Penn Medicine

Achieving Excellence in Sepsis Diagnosis –

Diagnosing Aberrant Host Immune Response

Nuala J. Meyer, MD MS

Director, Center for Translational Lung Biology

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The Problem

- Sepsis: “dysregulated host response to infection”
- *What defines a regulated host response to infection?*

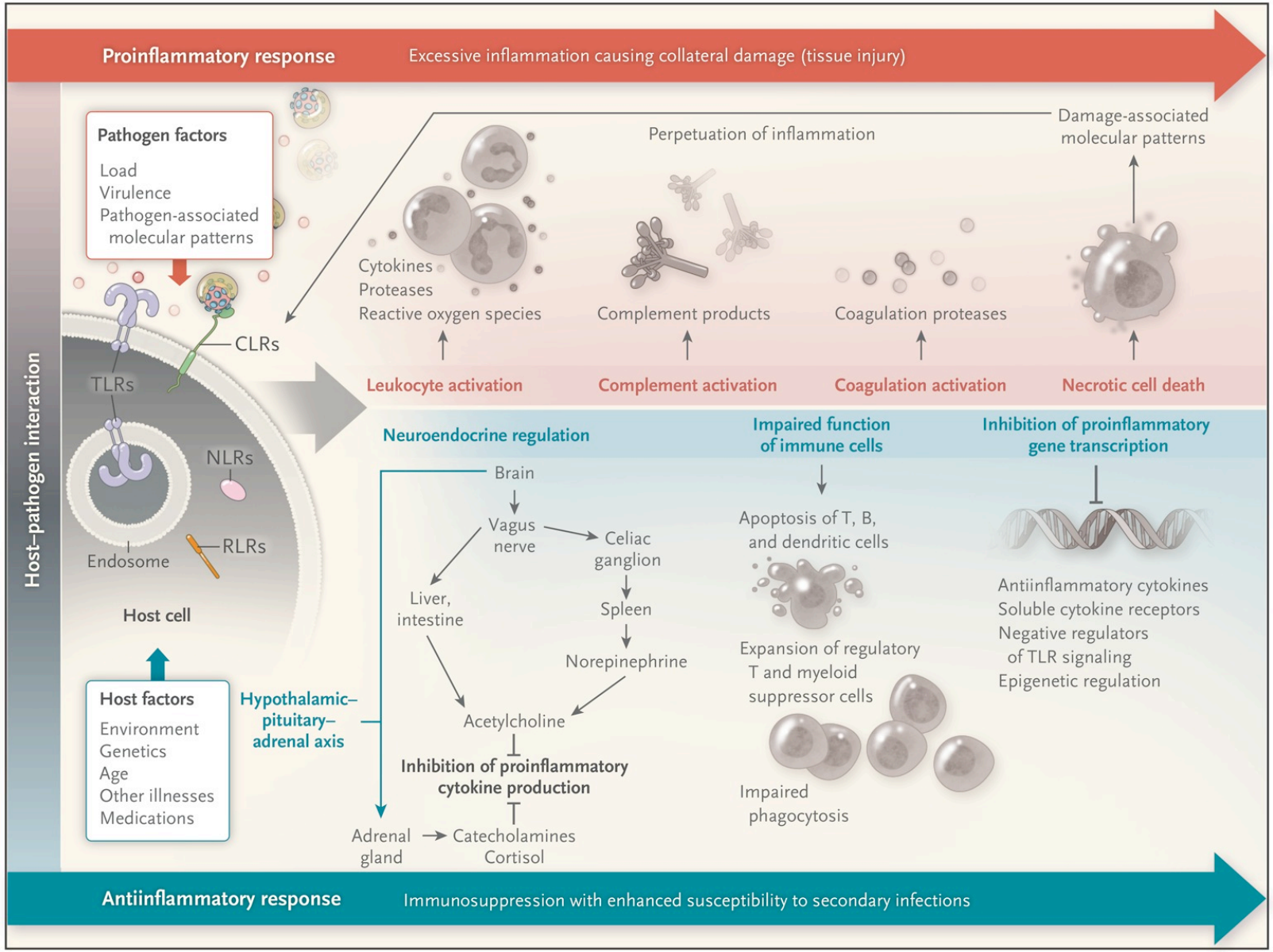
Focus on Inflammation

- *Regulated or Dysregulated?*
  - Pathogen- and site-dependent
  - Dynamic
  - Access to care and source control
- Systemic inflammatory response syndrome
  - Tachycardia, tachypnea, fever / hypothermia, WBC count
  - Reliably associates with mortality; yet misses 12% of shock

Lawrence, Willoughby, Gilroy Nat Rev Imm 2002; Kaukonen NEJM 2015

It's complicated

- Balance microbial killing & inflammation
- Simultaneous hyperinflammation, immune suppression



Angus NEJM 2013

Past Solutions

- Wait for organ dysfunction / Functio Laesa (Sepsis-3): too late?

