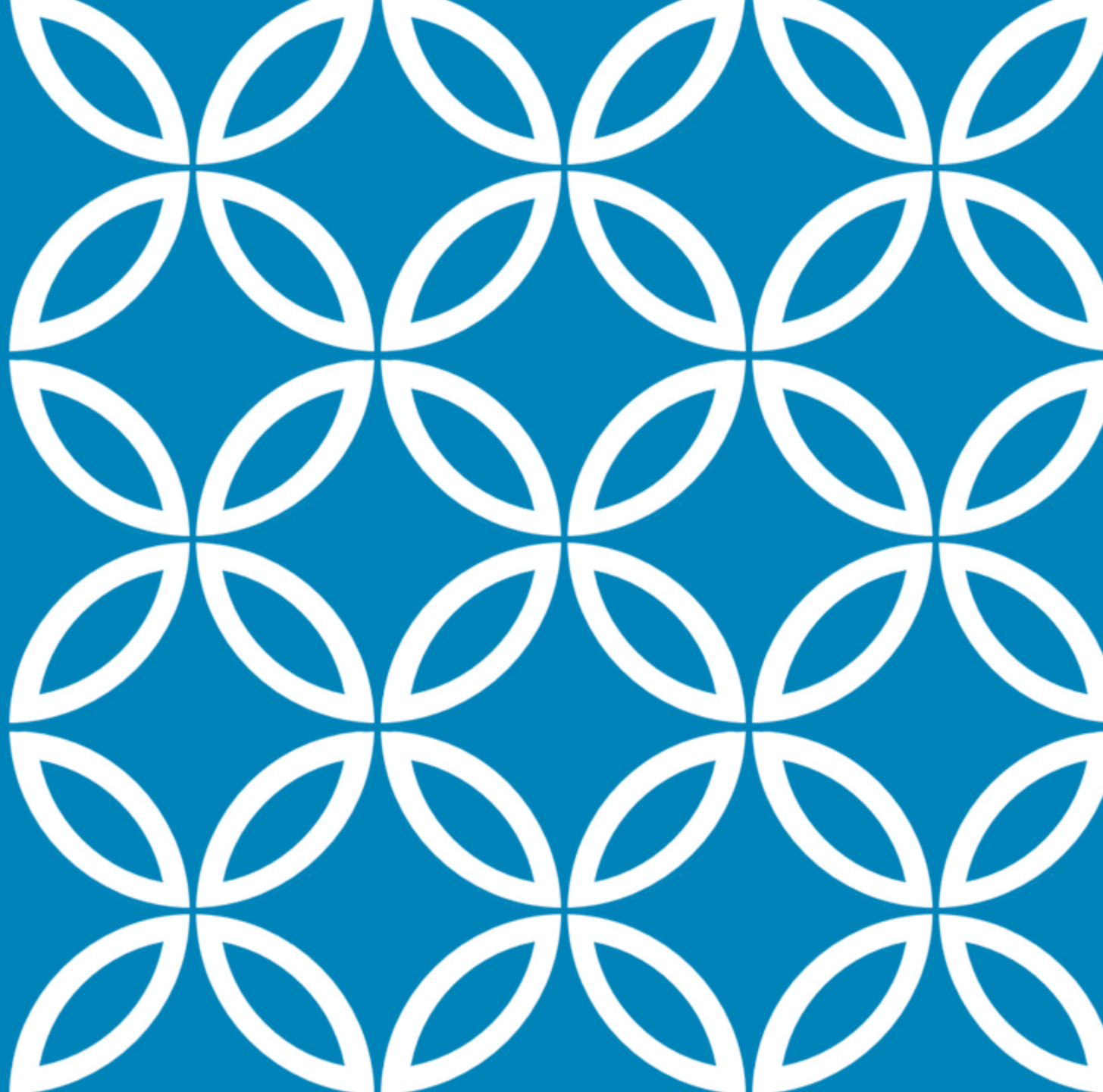


SEPSIS: THE CURRENT CONTROVERSIES

November 1, 2024

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OPPORTUNITY IN THE TIMELY AND CORRECT RECOGNITION OF SEPSIS

30% of antibiotics administered in the U.S. are suboptimal or unnecessary¹

Sepsis is prevalent, mortal, and expensive with the worst outcomes in those cases that were not present on admission

- Third most common cause of death in U.S. hospitals²
- Affecting 1.7 million people nationwide annually²
- Costing \$62 billion annually in hospitalizations and skilled nursing care³
- Overall inpatient death rate has been observed at 17.2% but higher in hospital-acquired sepsis (38.6% medical and 29.2% surgical)⁴

1. Centers for Disease Control and Prevention. Core elements of hospital antibiotic stewardship programs. CDC website. <https://www.cdc.gov/antibiotic-use/hcp/core-elements/hospital.html> . Published March 14, 2024. Accessed 10 Sept 2024.

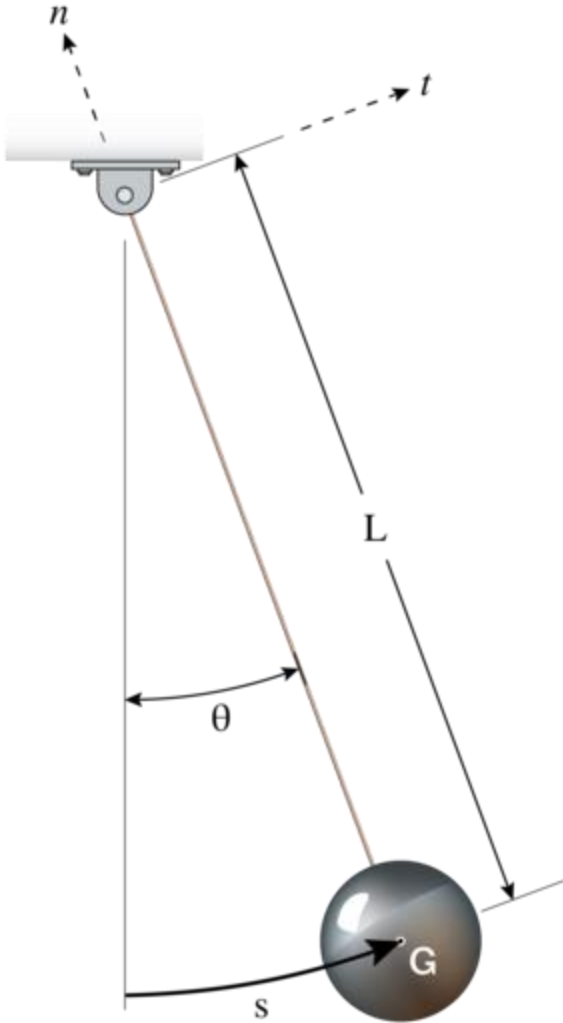
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3. Buchman, T. G. et al. Sepsis Among Medicare Beneficiaries: The Methods, Models, and Forecasts of Sepsis, 2012–2018. Critical Care Medicine 48(3):p 302-318, March 2020.

