



# All About Sepsis

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Dr. Pierre Kory  
Dr. Joe Varun  
9.6.2023

# RISE IN SEPSIS IS HITTING THE NEWS

## **Kentucky school districts cancel classes weeks into year amid COVID, flu and strep outbreaks**

By [Isabel Keane](#)

August 24, 2023 | 3:22pm | Updated

## **‘Very, very unusual’: MUSC doctors see spike in Invasive Strep cases**

## **Cases of flesh-eating Strep A infection surge across Australia**



By Allanah Sciberras | 6:37pm Aug 23, 2023

## **At least 3 kids die from Strep A as infections on rise among children in Canada**

On Friday, the WHO published an update on increased incidence of scarlet fever, invasive group A streptococcal infections in several countries.

Nova Scotia

## Serious infections rose last year in CBRM hospitals, but unexpected deaths down



Sepsis rate more than double national average, but officials say they are taking steps and seeing fewer deaths



[Tom Ayers](#) · CBC News · Posted: Jan 13, 2023 5:00 AM EST | Last Updated: January 13



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HEALTH NEWS

## Strep infection rates remain high in the U.S., even relative to pre-pandemic levels

Rates of strep throat diagnoses in February were nearly 30% higher than during the previous peak in February 2017, one report found.





Health > News Health

## **HEALTH CHECK** The 2 obscure signs of sepsis you must know as Strictly's Amy Dowden shares terrifying update

Isabel Shaw

Published: 11:17, 29 Aug 2023 | Updated: 12:10, 29 Aug 2023

# RISE IN SEPSIS IS HITTING THE NEWS

✍️ What I found was, the CDC and the media are engaged in a stealthy, all-out educational campaign to combat *sepsis*. They are rapidly pushing out new programs, materials, and requirements on the whole country's doctors and hospitals *through a fire hose*. But why?

From the New York Times, this week:

## *C.D.C. Sets New Standards for Hospitals to Combat Sepsis*

The agency outlined “core elements” needed to detect and treat the condition, a factor in 1.7 million hospitalizations in the U.S. each year.





## OPEN ACCESS

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# BNT162b2 COVID-19 vaccination in children alters cytokine responses to heterologous pathogens and Toll-like receptor agonists

Andrés Noé<sup>1,2\*</sup>, Thanh D. Dang<sup>1</sup>, Christine Axelrad<sup>1</sup>,  
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Kirsten P. Perrett<sup>2,3,4†</sup>, Nigel Curtis<sup>1,2,3†</sup> and Nicole L. Messina<sup>1,3†</sup>

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# FINDINGS

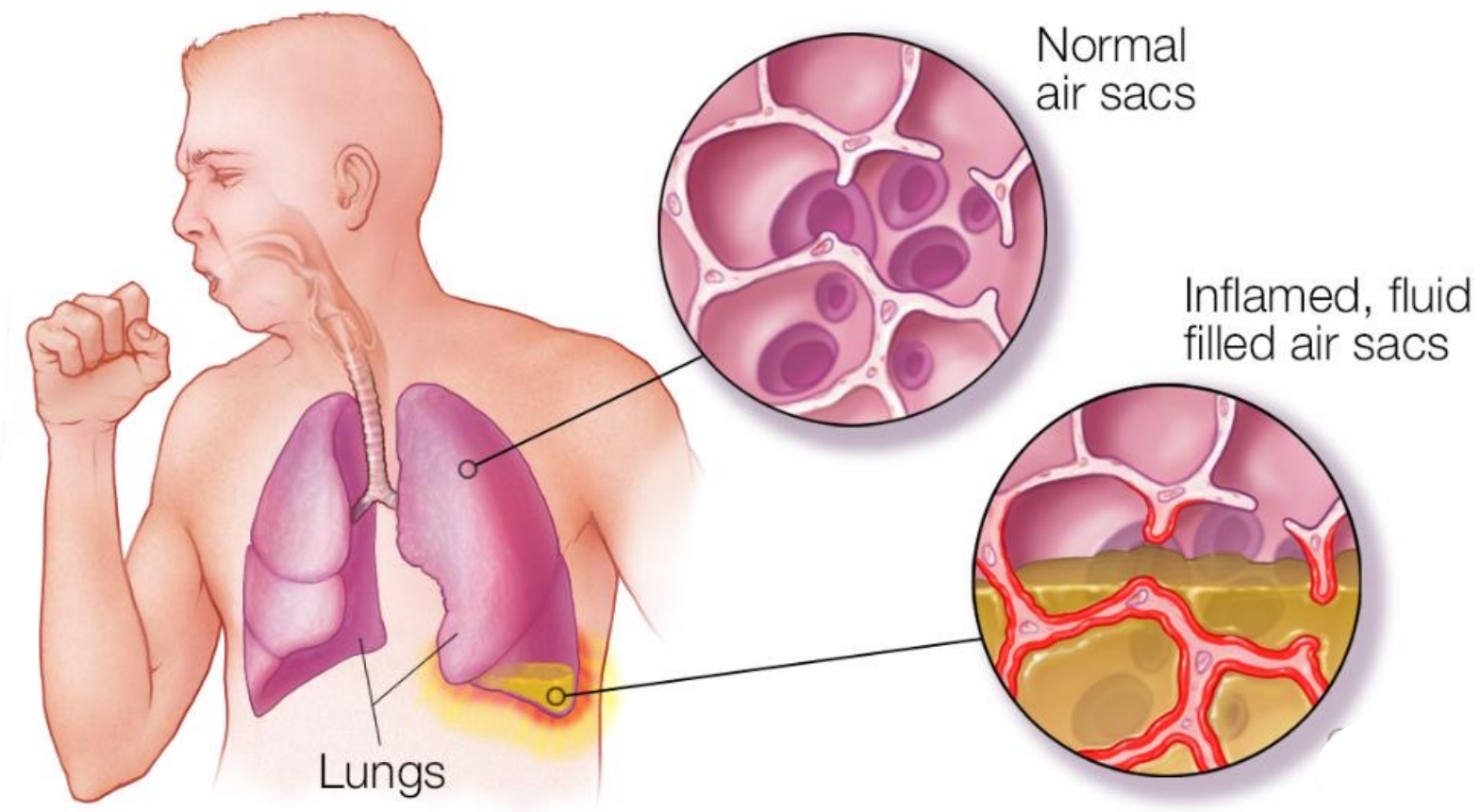
BNT162b2 vaccination is associated with a decrease in bacterial and viral stimulant-induced cytokine responses **one month** after vaccination

... BNT162b2 vaccination is associated with a sustained decrease in cytokine responses to viral, but not bacterial, stimulants **six months** after vaccination.

This is particularly relevant in children as they:

- Have extensive exposure to microbes at daycare, school, and social occasions;
- Are often encountering these microbes for the first time; and receive multiple vaccines as part of routine childhood vaccination schedules.
- There are currently no data on the clinical effects of COVID-19 vaccination-related heterologous effects in children.

