

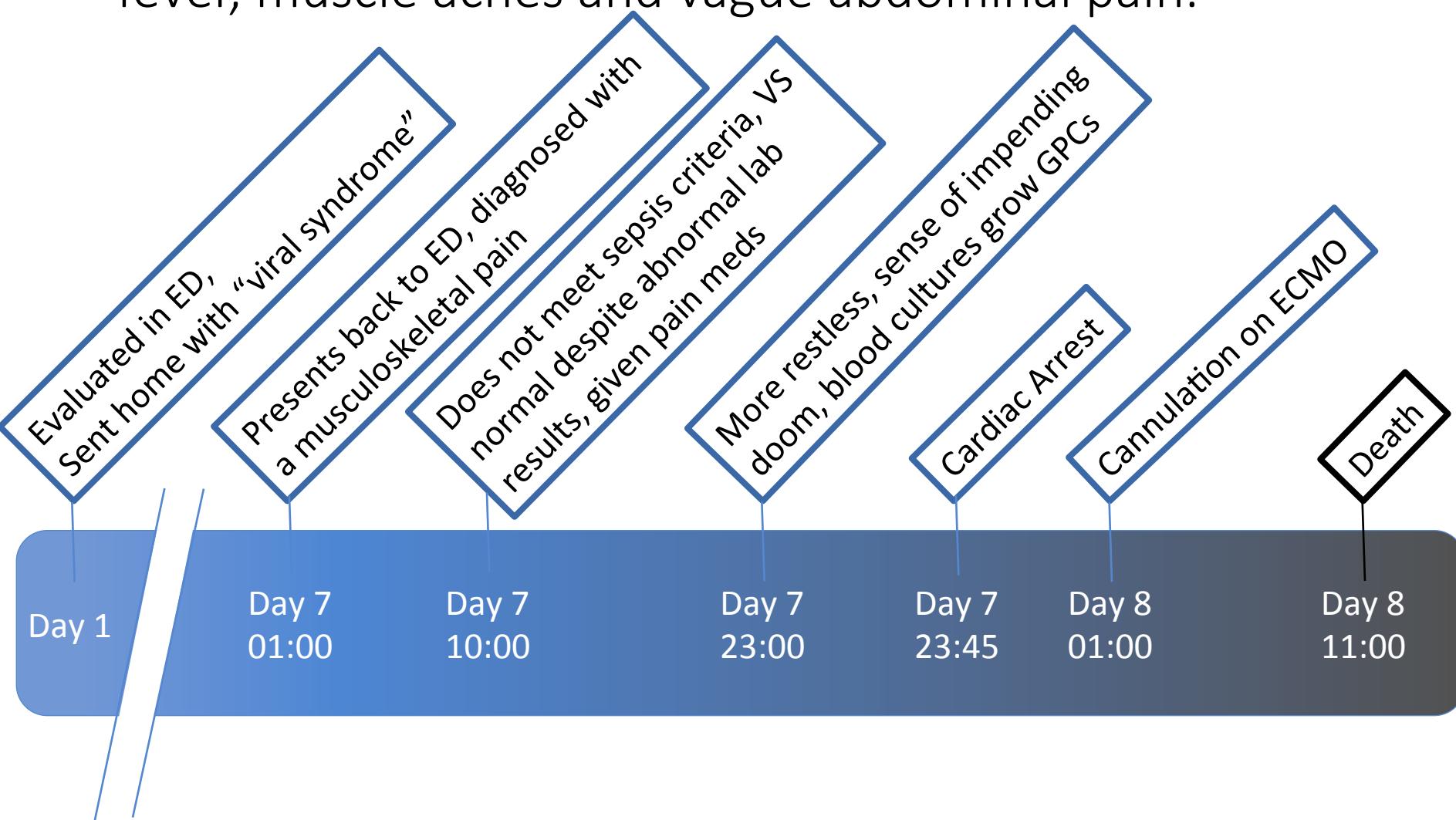
Heterogeneity in Critical Illness: Challenges and Opportunities

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International Summer Institute on Network Physiology

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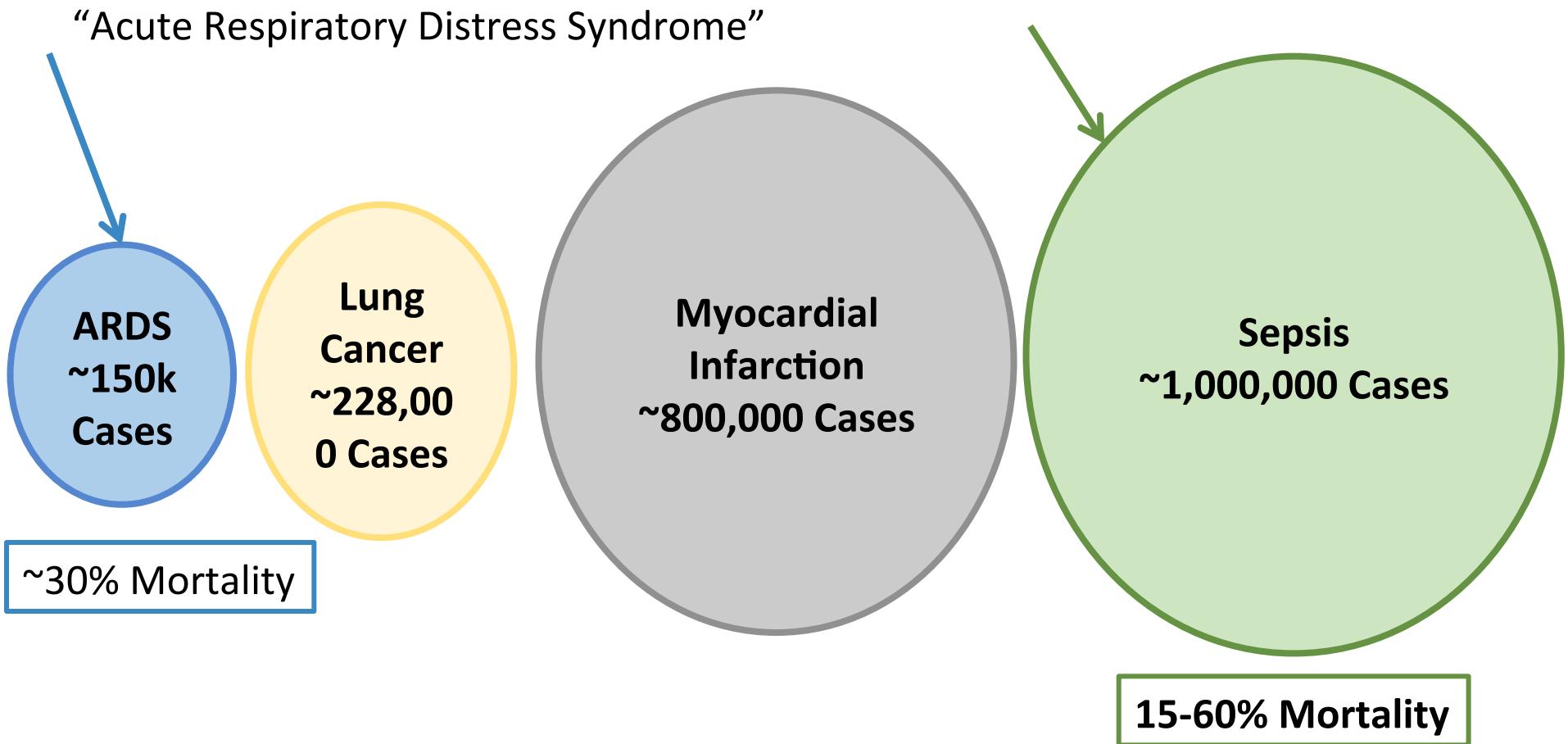
47 year old healthy man presents with subjective fever, muscle aches and vague abdominal pain.



Outline

- Context and Definitions
- Syndromes versus Diseases
- Impact of Heterogeneity
- Network Physiology Opportunities

Burden of Critical Illness – Incidence (US)



Significant morbidity, mortality, and cost associated with these conditions

Acute Respiratory Distress Syndrome

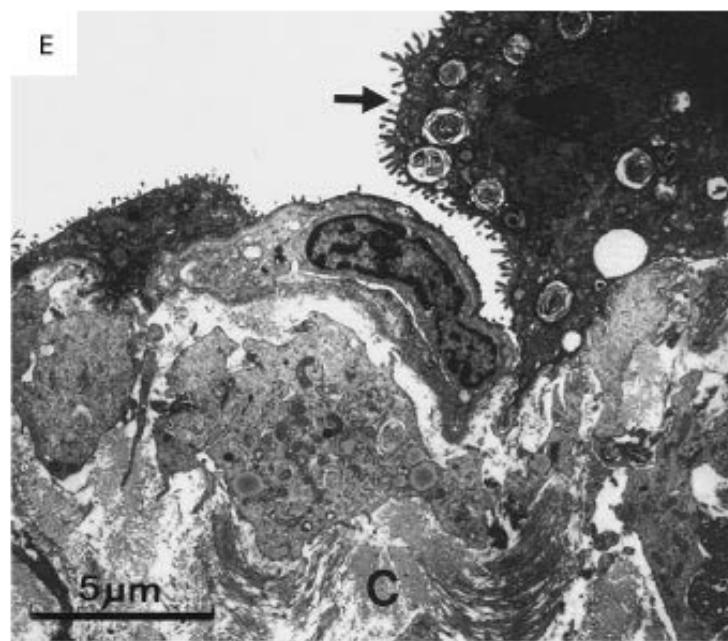
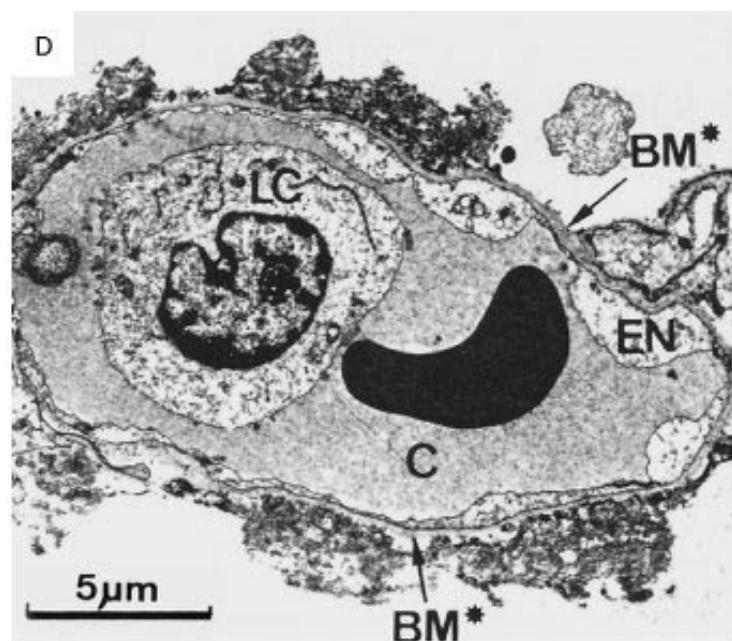
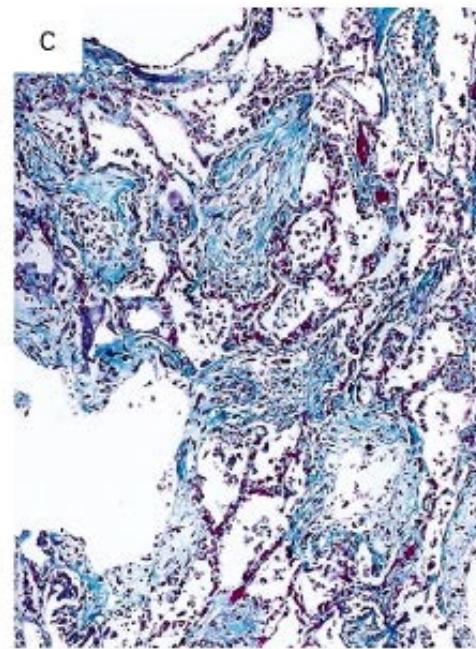
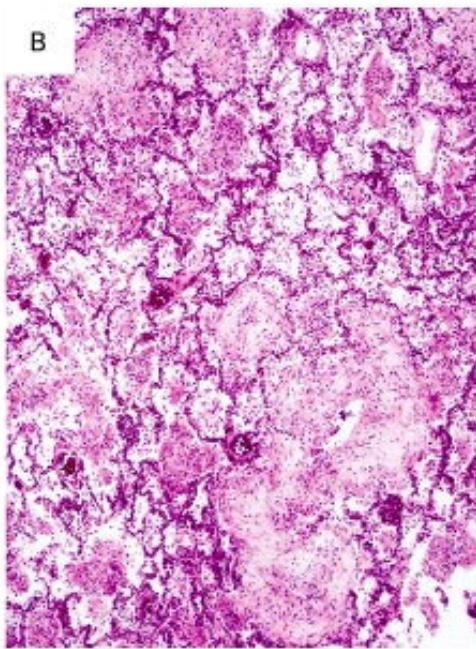
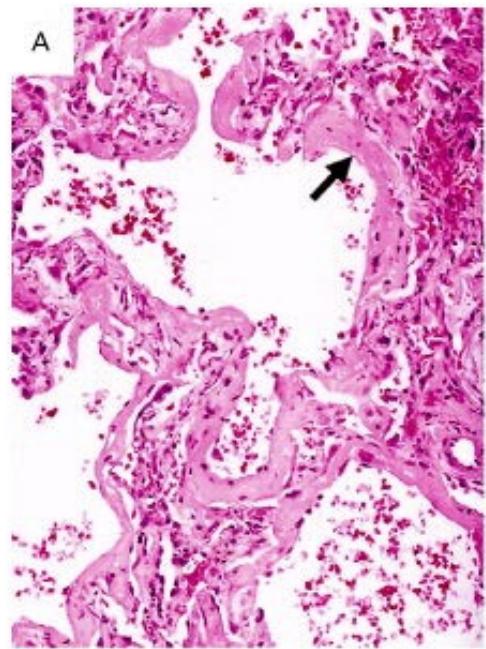
The Berlin Definition

