12.8</td>
<td>14</td>
<td>N (0.07)</td>
</tr>
<tr>
<td>LOS</td>
<td>=</td>
<td>=</td>
<td>N</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>24%</td>
<td>12%</td>
<td>Y (0.001)</td>
</tr>
<tr>
<td>Skin ischemia</td>
<td>6.5%</td>
<td>4%</td>
<td>N (0.09)</td>
</tr>
</tbody>
</table>

Dopamine vs. Norepinephrine for Shock: Subgroup

What About Vasopressin?

- Septic shock associated with
  - Low vasopressin levels
  - Down regulated vasopressin receptors
- Vasopressin (in low dose) dilates arteries
  - Renal
  - Pulmonary
  - Coronary
  - Cerebral
- OTOH, Vasopressin has been associated with
  - Intestinal ischemia
  - Skin necrosis
  - Cardiac arrest
VASST Study:

• 779 septic shock patients on > 5mcg/min levophed X 6 hrs + ≥ 1 organ failure
  – Vasopressin 0.03U/min or Norepinephrine 15 mcg/min
  – Open label vasopressors weaned by protocol
  – Outcome 28 day mortality
    • Stratified by severity of shock

Russell, JA et al NEJM 2008; 358:877-87
### VASST Results

<table>
<thead>
<tr>
<th></th>
<th>Vasopressin (% mortality)</th>
<th>Norepinephrine (% mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>28 day Mortality (all)</strong></td>
<td>35.4</td>
<td>39.3</td>
</tr>
<tr>
<td><strong>90 Day Mortality</strong></td>
<td>43.9</td>
<td>49.6</td>
</tr>
<tr>
<td>“Less Severe” Shock (&lt;15 mcg/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 Days</td>
<td>26.5*</td>
<td>35.7*</td>
</tr>
<tr>
<td>90 Days</td>
<td>35.8*</td>
<td>46.1*</td>
</tr>
</tbody>
</table>

Vasopressin use led to reduction in norepinephrine dosage, no change in organ dysfunctions. Digital ischemia more likely in vasopressin group (.06), cardiac arrest in norepinephrine group (.11)
Vasopressors: Tilt in favor of Norepinephrine

- No Knockout but maybe TKO in competition vs.
  - Dopamine
  - Norepinephrine

- Utility of vasopressin less clear:
  - ? Additive
  - Non-US use for “treating the vasoplegia” of shock
  - ? Reduce fluid requirements
Rethinking treatments and processes...
Improving Medical Care

Evidence → Guidelines, Bundles → Better Care → Better Outcomes
Natural Conflict in Implementation

• Need to Implement
  – Help patients
  – Act despite uncertainty
  – Generate “quality improvement” data

• Need to Accrue Sufficient information
  – Avoid harm
  – Avoid wasting energy/resources
Intensive Glucose Control
Single Center, 1548 mostly CV Surgery Patients

Pivotal interventional trial of a primarily cardiothoracic ICU population.

Insulin Use: 99% vs 39%

AM Glucose: 103 vs 153

\[ P = 0.01 \]

Van den Berghe, NEJM 2001
Intensive Glucose Control

Effects of Introducing a Tight Control Protocol

Mean Glucose: 152 mg/dL $\Rightarrow$ 131 mg/dL

Krinsley, Mayo Clin Proc, 2004
2nd Generation Multi-Center Studies

• Glucontrol*
  – Europe, Israel
    • Tight Control 8.6% hypoglycemia vs 2.4% (sig)
    • Tight Control 17% mortality vs. 15% (not sig)

• NICE-Sugar**
  – Australia, New Zealand, Canada, (US)
    • Tight Control 6.8% hypoglycemia vs. 0.5% (sig)
    • Tight Control 27.5 mortality vs. 24.9 (sig)

•Preiser, Intensive Care Medicine 2009
•** NICE-Sugar Invest., NEJM 2009
NICE-Sugar Outcomes

- Graph shows probability of survival over days after randomization for conventional and intensive glucose control groups.
- Table compares subgroups:
  - Operative admission
  - Diabetes
  - Severe sepsis
  - Trauma
  - APACHE II score
  - Corticosteroids
- Odds ratios and 95% confidence intervals for death are provided for each subgroup.
- P-values for heterogeneity are included.
Cautionary Tale: Tight Glucose Control

2001
Single Center Study: Tight Glucose Control Saves Lives

2003-2010
Adoption of “tight” regimens in guidelines, bundles and ICU protocols

2004-2006
Pre/post study
Tight glucose control saves lives

2010-2011
Multicenter Studies: Tight Glucose Control harmful
Tight Glucose Control Lessons

• Adoption based on not generalizable info
  – Single center
  – Unique management, limited population
• Expectation of unreasonably large benefit
• Inability to deliver the intervention safely
  – Lack of benefit associated with hypoglycemic events
This Does Not Mean Let Glucoses Soar

