Biomarkers

Stratification in Septic Shock

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Disclosures

• The Cincinnati Children’s Hospital Research Foundation and the Speaker have patent applications pending for the biomarker work described in this lecture.

• New Co. launch underway based on the stratification biomarkers described in this lecture—Persepsy Biomedical.
Outcome Risk Stratification for Septic Shock

• Early assessment (i.e. within 24 hours of admission) of mortality risk.
Why Do We Care?

• Reliable outcome risk stratification is fundamental for effective clinical practice and clinical research.
• Stratification for clinical trials.
• Informing individual patient decision making.
• Allocation of ICU resources.
• Quality metric.
• Risk-stratified analyses of clinical data.
• There is no reliable and validated outcome risk stratification tool specific for septic shock.
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Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe Sepsis
The ACCESS Randomized Trial

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Thierry Dugernier, MD
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Importance Eritoran is a synthetic lipid A antagonist that blocks lipopolysaccharide (LPS) from binding at the cell surface MD2-TLR4 receptor. LPS is a major component of the outer membrane of gram-negative bacteria and is a potent activator of the acute inflammatory response.

Objective To determine if eritran, a TLR4 antagonist, would significantly reduce sepsis-induced mortality.

Design, Setting, and Participants We performed a randomized, double-blind, placebo-controlled, multinational phase 3 trial in 197 intensive care units. Patients were enrolled from June 2006 to September 2010 and final follow-up was completed in September 2011.

Interventions Patients with severe sepsis (n=1961) were randomized and treated within 12 hours of onset of first organ dysfunction in a 2:1 ratio with a 6-day course of either eritran tetrasodium (105 mg total) or placebo, with n=1304 and n=567 patients, respectively.

Main Outcome Measures The primary end point was 28-day all-cause mortality. The secondary end points were all-cause mortality at 3, 6, and 12 months after beginning treatment.

Results Baseline characteristics of the 2 study groups were similar. In the modified intent-to-treat analysis (randomized patients who received at least 1 dose) there was no significant difference in the primary end point of 28-day all-cause mortality with 28.1% (366/1304) in the eritran group vs 26.9% (177/657) in the placebo group (P=0.59; hazard ratio, 1.05; 95% CI, 0.88–1.26; difference in mortality rate, −1.1; 95% CI, −5.3 to 3.1) or in the key secondary end point of 1-year all-cause mortality with 44.1% (290/657) in the eritran group vs 43.3% (565/1304) in the placebo group, Kaplan-Meier analysis of time to death by 1 year, P=0.79 (hazard ratio, 0.98; 0.85–1.13). No significant differences were observed in any of the prespecified subgroups. Adverse events, including secondary infection rates, did not differ between study groups.

Conclusions and Relevance Among patients with severe sepsis, the use of eritran, compared with placebo, did not result in reduced 28-day mortality.

Trial Registration clinicaltrials.gov Identifier: NCT00334828

Severe sepsis, a syndrome of acute infection complicated by organ dysfunction, is caused by a dysregulated systemic inflammatory response. Sepsis can progress to systemic hypotension (septic shock).
The ACCESS Randomized Trial

- Eritoran: Synthetic lipid A antagonist of the TLR4 receptor.
- Randomized 1,961 patients to placebo vs. drug.
- Primary outcome variable: 28-day all cause mortality.
- No efficacy.
The ACCESS Randomized Trial

• Enrollment criteria included an APACHE II score between 21 and 37: *high, but presumably modifiable, risk of death.*

• Predicted a mortality rate of 40% in the placebo group; basis for power calculations.

• The actual mortality rate was 27%.

• May have been underpowered.

• *Highlights the importance of developing stratification tools for septic shock to better inform the conduct of clinical trials.*
PERSEVERE

• PEidiatRic SEpsis biomarkEr Risk modEl.
• Multi-biomarker-based risk model to assign a mortality probability for children with septic shock.
• Have also developed a version for adults with septic shock: “ASSIST” (Adult Septic Shock Information and Stratification Technology).
• Models derived using CART methodology.
• Both models outperform physiology-based scoring systems (APACHE and PRISM).
Discovery of candidate stratification biomarkers for septic shock

Mining of genome-wide expression data to identify genes associated with 28-day mortality in children with septic shock.

