# Surviving Sepsis in 2024

## Understanding The Guidelines

Zaza Cohen, MD FCCP

HMH-Mountainside Medical Center

May 16, 2024

# Financial Disclosure

- Nothing to disclose

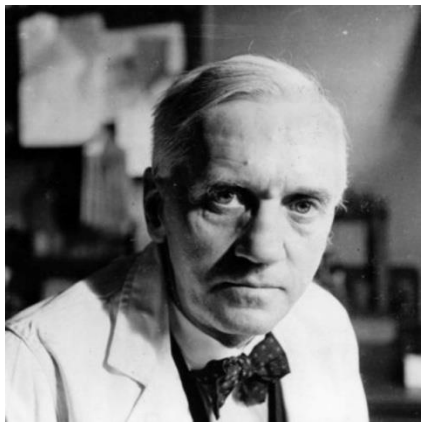
# Goals and Objectives

- Analyze the literature regarding diagnosis and treatment of sepsis
- Review the recent guidelines on sepsis
- Discuss the importance of a hospital-wide sepsis management initiative and barriers against its implementation

# Sepsis in March 2018:
# Long and Hard “Winter” Ahead


Game of Thrones was the hottest show on TV
Only virologists talked about Coronavirus

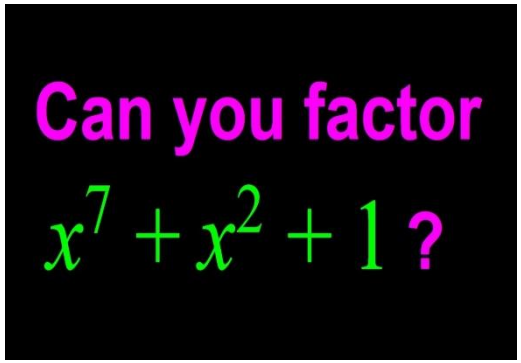
# Sepsis Revolution



- From Hippocrates to 20th Century
- Rivers et al. NEJM 2001
- Surviving Sepsis Campaign (SSC) 2002-Present
  - Barcelona Declaration (10/2/2002)
  - Multiple updates, most recent in 2021
- Sepsis-3 published in JAMA Feb 23, 2016
  - Has largely become a distant dot in the rearview mirror

# Let’s Play NY Times “Connections”

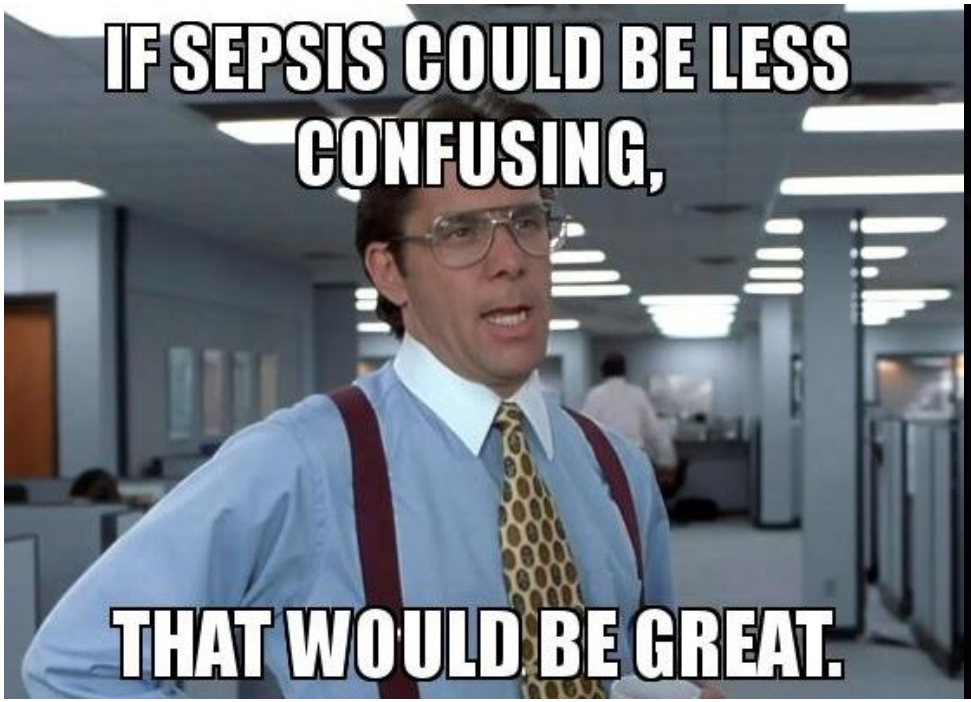

Septic Tank
Septic = sewage

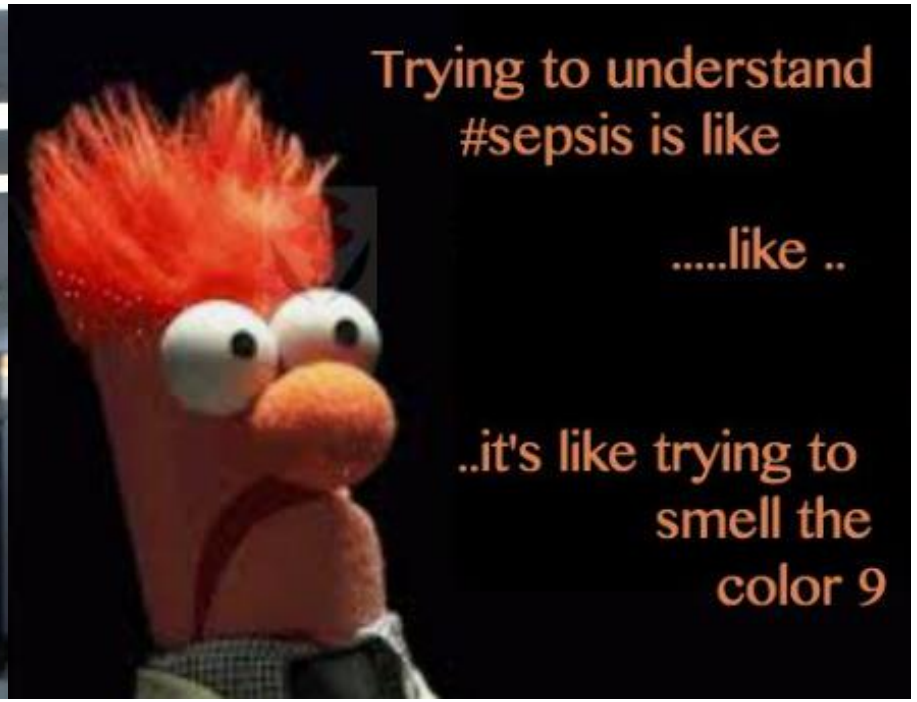



Septic polynomial
Septic = $7^{th}$ power


Septic patient
Septic = infection

# Sepsis – Why so Confusing?



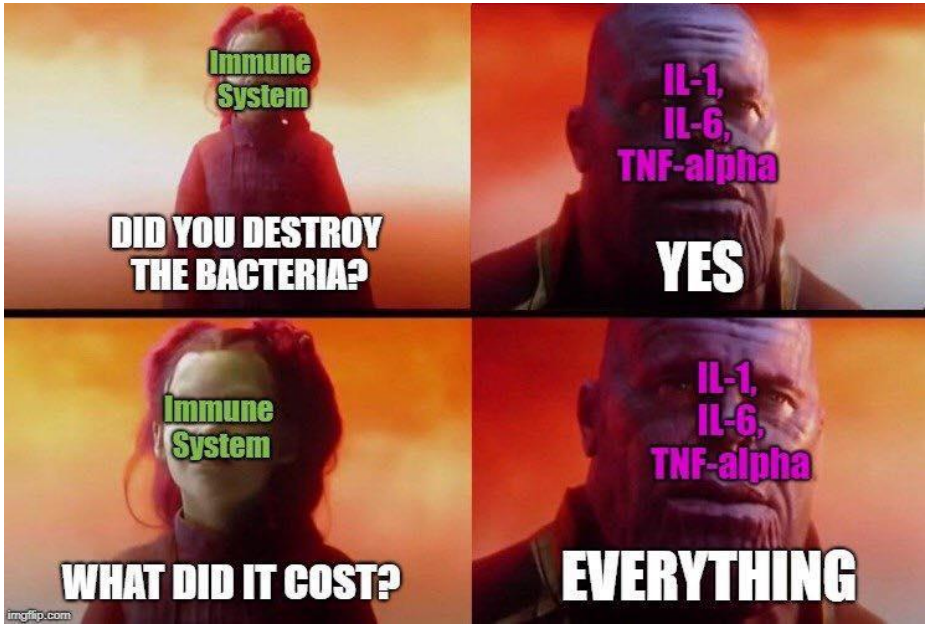
# Sepsis: Definition(s)

- A process by which flesh rots, swamps generate foul airs, and wounds fester
  - Hippocrates
- A laudable event, necessary for wound healing
  - Galen
- The result of the host's invasion by pathogenic organisms that then spread in the bloodstream
  - Pasteur et al.

