Sepsis: Definition & Management

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12/11/2025

SEPSIS IS A MAJOR HEALTH THREAT

>1.7 Million People In The U.S Are Diagnosed With Sepsis Every Year
>350K People Die From Sepsis Every Year

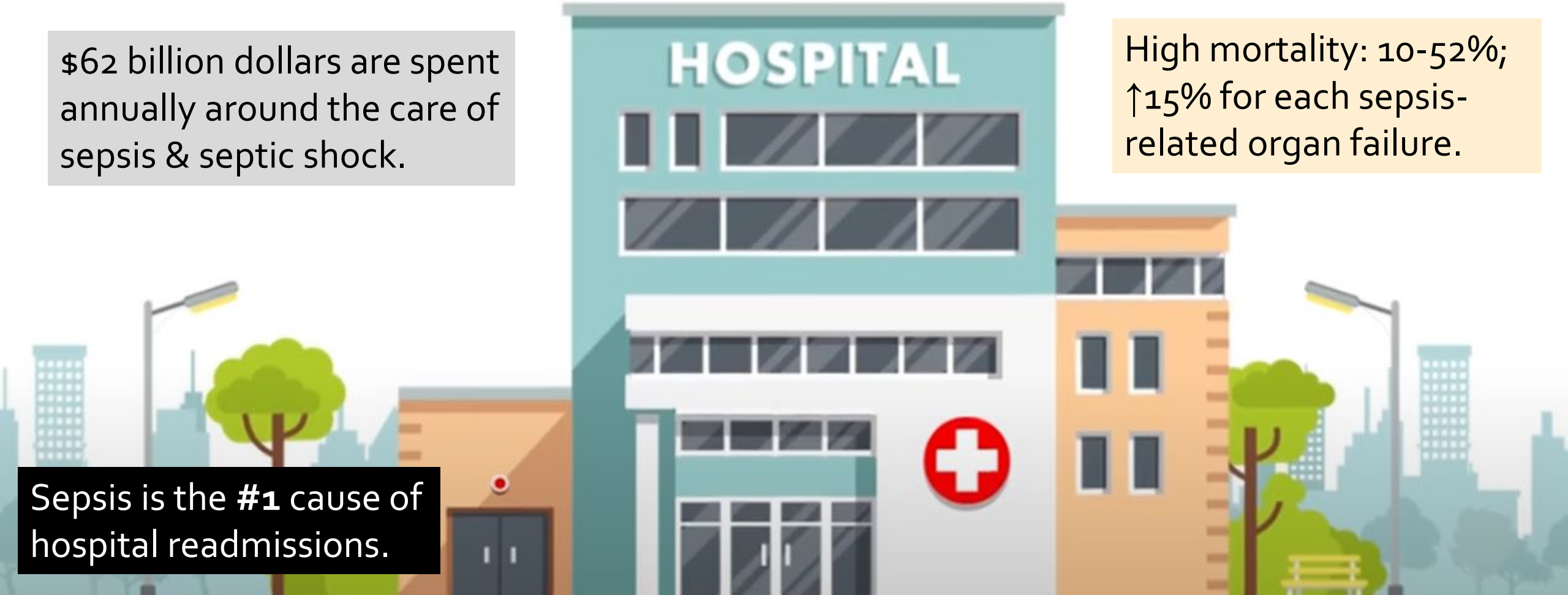
Rhee C, et al. JAMA 2017; 318:1241.

Sepsis Is The Leading Cause of Death In U.S. Hospitals

80% of cases of sepsis occur outside the hospital

$62 billion dollars are spent annually around the care of sepsis & septic shock.

High mortality: 10-52%; ↑15% for each sepsis-related organ failure.



Sepsis is the **#1** cause of hospital readmissions.

Sepsis definition

Life-Threatening Organ Dysfunction

Caused by

Dysregulated Host Response to Infection

Singer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315:801-810.

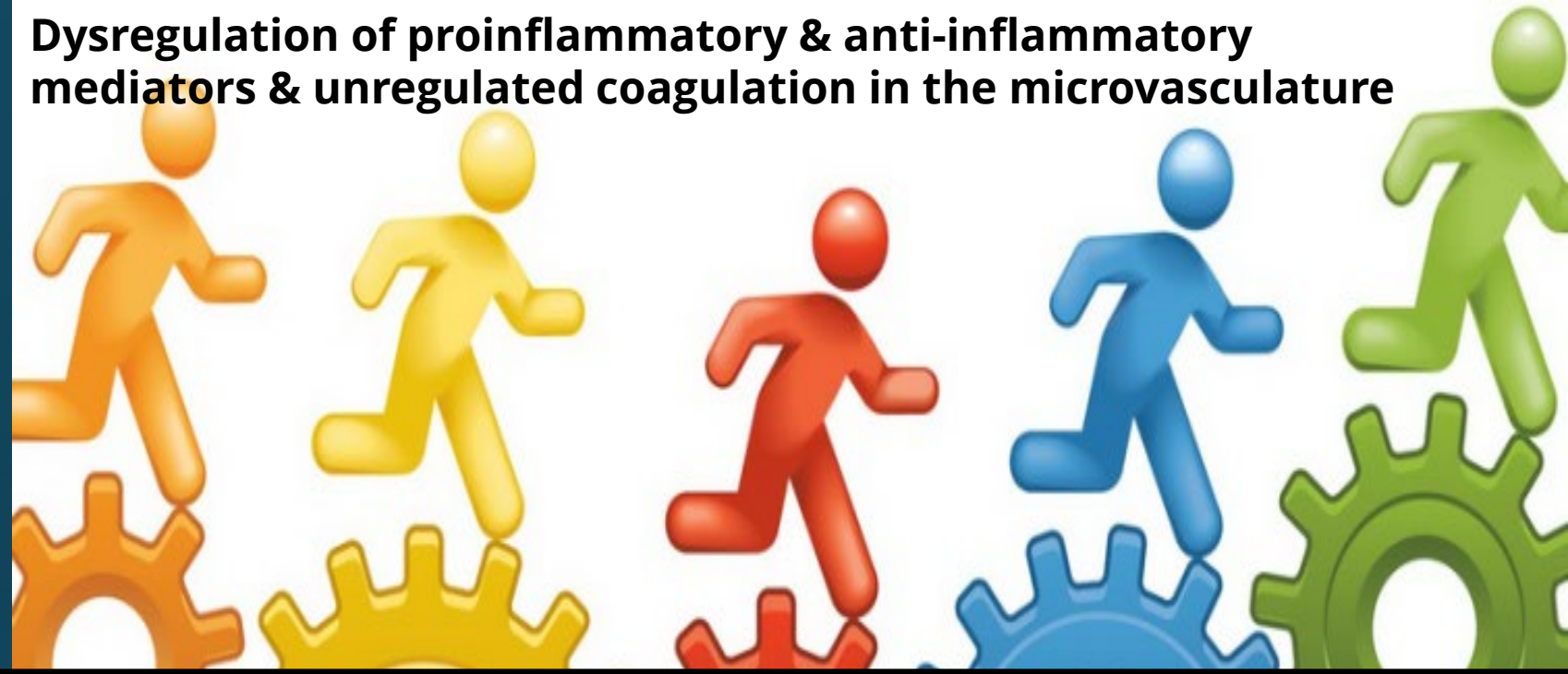
Sepsis Is A medical Emergency That Requires Immediate Medical Attention

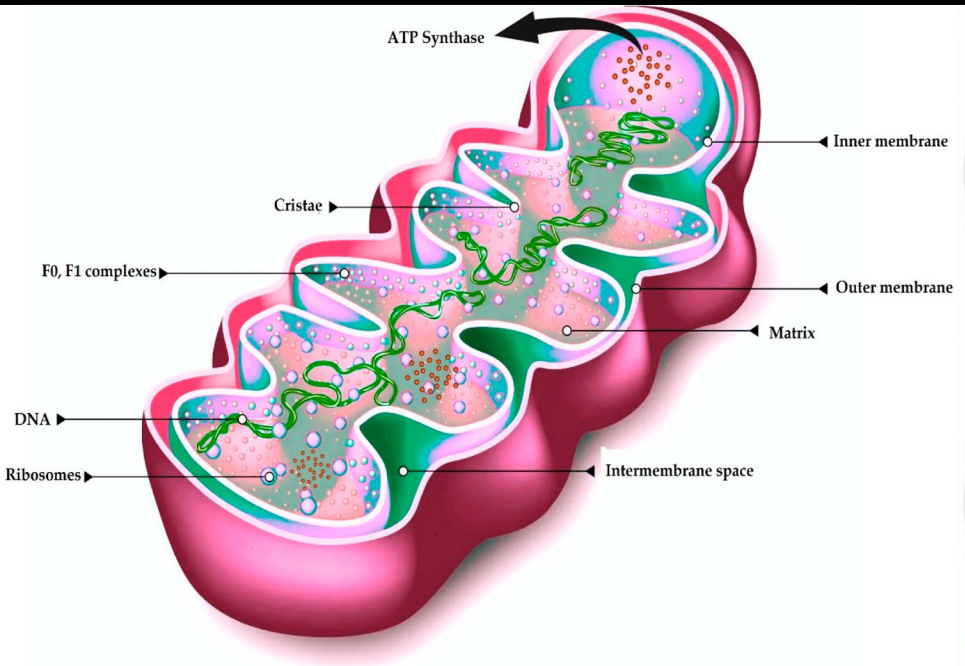
it takes sometimes as little as 12 hours from the earliest sign of infection to organ failure & death.

The risk of death increases by 4-9% for every hour the treatment is delayed.

The pathophysiology of sepsis is complex and involves dysfunction at many levels:

Dysregulation of proinflammatory & anti-inflammatory mediators & unregulated coagulation in the microvasculature





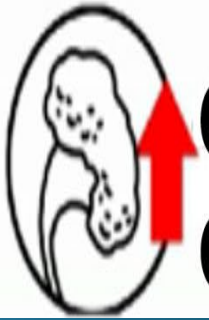
PaO_2/FiO_2

Hypotension Or Vasopressors

Platelets

Glasgow Coma Scale

Bilirubin



Creatinine Or Oliguria

Role of endotoxin and other bacterial components

Non-pathogen-mediated injury

Cell/tissue damage

Pathogen-mediated injury

PAMPs

DAMPs

Innate Immune System

-Executed by nearly all somatic cells via pattern recognition receptors (PRRs)

TLRs
NLRs
RLRs
MDL1R

NF-κB → Cytokine release

Infectious Inflammatory Response

Sterile Inflammatory Response

+Ag

Adaptive Immune Response

Uncontrolled response
Severe inflammatory process

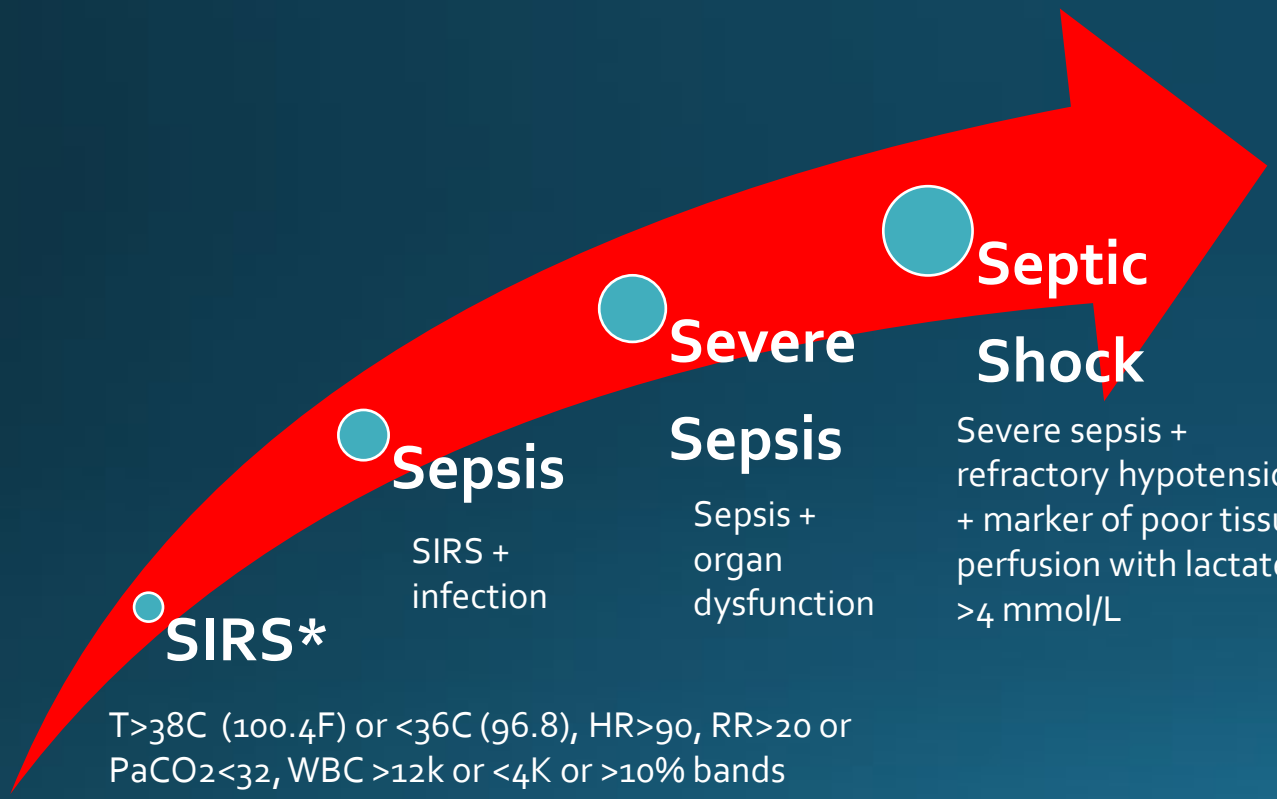
Controlled response
Resolution of the initial insult
Restauration & maintenance of homeostasis

DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors); Toll-like receptors (TLRs), nucleotide-oligomerization domain (NOD) leucine-rich repeat proteins (NLRs), & retinoic-acid-inducible gene I (RIG-I)-like helicases (RLRs); triggering receptor expressed on myeloid cell (TREM-1) and the myeloid DAP12-associating lectin (MDL-1) receptors

1-Piechota, M., et al. J. Intensive Care Med 2007; 22:232. 2-Ince, C. Crit. Care 2005; 9:S13. 3-Belousoviene, E., et al. Life 2021; 11:790.