117 genes with predictive capacity for mortality

12 gene products meeting the following criteria:
- Biological plausibility regarding sepsis biology.
- Gene product (i.e. protein) can be measured in serum/plasma.
## Final list of candidate stratification biomarkers

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Description</th>
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<td>CCL3</td>
<td>C-C chemokine ligand 3; a.k.a. MIP-1α</td>
</tr>
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<td>LCN2</td>
<td>Lipocalin 2; a.k.a. NGAL</td>
</tr>
<tr>
<td>MMP8</td>
<td>Matrix metallopeptidase 8; a.k.a. neutrophil collagenase</td>
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<tr>
<td>RETN</td>
<td>Resistin</td>
</tr>
<tr>
<td>THBS</td>
<td>Thrombospondin 1</td>
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<td>Granzyme B</td>
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<td>HSPA1B</td>
<td>Heat shock protein 70kDa 1B</td>
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<tr>
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<td>Lactotransferrin</td>
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<td>Neutrophil elastase 1</td>
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### HSPA1B

- **≤ 3.27E6**: N = 207
  - **Outcome**
    - Death: 8 (0.039)
    - Survived: 199 (0.961)

- **> 3.27E6**: N = 27
  - **Outcome**
    - Death: 6 (0.222)
    - Survived: 21 (0.778)

### CCL3

- **≤ 160**: N = 234
  - **Outcome**
    - Death: 14 (0.060)
    - Survived: 220 (0.940)

- **> 160**: N = 121
  - **Outcome**
    - Death: 27 (0.223)
    - Survived: 94 (0.777)

### IL8

- **≤ 507**: N = 55
  - **Outcome**
    - Death: 5 (0.091)
    - Survived: 50 (0.909)

- **≤ 829**: N = 174
  - **Outcome**
    - Death: 2 (0.011)
    - Survived: 172 (0.989)

- **> 829**: N = 33
  - **Outcome**
    - Death: 6 (0.182)
    - Survived: 27 (0.818)

### IL8 > 507

- **N = 66**
  - **Outcome**
    - Death: 22 (0.333)
    - Survived: 44 (0.667)

### GZMB

- **≤ 55**: N = 36
  - **Outcome**
    - Death: 17 (0.472)
    - Survived: 19 (0.528)

- **> 55**: N = 30
  - **Outcome**
    - Death: 5 (0.167)
    - Survived: 25 (0.833)

### MMP8

- **≤ 47513**: N = 40
  - **Outcome**
    - Death: 1 (0.025)
    - Survived: 39 (0.975)

- **> 47513**: N = 15
  - **Outcome**
    - Death: 4 (0.267)
    - Survived: 11 (0.733)

### Age

- **≤ 0.5 years**: N = 8
  - **Outcome**
    - Death: 5 (0.625)
    - Survived: 3 (0.375)

- **> 0.5 years**: N = 22
  - **Outcome**
    - Death: 0 (0.000)
    - Survived: 22 (1.000)
<table>
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<tr>
<th>Variable</th>
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**Low risk terminal nodes N = 236**

**Mortality risk: 0.0 to 2.5%**
Intermediate risk terminal nodes  
N = 75  
Mortality risk: 18.2 to 26.7%
High risk terminal nodes
\( N = 44 \)
Mortality risk: 47.2 to 62.5%
## Diagnostic Test Characteristics of PERSEVERE

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<td><strong>+Likelihood Ratio</strong></td>
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<td>0.2 (0.1 – 0.5)</td>
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<tr>
<td><strong>Area Under the Curve</strong></td>
<td>0.883 (0.832 – 0.933)</td>
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<td>0.883 (0.832 – 0.933)</td>
<td>0.811 (0.704 – 0.917)</td>
</tr>
</tbody>
</table>
If this model is valid, then perhaps the false positive subjects are “sicker” compared to the true negatives.
Compared to the true negative subjects, the false positive subjects have:

- Greater degree of organ failure burden.
- Greater duration of organ failure.
- Greater length of stay in the PICU.
RESEARCH

The pediatric sepsis biomarker risk model

Hector R Wong1,2*, Shelia Salisbury2, Qiang Xiao3, Natalie Z Cvijanovich4, Mark Hall5, Geoffrey L Allen6, Neal J Thomas7, Robert J Freishtat8, Nick Anas9, Keith Meyer10, Paul A Checchia11, Richard Lin12, Thomas P Shanley13, Michael T Bigham14, Anita Sen15, Jeffrey Nowak16, Michael Quasney17, Jared W Henricksen18, Arun Chopra19, Sharon Banschbach1, Eileen Beckman1, Kelli Harmon1, Patrick Lahni1 and Christopher J Lindsell20

Testing the Prognostic Accuracy of the Updated Pediatric Sepsis Biomarker Risk Model

Hector R. Wong1,2*, Scott L. Weiss3, John S. Giuliano Jr.4, Mark S. Wainwright5, Natalie Z. Cvijanovich6, Neal J. Thomas7, Geoffrey L. Allen8, Nick Anas9, Michael T. Bigham10, Mark Hall11, Robert J. Freishtat12, Anita Sen13, Keith Meyer14, Paul A. Checchia15, Thomas P. Shanley16, Jeffrey Nowak17, Michael Quasney16, Arun Chopra18, Julie C. Fitzgerald9, Rainer Gedeit19, Sharon Banschbach1, Eileen Beckman1, Patrick Lahni1, Kimberly Hart20, Christopher J. Lindsell20

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Potential Applications for PERSEVERE

• Stratification for clinical trials.
  – *Inform inclusion and exclusion criteria.*

• A quality metric to benchmark outcomes.
  – *Compare actual to predicted mortality.*

• Inform individual patient decision making.
  – *Reserve non-standard, higher risk therapies for higher risk patients.*

• Allocation of ICU resources.