The ARDS Definition Task Force*

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

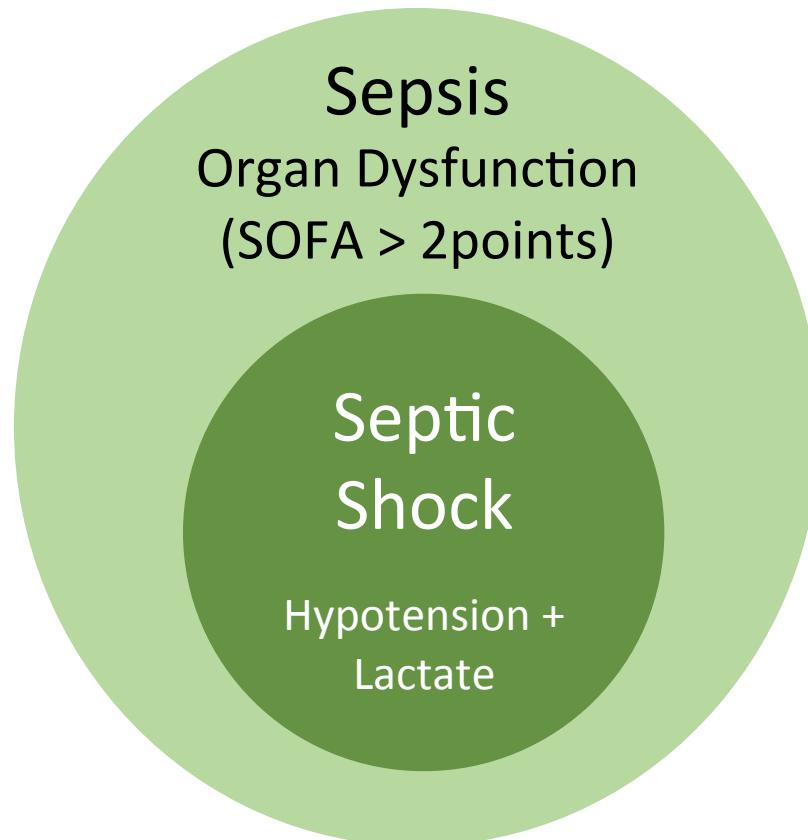
Acute Respiratory Distress Syndrome	
Acute	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Abn'l Imaging	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Not Something Else	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Low Oxygen Levels	$200 \text{ mm Hg} < \text{Pao}_2/\text{FIO}_2 \leq 300 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ cm H}_2\text{O}^c$ $100 \text{ mm Hg} < \text{Pao}_2/\text{FIO}_2 \leq 200 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm H}_2\text{O}$ $\text{Pao}_2/\text{FIO}_2 \leq 100 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm H}_2\text{O}$





Definition of Sepsis

“Life-threatening organ dysfunction caused by a dysregulated host response to infection”



Central Nervous System

Acute change or worsening mental status

Respiratory

Tachypnea
Increased need for O₂

Renal

Decrease urine output
Rising creatinine

Metabolic

Elevated lactate

Cardiovascular

Hypotension

Liver

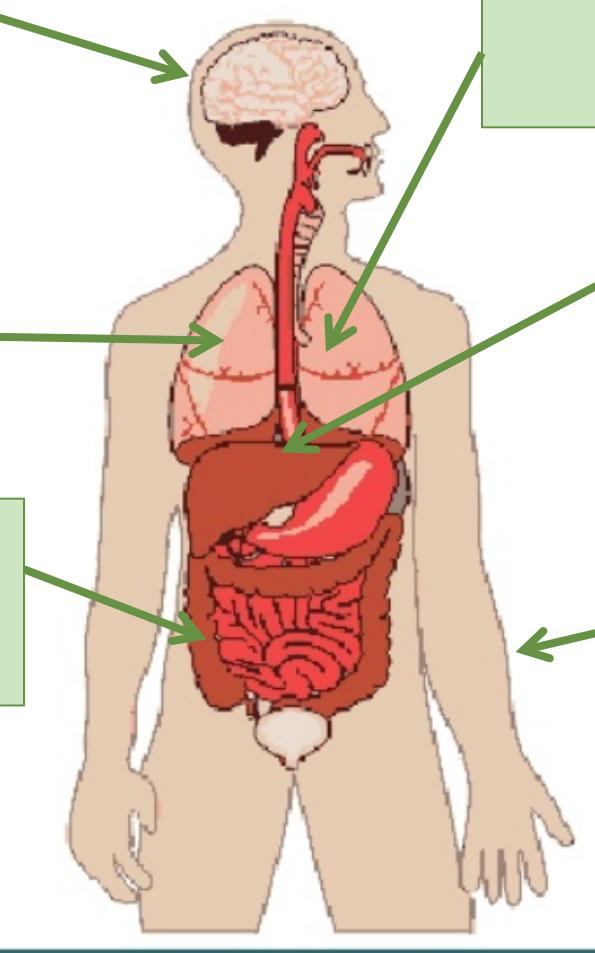
Elevated bilirubin, AST, ALT, Alk Phos

Circulatory

Poor capillary refill
Skin mottling

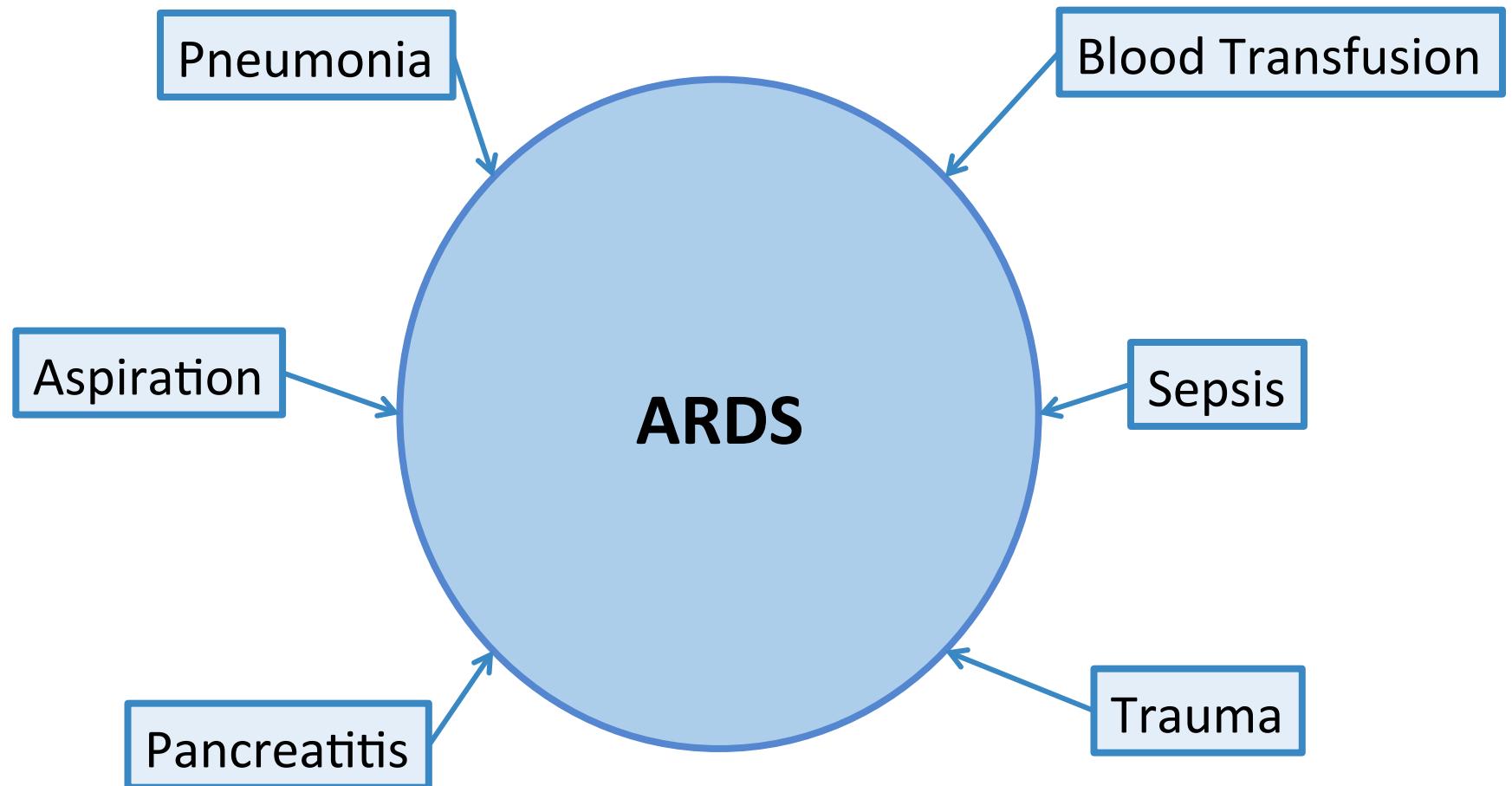
Hematologic

Thrombocytopenia
Coagulopathy (elevated INR, DIC)

