Unpacking an Engima:

SIMPLIFYING SEPSIS IN ADULTS

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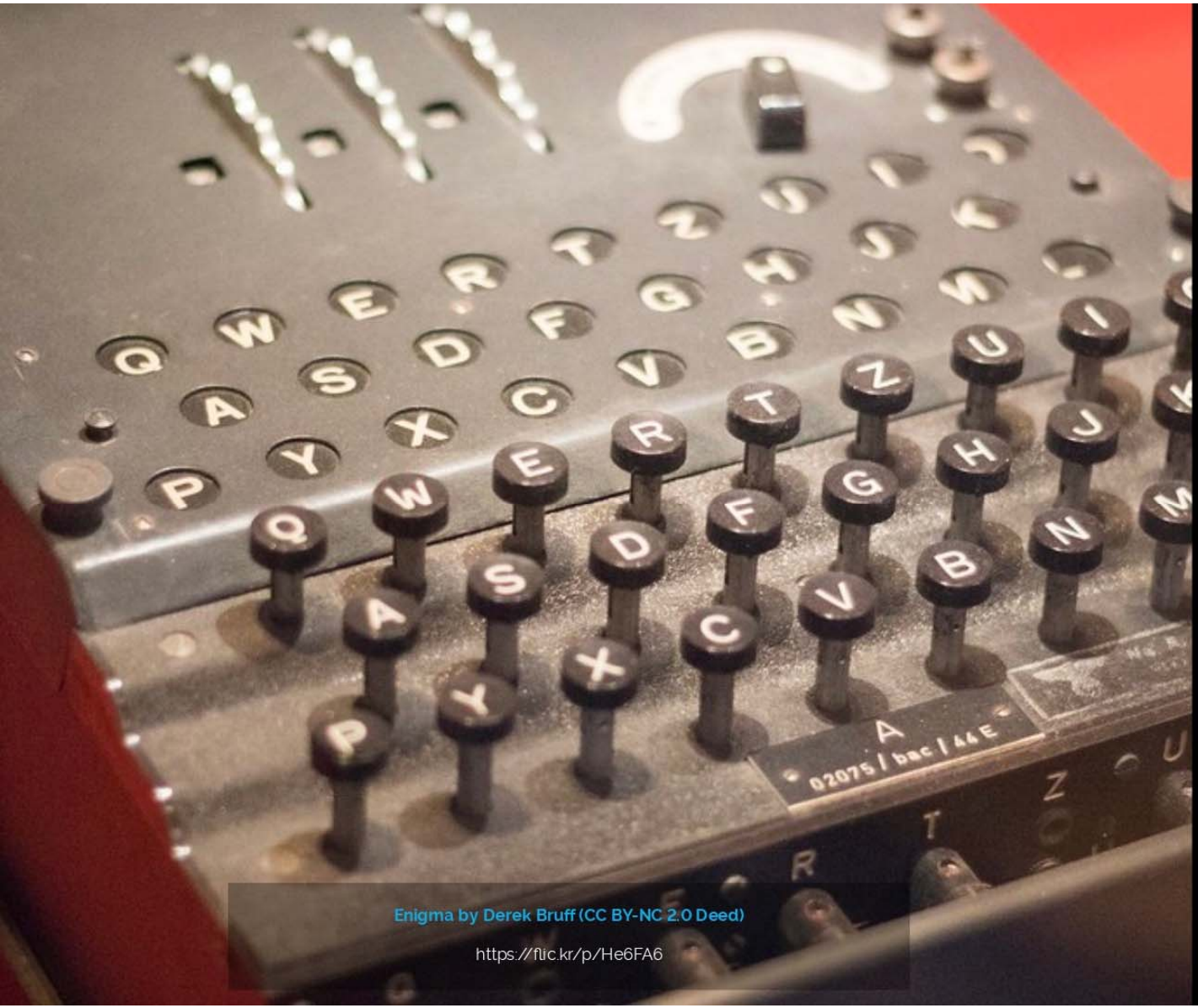
Open AI. DALL.E 3 (2024)

Non-Declaration Statement

I have no relevant relationships with ineligible companies to disclose within the past 24 months.



German Engima

Objectives

By the completion of the presentation, participants will be able to:

- **Summarize the evolution of diagnosis and treatment of sepsis**
- **Define uncomplicated infection, sepsis, and septic shock using pathophysiologic clues and clinical criteria**
- **Evaluate patient scenarios by key measures, and best practices in the identification and treatment of sepsis**
- **Identify current go-to antimicrobials for common septic patient scenarios**

Section 1

History/Epidemiology

"THE TRIUMPH OF DEATH," BY PIETER BRUEGEL THE ELDER (CC BY-NC 2.0 DEED)

"Sepsis"

- Comes from the Greek word "sepo" for "I rot"
- First documented in Homer's peom (2,700 years ago)
- First definition: 1914: Hugo Schottmuller
- Further defined in 1991 at a SCCM-ACCP conference by Roger Bone

Funk, Duane & Parrillo, Joseph & Kumar, Anand.

Gyawali, B., Ramakrishna, K., & Dhamoon, A. S.

33%

1/3 of all hospital deaths had sepsis during hospitalization

CDC

In a typical year...