4. Jones SL, et al. Outcomes and Resource Use of Sepsis-associated Stays by Presence on Admission, Severity, and Hospital Type. Med Care. 2016 Mar;54(3):303-10.

SEPSIS IS THE STORY OF PENDULUMS



“A great man once said the true symbol of the United States is not the bald eagle, it’s the pendulum, and when the pendulum swings too far in one direction, it will go back.”
-Ruth Bader Ginsburg

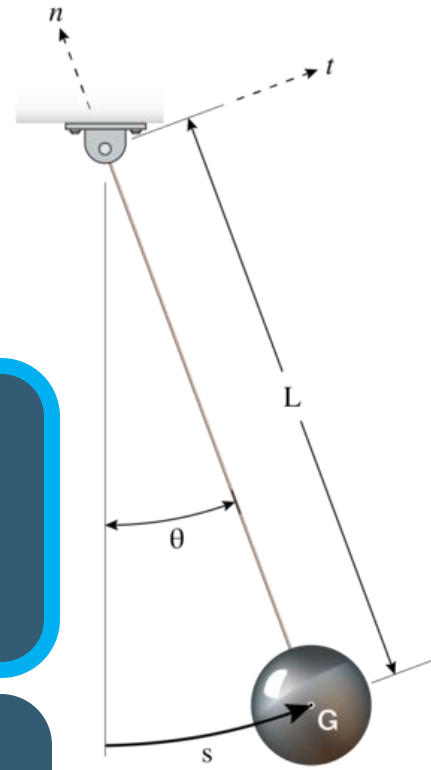


Image credit: Ruth Bader Ginsburg – The Oyez Project; Creative Commons License
Image credit: Wikimedia Commons

CURRENT CONTROVERSIES

How does one identify sepsis?

How does one support tissue perfusion through maladaptive responses?



SIRS $\rightarrow$ SOFA $\rightarrow$ SIRS ... OR... BOTH??

TIMELINE

1991
Consensus
Conference:
Sepsis-1
introduced
SIRS

2001
Consensus
Conference:
Sepsis-2 seeks
to expand
signs and
symptoms but
no change in
definition

2015 SEP-1
core measures
follows Sepsis-2

2016 Consensus
conference:
Sepsis-3 seeks
to redefine
sepsis around
organ
dysfunction and
SOFA with
qSOFA as
screening tool

2021 Surviving
Sepsis
Campaign
international
guidelines
recommends
against qSOFA
as screening

1. Levy MM et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31(4):1250.
2. Singer et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23; 315(8): 801-810.
3. Evans, L et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Medicine. 2021 Oct;47,1181-1247.

SEPSIS-1 1991: SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

Systemic activation of the innate immune response from any cause

- Localized infection, systemic infection, and noninfectious

At least 2 clinical indicators

- **$T < 96.8$ or ≥ 101**
- **$P > 90$**
- **$RR > 20$**
- **$WBC < 4000$ or $> 12,000$ or $> 10\%$ bands**
- **NOTE: Absence of hypotension as an indicator**

***Critically, one goal was to create
“standardization of research protocols”***

SEPSIS-2 2001: SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

Acknowledged the low specificity of SIRS

Emphasized the importance of early recognition

Specifically noted a future goal: biochemical or immunologic marker with high sensitivity and specificity

- 23 years later, still waiting...
- *Stay tuned for answers in transcriptomics, proteomics, metabolomics, cytomics...*

SEPSIS-2 SETTLED ON TWO PRINCIPLES:

SIRS should stand

- Criteria is broadly useful at the bedside and in research
- Sensitive enough to identify most patients with the syndrome
- Not overly cumbersome
 - Can be committed to memory and used in application

SIRS has limitations and additional signs should be evaluated

- **SIRS should prompt evaluation, it is *not* the definition of sepsis**

SEPSIS-2 TABLE 1 (SIRS IN BLUE)

Infection, documented as known or suspected, and **some** of the following (**not attributed to another cause**):

General variables

- Fever (core temperature 38.3°C)
- Hypothermia (core temperature 36°C)
- Heart rate $>90\text{bpm}$ or >2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance ($>20\text{ mL/kg}$ over 24 hrs)
- Hyperglycemia (plasma glucose $>120\text{ mg/dL}$) in the absence of diabetes

Inflammatory variables

- Leukocytosis (WBC count $>12,000$)
- Leukopenia (WBC count 4000)
- Normal WBC count with $>10\%$ immature forms
- Plasma C-reactive protein >2 SD above the normal value
- Plasma procalcitonin 2 SD above the normal value

Hemodynamic variables

- Arterial hypotension (SBP $<90\text{ mm Hg}$, MAP <70 , or an SBP decrease 40 mm Hg in adults or 2 SD below normal for age)
- $\text{SvO}_2 >70\%$
- Cardiac index >3.5

Organ dysfunction variables

- Arterial hypoxemia ($\text{PaO}_2/\text{FIO}_2 <300$)
- Acute oliguria (urine output $>0.5\text{ mL/kg/hr}$ for at least 2 hrs)
- Creatinine increase $>0.5\text{ mg/dL}$
- Coagulation abnormalities (INR >1.5 or aPTT $>60\text{ secs}$)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count $<100,000$)
- Hyperbilirubinemia (plasma total bilirubin $>4\text{ mg/dL}$)

Tissue perfusion variables

- Hyperlactatemia ($>1\text{ mmol/L}$)
- Decreased capillary refill or mottling

“Ultimately, this scheme seeks to codify the physical and laboratory findings that prompt an experienced clinician to conclude that an infected patient ‘looks septic.’”