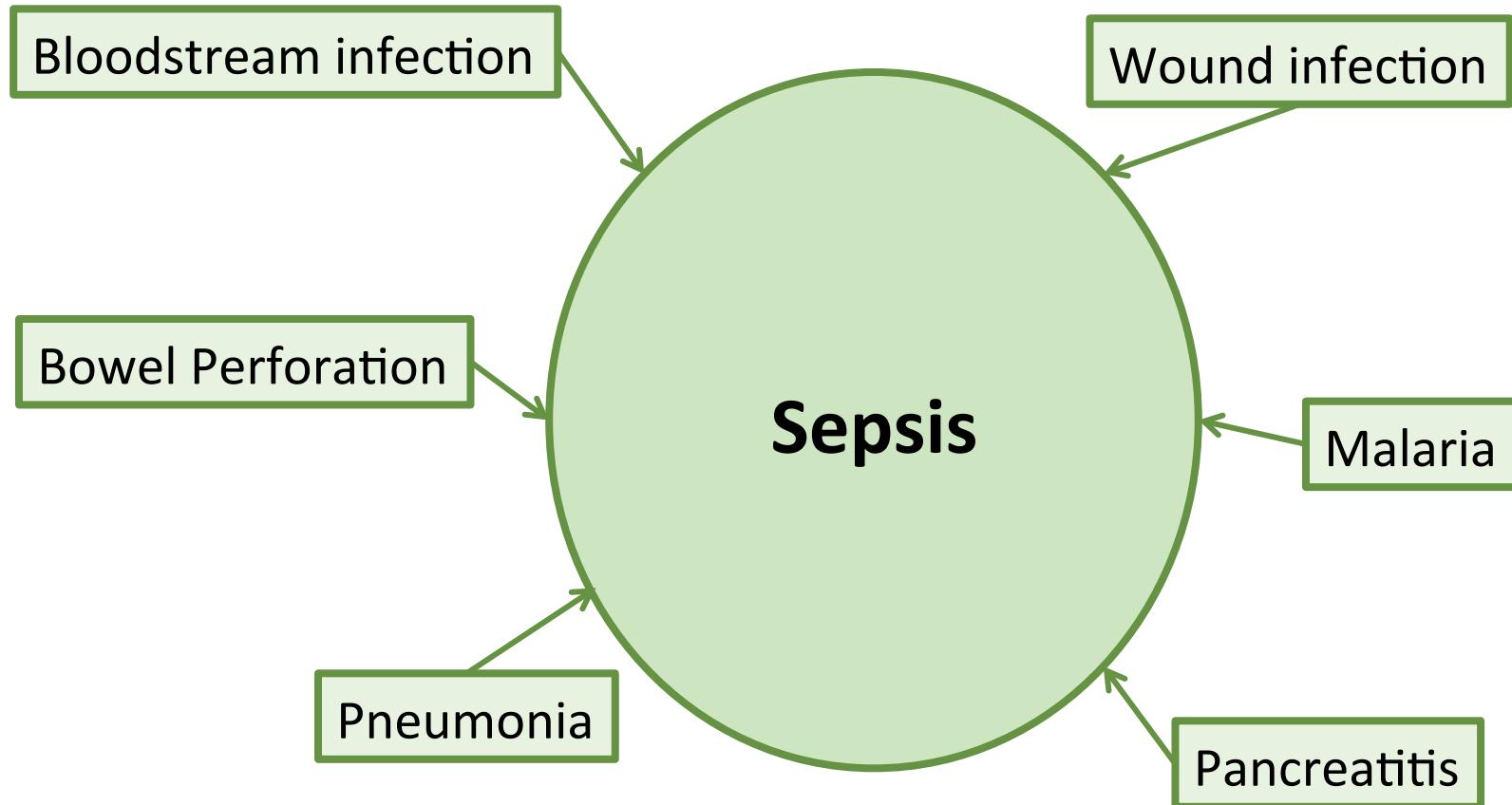


Overall Toxic Appearance

Critical Illness as Final Common Pathway?

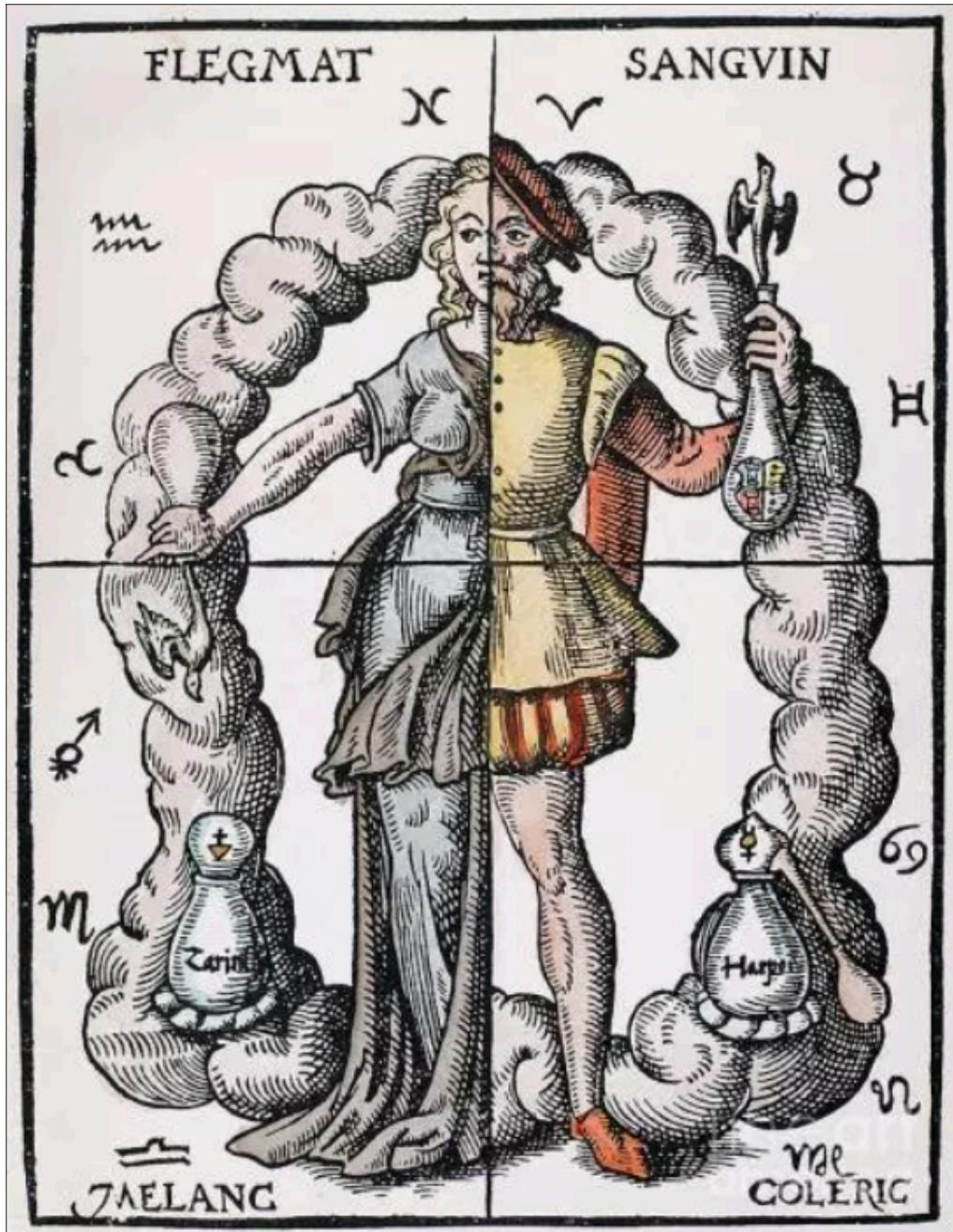


Critical Illness as Final Common Pathway?



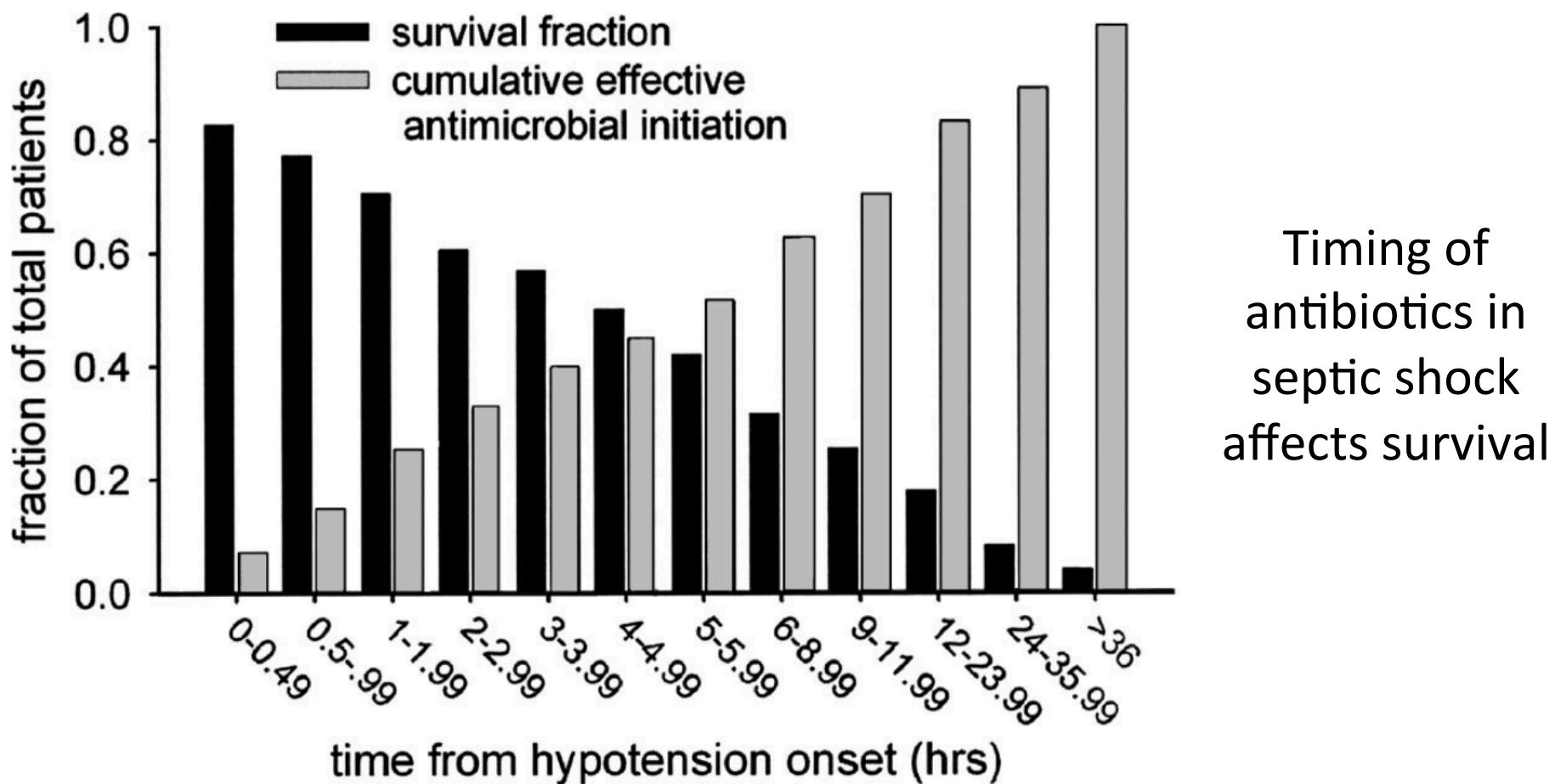
Sepsis and ARDS are Syndromes, not Diseases