American who will develop sepsis

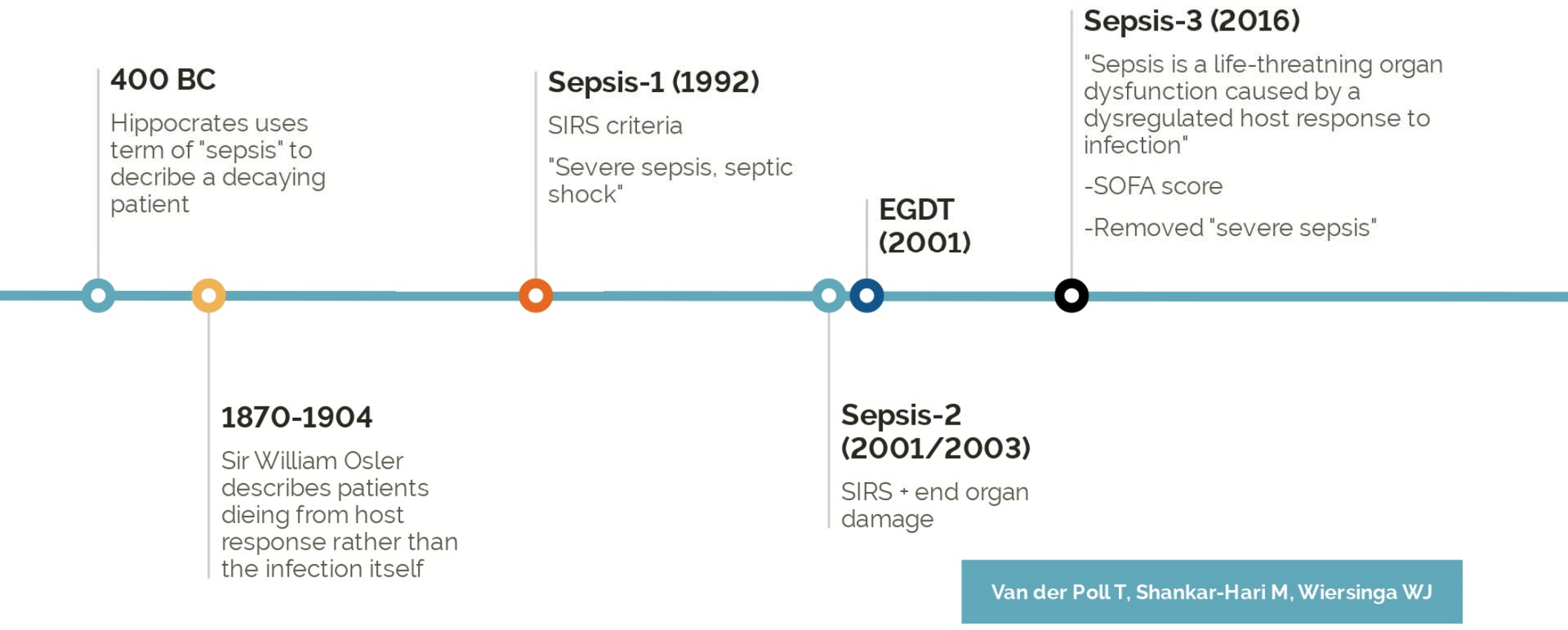
1.7 million

Sepsis Deaths

270,000

CDC

The Evolution of Sepsis



Van der Poll T, Shankar-Hari M, Wiersinga WJ

Evolution of the Term: Sepsis

Sepsis-1 (1991)

SCCM-ACCP

-Termed SIRS

-Sepsis = SIRS + Infection

-Purposely very sensitive to cast a wide net

Sepsis-2 (2001)

+Europeans

-Focus: many facets involved in sepsis

-Added complicated list of common signs/symptoms

-Little buy-in as Sepsis-1 was simpler

Sepsis-3 (2016)

-Focus: sepsis needs to be about worse case scenarios, i.e. end organ damage

-Septic shock: shock refractory to fluids/vasopressors, increased blood lactate levels

-SOFA score/qSOFA

-Removed 'Severe Sepsis'

Jean-Louis Vicent

Early Goal Directed Therapy (2001: Rivers et al)