SEPSIS-1 AND SEPSIS-2 DEFINITIONS

SIRS

Systemic disease with at least 2 clinical indicators. Can be infectious or noninfectious cause, ex trauma, pancreatitis, major surgery, burns.
 *$T < 96.8$ or ≥ 101 ; $P > 90$; $RR > 20$;
 $WBC < 4000$ or $> 12,000$ or $> 10\%$ bands*

SEPSIS

Documented (clinically assessed/suspected or culture-proven) infection with 2 or more SIRS indicators present

SEVERE SEPSIS

Sepsis and associate **acute organ dysfunction**

SEPTIC SHOCK

Hypotension not responsive to appropriate fluid resuscitation and often requiring vasopressor therapy

REFRACTORY SEPTIC SHOCK

Multiorgan system failure and hypotension refractory to vasoactive support

ACUTE ORGAN DYSFUNCTION

SOFA was part of sepsis-2: “Organ dysfunction can be defined using ...the Sequential Organ Failure Assessment (SOFA) score”

Additionally: elevated lactate

PaO ₂ /FiO ₂	Platelets	GCS	Bilirubin	MAP	Creatinine	Coded value
≥400	≥150	15	<1.2	No hypotension	<1.2	0
300-399	100-149	13-14	1.2-1.9	MAP <70	1.2-1.9	1
200-299	50-99	10-12	2.0-5.9	Dopamine ≤5 or dobutamine	2.0-3.4	2
100-199	20-49	6-9	6.0-11.9	Dopamine >5, epinephrine ≤0.1, norepinephrine ≤0.1	3.5-4.9 or UOP <500mL/day	3
<100	<20	<6	≥12.0	Dopamine >15, epinephrine >0.1, norepinephrine >0.1	≥5.0 or UOP <200mL/day	4

SEP-1 CORE MEASURES 2015

Follows Sepsis-2 closely

- Sepsis
- Severe Sepsis

Has some specific features of definitions unique to the core measures

- Severe sepsis with hypotension
- Threshold for septic shock*

• *Lactate ≥ 4 : Casserly, Brian; et al. Lactate Measurements in Sepsis-Induced Tissue Hypoperfusion: Results From the Surviving Sepsis Campaign Database. Critical Care Medicine 43(3):567-573, March 2015 [OR](#)

• Severe sepsis with hypotension not responding to crystalloid fluids [OR](#)

• Provider says so

SEPSIS-3
2016:
SEQUENTIAL
ORGAN FAILURE
ASSESSMENT
(SOFA)



SEPSIS-3 2016: SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA)



Noted that SIRS can simply represent normal host response to infection

- Sepsis indicates there is *dysregulated* host response
- SIRS does NOT necessarily indicate this



Asserted that SIRS was inadequately sensitive or specific

- Replaced SIRS with SOFA score (*change from baseline*) of 2 points or more



Asserted that the term severe was redundant

PROBLEMS WITH SEPSIS-3:

SIRS is not specific, SOFA is not sensitive¹

- In a study of patients of emergency department patients, 57% of patients meeting the old definition for septic shock did not meet the SEPSIS-3 definition for septic shock.
- The mortality of these patients was **14%**.
- SEPSIS-3 criteria did identify a group of patients with increased organ failure and higher mortality.

SOFA is a better prognostic tool than a diagnostic one

- Sepsis-3 definitions “**may actually decrease emphasis on the very group of patients most likely to derive benefit from early intervention.** Excluding this group of patients ... may inadvertently lead to under-recognition and treatment delays among a critically ill cohort of patients.”¹
- “Sepsis-3 criteria target a high mortality and omit patients with lower but significant mortality.”²

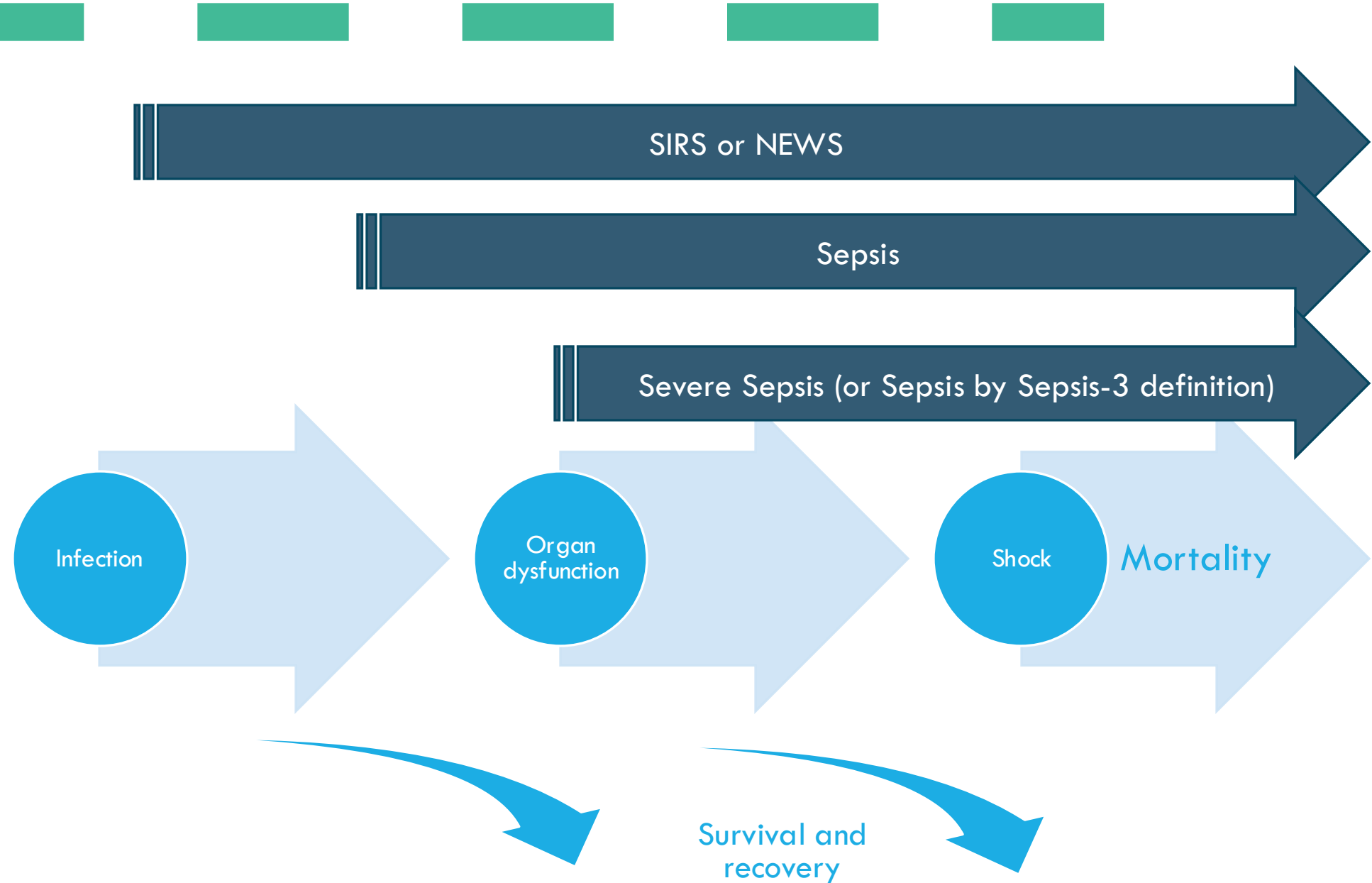
“Throwing out preclearance when it has worked and is continuing to work.... I like throwing away your umbrella in a rainstorm because you are not getting wet.”