*Angus, van der Poll, NEJM 2013 369:840*

# Sepsis: Definition

- Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection




*Surviving Sepsis Campaign CCM 2021 e1063*

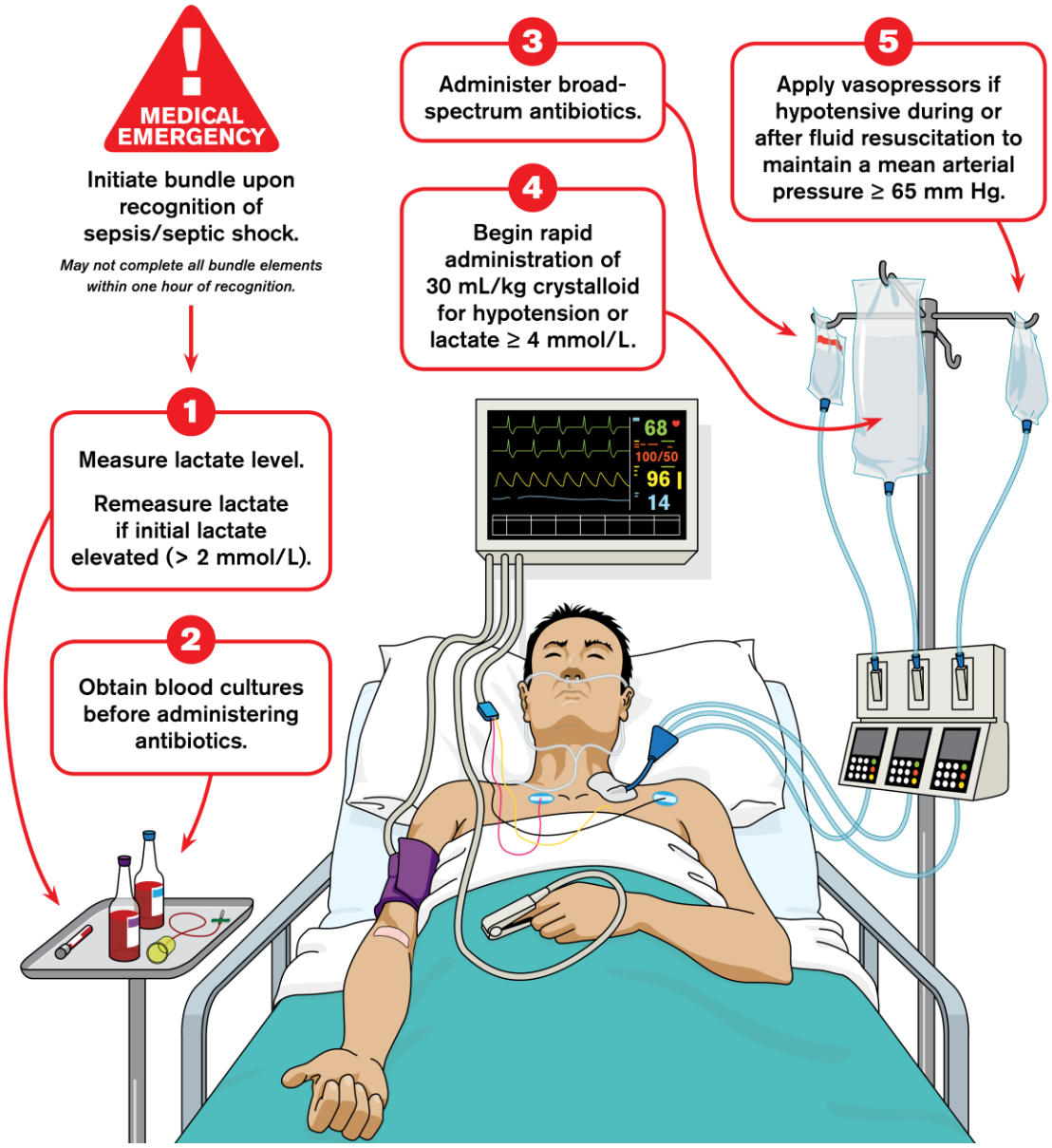
# Sepsis vs. Other Emergencies

- MI – ‘heart attack’
- Stroke – ‘brain attack’
- Sepsis – ‘bugs attack’
  - Overall goal: to gain the ‘emergency’ status and time-sensitive treatment approach like others

# Hour-1 Bundle

## Initial Resuscitation for Sepsis and Septic Shock

Surviving Sepsis Campaign®



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# Hour-1 Bundle Elements

1) Measure lactate level.*
2) Obtain blood cultures before administering antibiotics.
3) Administer broad-spectrum antibiotics.
4) Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate $\geq$ 4 mmol/L.
5) Apply vasopressors if hypotensive during or after fluid resuscitation to maintain a mean arterial pressure of $\geq$ 65 mm Hg.

*Remeasure lactate if initial lactate elevated (> 2 mmol/L).

# CMS SEP-1 Bundle

## Sepsis Bundle Algorithms

07-01-2022 (3Q22) through 12-31-2022(4Q22)

**SEP-1: Early Management Bundle, Severe Sepsis/Septic Shock (Composite Measure)**

**Numerator:**

**(Patients who received All of the following)**

Within three hours of presentation of severe sepsis:

- Initial lactate level measurement
- Broad spectrum or other antibiotics administered
- Blood cultures drawn prior to antibiotics

AND received within six hours of presentation of severe sepsis. ONLY if the initial lactate is elevated:

- Repeat lactate level measurement

AND within three hours of initial hypotension:

- Resuscitation with 30 mL/kg crystalloid fluids

OR within three hours of septic shock:

- Resuscitation with 30 mL/kg crystalloid fluids

AND within six hours of septic shock presentation, ONLY if hypotension persists after fluid administration:

- Vasopressors are administered

AND within six hours of septic shock presentation, if hypotension persists after fluid administration or initial lactate >= 4 mmol/L:

- Repeat volume status and tissue perfusion assessment is performed

**Denominator:**

Inpatients age 18 and over with an ICD-10-CM Principal or Other Diagnosis Code of sepsis, severe sepsis or septic shock as defined in Appendix A, Table 4.01 and not equal to U07.1 (COVID-19)