Sepsis Definition Over Time

Sepsis 1 & 2



Sepsis 3

- Complex clinical syndrome characterized by:

1. Life-threatening organ dysfunction (physiologic, pathologic, & biochemical abnormalities) caused by
2. Dysregulated host response to
3. Infection

***Keep in mind that SIRS and even the most recent SOFA score excluded pregnancy as normal pregnancy parameters overlap with criteria of sepsis. Pregnancy specific scores might be used instead.**

1-Bone RC, et al. Chest 1992; 101:1644. 2-Levy MM, et al. Intensive Care Med 2003; 29:530.3-Singer M, et al. JAMA 2016; 315:801.3- Albright CM, et al. Obstet Gynecol 2017; 130:747. Bowyer L, et al. Obstet Gynecol 2017; 57:540.

Problems With The 2016 Sepsis Definitions

No comprehensive specific criteria for identification of infection

Risk Factors For Sepsis

ICU admission: 18% of ICU pts have nosocomial infection and are intrinsically high risk for sepsis[1]

Bacteremia: In a study of 270 BCX, 95% of + BCX were associated w sepsis or septic shock[2]

Advanced age≥65[3]:Older pts ≥65 y of age account for the majority (60-85%) of all the episodes of sepsis

Immunosuppression: cancer was found to ↑ the risk of developing sepsis by 10-folds[4]

Diabetes and obesity: Higher ABSSSI, CAP, biliary dz, aspiration PNA, CLABSI,.. & higher mortality vs nl-wt pts.[5]

Community acquired pneumonia: Severe sepsis and septic sock develop in 48% and 5%, respectively of pts hospitalized with CAP.[6]

Previous hospitalization: It is associated with 3x ↑sed of developing sepsis in the subsequent 90 d.[7]

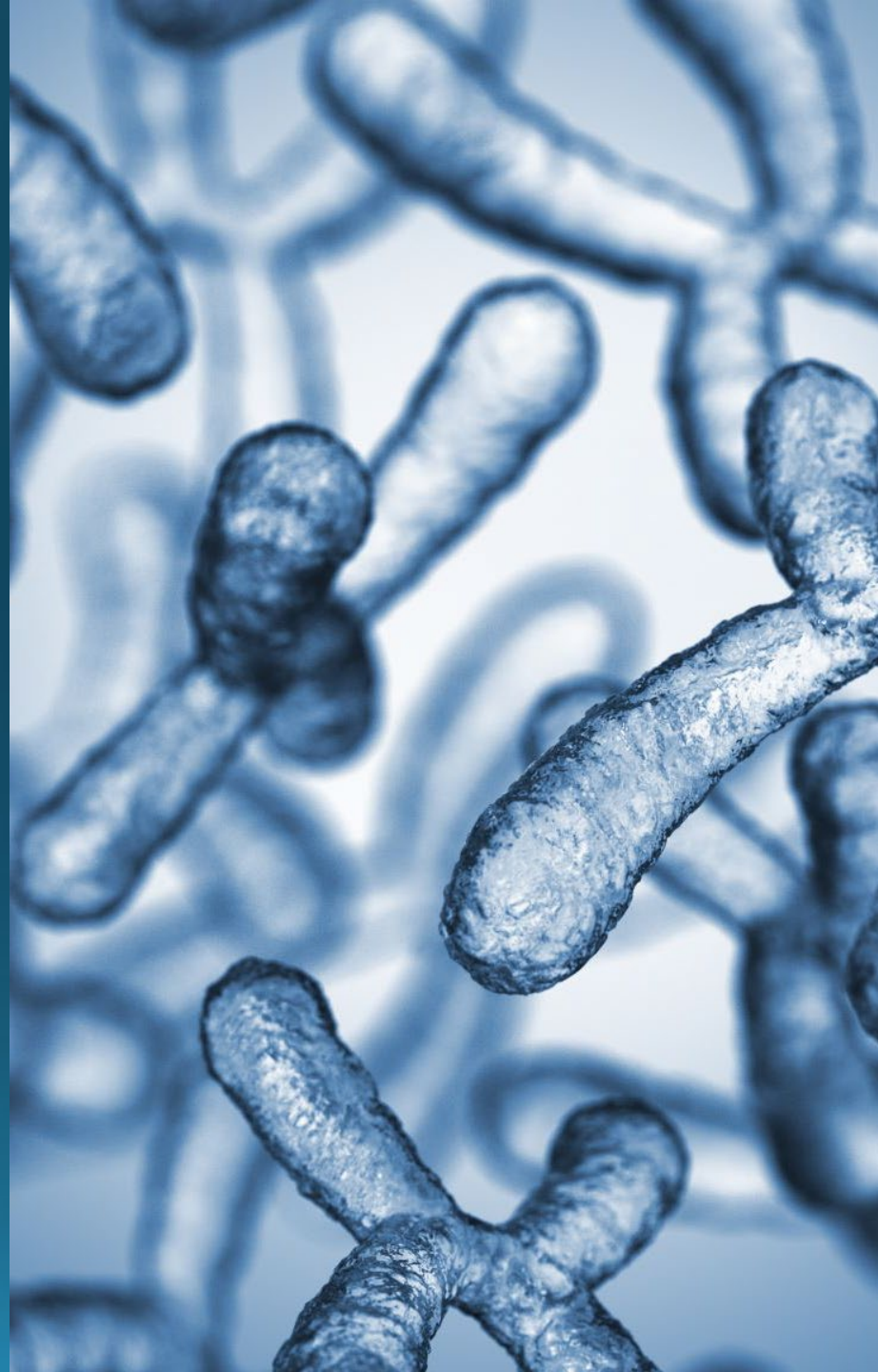
Genetic polymorphisms: defects of innate immunity leading to lack of recognition of pathogens, defect in antibody production, or a lack of T cells, phagocytes, natural killers, or complement.[8]

There are disparities in sepsis rates among different demographic groups. The incidence is higher among older folks and AA males & during wintertime (respiratory infections)[9,10]

1-Donowitz L., et al. Critical Care Medicine1982;10:355. 2-Jones GR, et al. QJM 1996; 89:515. 3-Martin GS, et al. Crit Care Med 2006;34:15. 4-Williams MD, et al. Cit Care 2004; 8:R291. 5-Falagas ME, et al. Lancet Infect Dis 2006; 6:438. 6-Dremsizov T, et al. Chest 2006; 129:968. 70-Prescott HC, et al. Am J Respir Crit Care Med 2015; 192:581. 8-Netea MG, et al. N Engl J Med 2011; 364:60. 9-Martin GS, et al. N Engl J Med 2003; 348:1546. 10-Danai PA, et al. Crit Care Med 2007; 35:410.

Microbiology

- The identification of organism in Cultures in a patient who fulfills the definition of sepsis is highly supportive of the dg of sepsis, but it is not necessary.[1,2]
  - **Negative culture in >50% of cases of sepsis**
  - **Positive culture is not required to decide on empirical antimicrobials**
- Blood cultures are frequently negative (+ BCX= 31.4% prior to administration of Abx) [3]
- No radiographic signs that are specific for sepsis (PNA, empyema, GIT infection, …)



1-Gupta S, et al. Chest 2016; 150:1251. 2-Cohen J, et al. Lancet Infect Dis 2015; 15:581. 3-Chang MP, et al. Ann Intern Med 2019; 171:547.

Sepsis & Severe Sepsis Core Measure Compliance

❑SIRS requires ≥2 of the following:

1. T >38.3°C (100.9°F) or <36°C (96.8°F)
2. P >90/min
3. RR >20/min
4. WBC >12k or <4k or >10% immature band forms

❑Sepsis = SIRS + confirmed or presumed infections

❑Severe Sepsis = sepsis with ≥ 1organ dysfunction or hypo-perfusion:

- Cardiovascular:
  - SBP <90 mmHg or drop ≥ 40 mm Hg of normal or MAP < 65 mmHg
- Lactate >2.0 mmol/L
- AKI:
  - sCr>2 mg/dL (↑by 0.5 mg/dL)
  - Urine output <0.5 mL/kg/h for ≥2 h) despite adequate
- DIC:
  - INR >1.5; aPTT >60 sec
  - Platelets <100 $\times 10^9$/L
- Pulmonary:
  - ALI (PaO_2/FiO_2 <250) (No PNA)
  - ALI (PaO_2/FiO_2 <200) (PNA)
- Bilirubin >2 mg/dL µmol/L
- Adrenal insufficiency: ↓Na &↑K

Septic Shock =

❑Sepsis with refractory hypotension within the hour after fluid challenges :

- Refractory means SBP <90 mmHg, SBP drop by >40 mm Hg drop from baseline or MAP <65 mmHg that persists after 30 mL/kg crystalloid (NS 0.9% or LR) And/Or

❑ Lactate levels ≥4 mmol/L

1-Definitions according to the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) in 1992 . 2-Levy MM, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:1250. 3-Evans L, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Medicine 2021:49;e1063-e1143.

SIRS lacks sensitivity for defining sepsis (face validity)

SIRS +	SIRS -
87.9%	12.1%

Will miss 1 in 8 pts with infection & organ dysfct

SIRS lacks specificity for infection

SIRS + w/o infection
80%

4 in 5 ICU pts w/o infection have SIRS criteria

The Truth

Test Score:	Has the disease	Does not have the disease	
Positive	True Positives (TP) a	False Positives (FP) b	PPV = $\frac{TP}{TP + FP}$
Negative	False Negatives (FN) c	True Negatives (TN) d	NPV = $\frac{TN}{TN + FN}$

Sensitivity $\frac{TP}{TP + FN}$ **Specificity** $\frac{TN}{TN + FP}$

Or, $\frac{a}{a + c}$ $\frac{d}{d + b}$

Kaukonen KM, et al. N Engl J Med 2015;372:1629-1638. Seymour CW, et al. JAMA 2016; 315:762

SIRS To Organ Dysfunction

- **SIRS requires ≥2 of the following:**
  1. T >38.3°C (100.9°F) or <36°C (96.8°F)
  2. P >90/min
  3. RR >20/min or PaCO2 <32 mmHg
  4. WBC >12k or <4k/mm^3 or >10% immature band forms

Acute change of SOFA ≥2 : >10% mortality

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
PaO_2/FIO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10^3/μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: FIO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

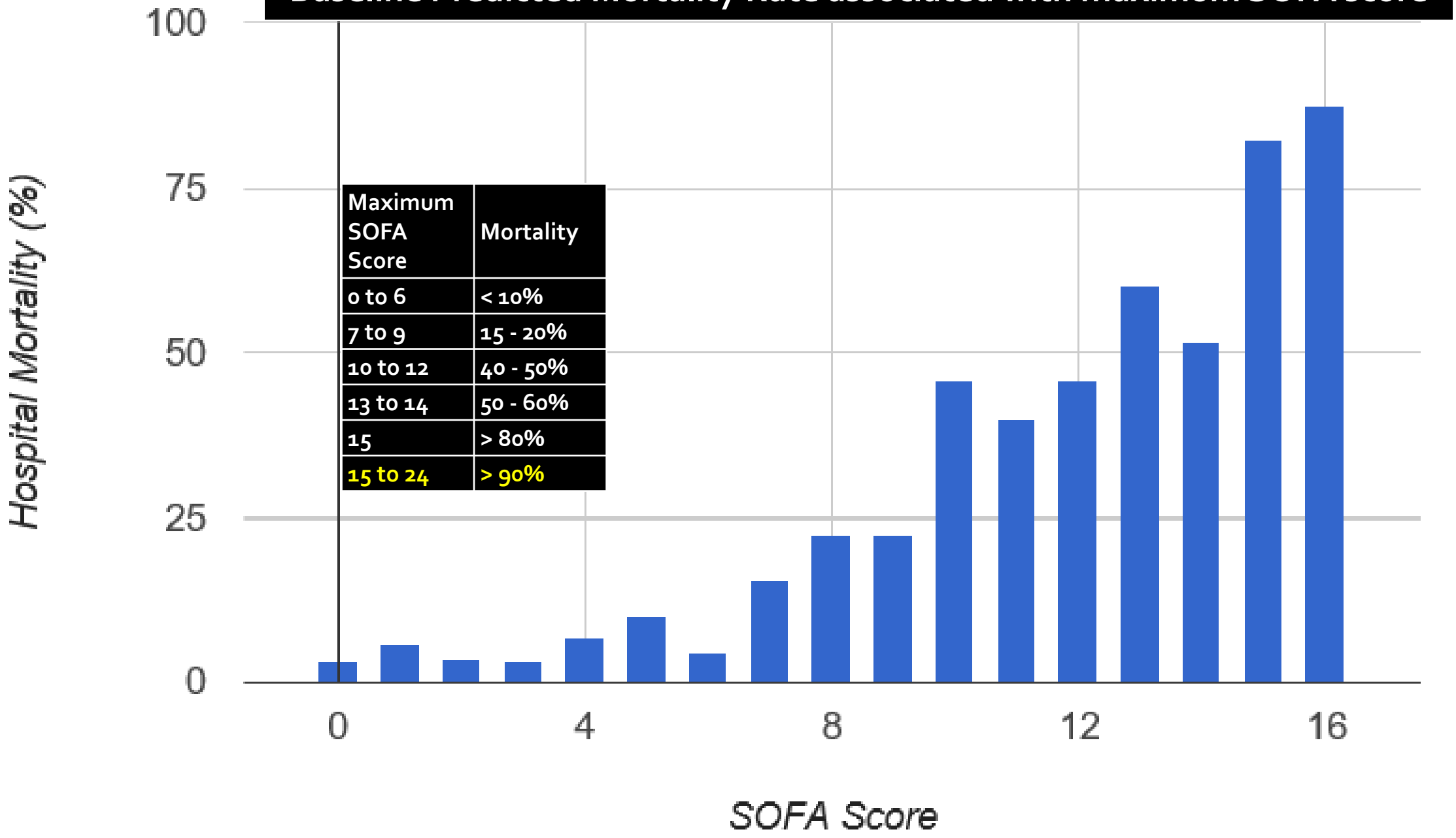
[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

1-Levy MM, et al. Intensive Care Med 2003; 29:530.2-Singer M, et al. JAMA 2016; 315:801. Evans L, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Medicine 2021:49;e1063-e1143.