-Ruth Bader Ginsburg

1. Sterling SA, Puskarich MA, Glass AF, et al. The Impact of the Sepsis-3 Septic Shock Definition on Previously Defined Septic Shock Patients. Crit Care Med 2017; 45:14361442
2. Sprung, Charles and Trahtenberg, Uriel. What Definition Should We Use for Sepsis and Septic Shock? Editorial. Crit Care Med. 2017 Sep;45(9):1564-1567. doi: 10.1097/CCM.00000000000002544.
3. Image credit: Library of Congress



Presents for care at any point (including developing infection and sepsis mid hospital stay)



SEPSIS-3 REMAINS HUGELY CONTROVERSIAL

CMS published response to the Sepsis-3 Criteria:

- “The Sepsis-3 definition structure does not clearly identify patients in the early stages of sepsis where rapid resuscitation provides the greatest patient benefit and improves survival. [A change to the existing definition could disrupt the 15-year trend toward further reduction in sepsis mortality.](#)”

Explicitly **not** endorsed by:

- Infectious Disease Society of America
- American College of Emergency Physicians
- The American College of Chest Physicians

It doesn't have to be either/or! Sepsis-3 itself notes:

- “There are, as yet, no simple and unambiguous clinical criteria or biological, imaging, or laboratory features that uniquely identify a septic patient.... Neither qSOFA nor SOFA is intended to be a stand-alone definition of sepsis.”

1. ISDA Sepsis Task Force. Infectious Disease Society of America Position Statement: Why IDSA Did not Endorse the Surviving Sepsis Campaign Guidelines. Clin Infect Dis. 2018 May 2;66(10):1631-1635. doi: 10.1093/cid/cix997.
2. Sepsis – 3, a New Definition. Solutions or New Problems? American College of Emergency Physicians Quality Improvement and Patient Safety Newsletter. July 2016. Online 21 Dec 2021.
3. Simpson, Steven. SIRS in the Time of Sepsis. Chest. 2018 Jan;153(1):34-38. doi: 10.1016/j.chest.2017.10.006. Epub 2017 Oct 14
4. Townsend, S. R.; Rivers, E; Tefera, L. Definitions for Sepsis and Septic Shock. JAMA. 2016;316(4):457-458. doi:10.1001/jama.2016.6374
5. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–810.

TAKE HOMES: THE ART OF MEDICINE



01

Sepsis is heterogeneous and complex; screening tools help but diagnosis requires critical thinking

02

SIRS is very sensitive but possibly overly so. Is the host response maladaptive with risk for decompensation? Do they “look septic?”

03

SOFA is a good prognostic tool but lacks sensitivity for diagnosis and screening

04

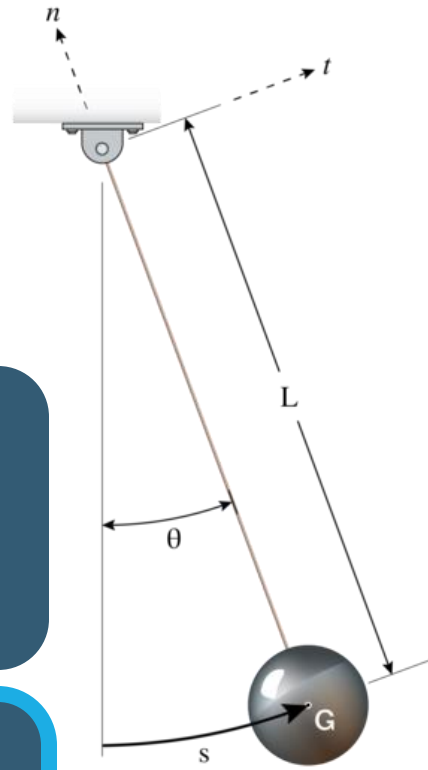
Both sepsis-2 and sepsis-3 have valid points

- In the end, use all the available data, your best judgment, and evolve your assessment as the case unfolds

CURRENT CONTROVERSIES

How does one identify sepsis?

How does one support tissue perfusion through maladaptive responses?



FLUID STRATEGIES AND PRESSORS

LANDMARK EGDT RIVERS 2001

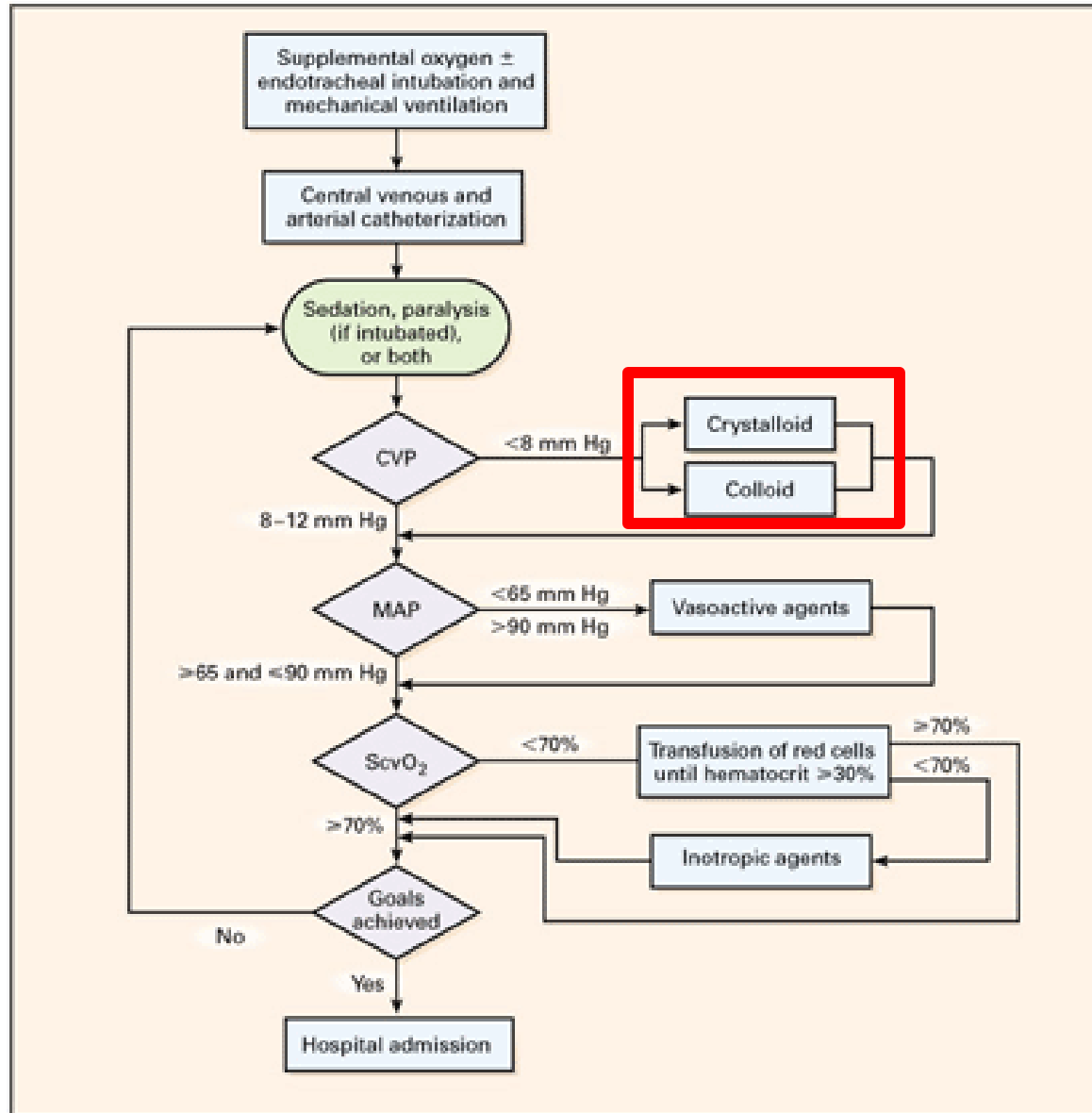
The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S.,
ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D.,
FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