# Defining Infection vs Diagnosing Sepsis



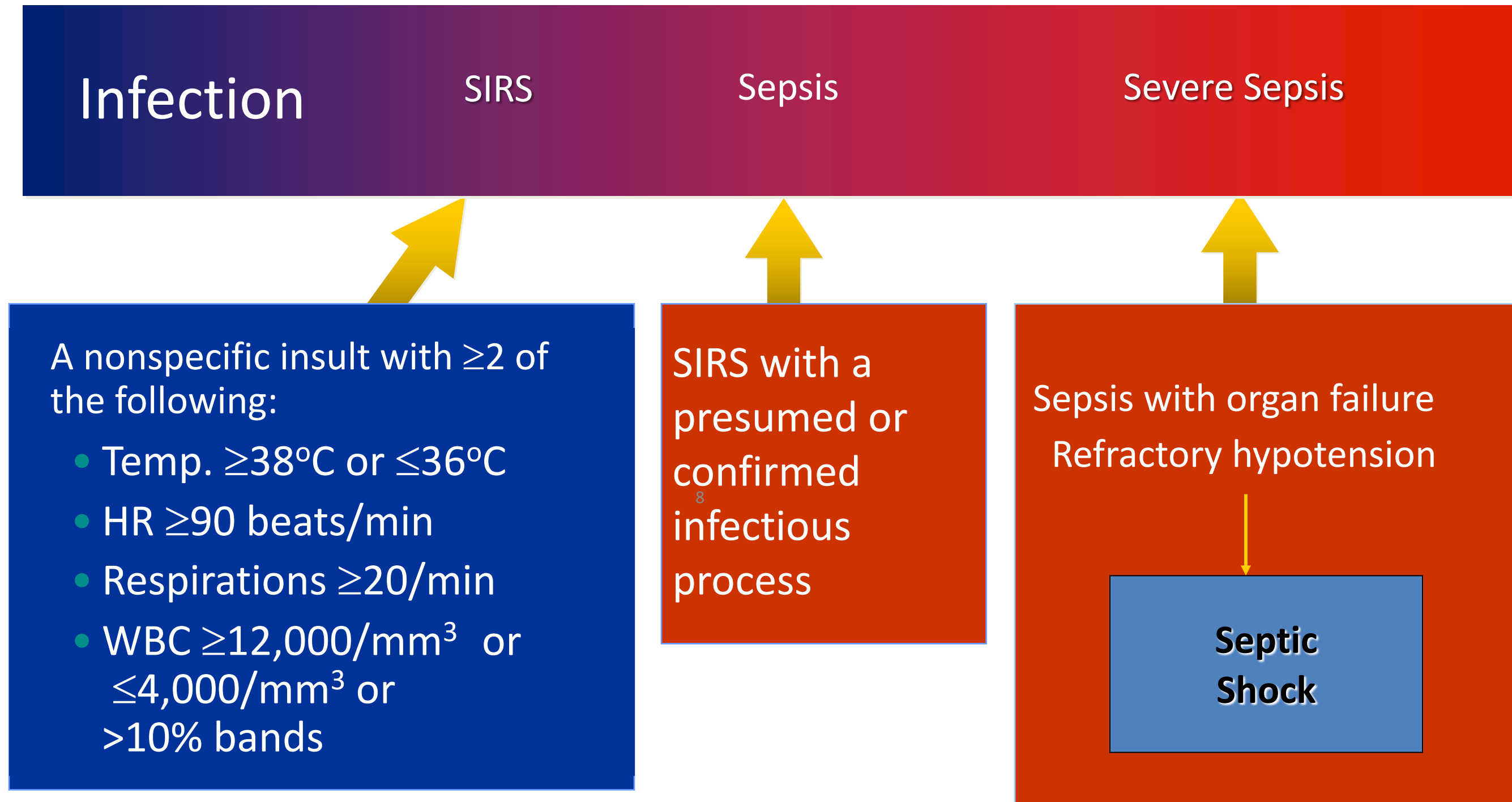
**Pneumonia**

**Cellulitis**





# Sepsis II: Defining a Disease Continuum



Bone et al. Chest. 1992;101:1644

# What is sepsis?

Infection

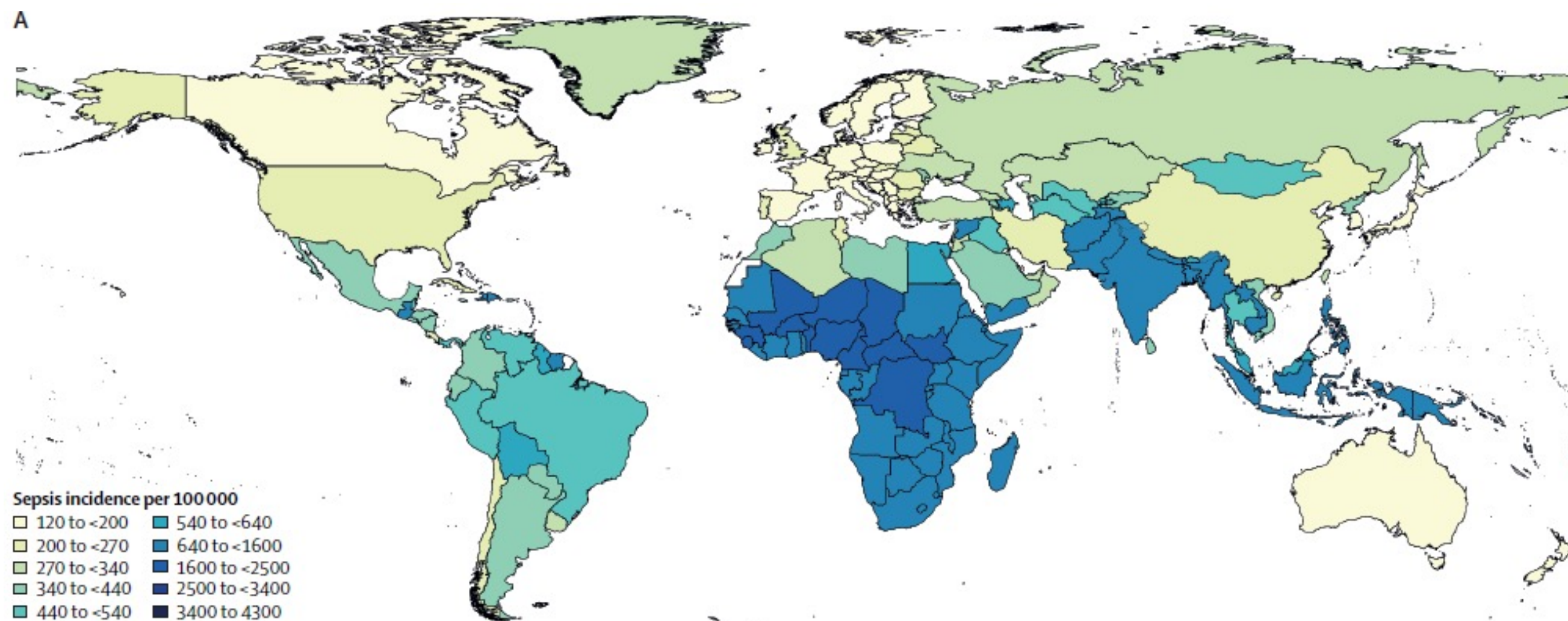
plus

organ

dysfunction

# Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study

*Kristina E Rudd, Sarah Charlotte Johnson, Kareha M Agesa, Katya Anne Shackelford, Derrick Tsoi, Daniel Rhodes Kievlan, Danny V Colombara,*



**Findings** In 2017, an estimated 48·9 million (95% uncertainty interval [UI] 38·9–62·9) incident cases of sepsis were recorded worldwide and 11·0 million (10·1–12·0) sepsis-related deaths were reported, representing 19·7% (18·2–21·4) of all global deaths. Age-standardised sepsis incidence fell by 37·0% (95% UI 11·8–54·5) and mortality decreased by



# National Inpatient Hospital Costs: The Most Expensive conditions by Payer, 2013

## STATISTICAL BRIEF #204

Rank	CCS principal diagnosis category	Aggregate hospital costs, \$ millions	National costs, %	Number of hospital stays, thousands	Hospital stays, %
1	Septicemia	23,663	6.2	1,297	3.6
2	Osteoarthritis	16,520	4.3	1,023	2.9
3	Liveborn	13,287	3.5	3,765	10.6
4	Complication of device, implant or graft	12,431	3.3	632	1.8
5	Acute myocardial infarction	12,092	3.2	602	1.7
6	Congestive heart failure	10,218	2.7	882	2.5
7	Spondylosis, intervertebral disc disorders, other back problems	10,198	2.7	555	1.6
8	Pneumonia	9,501	2.5	961	2.7
9	Coronary atherosclerosis	9,003	2.4	458	1.3
10	Acute cerebrovascular disease	8,840	2.3	585	1.6
11	Cardiac dysrhythmias	7,178	1.9	710	2.0
12	Respiratory failure, insufficiency, arrest (adult)	7,077	1.9	387	1.1
13	Complications of surgical procedures or medical care	6,079	1.6	465	1.3
14	Rehabilitation care, fitting of prostheses, and adjustment of devices	5,373	1.4	390	1.1
15	Mood disorders	5,246	1.4	836	2.3
16	Chronic obstructive pulmonary disease and bronchiectasis	5,182	1.4	645	1.8
17	Heart valve disorders	5,151	1.4	123	0.3
18	Diabetes mellitus with complications	5,142	1.3	531	1.5
19	Fracture of neck of femur (hip)	4,861	1.3	303	0.9
20	Biliary tract disease	4,722	1.2	405	1.1
<b>Total for top 20 conditions</b>		181,762	47.7	15,554	43.7
<b>Total for all stays</b>		381,439	100.0	35,598	100.0
Abbreviation: CCS, Clinical Classifications Software					
Source: Agency for Healthcare Research and Quality (AHRQ), Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project (HCUP), National Inpatient Sample (NIS), 2013					