# SEP-1 Bundle

**TABLE 3** ] Element-Level Unadjusted and Adjusted Conditional Treatment Effects Based on the Hierarchical Generalized Linear Model Logistic Regression Model

| Bundle: Treatment Section and Elements | No. of Eligible Cases | Pass Rate (%) | Compliant 30-d Mortality (%) | Noncompliant 30-d Mortality (%) | Conditional Adjusted OR | Conditional Adjusted OR 95% CI | *P* Value |
|---|---|---|---|---|---|---|---|
| Complete SEP-1 bundle[a] | 333,770 | 42.1 | 21.7 | 30.3 | 0.829 | 0.812-0.864 | < .001 |
| Severe sepsis 3 h: initial lactate level | 159,646 | 86.0 | 26.2 | 32.0 | 0.772 | 0.743-0.802 | < .001 |
| Severe sepsis 3 h: antibiotic administration | 137,252 | 88.5 | 25.8 | 29.0 | 0.844 | 0.798-0.892 | < .001 |
| Severe sepsis 3 h: blood culture | 121,454 | 90.0 | 25.3 | 30.8 | 0.867 | 0.827-0.908 | < .001 |
| Severe sepsis 3-h bundle | 159,646 | 68.5 | 25.3 | 30.8 | 0.803 | 0.779-0.828 | < .001 |
| Severe sepsis 6-h bundle: repeat lactate level | 74,349 | 62.6 | 27.0 | 26.9 | 0.885 | 0.851-0.921 | < .001 |
| Shock 3-h bundle: crystalloid fluid administration | 24,357 | 62.2 | 34.1 | 34.8 | 0.915 | 0.855-0.980 | .011 |
| Shock 6 h: vasopressors | 5,332 | 77.3 | 39.3 | 29.1 | 1.317 | 1.126-1.541 | < .001 |
| Shock 6 h: reassessment | 9,931 | 38.1 | 38.0 | 36.5 | 1.012 | 0.920-1.114 | .807 |
| Shock 6 h: vasopressors and reassessment | 4,122 | 42.5 | 40.8 | 38.3 | 1.014 | 0.879-1.169 | .846 |
| Shock 6-h bundle | 11,141 | 34.0 | 38.0 | 35.3 | 1.048 | 0.955-1.149 | .326 |

[a]Data inclusive from quarter 4, 2015, to quarter 1, 2017; data in all other rows represent quarter 4, 2015, to quarter 2, 2016.

*Townsend et al; Chest 2021*

# Surviving Sepsis Guidelines (SSG)

- A total of 93 statements (‘commandments’)
- Grading
  - Strong 15 (16%)
  - Weak 54 (58%)
  - Best practice statement (BPS) 15 (16%)
  - No recommendation 9 (10%)
- A separate section on “Ventilation”
  - Statements (‘commandments’) 46-57

*Surviving Sepsis Campaign CCM 2021 e1063*

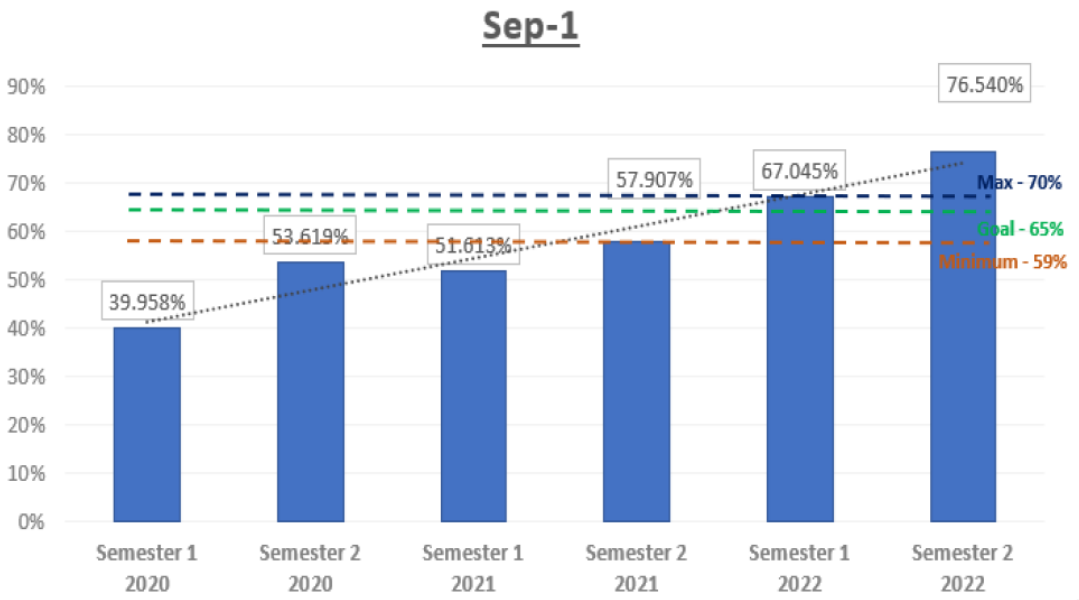
# Recommendations – General

1. For hospitals and health systems, we recommend using a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients and standard operating procedures for treatment.

*Surviving Sepsis Campaign CCM 2021 e1063*

# Sepsis Initiative at HMH-MMC

## Sepsis: Sep-1 Bundle Compliance

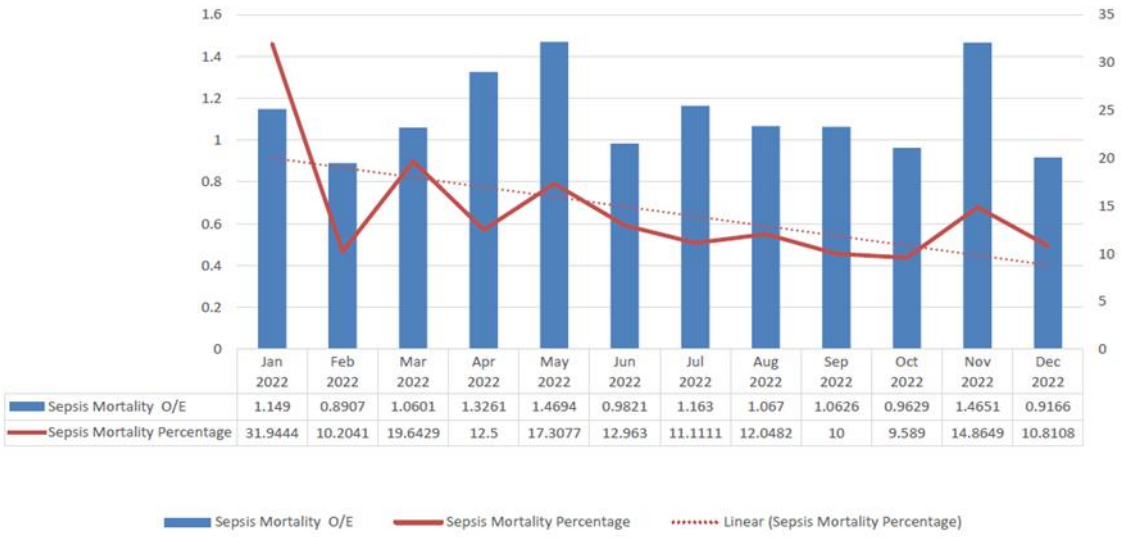



Hackensack Meridian
Mountainside Medical Center

*Courtesy of Candise Maiore, HMH-MMC Quality Manager*

# Sepsis Initiative at HMH-MMC

## Sepsis Mortality (O/E vs Rate 2022)




| | Jan 2022 | Feb 2022 | Mar 2022 | Apr 2022 | May 2022 | Jun 2022 | Jul 2022 | Aug 2022 | Sep 2022 | Oct 2022 | Nov 2022 | Dec 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sepsis Mortality O/E | 1.149 | 0.8907 | 1.0601 | 1.3261 | 1.4694 | 0.9821 | 1.163 | 1.067 | 1.0626 | 0.9629 | 1.4651 | 0.9166 |
| Sepsis Mortality Percentage | 31.9444 | 10.2041 | 19.6429 | 12.5 | 17.3077 | 12.963 | 11.1111 | 12.0482 | 10 | 9.589 | 14.8649 | 10.8108 |