- "Inflammatory markers"
  - C reactive protein, ESR, LDH, ferritin
  - Cytokines
  - Leukocyte gene expression or leukocyte populations
  - *May reliably prognosticate worse outcomes, but actionable?*

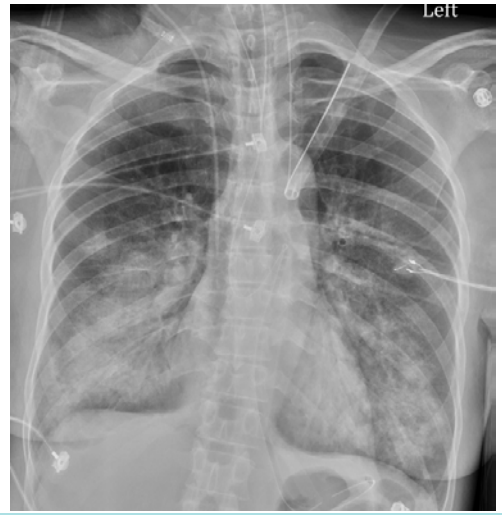
Procalcitonin: Success?

- Strong test characteristics for bacteremia, bacterial infection
  - ~79% sensitivity for bacteremia in ED settings
  - Dynamic with treatment, response indicator

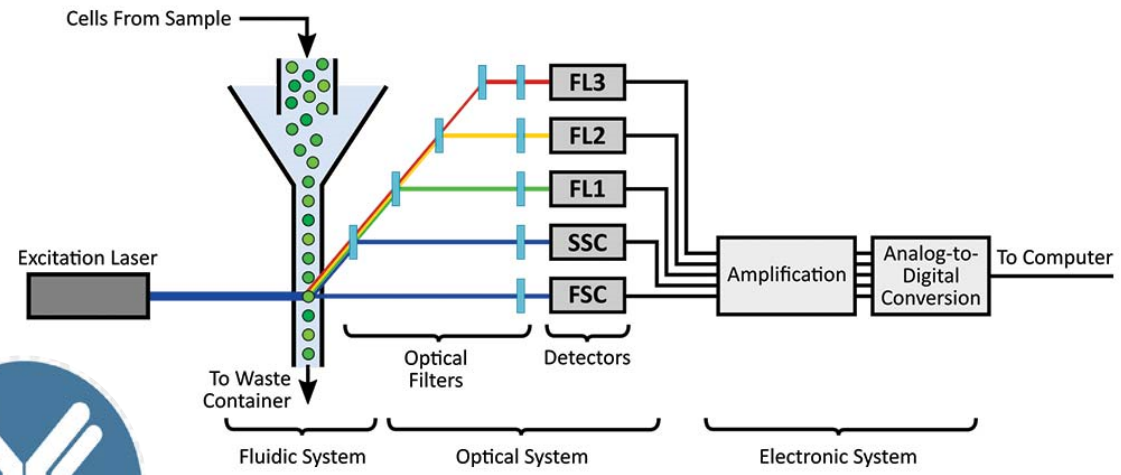
- But … not specific to infection, may indicate sterile inflammation
  - Viral sepsis not detected
  - Different test performance characteristics for pneumonia vs bacteremia