# The Human Cost



- ~ 300 000 deaths/year USA
- Sepsis survivors have a shortened life expectancy
- Increased risk of major adverse cardiovascular events
- High incidence of cognitive dysfunction and PTSD
- Impaired quality of life
- 42% more likely to commit suicide



# William Osler...

“Except for a few occasions patients’ appear to die from the body’s response to infection rather than from it”

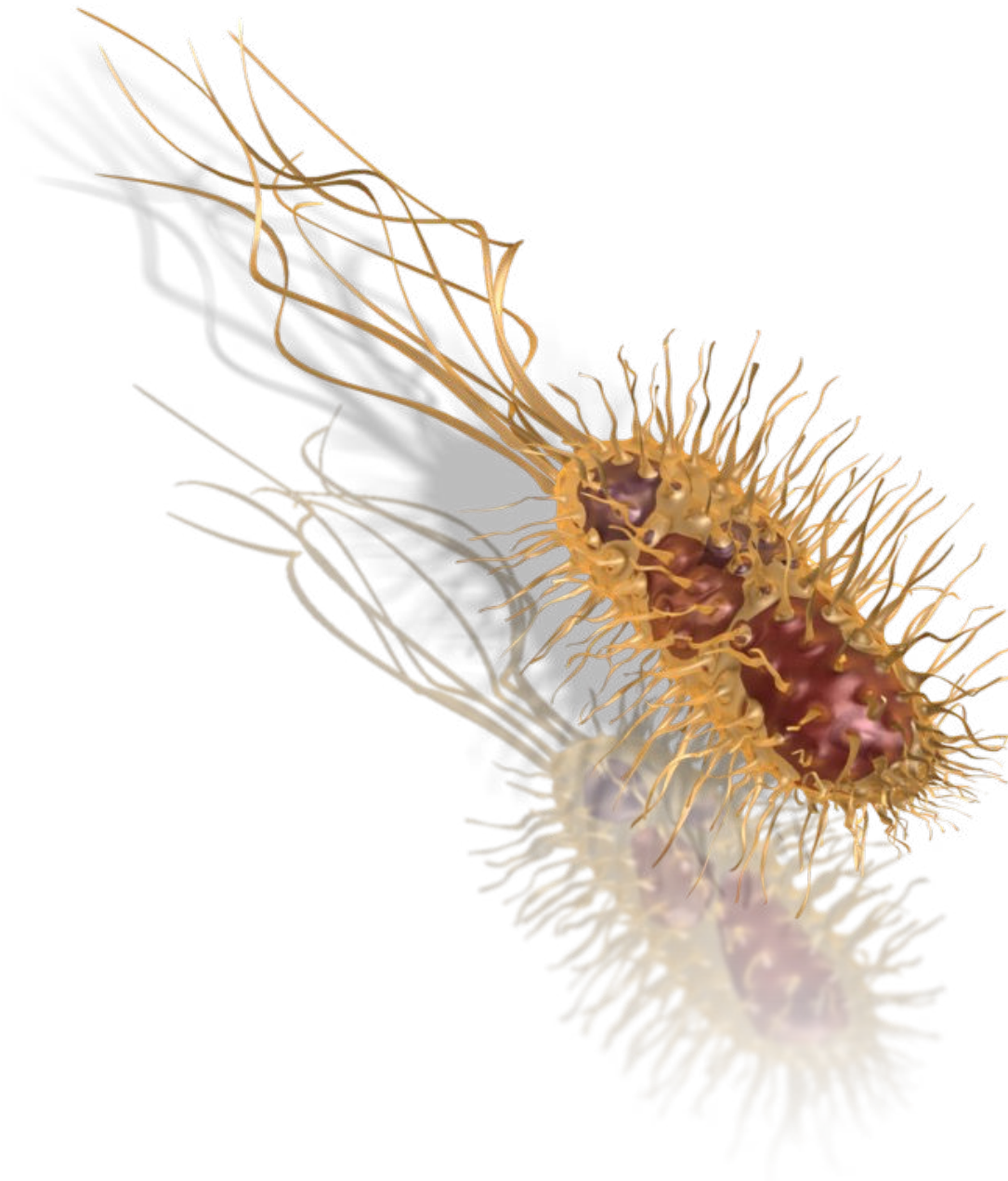


*The General Practitioner, Nov. 1902*

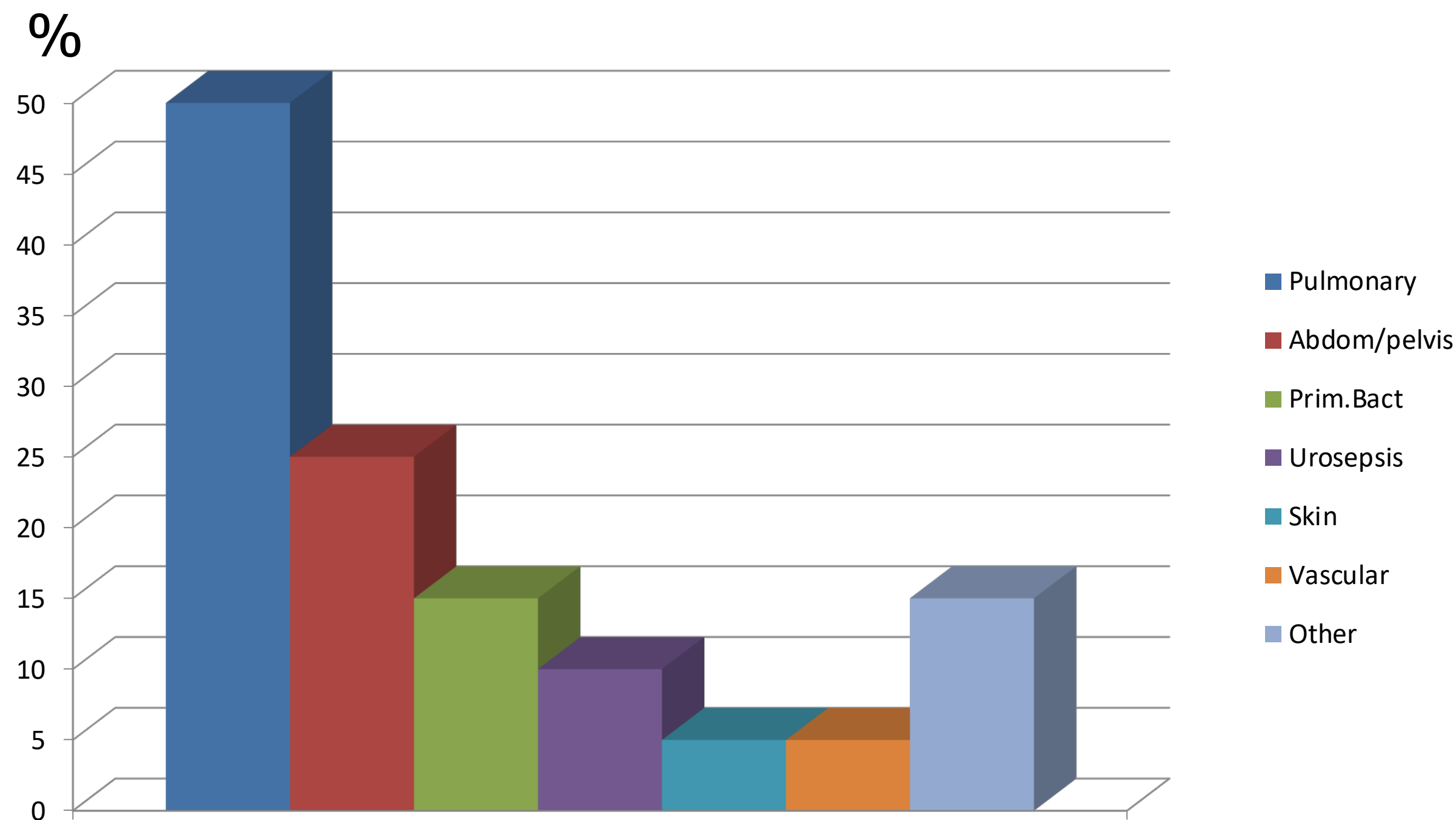


# Microbiology

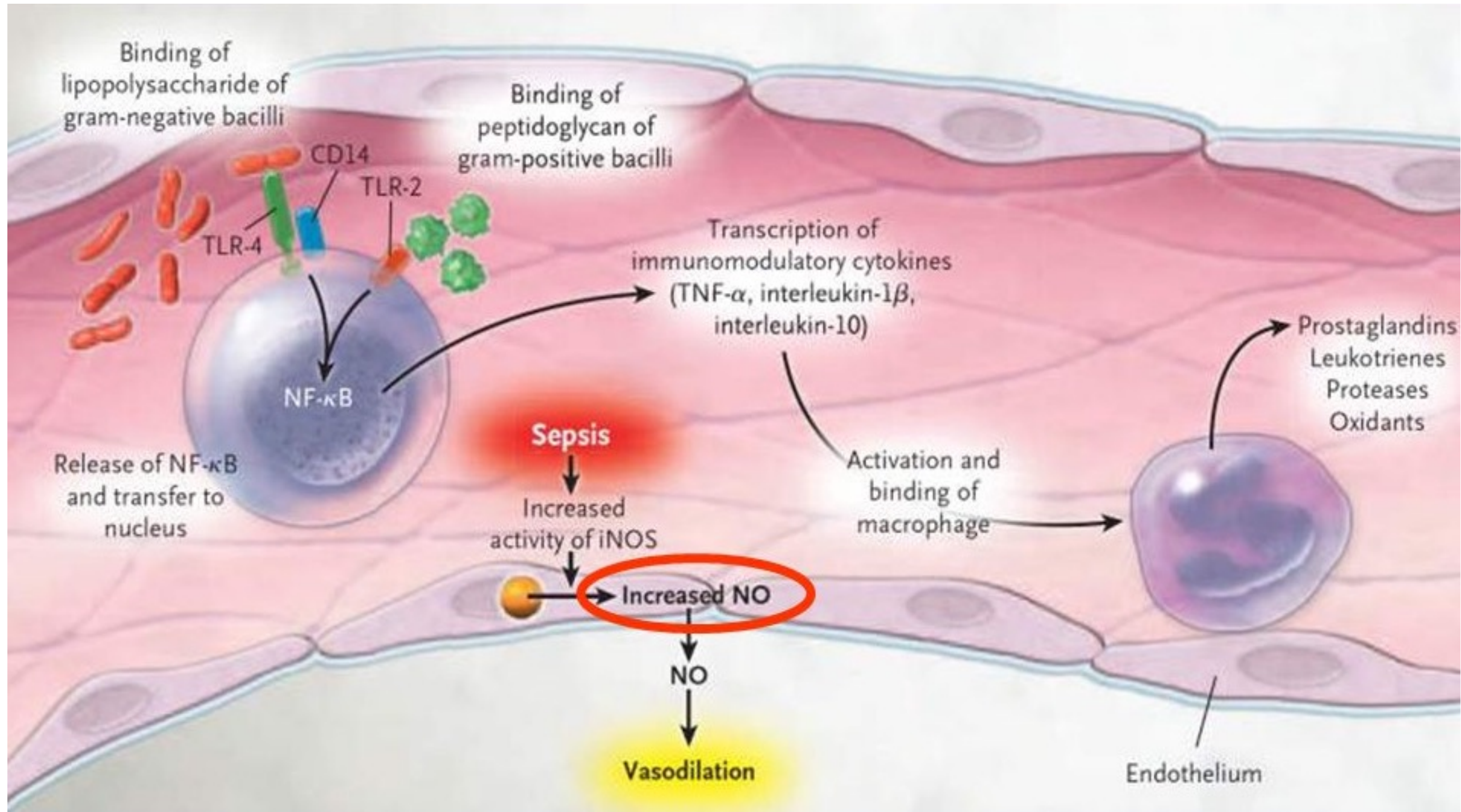
- 25% Gram negatives
- 25% Gram positives
- 20% Mixed gram negative/positive
- 3% Fungal (candida)
- 2% Anaerobes
- 25% Unknown