Hackensack Meridian
Mountainside Medical Center

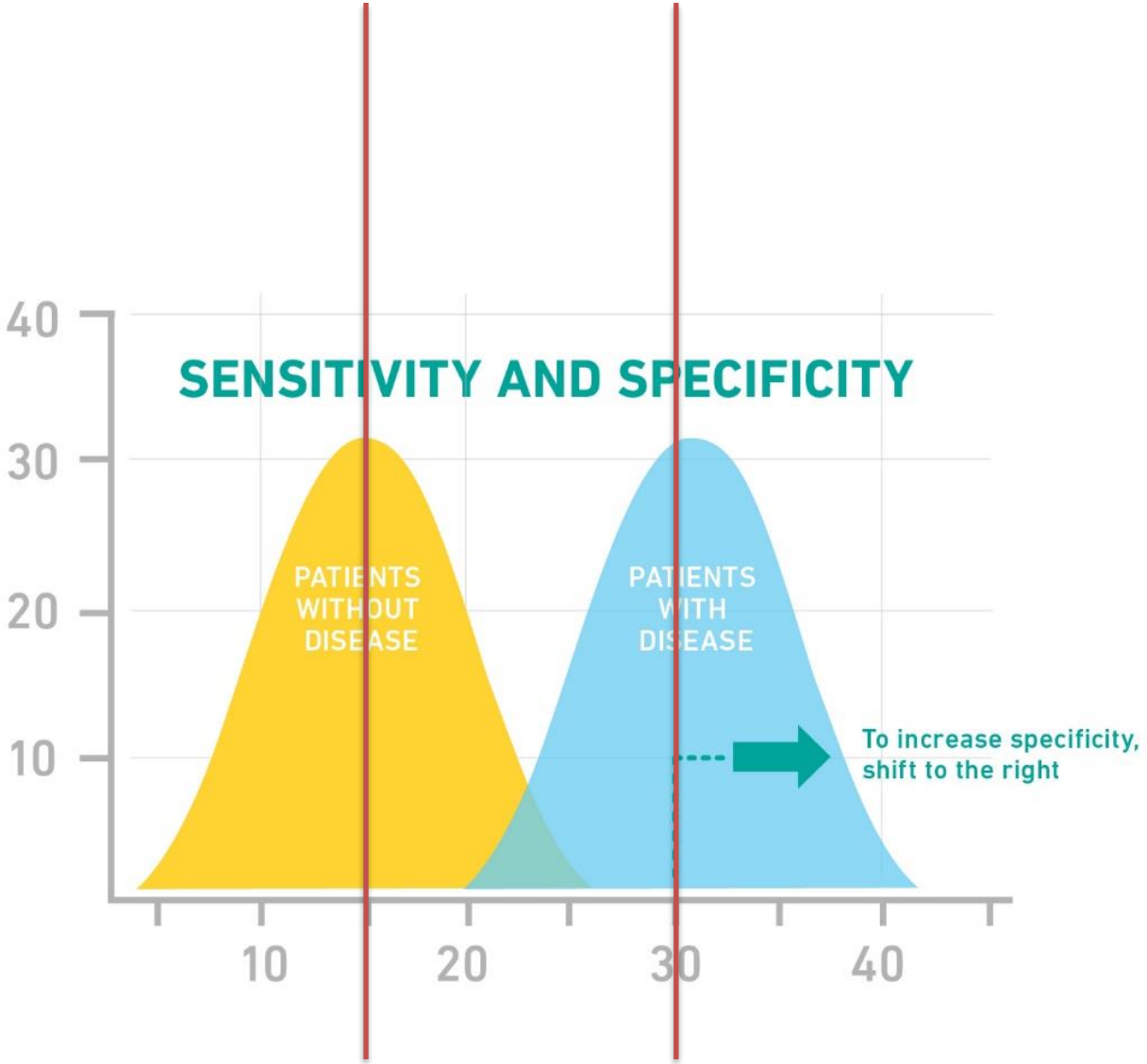
*Courtesy of Candise Maiore, HMH-MMC Quality Manager*