Any patient with SIRS criteria, SBP ≤90mmHg,

OR

lactate ≥4 mmol/liter

All patient received

Vitals

Labs

Cardiac monitoring

Pulse oximetry

Urinary catheterization

Arterial line

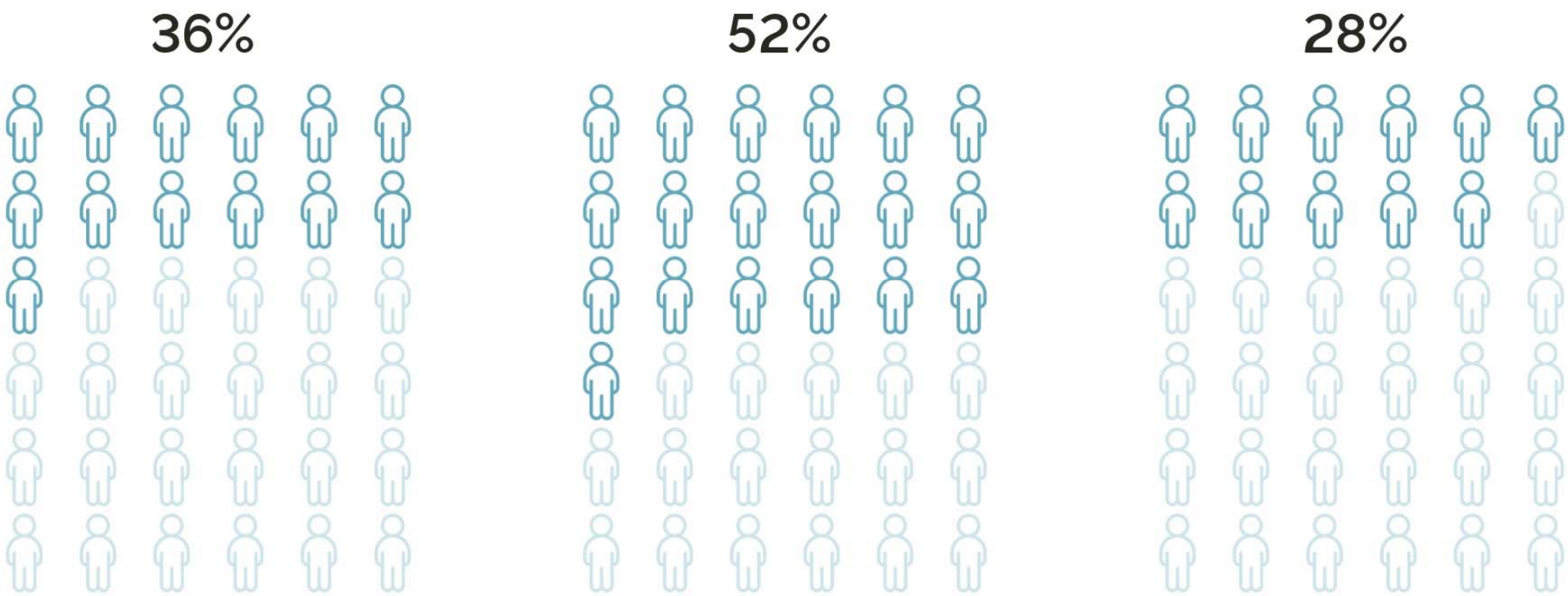
Central venous catheter

Comparison

Standard care vs "Earl Goal-directed therapy witin SIX hours"

Strict hemodynamic criteria

EGDT Outcomes : Reductions in Mortality



Rivers et al.

Since Rivers et al

- **Approach not replicated in multiple RCT**
  ProCESS, ProMISe, ARISE: EGDT not superior than usual care
- **Not seen as harmful**
- **Useful in terms of big picture**

Rhodes, A., Evans, L. E., Alhazzani, W., et al

Evolution of the Term: Sepsis

Sepsis-"4" (2021)

-Don't recommend qSOFA

-Providers may use clinical judgment with administering ABx, and if shock absent + lower suspicion of infectious causes, delay ABx to THREE hours after presentation

-Balanced crystalloids > normal saline

-Start vasopressors peripherally if needed

-After initial bolus, no difference between restrictive vs. liberal fluid administration (CLOVERS/CLASSIC trials)

Evans L, Rhodes A, Alhazzani W, et al.

Section 2

Patho-

Pathogenesis

Starts with innate immunity

Macrophages

Monocytes

Neutrophils

NKC

Activated by:

Pathogen-associated molecular patterns (PAMPs)

Damage-associated molecular patterns (DAMPs)

(intracellular material/molecules released from dead/dying cells)

Causes

Transcription (inside innate immune cells of proinflammatory cytokines)

Gyawali, B., Ramakrishna, K., & Dhamoon, A. S.

Pathogenesis

Proinflammatory cytokinds

Activate and cause proliferation of:

- Leukocytes
- Compliment system
- Tissue factor production

Hypercoagulability

Tissue factor activates coag. cascade

Microthrombi cause local perfusion defects (local hypoxia ensues)

Depressed protein C leads to un-inhibited clot formation

Gyawali, B., Ramakrishna, K., & Dhamoon, A. S.

Pathogenesis

Immunosupression

Th and Tc cells apoptose

Neutrophil's chemokine receptors stop working

Cardiovascular Malfunction

Circulating cytokines interfere with cardiac myocytes' mitochondrial function

Systolic AND diastolic dysfunction

Arterial AND venous dilation

Failing junctions cause leaking fluid into intersititum

Gyawali, B., Ramakrishna, K., & Dhamoon, A. S.

Pathophysiology

Pulmonary

Fluid enters lungs

V-Q mismatch

Worsening hypoxia

Renal

Decreased renal perfusion and ATN

leads to AKI

Gastrointestinal

Leaky linings cause bacteria to leave bowel

Neural

Blood-brain barrier changes

Cerebral edema

Can lead to encephalopathy

Gyawali, B., Ramakrishna, K., & Dhamoon, A. S.

The balance of immune activation in sepsis

Adapted from Giamarellos-Bourboulis, Aschenbrenner, Bauer, et al

Beneficial: Pro-inflammatory immune response

Local activation of cytokines
Activate phagocytes, killing cells
Local endothelial recruit

Beneficial: Counter-regulatory immune response

Regulation and control of inflammation
Increase tissue repair

Deleterious: Pro-inflammatory immune response

Systemic cytokine release, endothelial activation causes hypotension
Systemic complement activation
DIC
Organ Dysfunction

Deleterious: Counter-regulatory immune response

Too strong inhibition of antimicrobial mechanism
Immunosuppression
Opportunistic infections

Section 3

Definitions/Constructs

Definition

> "Sepsis is a highly heterogeneous clinical syndrome that affects a broad range of patients with a great variety of underlying comorbidities..."