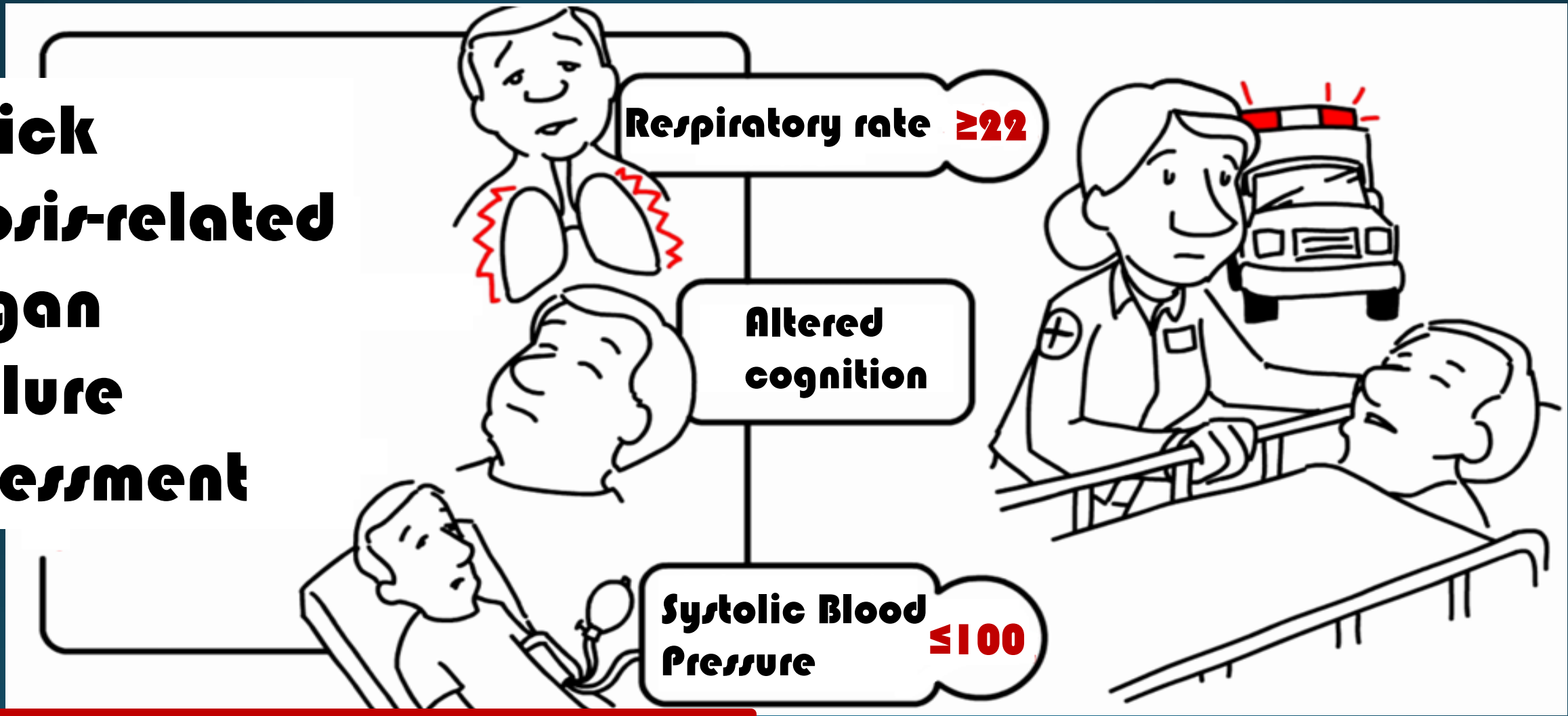
Baseline Predicted Mortality Rate associated with maximum SOFA score



Maximum SOFA Score	Mortality
0 to 6	< 10%
7 to 9	15 - 20%
10 to 12	40 - 50%
13 to 14	50 - 60%
15	> 80%
15 to 24	> 90%

Bed side clinical assessment (qSOFA)

Quick Sepsis-related Organ Failure Assessment



Score interpretation & mortality:

- zero or 1 → 1-2%: 2 →8%: 3 → >20%

1-Singer, M., et al. Sepsis-3. JAMA 2016, 315, 801–810.

IDENTIFICATION OF EARLY SEPSIS (qSOFA or NEWS)

- Early detection of sepsis saves lives
- **The 2021 sepsis guidelines: The National Early Warning Score (NEWS) score & SIRS outperform qSOFA in predicting in-hospital death & need for ICU admission.**

- **SIRS requires ≥2 of the following:**

1. T >38.3°C (100.9°F) or <36°C (96.8°F)
2. P >90/min
3. RR >20/min or PaCO2 <32 mmHg
4. WBC >12k or <4k/mm^3 or >10% immature band forms

Table 1. **The adapted NEWS tool**

Element	Score						
	3	2	1	0	1	2	3
Respiratory rate	≤8		9-11	12-20		21-24	≥25
SpO_2	≤91	92-93	94-95	≥96			
Oxygen		Yes		No			
Systolic blood pressure	≤90	91-100	101-110	111-219			≥220
Pulse	≤40		41-50	51-90	91-110	111-130	≥131
ACVPU				A			C,V,P,U
Temperature, °C	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	

Complete a sepsis screen on all patients with NEWS ≥3 with signs of infection.

ACT = acute clinical team; ACVPU = Alert, Confusion, Voice, Pain, Unresponsive; SPO_2 = peripheral capillary oxygen saturation; NEWS = National Early Warning Score.

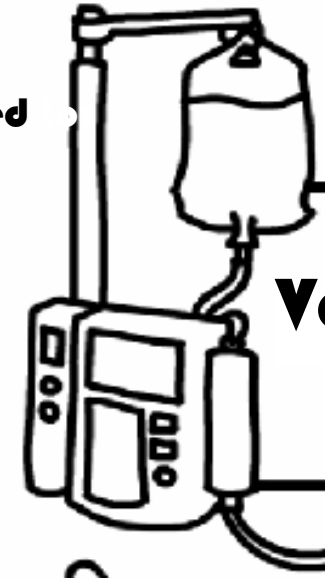
1-Singer M, et al. JAMA 2016; 315:801. 2-Shankar-Hari M, et al. JAMA 2016; 315:775.
3-Seymour CW, et al. JAMA 2016; 315:762. 4-Seetharaman S, et al. Am J Med 2019; 132:862.
5-Evans L, et al. Crit Care Med 2021; 49:e1063 6-Covino M, et al. Resuscitation 2023; 190:109876. 7-Evans L, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Medicine 2021:49;e1063-e1143.

Septic shock

The combination circulatory and cellular abnormities gave a mortality of >42% compared

- **26% for those with ↑lactate alone**
- **30% for those with hypotension alone**
- **19% for those with sepsis & organ dysfct w/o ↑ in lactate levels or ↓ in SBP**

Sepsis +



Abnormalities in both:
1-Circulatory physiology &
2-Cellular metabolism

Vasopressors To Maintain MAP ≥65 mmHg

+

Serum lactate level ≥18 mg/dl (2 mmol/l)

In The Absence of Hypovolemia

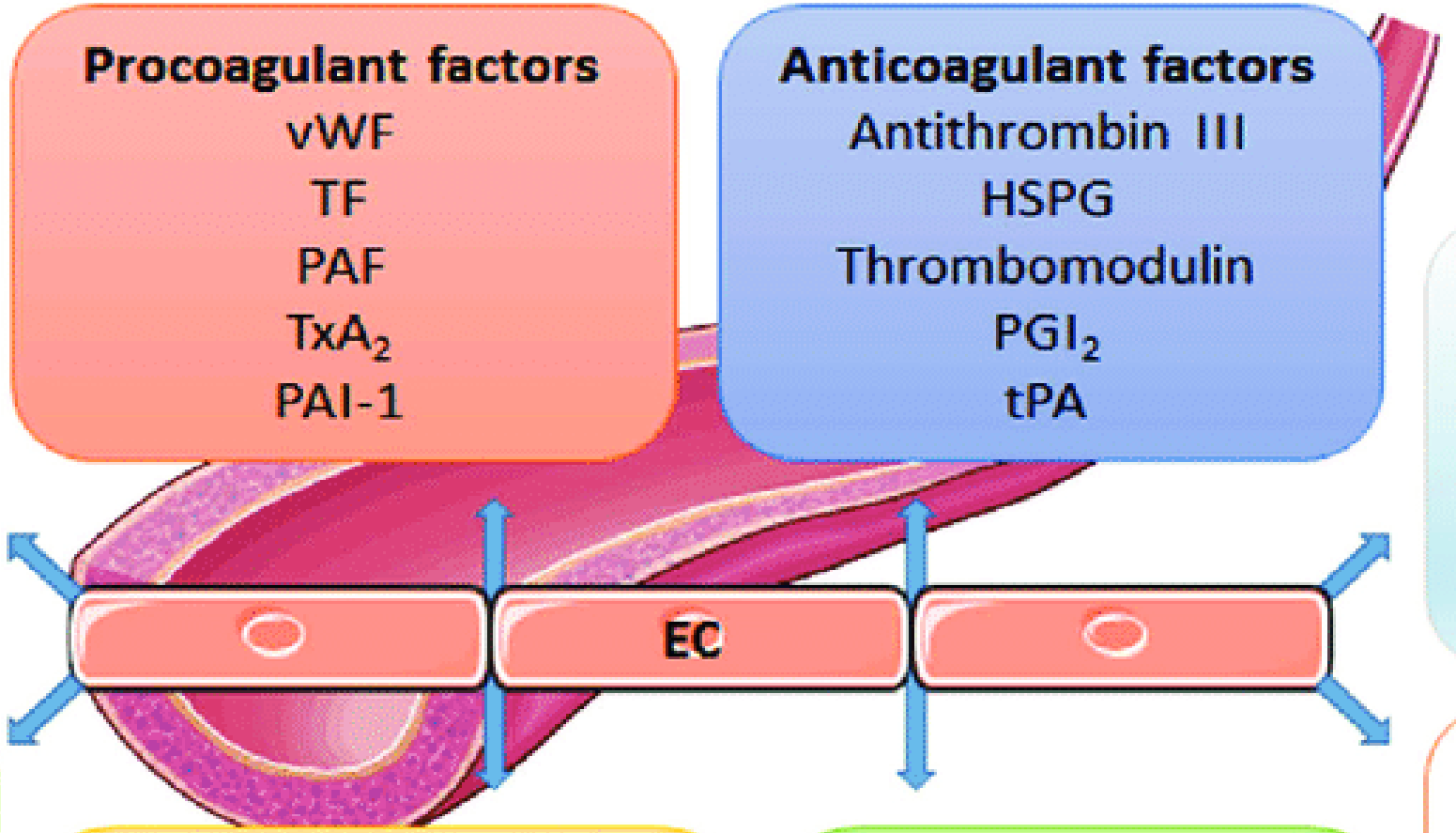
1-Singer, M., et al. Sepsis-3. JAMA 2016, 315, 801–810.