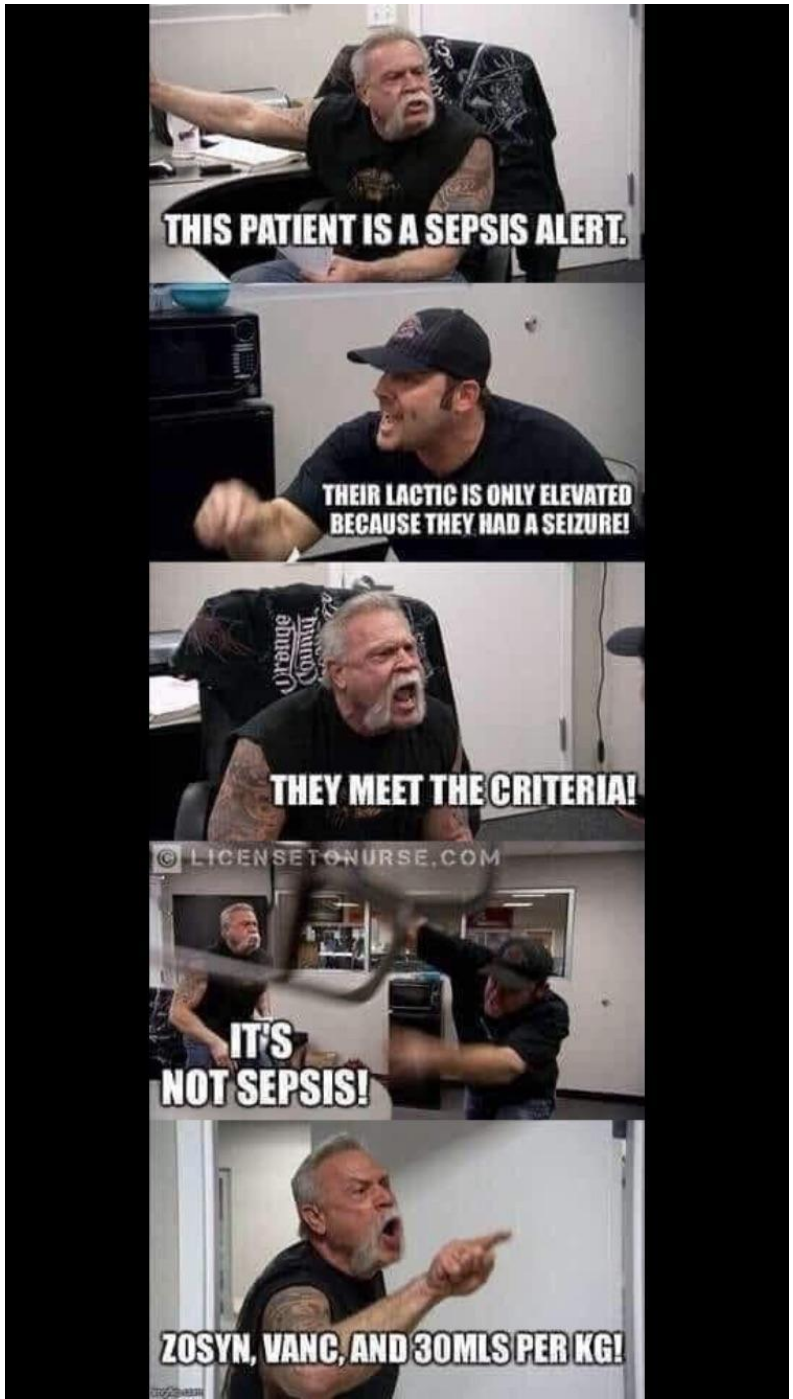
# General

2. We **recommend against** using qSOFA compared with SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock.

*Surviving Sepsis Campaign CCM 2021 e1063*

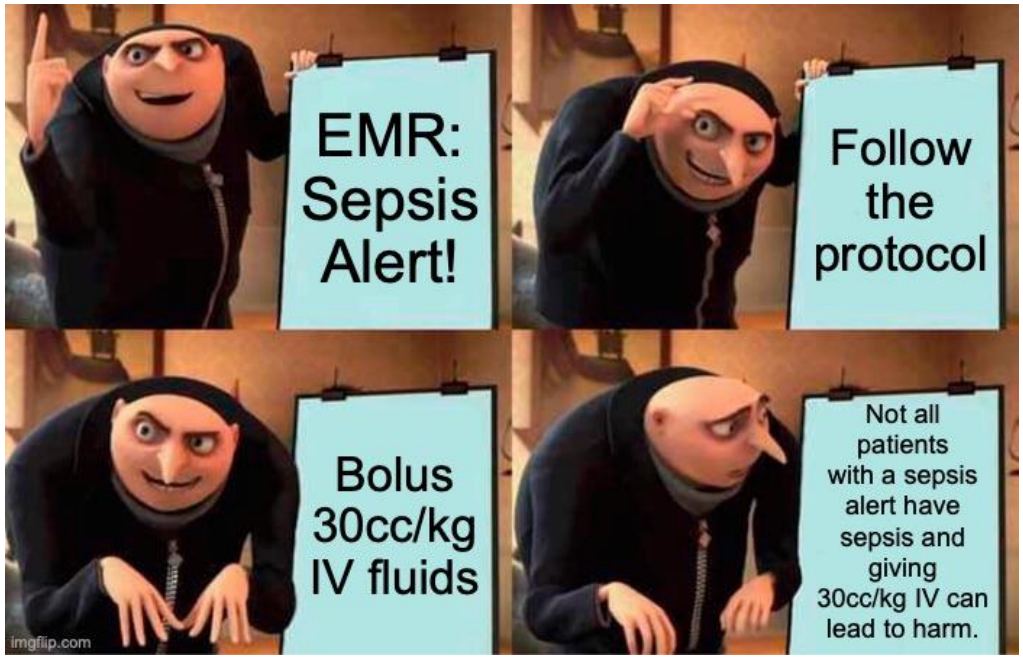
# SIRS vs qSOFA






**The patient has SEPTIC SHOCK, they need 30 cc/kg fluid NOW !**

**Meh, this is influenza pneumonia with mild hyperlactatemia.**



# Antibiotics

12. For adults with possible septic shock or a high likelihood for sepsis, we recommend administering antimicrobials immediately, ideally within 1 hour of recognition.

*Surviving Sepsis Campaign CCM 2021 e1063*

# Choice of Fluids

32. For adults with sepsis or septic shock, we recommend using crystalloids as first-line fluid for resuscitation.

35. For adults with sepsis or septic shock, we recommend **against** using starches for resuscitation.

*Surviving Sepsis Campaign CCM 2021 e1063*

# Hemodynamics

9. For adults with septic shock on vasopressors we recommend an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets.

37. For adults with septic shock, we recommend using norepinephrine as the first-line agent over other vasopressors.

*Surviving Sepsis Campaign CCM 2021 e1063*

# Miscellaneous

60. Use restrictive transfusion policy

64. Use VTE prophylaxis unless contraindicated

65. Use low molecular weight over unfractionated heparin for VTE prophylaxis

69. Initiate insulin therapy to keep glucose < 180 mg/dL

*Surviving Sepsis Campaign CCM 2021 e1063*

# Vent Management Statements

- A total of 12 statements (#46-57)
- Strong recommendations – 4
- Weak recommendations – 6
- No recommendations – 2

# Vent Management – Strong Rec's

49. Use low tidal volume – 6ml/kg (IBW)
50. Keep plateau pressure below 30 cm H2O
54. Do not use incremental PEEP as 'recruitment maneuver'
55. Use prone ventilation for at least 12 hours in patients with moderate to severe ARDS

*Surviving Sepsis Campaign CCM 2021 e1063*

# Vent Management – Other Rec's

- 46. There is insufficient evidence to make a recommendation on the use of conservative oxygen targets in adults with sepsis-induced hypoxemic respiratory failure

- (No Recommendation)

# Vent Management – Other Rec's

- 47. For adults with sepsis-induced hypoxemic respiratory failure, we suggest the use of high flow nasal oxygen over noninvasive ventilation.

- Weak Recommendation
- Low quality of evidence
- New in 2021

# Vent Management – Other Rec's

- 48. There is insufficient evidence to make a recommendation on the use of noninvasive ventilation in comparison to invasive ventilation for adults with sepsis-induced hypoxemic respiratory failure.

- No recommendation

# Vent Management – Other Rec's

51. For adults with moderate to severe sepsisinduced ARDS, we suggest using higher PEEP over lower PEEP.

- Weak Recommendation
- Moderate quality evidence

# Vent Management – Other Rec's

52. For adults with sepsis-induced respiratory failure (without ARDS), we suggest using low tidal volume as compared with high tidal volume ventilation.

- Weak Recommendaton
- Low quality evidence

# Vent Management – Other Rec's

53. For adults with sepsis-induced moderatesevere ARDS, we suggest using traditional recruitment maneuvers.

- Weak recommendation
- Moderate quality evidence

# Vent Management – Other Rec's

56. For adults with sepsis induced moderatesevere ARDS, we suggest using intermittent NMBA boluses, over NMBA continuous infusion.

- Weak recommendation
- Moderate quality evidence

# Vent Management – Other Rec's

57. For adults with sepsis-induced severe ARDS, we suggest using veno-venous (VV) ECMO when conventional mechanical ventilation fails in experienced centers with the infrastructure in place to support its use.

- Weak recommendation
- Low quality evidence
- New recommendation

# Some Disputed Topics

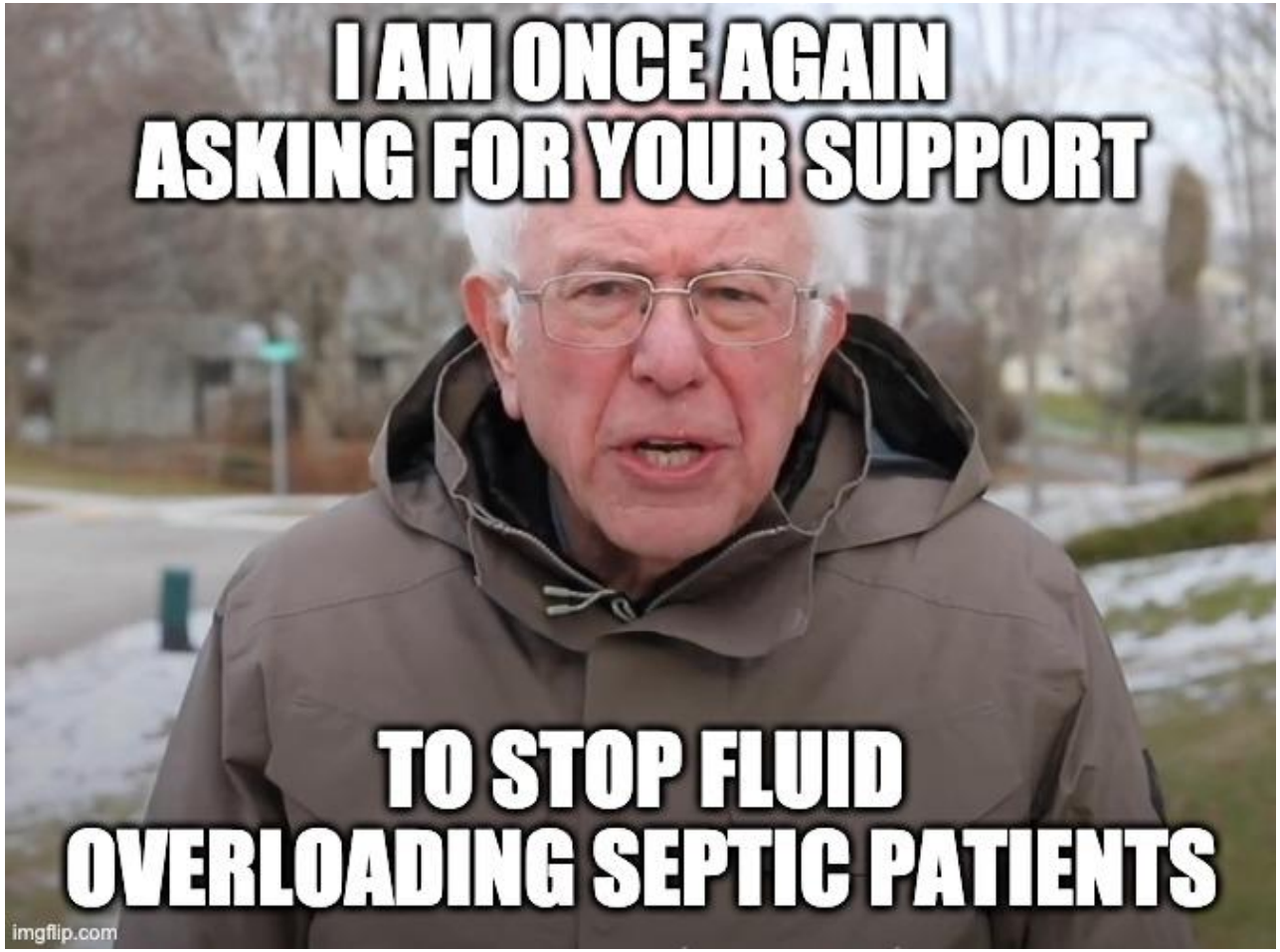
- Amount of fluids to be administered
- Choice of fluids to be administered
- Vitamin C for sepsis

