Heterogeneity in Critical Illness: Challenges and Opportunities

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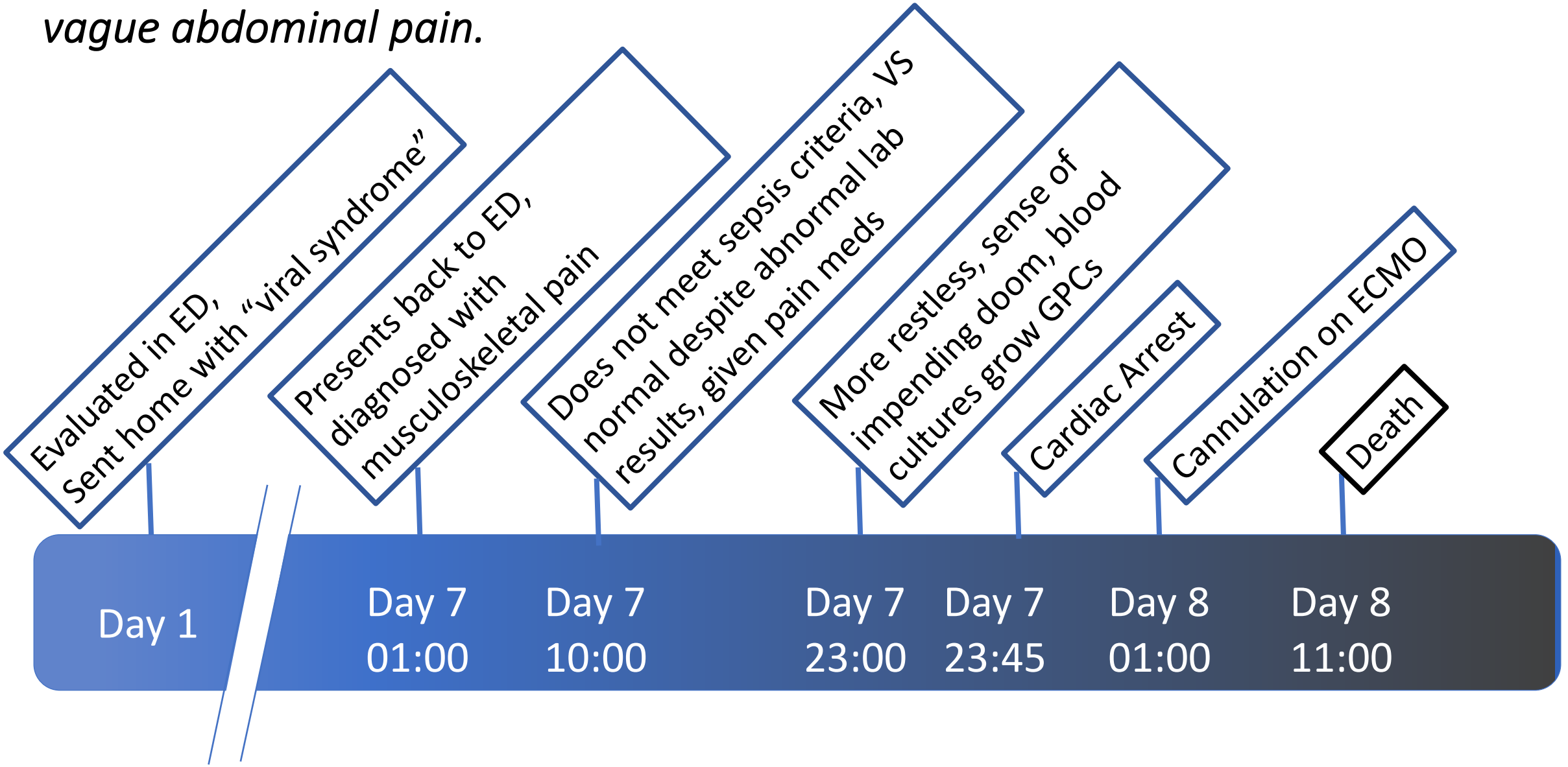
24 July, 2022

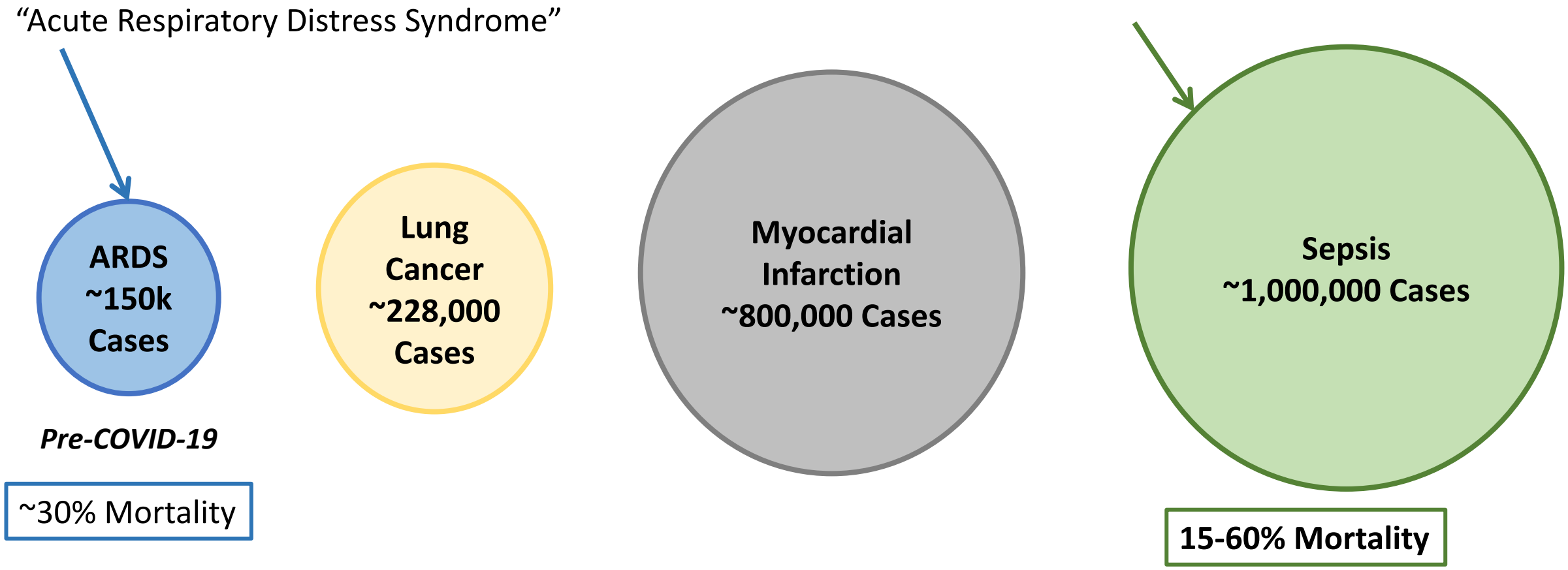
47 year old healthy man presents with subjective fever, muscle aches and vague abdominal pain.



Outline

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

Burden of Critical Illness – Annual Incidence (United States)



Significant morbidity, mortality, and health care burden associated with these conditions

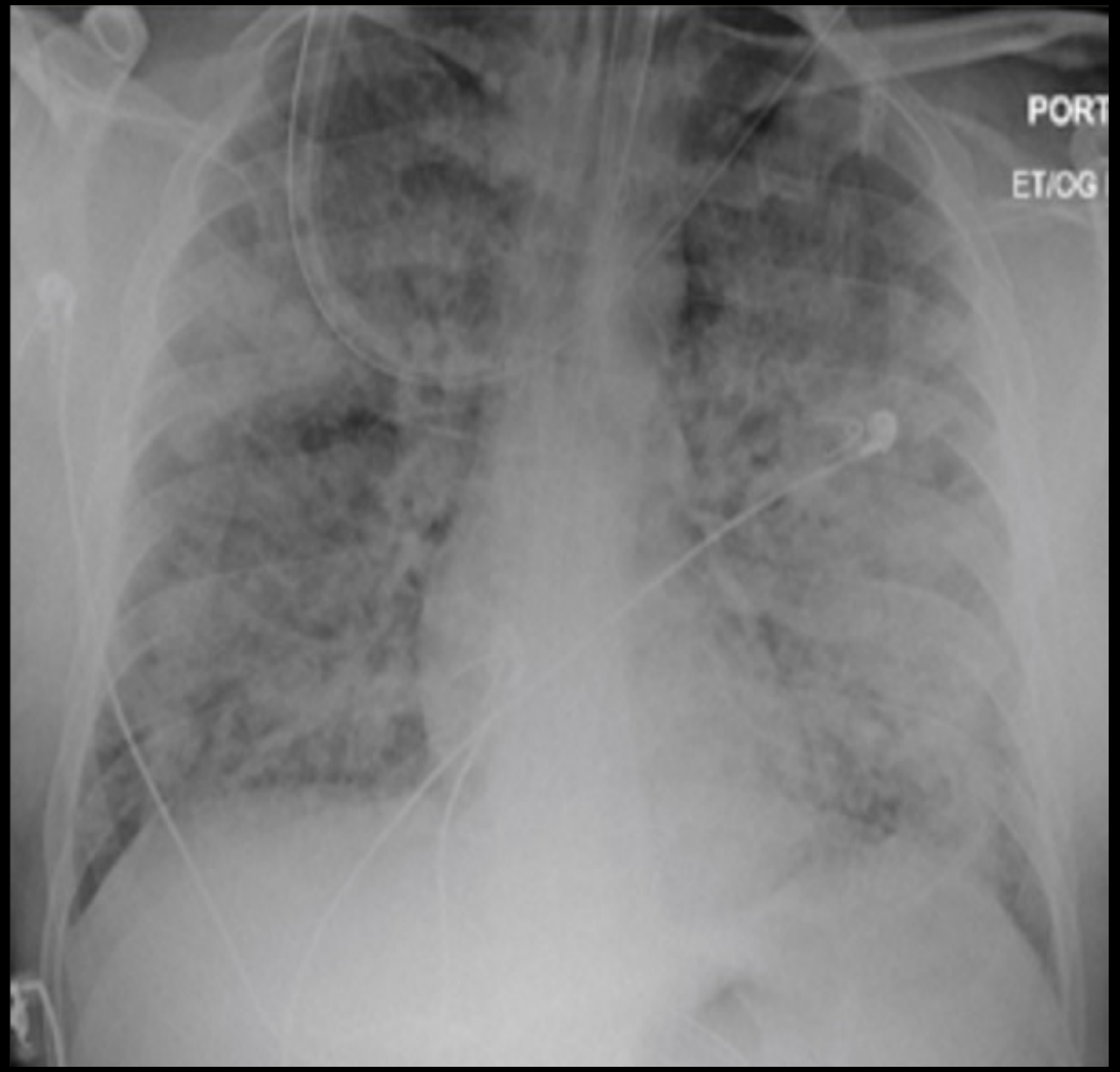
Acute Respiratory Distress Syndrome
The Berlin Definition

