Sepsis Management in 2024

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HARVARD MEDICAL SCHOOL

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- **Royalties**
  - UpToDate (Procalcitonin chapter)
- **Grant Funding** (related to sepsis surveillance and quality)
  - Centers for Disease Control and Prevention
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- **Committee Membership**
  - IDSA Sepsis Advisory Panel (Chair)
  - CMS Sepsis Measure Development Technical Advisory Group (Member)
  - ATS/IDSA Hospital-Acquired/Ventilator-Associated Pneumonia Guidelines Panel (Member)
- **Editorial**
  - Associate Editor, *Clinical Infectious Diseases*
  - Editorial Board, *Critical Care Medicine* and *Critical Care Explorations*

No financial conflicts related to this presentation

Outline

- Sepsis Screening
- Fluid Resuscitation
- Vasopressors
- Antibiotic and Infection Management
- Corticosteroids

GUIDELINES

Surviving sepsis campaign: int national guidelines fo anage ent epsis and septic shock 2021

Laura Evans[1*], Andrew Rh
Craig French[6], Flávia R. M
Christa Schorr[11], Steven Simp gus[15], Yaseen Arabi[16],
Luciano Azevedo[17], Richard Beale aurizio Cecconi[21,22],
John Centofanti[23], Angel Coz Ya
Elisa Estenssoro[28], Ricard Fe lander Møller[32],
Theodore Iwashyna[33], Shevin Jacob[34], Rut ck Koh[38], Anand Kumar[39],
Arthur Kwizera[40], Suzana Lobo[41], Henry M Sange hta[44], Yatin Mehta[45],
Mervyn Mer[46], Mark Nunnally[47], Simon owski Osb zabeth Pap anassoglou[49],
Anders Perner[50], Michael Puskarich[51], Jason Robert 4,55], Willia hweickert[56], Ma reen Seckel[57],
Jonathan Sevransky[5], Charles L. Sprung[58,59], Tobias e[60], Janice Z merman[61] and Mitchell Levy[62]

UPDATE IN PROGRESS

Evans, *Crit Care Med* 2021; e1063-e1143
Evans, *Intensive Care Med* 2021; 47:181-1247

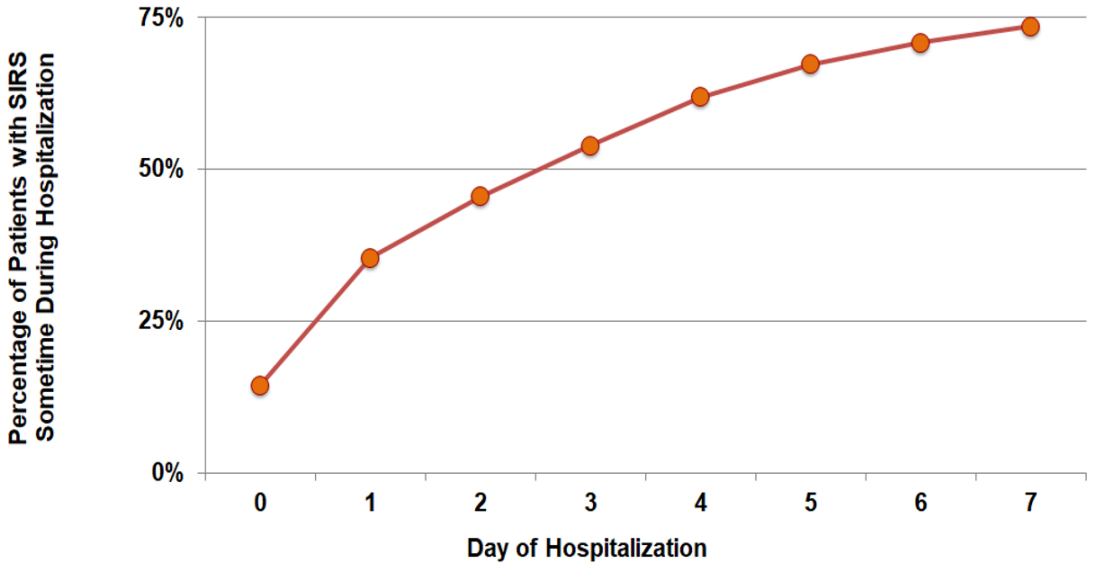
SEPSIS SCREENING

Sepsis Screening: The Million Dollar Question

Problems with SIRS

Too Nonspecific

269,951 patients admitted to non-ICU wards in 5 Chicago hospitals

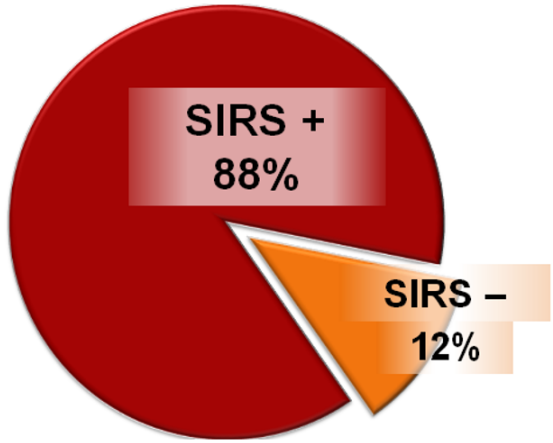


47% of ward patients met SIRS criteria at least once

Churpek, *AJRCC* 2015; 192(8):958-64

Not Perfectly Sensitive

109,663 patients with infection and organ dysfunction admitted to 172 ICUs in Australia and New Zealand, 2000-2013



SIRS misses 1 in 8 patients with infection-associated organ dysfunction

Kaukonen, *NEJM* 2015; 372(17):1629-38

Sepsis-3 (2016)

"Sepsis is defined as <u>life-threatening organ dysfunction</u> caused by a dysregulated host response to infection"

- Eliminated SIRS as part of sepsis definition

<u>Quick SOFA (qSOFA) proposed for rapid screening</u>
2 of 3 criteria:
- **Systolic Blood Pressure ≤100 mmHg**
- **Respiratory Rate ≥ 22 bpm**
- **Altered Mental Status (GCS <15)**

- Supported by retrospective analyses in large databases comparing **prognostic significance** of various clinical criteria **in patients with suspected infection**

Singer, *JAMA* 2016, 315:801-10
Seymour, *JAMA* 2016; 315(8):762-74

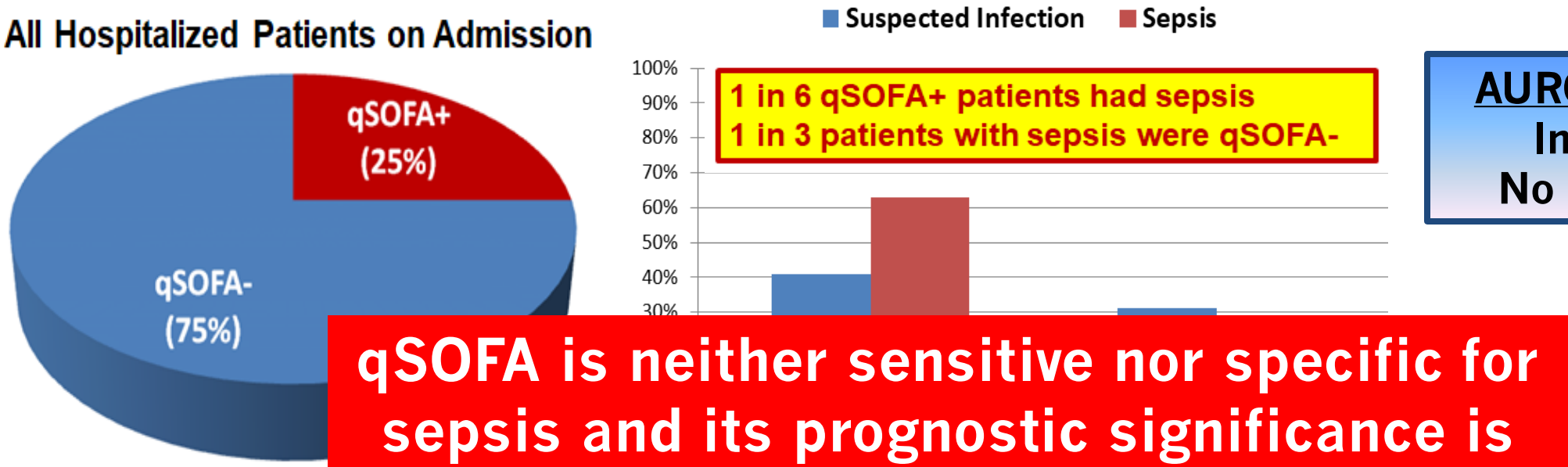
How Useful is qSOFA in Undifferentiated Patients?

Epidemiology of Quick Sequential Organ Failure Assessment Criteria in Undifferentiated Patients and Associated with Suspected Infection and Sepsis

CHEST

Vijay Anand DO; Zilu Zhang, MS; Sameer S. Kadri MD; Michael Klompas MD MPH; Chanu Rhee MD MPH