Giamarellos-Bourboulis et al.

Definition

> “...there is also a broad range of causitve pathogens and disease entities, with diverse pathogenesis and pathophysiology„

Giamarellos-Bourboulis et al.

Sepsis as a "construct"

> "...'sepsis' is only a **construct** that we use to define a situation that can be associated with a number of criteria (or characteristics) and we should not confuse the definition per se with the criteria"

Jean-Louis Vincent
Evolution of the Concepts of Sepsis

Sepsis as a "construct"

> "Moreover, when speaking about sepsis, we should not talk about diagnosis, which can be defined as the determination of a specific disease entity...As a construct or syndrome, sepsis cannot be 'diagnosed' but is 'recognized' or 'identified'"

Jean-Louis Vincent
Evolution of the Concepts of Sepsis

Section 4

Scenarios

Jess

20 year old female

Hx: ALL, currently undergoing treatment

Presents to the ER for malaise

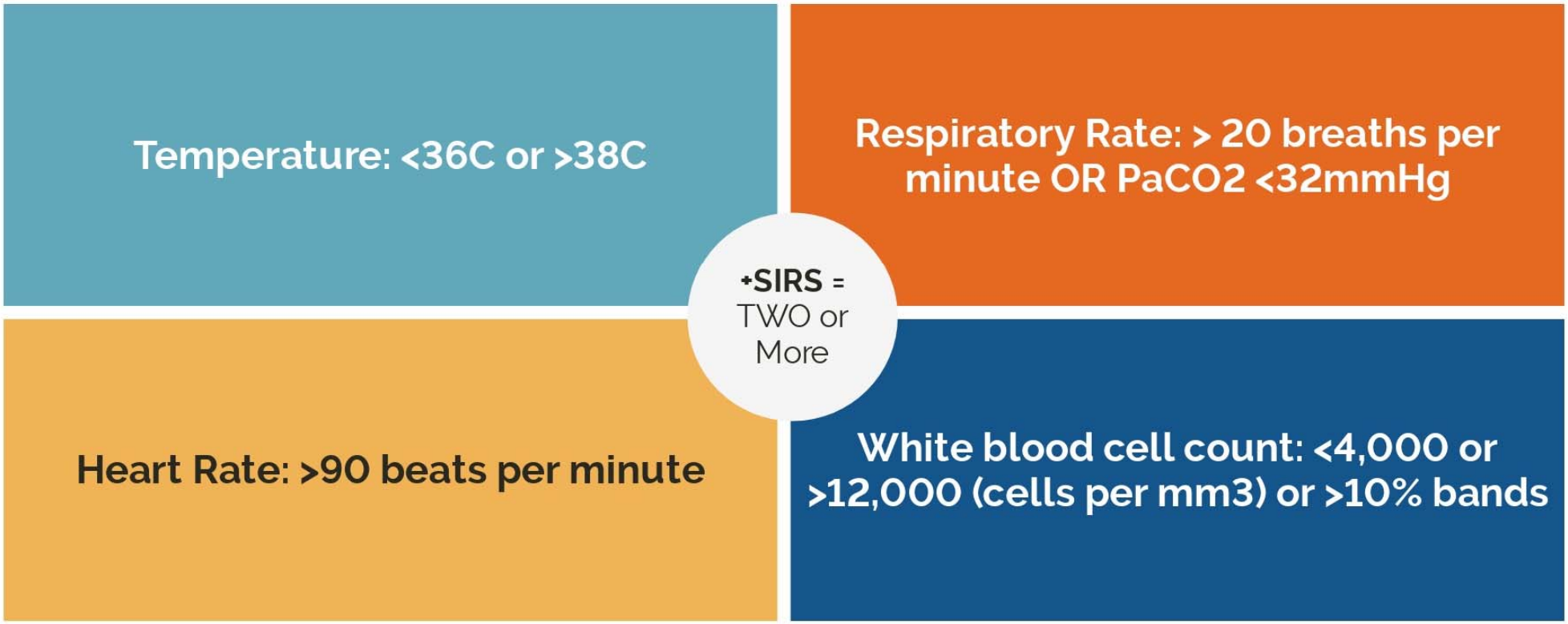
HR: 120

Temp: 37C

RR: 22/min

CBC: WBCs = 2,000/mmm3

Systemic **I**nflammatory **R**esponse **S**yndrome (**SIRS**)



Sequential **O**rgan **F**ailure **A**ssessment **S**core (**SOFA**)

System	0	1	2	3	4
Respiratory (PaO2/FiO2)	≥400mmHg	<400mmHg	<300mmHg	<200mmHg w/ respiratory support	<100 mmHg w/ respiratory support
Coagulation (Platelets x10^3)	≥150	<150	<100	<50	<20
Liver (Bilirubin, mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12
Cardiovascular	MAP≥ 70mmHg	MAP<70mmHg	Dopamine <5 or any dobutamine	Dopamine 5.1-15 or Epi ≤0.1 or Norepi ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepi >0.1
CNS (GCS)	15	13-14	10-12	6-9	<6
Renal (Creatinine, mg/dL)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
Renal (Urine output)				<500	<200

Singer M, Deutschman CS, Seymour CW, et al.