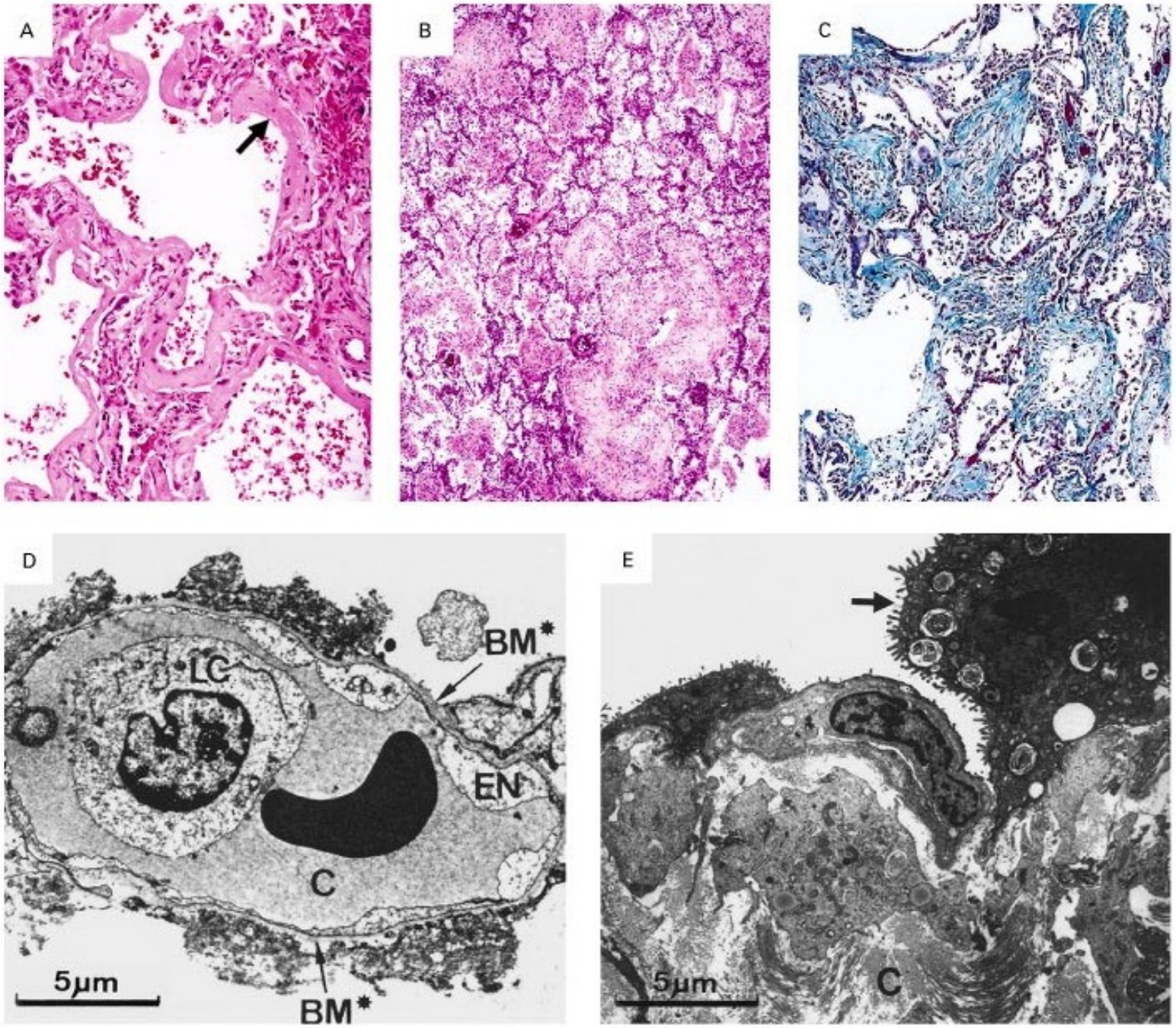
The ARDS Definition Task Force*

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 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
	100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
	Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

The ARDS Definition Task Force, JAMA 2012


PORT
ET/OG

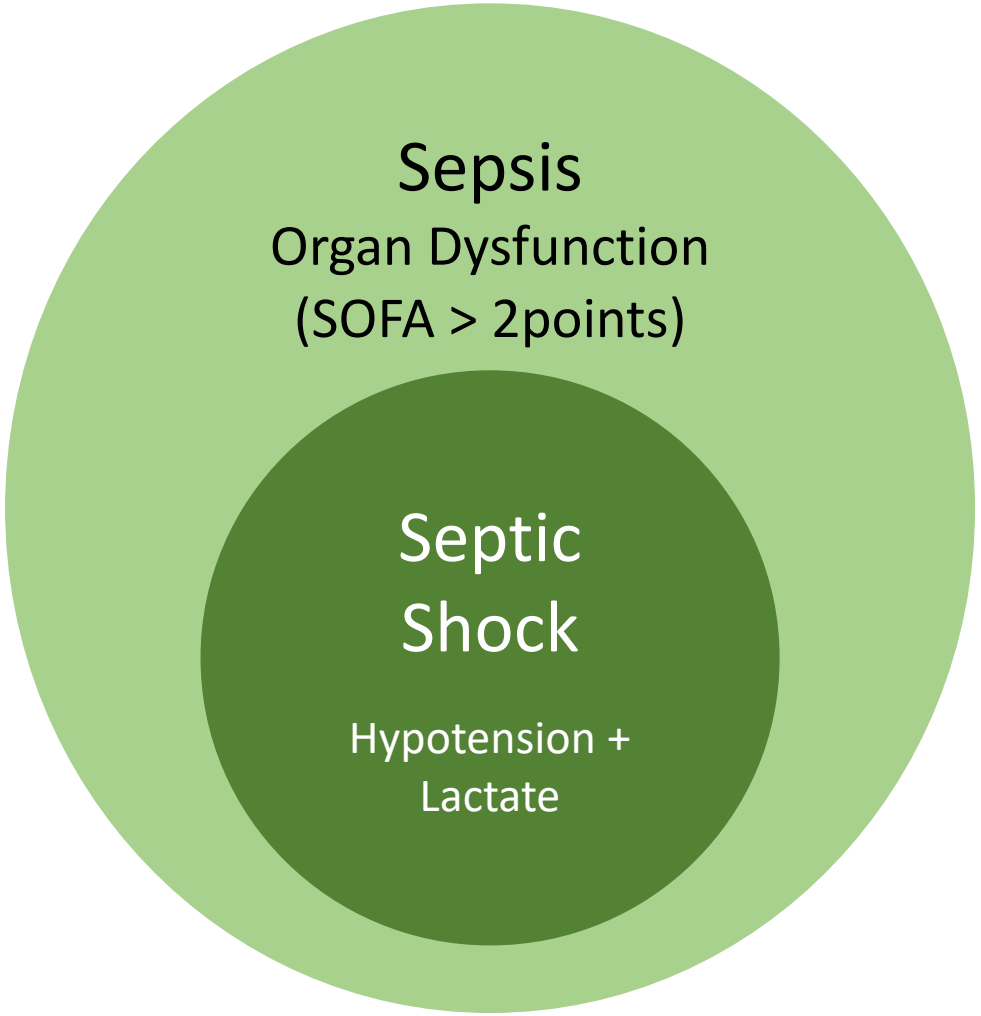


Pathologic features

- Loss of endothelial integrity
- Alveolar flooding and hyaline membrane formation
- Later fibrosis with maladaptive injury repair

Ware & Matthay. NEJM 2000

Definition of Sepsis



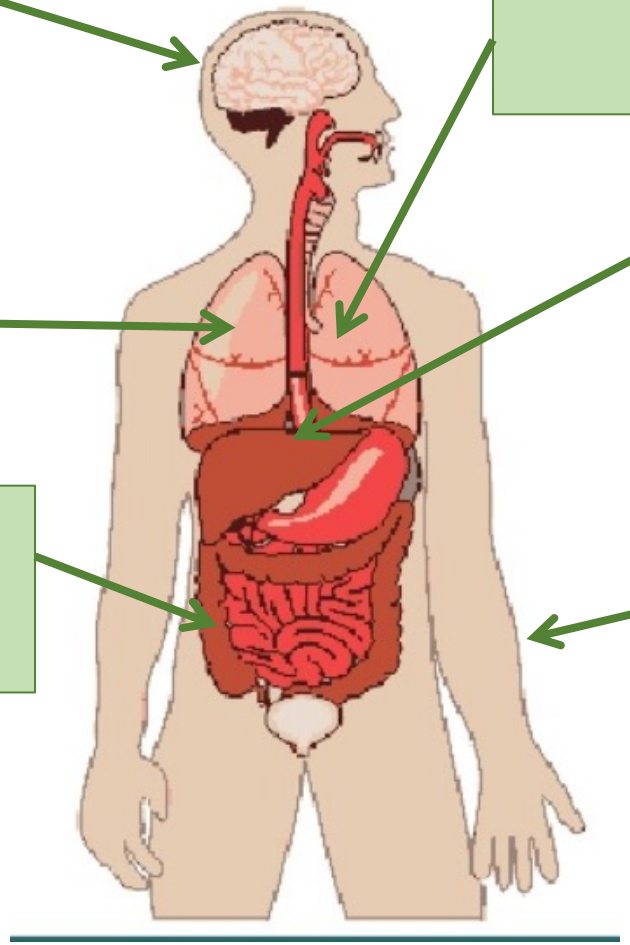
"Life-threatening organ dysfunction caused by a dysregulated host response to infection"

Cental Nervous System
Acute change or worsening mental status

Respiratory
Tachypnea
Increased need for O_2

Renal
Decrease urine output
Rising creatinine

Metabolic
Elevated lactate



Cardiovascular
Hypotension

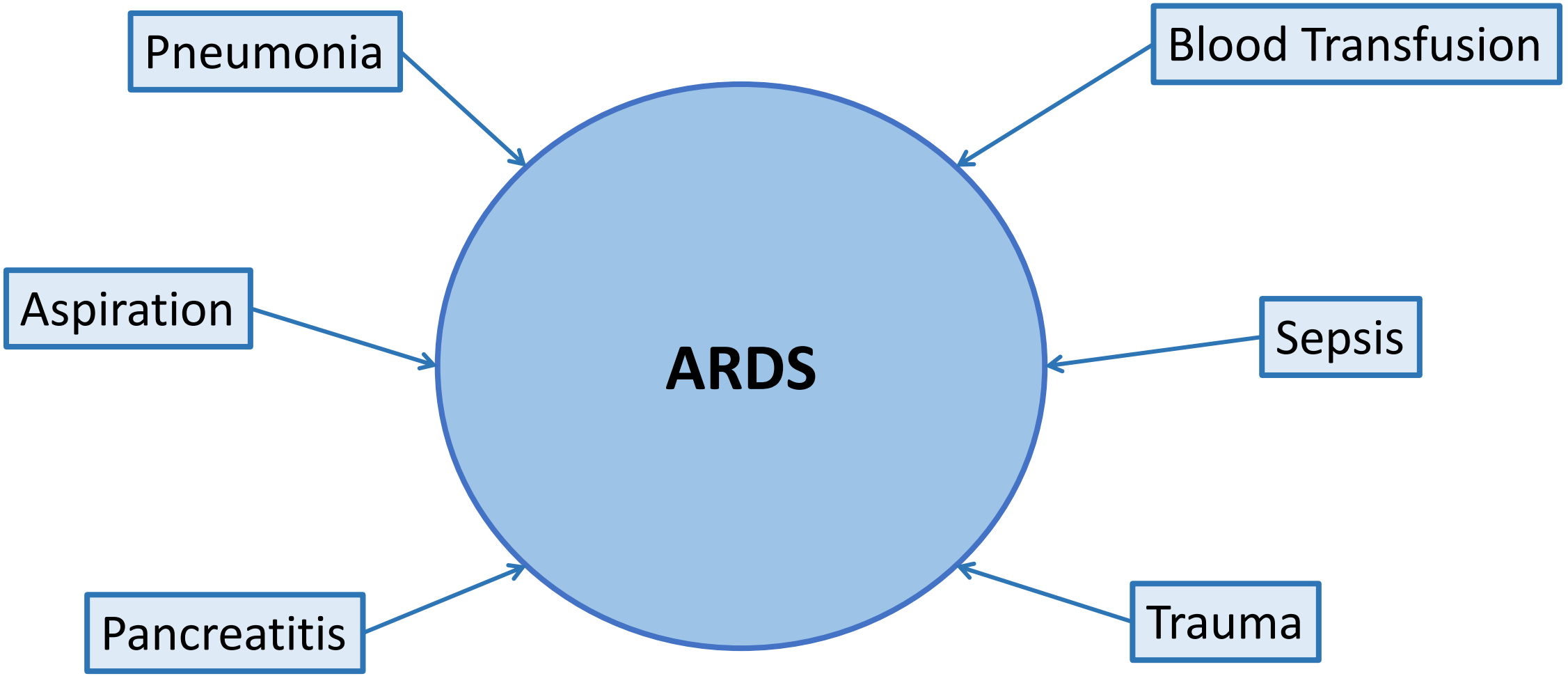
Liver
Elevated bilirubin, AST, ALT, Alk Phos