1 million adult patients admitted to 85 U.S. hospitals from 2013-2015



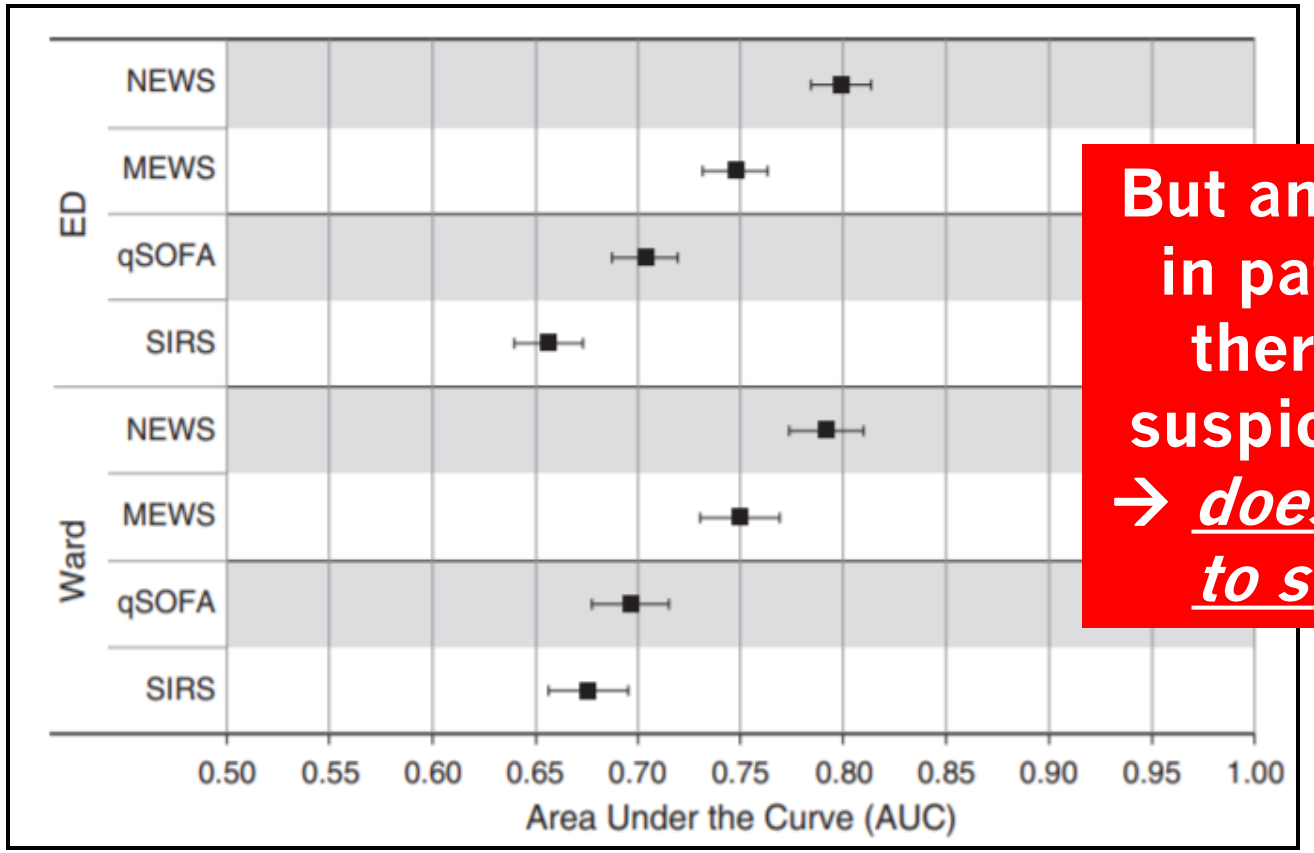
AUROC for Mortality
Infection: 0.81
No Infection: 0.88

qSOFA is neither sensitive nor specific for sepsis and its prognostic significance is unrelated to infection

Anand, *Chest* 2019; 156:289-297

Early Warning Scores Perform Better than qSOFA and SIRS

30,677 patients in the **ED or ward** **with suspected infection**
Criteria compared for predicting **death or ICU transfer**



But analysis was done in patients in whom there was already suspicion of infection → *doesn't tell us when to suspect sepsis*

NEWS > MEWS > qSOFA > SIRS

Churpek, *Am J Resp Crit Care Med* 2017; 195(7):906-11

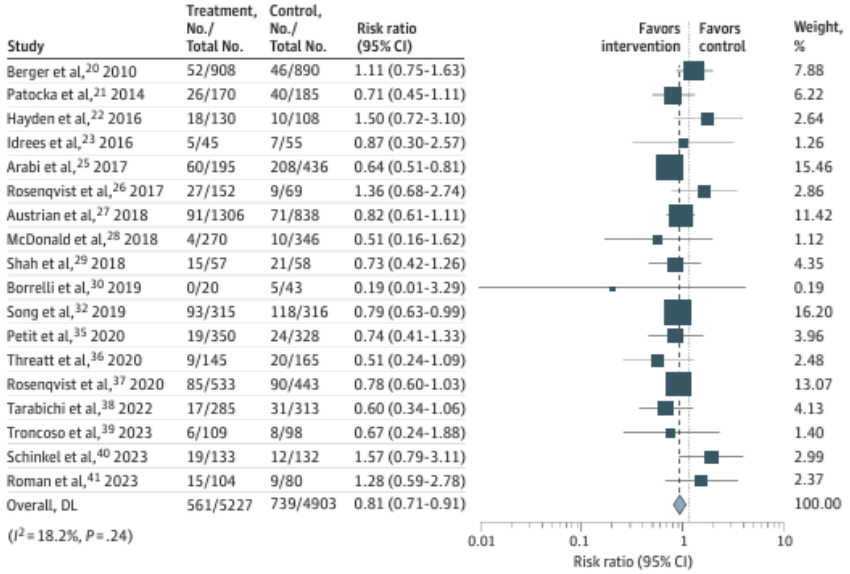
JAMA Network Open

Original Investigation | Critical Care Medicine

Sepsis Alert Systems, Mortality, and Adherence in Emergency Departments

A Systematic Review and Meta-Analysis

Systematic review of 22 studies of sepsis alert systems in the ED (n=19,580 patients)



Study	Treatment, No./ Total No.	Control, No./ Total No.	Risk ratio (95% CI)	Weight, %
Berger et al,[20] 2010	52/908	46/890	1.11 (0.75-1.63)	7.88
Patocka et al,[21] 2014	26/170	40/185	0.71 (0.45-1.11)	6.22
Hayden et al,[22] 2016	18/130	10/108	1.50 (0.72-3.10)	2.64
Idrees et al,[23] 2016	5/45	7/55	0.87 (0.30-2.57)	1.26
Arabi et al,[25] 2017	60/195	208/436	0.64 (0.51-0.81)	15.46
Rosenqvist et al,[26] 2017	27/152	9/69	1.36 (0.68-2.74)	2.86
Austrian et al,[27] 2018	91/1306	71/838	0.82 (0.61-1.11)	11.42
McDonald et al,[28] 2018	4/270	10/346	0.51 (0.16-1.62)	1.12
Shah et al,[29] 2018	15/57	21/58	0.73 (0.42-1.26)	4.35
Borrelli et al,[30] 2019	0/20	5/43	0.19 (0.01-3.29)	0.19
Song et al,[32] 2019	93/315	118/316	0.79 (0.63-0.99)	16.20
Petit et al,[35] 2020	19/350	24/328	0.74 (0.41-1.33)	3.96
Threatt et al,[36] 2020	9/145	20/165	0.51 (0.24-1.09)	2.48
Rosenqvist et al,[37] 2020	85/533	90/443	0.78 (0.60-1.03)	13.07
Tarabichi et al,[38] 2022	17/285	31/313	0.60 (0.34-1.06)	4.13
Troncoso et al,[39] 2023	6/109	8/98	0.67 (0.24-1.88)	1.40
Schinkel et al,[40] 2023	19/133	12/132	1.57 (0.79-3.11)	2.99
Roman et al,[41] 2023	15/104	9/80	1.28 (0.59-2.78)	2.37
Overall, DL	561/5227	739/4903	0.81 (0.71-0.91)	100.00

(I^2 = 18.2%, P = .24)

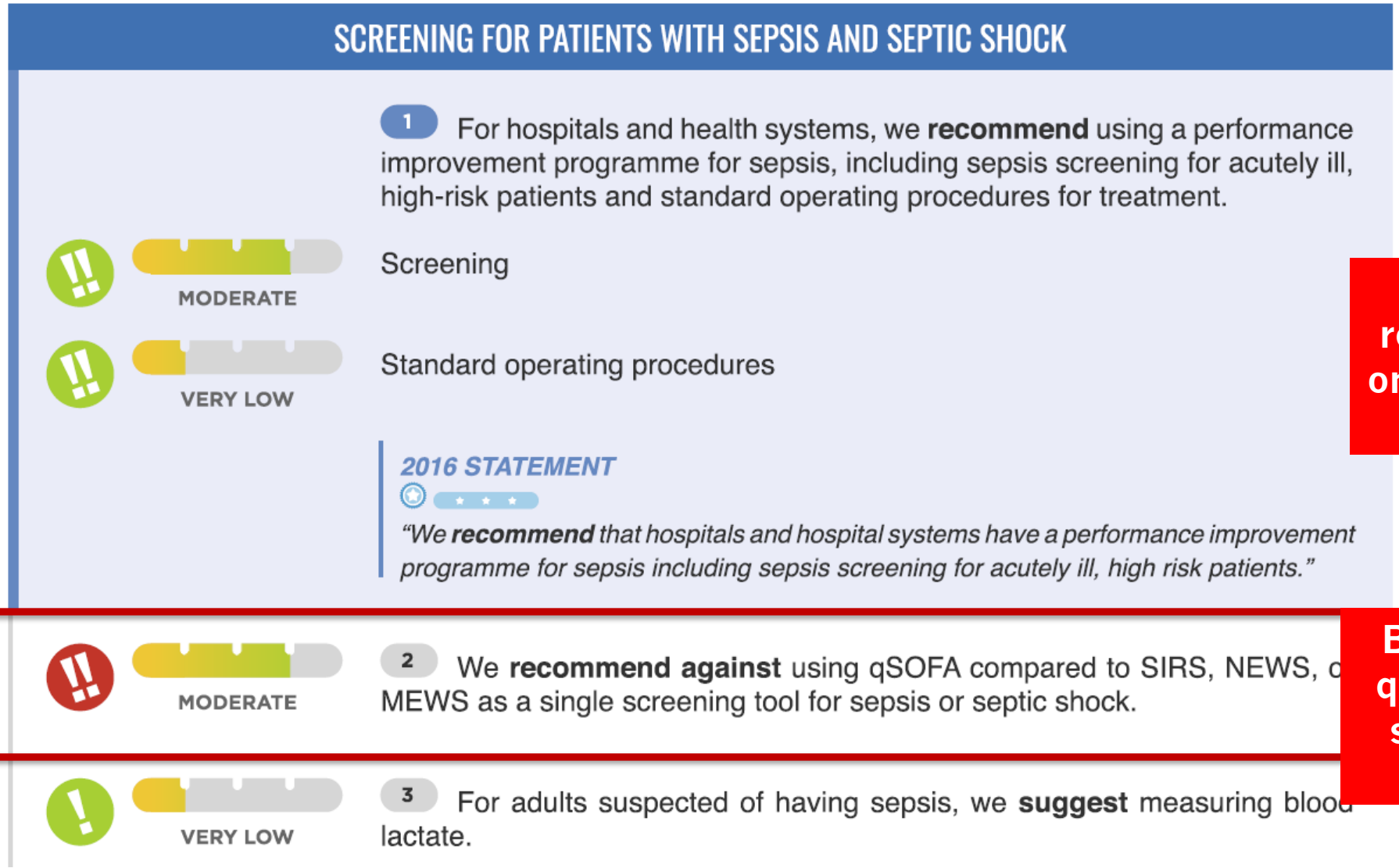
↓Mortality (RR 0.78, 95% CI 0.67-0.92)
↑Adherence with bundle elements