1368 • N Engl J Med, Vol. 345, No. 19 • November 8, 2001 • www.nejm.org

STEP 1: OPTIMIZE PRELOAD TO IMPROVE CARDIAC OUTPUT



Volume resuscitation remains a mainstay of sepsis care...
... with some caution

PRELOAD THINKING HAS ADJUSTED

The septic heart may have Starling curve shifted down and to the right

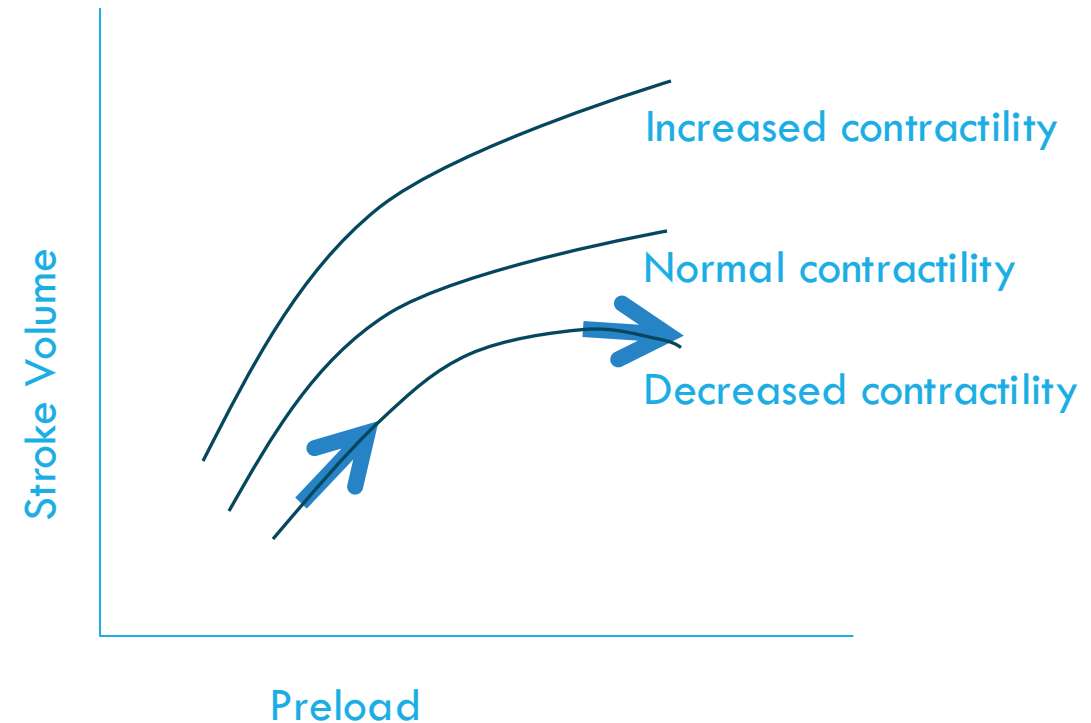
- With decreased contractility

End-organ dysfunction is related to bioenergetic failure *and* impaired perfusion

- Tissue edema can make cellular dysfunction worse

About 50% of septic shock patients are fluid responsive

- Rapidly become nonresponsive to further fluid challenges



“Individualized, conservative
and physiologic guided
approach to fluid
resuscitation.”

CLASSIC AND CLOVERS TRIAL

Randomized, open-label trial and randomized, unblinded superiority trial

Very large (one US focused with 60 centers, another international with 31 ICUs in 8 countries); total more than 3000 patients

Followed for entirety of ICU stay with sepsis after initial 1L IV fluids and for intervention period of 24 hours for those with hypotension refractory to initial 1-3L IV fluids

90-day mortality

Restrictive fluid strategy

Lower IV fluid volumes

- Given for prespecified indications suggesting severe intravascular volume depletion
- Difference of medians $>2L$ less fluid