Circulatory
Poor capillary refill
Skin mottling

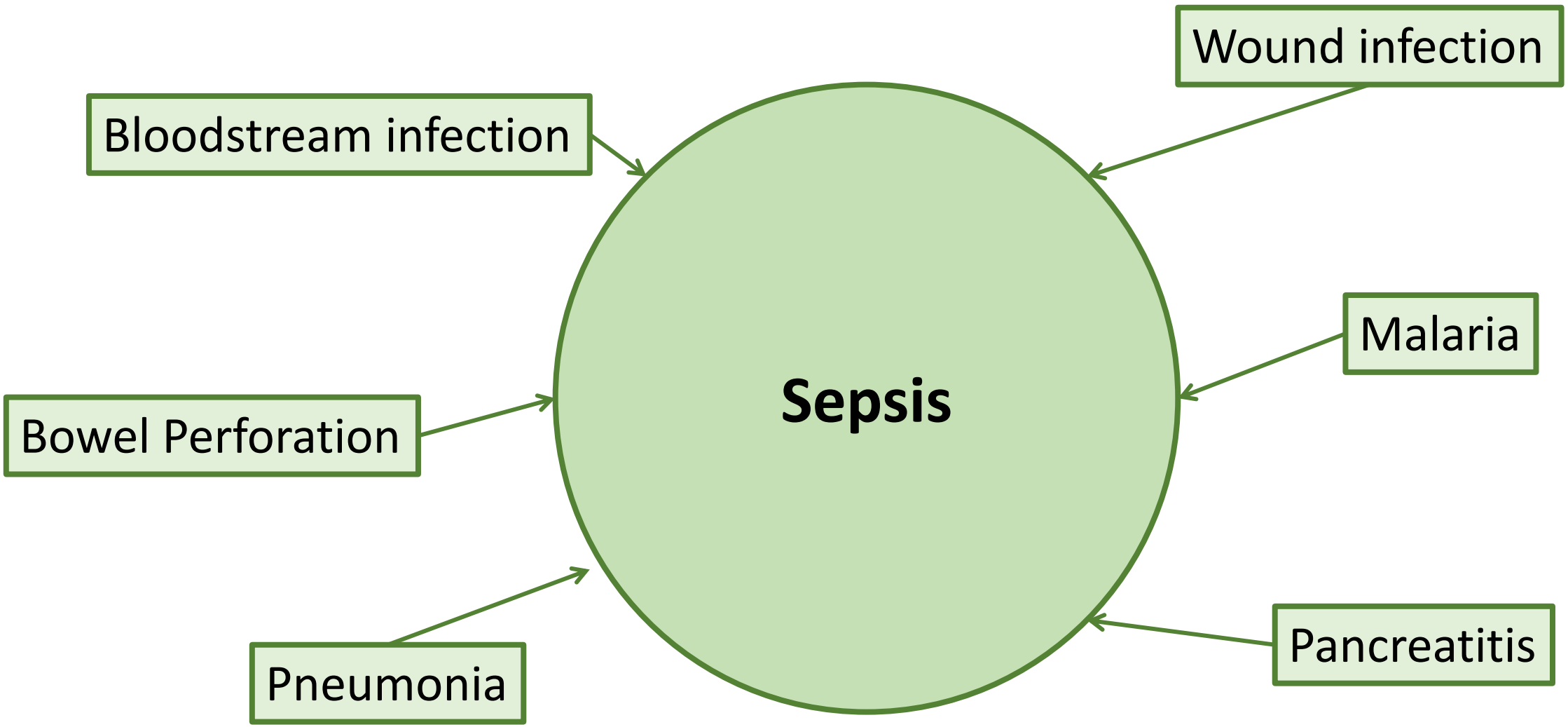
Hematologic
Thrombocytopenia
Coagulopathy (elevated INR, DIC)

Overall Toxic Appearance

Critical Illness as Final Common Pathway

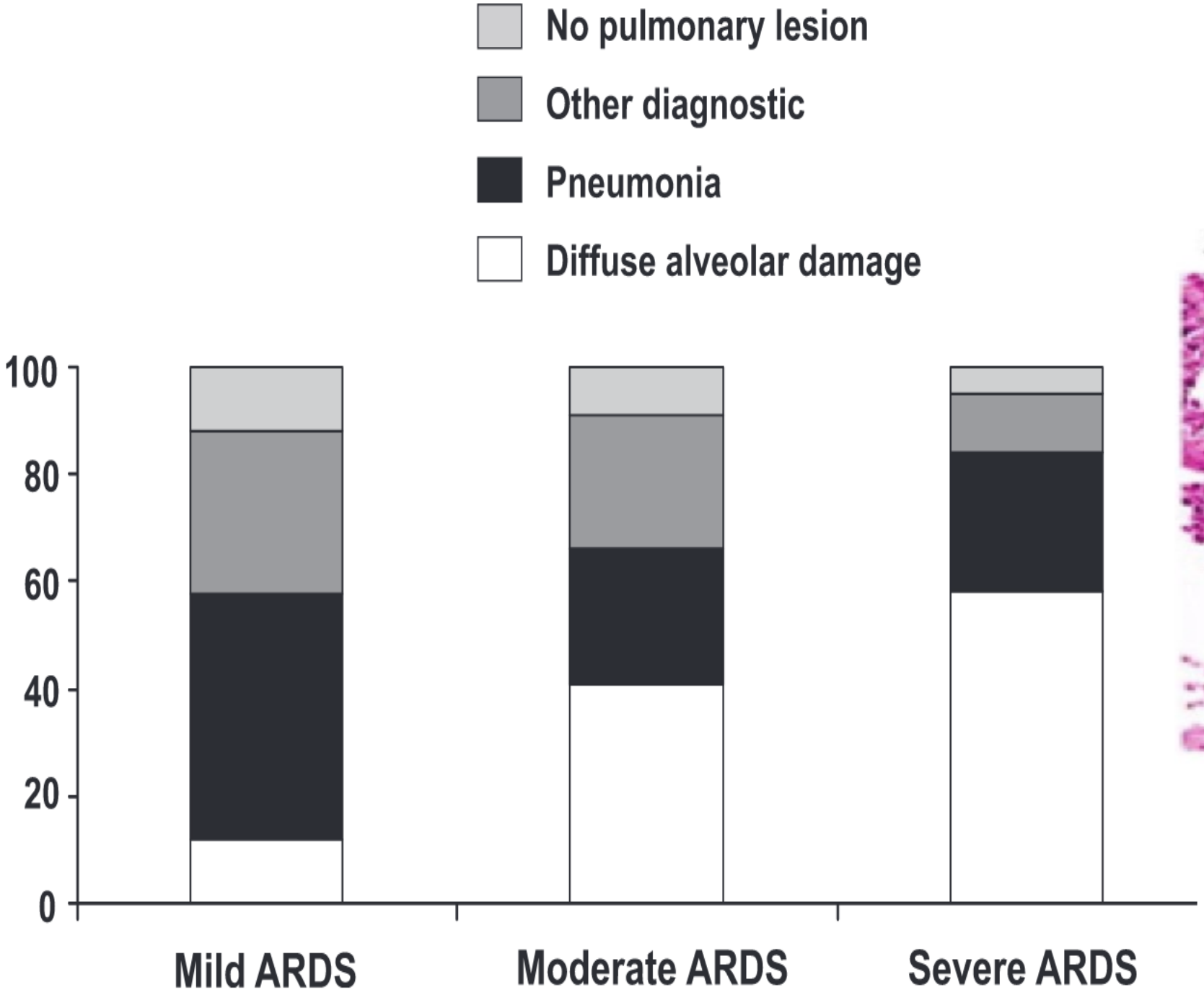


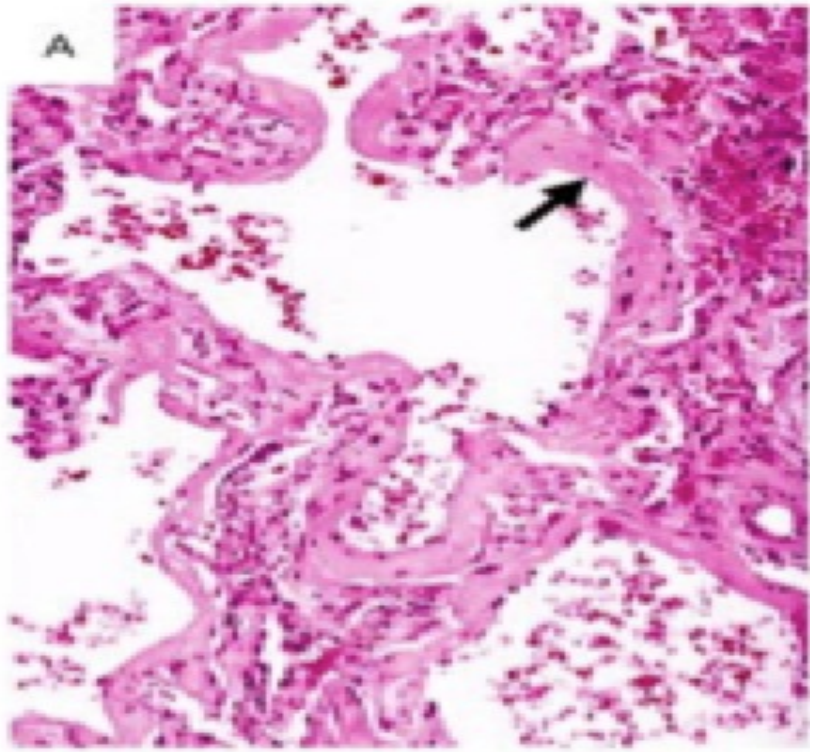
Critical Illness as Final Common Pathway



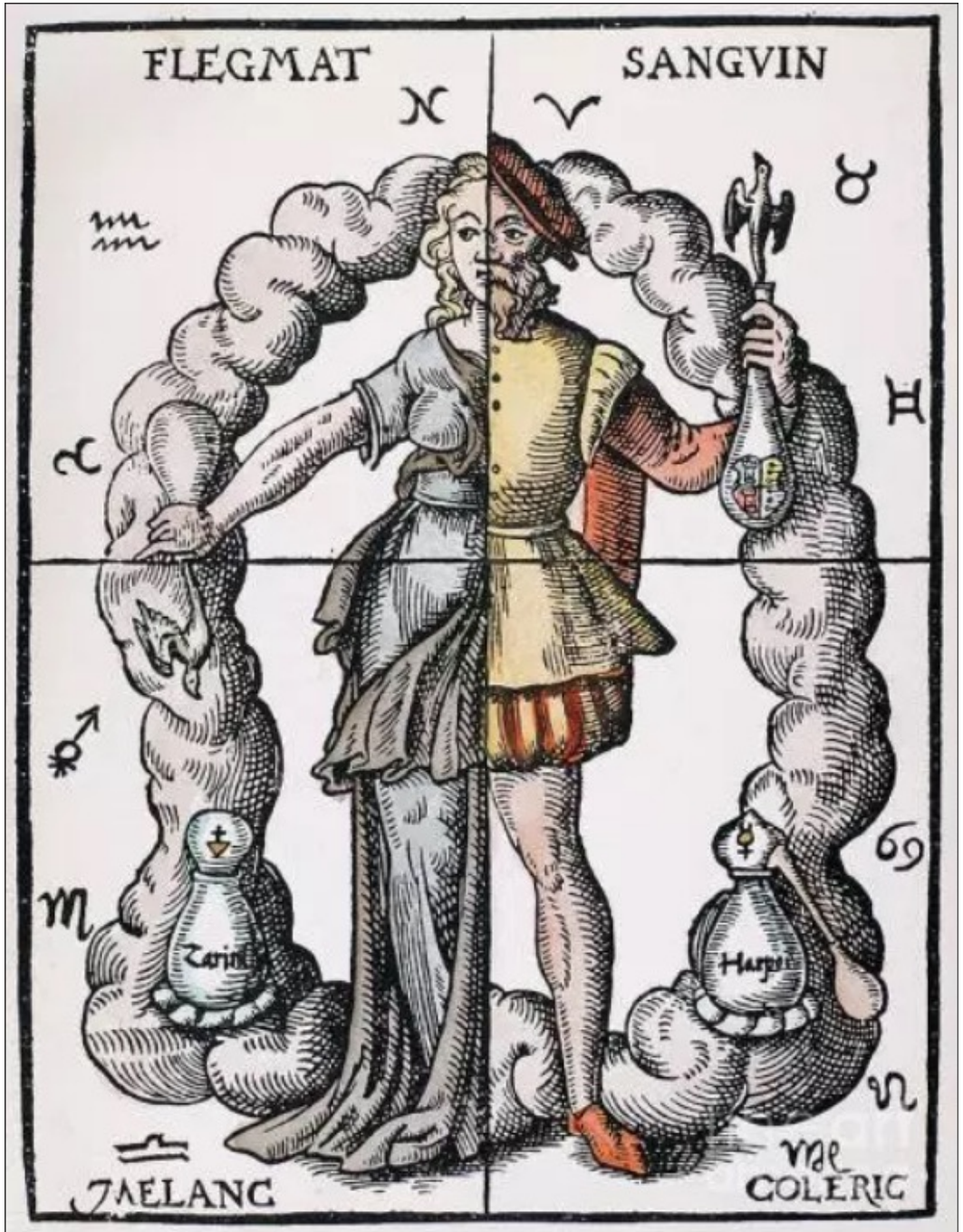
Sepsis and ARDS are *Syndromes*, not Diseases

- 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 for research and early intervention