But most studies at high risk of confounding and ascertainment bias

And no guidance on what sepsis alert criteria are best

Kim H, *JAMA Netw Open* 2024; 7:e2422823

Sepsis Screening

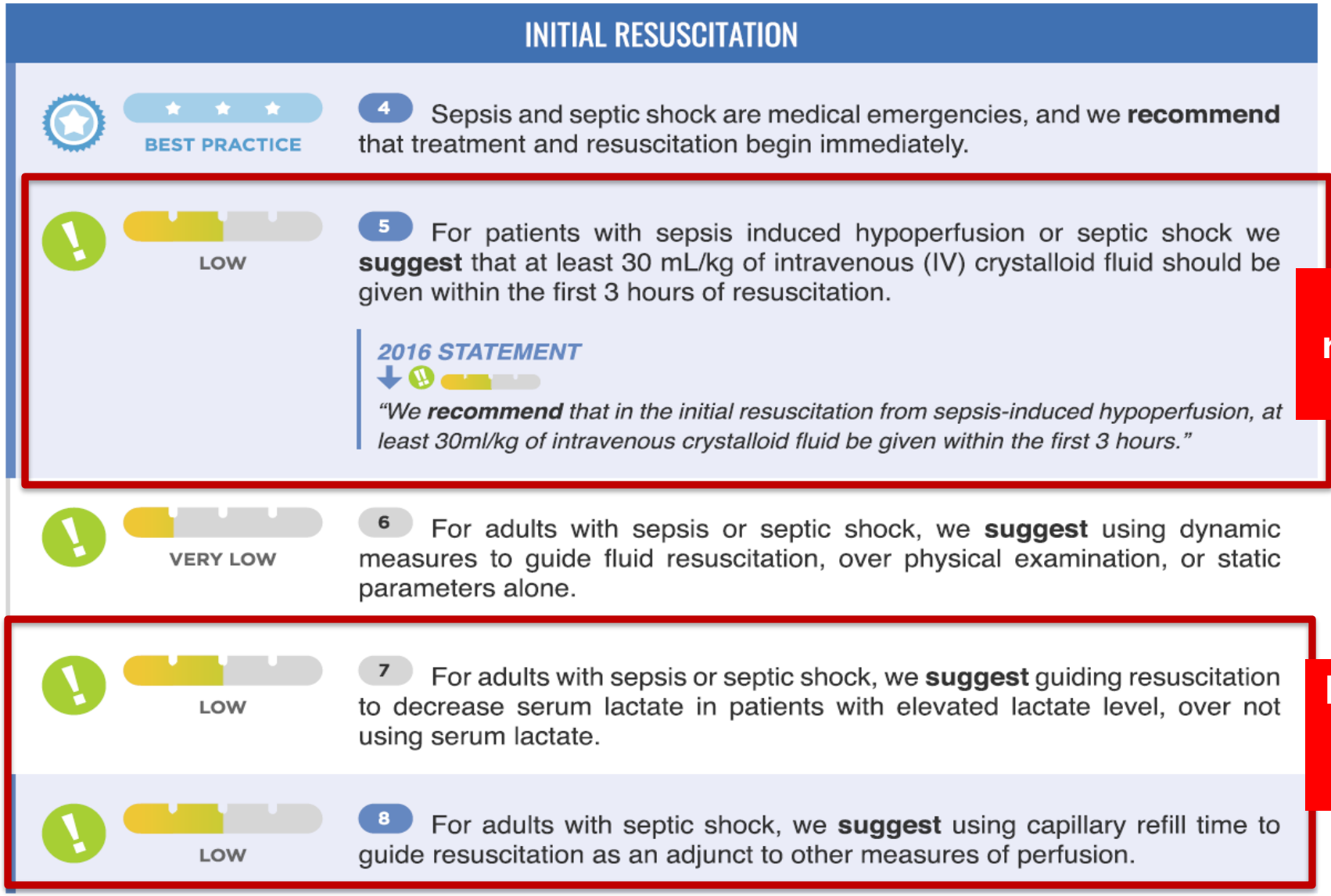


No specific recommendation on what screening tool is best

But avoid using qSOFA alone for screening (low sensitivity)

FLUID RESUSCITATION

Initial Fluid Resuscitation



30 cc/kg fluid recommendation downgraded

Recs informed by ANDROMEDA-SHOCK Trial

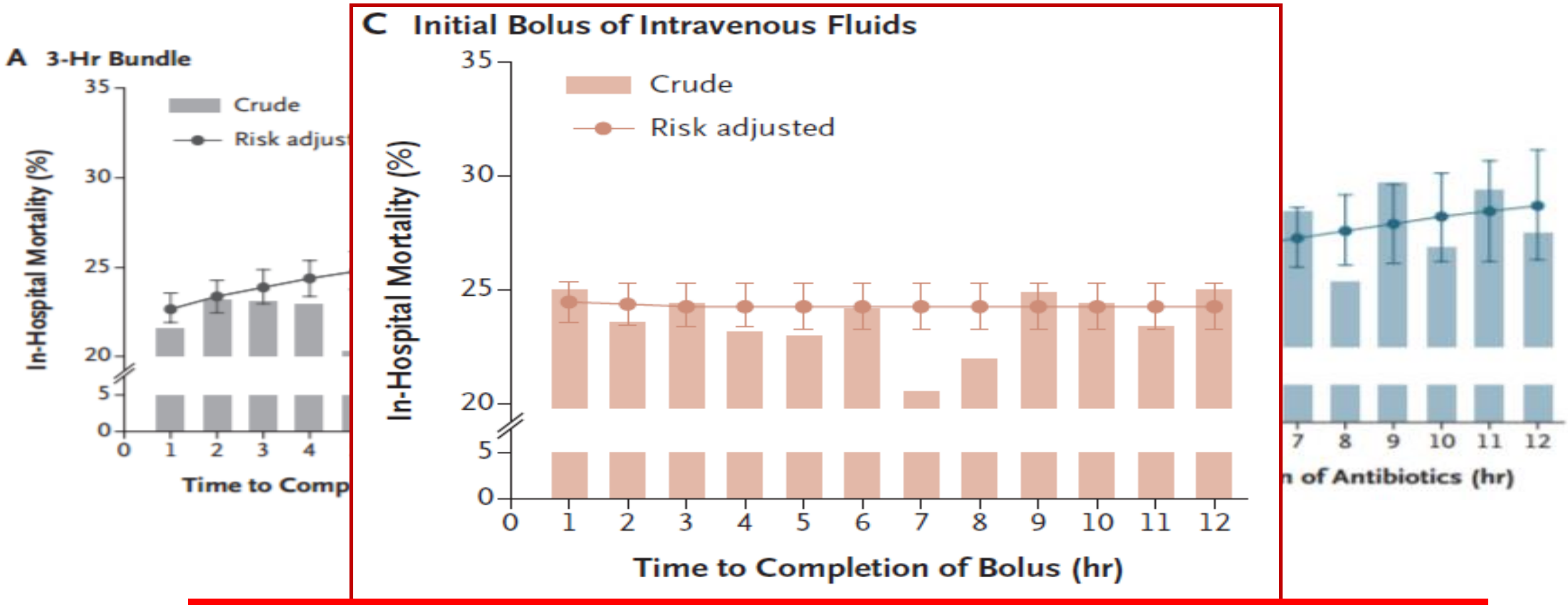
30 cc/kg Fluid Bolus

- 30 cc/kg threshold not rigorously studied in RCTs
- Potential for fluid overload in patients with heart failure, ESRD, respiratory dysfunction
- Increasing evidence about the harmful effects of over-resuscitation and positive fluid balance[1-4]

1. Brandt, *Crit Care* 2009; 13:R186
2. Micek, *Crit Care* 2013; 17:R246
3. Acheampong, *Crit Care* 2015; 19:251
4. Maitland, *NEJM* 2011; 364:2483-95

NY State Analysis: What Matters?

Association between each hour of delay until bundle completion and risk-adjusted mortality amongst 49,331 patients in New York State



No difference with time-to-30 cc/kg fluid bolus

Seymour, *NEJM* 2017;376:2235-2244

Lactate-Guided Resuscitation?

- **ANDROMEDA-SHOCK:** Multinational trial of 424 patients with septic shock comparing fluid resuscitation protocol based on **normalizing capillary refill vs lactate-clearance strategy**
  - **No difference in 28-day mortality**
  - **Peripheral perfusion strategy associated with less organ dysfunction at 72 hours** (potentially related to lower volume of administered fluids?)
  - And **lower mortality in subgroup of septic shock patients with less severe organ dysfunction** (SOFA score <10)

  - ***Argues against using lactate clearance to guide fluids!***

Hernandez, *JAMA* 2019;321:654-64

Early Liberal vs Restrictive Fluid Resuscitation

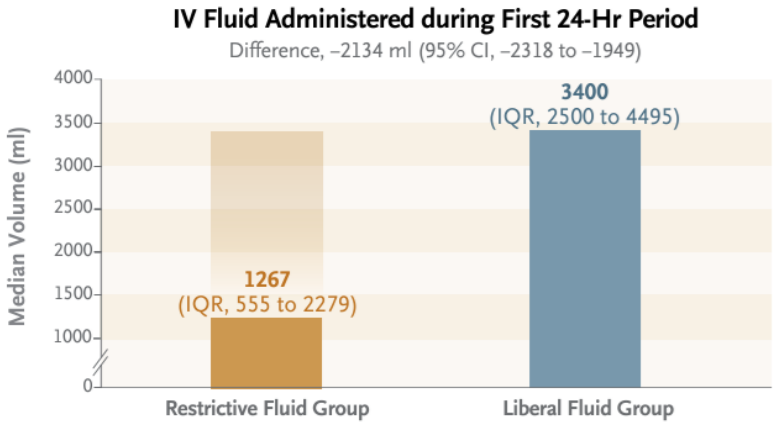
45 There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hours of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after the initial resuscitation.