Shehabi AJRCCM 2014

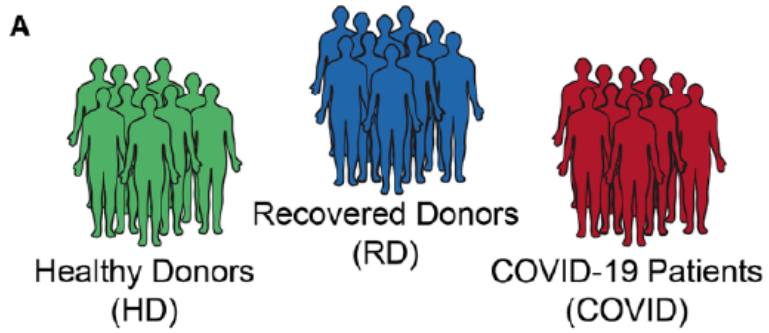
A case for discovery: COVID-19 example



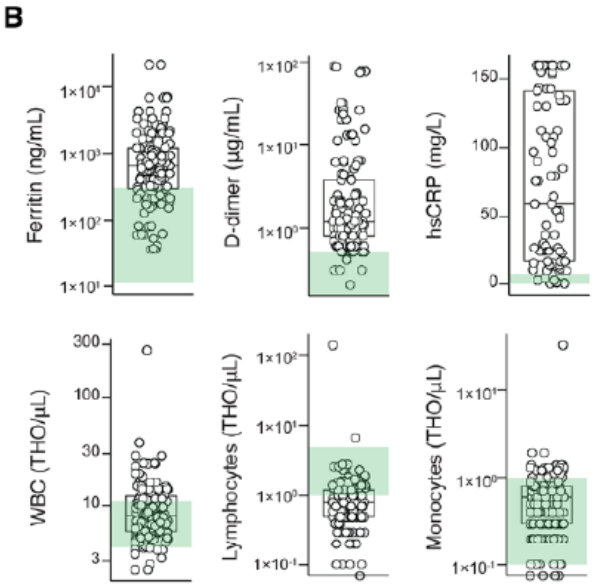
Flow Cytometry

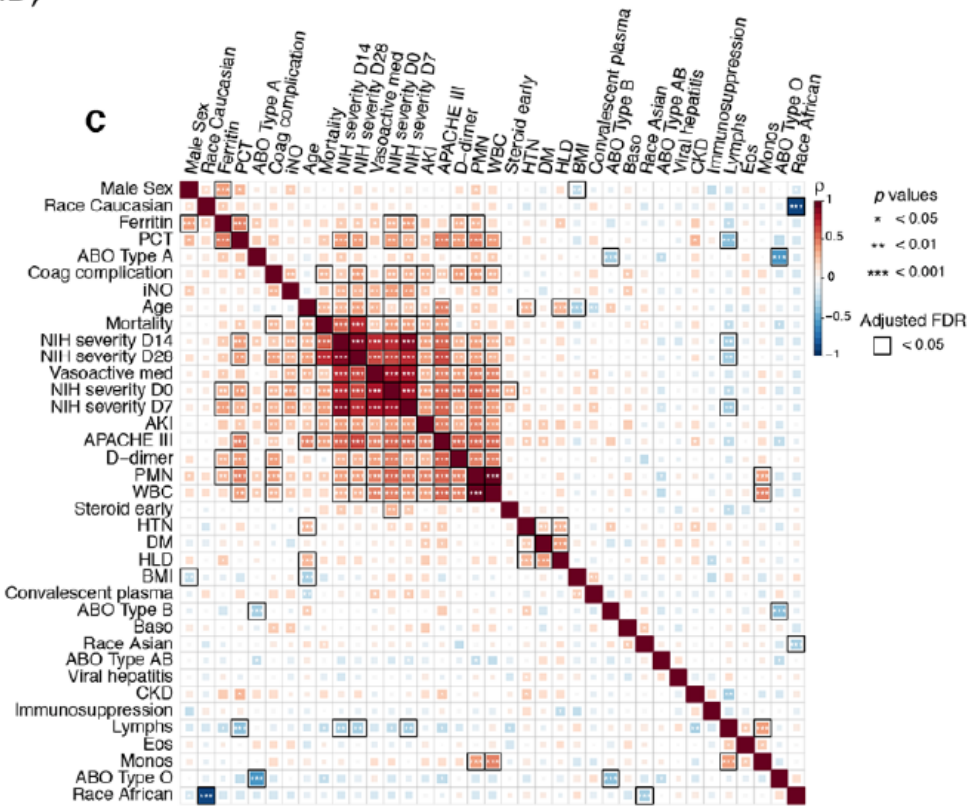


Proteins, Metabolites, Lipids



		Healthy Donors	Recovered	COVID-19
Whole Study	Number	70	46	149
	Age (yr)	41 [22–62]	30 [20–61]	60 [22–90]
	Gender (F/M)	14 (44%) / 18 (56%)	11 (50%) / 11 (50%)	67 (46%) / 80 (54%)
Flow Study	Number	60	36	125
	Age (yr)	41 [22–62]	29 [20–61]	60 [22–90]
	Gender (F/M)	12 (48%) / 13 (52%)	9 (50%) / 9 (50%)	60 (49%) / 63 (51%)