qSOFA

Altered Mental State

GCS<15

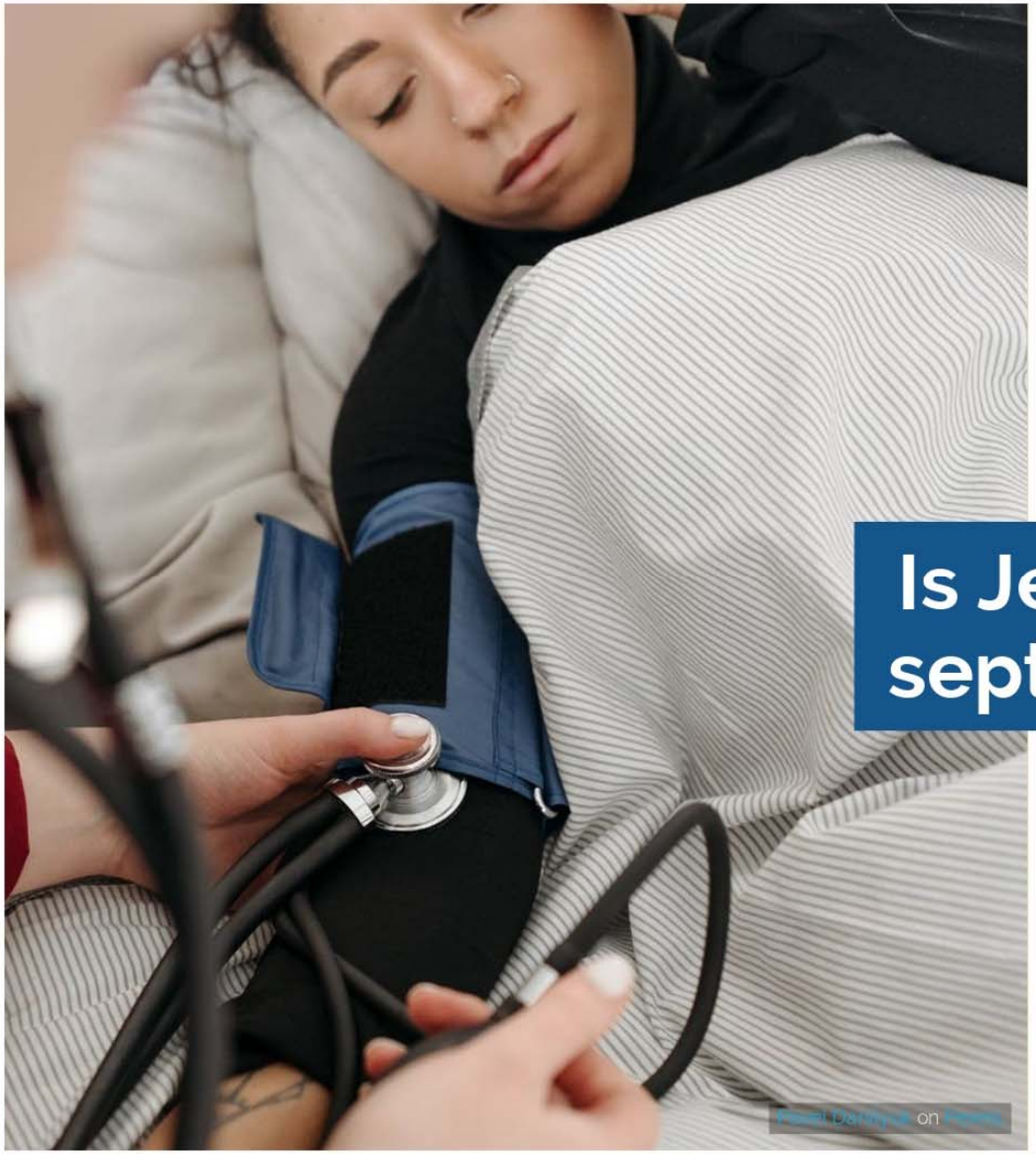
Tachypnea

Respiratory Rate ≥22/min

Hypotensive

SBP ≤100mmHg

Singer M, Deutschman CS, Seymour CW, et al.



Is Jess septic?

Jess

20 year old female

Hx: ALL, currently undergoing treatment

Presents to the ER for malaise

HR: 120

Temp: 37C

RR: 22/min

WBCs = 2,000/mmm3

New Definitions

1 **Sepsis**

Dysregulated host response to infection that leads to acute organ dysfunction

2 **Septic Shock**

Subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality risk

3 **Uncomplicated Infection**

Infections that doesn't lead to organ dysfunction, poor course, or death

SEVERE SEPSIS is NO LONGER part of *medical* terminology

Singer M, Deutschman CS, Seymour CW, et al.

Is Sarah septic?