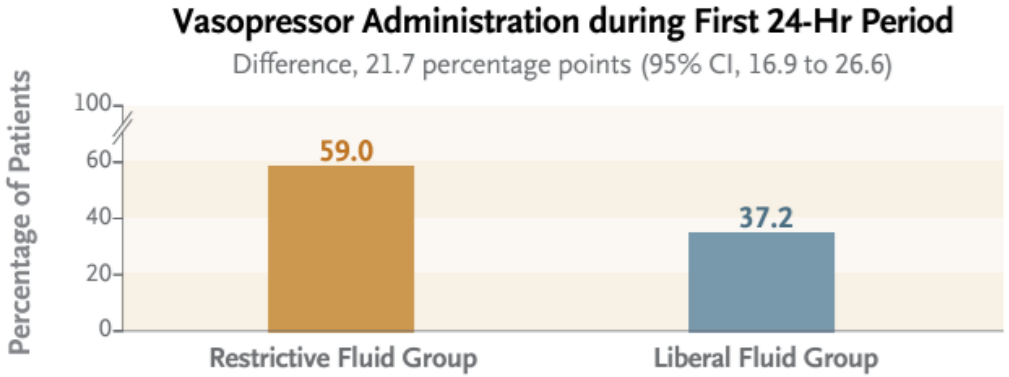
> ***2016 STATEMENT***
>
> *"We **suggest** using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock."*
>
> *"We **suggest** using crystalloids over gelatins when resuscitating patients with sepsis or septic shock."*

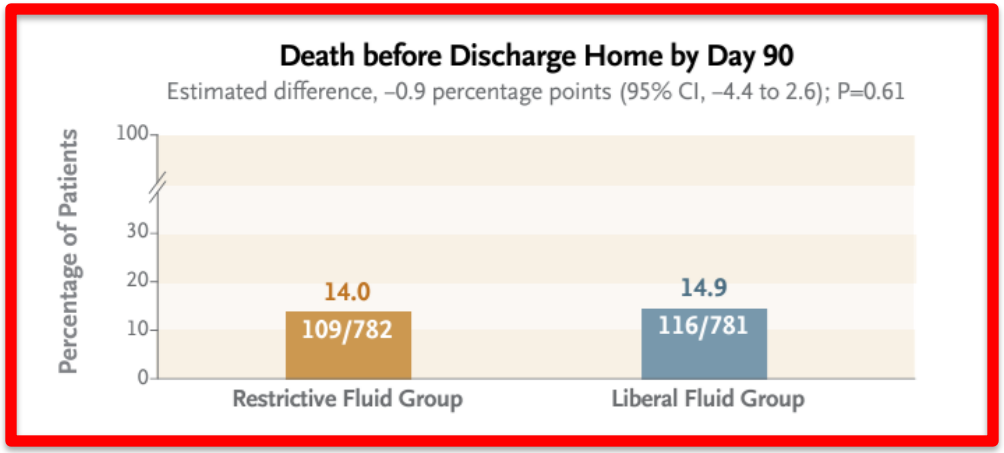
Prior to CLOVERS trial

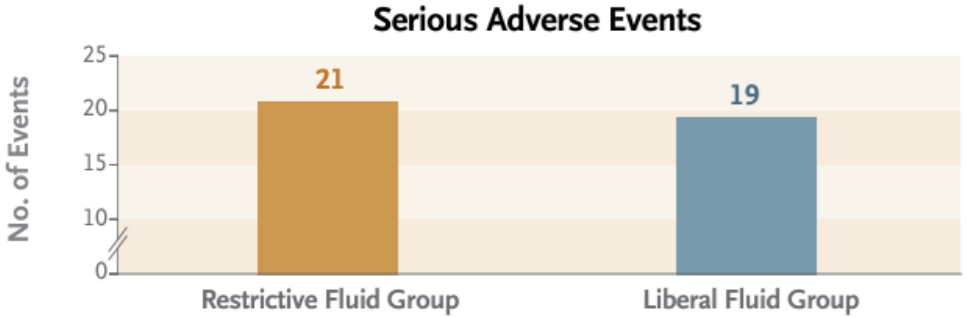
Early Vasopressors or Liberal Fluids?

CLOVERS Trial: RCT of 1563 patients with sepsis-induced hypotension comparing restrictive fluid strategy (early vasopressors) vs liberal fluid strategy x 24 hours after an initial 1-3 L of resuscitation in 60 US hospitals



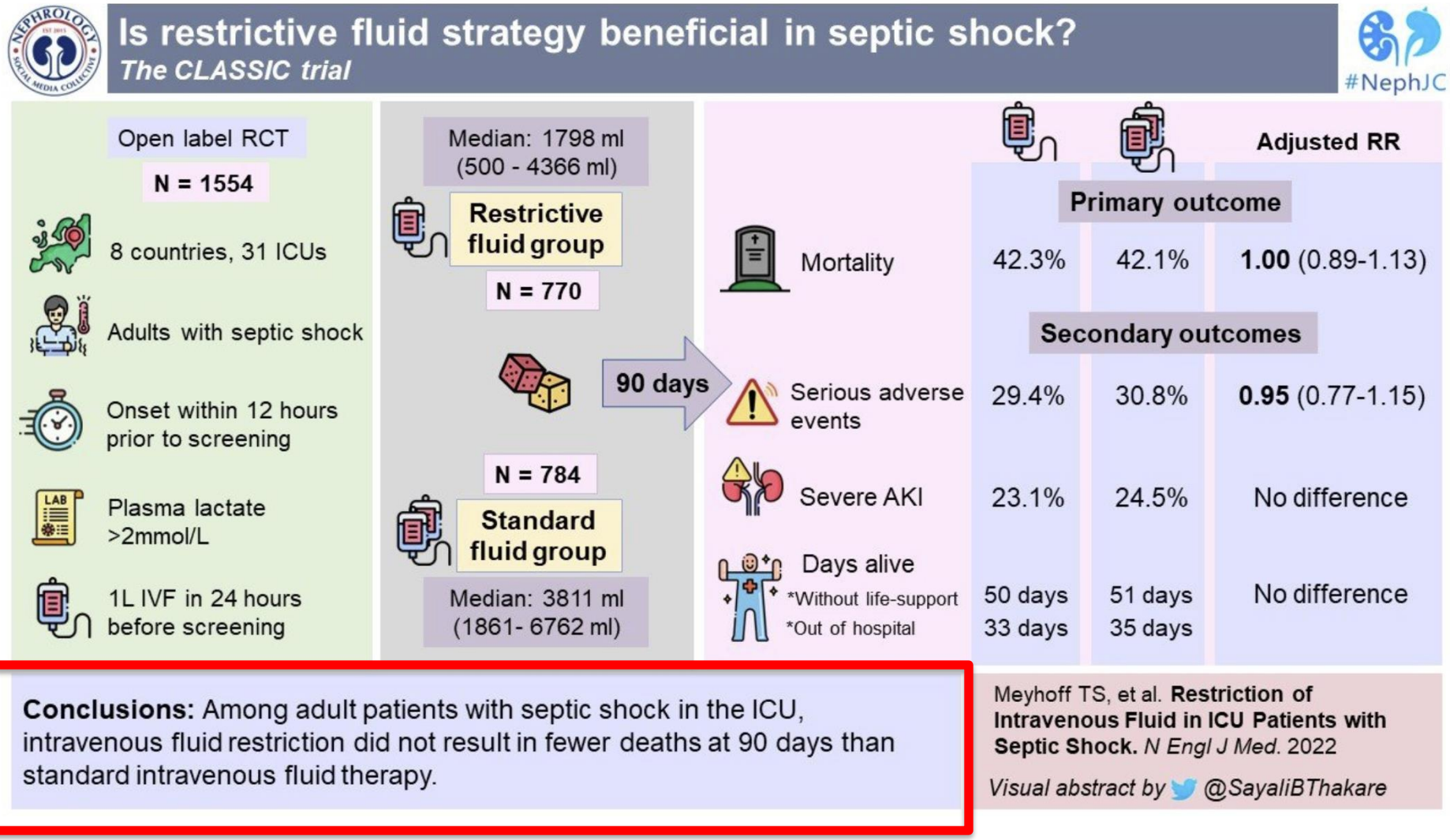






Shapiro NI, *NEJM* 2023; 388:499-510

Restrictive vs Standard Fluid Strategies in the ICU
(Post-Initial Resuscitation)



Meyhoff, TS. *NEJM* 2022; 386(26):2459-2470

Fluid Choice

MODERATE

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

LOW

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

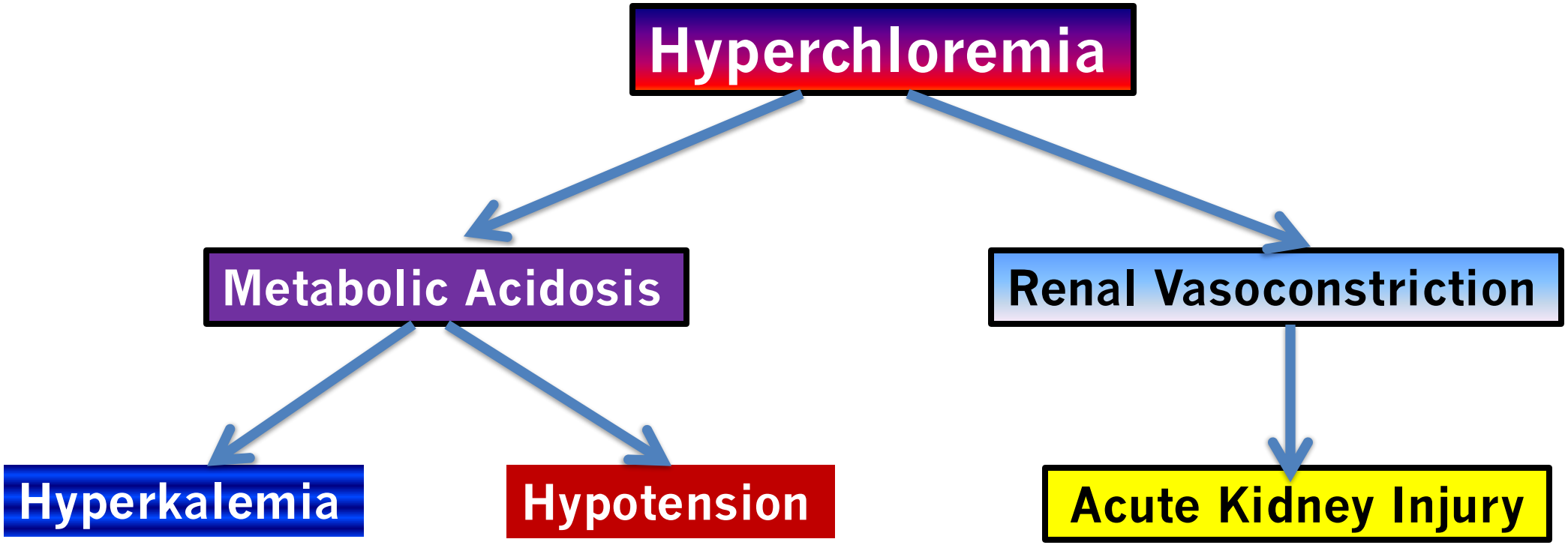
> ***2016 STATEMENT***
>
> *"We **suggest** using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock"*

Recs informed by SMART Trial (but before PLUS Trial)

MODERATE

34 For adults with sepsis or septic shock, we **suggest** using albumin in patients who received large volumes of crystalloids.