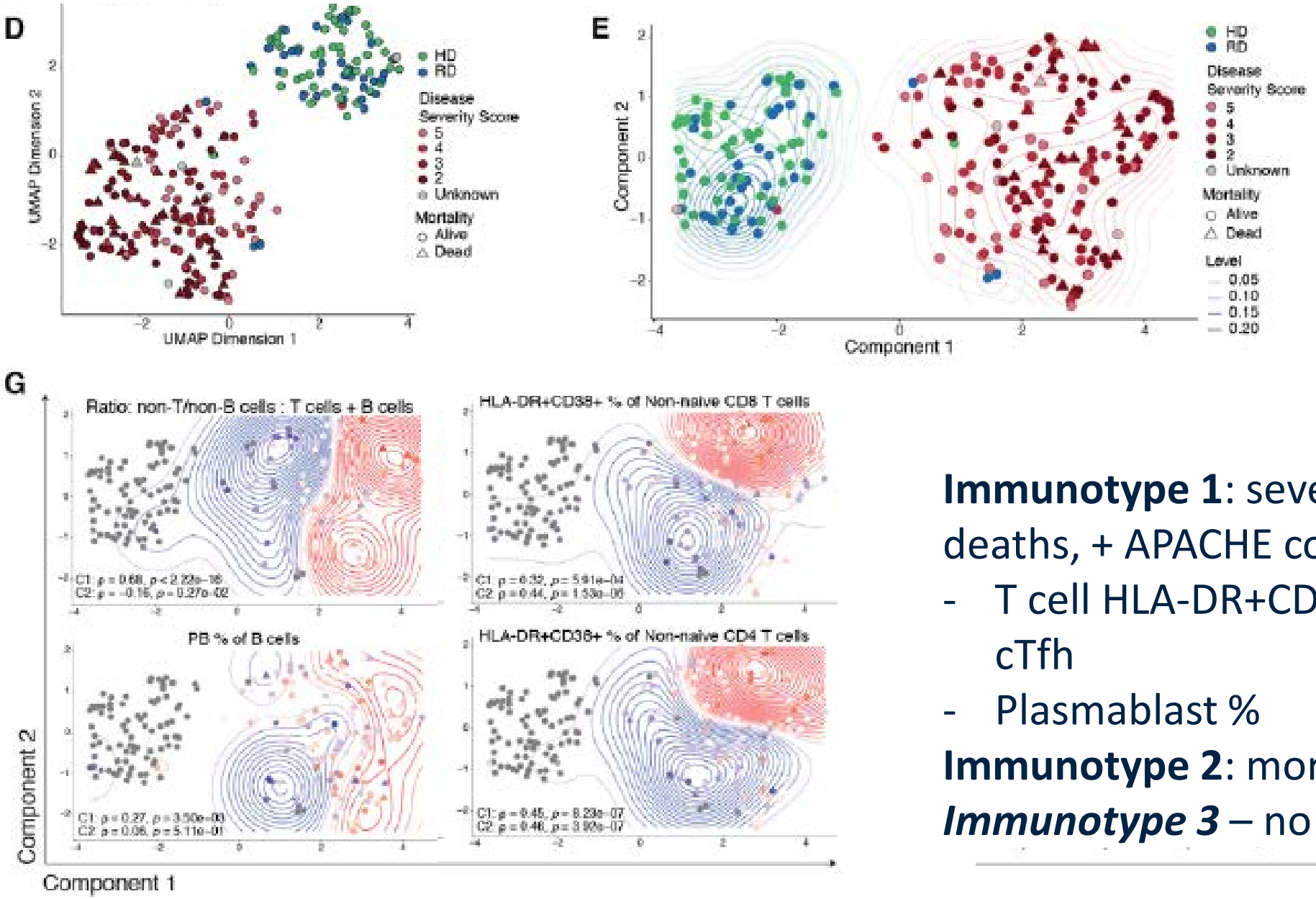


First 125 COVID Inpatients

High dimensional flow + clinical data

Data reduce immune features into 2-D components, “immunotypes”

Mathew et al *Science* 2020



Immunotype 1: severe disease, majority of deaths, + APACHE correlation, IL6, CRP

- T cell HLA-DR+CD38+, Ki67+PD1+, low cTfh
- Plasmablast %

Immunotype 2: more balanced, cTfh cells

Immunotype 3 – no B or T activation

Mathew et al *Science* 2020

Towards an Immune Health Readout in the context of COVID-19

- Require external replication and validation of immunotypes
  - Qualification process for cytometric features
  - *Learning the immune profile when things go well – regulated response*
- Integrate with gene expression, secreted protein/metabolite analysis
- Test immunotype response to different therapies

Could we apply this strategy to all forms of sepsis?

- Partner with advanced pathogen detection techniques
- Define pathogen-specific favorable and unfavorable patterns
  - Integrative analysis: EMR, routine labs, gene expression, secreted proteins, inflammatory cell populations
- Iterate within clinical trials
  - Expanded cost and complexity, but major payoff
- Public buy-in – PR campaign to encourage participation