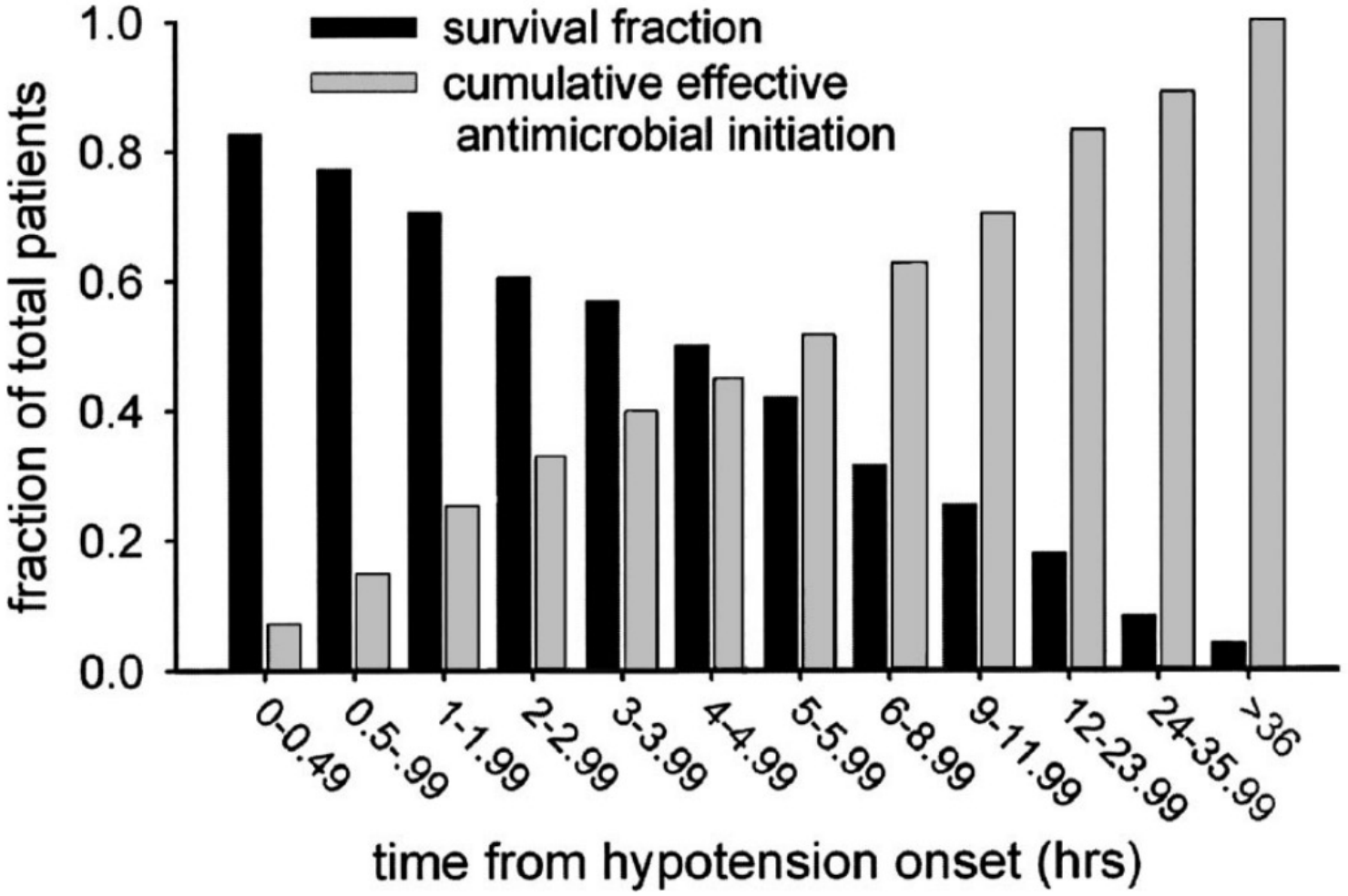


Thille AW, et al. AJRCCM 2013



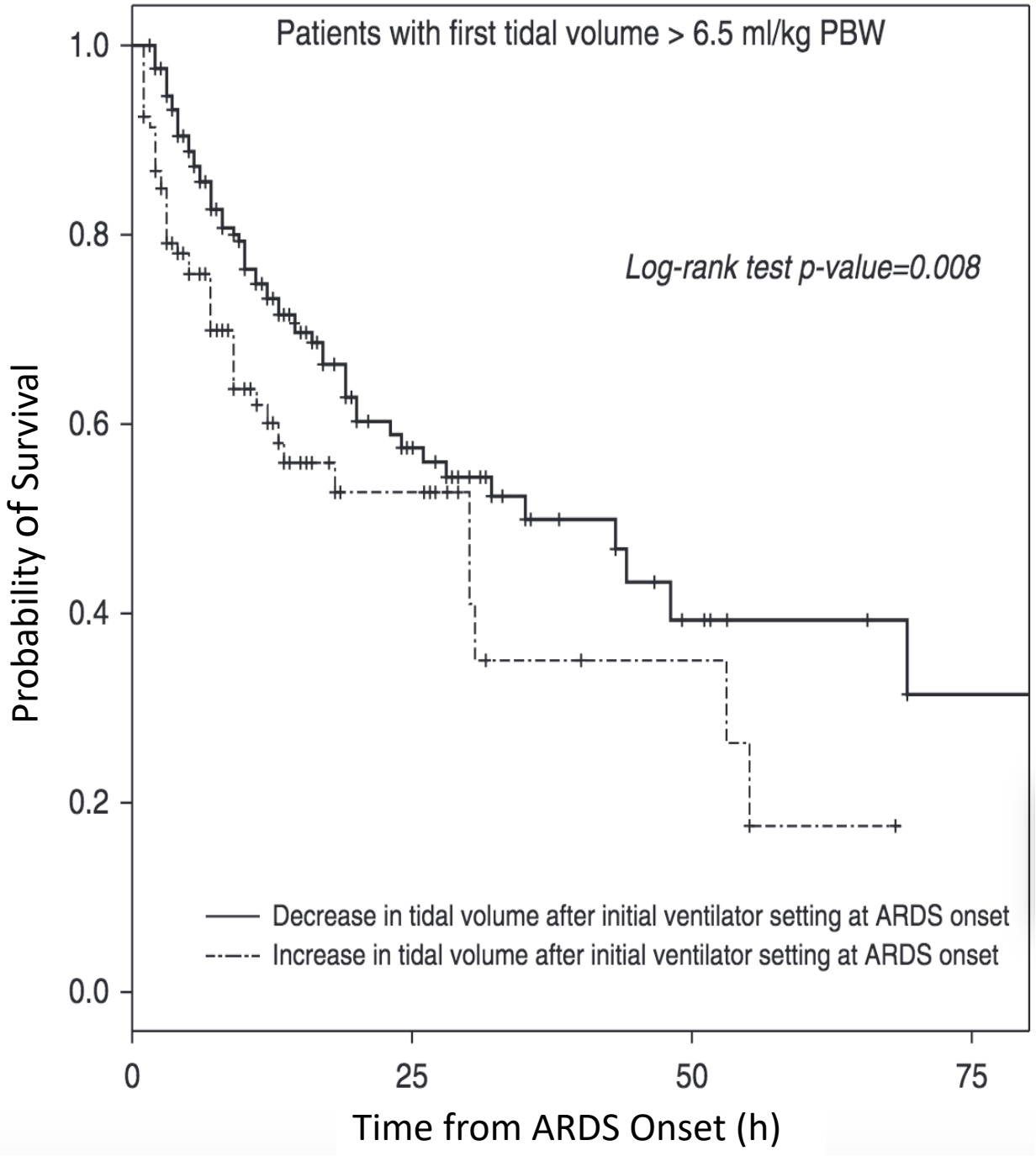
Have we really come that far?

Early Identification → Early Intervention



Timing of antibiotics in septic shock affects survival

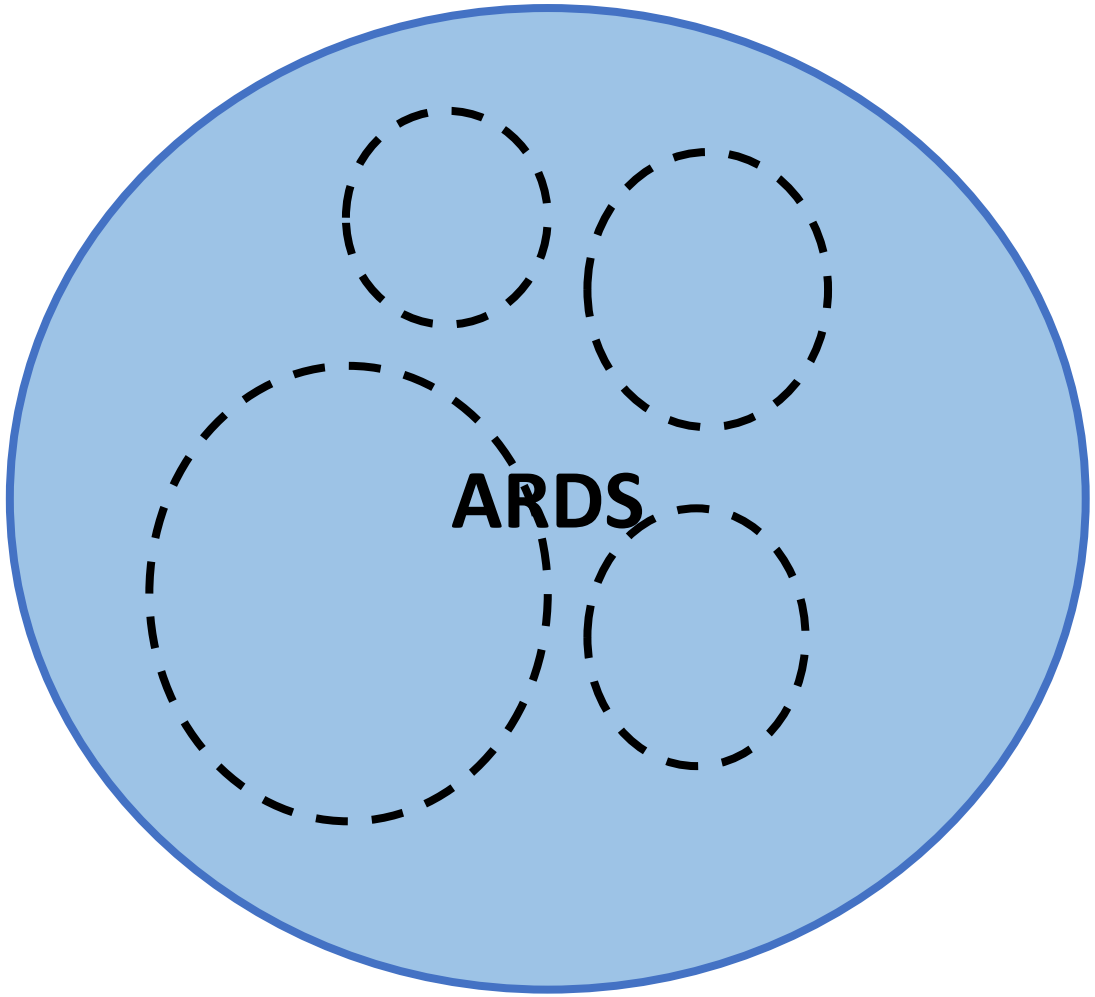
Kumar A, et al. Crit Care Med 2006



Ventilator management at ARDS onset impacts survival

Needham DM, et al. AJRCCM 2015

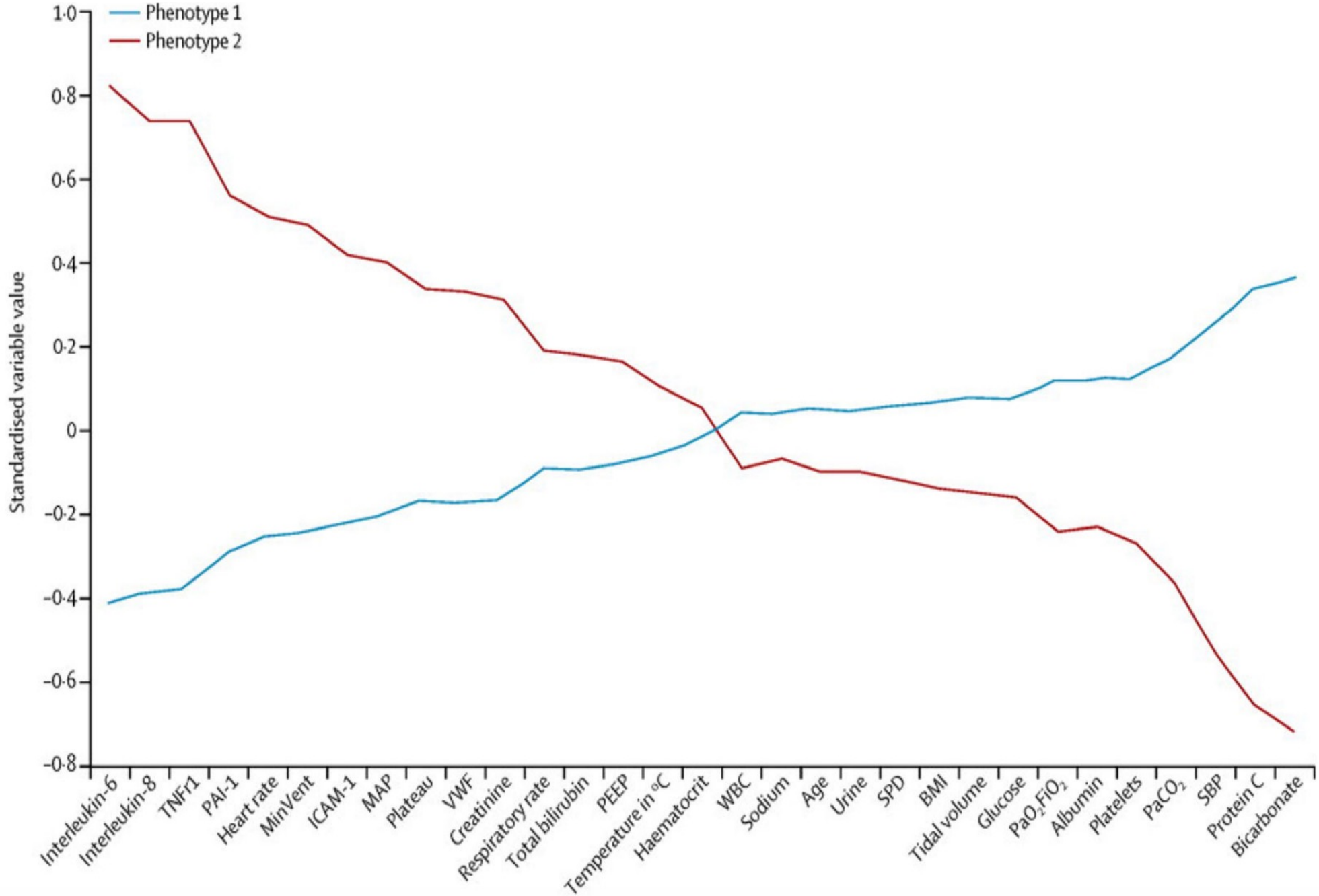
A Challenge of Syndromic Definitions: Heterogeneity!!