Physiologic Effects of (Ab)Normal Saline

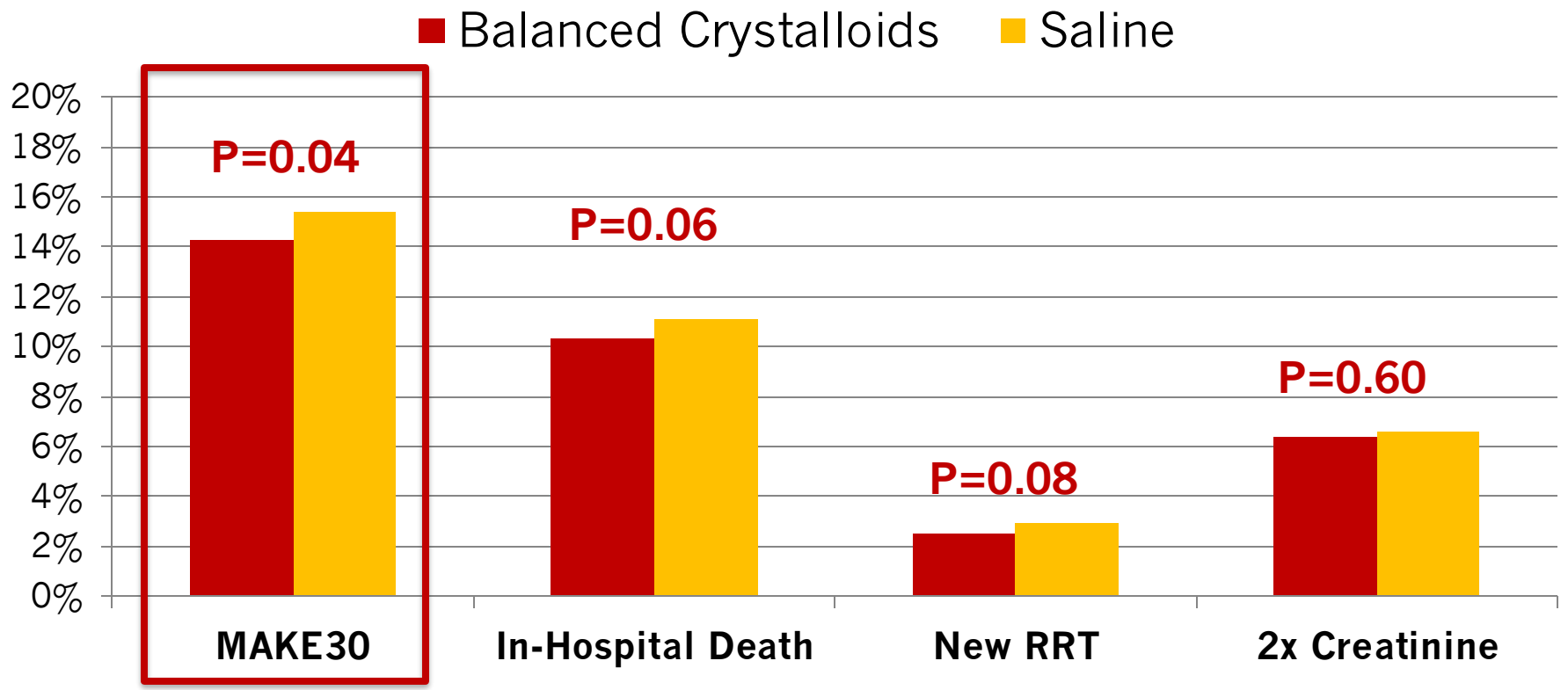


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

"SMART Trial": Cluster-randomized cross-over trial of 15,800 patients in 5 ICUs at Vanderbilt

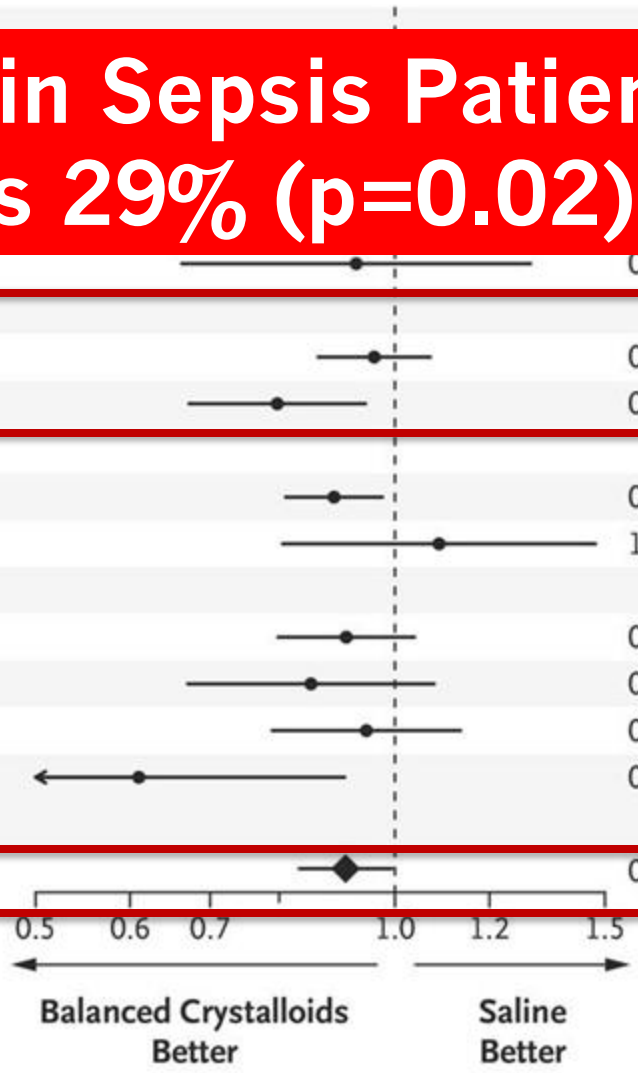


PRIMARY COMPOSITE OUTCOME

Semler, *NEJM* 2018; 378:829-39

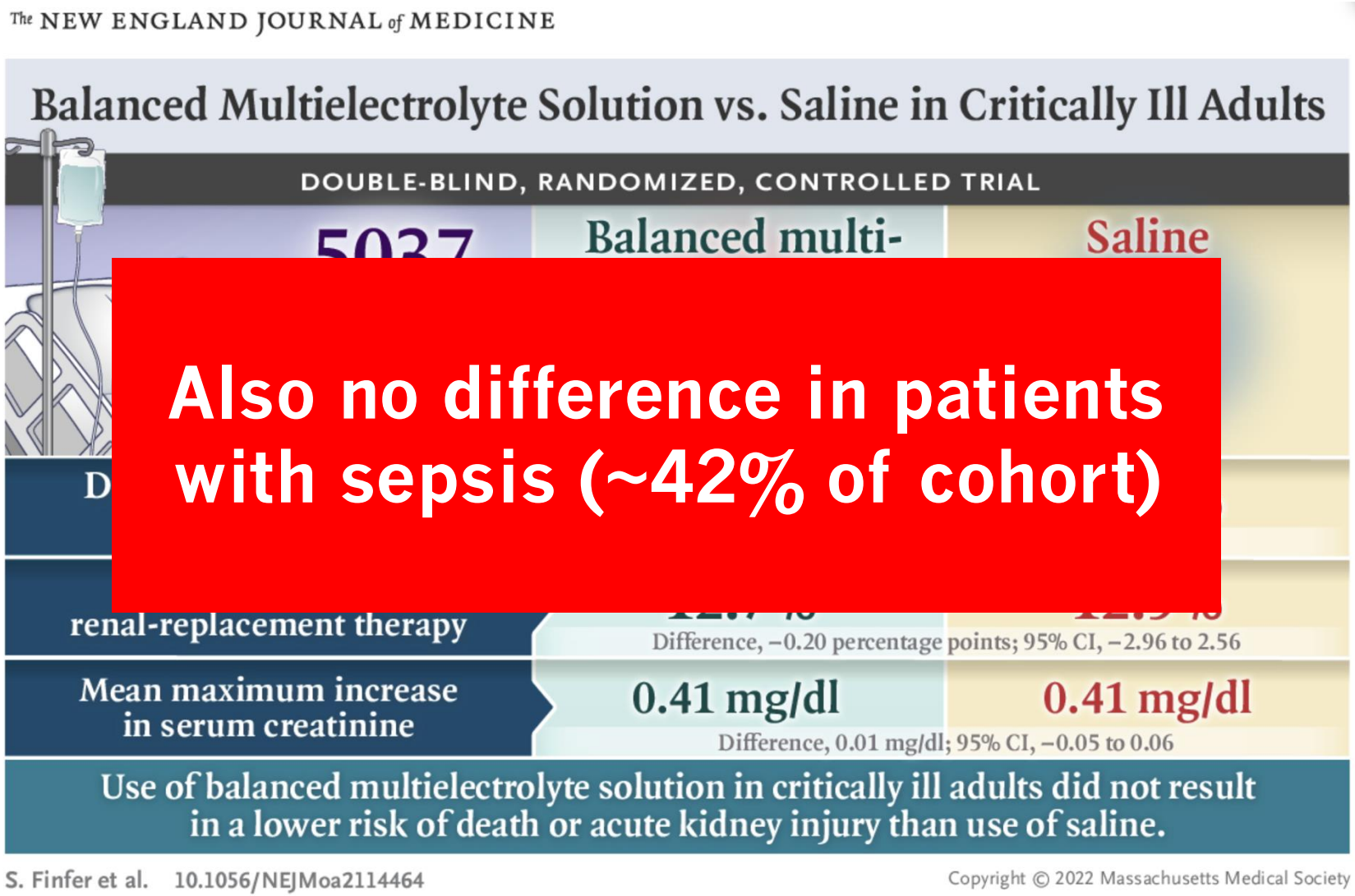
Mortality in Sepsis Patients: 25% vs 29% (p=0.02)