Procoagulant factors
vWF
TF
PAF
TxA_2
PAI-1

Anticoagulant factors
Antithrombin III
HSPG
Thrombomodulin
PGI_2
tPA

Vasodilators
NO
PGI_2
EDHF
H_2S

VSMC proliferation
NO
TXA_2
ROS (eg. $O^{\bullet -}$)
PGH_2



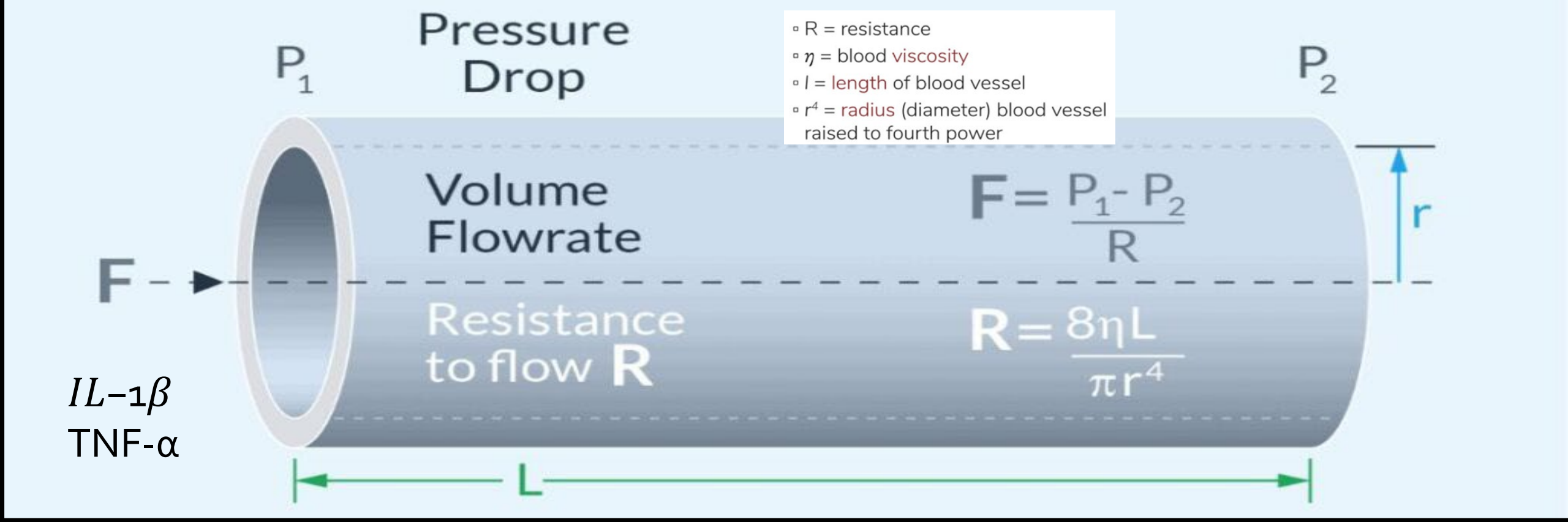
Vasoconstrictors
Ang II
ET-1
TXA_2
ROS (eg. $O^{\bullet -}$)
PGH_2

Inflammatory mediators
Leukotrienes
Chemoattractants (eg. CCL2, CCL3, CCL5)
CAMs (selectins, integrins, immunoglobulins)
Interleukins

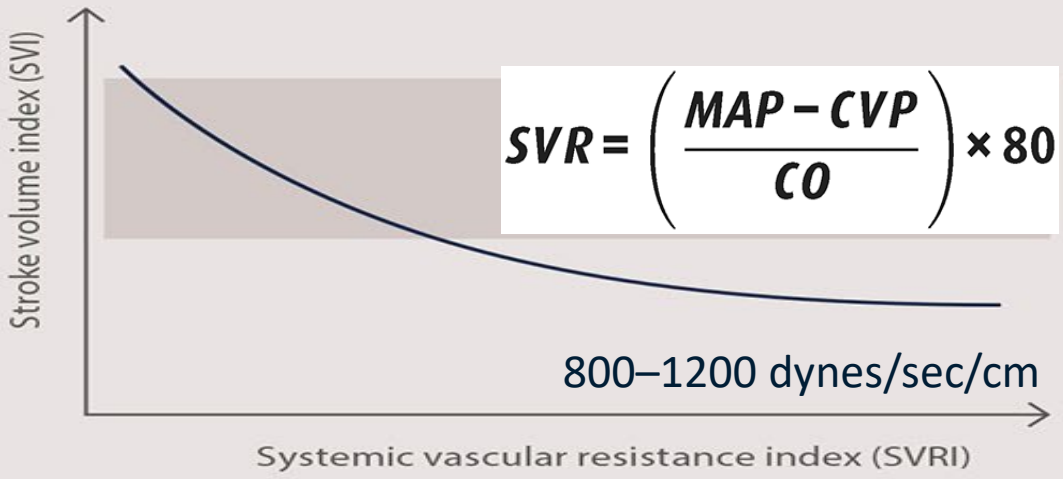
Angiogenic factors
VEGF (VEGFA, VEGFB)
PDGF
TGF-β
FGF
EGF

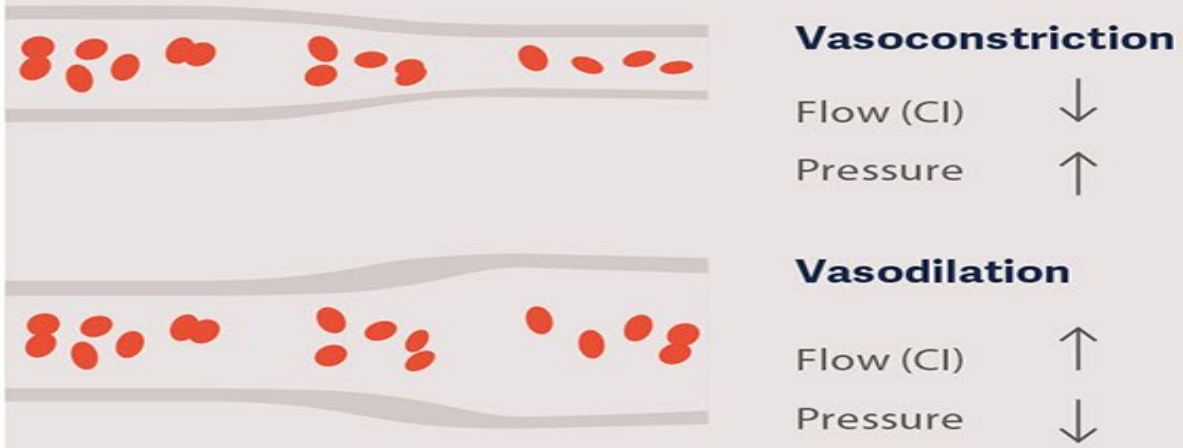
Permeability
NO
PGI_2
ROS

1-Piechota, M., et al. J. Intensive Care Med 2007; 22:232. 2-Ince, C. Crit. Care 2005; 9:S13. 3-Belousoviene, E., et al. Life 2021; 11:790.



$IL\text{–}1\beta$
TNF-α





Management

- The treatment of sepsis/septic shock is challenging
- Successful treatment of severe sepsis and septic shock depends on 3 pillars:
  1. **Early administration of antimicrobials**
  2. **Supporting organ perfusion and function**
  3. **Controlling the infection**

- **To that end, the following interventions should be performed concomitantly rather than sequentially.**

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801-10.

Sepsis & Severe Sepsis Core Measure Compliance (SEP-1)

The "sepsis bundle" is a created time-based performance improvement metrics

3 Hours

1-Initial Lactate Level Collection

2-Blood Culture Collection Prior to Antibiotics (2 sets)

→Consider need for source control

3-Broad Spectrum Antibiotic Administration (within 3 hrs in the ED, within 1 hr in the ICU)

4-Administer 30 mL/Kg crystalloid IVF (NS or LR) (if low BP or High Lactate ≥4mmol/L)

6 Hours

1-If initial lactate level is ≥ 2.0 mmol/L →

Re-measure Lactate within 6 hours

2-Administer vasopressors if MAP <65mmHg that does not respond to initial resuscitation

3-Reassess Volume Status & Tissue perfusion (persistent low BP after IVF or high lactate ≥4mmol/L)

Time of presentation" is defined as the time of triage in the ED or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis, severe sepsis or septic shock ascertained through chart review.
Time Zero= Suspected Infection + SIRS + Acute Organ Dysfunction (within a 6h window)

Levy MM, et al. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med 2018; 44:925.

Sepsis & Severe Sepsis Core Measure Compliance

- ❑ The "sepsis bundle" has been central to the implementation of the surviving sepsis campaign (SSC)
- ❑ In 2018, the 2016 3- and 6-hour bundles were revised and combined into a single 1-hour performance improvement bundle

Hour 1 bundle

1-Initial Lactate Level Collection*

2-Blood Culture Collection Prior to Antibiotics (2 sets)

3-Broad Spectrum Antibiotic Administration

4-Administer 30 mL/Kg crystalloid IVF (NS or LR) (if low BP or High Lactate ≥4mmol/L) & vasopressors if refractory hypotension

*If lactate level is ≥ 2.0 mmol/L → Re-measure Lactate within 6 hours

"Time of presentation" is defined as the time of triage in the ED or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis, severe sepsis or septic shock ascertained through chart review.

Levy MM, et al. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med 2018; 44:925.

Sepsis & Severe Sepsis Core Measure Compliance (SEP-1)

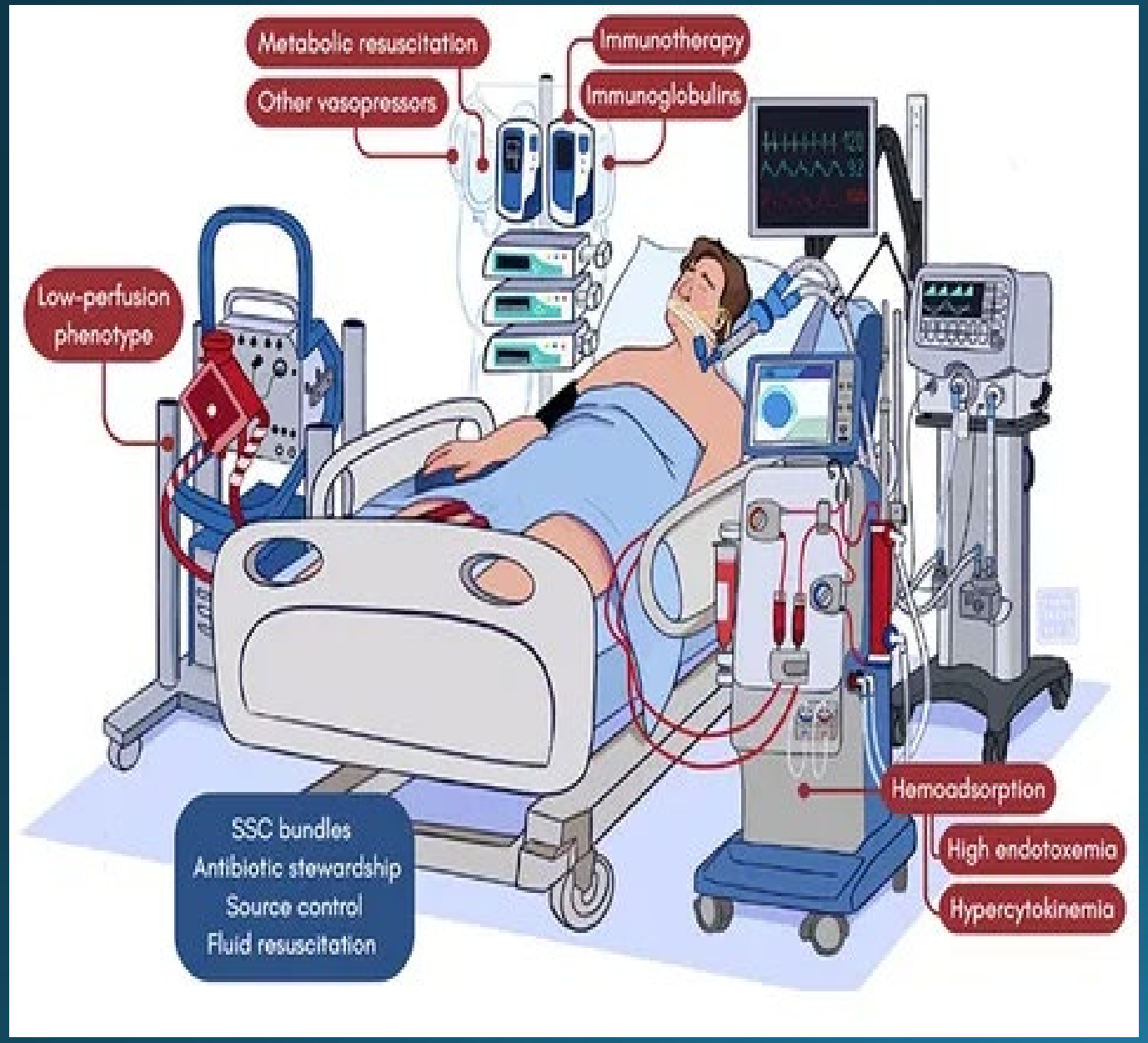
3 Hours

6 Hours

ALL OR NOTHING MEASURE (MUST PERFORM ALL BUNDLE ELEMENTS TO GET "CREDIT")

To get credit we must master the sepsis piece

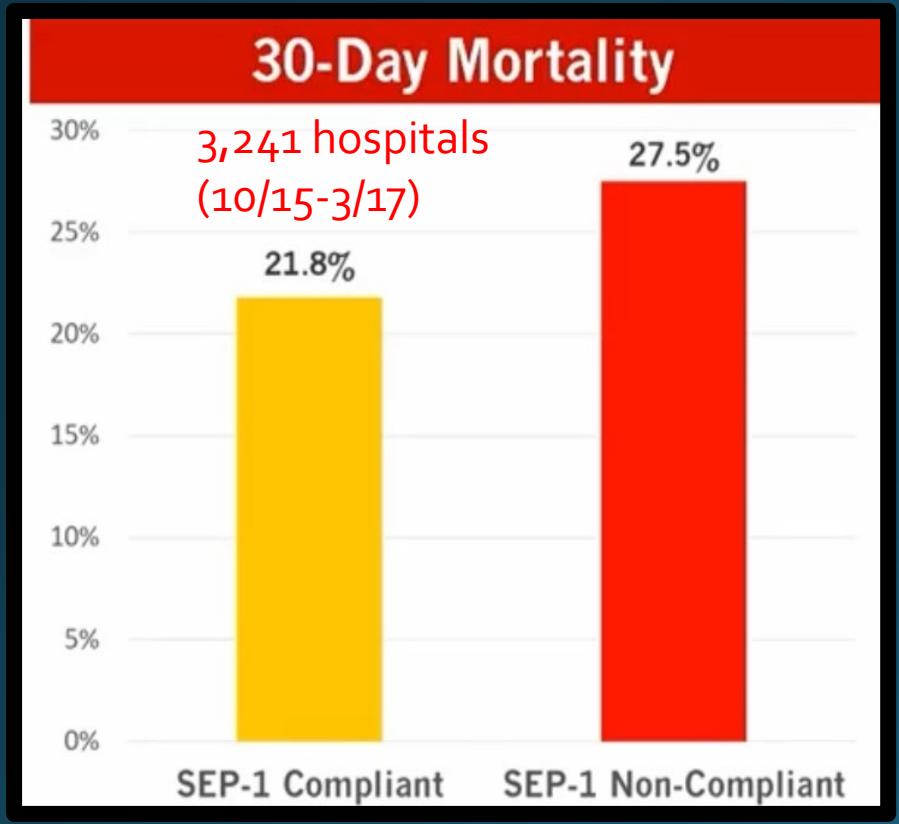
Time of presentation" is defined as the time of triage in the ED or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis, severe sepsis or septic shock ascertained through chart review.
Time Zero= Suspected Infection + SIRS + Acute Organ Dysfunction (within a 6h window)



The implementation of Sepsis-1 can lead to faster treatment, a reduction in mortality rates, and better outcomes, particularly for septic shock.