Liberal fluid strategy

Either no limit or 5L fluid limit

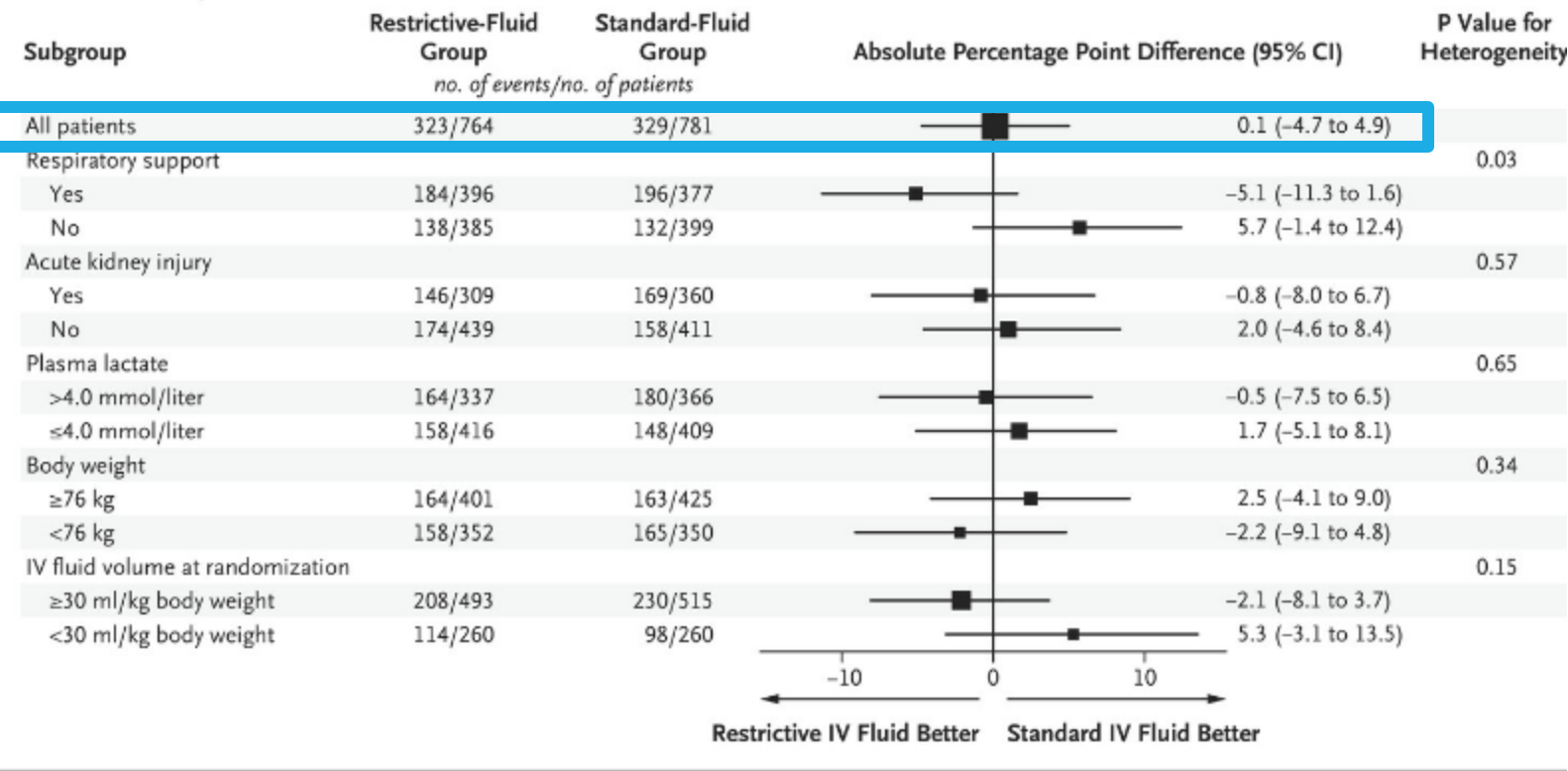
Fluids given under multiple conditions, including if any improvement in hemodynamic factors

Rescue conditions for pressors defined in CLOVERS

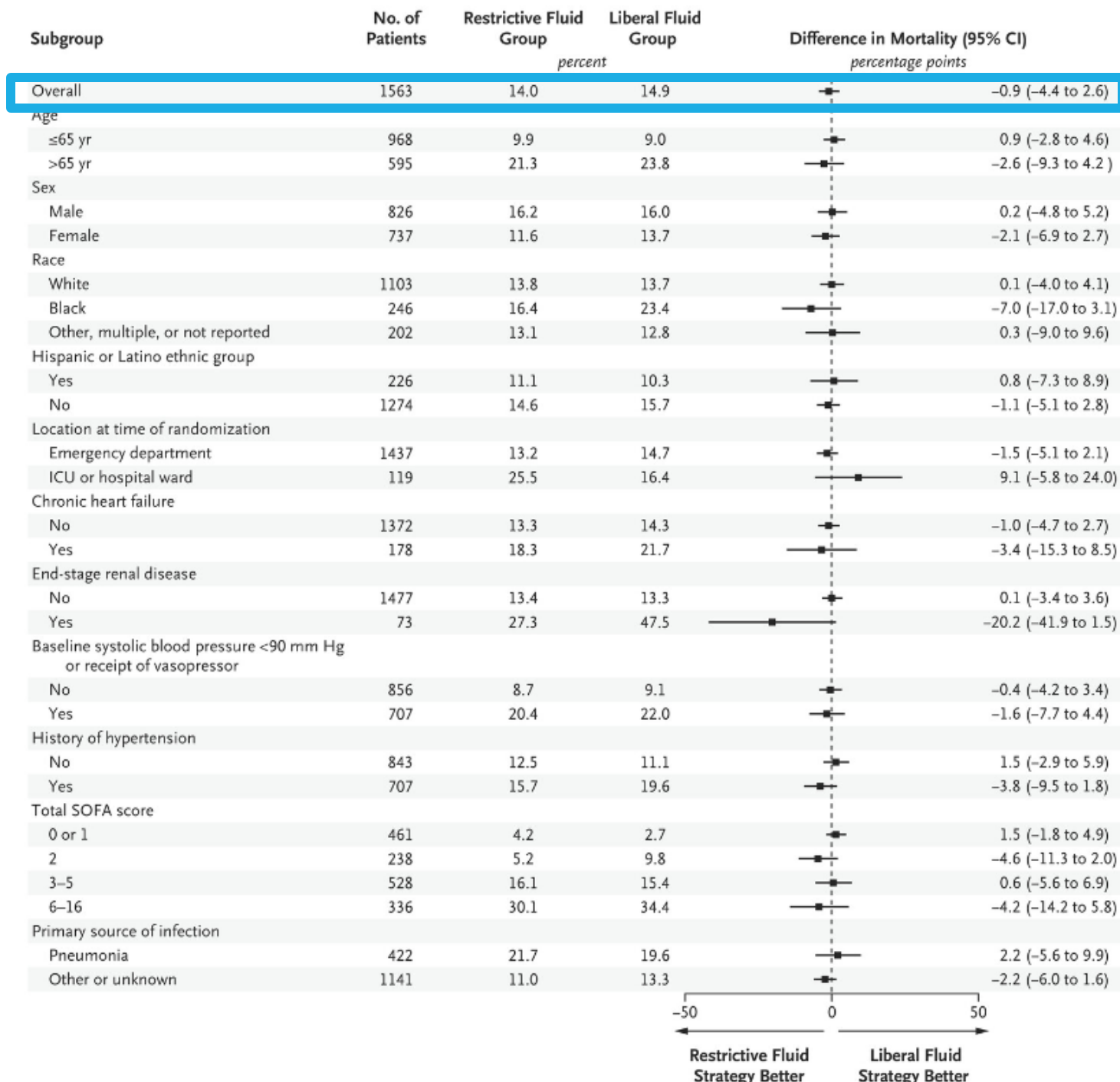
1. CLASSIC Trial Group. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. N Engl J Med. 2022 Jun 30;386(26):2459-2470. doi: 10.1056/NEJMoa2202707. Epub 2022 Jun 17.
2. National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network. Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension. N Engl J Med. 2023 Feb 9;388(6):499-510. doi: 10.1056/NEJMoa2212663. Epub 2023 Jan 21.