Subgroup	Balanced Crystalloids	Saline	Odds Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no. (%)				
Unit					0.27
Medical				0.04	
Cardiac				0.38	
Neurologic				0.04	
Trauma				0.66	
Surgical	75/657 (11.4)	79/648 (12.2)	0.93 (0.66–1.30)	0.66	
Sepsis					0.06
No	744/6775 (11.0)	756/6691 (11.3)	0.96 (0.86–1.07)	0.47	
Yes	395/1167 (33.8)	455/1169 (38.9)	0.80 (0.67–0.94)	0.01	
Traumatic brain injury					0.24
No	1034/7244 (14.3)	1118/7195 (15.5)	0.89 (0.81–0.98)	0.01	
Yes	105/698 (15.0)	93/665 (14.0)	1.09 (0.81–1.47)	0.58	
Categories of kidney function					0.19
Normal	476/5596 (8.5)	514/5561 (9.2)	0.91 (0.80–1.04)	0.16	
Acute kidney injury	315/574 (54.9)	316/537 (58.8)	0.85 (0.67–1.08)	0.18	
Chronic kidney disease	301/1388 (21.7)	307/1360 (22.6)	0.95 (0.79–1.13)	0.55	
Previous renal-replacement therapy	47/384 (12.2)	74/402 (18.4)	0.61 (0.41–0.91)	0.01	
Overall	1139/7942 (14.3)	1211/7860 (15.4)	0.91 (0.83–0.99)	0.04	



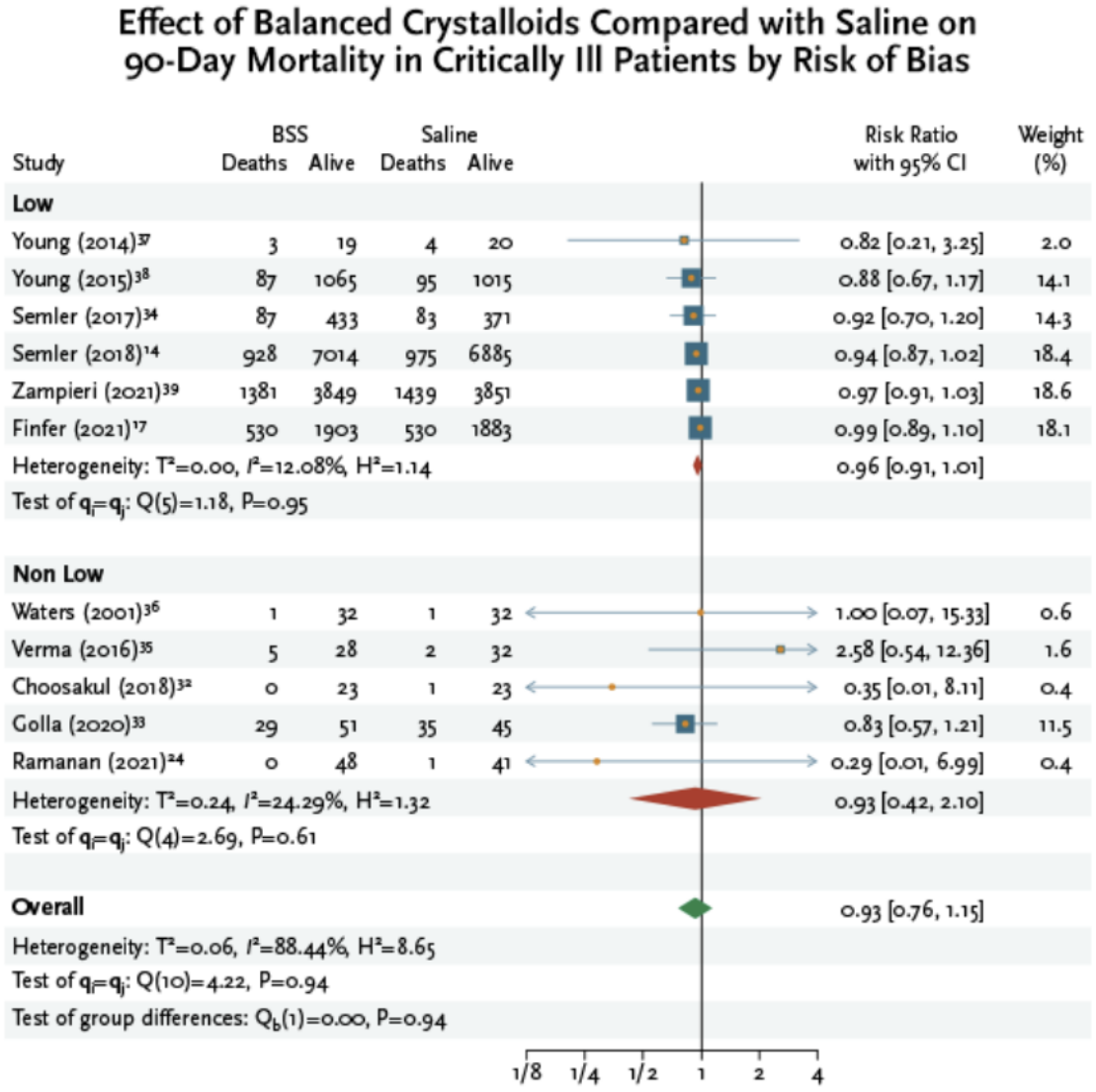
Semler, *NEJM* 2018; 378:829-39

The PLUS Trial



Finfer, *NEJM* 2022; 386:815-826

Updated Meta-Analysis of RCTs



89.5% probability that balanced crystalloids reduce mortality

Trend towards better renal outcomes with balanced solutions:

- **AKI: RR 0.96 [95% CI 0.89-1.02]**
- **RRT: RR 0.95 [95% CI 0.81-1.11]**

Hammond, *NEJM Evidence* 2022; 1 (2)

VASOPRESSORS AND HEMODYNAMIC TARGETS

Vasopressor Management

!!

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

HIGH	Dopamine
MODERATE	Vasopressin
LOW	Epinephrine
LOW	Selepressin
VERY LOW	Angiotensin 2

1st line NE over dopamine supported by SOAP II trial → equivalent mortality but more adverse effects with dopamine (NEJM 2010)

Combination of vasopressin + NE weakly supported by VASST trial – no difference in mortality overall, but lower mortality with combo pressors in less severe septic shock (NEJM 2008)

!

MODERATE

38 For adults with septic shock on norepinephrine with inadequate mean arterial pressure levels, we **suggest** adding vasopressin instead of escalating the dose of norepinephrine.

!

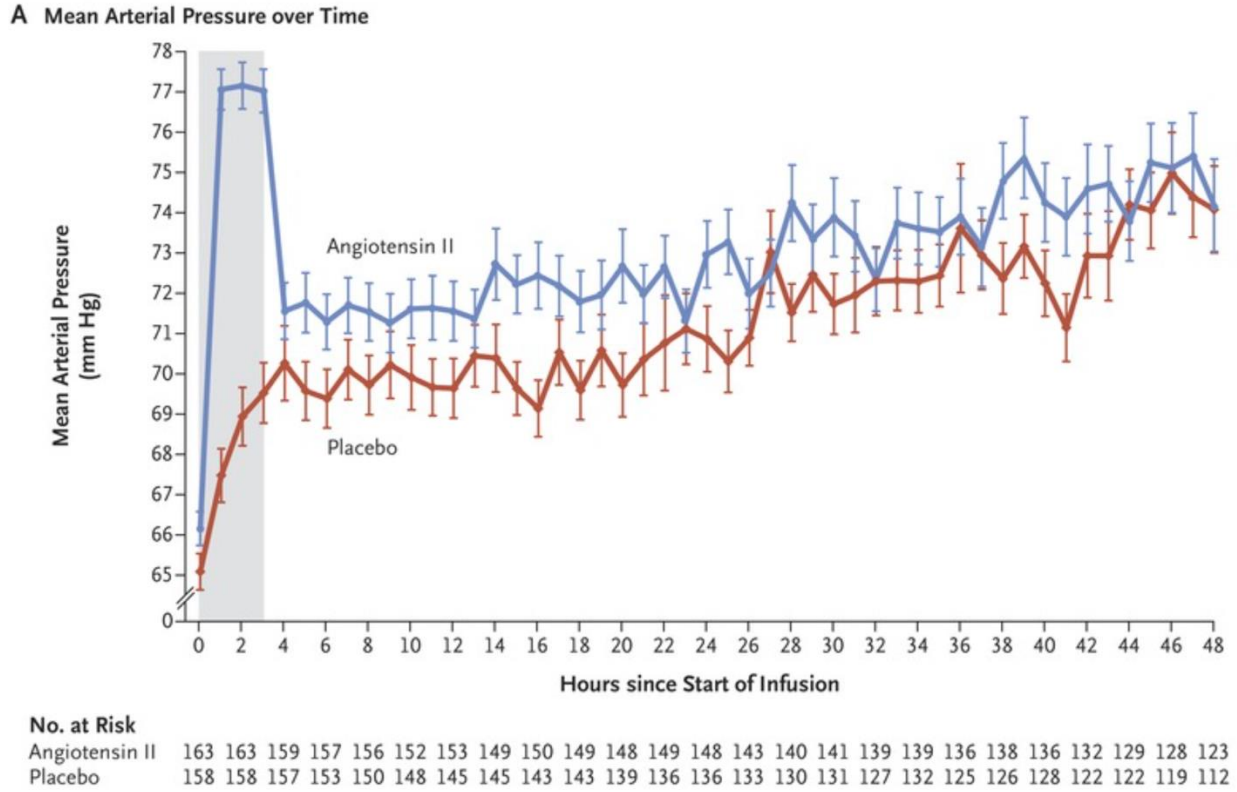
LOW

39 For adults with septic shock and inadequate mean arterial pressure levels despite norepinephrine and vasopressin, we **suggest** adding epinephrine.