Effects of Compliance With the Early Management Bundle (SEP-1) on Mortality Changes Among Medicare Beneficiaries With Sepsis

A Propensity Score Matched Cohort Study



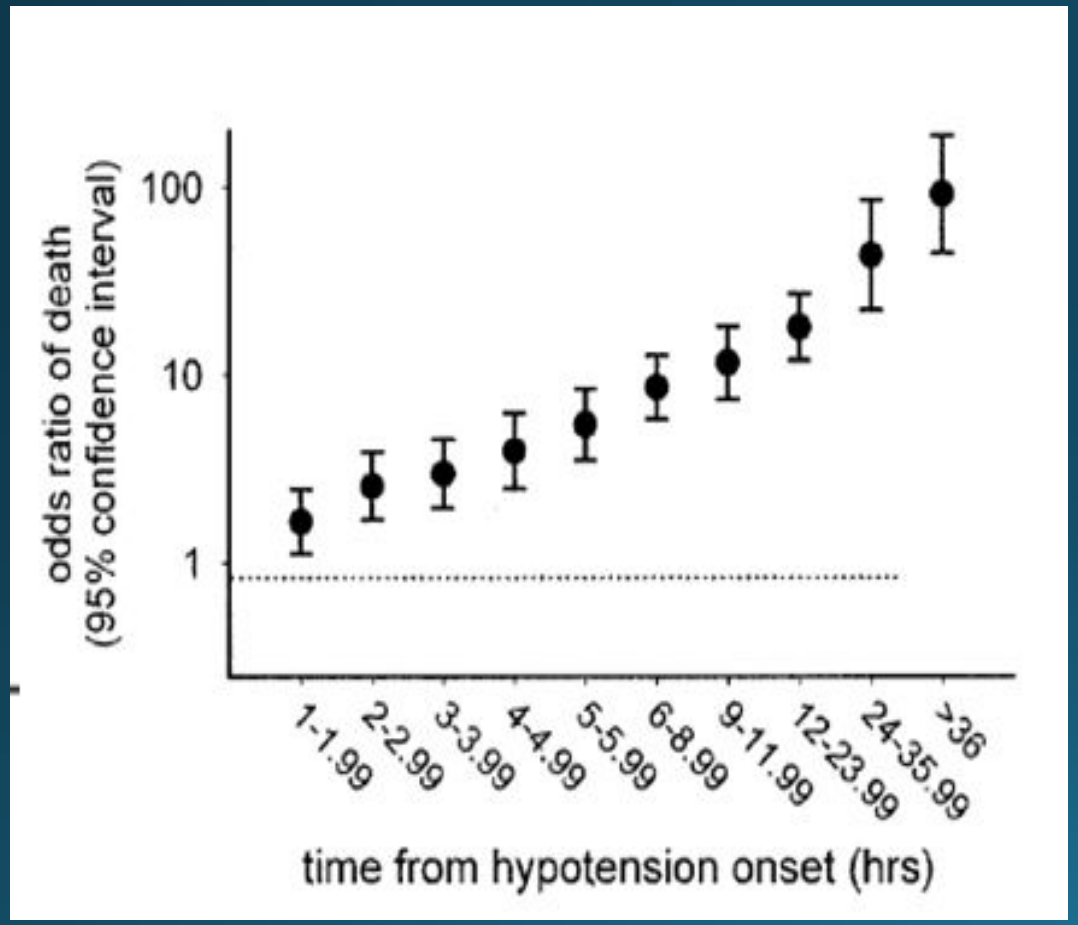
US hospitals have reported compliance with the SEP-1 quality measure to CMS since 2015:
Compliance was defined as completion of all qualifying SEP-1 elements including lactate measurements, BCx collection, broad-spectrum antibiotic administration, 30 mL/kg crystalloid fluid administration, application of vasopressors, & patient

- Retrospective analysis of 122,870 Medicare patients with sepsis diagnoses who received SEP-1 compliant care matched to 122,870 patients who received non-compliant care (10/15-3/17)
- Standard match: Compliance was associated with a reduction in 30-day mortality (21.81% vs. 27.48%, respectively) → ARR=5.67% p=s
- Stringent match: Compliance was associated with a reduction in 30-day mortality (22.22% vs. 26.28%, respectively) → ARR=4.06% p=s
- Median LOS was shorter among cases whose care was compliant (5 vs 6 d; IQR, 3-9 vs 4-10 d; p=s)

Townsend S, et al. Chest 2022; 161:392.

1-Antibiotic therapy

Antibiotics in septic shock: Go Big Early

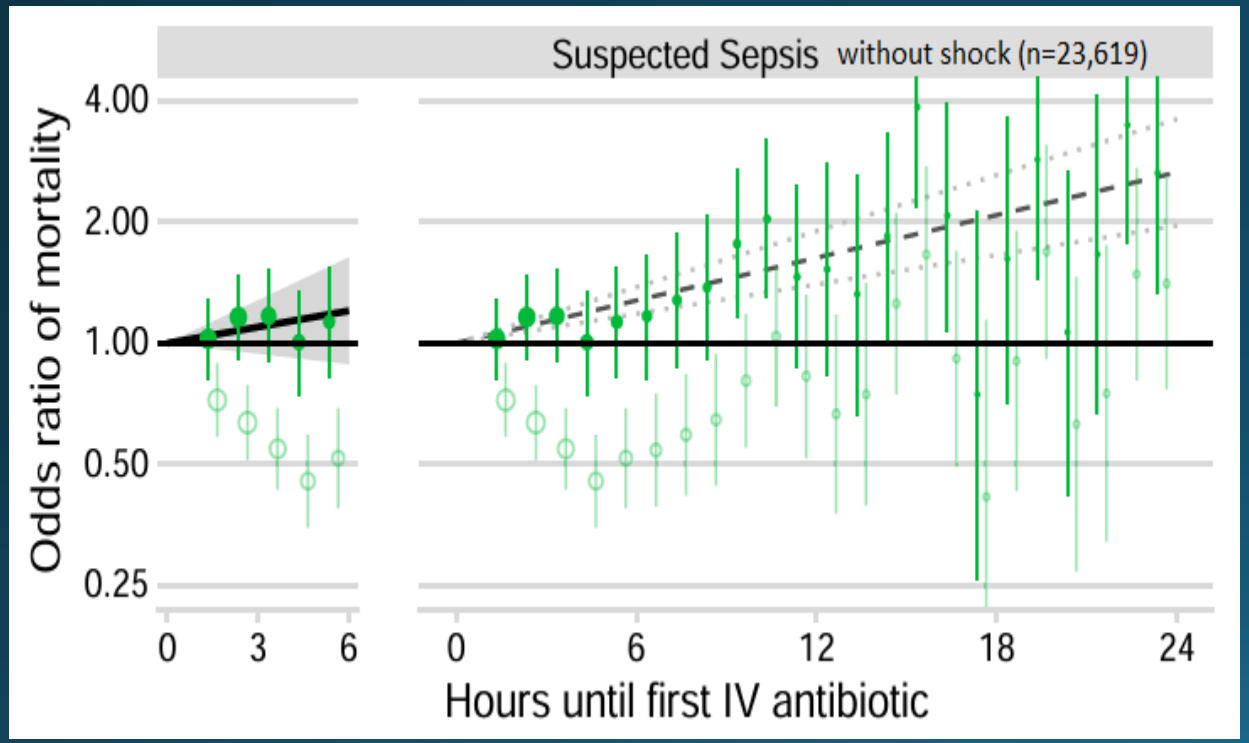


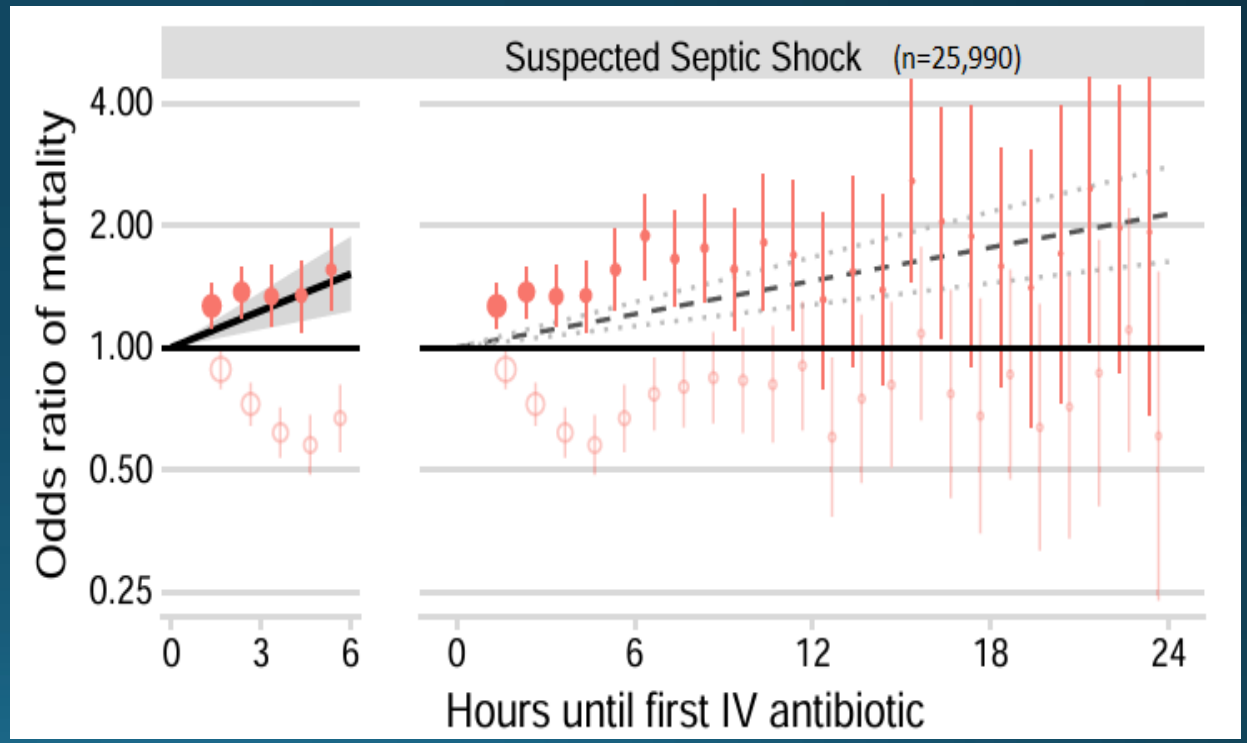
- Septic shock (refractory hypotension + pressors): 7.6% mortality increase per hour delay in antibiotics[1]
- Median time to appropriate Abx=6h[1]
- Sepsis (adjustment of outliers): Most important to administer Abx within 6 hours[2]

1-Kumar A, et al. Crit Care Med 2006; 34:1589. 2-Pal TR, et al. Clin Infect Dis 2023; 2:ciad450.

Timely Antibiotics & Mortality: Sepsis vs Septic Shock

- Retrospective analysis of 104,248 patients admitted to 5 Massachusetts hospitals with suspected infection (BCx + IV Abx within 24h of ED arrival) → modeled association between hourly delays in Abx & risk-adjusted mortality





↑mortality seen with hourly delays for septic shock (aOR=1.07; 95% CI: 1.04-1.11) but only >6h for sepsis without shock (aOR=1.03; 95% CI:0.98-1.09)

Pak TR, et al. Clin Infect Dis 2023; 77:1534.

Clinical Infectious Diseases

MAJOR ARTICLE

Administration of a β-Lactam Prior to Vancomycin as the First Dose of Antibiotic Therapy Improves Survival in Patients With Bloodstream Infections

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(See the Editorial Commentary by Cutrell and Sanders on pages 105–6.)

Background. Prompt initiation of antibiotic therapy improves the survival of patients with bloodstream infections (BSIs). We sought to determine if the sequence of administration of the first dose of antibiotic therapy (ie, β-lactam or vancomycin, if both are deemed necessary and cannot be administered simultaneously) impacts early mortality for patients with BSI.

Methods. We conducted a multicenter, observational study of patients ≥13 years with BSIs to evaluate the association of the sequence of antibiotic administration with 7-day mortality using inverse probability of treatment weighting (IPTW) incorporating propensity scores. Propensity scores were generated based on demographics, Pitt bacteremia score, intensive care unit status, highest lactate, highest white blood cell count, Charlson comorbidity index, severe immunocompromise, administration of active empiric therapy, combination therapy, and time from emergency department arrival to first antibiotic dose.