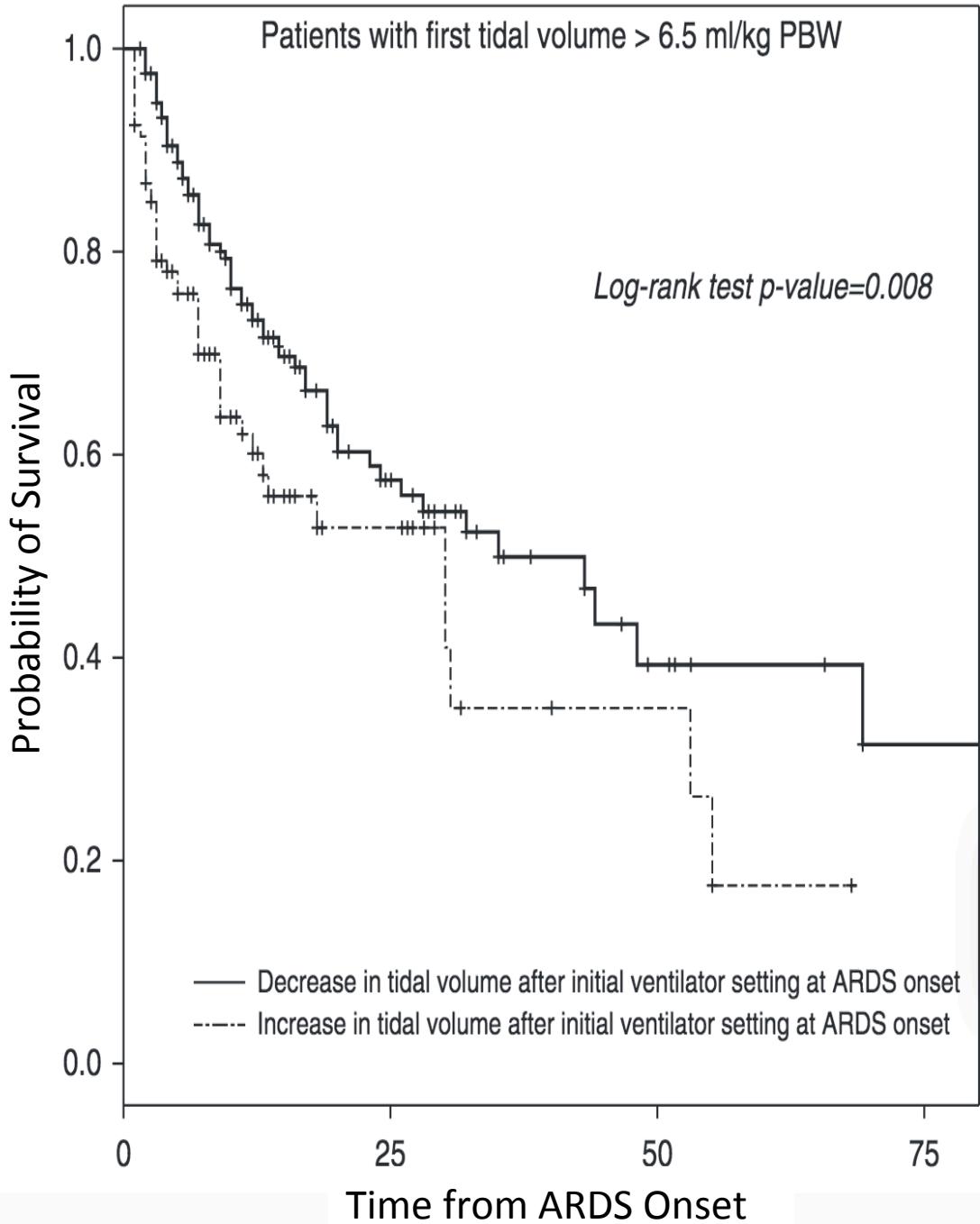
- No specific biomarker (e.g. a blood test) to identify either “sepsis” or ARDS
- Diagnosis can be made at the bedside, but may not be specific (or even that sensitive)
- Purposefully inclusive definitions based on easily accessible clinical information
- Developed from need for a case definition



Have we really
come that far?

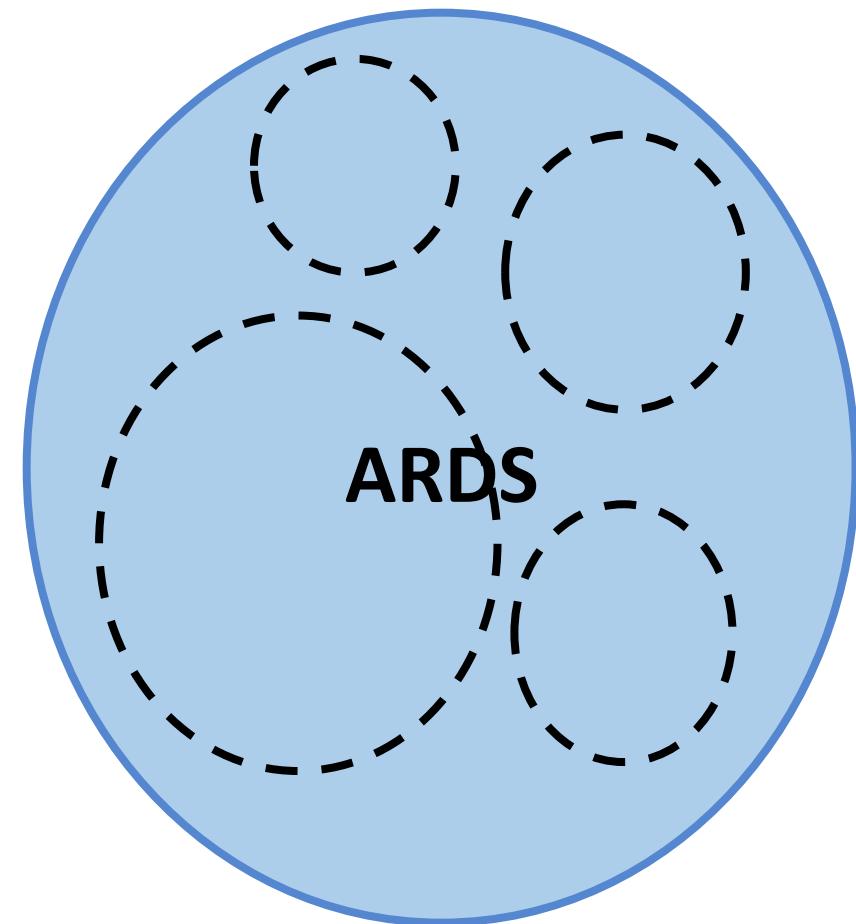
Early Identification → Early Intervention



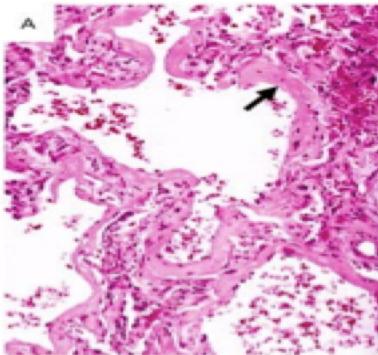


Ventilator management
at ARDS onset impacts
survival

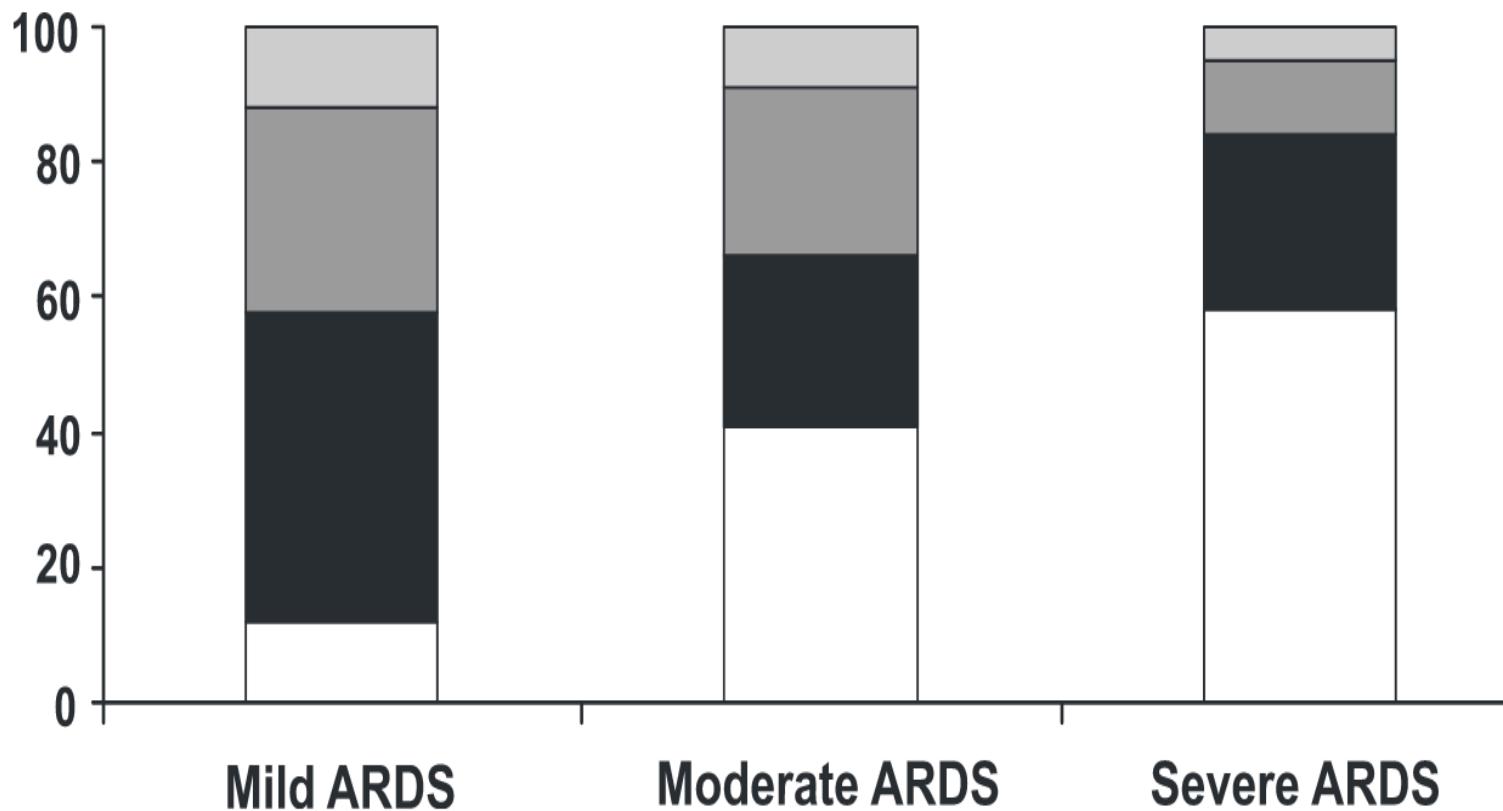
A Challenge of Syndromic Definitions: Heterogeneity!!