# Severe Sepsis: Primary Source

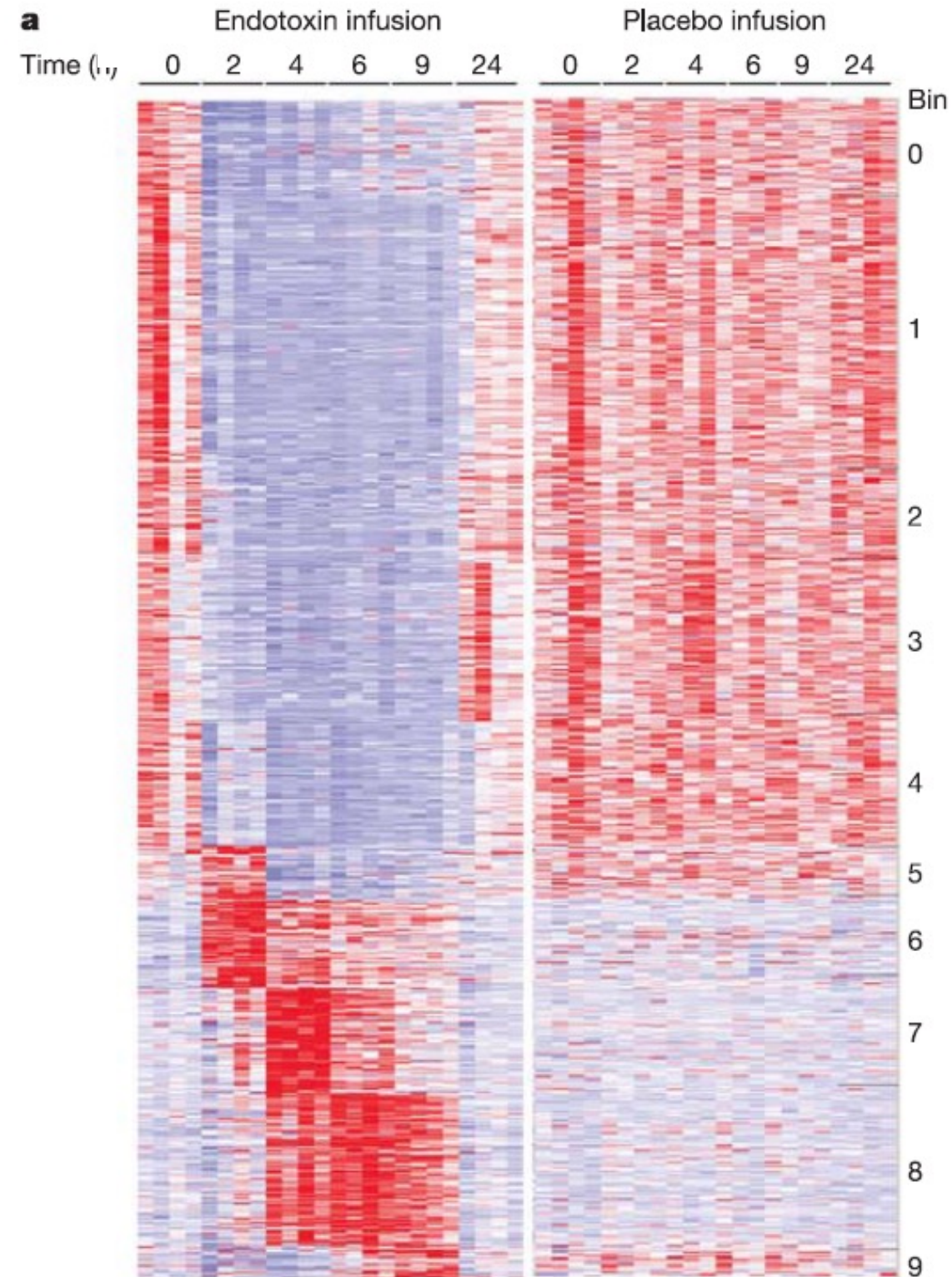


# PAMPs and activation of the inflammatory cascade





# A Network-Based Analysis of Systemic Inflammation in Humans

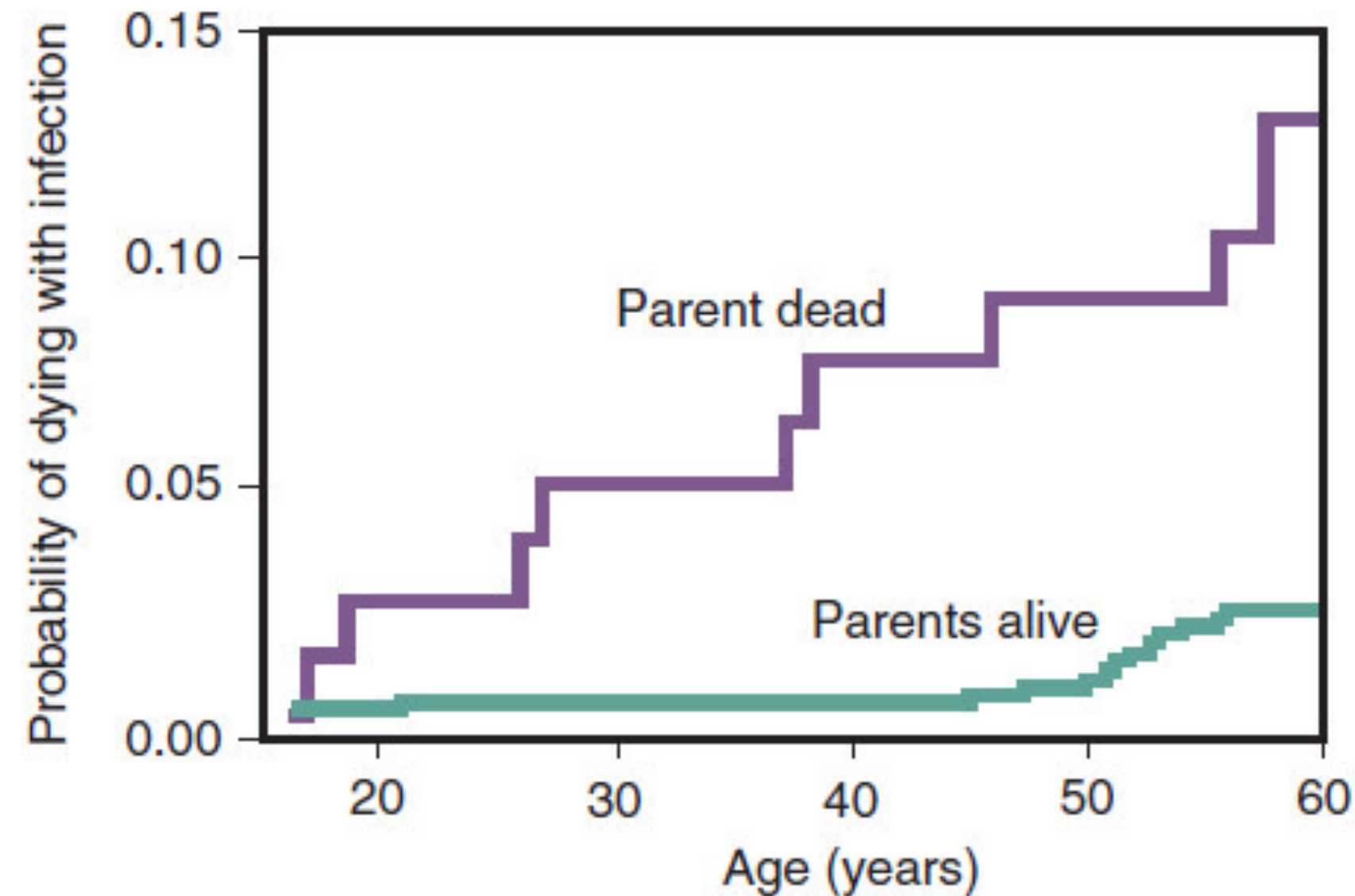


3714 unique genes

- Pro-inflammatory cytokines
- Anti-inflammatory cytokines
- Chemokines
- Adhesion molecules