Results. Of 3376 eligible patients, 2685 (79.5%) received a β-lactam and 691 (20.5%) received vancomycin as their initial antibiotic. In the IPTW cohort, exposed and unexposed patients were similar on all baseline variables. Administration of a β-lactam agent prior to vancomycin protected against 7-day mortality (adjusted odds ratio [aOR], 0.48 [95% confidence interval {CI}, .33–.69]). Similar results were observed when evaluating 48-hour mortality (aOR, 0.45 [95% CI, .24–.83]). Administration of vancomycin prior to a β-lactam was not associated with improved survival in the subgroup of 524 patients with methicillin-resistant *Staphylococcus aureus* BSI (aOR, 0.93 [95% CI, .33–2.63]).

Conclusions. For ill-appearing patients likely to be experiencing a BSI, prioritizing administration of a β-lactam over vancomycin may reduce early mortality, underscoring the significant impact of a relatively simple practice change on improving patient survival.

Keywords. antibiotics; bacteremia; mortality; sepsis; β-lactam.

Penicillin (PCN) allergy

- **True PCN allergy is rare: 10% of population in the US reported being allergic to PCN but >90% are not truly allergic**
  - 80% with IgE-mediated (type 1) allergy lose sensitivity in 10 years
- Patients with reported PCN allergy are more often prescribed inappropriate antimicrobials:
  - Higher risk of *Clostridioides difficile* & antimicrobial-resistant infections

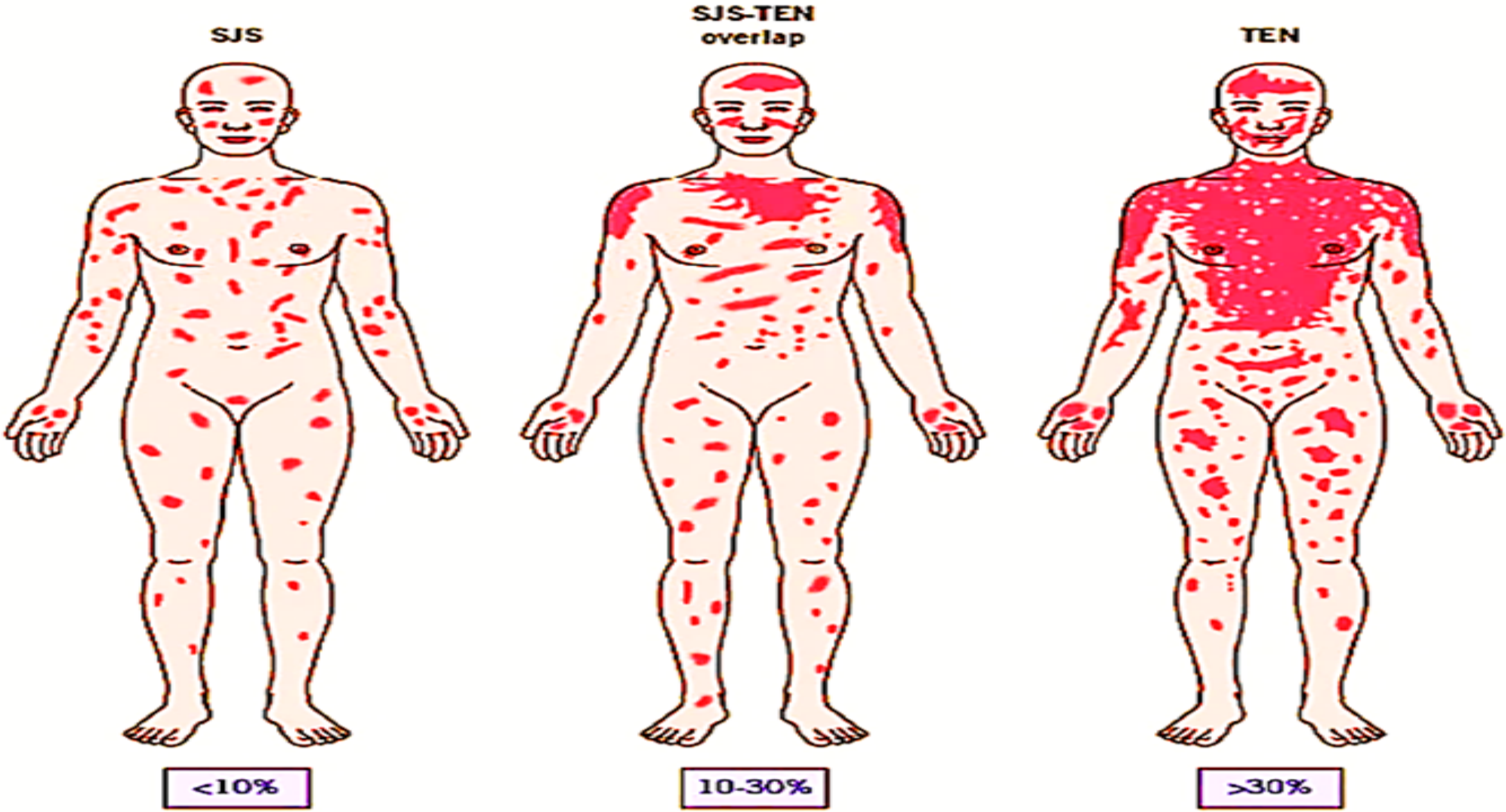
AB-R, antibiotic resistance; CDI, Clostridioides difficile infection

1-https://www.cdc.gov/antibiotic-use/media/pdfs/penicillin-factsheet-508.pdf. 2-Jaffa RK, et al. Am J Emerg Med 2021; 48:255. macy E, Contreras R. j Allergy Clin Immunol 2014; 133:790.

PEN-FAST Tool		
PEN	Patient reported penicillin allergy	
F	Five years or less since reaction	2 points
A S	Anaphylaxis or angioedema OR Severe cutaneous reaction	2 points
T	Treatment required for reaction	1 point

Interpretation	
0 points	Very low risk of positive penicillin allergy test (0.6% risk)
1 or 2 points	Low risk of positive penicillin allergy test (<5% risk)
3 points	Moderate risk of positive penicillin allergy test (<20% risk)
4 or 5 points	High risk of positive penicillin allergy test (50% risk)

What was reaction to PCN: DRESS (Drug fever & liver, kidney, heart, or lung dysfunction; delayed type 4 T cell-mediated), skin blistering/rash, mucosal involvement (mouth, eye, genital ulcers), angioedema, SOB


SJS
SJS-TEN
overlap
TEN
<10%
10-30%
>30%

2-Controlling the infection (source control)

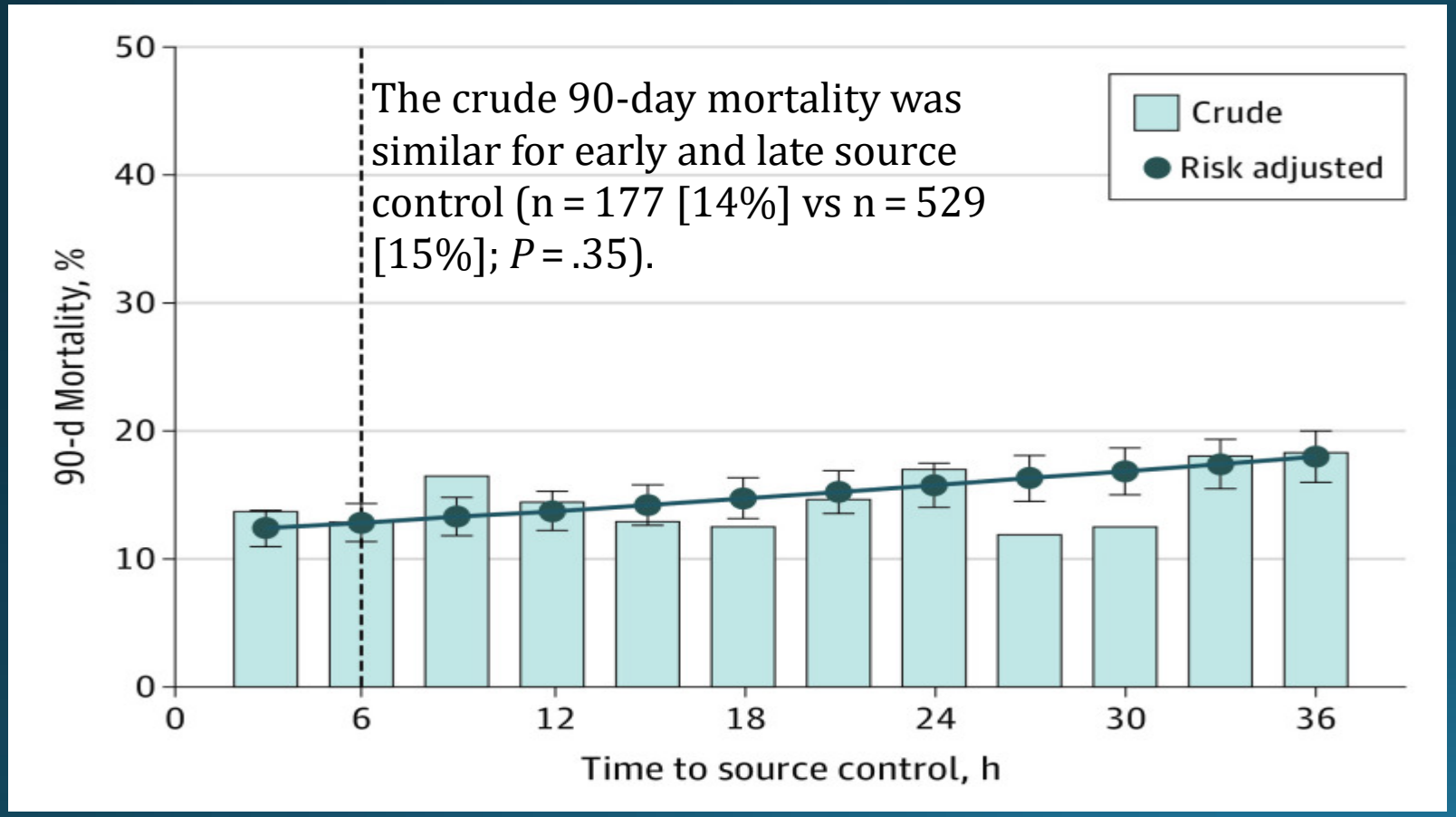
- **Prompt identification & control of any potential source of infection is essential in the management of sepsis.**
  - **Drainage** of abscesses
  - **Removal** of possibly infected catheters or devices (CVC, cardiac devices, pain pump, nerve stimulator, hardwares, implants,…)
    - One exception is necrotizing pancreatitis: definitive resection should be delayed until the extent of necrosis is clear.

Source o sepsis	Potential need for source control
Colitis/diverticulitis	Abscess
Cholangitis	Biliary stone
Cholecystitis	Cholecystostomy vs Sx
UTI	Renal abscess, ureteral stone
Line-related	CVC, HDC, PICC
CIED	Cardiac device removal
IE	Valve surgery
Joint/bone infections	drainage
Skin/soft tissue infection	Abscess, NSTI,

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801-10.

Source Control In Sepsis

Cohort study of 4962 patients with sepsis undergoing source control interventions in a 14-hospital integrated health care system



Observed and Risk-Adjusted 90-Day Mortality for the Primary CohortError bars indicate 95% CIs; dashed line, the 6-hour time point delineating early and late source control.

- Median source control after sepsis = 15.4 h (5.5-21.7)
- MVA: Early (<6h) source control (1315 pts; 27%) associated with 29% decreased risk-adjusted odds of 90-d mortality (aOR=0.71; 95%: 0.63-0.80)
- Greater benefit among GI (aOR=0.56; 0.43-0.8) & soft tissue (aOR=0.72: 0.55-0.95) interventions vs orthopedic & cardiac interventions (aOR=1.33: 0.96-1.83; p<0.001)

Reitz KM, et al. JAMA Surg 2022; 157:817.

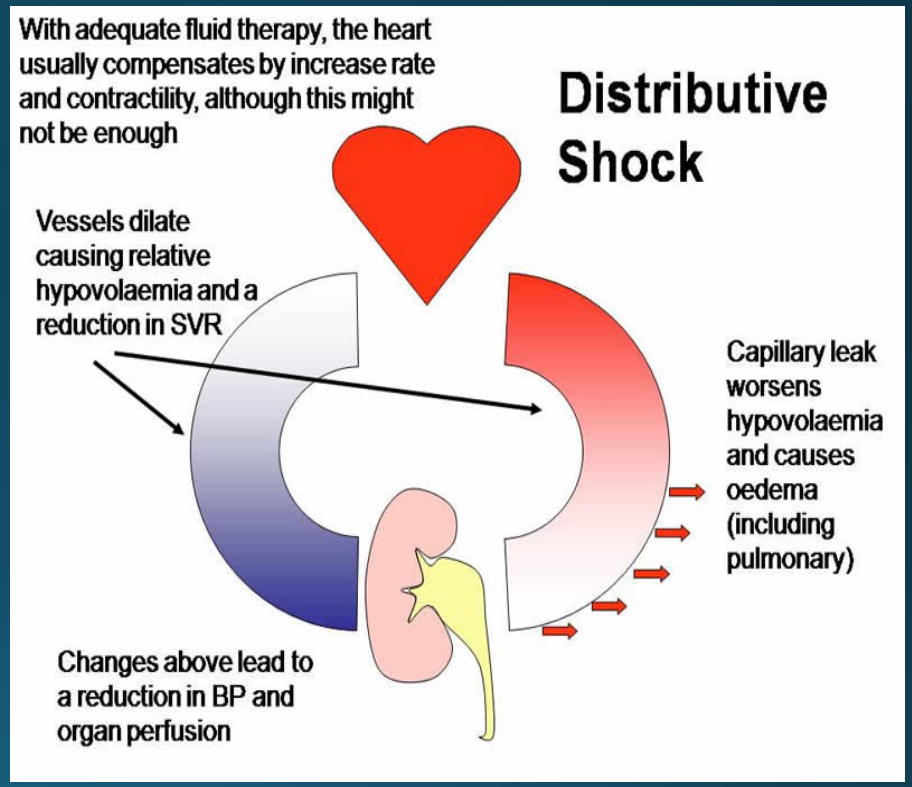
3-Riding the wave Navigating fluids in the storm of septic shock

How much fluid should you give to a patient with sepsis-induced hypotension???