- **Subphenotypes:** groups that appear different in some way
- **Endotypes:** groups with distinct disease processes

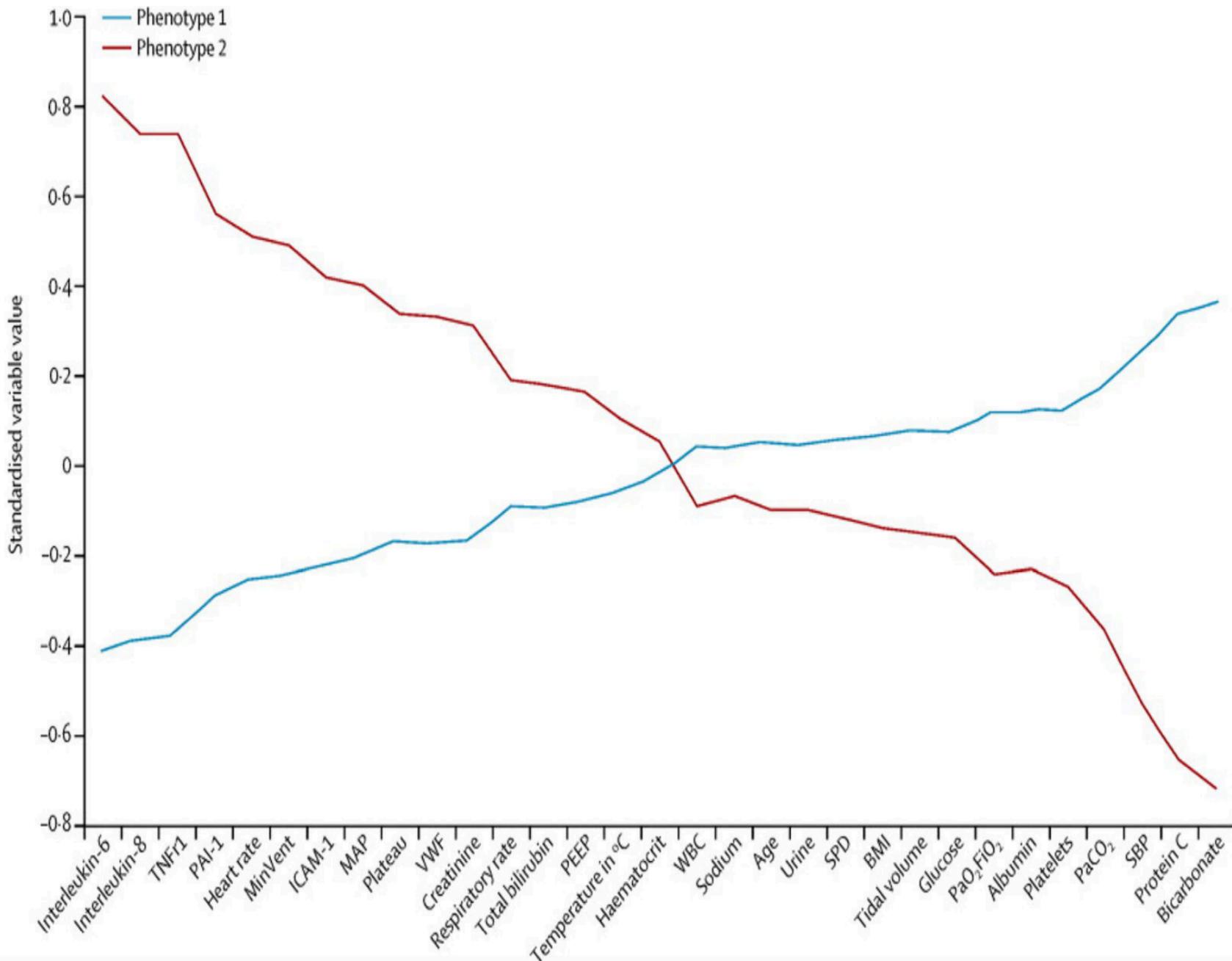


- No pulmonary lesion
- Other diagnostic
- Pneumonia
- Diffuse alveolar damage



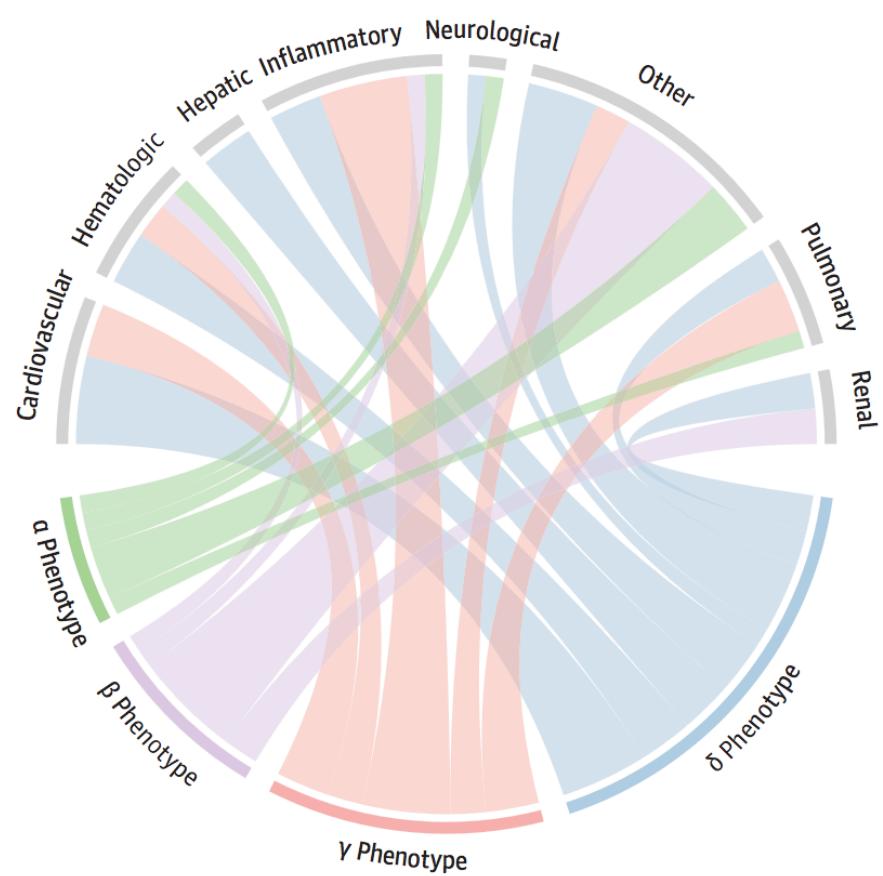
How to Identify Subgroups in ARDS

- What caused it?
 - Direct versus indirect injury
- What does it look like? (anatomic)
 - Focal versus diffuse
- What does it look like? (biomarker profile)
 - Latent class analysis