- Transcription factors
- Enzymes
- Clotting factors
- Stress proteins
- Etc., etc..

Calvano SE et al. Nature 2005;437:3985

# The Genetics of Sepsis

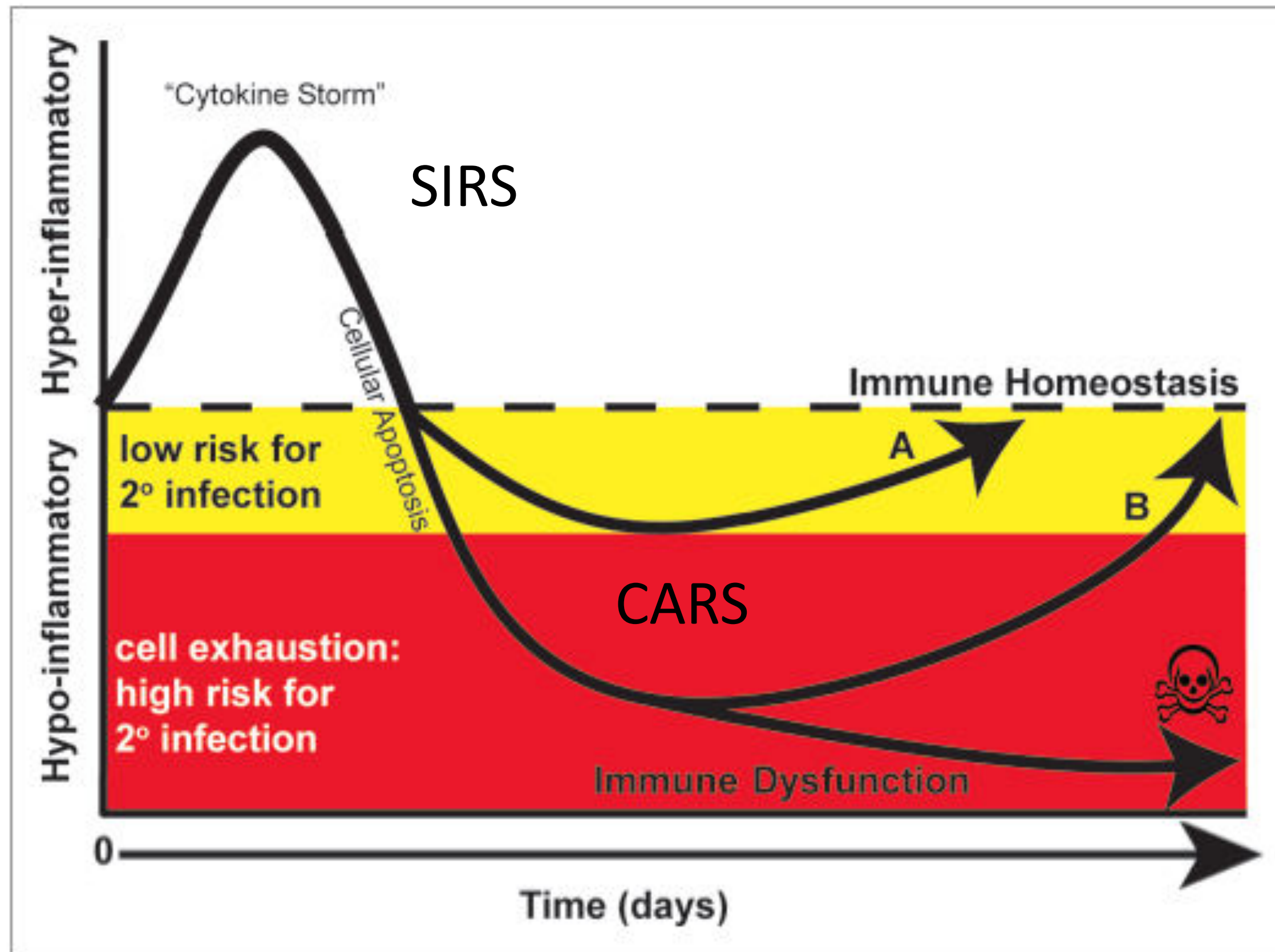


Probability of dying from an infection with at least one biologic parent who died before age 50 of an infection versus adoptees whose biologic parents were alive at that age.