CLASSIC TRIAL

B Death at 90 Days



There was no difference in mortality



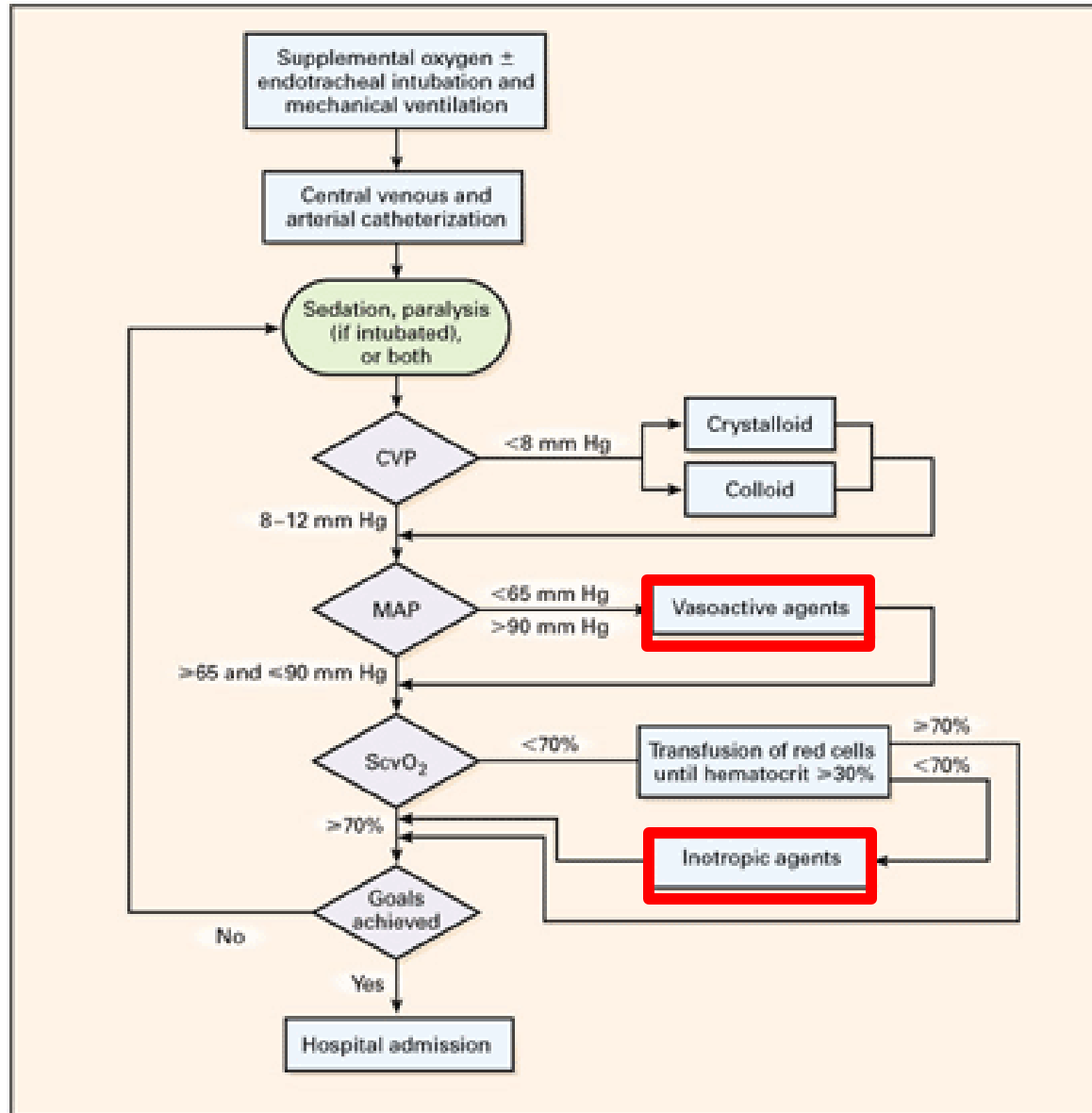
CLOVERS TRIAL

There was no difference in mortality

Bottom lines:

1. Perfusion is the issue
2. Don't hesitate on pressors
 - Severe hypotension (SBP <70, MAP <50)
 - Not fluid responsive
 - Lactate >4 or increasing after 2 hours

STEP 2: MAINTAIN TISSUE PERFUSION



Escalation to pressors without undue delay remains a mainstay, with norepinephrine first line preferred agents, addition of dobutamine if cardiac dysfunction^{1, 2}

Graphic: Rivers E, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001 Nov 8;345(19):1368-77.

1. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Critical Care Medicine* 49(11):p e1063-e1143, November 2021.
2. Jia, Lu; Wang, Pufeng; Li, Cong; Xie, Jianfeng. The Efficacy and Safety of Vasopressors for Septic Shock Patients: A Systemic Review and Network Meta-Analysis. *Shock* 60(6):p 746-752, December 2023.

RECENT CONTROVERSY: TYPE OF FLUID

1. Long settled: Crystalloid over colloid (like heta-starch)
2. But which crystalloid? Normal saline (“unbalanced”) or **lactated ringers** (“balanced”)
3. Problem: Infusion of large quantities of 0.9% saline will result in hyperchloremic acidosis.

4. Evidence:

- Multicenter prospective cohort study of 53,448 nonsurgical sepsis patients 2014. Few patients received *only* balanced or unbalanced so % of balanced fluids were calculated and propensity matched **Lower in-hospital mortality** (16.9 versus 22.8)
- Meta analysis 2014 found that septic patients that received balanced fluids had a **trend towards a lower mortality** than those that received NS (OR 0.78; 0.58-1.05).
- SALT 2017: The incidence of **major adverse kidney events** within 30-days was less in the sepsis/septic shock subgroup that received balanced fluids vs. normal saline (OR 0.56; 0.33–0.94).
- SMART 2019: In a pre-specified subgroup of septic ICU patients, there was **lower 30-day mortality** in those receiving balanced solutions compared to normal saline (OR 0.80; 0.67-0.94). Furthermore, in a secondary analysis of 1,641 patients admitted to the ICU with sepsis, balanced solutions were associated with **reduced 30-day hospital mortality, major adverse kidney events in 30 days, and increased vasopressor- and RRT-free days.**
- BaSICS 2021: Subgroup analysis of 90-day survival of patients with sepsis did not find any differences between the balanced and normal saline groups (OR 0.93; 0.82-1.06).
- PLUS: Subgroup analysis of death from any cause in patients with sepsis did not find any differences in mortality between the balanced and normal saline groups (OR 1.01; 0.83–1.23).