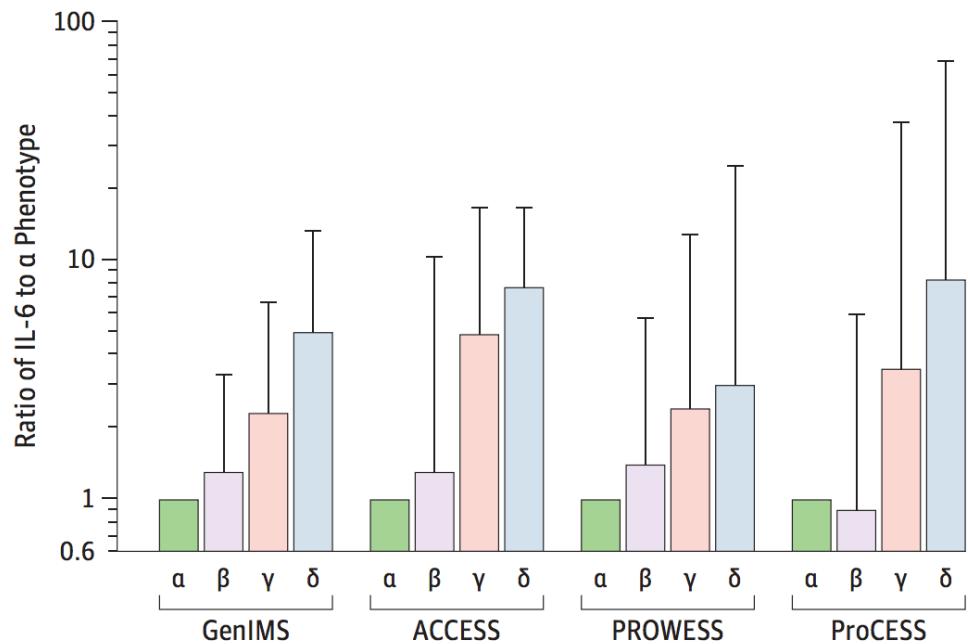


Sepsis Phenotypes

A All phenotypes combined

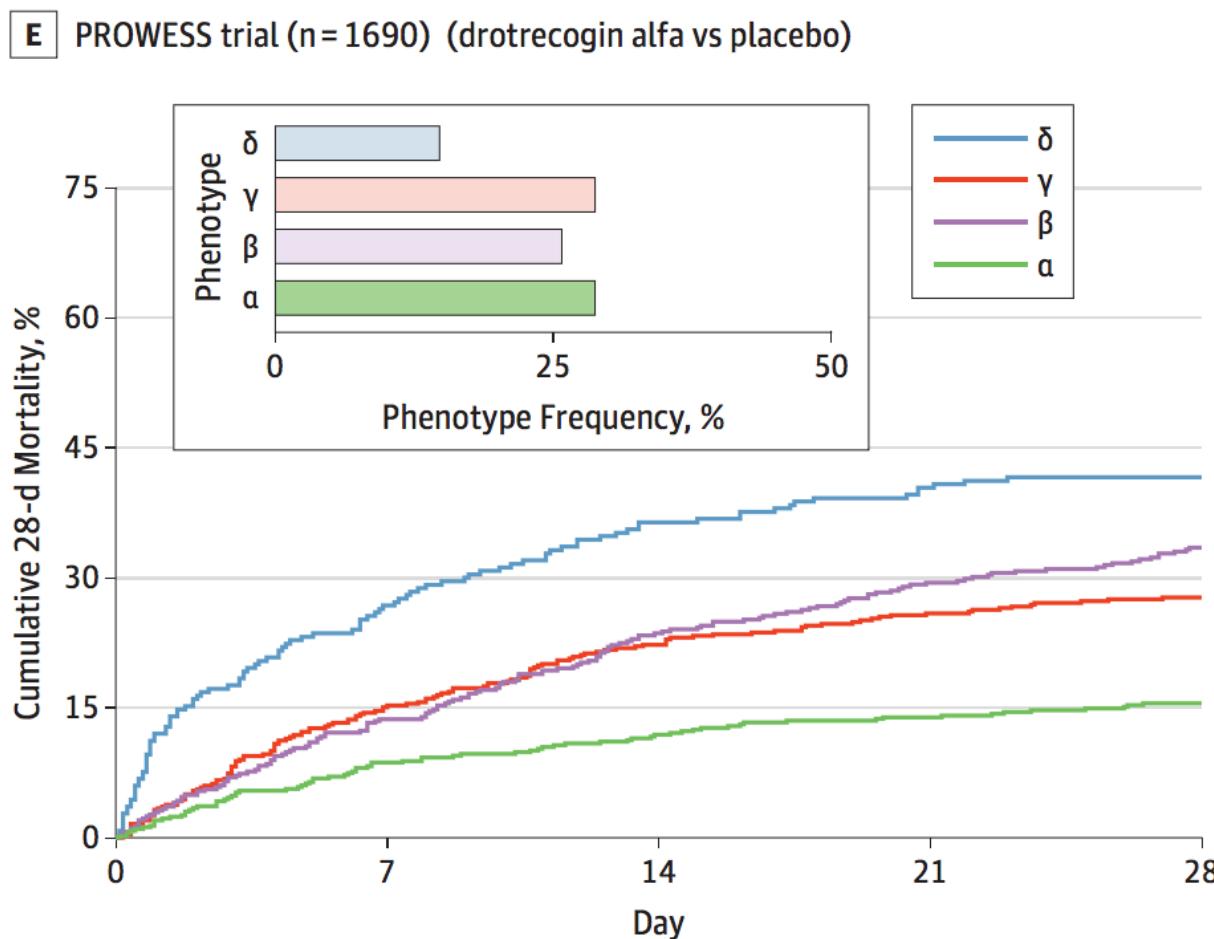


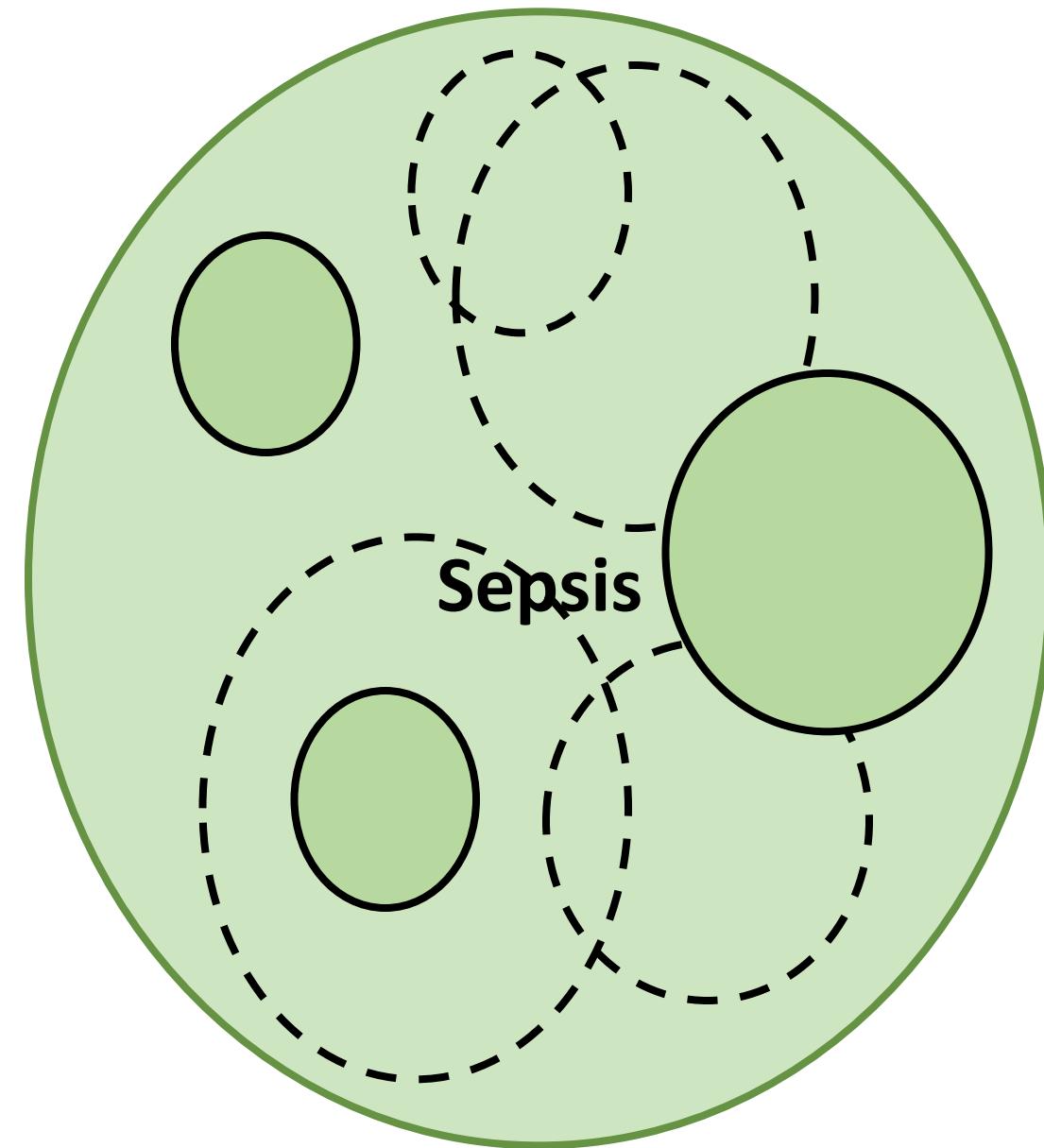
A Ratio of IL-6 to a phenotype



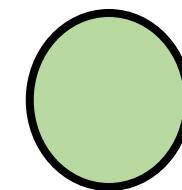
How do we know our subgroups are real?

- Do they behave differently? Prognosis or Therapeutic Response

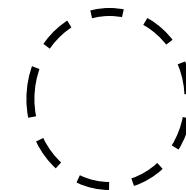


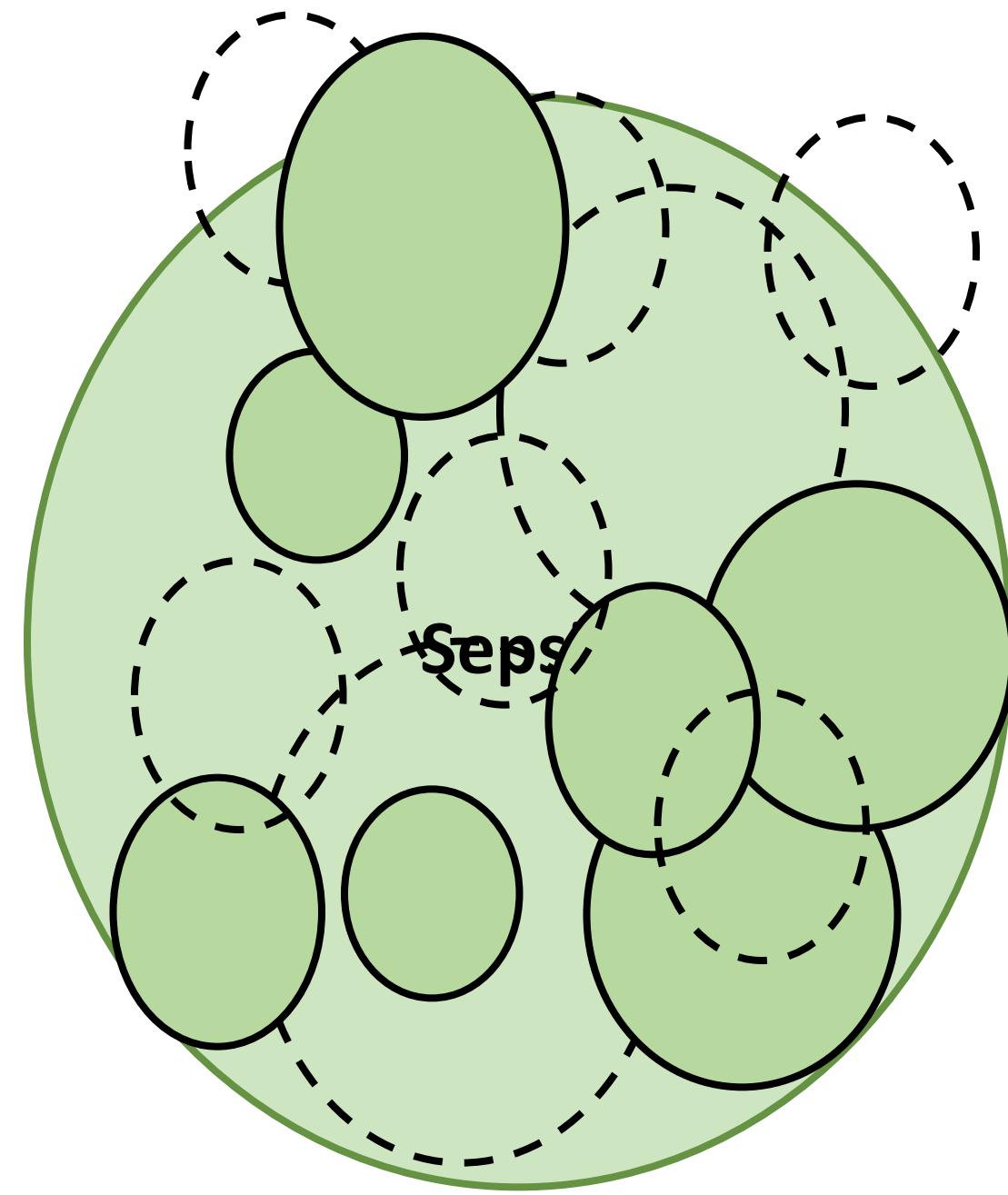


Some subgroups are identifiable



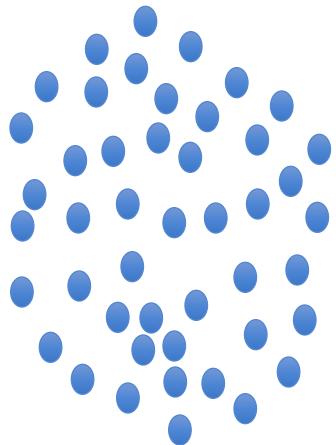
Some subgroups are
not identifiable



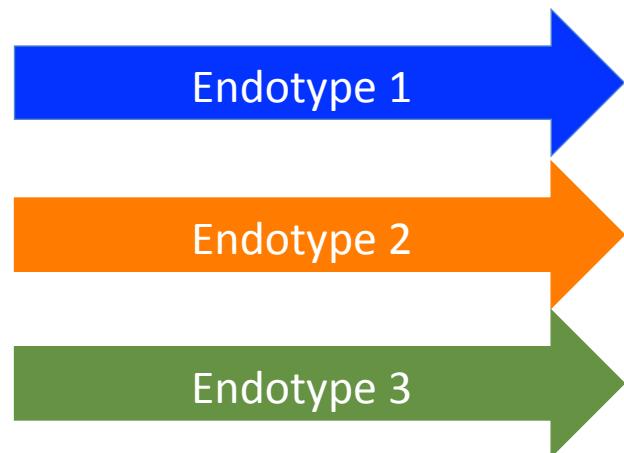
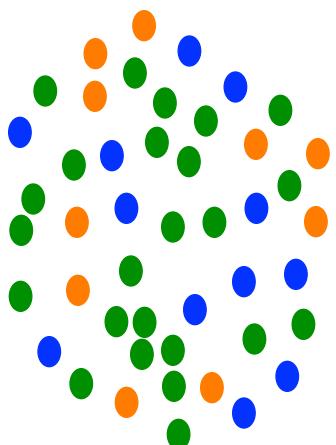


*And it's probably even
worse than we
know....*

Why Does Heterogeneity Matter?