*Sorensen TIA, et al. Genetic and environmental influences on premature death in adult adoptees.*

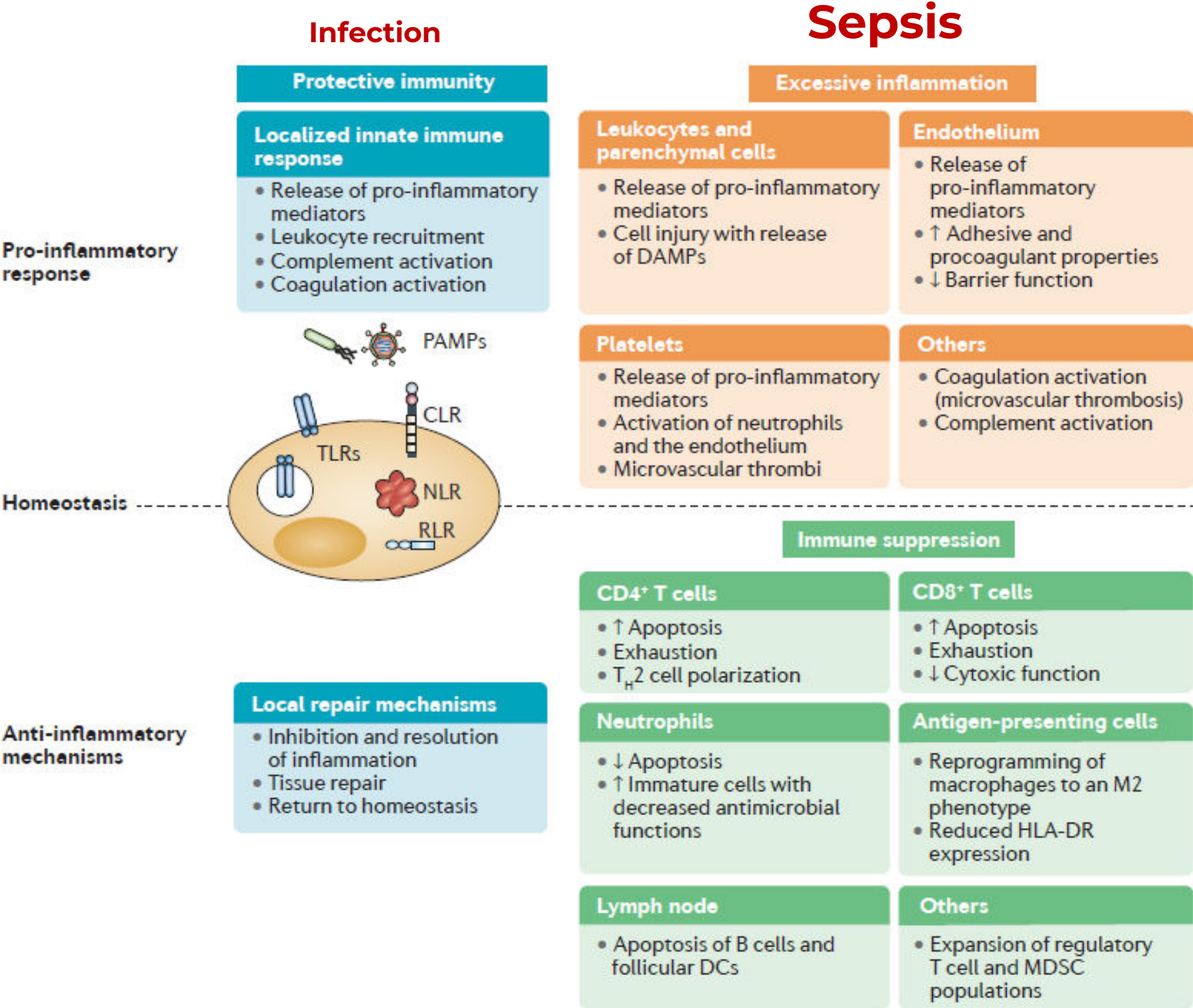
*N Engl J Med. 1988;318:727-732*

# Traditional Model





# It's more complicated...



# Acute Organ Dysfunction in Severe Sepsis

Altered  
Consciousness  
Confusion  
Psychosis

Tachypnea  
 $\text{PaO}_2 < 70 \text{ mm Hg}$   
 $\text{SaO}_2 < 90\%$   
 $\text{PaO}_2/\text{FiO}_2 \leq 300$

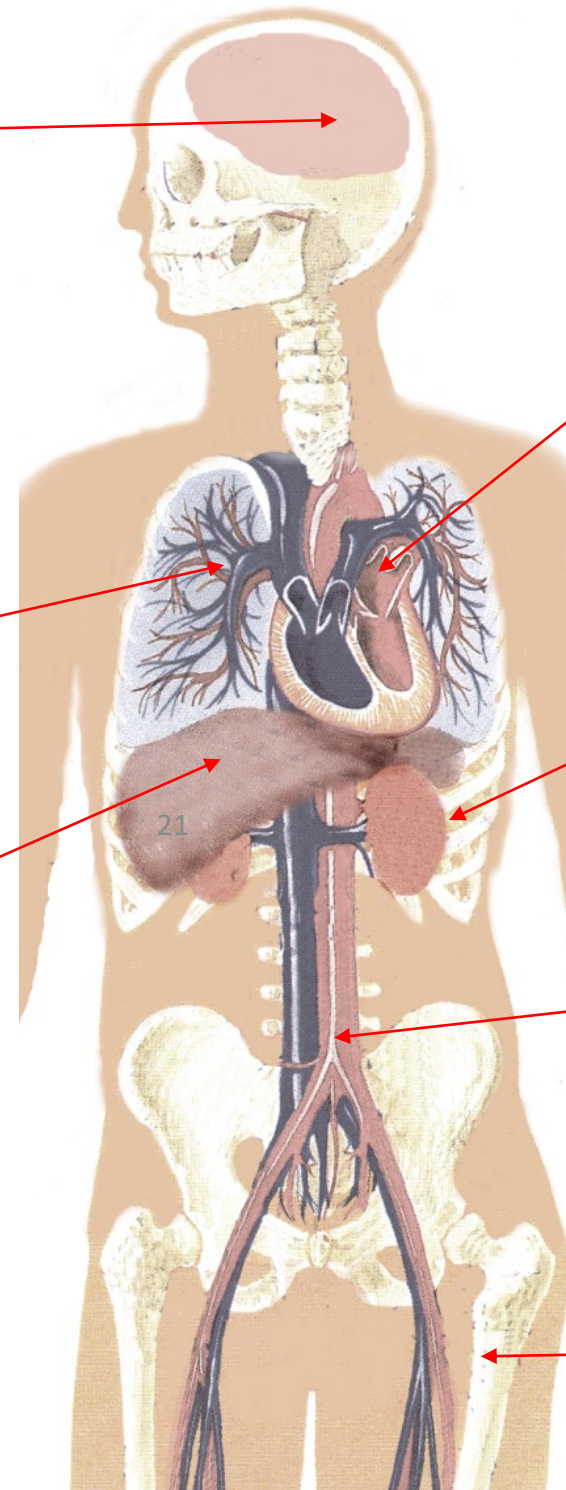
Jaundice  
 $\uparrow$  Enzymes  
 $\downarrow$  Albumin  
 $\uparrow$  PT

Tachycardia  
Hypotension  
Vasodilatation  
 $\downarrow$  Contractility

Oliguria  
Anuria  
 $\uparrow$  Creatinine

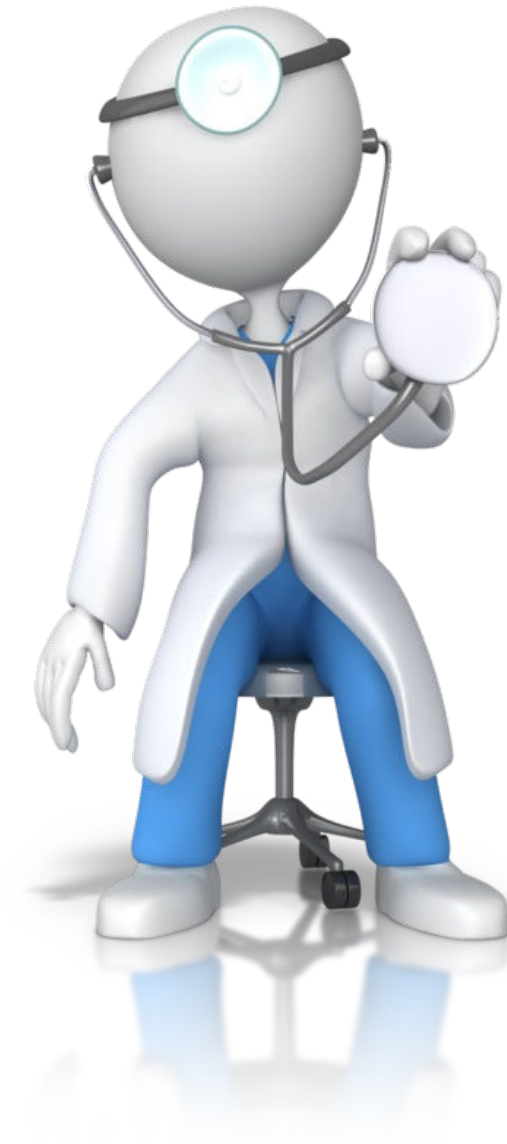
$\downarrow$  Platelets  
 $\uparrow$  PT/APTT  
 $\downarrow$  Protein C  
 $\uparrow$  D-dimer