Sarah

20 year old female

No past medical history

Presents to the ER upper respiratory symptoms

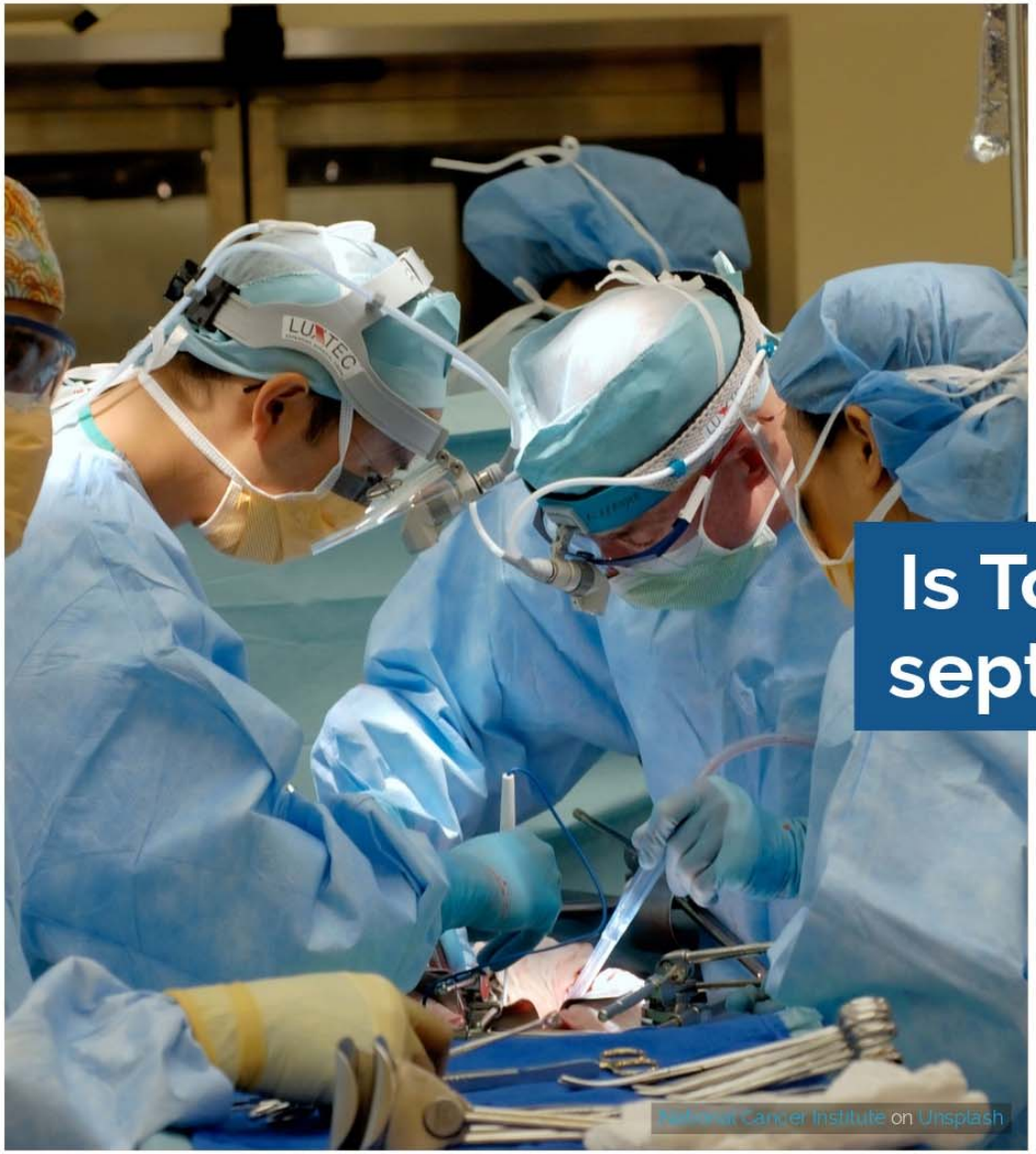
HR: 120

Temp: 39C

RR: 24/min

WBCs = WNL

COVID Positive



Is Tom septic?

Tom

20 year old male

No past medical history

Presents to the ER RLQ pain that started two hours ago

HR: 120

Temp: 39C

RR: 24/min

BP: 120/80

WBC: WNL

CT Abdomen: Appendicitis with perforation

Is Frank septic?

Frank

20 year old male

PMHx: IVDU

Presents to ED unconscious

HR: 120

Temp: 39C

RR: 24/min

WBCs = 20,000

BP: 80/40mmHg

Lactate: 5

Section 5

The NEW Science

Surviving Sepsis Campaign: 2021 Updates

Practice Changing Updates

Don't use qSOFA

Capillary Refill Matters

Use to guide resuscitation

Balanced Fluids > Normal Saline

Remember to consider IBW instead of actual weight

If 30mL/kg would be harmful, document!

Evans et al.

Surviving Sepsis Campaign: 2021 Updates

Practice Changing Updates

Norepinephrine should be FIRST-line agent

Add Vasopressin instead of escalating NorEpi

If that fails, consider Epinephrine

Aim for MAP of 65mmHg

Permissive hypotension (60-65mmHg) may not be a bad thing

Evans et al.

Surviving Sepsis Campaign: 2021 Updates

Practice Changing Updates

Continued shock? Consider adding corticosteroids

IV Hydrocortisone

(50mg q 6 hours for 200mg/day)

Vitamine C doesn't work

Antibiotic Timing

Shock: give within an hour

No shock, but septic: give within an hour

No shock, don't know what it is: give within THREE hours

Evans et al.