Variable outcomes
and response to
therapy

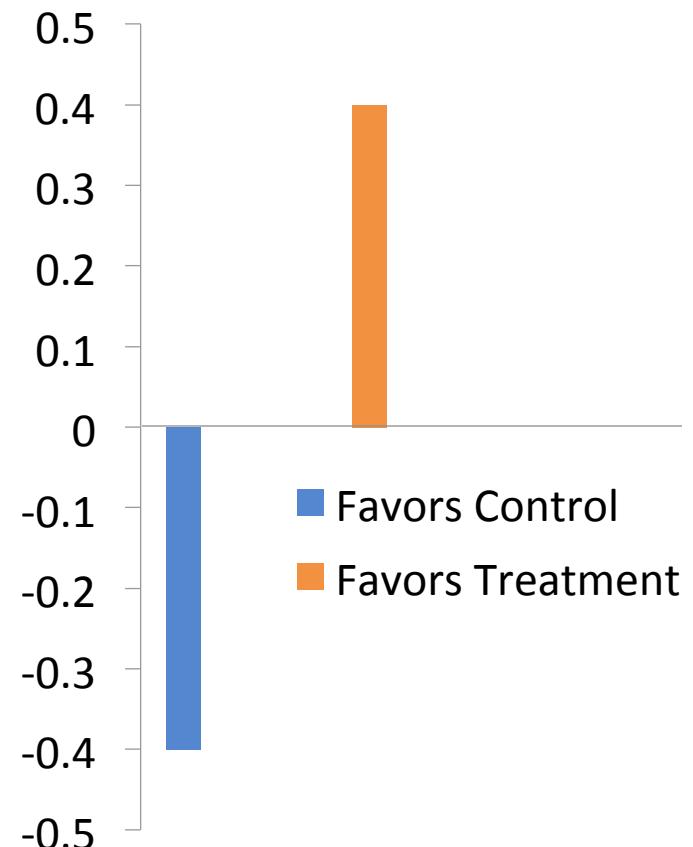
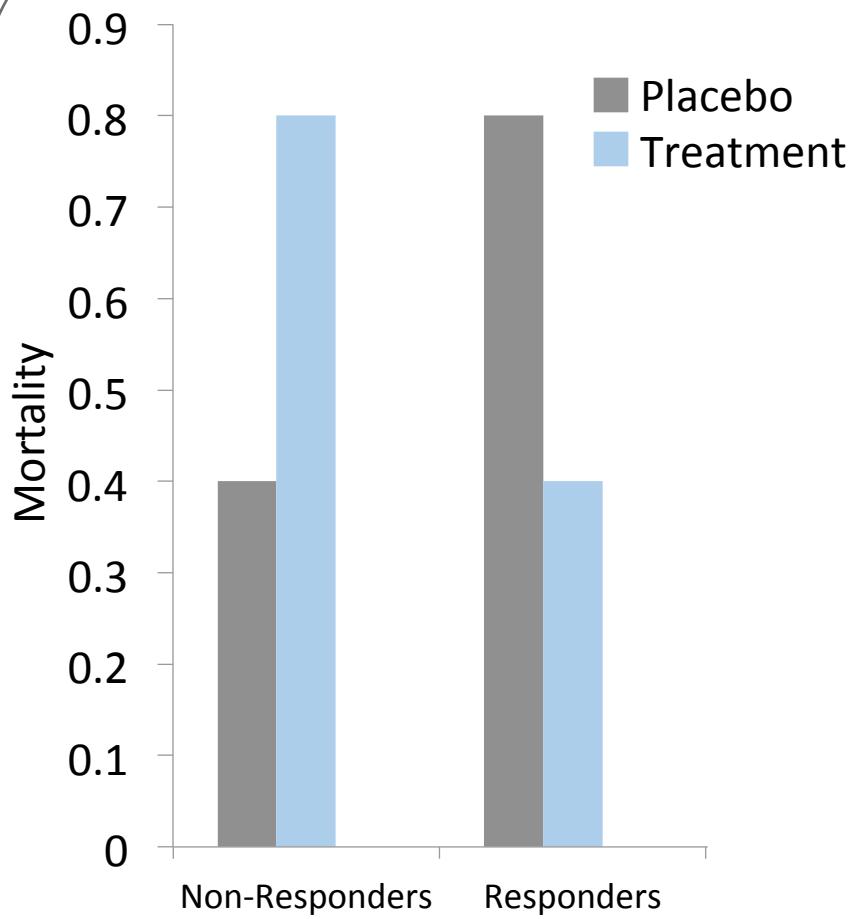


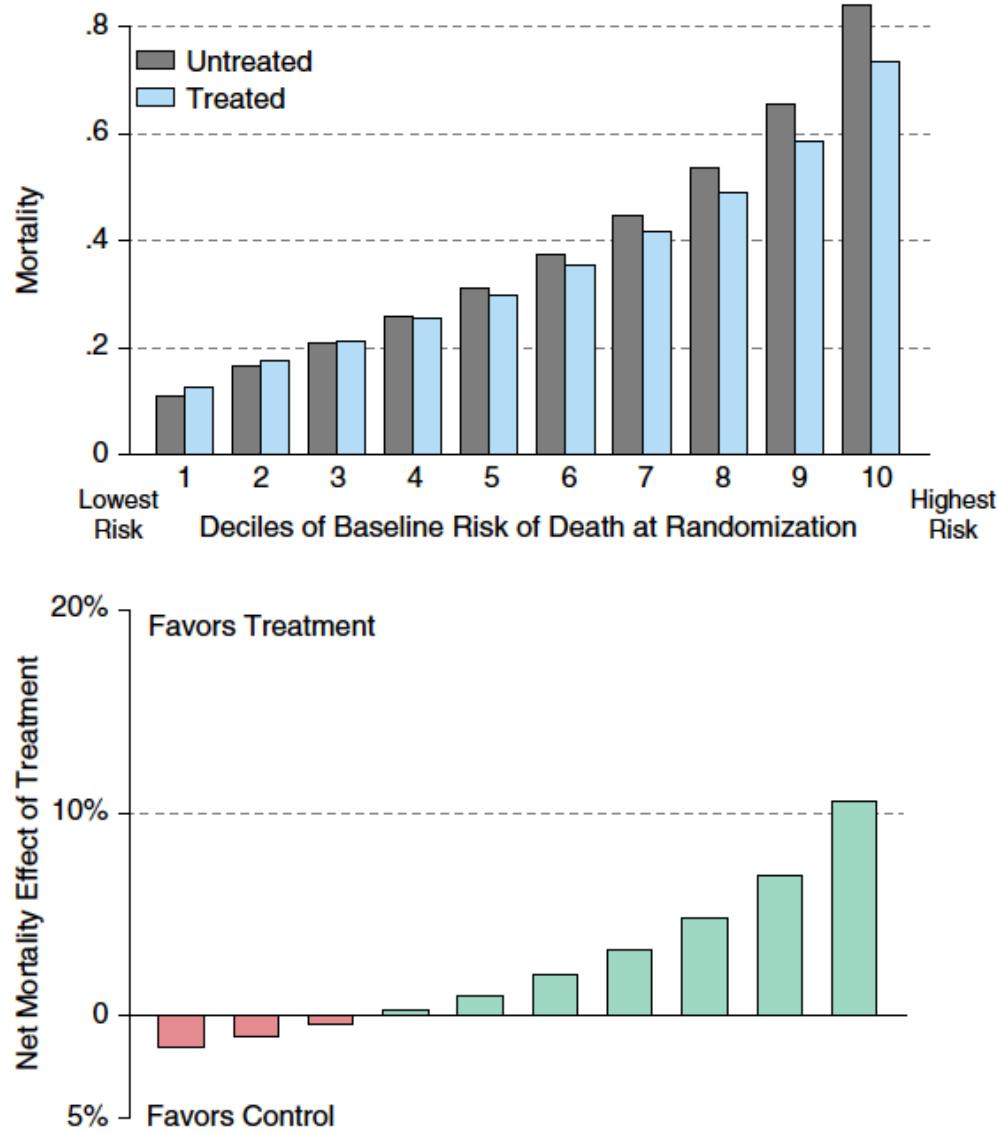
Accurate Prognosis
&
Personalized and
Effective Therapy

Nitric Oxide
Surfactant/perflourocarbon
Corticosteroids
Prostaglandin E1
Lysophyline
Ibuprofen
Procysteine
Anticytokine/antiendotoxin
Ketorconazole
Streptokinase
Neutrophil elastase inhibitor
sPLA2 inhibitor
rhAPC
Albuterol/salmeterol
Furosemide
Cisatracurium
GM-CSF
Beta Agonists
Statins

Alkaline Phosphatase
Granulocyte Colony-stimulating Factor
Anti-tumor Necrosis Factor Ab
Recombinant human tissue pathway (-)
Ibuprofen
N-acetylcysteine
Nitric Oxide Inhibitors
Growth Hormone
Bradykinin Antagonists
Levosimendan
Hypothermia
Hyperoxia
Hypertonic saline
Hemoperfusion through Polymyxin B
Interleukin 1 Receptor Antagonist
TLR-4 Antagonist
Anti-Endotoxin Antibody
Activated Protein C
Recombinant Thrombomodulin

Why Heterogeneity Matters





Heterogeneity of Treatment Effect

Summary So Far...

Common and Highly Morbid Conditions

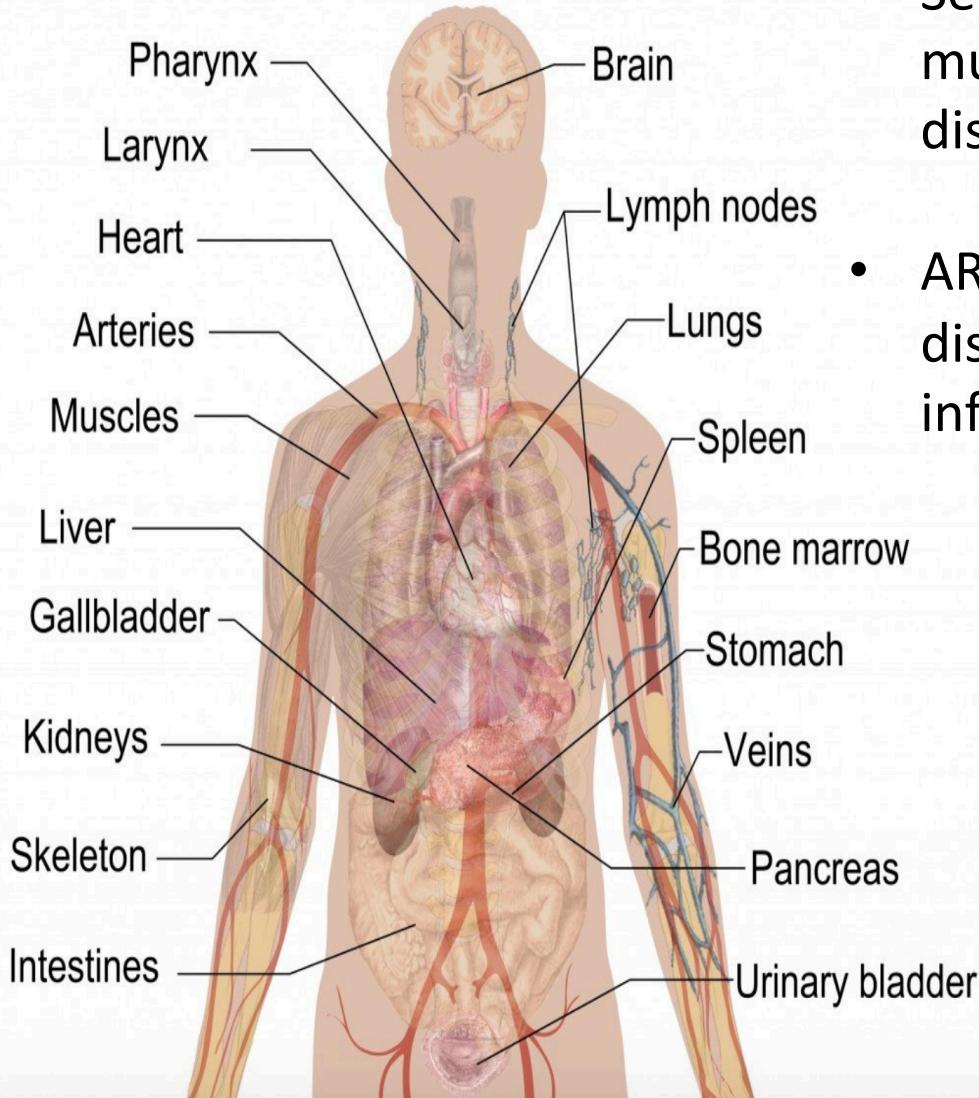
+ Importance of Early Recognition and Intervention