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

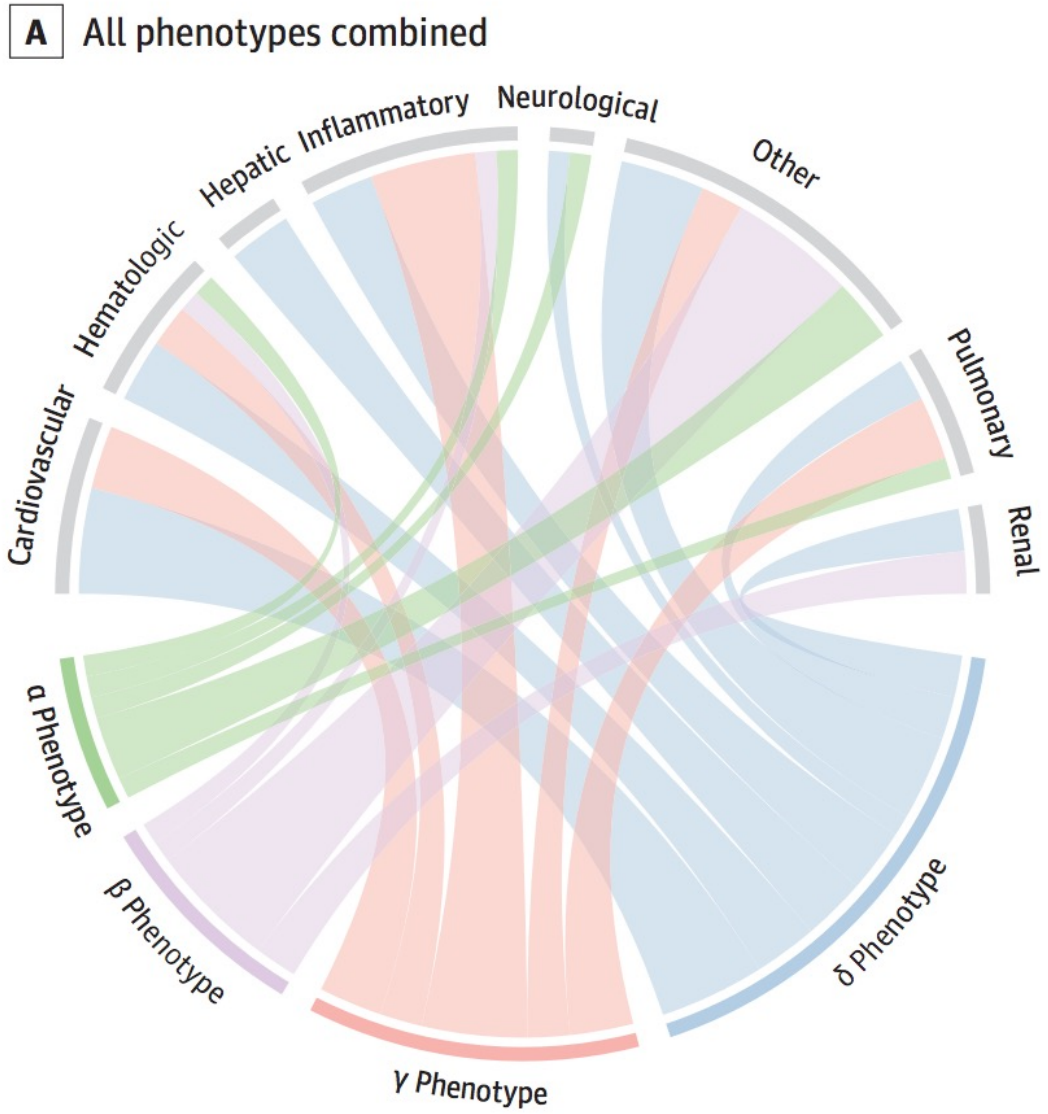
How to Identify Subgroups in ARDS

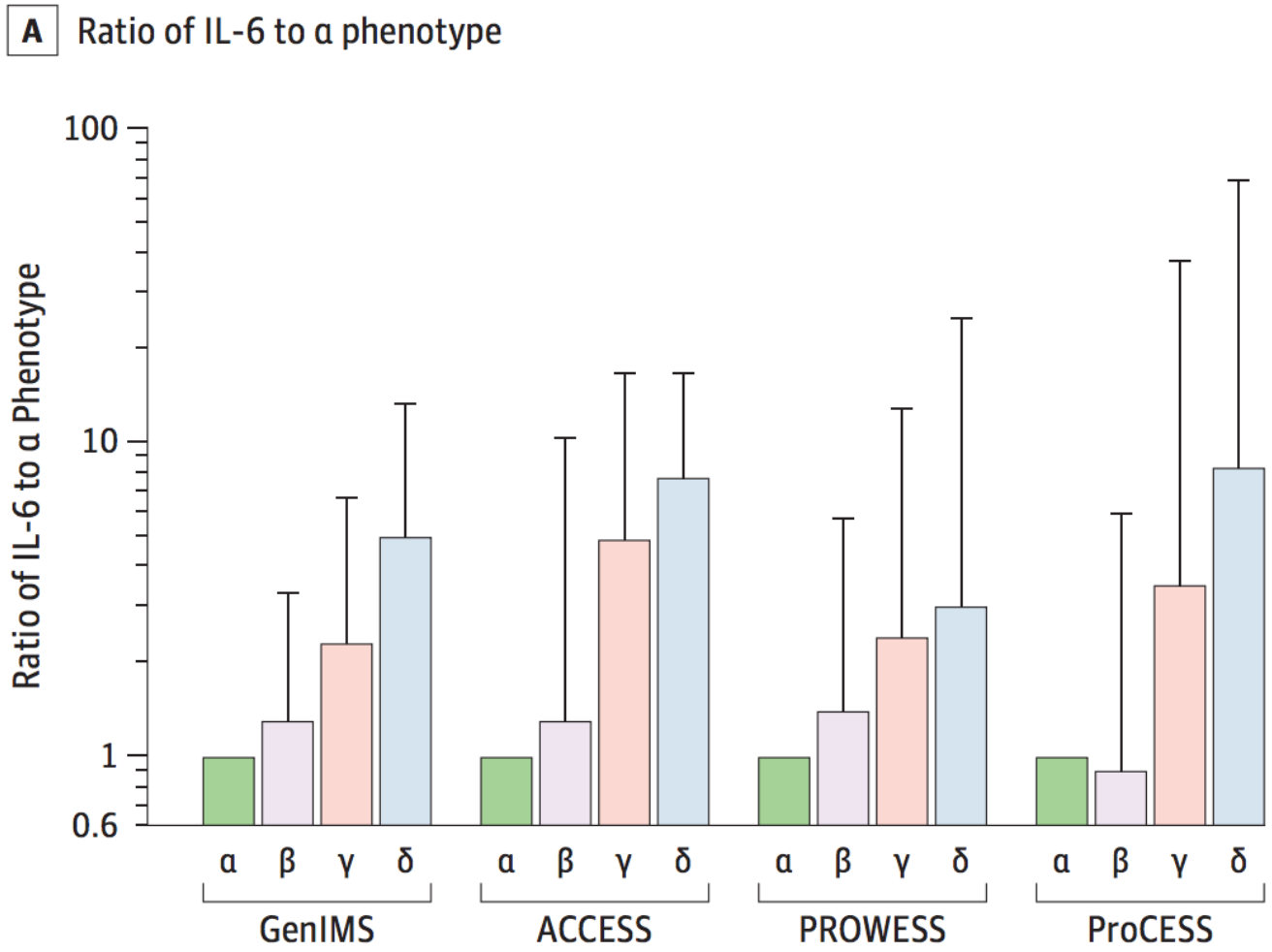
- What caused it?
  - Direct versus indirect injury
- What does it look like? (anatomic)
  - Focal versus diffuse
- What does it look like? (biomarker profile)
  - Latent class analysis