# Channeling My Inner Student

I LOVIT when a CLASSIC CLOVER PETAL
PLUS BaSICS pattern is SPLIT up and paired with
SMART color choices like SALT-ED CITRIS

A lovely poem brought to you by ChatGPT

# Channeling My Inner Bernie Sanders

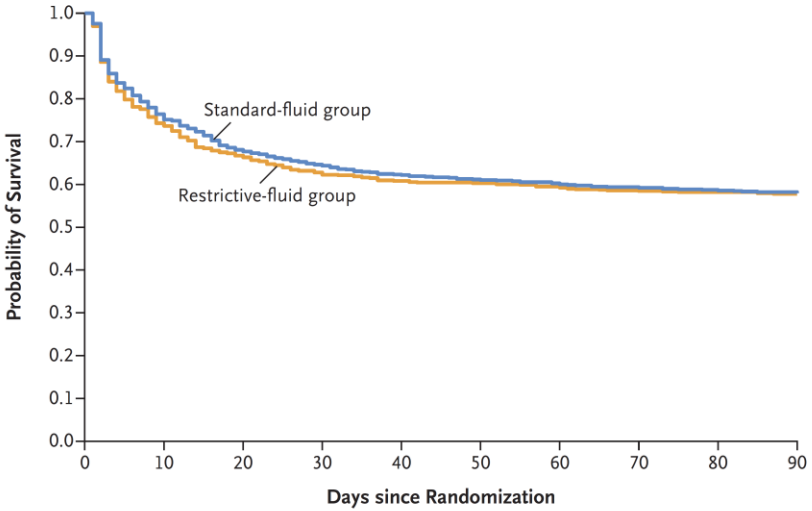


# IV Fluids – How Much Is Too Much?

- CLASSIC
  - International (Europe), stratified, parallel-group, open-label, randomized study
  - Septic patients within 12 hours of onset
  - About 1/3 patients in each group received 30ml/kg bolus
  - Restrictive vs. Liberal fluid protocol

*Meyhoff et al; NEJM 2022*

**A Overall Survival**

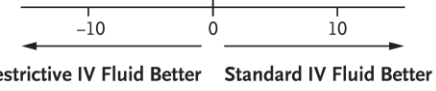



**No. at Risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Standard-fluid group | 780 | 596 | 531 | 504 | 486 | 477 | 470 | 463 | 458 | 454 |
| Restrictive-fluid group | 763 | 567 | 509 | 479 | 464 | 460 | 454 | 447 | 444 | 441 |

**B Death at 90 Days**

| Subgroup | Restrictive-Fluid Group *no. of events/no. of patients* | Standard-Fluid Group *no. of events/no. of patients* | Absolute Percentage Point Difference (95% CI) | P Value for Heterogeneity |
|---|---|---|---|---|
| All patients | 323/764 | 329/781 | 0.1 (−4.7 to 4.9) | |
| Respiratory support | | | | 0.03 |
| Yes | 184/396 | 196/377 | −5.1 (−11.3 to 1.6) | |
| No | 138/385 | 132/399 | 5.7 (−1.4 to 12.4) | |
| Acute kidney injury | | | | 0.57 |
| Yes | 146/309 | 169/360 | −0.8 (−8.0 to 6.7) | |
| No | 174/439 | 158/411 | 2.0 (−4.6 to 8.4) | |
| Plasma lactate | | | | 0.65 |
| >4.0 mmol/liter | 164/337 | 180/366 | −0.5 (−7.5 to 6.5) | |
| ≤4.0 mmol/liter | 158/416 | 148/409 | 1.7 (−5.1 to 8.1) | |
| Body weight | | | | 0.34 |
| ≥76 kg | 164/401 | 163/425 | 2.5 (−4.1 to 9.0) | |
| <76 kg | 158/352 | 165/350 | −2.2 (−9.1 to 4.8) | |
| IV fluid volume at randomization | | | | 0.15 |
| ≥30 ml/kg body weight | 208/493 | 230/515 | −2.1 (−8.1 to 3.7) | |
| <30 ml/kg body weight | 114/260 | 98/260 | 5.3 (−3.1 to 13.5) | |




*Meyhoff et al; NEJM 2022*

# CLOVERS

- Unblinded superiority trial
- 60 Centers across US
- Prioritizing fluids vs pressors

**Table 2. Therapies Administered during the Trial Intervention Period.***

| Therapies | Restrictive Fluid Group (N=782) | Liberal Fluid Group (N=781) | Difference (95% CI)† |
|---|---|---|---|
| Median volume of IV fluid administered (IQR) — ml‡ | | | |
| Over 6-hr period | 500 (130 to 1097) | 2300 (2000 to 3000) | −1800 (−1889 to −1711) |
| Over 24-hr period | 1267 (555 to 2279) | 3400 (2500 to 4495) | −2134 (−2318 to −1949) |
| Vasopressor administration during first 24-hr period — no./total no. (%) | 460/780 (59.0) | 290/779 (37.2) | 21.7 (16.9 to 26.6) |
| Time from randomization to first vasopressor among patients who had vasopressors administered — hr§ | 1.8±3.4 | 3.2±4.7 | −1.4 (−2.0 to −0.8) |
| Duration of vasopressor use during first 24-hr period among patients who received vasopressor therapy — hr¶ | 9.6±10.0 | 5.4±8.6 | 4.2 (3.3 to 5.2) |