BOTTOM LINE 2021 SSC GUIDELINE:

33. For adults with sepsis or septic shock, we **suggest** using balanced crystalloids instead of normal saline for resuscitation
Weak recommendation, low quality of evidence

1. R. Phillip Dellinger, MD. Jour CCM. 2013;41(2):580-620
2. Poorna M, et al. BioMed Research International, vol. 2014, Article ID 984082, 9 pages, 2014. doi:10.1155/2014/984082
3. Rochwerg et al. Ann Intern Med 2014;161:347-355.
4. Raghunathan K et al. Crit Care Med. 2014 Jul;42(7):1585-91.
5. Semler MW et al. Am J Respir Crit Care Med. 2017 May;195(10):1363-72.
6. Semler MW et al. N Engl J Med. 2018 Mar;378:829-39.
7. Brown RM et al. Am J Respir Crit Care Med. 2019 Dec;200(12):1487-95.
8. Zampieri FG et al. JAMA. 2021 Aug;326(9):818-29.
9. Finfer S et al. N Engl J Med. 2022 Mar;386:815-25.

TAKE HOMES: THE ART OF MEDICINE



01
Early fluid resuscitation remains a
mainstay

- With careful attention to
individual fluid needs

02
Pressors should be started without
delay if inadequate response to
fluid resuscitation

03
Lactated ringers is preferred to
normal saline

TOPICS WE DON'T HAVE TIME TO COVER TODAY

- SEP-1 core measure dissent

- Barbash et al. Treatment patterns and clinical outcomes after the introduction of the Medicare Sepsis Performance Measure (SEP-1). *Annals Int Med.* 2021;174(7):927-935.
- “CMS Sepsis Measurement Under Fire.” 2022. [CMS Sepsis Measurement Under Fire | MedPage Today](#) Online. Accessed 10 March 2022.
- Klompas M K and Rhee C. Has the Medicare Sepsis Performance Measure (SEP-1) Catalyzed Better Outcomes for Patients with Sepsis? *Annals Int Med.* 2021;174(7):1010-1011

- Machine learning and Artificial Intelligence in predictive models

- Boussina, A., Shashikumar, S.P., Malhotra, A. *et al.* Impact of a deep learning sepsis prediction model on quality of care and survival. *npj Digit. Med.* 7, 14 (2024).
- Cull J, Brevetta R, Gerac J, Kothari S, Blackhurst D. Epic Sepsis Model Inpatient Predictive Analytic Tool: A Validation Study. *Crit Care Explor.* 2023 Jun 30;5(7):e0941.
- Kamran, F, et al. Evaluation of Sepsis Prediction Models before Onset of Treatment. *NEJM.* 2024 Feb 7;1(3).

- Biomarkers

- Póvoa P, Coelho L, et al. How to use biomarkers of infection or sepsis at the bedside: guide to clinicians. *Intensive Care Med.* 2023;49(2):142-53.
- Chambliss AB, Patel K, et al. AACC guidance document on the clinical use of procalcitonin. *J Appl Lab Med* 2023;8:598-634.

TOPICS WE DON'T HAVE TIME TO COVER TODAY

- New thinking on antibiotic duration and impact on resistance patterns

- Metlay JP, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019 Oct 1;200(7):e45-e67.
- Grant J, Saux NL; members of the Antimicrobial Stewardship and Resistance Committee (ASRC) of the Association of Medical Microbiology and Infectious Disease (AMMI) Canada. Duration of antibiotic therapy for common infections. *J Assoc Med Microbiol Infect Dis Can*. 2021 Sep 30;6(3):181-19

- Surviving Sepsis Campaign recommends *against* qSOFA

- Dykes et al. Contrasting qSOFA and SIRS Criteria for Early Sepsis Identification in a Veteran Population. *Federal Prac Spec Issue*. 2019 Mar 24 (Suppl 2):S21-24.
- Serafim R, Gomes JA, Salluh J, Póvoa P. A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome criteria for the diagnosis of sepsis and prediction of mortality: a systematic review and meta-analysis. *Chest*. 2018;153(3):646–655.
- Evans, L et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Medicine*. 2021 Oct;47,1181-1247.

- ProCESS, PROMISe, and ARISE draw some conclusions not necessarily borne out in the data

- De Backer, D., Vincent, JL. Early goal-directed therapy: do we have a definitive answer?. *Intensive Care Med* **42**, 1048–1050 (2016)
- Yu H, Chi D, Wang S, Liu B. Effect of early goal-directed therapy on mortality in patients with severe sepsis or septic shock: a meta-analysis of randomised controlled trials. *BMJ Open*. 2016 Mar 1;6(3):e008330.
- Nguyen, H.B., Jaehne, A.K., Jayaprakash, N. *et al*. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. *Crit Care* **20**, 160 (2016).

TOPICS WE DON'T HAVE TIME TO COVER TODAY

- It has been suggested to not use CVP any longer and consider noninvasive fluid management monitoring systems.... Or even just passive leg raise
 - P. E. Marik, M. Baram, and B. Vahid, "Does the central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares," *Chest*, vol. 134, no. 1, pp. 172–178, 2008.
 - Cavallaro F., Sandroni C., Marano C., La Torre G., Mannocci A., De Waure C., et. al.: Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Med* 2010; 36: pp.
- Consider lactic acid clearance in addition to or in lieu of ScVO₂
 - Baysan, Meryem et al. The Added Value of Lactate and Lactate Clearance in Prediction of In-Hospital Mortality in Critically Ill Patients With Sepsis. *Critical Care Explorations* 2(3):p e0087, March 2020.
 - Jones AE, Shapiro NI, Trzeciak S, et al. Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy: A Randomized Clinical Trial. *JAMA*. 2010;303(8):739–746.
 - Simpson SQ, Gaines M, Hussein Y, Badgett RG. Early goal-directed therapy for severe sepsis and septic shock: A living systematic review. *J Crit Care*. 2016 Dec;36:43-48.
 - Gu WJ, Zhang Z, Bakker J. Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials. *Intensive Care Med*. 2015 Oct;41(10):1862-3.

TOPICS WE DON'T HAVE TIME TO COVER TODAY

- Steroids for severe CAP

- Dequin PF, et al. CRICS-TriGGERSep Network. Hydrocortisone in Severe Community-Acquired Pneumonia. *N Engl J Med*. 2023 May 25;388(21):1931-1941

- The importance of administering β lactam prior to vancomycin in bacteremic patients

- Amoah J, Klein EY, Chiotos K, Cosgrove SE, Tamma PD. Administration of a β -Lactam Prior to Vancomycin as the First Dose of Antibiotic Therapy Improves Survival in Patients With Bloodstream Infections. *Clin Infect Dis*. 2022 Aug 24;75(1):98-104.

- Vitamin C

- de Man A et al. Vitamin C for all? *Curr Opin Crit Care*. 2024 Aug 1;30(4):298-304.

- Post sepsis syndrome

- van der Slikke EC et al. Understanding Post-Sepsis Syndrome: How Can Clinicians Help? *Infect Drug Resist*. 2023 Sep 29;16:6493-6511.



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mn.us\)](https://mnvotes.sos.state.mn.us)

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