• Recalibrate expectations of magnitude of benefit
• Slow down.
• Treat glucose to 140 range
  – Don’t go back to bad old days
• Try to identify groups most likely to benefit
  – Surgical
• Innovate to prevent hypoglycemia
Infectious Disease Society (IDSA): Quality of Evidence for Guidelines

All Guidelines

Guidelines By Date

- Management of intravascular catheter-related bloodstream infections
- Candidiasis
- Aspergillosis
- Intra-abdominal infections
- Cryptococcal disease
IDSA Hospital Acquired Pneumonia Guidelines

• IDSA/ATS recommendations for treatment of hospital acquired pneumonia

• Multidrug resistant organism risk:
  – Late onset ventilator associated pneumonia
  – Immunosuppression
  – Chronic HD
  – Home infusion or wound care
  – Other

• Pts at risk of multi-drug resistant organisms:
  – an anti-pseudomonal cephalosporin, carbapenem, or β-lactam and β-lactamase inhibitor
  – aminoglycoside or antipseudomonal fluoroquinolone
  – linezolid or vancomycin
IMPACT-HAP

• Improving Medicine through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (IMPACT-HAP).

• Improve guideline compliance in 4 academic medical centers
  – Development of an antibiotic algorithm
  – Education for MD, RN, Pharmacy staff

• Assess relationship of guideline adherence to outcome
Outcome IMPACT-HAP

- Compliance increased from 33% -> 47% over study
- 174/303 Non-compliant
  - 154 no 2nd Gram –
  - 24 no 1st Gram –
  - 24 no Gram +
- Mortality
  - 35% Compliant
  - 21% Non-compliant
- No correction for any clinical data changed the finding
Outcomes IMPACT-HAP

• Why?
  – Additional Gram negative may not help
    • 1 controlled study, several meta-analyses concur
  – Aminoglycosides, colistin toxic?
  – Local physician judgment superior to guideline?

• What next?
  – IDSA reviewing guidelines
  – Randomized trial?
Detection of “Failure” can be an indication that our system is self-correcting, though not as fast as I would like

- Bundles/Guidelines need to be continually tested and reviewed
- Our enthusiasms are double-edged swords
  - Pushing care forward
  - Blinding us to contradictory information

So, let’s be careful out there..
New treatments??
Other Possible Interventions

• Endotoxin and TLR-4 blockade
  – Hemofiltration
    • Early outcome data
  – Medication Eritoran
    • Phase 3 completed/not officially reported
Endotoxin/Receptors as Pharmacologic Target

– LPS levels correlate with
  • shock,
  • gut hypoperfusion,
  • adverse outcomes in human sepsis
  • Gram -/+ and Fungal pathogens

– Upstream point of sepsis cascade

– Strategies in Clinical Trials
  • Polymixin Hemoperfusion
  • E5564 aka Eritoran
    – Lipid A-like structure blocks signaling at MD2/TLR 4
Polymyxin Hemoperfusion

- Used in Japan x years despite no clinical trials (made in Japan)
- Does absorb endotoxin
- Endotoxin levels elevated in many types of sepsis
Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis [EUPHAS]

- 10 Italian ICU’s over 3 years
- Emergency Abdo Surgery + Sepsis
- “Standard Care” or Standard + 2 2hr hemofilter sessions

Cruz et al, JAMA 2009
EUPHAS Outcome

Survival Proportion

Log-rank $P = .03$

Time, d

<table>
<thead>
<tr>
<th>Time, d</th>
<th>Polymyxin B hemoperfusion therapy</th>
<th>Conventional therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>19</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>15</td>
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<tr>
<td>20</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>25</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>30</td>
<td>18</td>
<td>11</td>
</tr>
</tbody>
</table>
EUPHAS Issues

• Trial stopped for “ethical” reasons?!?!?!
• Designed to detect hemodynamic changes
  – Modest effect of hemoperfusion
• Very low enrollment, accrual rates
  – Small studies very subject to influence by minimal number of events
  – Uncertain applicability
• Placebo mortality much higher than anticipated. Treatment group mortality about anticipated.
• Larger, randomized trial in progress now.
- Short fatty acids, unsaturated 18 carbon fatty acid, and absence of dodecanoic acid leads to the antagonistic properties of E5564
- C.3 and C.3' ether linkages and methyl group at C.6' site confers stability
1900 Patients with severe sepsis
Randomized to standard tx+ placebo or standard tx+ eritoran
Able to “see” about 6% drop

