Sepsis Endotypes

Hector R. Wong, MD
Division of Critical Care Medicine
Cincinnati Children’s Hospital Medical Center
Cincinnati Children’s Research Foundation

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What is an Endotype?

- A subclass or subgroup of a disease/condition based on a biological or physiological process.
- Especially relevant to critical care medicine because we mostly manage syndromes: ARDS, septic shock, etc.
- We already consider this to some extent:
  - Cardiogenic vs. distributive vs. hypovolemic shock
  - Gram negative vs. gram positive sepsis
- We are starting to do even better......
• Latent class modeling to identify endotypes of ARDS.

• Biological and clinical data.

• Two endotypes identified based on the degree of inflammation, vasopressor need, serum bicarbonate, and sepsis prevalence.

• Endotype 2 had higher mortality and organ failure burden.

• Differential response to PEEP.
Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study

Emma E Davenport, Katie L Burnham*, Jayachandran Radhakrishnan*, Peter Humberg, Paula Hutton, Tara C Mills, Anna Reutonen, Anthony C Gordon, Christopher Gerrard, Adrian V Hill, Charles J Hinds, Julian C Knight

• *Lancet Respir Med 2016; 4:259
• Transcriptomic analyses to identify septic shock endotypes.
• Sepsis Response Signatures (SRS) 1 and 2.
• SRS1: characterized by immune suppression.
• Higher mortality in SRS1.
Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock

Hector R. Wong¹,², Natalie Z. Cvijanovich³, Nick Anas⁴, Geoffrey L. Allen⁵, Neal J. Thomas⁶, Michael T. Bigham⁷, Scott L. Weiss⁸, Julie Fitzgerald⁸, Paul A. Checchia⁹, Keith Meyer¹⁰, Thomas P. Shanley¹¹, Michael Quasney¹¹, Mark Hall¹², Rainer Gedeit¹³, Robert J. Freishtat¹⁴, Jeffrey Nowak¹⁵, Raj S. Shekhar¹⁶, Shira Gertz¹⁷, Emily Dawson¹⁸, Kelli Howard¹, Kelli Harmon¹, Eileen Beckman¹, Erin Frank¹, and Christopher J. Lindsell¹⁹


• Transcriptomic analyses to identify septic shock endotypes.
• Gene expression mosaics representing 100 genes.
• Reference mosaics.
• Endotype assignment using computer assisted-image analysis.
Endotype A
Endotype B

"GENE EXPRESSION SCORE": GES

Metric to quantify range of variability in expression of the 100 genes.

Less variability, lower GES $\rightarrow$ Endotype A

Greater variability, higher GES $\rightarrow$ Endotype B

AUROC = 0.98 (95% C.I. 96 to 99)

$$GES = \sum_{Genes,i} \frac{(e_i - \mu_g)^2}{1 \times 10^6}$$
• The 100 endotype-defining genes reflect:
  • Adaptive immunity
  • Glucocorticoid receptor signaling
• Repressed in endotype A.
Endotype A subjects have higher absolute lymphocyte counts compared to endotype B.

That just reflects lymphopenia!
• Endotype A subjects have greater mortality and organ failure burden.

• Logistic regression, accounting for illness severity, age, and co-morbidity:
  • Allocation to endotype A independently associated with increased mortality.
  • Corticosteroid prescription independently associated with increased mortality among endotype A subjects.
Temporal Considerations

• All data so far represent the first 24 hours of a sepsis diagnosis.

• *Do patients change endotypes over time, and do those changes associate with outcome?*
Temporal Considerations
## Temporal Considerations

### Temporal Endotype Grouping, Day 1 → Day 3, n = 375

<table>
<thead>
<tr>
<th></th>
<th>A → A</th>
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<td>Mortality, n (%)</td>
<td>12 (16)</td>
<td>10 (18)</td>
<td>8 (5)</td>
<td>1 (1)</td>
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<tr>
<td>Complicated course, n (%)</td>
<td>37 (49)</td>
<td>22 (39)</td>
<td>36 (22)</td>
<td>9 (12)</td>
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Among “A $\rightarrow$ A” subjects, corticosteroid prescription independently associated with increased odds of mortality: O.R. 15.0 (95% C.I. 2.8 to 80.8), p = 0.002.
Logistic regression using the GES metric

\[
GES = \sum_{Genes,i} \frac{(e_i - \mu_g)^2}{1 \times 10^6}
\]
Logistic regression using the GES metric

• Log transformed the GES values.
• Considered:
  • Day 1 GES
  • Day 3 GES
  • Day 1 GES + Day 3 GES
• Primary outcome: 28 day mortality.
• Adjusted for illness severity (PRISM), age, and co-morbidity burden.
Logistic regression using the GES metric

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<tr>
<td>Sum_Day 1 + Day 3 GES</td>
<td>0.5</td>
<td>0.3 to 1.0</td>
<td>0.033</td>
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Application?

• **Predictive** enrichment.

• Selection of patients more likely to respond to a therapeutic intervention, compared to an unselected cohort.

• **Prognostic** enrichment.

• Selection of patients more likely to have an outcome of interest, compared to an unselected cohort.
Can we identify patients who may benefit from corticosteroids?

“PERSEVERE”: A multi-biomarker stratification tool to assign a baseline mortality probability

Endotype A

Endotype B

Endotype B patients have higher expression of glucocorticoid receptor pathway genes
Can we identify patients who may benefit from corticosteroids?

Endotype B + Intermediate to high baseline mortality risk

- Increased expression of GCR genes. *Predictive enrichment*
- Higher likelihood of disease-related event. *Prognostic enrichment*

>10 fold **decreased** risk for poor outcome when prescribed corticosteroids.
O.R. 0.07
95% CI: 0.10-0.48
P = 0.007
- Gene expression mosaics representing 100 genes.
- Reference mosaics.
- Endotype assignment using computer assisted-image analysis.
Reducing the number of genes necessary for endotype assignment

• Classification and regression tree (CART) methodology.
• Considered all 100 genes as candidate predictors.
• Outcome: endotype A vs. endotype B.
• Reference criterion: gene expression mosaics and computer assisted image analysis.
Decision tree consisting of just 4 genes: Janus kinase 2 (JAK2), Protein kinase C, β (PRKCB), SOS Ras/Rho guanine nucleotide exchange factor 2 (SOS2), LYN proto-oncogene, Src family tyrosine kinase (LYN).
High probability of being an endotype A
High probability of being an endotype B
**AUROC = 0.97 (0.95 to 0.99)**

Validation cohort (n = 43) **AUROC = 0.97 (0.93 to 1.00)**
Thank You

Endotype A

Endotype B