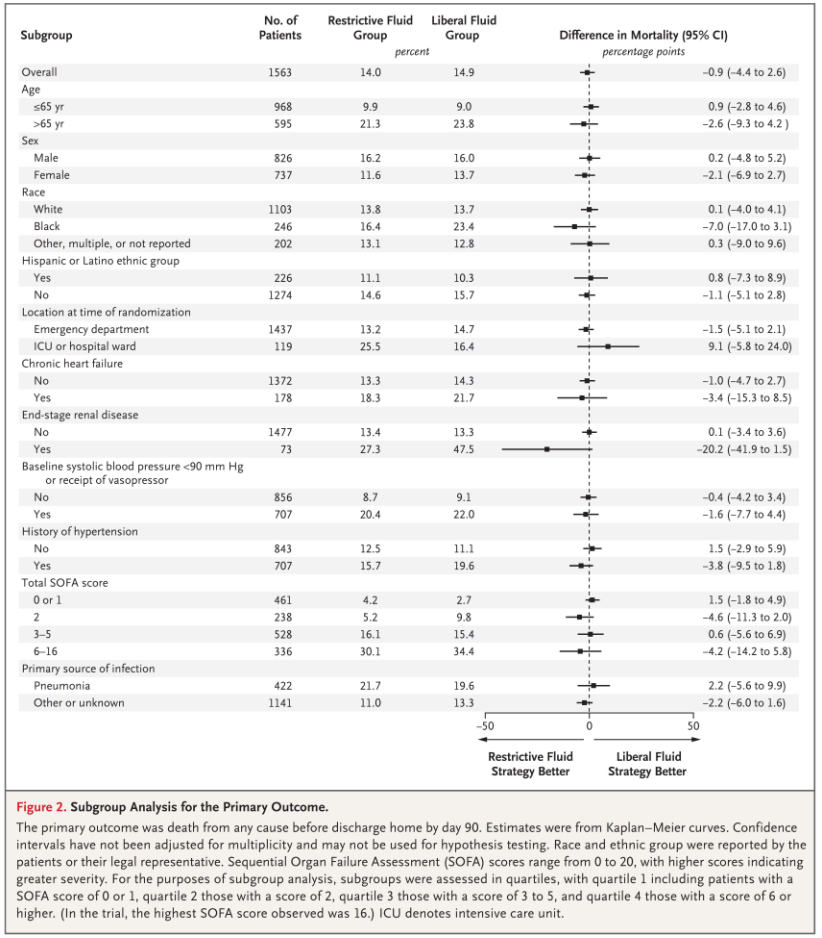


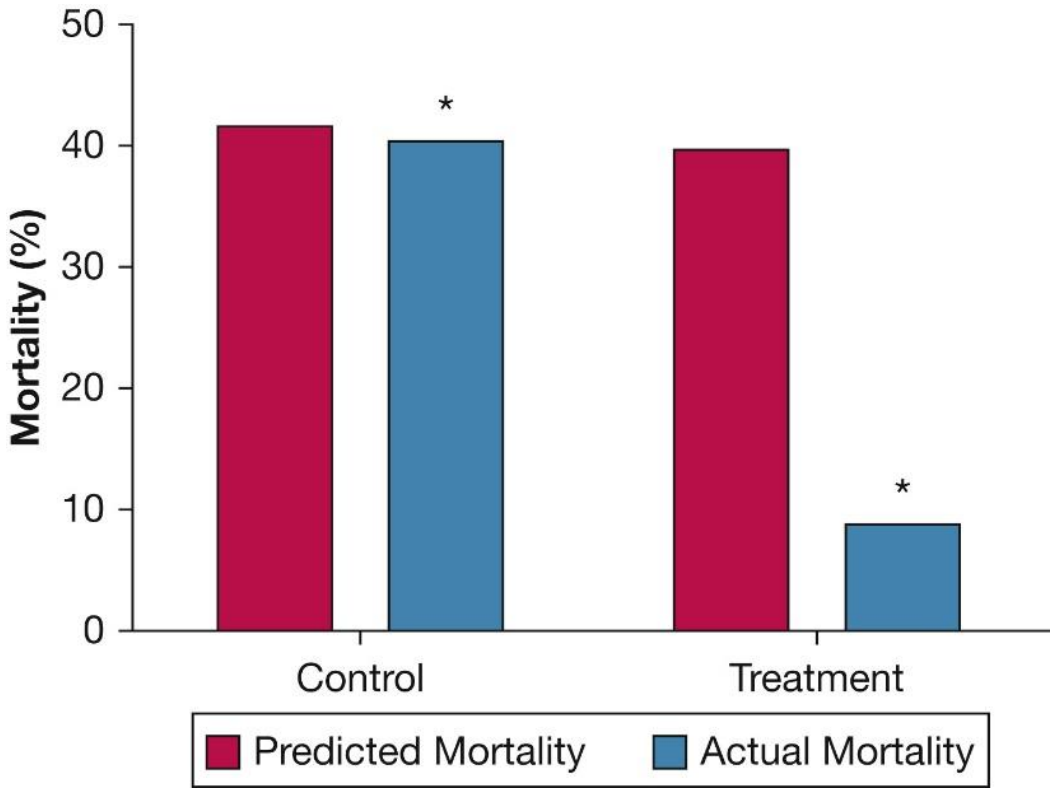

**Figure 2. Subgroup Analysis for the Primary Outcome.**

The primary outcome was death from any cause before discharge home by day 90. Estimates were from Kaplan–Meier curves. Confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing. Race and ethnic group were reported by the patients or their legal representative. Sequential Organ Failure Assessment (SOFA) scores range from 0 to 20, with higher scores indicating greater severity. For the purposes of subgroup analysis, subgroups were assessed in quartiles, with quartile 1 including patients with a SOFA score of 0 or 1, quartile 2 those with a score of 2, quartile 3 those with a score of 3 to 5, and quartile 4 those with a score of 6 or higher. (In the trial, the highest SOFA score observed was 16.) ICU denotes intensive care unit.

*CLOVERS Trial, NEJM 2023*

# Who Is This What Is He Selling?

# Snake Oil




Marik PE et al; Chest 2017(151):1229

# LOVIT Trial – Vitamin C in Sepsis

- Randomized placebo-controlled trial (RCT)
- 872 patients in ICU (less than 24 hours in ICU)
- Suspected infection
- Receiving vasopressors
- Randomized to Vitamin C 50mg/kg every 6 hours for 96 hours vs. placebo
- Primary outcome: death or organ dysfunction

*Lamontagne et al; NEJM 2022*

# LOVIT Trial – Vitamin C in Sepsis

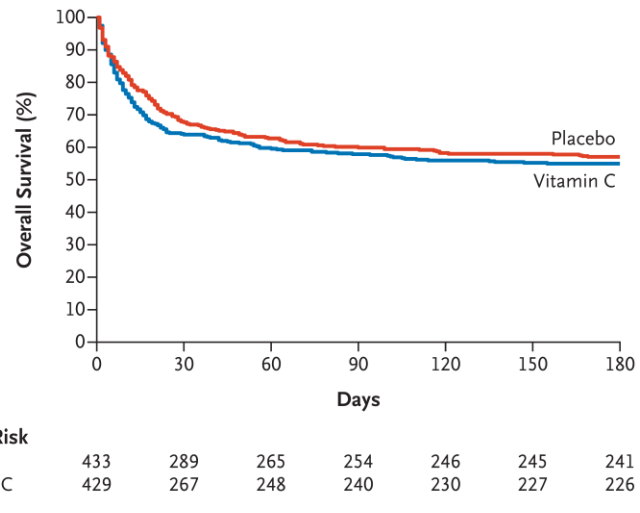
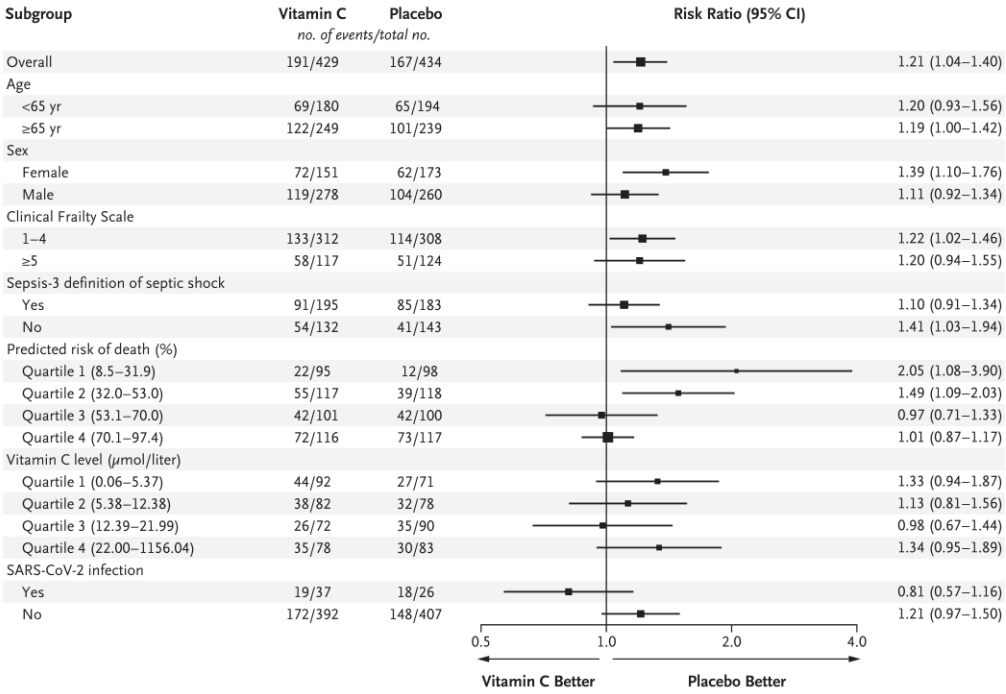