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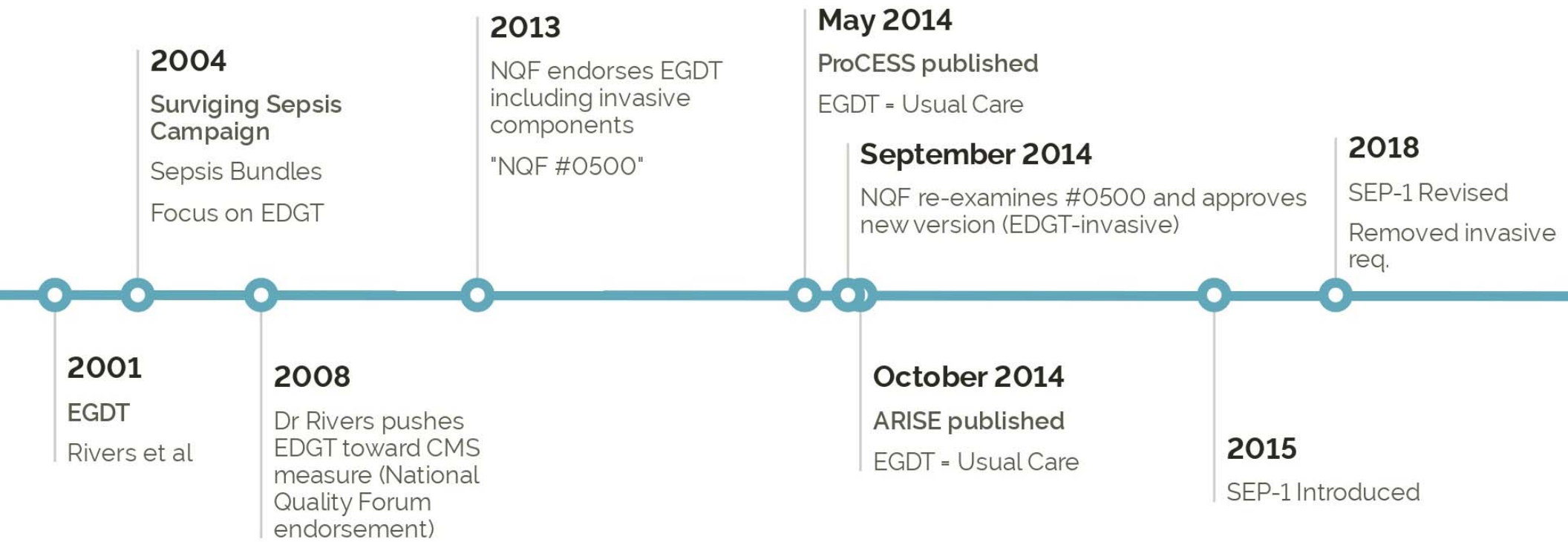
Section 6

Now Entering Reality

Sepsis History



Faust & Weingart

SEP-1 Definitions

Sepsis

1) Source of Infection

2) TWO (or more) SIRS criteria

Severe Sepsis

1) Sepsis

2) Organ dysfunction

- Eleveted serum lactate (above ULN)
- SBP <90mmHg
- Drop of BP>40mmHg

Septic Shock

1) Severe Sepsis

2) Hypotension despite adequae fluid resucitation

SEP-1: CMS, October 2023

SEP-1: Severe Sepsis Bundle

THREE (3) Hour Bundle

Lactate drawn

**If elevated (>2), must redraw within SIX (6) hours

Blood Cultures drawn

and drawn BEFORE antibiotics

Antibiotics given

SEP-1: CMS, October 2023

SEP-1: Septic Shock Bundle

All of the SEVERE sepsis bundle

30mL/kg of crystalloid fluids administered

within **three hours** of recognition

Provider judgment/documentation can justify not administering all fluids

Fluid assessment within SIX (6) hours

If vasopressors are started

SEP-1: CMS, October 2023

Final Section

Emperic Antimicrobials

Sepsis Deaths

Total sepsis deaths

270,000

Attributed to antibiotic resistance

35,000

Strich JR, Heil EL, Masur H.

CAP

Beta-lactam (ampicillin+sulbactam/ceftriaxone)
AND **Macrolide** (azithro/clarithromycin)

Monotherapy: **respiratory fluoroquinolone**
(levofloxacin or moxifloxacin)