Angiotensin II

- Non-catecholamine vasopressor FDA approved in Dec 2017 for septic / distributive shock based on ATHOS-3 Trial

- **Patients on high dose NE had good BP response to angiotensin II vs placebo**
  - **With no difference in serious adverse events**
  - **And trend towards lower 28-day mortality (46% vs 54%, p=0.12)**



Khanna, *NEJM* 2017; 377:419-30

Methylene Blue?

- Inhibits guanylate cyclase (enzyme that produces cGMP) and nitric oxide → inhibits vascular smooth muscle relaxation
- **Most common refra… following CP bypass**
- **Very lim…**
- Side effect…
  - Interfere with O2 sa…
  - Serotonin syndro… in pat… n ser… gic agents (… artial MAO inhibitor)
  - Potential methemoglobinem…
  - Blue discoloration of skin, mucosa, urine (temporary)
  - Contraindicated with G6PD deficiency (hemolytic anemia)

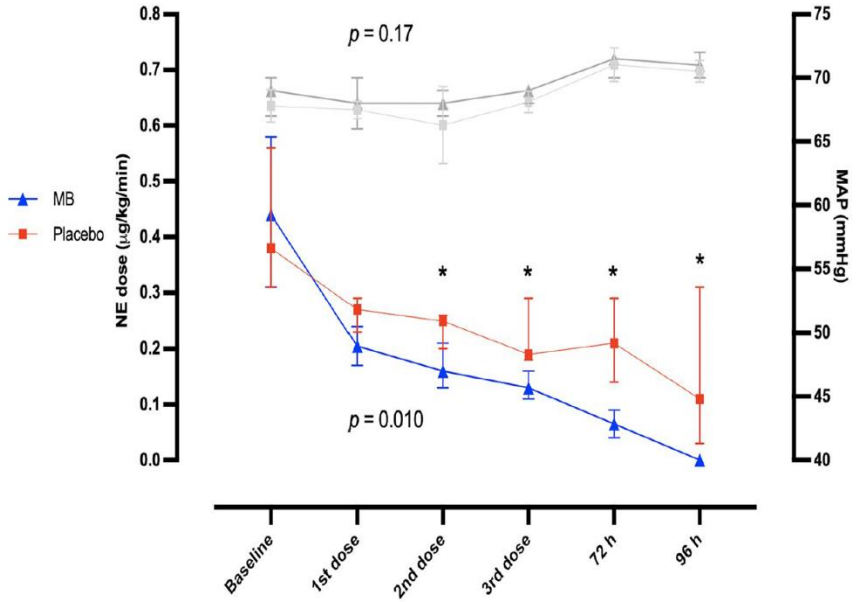
TYPICALLY A DRUG OF LAST RESORT; NOT MENTIONED IN SSC GUIDELINES

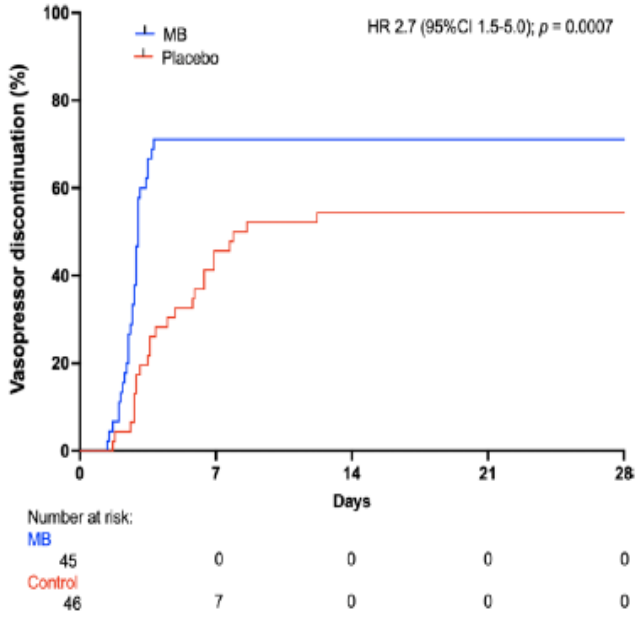
1. Kirov, *Crit Care Med* 2001; 29:1860-7
2. Memis, *Anaesth Intensive Care* 2002; 30:755-62

RESEARCH Open Access

Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial

Single center RCT of 91 patients with septic shock comparing early adjunctive methylene blue (within 24h) vs standard care





- ↓Time to vasopressor discontinuation (69 h vs 94 h, p<0.001)
- ↓ICU LOS by 1.5 days (p=0.039)
- Similar mortality rates
- No serious adverse effects

Ibarra-Estrada M, *Crit Care* 2023; 27:110

Hemodynamic Management: Beta-Blockers?

Theory: Adrenergic stress in septic shock may cause adverse cardiac, immune, inflammatory, and metabolic consequences that are attenuated with beta-blockers (supported by some animal models and retrospective studies of sepsis patients on chronic beta-blockers)


Research

Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

- Open-label phase 2 single-ICU RCT of 154 patients in the Netherlands with septic shock with HR ≥95 requiring high-dose NE comparing esmolol vs usual care
- **Achieved primary outcome of reduced heart rate, without adverse hemodynamic and organ function measures**
- **Secondary outcome: lower 28-day mortality with esmolol 49.4% vs 80.5% in control (p<0.001)**

Morelli A, JAMA 2013; 310:1683-91


Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Landiolol and Organ Failure in Patients With Septic Shock
The STRESS-L Randomized Clinical Trial

- Open-label RCT in 40 UK ICUs comparing landiolol vs usual care in 126 patient with septic shock with HR ≥ 95 and ≥24 hours of NE
- **Trial stopped early: No signal for reduction in SOFA scores at 14 days; increased hypotension, pressor requirements, and lactate levels**
- **Also higher 28-day mortality: 37.1% in landiolol group vs 25.4% in standard care group (p=0.16)**

Whitehouse T, JAMA 2023; 330:1641-1652

MAP Goal

MEAN ARTERIAL PRESSURE

MODERATE

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.

Supported by lack of benefit for higher MAP targets, and lack of harm with permissive hypotension in elderly patients (65 trial)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO. 17

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D., for the SEPSISPAM Investigators*

- Multicenter RCT in 29 French hospitals
- 776 adults with septic shock randomized to high vs low MAP targets (80-85 vs 65-70 mmHg) using vasopressors
- No difference in 28-day mortality (or 90-day mortality)

- **More renal failure in chronic HTN pts in low MAP group**
- **More a-fib in high MAP group**

Asfar, NEJM 2014; 370:1583-93

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension
A Randomized Clinical Trial

François Lamontagne, MD; Alvin Richards-Belle, BSc; Karen Thomas, MSc; David A. Harrison, PhD; M. Zia Sadique, PhD; Richard D. Grieve, PhD; Julie Camsooksai, BSc; Robert Darnell, BA; Anthony C. Gordon, MD; Doreen Henry, MSc; Nicholas Hudson, BA; Alexina J. Mason, PhD; Michelle Saull, BSc; Chris Whitman, BSc; J. Duncan Young, DM; Kathryn M. Rowan, PhD; Paul R. Mouncey, MSc; for the 65 trial investigators

- "65 Trial" = multicenter RCT done in 65 U.K. ICUs
- Enrolled ~2600 patients ≥65 years old with vasodilatory shock to vasopressors with MAP goal 60-65, vs usual care (MAP ≥65)
- **Permissive hypotension → similar 90-day mortality** (trend toward benefit), with shorter duration of vasopressors and no adverse events in any subgroups

➢Implication: Can have a low threshold to decrease MAP goal to 60 for elderly patients (especially if close to weaning off pressors, or having arrhythmias or other problems with high-dose pressors)

Lamontagne, *JAMA* 2020; 323:938-949

ANTIBIOTIC AND INFECTION MANAGMENT

Empiric Antimicrobial Therapy

19 For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we **suggest** using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent.

20 For adults with sepsis or septic shock and low risk for multidrug resistant (MDR) organisms, we **suggest against** using two gram-negative agents for empiric treatment, as compared to one gram-negative agent.

21 For adults with sepsis or septic shock, we **suggest against** using double gram-negative coverage once the causative pathogen and the susceptibilities are known.