Calfee CS, et al. Lancet Respir Med 2014

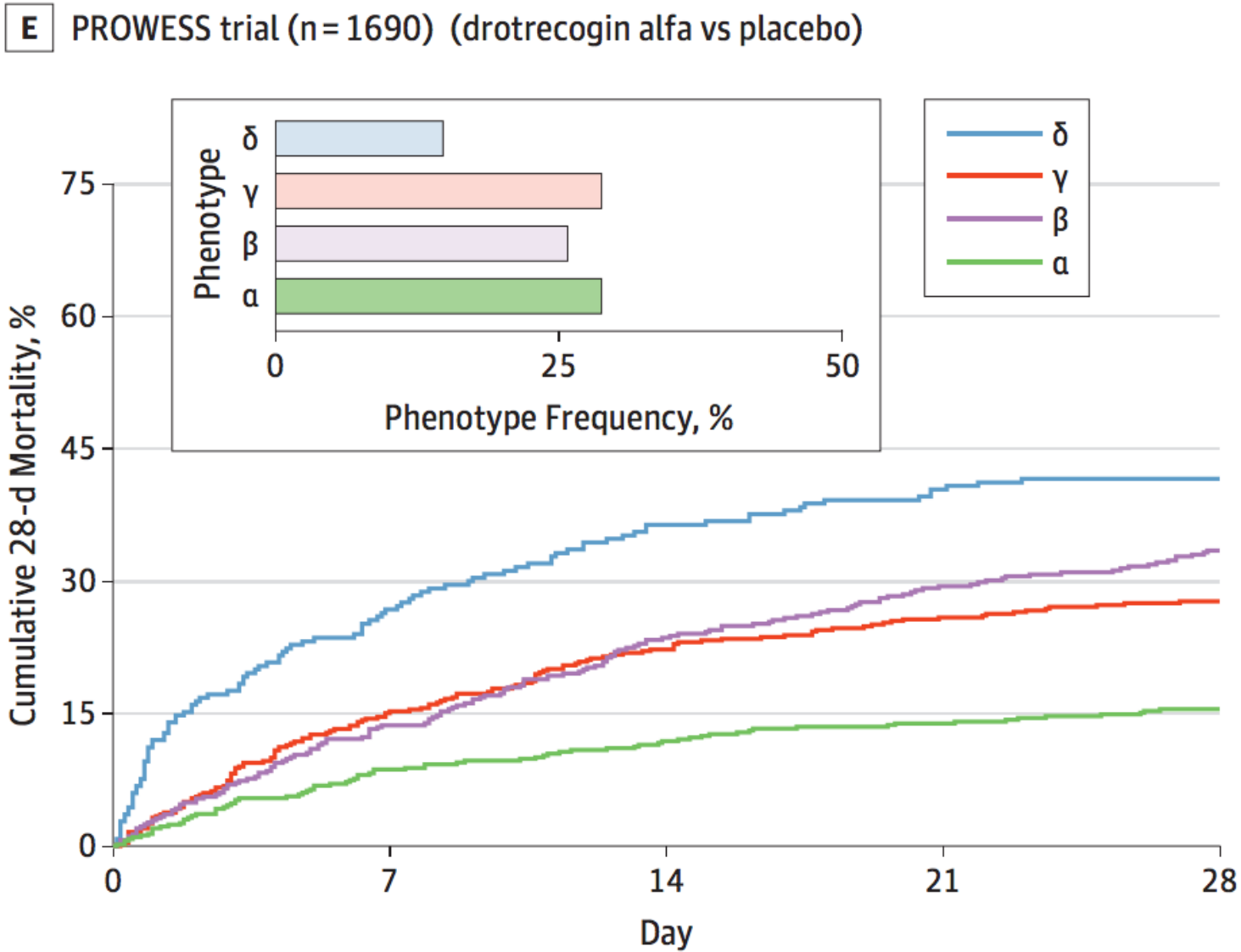
Sepsis Phenotypes

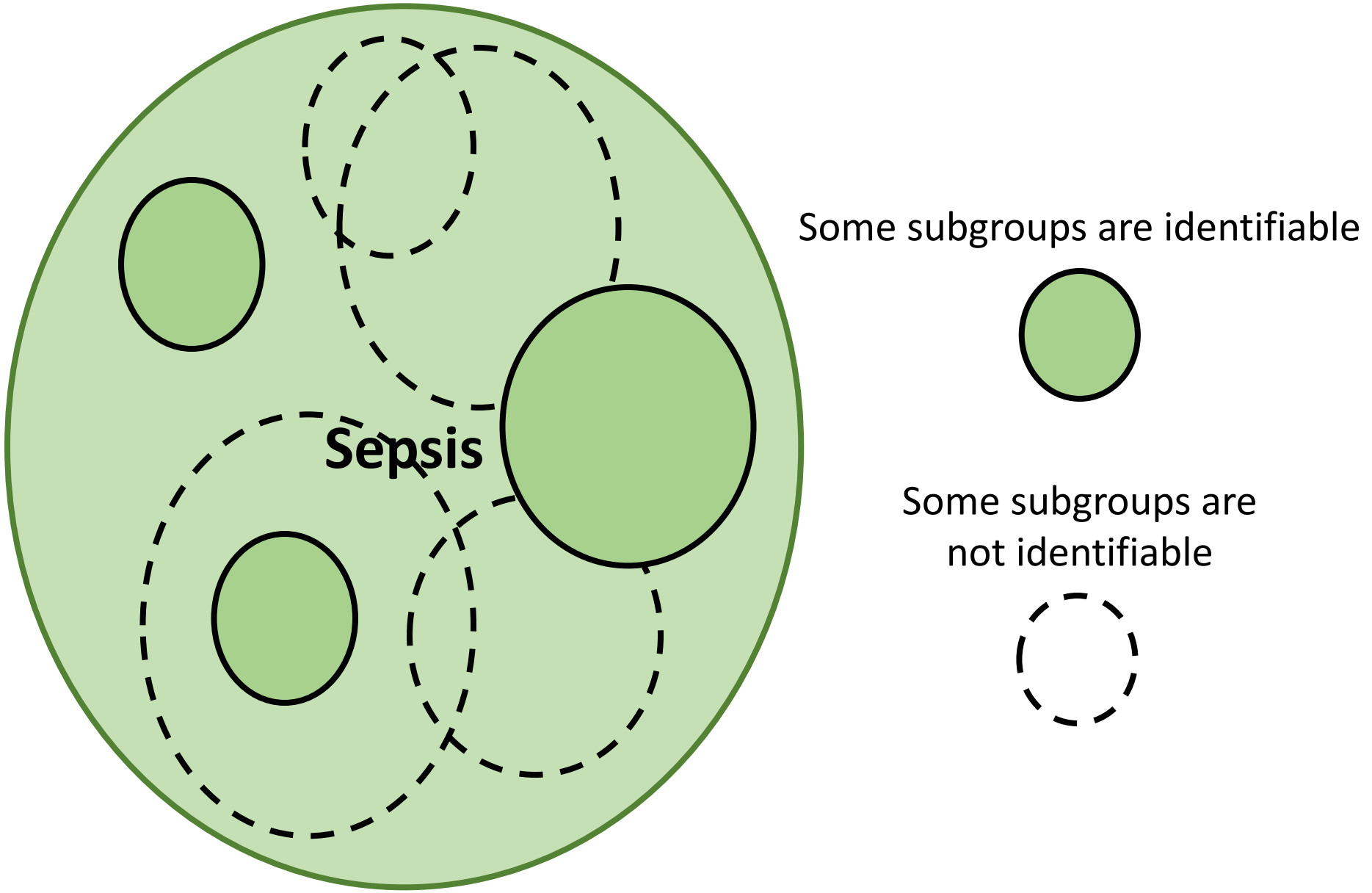


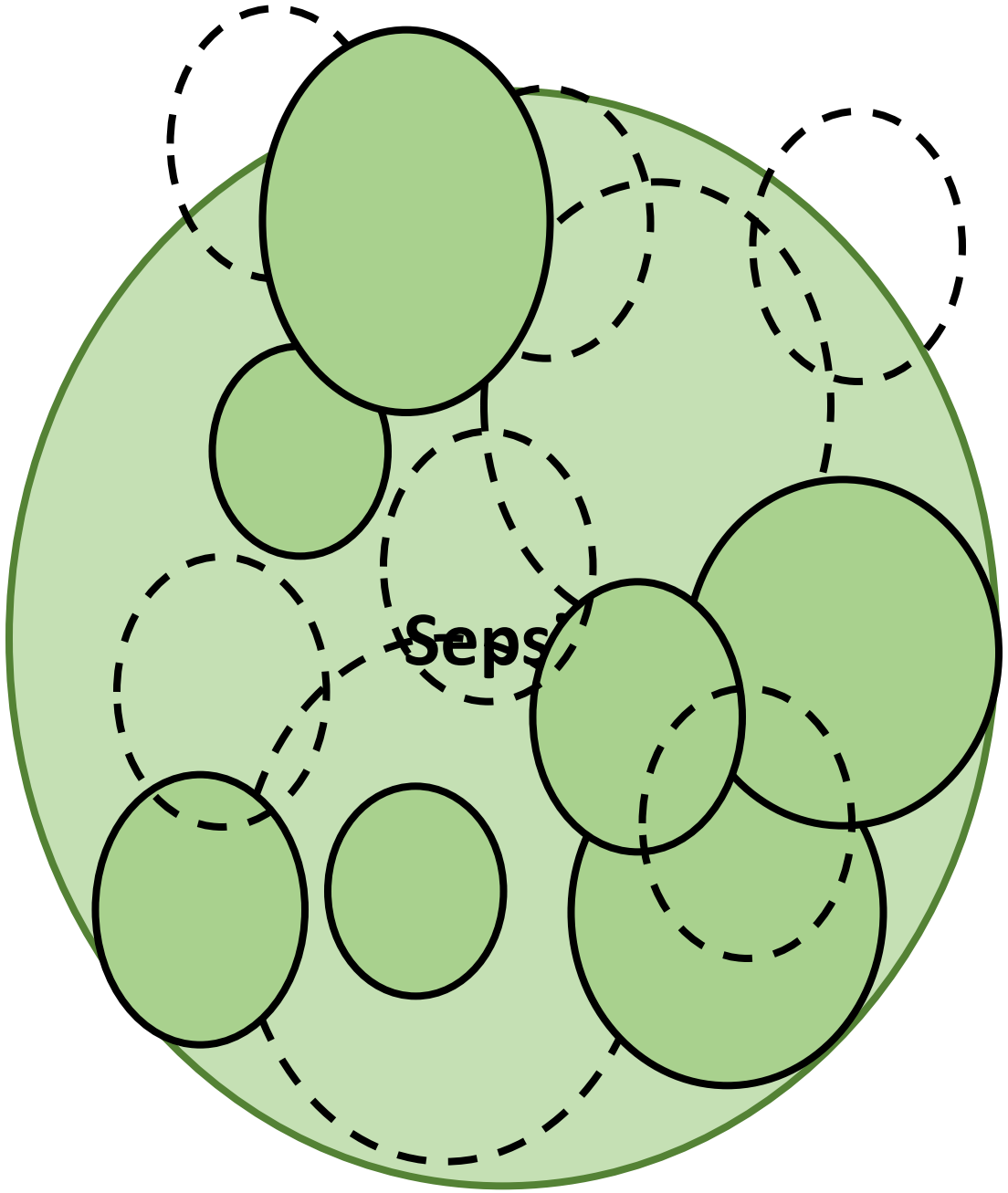


Seymour C, et al. JAMA 2019

How do we know our subgroups are real?

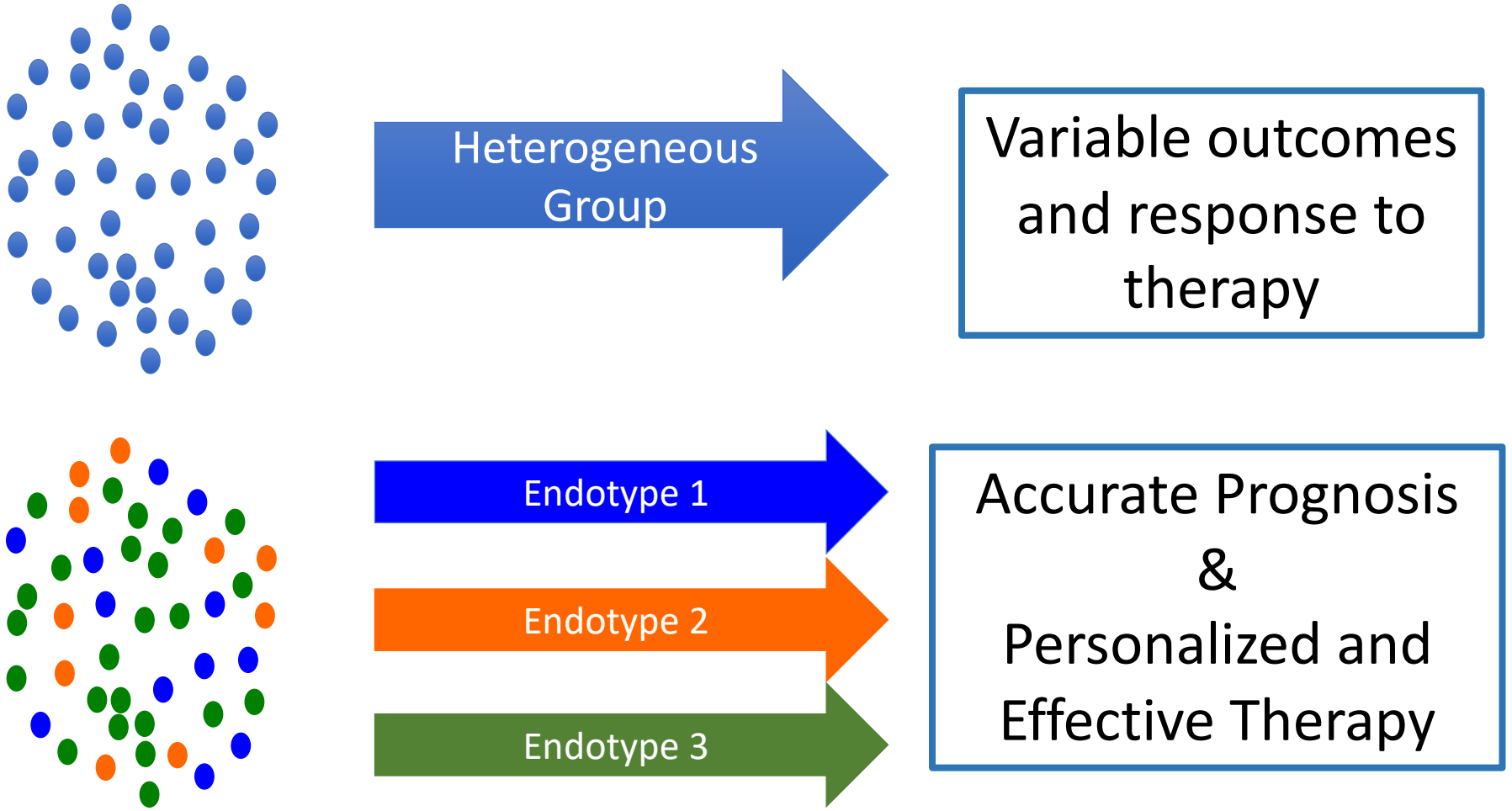



Sepsis
Some subgroups are identifiable
Some subgroups are not identifiable



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

Why Does Heterogeneity Matter?