**Figure 2. Kaplan–Meier Analysis of Survival at 6 Months.**

Shown is the percentage of patients who were alive at the 6-month follow-up (226 patients [54.2%] in the vitamin C group and 241 [56.6%] in the placebo group), which was a secondary outcome in the trial.




*Lamontagne et al; NEJM 2022*

# Frequentist vs Bayesian


ORIGINAL ARTICLE

# Balanced Crystalloids versus Saline in Critically Ill Adults

- Pragmatic
- Cluster-randomized
- Multiple-crossover
- Unblinded
- Conducted in five intensive care units at a single academic center
- Composite vs patient centered outcome

*Semler et al; NEJM 2018*

# Statistical vs. Biological Significance

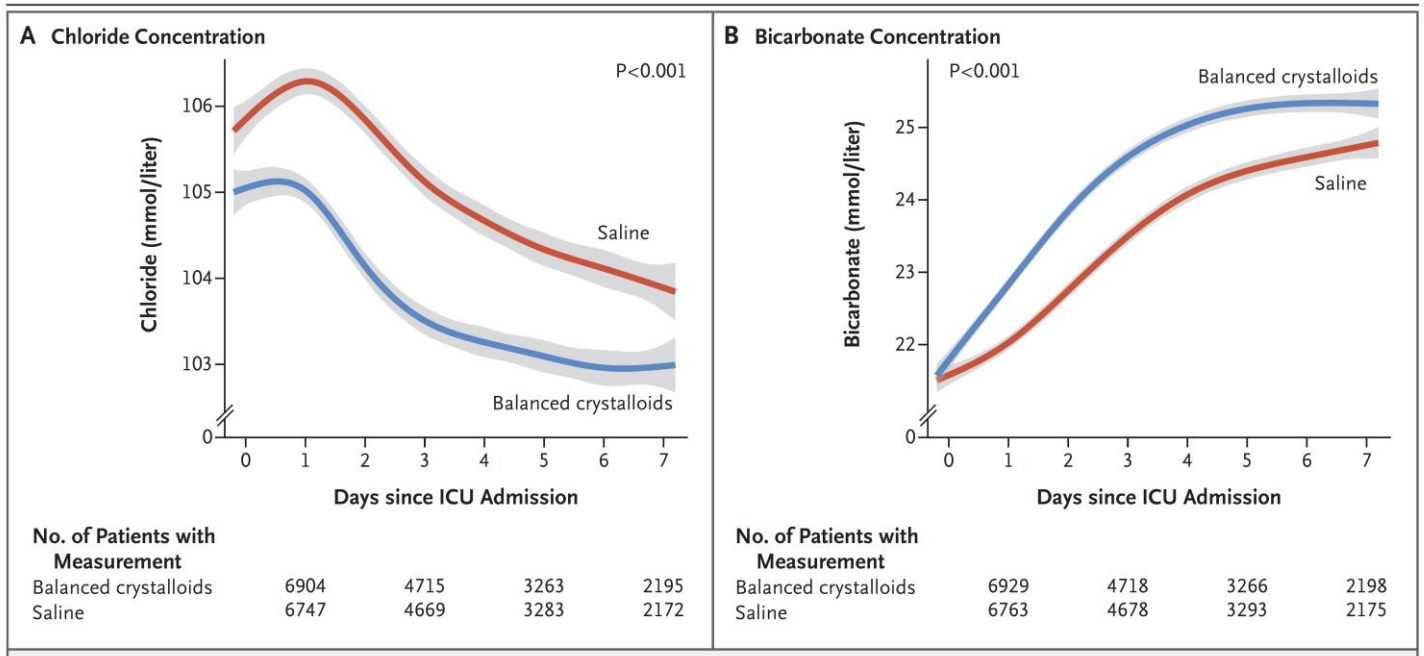



**Figure 2. Plasma Chloride and Bicarbonate Concentration According to Group.**

The mean and 95% confidence interval (denoted by gray shading) for the first measurement of plasma chloride concentration (Panel A) or bicarbonate concentration (Panel B) on the first 7 days since admission to the intensive care unit (ICU) are shown for patients in the balanced-crystalloids group and in the saline group with locally weighted scatterplot smoothing. Plasma chloride and bicarbonate concentrations were similar between groups at presentation (Table S3 in the Supplementary Appendix), but because fluid therapy in the emergency department and operating room was coordinated with the ICU to which patients were being admitted, plasma chloride concentration differed between the balanced-crystalloids and saline groups at the time of ICU admission.

*Semler et al; NEJM 2018*

ORIGINAL ARTICLE

# Balanced Crystalloids versus Saline in Critically Ill Adults

There was no different between the groups in:

- In-hospital mortality,
- ICU-free days,
- Ventilator-free days,
- Vasopressor-free days,
- RRT-free days,
- Creatinine level

*Semler et al; NEJM 2018*

# “Balanced” vs NS Trials

- In conclusion, in this trial involving critically ill adults, intravenous administration of balanced crystalloids rather than saline had a favorable effect on the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction.
  - Semler et al; NEJM 2018
  - SMART Trial

- Among patients with sepsis in a large randomized trial, use of balanced crystalloids was associated with a lower 30-day in-hospital mortality compared with use of saline.
  - Brown et al; AJRCCM 2019
  - Secondary analysis of the SMART Trial

# “Balanced” vs NS Meta-analysis

- Torture the numbers long enough and they’ll tell you what you want to hear
- They use data like a drunk uses lampposts – for support, not for illumination

# “Balanced” vs NS Meta-analysis

- Total of 13 trials included
- 6 out of 13 labeled as “low risk of bias”
- The overall impact on mortality based on these 6 trials was reported as relative risk of 0.96 with confidence interval of 0.91 to 1.01
    - Absolute risk reduction ~1%
    - NNT ~ 100
    - Minimal biological significance
    - Arguably no statistical significance

*Hammond et al; NEJM Evid 2022*

# “Balanced” vs NS Meta-analysis

- “In this systematic review and meta-analysis, the estimated effect of using balanced crystalloids versus saline for fluid therapy in critically ill adults ranged from a 9% relative reduction to a 1% relative increase in risk of death by 90 days or the nearest reported time point”
- “The inferences drawn from our study will depend on individual’s preference for a frequentist or Bayesian approach to interpreting data”

*Hammond et al; NEJM Evid 2022*

# Some Disputed Topics

- The amount of fluids to be administered
  - Beware of “enough is enough” moment
- Choice of fluids to be administered
  - LR is probably (definitely, maybe?!?) better than NS, but more convincing studies are needed
- Vitamin C for sepsis
  - Multiple well-designed studies show no benefit

# Surviving Sepsis in 2024 – Summary

- Sepsis is an emergency
  - Early recognition and aggressive goal-directed treatment
- Follow SEP-1
  - It’s not just a CMS rule, it saves lives
- Judicious use of fluids
  - Choose carefully – type and amount of fluids
- Don’t be shy to use vasopressors
- Fluids and antibiotics remain the mainstay of therapy