Neuropathy  
Myopathy



# The Hemodynamic derangements of sepsis

- Vasoplegic shock/vasodilatory shock (**VENODILATION**)
  - Nitric oxide
  - $K_{ATP}$
  - Vasopressin
- Leaky capillaries
  - Glycocalyx
  - Endothelial junctions
- Myocardial depression + diastolic dysfunction
  - Nitric Oxide
  - Tissue edema





# Presenting Symptoms Independently Predict Mortality in Septic Shock: Importance of a Previously Unmeasured Confounder\*

- Objective
  - To determine the frequency and impact of vague symptoms not specific for infection on outcome of septic shock
- Methods
  - Retrospective chart review study of adult patients with septic shock
  - Explicit symptoms: fever, chills, or rigors, cough with productive sputum, dysuria, reported skin redness, etc.
  - Vague symptoms: fatigue, weakness, and abdominal or generalized pain without fever, etc.
- Results
  - Of 654 cases **37% presented with vague symptoms**
  - Time to antibiotics significantly longer 1.6 vs 0.8 hr.
  - Vague symptoms independently associated with mortality (OR 2.12, CI 1.3 -3.4)

# Early Detection of Sepsis

- Heart rate > 90/min
- Resp. Rate > 20/min
- Temp > 38.0° or < 36°
- WBC > 12 or < 4
- Confusion
- Hypotension (SBP < 90 mmHg)
- **PCT > 0.5 ng/ml**
- **Band count > 5%**
- **Lymphocytopenia < 0.5 x 10<sup>3</sup>uL**
- **Thrombocytopenia < 150 x 10<sup>3</sup>uL**
- **Neutrophil/lymphocyte > 10**

SIRS Criteria

# Steps to the Cure.....

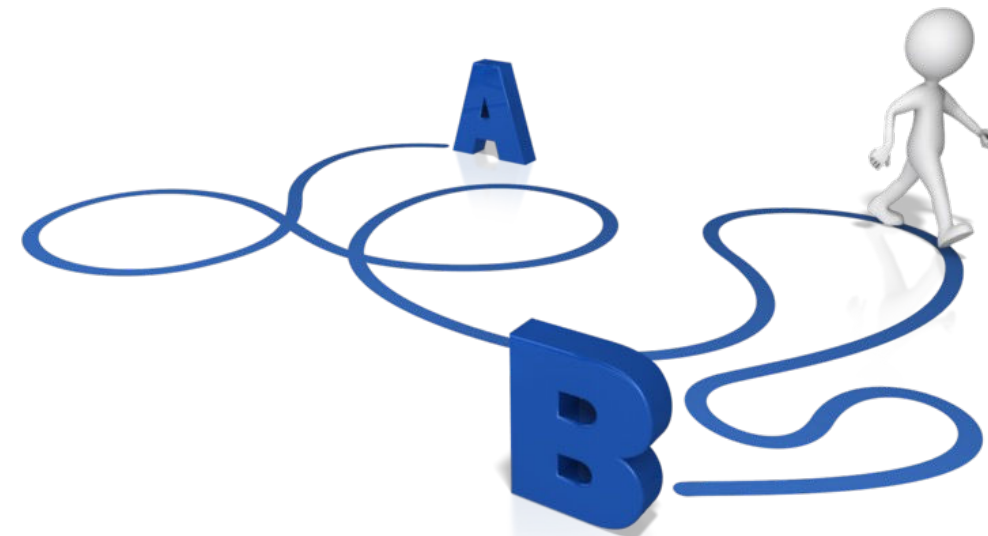
- Early Diagnosis
- Early administration of the correct antibiotics, in the correct dose
- Source Control
- Conservative, physiologic approach to fluid resuscitation
- Early use of Norepinephrine
- The “Metabolic Resuscitation Protocol”
  - Steroids, Vitamin C and Thiamine
- Multidisciplinary, team approach to patient care
- State-of-the-art evidence based supportive care





# Goals of Hemodynamic Support

- **MAP > 60-65 mmHg**
- HR < 100/min
- Adequate tissue perfusion
  - Clinical examination
  - CI > 2.2 l/min/m<sup>2</sup>
- CVP < 8 mmHg



# The Hemodynamic derangements of sepsis

- **FLUIDS INCREASE** Vasoplegic shock/vasodilatory shock
  - Nitric oxide
  - $K_{ATP}$
  - Vasopressin
- **FLUIDS INCREASE** Leaky capillaries
  - Glycocalyx
  - Endothelial junctions
- **FLUIDS INCREASE** Myocardial depression
  - Nitric Oxide
- **FLUIDS INCREASE** diastolic dysfunction

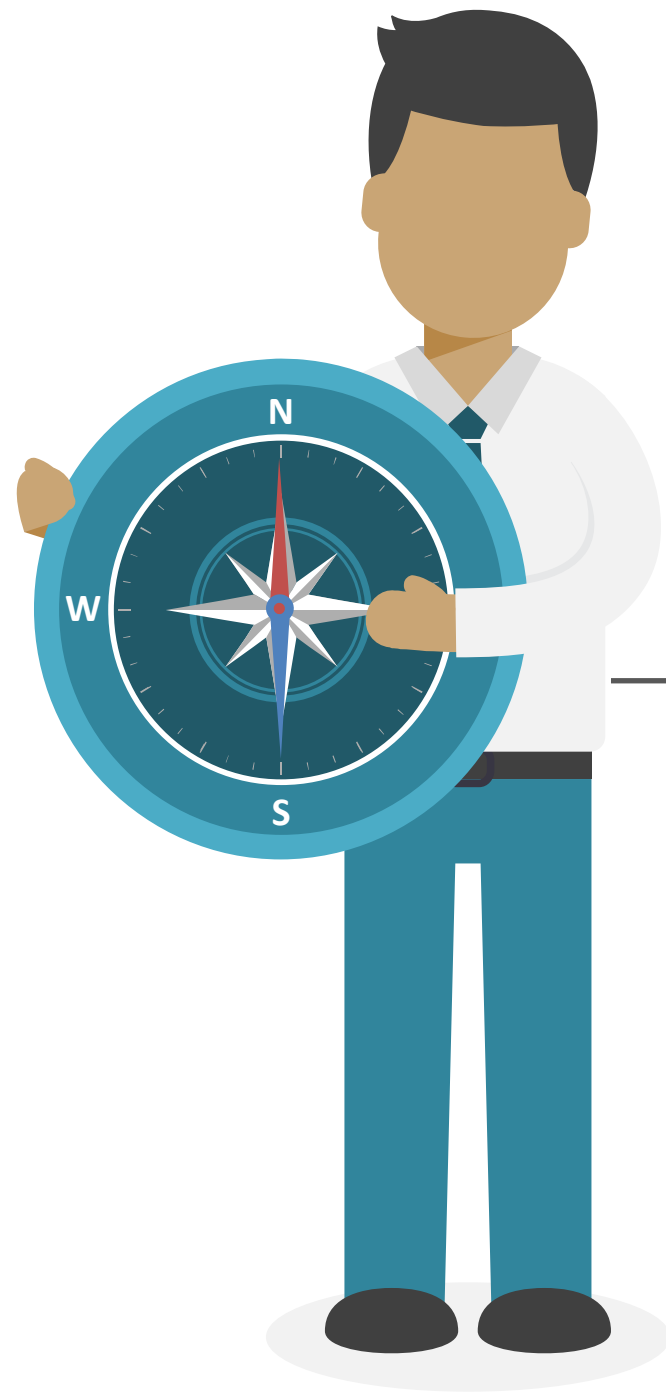


# Key Roles of Vitamin C in Sepsis

Key Role	Mechanism
Free radical scavenger	Scavenges extracellular, intracellular and mitochondrial ROS; limits oxidation of mitochondrial proteins, enzymes, lipoproteins, cell membrane, etc.
Anti-inflammatory	Inhibits activation of NFκB, decreases HMGB1, inhibits histamine, prevents NETosis, inactivates HIF-1α
Microcirculation	Increases eNOS, decreases iNOS, preserves tight junctions
Immune function	Supports lymphocyte proliferation, increases neutrophil bacteriocidal action, improves chemotaxis, stimulates interferon production, decreases T regulatory cells (Tregs)
Anti-thrombotic	Decreases platelet activation and tissue factor expression, increases thrombomodulin
Synthesis of catecholamines	Acts cofactor in synthesis of epinephrine, dopamine and vasopressin. Increases adrenergic sensitivity
Wound Healing	Hydroxylation of procollagen, increased expression of collagen mRNA