Nitric Oxide

Surfactant/perflourocarbon

Prostaglandin E1

Lysophyline

Ibuprofen

Procysteine

Anticytokine/antiendotoxin

Ketoconazole

Streptokinase

Neutrophil elastase inhibitor

sPLA2 inhibitor

rhAPC

Albuterol/salmeterol

Furosemide

Cisatricurium

GMCSF

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

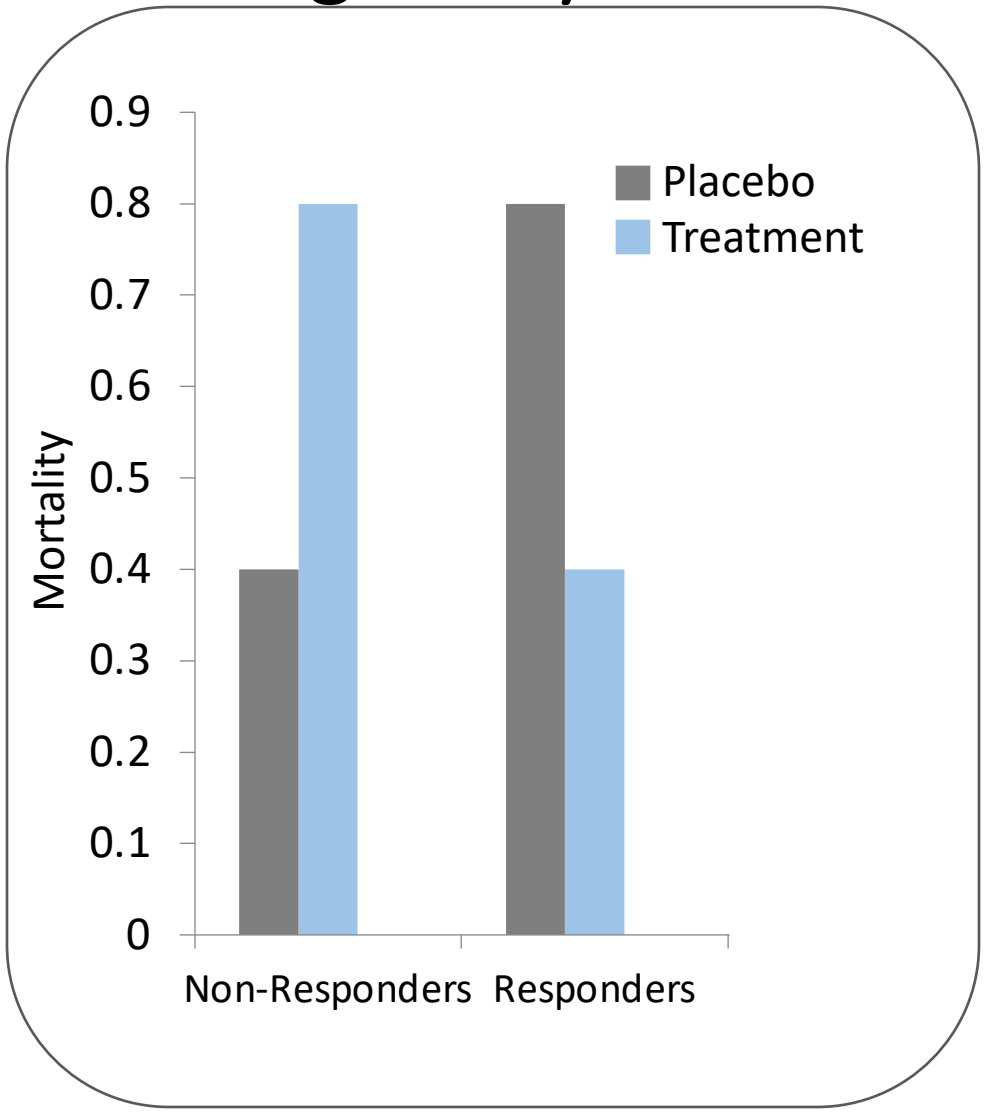
TLR-4 Antagonsist

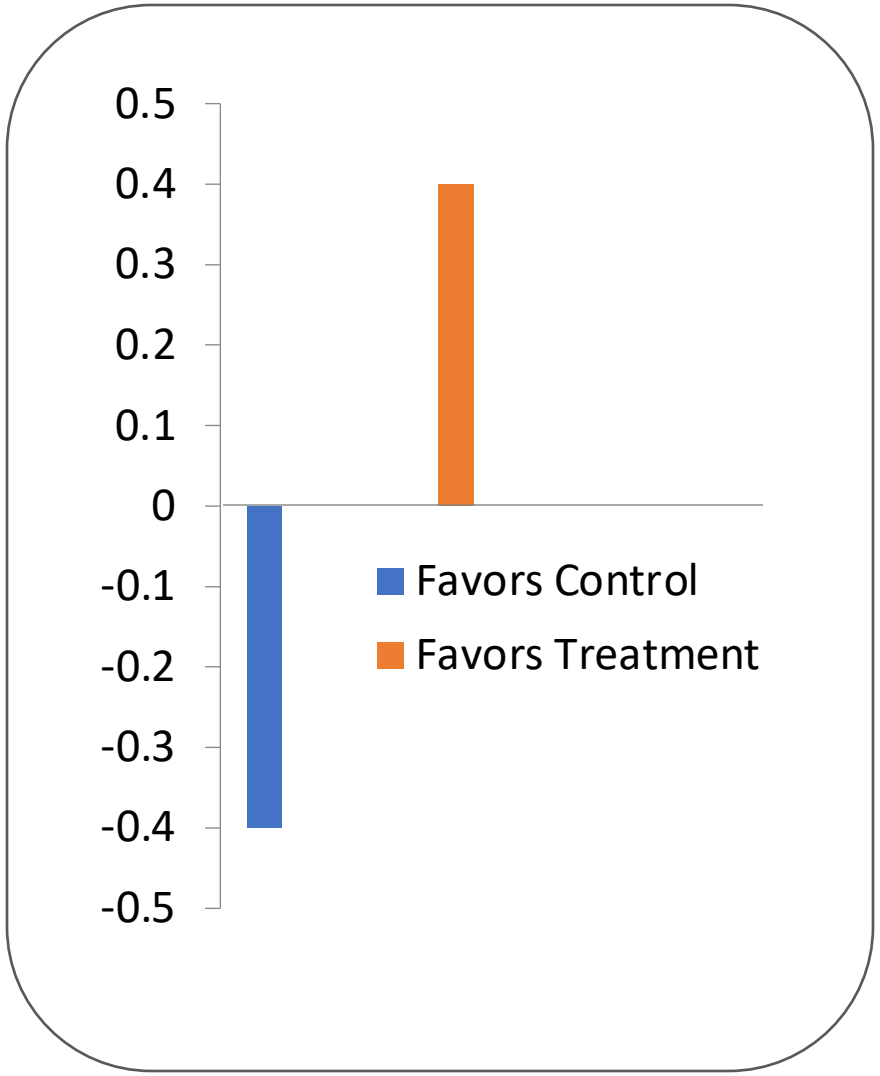
Anti-Endotoxin Antibody

Activated Protein C

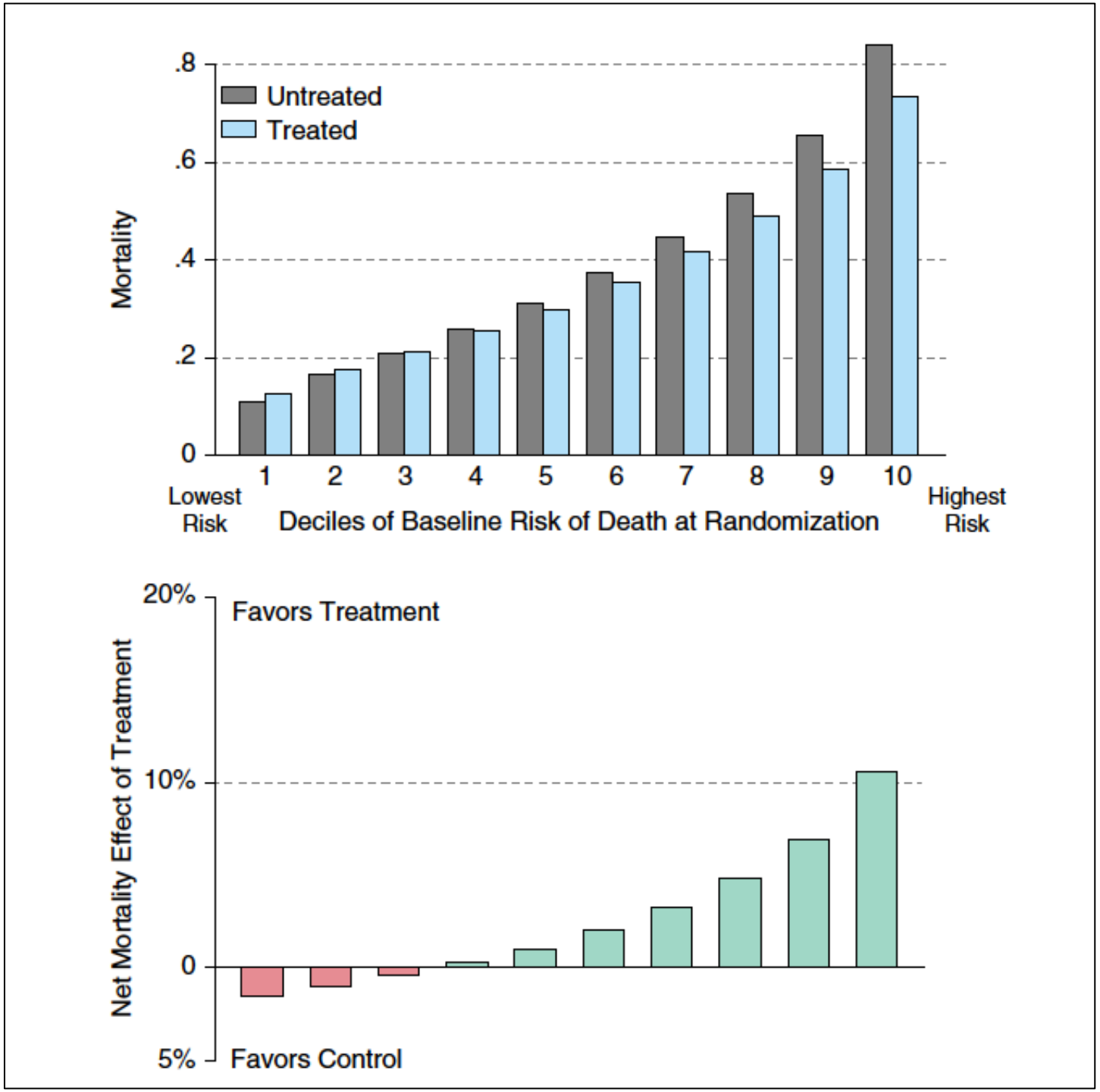
Recombinant Thrombomodulin

Why Heterogeneity Matters





Iwashyna JI, et al. AJRCCM 2015



Heterogeneity of Treatment Effect

Iwashyna JI, et al. AJRCCM 2015

Summary So Far…

Common and Highly Morbid Conditions

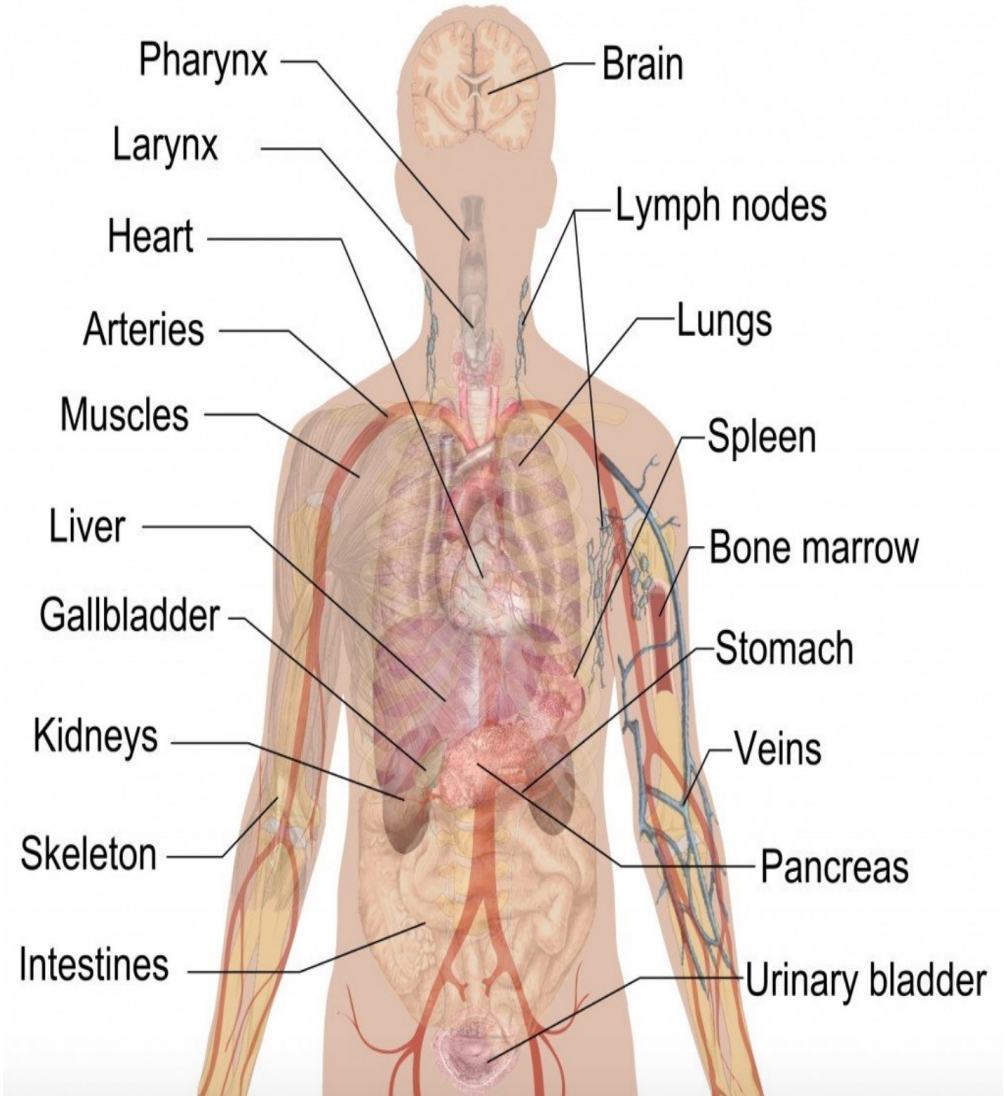
\+ Importance of Early Recognition and Intervention