ACCESS TRIAL
A CONTROLLED COMPARISON OF ERITORAN AND PLACEBO IN PATIENTS WITH SEVERE SEPSIS
# 28-day mortality

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eritoran</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MITT population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>657</td>
<td>1304</td>
</tr>
<tr>
<td>Mortality (Dead or Unknown)</td>
<td>26.9%</td>
<td>28.1%</td>
</tr>
<tr>
<td>P value vs Placebo</td>
<td>--</td>
<td>0.5986</td>
</tr>
<tr>
<td><strong>Per Protocol population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>584</td>
<td>1176</td>
</tr>
<tr>
<td>Mortality (Dead or Unknown)</td>
<td>25.0%</td>
<td>27.0%</td>
</tr>
<tr>
<td>P value vs Placebo</td>
<td>--</td>
<td>0.3802</td>
</tr>
<tr>
<td><strong>Japanese population (MITT)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>52</td>
<td>80</td>
</tr>
<tr>
<td>Mortality (Dead or Unknown)</td>
<td>23.1%</td>
<td>15.0%</td>
</tr>
<tr>
<td>P value vs Placebo</td>
<td>--</td>
<td>0.2398</td>
</tr>
</tbody>
</table>
1-year mortality (Secondary endpoint)

Log-Rank Test p-value: 0.7924
Hazard Ratio (95% CI): 0.98 (0.85, 1.13)
Talactoferrin

• Analog of Lactoferrin
  – Phase 2 sepsis trial 190 patients
    • Approx 65% with Cardiovascular dysfunction

• Dendritic cell recruiter
Oral Talactoferrin’s Effects are Mediated through the Gut

Where 75% of Immune System Resides

**Action on GI Tract**
- Binds epithelial cells and modulates intra-cellular signaling pathways impacting cytokine secretion
- Increases levels of key chemokines (e.g., CCL20) and cytokines (e.g., IFN-γ) derived from the GI tract
- Decreases production of Th2 cytokines (IL-4, IL-6, IL-10)

**Systemic Consequences**
- Decreases GI tract-induced systemic pro-inflammatory cytokine surges that contribute to the systemic multi-organ damage in sepsis
- Normalizes GI permeability and decreases bacterial translocation across the gut
- Minimizes the increase in circulating neutrophils in response to inflammation
Lactoferrin LF11 Peptide Bound to LPS

- Cationic LPS binding protein
  - competes for LPS with LBP, CD14
- Fe$^{2+}$ chelator,
  - limits oxidant tissue injury
- Bacteriostatic
- Promotes neutrophil binding and activity
- Promotes efficient antigen presentation and clearance by GALT

Phase II Trial of Talactoferrin in Patients with Severe Sepsis

190 patients*, severe sepsis <24 hours

- Standard Care + Talactoferrin 1.5 gm tid up to 28 days (n= 96)
- Standard Care + placebo tid up to 28 days (n= 94)

28-Day All Cause Mortality

*194 patients enrolled, 190 treated
### Primary Endpoint: 28-Day All-Cause Mortality

#### 28-Day All-Cause Mortality (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Talactoferrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-Day All-Cause Mortality (%)</td>
<td>26.6%</td>
<td>14.6%</td>
</tr>
</tbody>
</table>

- **Absolute reduction**: 12%
- **Relative reduction**: 45%

#### Odds-ratio and p-values

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds-ratio</td>
<td>0.47</td>
<td>0.49</td>
</tr>
<tr>
<td>p-value (1-tail)</td>
<td>0.02</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>p-value (2-tail)</td>
<td>0.04</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*adjusted for CV dysfunction*
28-Day All-Cause Mortality by CV Status

**With CV Dysfunction**
- Placebo: 28.6% (n = 121)
- Talactoferrin: 22.4%

**No CV Dysfunction**
- Placebo: 22.6% (n = 69)
- Talactoferrin: 2.6%

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Talactoferrin</th>
<th>Odds-ratio</th>
<th>p-value (2-tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Dysfunction</td>
<td>28.6%</td>
<td>22.4%</td>
<td>0.72</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CV Dysfunction</td>
<td>22.6%</td>
<td>2.6%</td>
<td>0.09</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Talactoferrin

• Talactoferrin early results encouraging
  – Phase 2 sepsis
  – 1 Pediatric trial necrotizing enterocolitis
  – Early Phase Oncology development

• Uncertainty
  – Very large effect in pt’s without shock?
  – Big randomization problem
    • 22 Subjects received active drug + placebo!!!!

• Phase 3 Study in start-up phase
For the moment,

Talactoferrin:

When it comes to infection, listen to your mom!
Conclusions (1)

• Numerous trials in critical care continue to refine our understanding of how to treat patients

• Information must be understood in the context of
  – Limitations of the endpoints we choose to follow
  – The size of effects we can see with < ideal sample sizes
  – “ABSENCE OF PROOF ≠ PROOF OF ABSENCE”

• Innovative trial design will minimize these problems
Conclusions (2)

- Norepinephrine best “default” vasopressor for shock
- Role of vasopressin supportive rather than starring
- “Tight” glucose control on the back burner
- TLR4 blocker (E5564) pretty convincingly ineffective for severe sepsis
- Guidelines/Bundles need to be continually tested
- Anticipate results
  - Talactoferrin
  - Filtration for sepsis
  - Corticosteroids for severe CAP
  - 2 large early goal directed therapy sepsis trials
  - Many more to come!!!