RF for MRSA/Pseudomonas? + Vanc/Linezolid

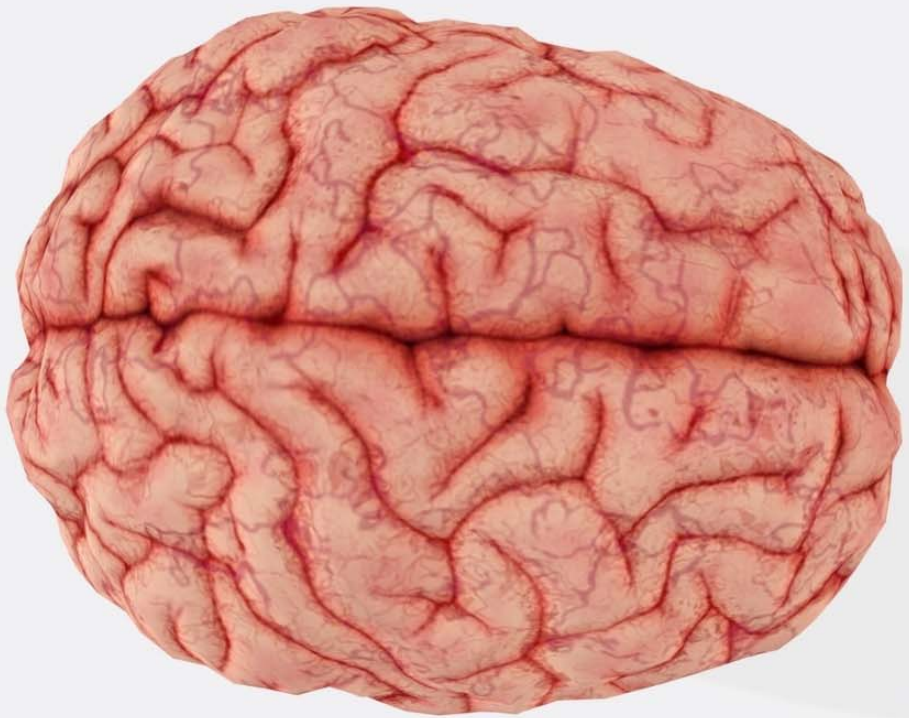
HAP/VAP

Vancomycin/Linezolid

Pip-Tazobactam

Cefepime

Strich, Heil, Masur



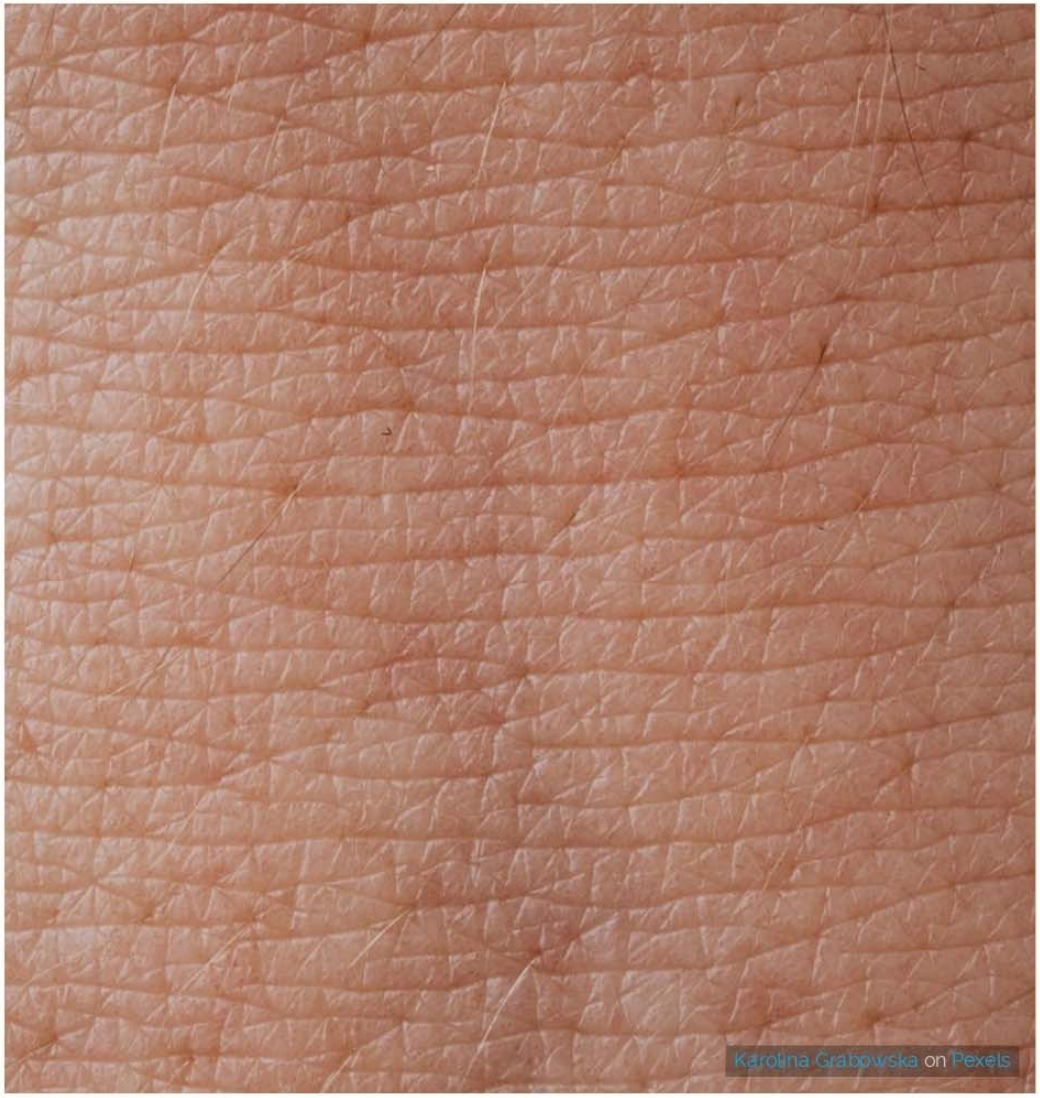
BUDDHI Kumar SHRESTHA on Unsplash

Meningitis

Vancomycin + Ceftriaxone

Age>50, Alcohol abuse, Immunocompromised?
Add Ampicillin

Strich, Heil, Masur



Nec Fasc

Vancomycin/Linezolid

AND

Pip/Tazo, Carbapenam, Ceftriaxone+Metronidazole

Severe Cellulitis

Vancomycin AND Pip-Tazo

Strich, Heil, Masur

Pyelonephritis

Fluoroquinolone

Aminoglycoside

Extended-spectrum Cephalosporin

Strich, Heil, Masur


TAKE
AWAY

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