\+ Heterogeneous Groups

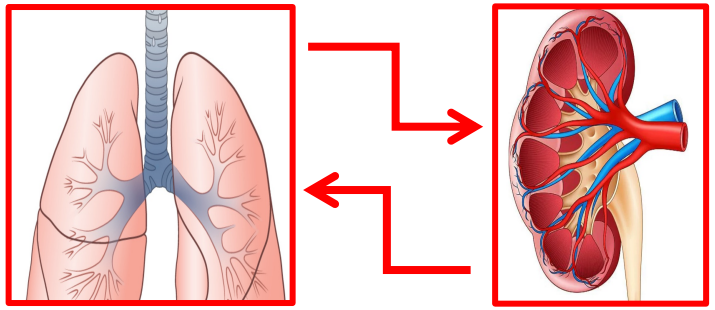
\+ Need for More Targeted Trials and Therapies

= Opportunity for Network Physiology??

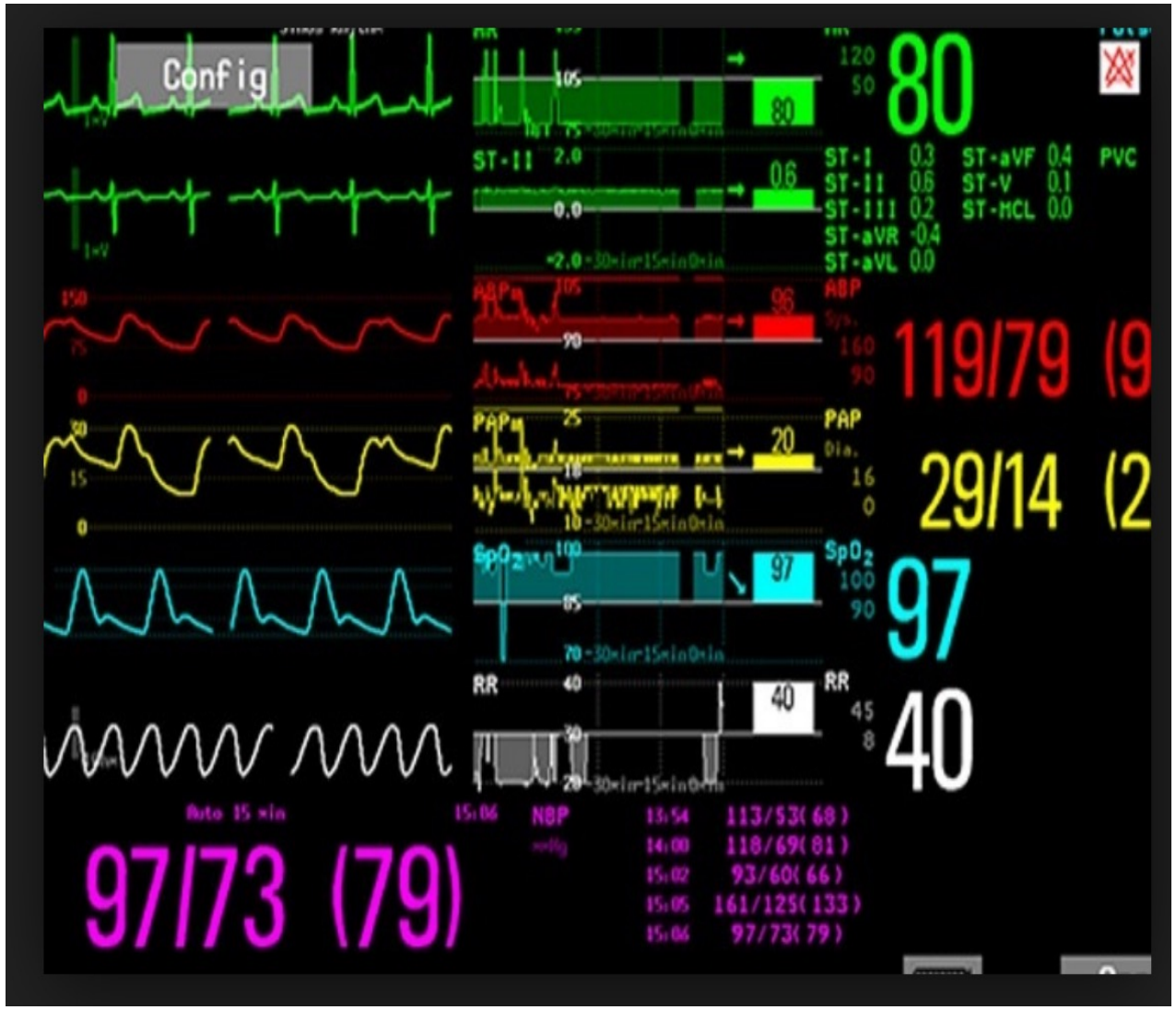
Critical Illness and Network Physiology: Multi-organ Failure



- 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

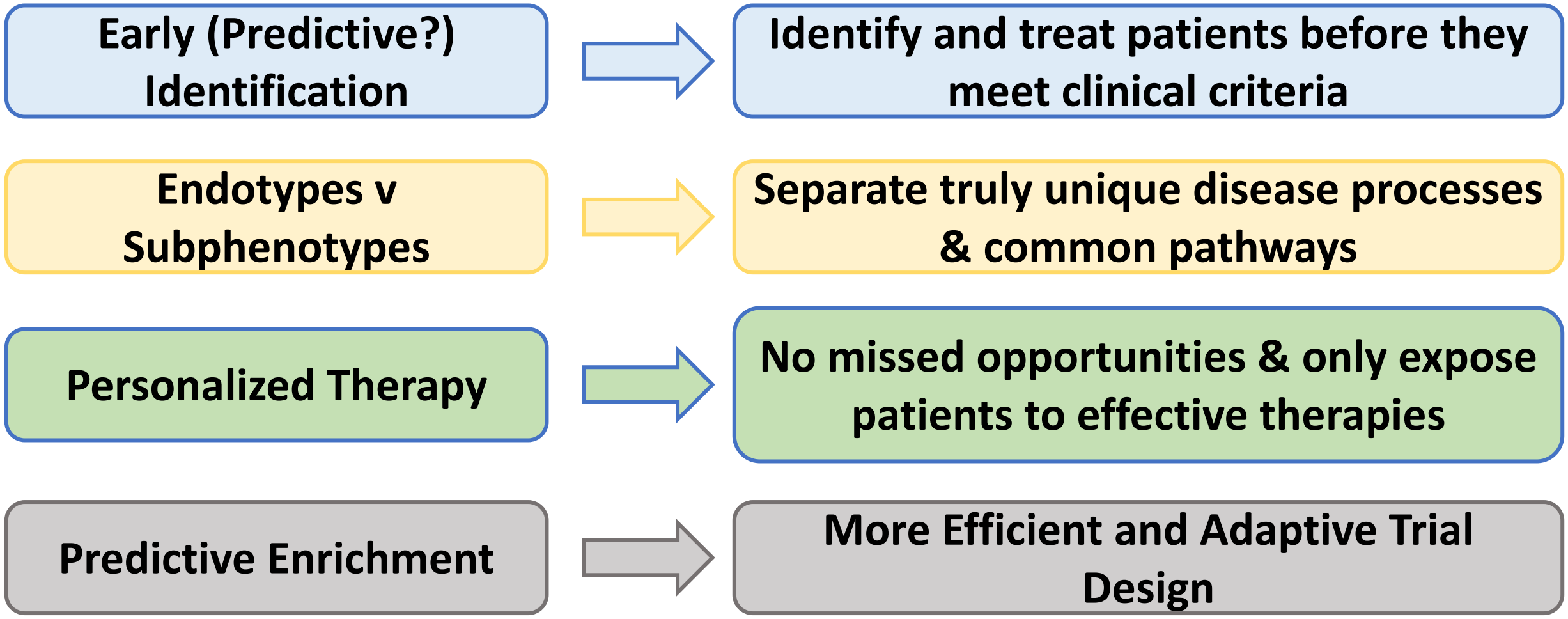


- The ICU is a data rich environment…
- Standard of care* is continuous monitoring of multiple organ systems
- Electronic medical record and central storage of monitoring data

* In well resourced settings


NEC NEW ENGLAND CONSERVATORY

Critical Care and Network Physiology



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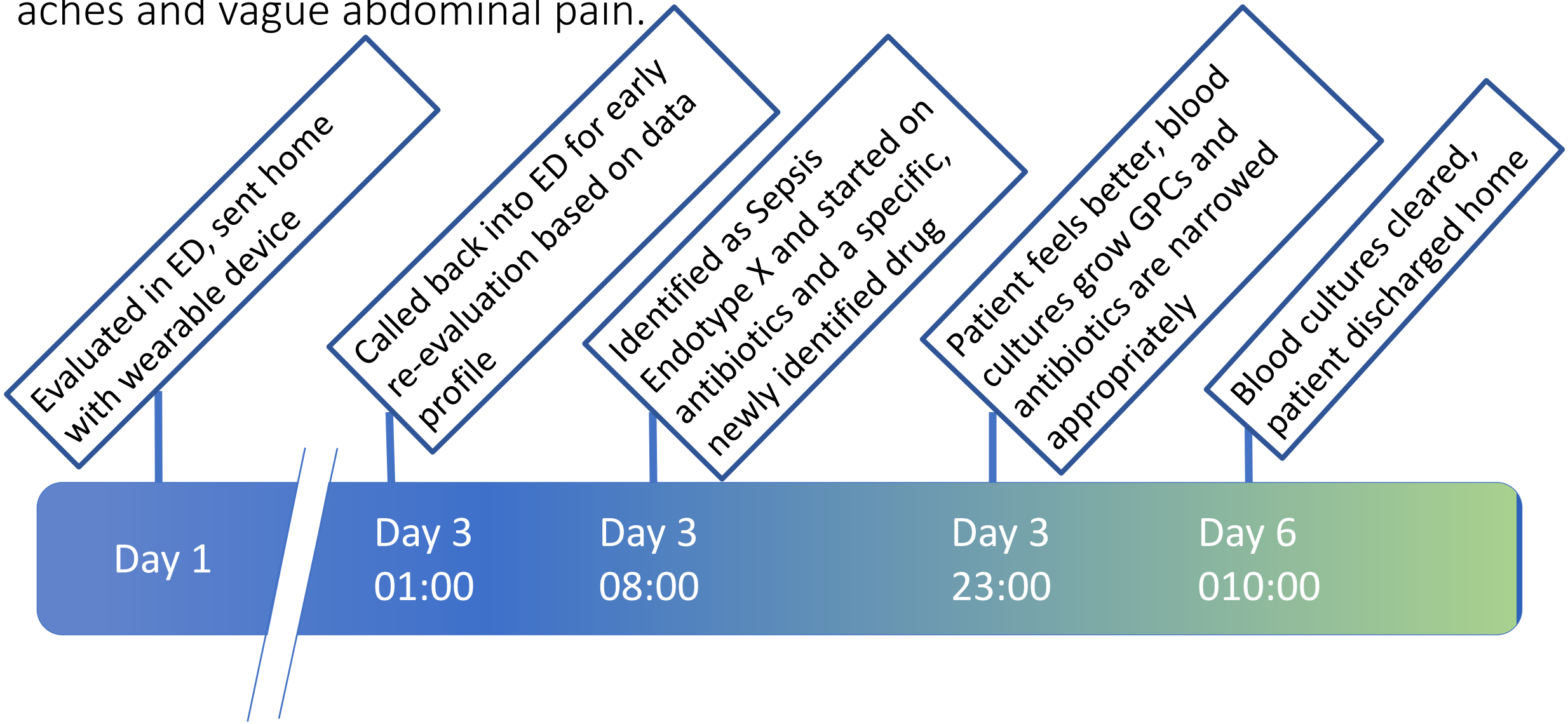

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