3-Initial Resuscitation[1]:

→Crystalloid (Normal saline 0.9%)+
→Balanced crystalloid (Lactate Ringer)++
→Colloid (albumin)

- ❑Sepsis serious hemodynamic effects:
  - ↓ preload (due to capillary leak),
  - Impaired cardiac contractility, and
  - Decreased vascular tone (↓SVR)
- ❑Lactate≥4 or hypotension (SBP<90 mmHg):
  - Early & aggressive fluid resuscitation: with an initial bolus of 30 mL/kg followed by maintenance fluid
- ❑Patients with severe sepsis/septic shock who did not receive fluid challenges 30 cc/kg of crystalloid within the 1st 3 h after diagnosis had 52% ↑ in odds of in-hospital mortality[2]



SVR (systemic vascular resistance)=$80\times(MAP-CVP)/CO$= 700-1500 dynes·sec·cm^{-5}

LR: has an electrolyte composition similar to plasma with the addition of a buffer, such as lactate
Large volume fluid resuscitation: LR and albumin are associated with better outcome compared to NS

1-Singer M, et al. JAMA. 2016;315:801-10. 2-Kuttab HI, et al. Crit Care Med. 2019;47:1582-1590.

Surviving Sepsis Campaign: Evolution of the 30 cc/kg guideline

Surviving Sepsis Campaign

- **30cc/kg initial resuscitation is generally considered standard of care and should be initiated within the first hour of presentation.**

2001: Recommended Early Goal-Directed Therapy

2016: Recommended 30 cc/kg (Strong-graded)

2021: Suggest 30 cc/kg (weak-graded)

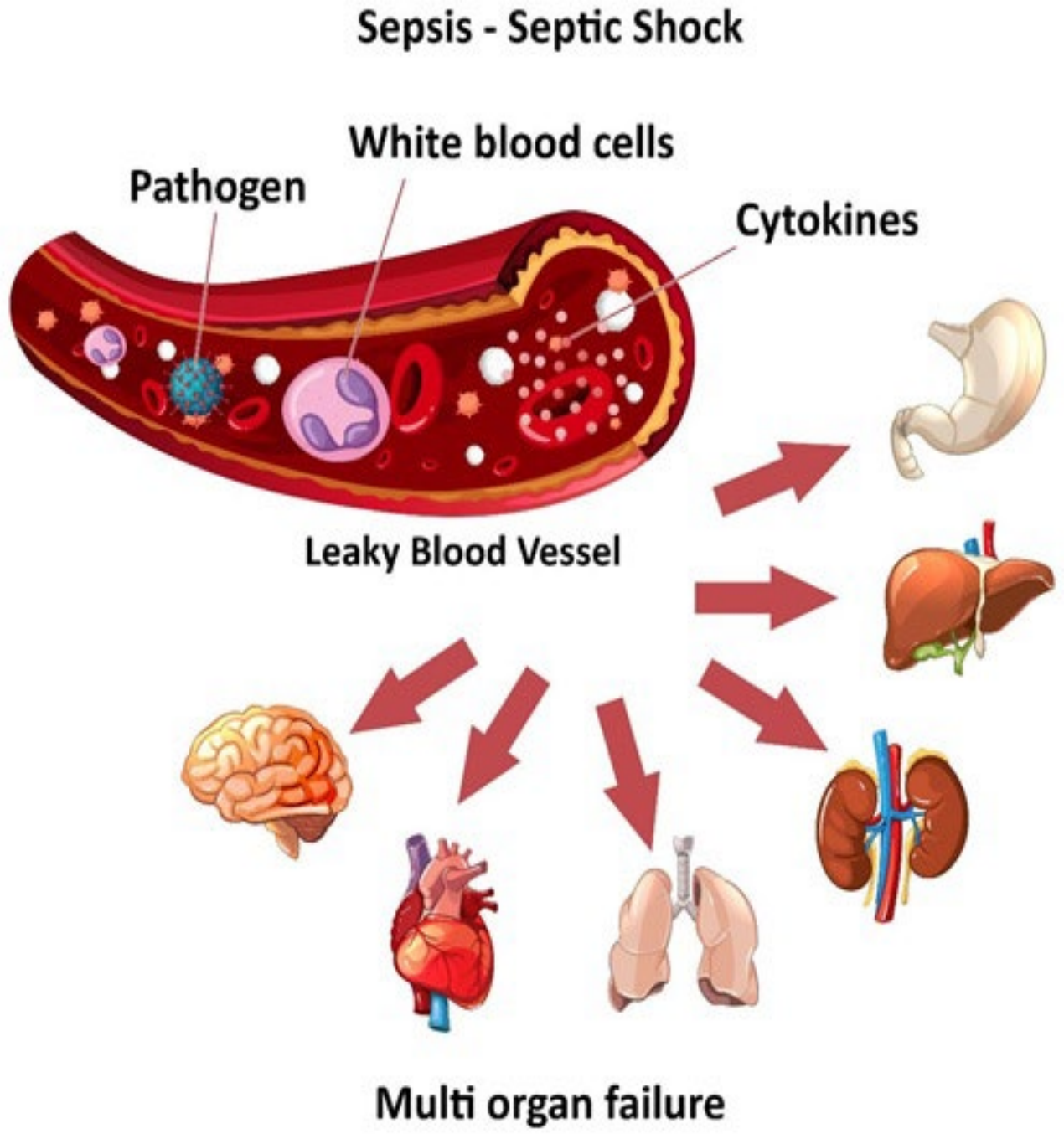
-**We recommend (strong):** All or almost all informed persons would choose the intervention (95%)

-**We suggest (weak):** Most informed persons would choose the interventions (66%), but still important variation among informed persons

→ Requires consideration, shared decision-making

Why give fluids?

- Restore intravascular volume
- Treat hypotension
- Improve organ perfusion



Farhanah N., et al. J. Med. Chem. Sci 2023; 6:2650.

Harm of fluids: evidence

- >20,000 patients with sepsis in Premier database (2013)
- Receiving >5 L on day 1
- 2.3% increase mortality/liter
- $999 increase in hospital cost/liter

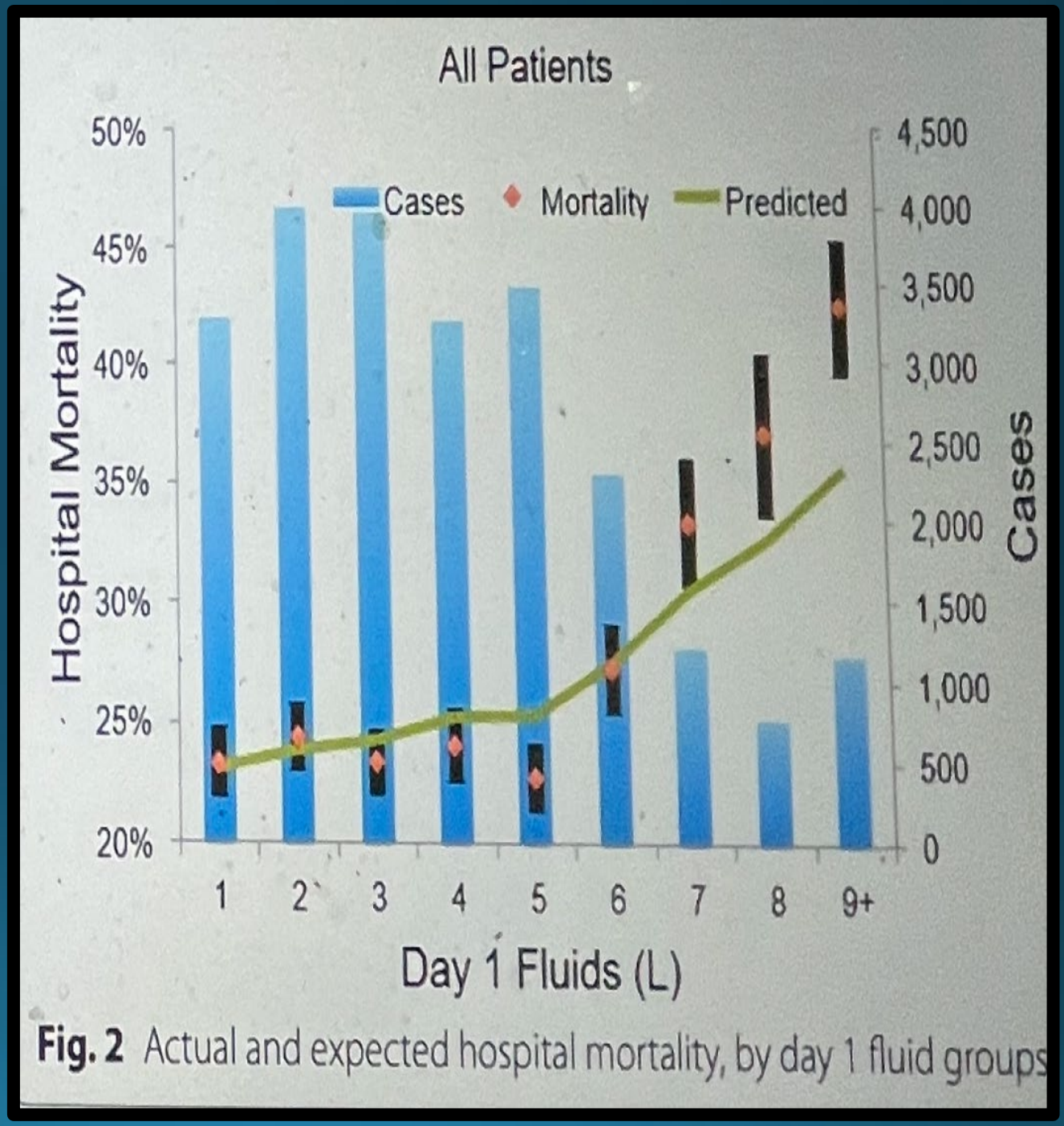
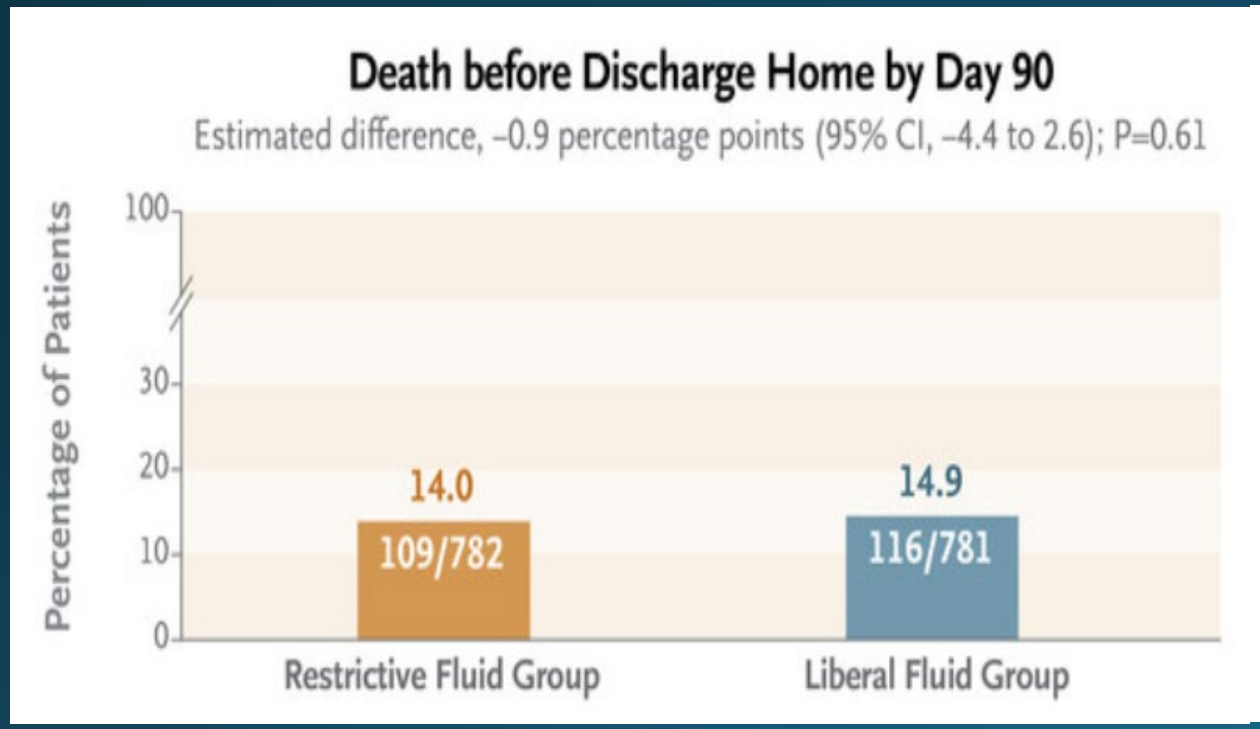
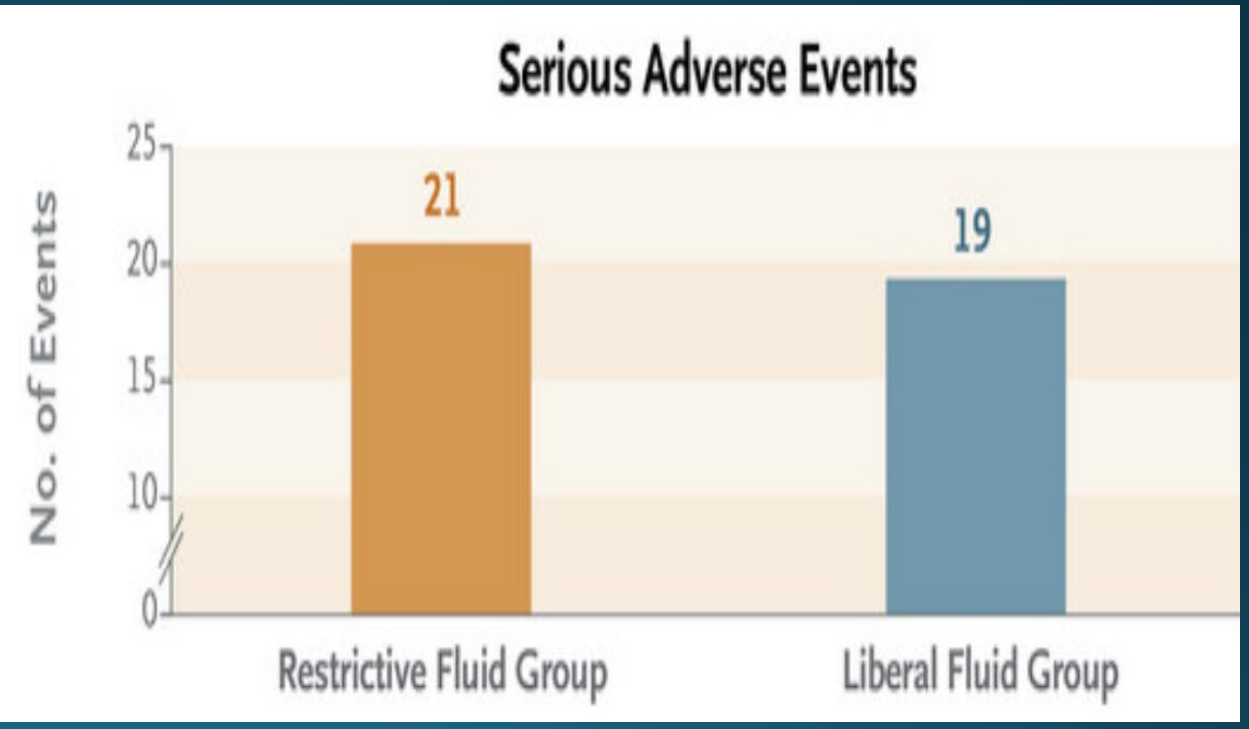