+ Heterogeneous Groups

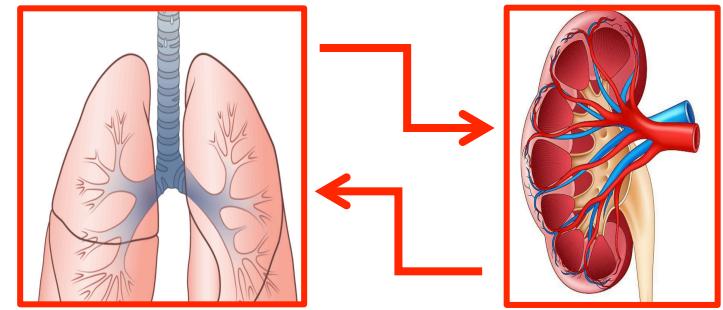
+ Need for More Targeted Trials and Therapies

= *Opportunity for Network Physiology??*

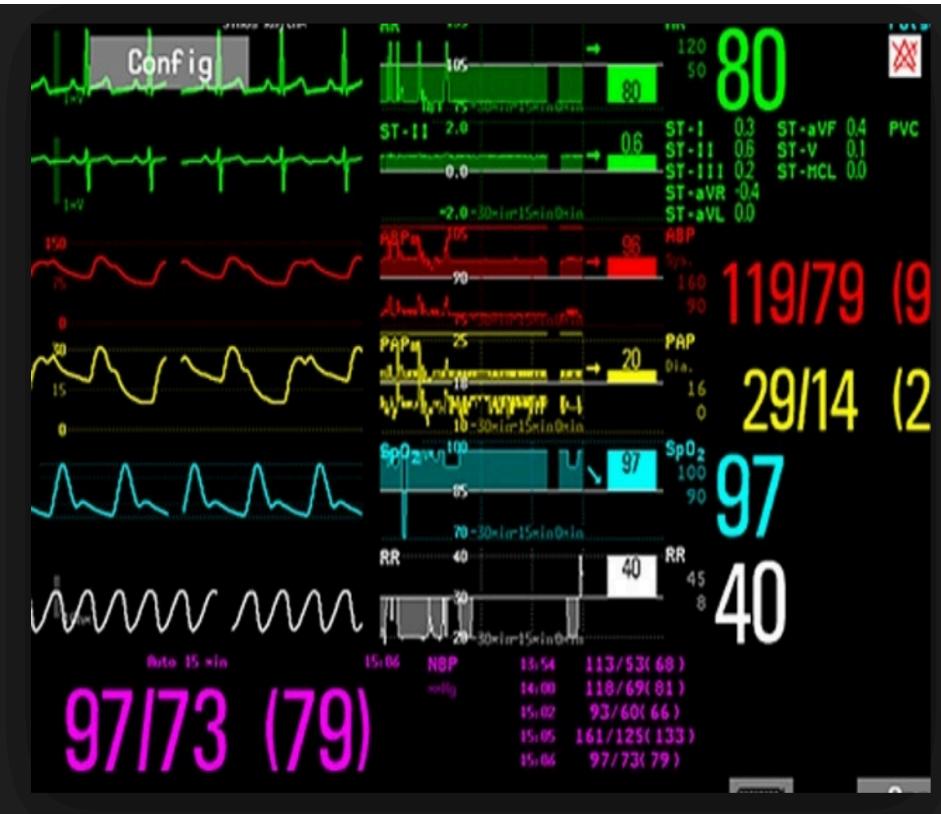
Critical Illness and Network Physiology: Multiorgan Failure



- Sepsis is defined by dysfunction of multiple organs and is a systems disease
- ARDS (although a “pulmonary” disease) is often part of a cycle of inflammation and organ failure



Critical Illness and Network Physiology: The Data



- Critical illness is a data rich condition...
- Standard of care* is continuous monitoring of multiple organ systems
- Electronic medical record and central storage of monitoring data

* In resource-rich settings



Critical Care and Network Physiology

Early (Predictive?) Identification



Identify and treat patients before they meet clinical criteria

Endotypes v Subphenotypes



Separate truly unique disease processes & common pathways

Personalized Therapy



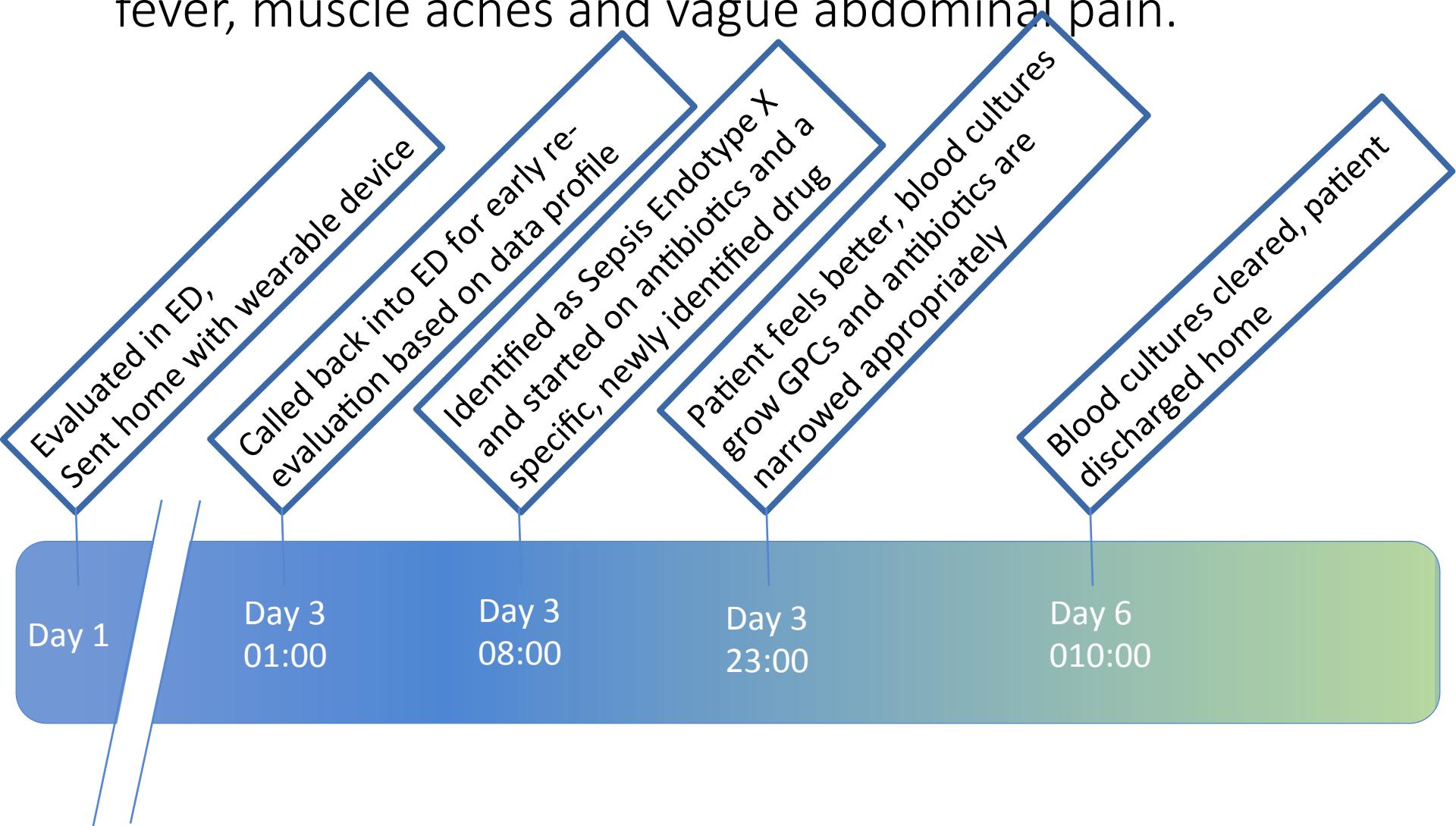
No missed opportunities & only expose patients to effective therapies

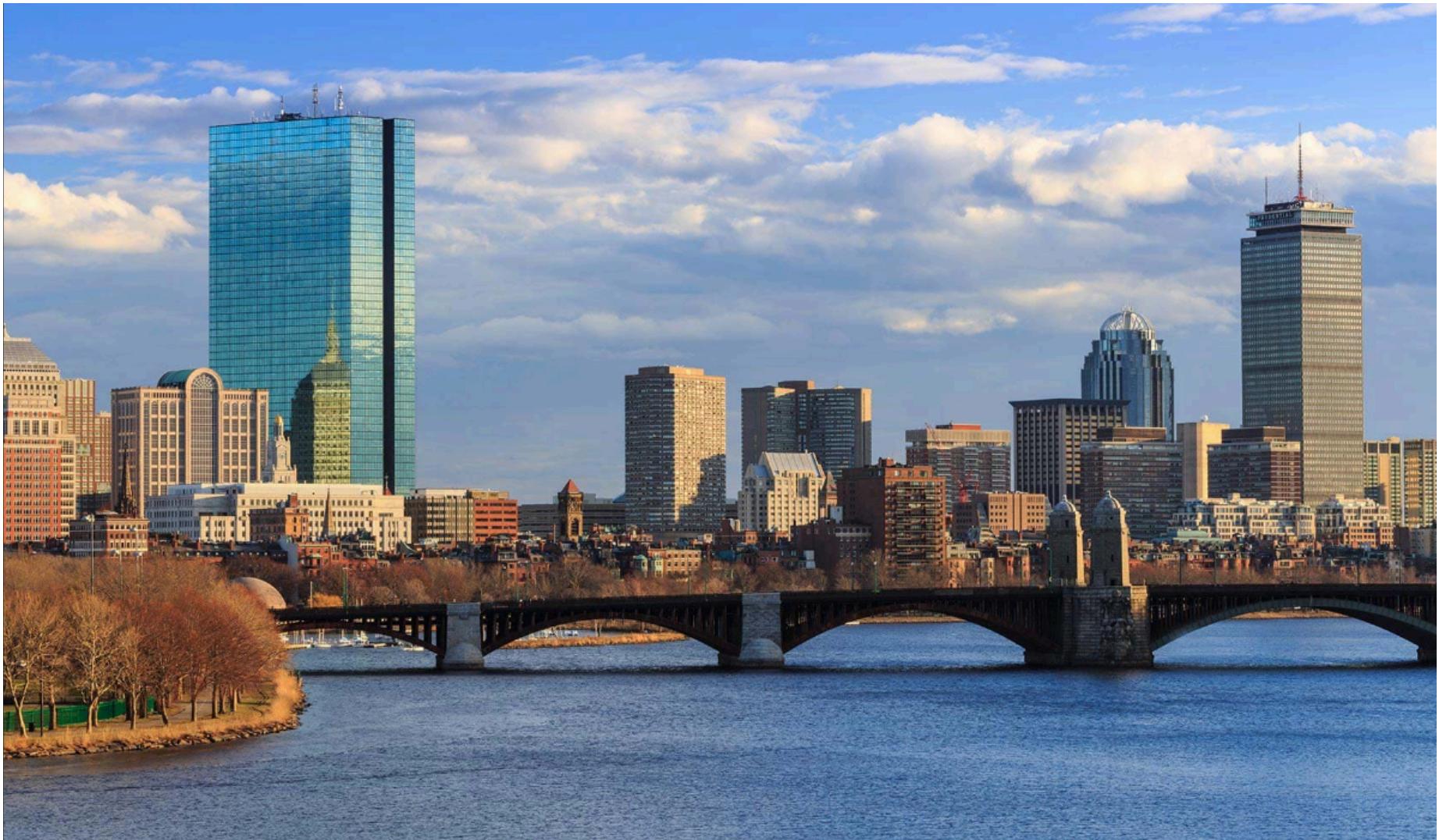
Predictive Enrichment



More Efficient and Adaptive Trial Design

47 year old healthy man presents with subjective fever, muscle aches and vague abdominal pain.





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