• Risk stratified analysis of clinical data.
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Fluid is now the cause of all evil in the intensive care unit........

• “Fluid overload” or a positive fluid balance associated with poor outcomes in multiple studies:
  – Adult and pediatric studies.
  – Sepsis, ALI, and other forms of critical illness.
• Is “fluid overload” really a direct cause of poor outcomes?
• Is the reported association between fluid overload and poor outcome a reflection of cofounding by illness severity (epiphenomenon)?
• Do sicker patients simply have more vascular leak and more fluid requirements?
Stratified 317 patients with septic shock into 3 mortality risk groups:

- **Low**
- **Intermediate**
- **High**

Tested the association between positive fluid balance and poor outcome within each risk strata.

Some associations were found between positive fluid balance and poor outcome in the low risk group.

A positive fluid balance was **NOT** associated with poor outcomes in the intermediate and high mortality risk groups.
Risk Stratified Analysis of Adjunctive Corticosteroids and Pediatric Septic Shock Outcomes

- 496 subjects with septic shock.
- About $\frac{1}{2}$ received adjunctive corticosteroids.
- Stratified the cohort into three mortality risk strata and tested the association between steroids and outcomes within each risk strata.
  - Hypothesized that higher mortality risk patients may benefit the most from adjunctive corticosteroids.
- Could not detect any outcome benefit from adjunctive corticosteroids in any of the risk strata.
  - Possible harm.
- Manuscript in press (*PLOS ONE*).
- Therapies for Sepsis and ARDS: Saturday, 15:00, Grand East
Potential Applications for PERSEVERE

• Stratification for clinical trials.
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• A quality metric to benchmark outcomes.
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• Inform individual patient decision making.
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• Allocation of ICU resources.

• Risk stratified analysis of clinical data.
A Multibiomarker-Based Outcome Risk Stratification Model for Adult Septic Shock

Hector R. Wong, MD; Christopher J. Lindsell, PhD; Ville Pettilä, MD, PhD; Nuala J. Meyer, MD, MS; Simone A. Thair, BSc; Sari Karlsson, MD, PhD; James A. Russell, MD; Christopher D. Fjell, PhD; John H. Boyd, MD; Esko Ruokonen, MD, PhD; Michael G. S. Shashaty, MD, MS; Jason D. Christie, MD; Kimberly W. Hart, MS; Patrick Lahni, BS; Keith R. Walley, MD.


- A version of the model for adults with septic shock.
- 881 subjects from 3 different countries.
- Outperforms APACHE II, APACHE III, and IL6.

Dr. Wong’s institution received grant support from the National Institutes of Health (NIH). Dr. Wong has a patent pending for a biomarker model with U.S. Patent Office and received support for article research from the NIH. Dr. Lindsell’s institution received grant support from the NIH. His contributions to this work were supported, in part, by an institutional Clinical and Translational Science Award (CTSA) from the NIH. Dr. Lindsell and his institution have a patent (he was named as co-inventor on a patent for a multibiomarker-based risk stratification model for pediatric sepsis). Dr. Lindsell received support for article research from the NIH. Dr. Meyer’s institution received grant support from the NIH (HL102254 and Submitted RO1) and GlaxoSmithKline (research grant to support plasma collection). Dr. Meyer received support for article research from the NIH. Ms. Thair consulted for IXL Consulting and received grant support from University of British Columbia (grant for PhD graduate studies). Dr. Russell served as board member for Sirius Genomics; consulted for Ferring, Astra Zeneca, Medimmune, Grifols, and Sirus Genomics; has a patent with the University of British Columbia; and has stock options with Sirus Genomics. Dr. Russell’s institution received grant support from Ferring, Astra Zeneca, and Sirus Genomics. Dr. Shashaty’s institution received grant support from the NIH (Career Development Award to study the association of adiposity with acute kidney injury in critically ill trauma patients). Dr. Christie provided expert testimony for various law firms (expert testimony on asbestos litigation in brake workers) and received support for article research from the NIH. Dr. Lahni received support for article research from the NIH. Dr. Walley is employed by the University of British Columbia and received grant support from Canadian Institutes of Health Research. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Objectives: Clinical trials in septic shock continue to fail due, in part, to inequitable and sometimes unknown distribution of baseline mortality risk between study arms. Investigators advocate that intervention trials in septic shock require effective outcome risk stratification. We derived and tested a multibiomarker-based approach to estimate mortality risk in adults with septic shock.