Fig. 2 Actual and expected hospital mortality, by day 1 fluid groups

Marik PE, et al. Intensive Care Med 2017; 43:625.

2023 CLOVERS results: Outcome of early restrictive vs. liberal fluid management after initial resuscitation



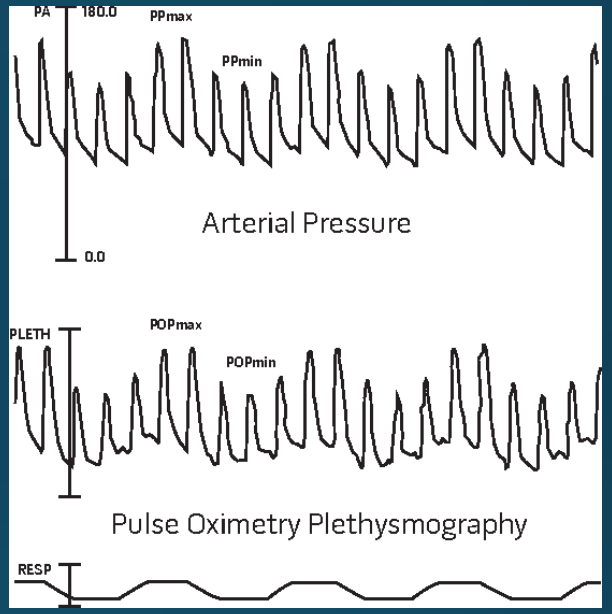


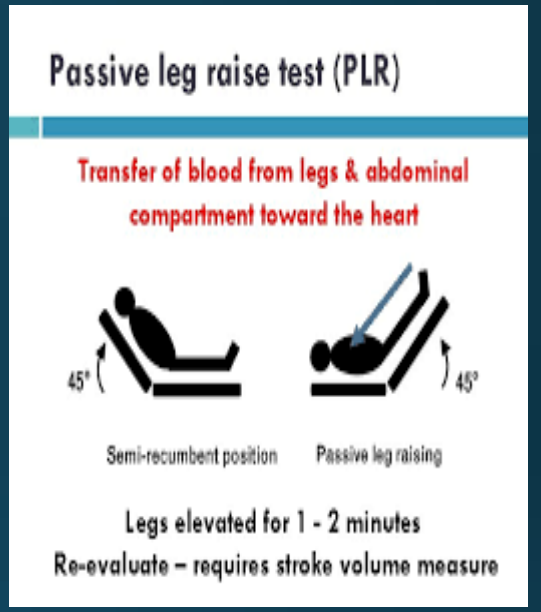
- In pts with sepsis-induced hypotension, a restrictive fluid strategy that prioritized vasopressors in the 1st 24 h after resuscitation did not result in significantly lower or higher mortality before discharge home by day 90 than a liberal fluid strategy

NHLBI PETAL Network. N Engl J Med 2023;388:499.

Techniques used as indicators of adequate fluid:

- **Static parameters:**
  - Mean arterial pressure [(SBP+2DBP)/3]
  - Change in serum lactate level
  - Capillary refill time (CRT)
  - Central venous pressure (CVP)
  - Pulmonary artery occlusion pressure (PAOP)
  - Left & right ventricular end-diastolic volume
  - Corrected flow time
- **Dynamic parameters:**
  - Pulse pressure variation (PPV): arterial waveform
  - Stroke volume variation (SVV)
  - Bedside echo assessment of inferior vena cava filling (IVCCI-Inspiratory collapsibility index ≥50%)
  - Plethysmography variation index (PVI) during respiratory cycle: [(PImax–PImin)/PImax]×100
  - Aortic blood flow (doppler or echocardiographic)
- **Techniques based on real or virtual fluid challenges:**
  - Passive leg raise (PLR)
  - Mini fluid boluses (100-200 mL)





Perfusion index (PI)

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801-10.

Recommendation: Focus on Sepsis Outcomes

Viewpoint

January 20, 2023

The Importance of Shifting Sepsis Quality Measures From Processes to Outcomes

Michael Klompas, MD, MPH[1,2]; Chanu Rhee, MD, MPH[1,2]; Mervyn Singer, MD[3]

- Shift the emphasis to what matters to most patients and clinicians
- Avoid some of the SEP-1's potentially harmful effects (e.g., overly aggressive Abx and fluid administration)
- Allow clinicians the freedom to tailor care to patient's various syndromes, underlying conditions, and precipitating pathogens
- Incentivize hospitals to address the full continuum of sepsis care

Klompas M, et al. JAMA 2023; 329:535.

Other potential opportunities

- Speeding identification of causative pathogens & Abx susceptibilities
- Implementing processes to facilitate timely source control
- Optimizing Abx dosing & administration regimens
- Encouraging timely Abx de-escalation
- Minimizing sedation & delirium in ICU patients
- Using appropriate lung protective ventilation
- Preventing hospital-acquired infections
- Preventing pressure injuries and venous thromboembolism
- Improving rehabilitation programs
- And more…..

Sepsis Innovations can revolutionize sepsis screening, diagnosis and treatment

Examples of FDA-Cleared Sepsis-Related Tests

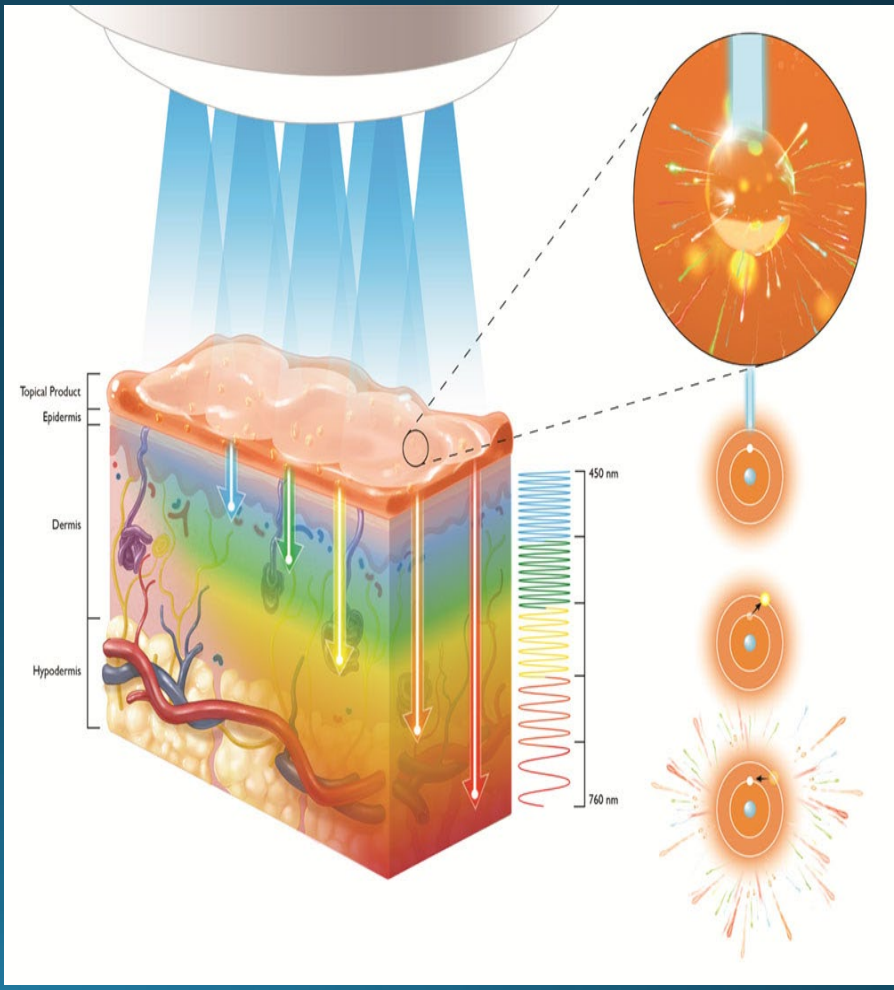
- **SeptiCyte RAPID (Immunexpress):** This PCR-based test identifies the pattern of immune system gene expression consistent with severe infection within approximately one hour.
- **IntelliSep Test (Cytovale):** This is described as the first and only test FDA-cleared for sepsis detection itself. It analyzes the biophysical changes (e.g., deformability) in white blood cells that occur in response to systemic infection, providing a high, medium, or low probability result within about 10 minutes.
- **Sepsis ImmunoScore (Prenosis):** This is the first-ever FDA-authorized AI diagnostic tool for sepsis. It uses machine learning to evaluate a patient's biological status (based on 22 biomarkers and clinical data) to provide a risk score for having or progressing to sepsis within 24 hours.
- **TriVerity Test System (Inflammatix):** This test measures the expression of 29 immune-related genes and uses AI to help differentiate between bacterial, viral, or non-infectious causes of illness, and assesses the risk of severe outcomes, such as the need for mechanical ventilation.
- **IVD Capsule PSP (Abionic):** This test detects sepsis earlier than some current standards by measuring levels of the pancreatic stone protein (PSP) biomarker from a drop of blood.

Noninvasive Light-Based Treatment Offers Hope in Sepsis Care

The use of vascular photobiomodulation (VPBM) significantly improved critical metabolic parameters including WBC (d3-5), ph (d5), SpO_2 (d2-5) and lactate levels (d3-5) in patients with sepsis

RCT at a hospital in Brazil to evaluate the effects of VPBM in 30 patients with a confirmed diagnosis of sepsis who were clinically stable and did not require vasopressors.

The VPBM group (mean age, 41 years) received 30-minute applications of a 660-nm red laser delivering 180 J of energy to the radial artery over 5 consecutive days, whereas the control group (mean age, 39 years) received the same procedure with the laser turned off.



de Sousa AC, et al. Lasers in Surgery and Medicine 2025;57:677.

Coming our Way Soon

- **CMS' Electronic Sepsis Mortality Measure**
  - CMS is developing a **community–onset sepsis 30-d mortality electronic clinical quality measure (eCQM)** that can be implemented and risk-adjusted using electronic health record data
    - Draft specifications released in June 2022
    - Currently in testing/pilot phase
  - Much more work still needs to be done in developing optimized and objective sepsis criteria, developing robust risk-adjustment methodology, and ensuring feasible implementation on a national level

Sepsis awareness, prevention, and treatment:
We must stay ahead to improve the quality of sepsis care

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For Disease-specific Care in Sepsis

PMC Team Sepsis Journey to TJC Certification

People

- Dedicated Sepsis Team
- Sepsis Champions
- Frontline Staff

Process

- What is Working/Not Working
- Sepsis Screenings
- Sepsis Order Sets
- Workflows

Policy

- Ensuring policy reflects Sep-1
- Ensuring all existing policies related to the management of sepsis are current and correct

Education

- Annual Staff Education
- Nurse/Provider Onboarding
- Patient/Community Education

Monitoring

- Concurrent Reviews
- Immediate Education for Sep-1 Fallouts
- Rounding/Huddles

- Application submitted to THJ May 7, 2025
- Surveyed June 21, 2025
- Awarded Certification July 15 2025

Thank you