# Philosophy of the Hydrocortisone, Ascorbic Acid and Thiamine (HAT) Protocol



Targets the hosts response to infection  
Anti-inflammatory + antioxidant



Multiple agents with overlapping and  
synergistic actions



**SAFE – No side effects**



**CHEAP and readily available**

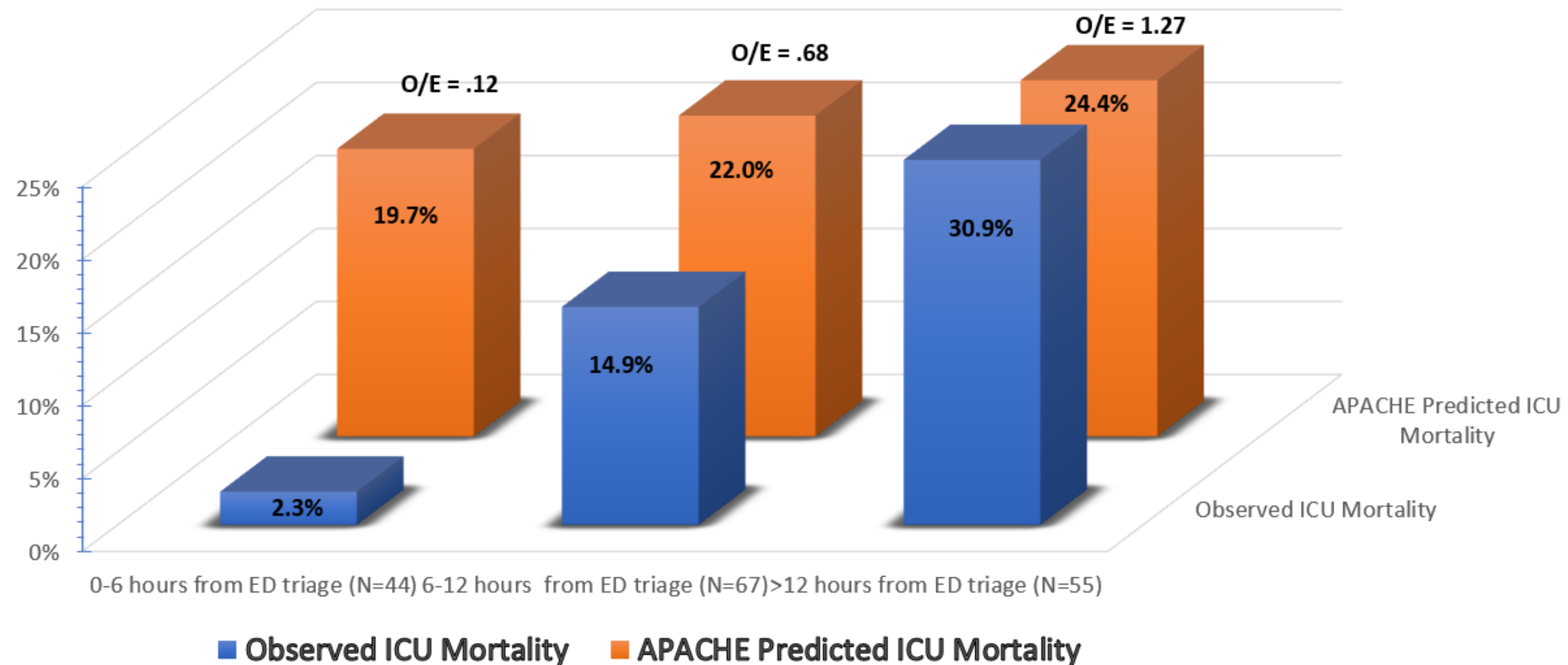
## SNGH – Hospital Sepsis Mortality



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HEALTH ANALYTICS<sup>®</sup>  
IBM Watson Health<sup>™</sup>

**FLCCC**<sup>®</sup>  
ALLIANCE

# Septic Shock patient cohorts by time period from Emergency Room triage to HAT therapy initiation

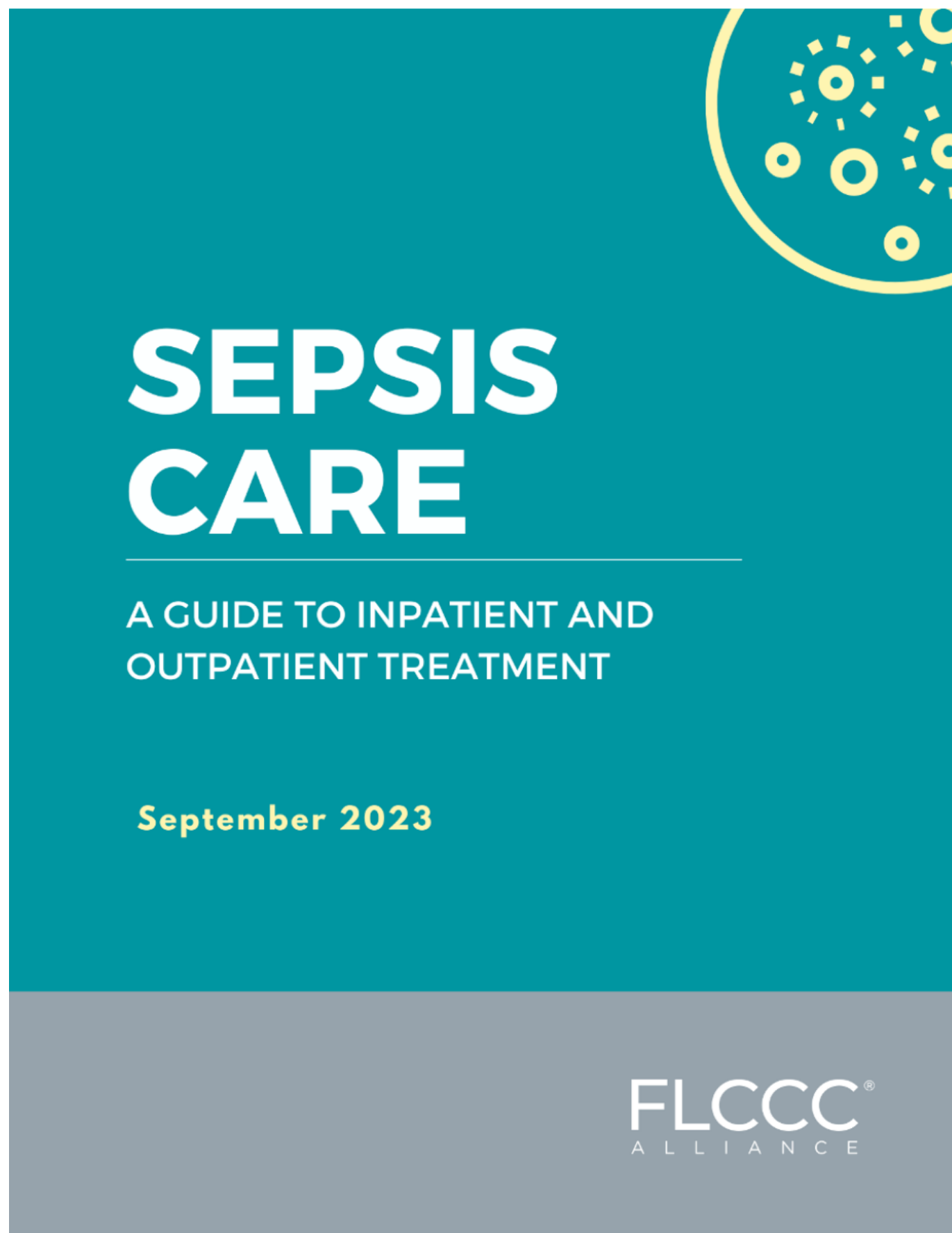


Kory P, et al. *Crit Care shock* 2020;23:23



# HAT Rx: Characteristics of RCTs

Study	n	Mean time to Rx	Mortality	SOFA/Pressor
Marik -2017	94	< 6 hours	8.5 vs. 40.4%	YES
Vitamins-2020	216	> 18 hours	28.6 vs. 24%	NO
Oranges-2020	137	< 10 hours	16.4 vs. 19%	YES
ACTS-2020	205	> 14.5 hours	34.7 vs. 29.3	NO
Wani-2020	100	< 10 hours	40 vs. 42%	YES
VICTAS -2021	501	> 14.7 hours	22 vs.24%	NO
Feng - 2021	136	1.7 hours	8 vs. 15%	YES



# Find the: Sepsis Care Protocol

**Under the  
“Treatment Protocols” tab  
FLCCC.net**