Endotypes: Kids and Adults

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What is an Endotype?

• A subclass of a disease based on a defining biological mechanism(s).

• Endotype → Therapy → *Predictive Enrichment*.

• We already do this to some extent:
  • Cardiogenic vs. distributive vs. hypovolemic shock
  • Gram negative vs. gram positive sepsis

• We are starting to do even better.......
Clinical Data

Endotyping

Biological Data
Whole genome expression profiling
Whole blood-derived RNA
_Transcriptomics_

Endotyping
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 Rautanen, Anthony C Gordon, Christopher Garrard, Adrian V S Hill, Charles J Hinds, Julian C Knight

- UK Genomic Advances in Sepsis (GAinS).
- Transcriptomic analyses to identify sepsis endotypes (CAP).
- Sepsis Response Signatures (SRS) 1 and 2.
- SRS1: characterized by immune suppression.
- Higher mortality in SRS1.
Shared and Distinct Aspects of the Sepsis Transcriptomic Response to Fecal Peritonitis and Pneumonia

Katie L. Burnham¹, Emma E. Davenport¹, Jayachandran Radhakrishnan¹, Peter Humbug¹, Anthony C. Gordon², Paula Hutton³, Eduardo Svoren-Jabalera⁴, Christopher Garrard⁵, Adrian V. S. Hill¹, Charles J. Hinds⁴, and Julian C. Knight¹

¹Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom; ²Section of Anaesthetics, Pain Medicine and Intensive Care, Imperial College London, London, United Kingdom; ³Adult Intensive Care Unit, John Radcliffe Hospital, Oxford, United Kingdom; and ⁴William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University, London, United Kingdom

• *Am J Respir Crit Care Med* 2017; 196:328.
• Sepsis secondary to fecal peritonitis.
• Validated SRS1 and SRS2.
Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study

Brendon P Scicluna, Lonneke A van Vught, Aelko H Zwinderman, Maryse A Wiewel, Emma E Davenport, Katie L Burnham, Peter Nürnberg, Marcus J Schultz, Janneke Horn, Olaf L Cremer, Marc J Bonten, Charles J Hinds, Hector R Wong, Julian C Knight, Tom van der Poll, on behalf of the MARS consortium

- Molecular Diagnosis and Risk Stratification of Sepsis (MARS).
- Four endotypes: MARS 1 through 4.
- Validated in the GAInS cohort.
- MARS1 characterized by suppression of innate and adaptive immunity related genes.
- Higher mortality in the MARS 1 group.
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 Fitzgerald⁹, Paul A. Cucchia⁹, 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.
Endotype A  
Endotype B  

- Gene expression mosaics representing 100 genes.
- Reference mosaics.
- Endotype assignment using computer assisted-image analysis.
• 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 septic shock diagnosis.
• Sepsis is a highly dynamic process.
• *Do patients “transition” endotypes during the acute phase of illness, and do those transitions associate with outcome and treatment response?*
Temporal Considerations

Day 1 → Day 3

Day 1

Day 3

Day 1 → Day 3

Day 1

Day 3

Day 1 → Day 3

Day 1

Day 3

Day 1 → Day 3

Day 1

Day 3
Summary of Temporal Endotyping

• About one-third of children with sepsis transition endotype over the first three days of illness.
• The day 1 endotype assignment is most strongly associated with outcome.
• But, the day 3 assignment modifies the association with outcome.
• “Persistence” of endotype A is most strongly associated with poor outcome.
• Corticosteroid prescription associated with a 15 fold mortality increase among patients who persist as endotype A.
Common Theme Across Three Studies

“GAinS”, “MARS”, and “Wong”

Transcriptomics and unsupervised clustering

Gene expression based subgroups of sepsis

One group with a higher mortality rate (validated)

Suppression of adaptive immunity genes
So are we all saying the same thing?
So are we all saying the same thing? 

*yes and no*

- There is a subgroup of patients with sepsis characterized by repression of genes corresponding to adaptive immunity.
- And these patients are at higher risk of poor outcome.
So are we all saying the same thing?

*yes and no*

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- Some overlap of pathway enrichment between endotype A and SRS1, but minimal gene overlap
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Wong Cohort

- Some overlap of pathway enrichment between endotype A and SRS1, but minimal gene overlap
- Classified in Mars-1, -2, and -4, but not -3. No differences in mortality.
So are the all saying the same thing? *yes and no*

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Pediatric sepsis endotypes among adults with sepsis

- Downloaded the GAinS study expression data.
- Classified the cohort into endotype A or B.
- 163 subjects (30%) allocated to endotype A and 386 to endotype B.
- No difference in mortality: 23 vs. 25%.
- Weak correlation between endotype assignment and SRS membership.
Pediatric sepsis endotypes among adults with sepsis

• The median age of the GAinS cohort = 68 years, range = 18 to 92.

• Is there an interaction between age and endotype assignment?
  • Younger age X endotype A = higher risk of mortality.

• Is there an interaction between endotype assignment and SRS membership.
  • Mortality in the “A1” group = 47%, $p = 0.001$ vs. other co-assignment groups.
Pediatric sepsis endotypes among adults with sepsis
Pediatric sepsis endotypes among adults with sepsis

So what does all this mean?

Public sharing of transcriptomic data is a powerful thing!
So what does all this mean?

• Three independent research groups:
  • Subset of patients with sepsis characterized by repression of adaptive immunity-related genes.
  • Higher mortality.

• The endotyping strategy for adults might not be applicable to children, and *vice versa*.
  • But “A1” patients might be particularly vulnerable.

• But increase mortality risk is NOT the important point here.

• The important point is the potential for *predictive enrichment*. 
Predictive Enrichment

- *Enrichment*: The selection of patients in whom an intervention is more likely to be effective compared to an unselected cohort.

- *Predictive Enrichment*: The selection of patients in whom an intervention is more likely to be effective based on a biological mechanism.

- Perhaps patients classified as “SRS1”, “MARS1”, or “Endotype A” are the best candidates for immune enhancing therapies.

- And in children, we might want to avoid corticosteroids among endotype A patients.
Can we identify patients who may benefit from corticosteroids using prognostic and predictive enrichment?

**Prognostic Enrichment**

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

**Predictive Enrichment**

Endotype A

Endotype B

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

- 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. 0.09
95% CI: 0.01-0.54
P = 0.007
Is any of this feasible?

• Diagnostic testing among critically ill patients is time sensitive.

• mRNA-based strategies are technically more challenging than “traditional” biomarkers.

• Complex expression signatures.

• All three groups have distilled their respective strategies to a handful of classifier genes:
  • Knight: 7 genes.
  • van der Poll: 8 genes.
  • Wong: 4 genes.
A Randomized Controlled Trial of Corticosteroids in Pediatric Septic Shock: A Pilot Feasibility Study

Kusum Menon, MSc, MD; Dayre McNally, MD, PhD; Katharine O’Hearn, MSc; Anand Acharya, PhD; Hector R. Wong, MD; Margaret Lawson, MSc, MD; Tim Ramsay, PhD; Lauralyn McIntyre, MD; Elaine Gilfoyle, MEd, MD; Marisa Tucci, MD; David Wensley, MBBS; Ronald Gottesman, MD; Gavin Morrison, MD; Karen Choong, MSc, MB; for the Canadian Critical Care Trials Group
Thank You

MARS 1 to 4

Endotype A

Endotype B

SRS1 and 2