Design: Previous genome-wide expression studies identified 12 plasma proteins as candidates for biomarker-based risk stratification. The current analysis used banked plasma samples and clinical data from existing studies. Biomarkers were assayed in plasma samples obtained from 341 subjects with septic shock within 24 hours of admission to the ICU. Classification and
Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

**Post hoc analysis of VASST outcome data based on risk stratification**

- VASST tested the efficacy of vasopressin in adults with septic shock.
- No efficacy.
- **Post hoc:** divided the patients into 3 risk categories based on the biomarker model.
  - Low risk: <10% (n = 135)
  - Intermediate risk: 10% to 50% (n = 163)
  - High risk: >58 to 75% (n = 43)
- Analyzed outcome in vasopressin arm vs. control arm based on these categories.
Post hoc analysis of VASST outcome data based on risk stratification

<table>
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<tr>
<th>Risk Category (mortality prob.)</th>
<th>Control Deaths/Total (%)</th>
<th>Vasopressin Deaths/Total (%)</th>
<th>Vasopressin Size Effect (95% CI)</th>
<th>P value</th>
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<td>Low (&lt;10%)</td>
<td>5/64 (7.8)</td>
<td>7/71 (9.9)</td>
<td>2.1% (-8.4 to 12.2)</td>
<td>0.677</td>
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Low Risk Group; $p = 0.680$

Intermediate Risk Group; $p = 0.195$

High Risk Group; $p = 0.844$
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- 11% absolute mortality decrease in the vasopressin arm.
- Would need 313 patients, in each arm, from the intermediate risk category, to detect a difference in mortality.
Failed to demonstrate efficacy.
Assumed a 60% mortality in the control arm.
Actual mortality in the control arm was 39.3%.
Targeted at a 10% absolute reduction in mortality.
Needed 388 patients in each arm.
Enrollment in the next sepsis trial...

Patient meets stringent clinical (ideally biological) criteria

→ Patient is stratified based on initial mortality risk

Exclude if at extremes of low or high risk

Randomize

Include all risk groups with *a priori*, planned stratified analysis

Randomize
Enrollment in the next sepsis trial...

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Exclude if at extremes of low or high risk

Include all risk groups with *a priori*, planned stratified analysis

Randomize

Patient is also stratified based on the “biological phenotype” of sepsis
Collaborators for developing the adult risk model

• University of British Columbia and St. Paul’s Hospital.
  – Keith Walley, MD
  – James Russell, MD
  – Simone Thair, BSc
  – Christopher Fjell, PhD
  – John Boyd, MD

• FINNSEPSIS Investigators
  – Ville Pettilä, MD, PhD
  – Sari Karlsson, MD, PhD
  – Esko Ruokonen, MD, PhD

• University of Pennsylvania
  – Nuala Meyer, MD, MS
  – Michael Shashaty, MD, MS
  – Jason Christie, MD
Acknowledgements: Contributing Centers

- **Natalie Cvijanovich, MD**: Children’s Hospital & Research Center Oakland, Oakland, CA.
- **Thomas Shanley, MD**: University of Michigan, C.S. Mott Children’s Hospital, Ann Arbor, MI.
- **Geoffrey Allen, MD**: Children’s Mercy Hospitals & Clinics, Kansas City, MO.
- **Neal Thomas, MD**: Penn State Hershey Children’s Hospital, Hershey, PA.
- **Robert Freishtat, MD**: Children’s National Medical Center, Washington, DC.
- **Nick Anas, MD**: Children’s Hospital of Orange County, Orange, CA.
- **Keith Meyer, MD**: Miami Children’s Hospital, Miami, FL.
- **Paul Checchia, MD**: Texas Children’s Hospital, Houston, TX.
- **Michael Bigham, MD**: Akron Children’s Hospital, Akron, OH.
- **Mark Hall, MD**: Nationwide Children’s Hospital, Columbus, OH.
- **Anita Sen, MD**: New York-Presbyterian, Morgan Stanley Children’s Hospital, Columbia University Medical Center, New York, NY.
- **Jeffery Nowak, MD**: Children’s Hospital and Clinics of Minnesota, Minneapolis, MN.
- **Michael Quasney, MD, PhD**: Children’s Hospital of Wisconsin, Milwaukee, WI.
- **Jared Henricksen, MD**: Primary Children’s Medical Center, Salt Lake, UT.
- **Arun Chopra, MD**: St. Christopher’s Hospital for Children, Philadelphia, PA.
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