Timing of Antibiotics

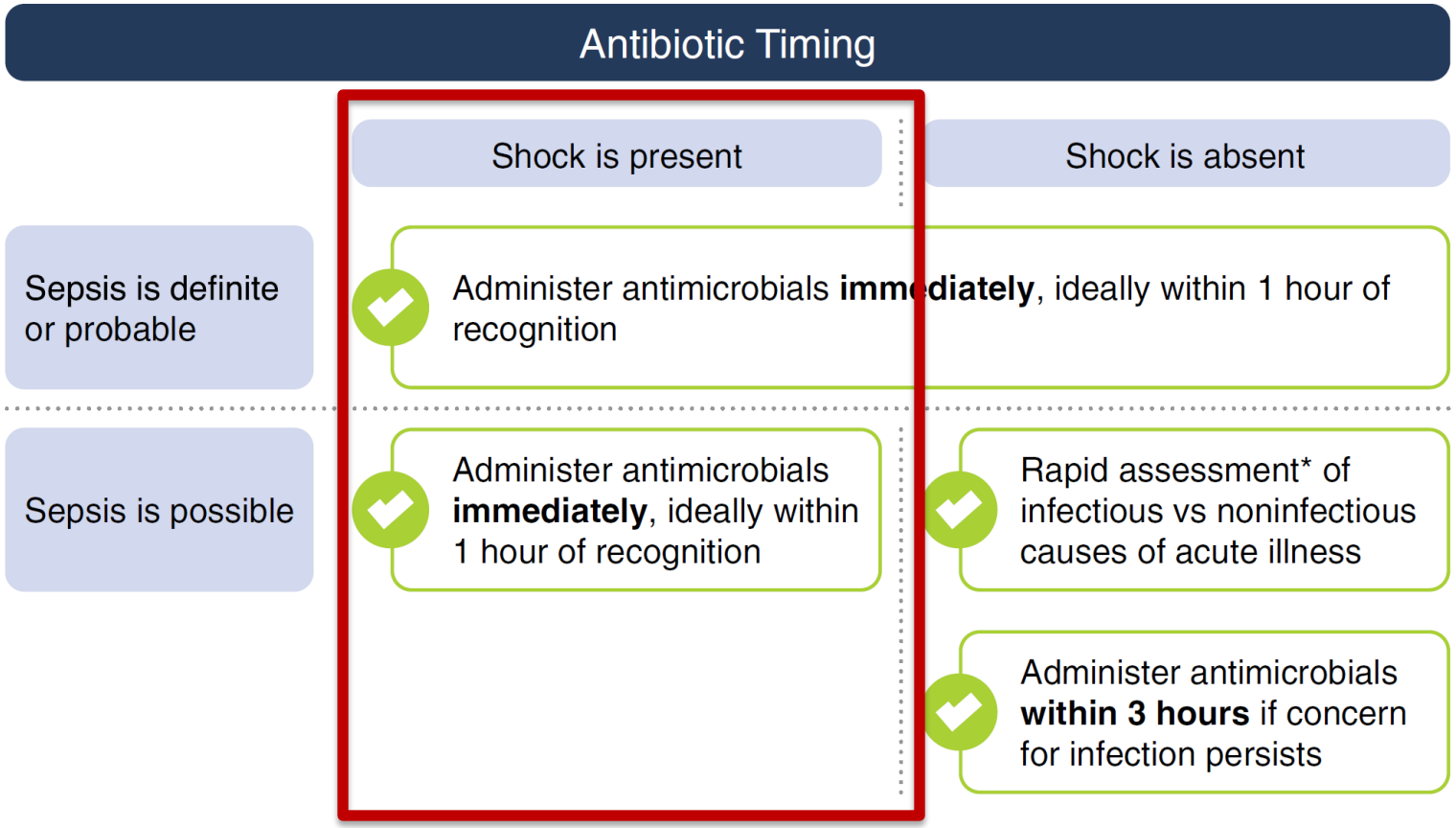
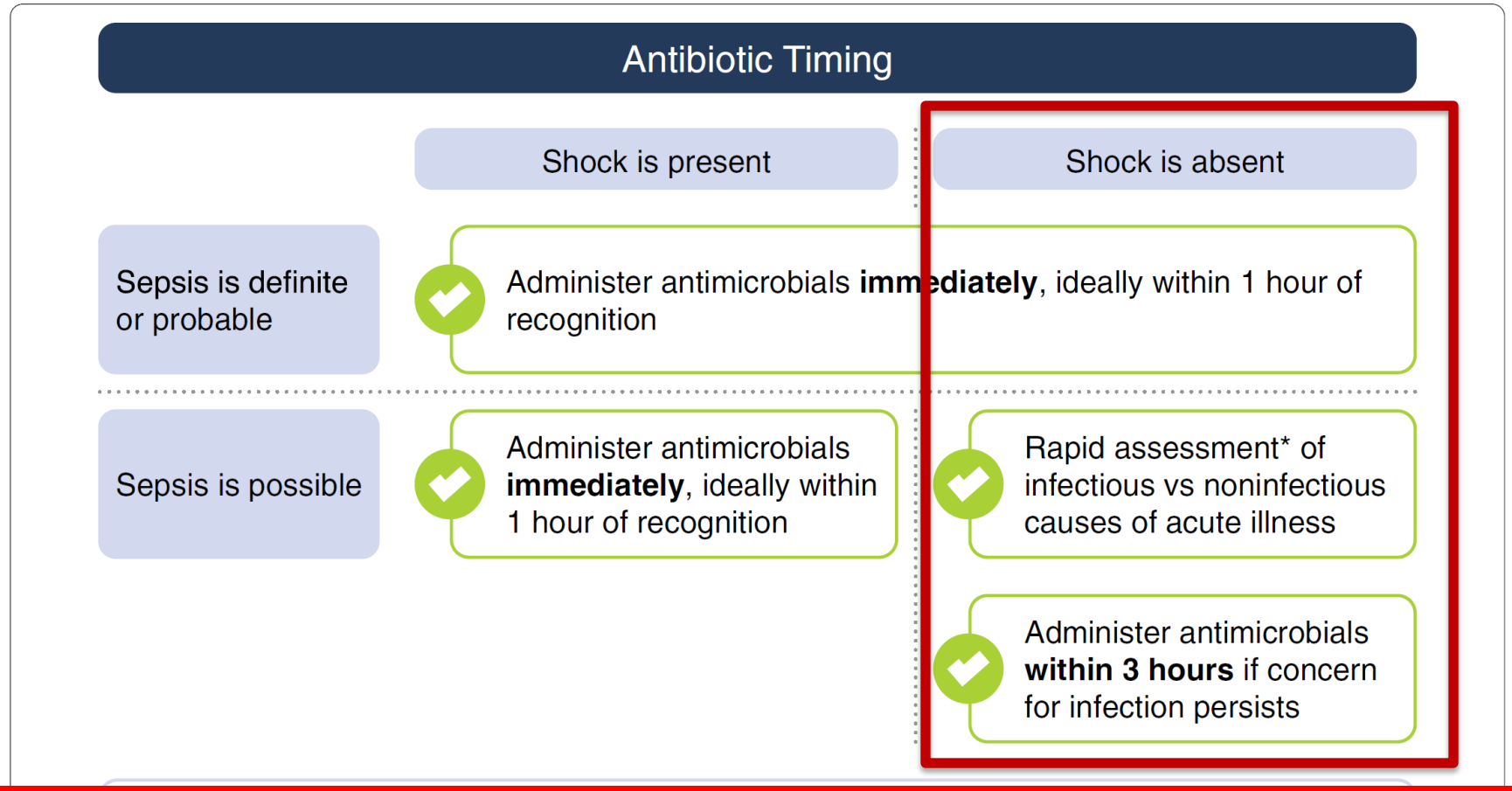


Fig. 1 Recommendations on timing of antibiotic administration

Timing of Antibiotics



Driven by a large body of observational studies suggesting that hourly delays in antibiotics are associated with higher mortality in patients with septic shock but not sepsis without shock

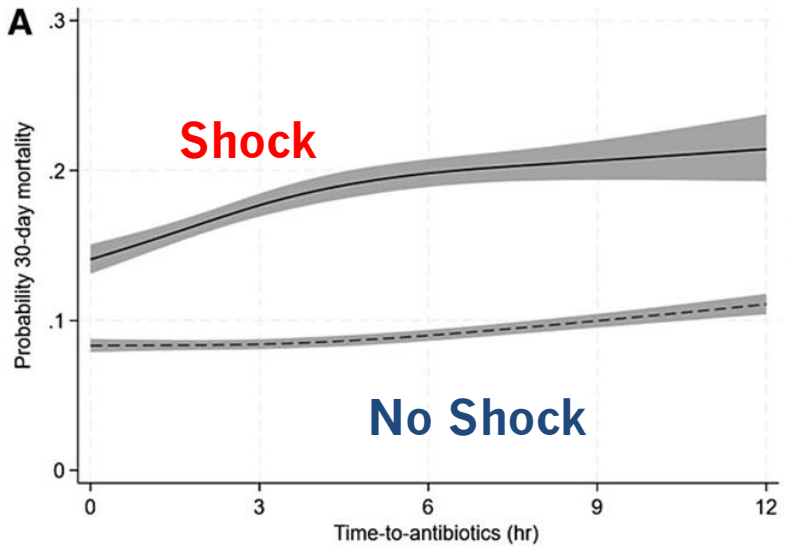
ORIGINAL ARTICLE

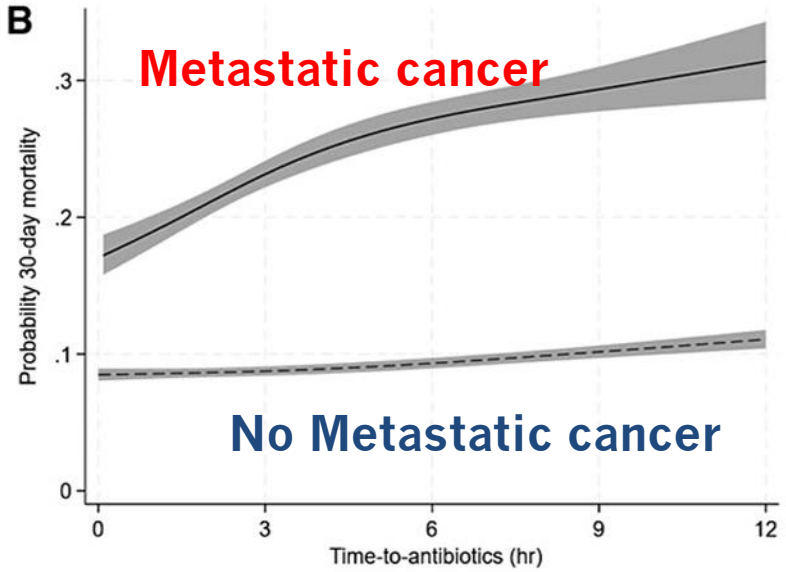
Heterogeneity of Benefit from Earlier Time-to-Antibiotics for Sepsis

Rachel K. Hechtman[1], Patricia Kipnis[2], Jennifer Cano[3], Sarah Seelye[3], Vincent X. Liu[2], and Hallie C. Prescott[1,3]

Retrospective cohort study of 273,255 patients with community-onset sepsis at 173 hospitals and treated with antibiotics within 12 hours of arrival

Greatest benefit of early antibiotics in patients with shock (vs no shock) and metastatic cancer (vs no metastatic cancer)
Also: patients with multiple organ dysfunctions





Hecthman RK, AJRCC 2024 ; 209:852-860

Antibiotic Dosing Strategy

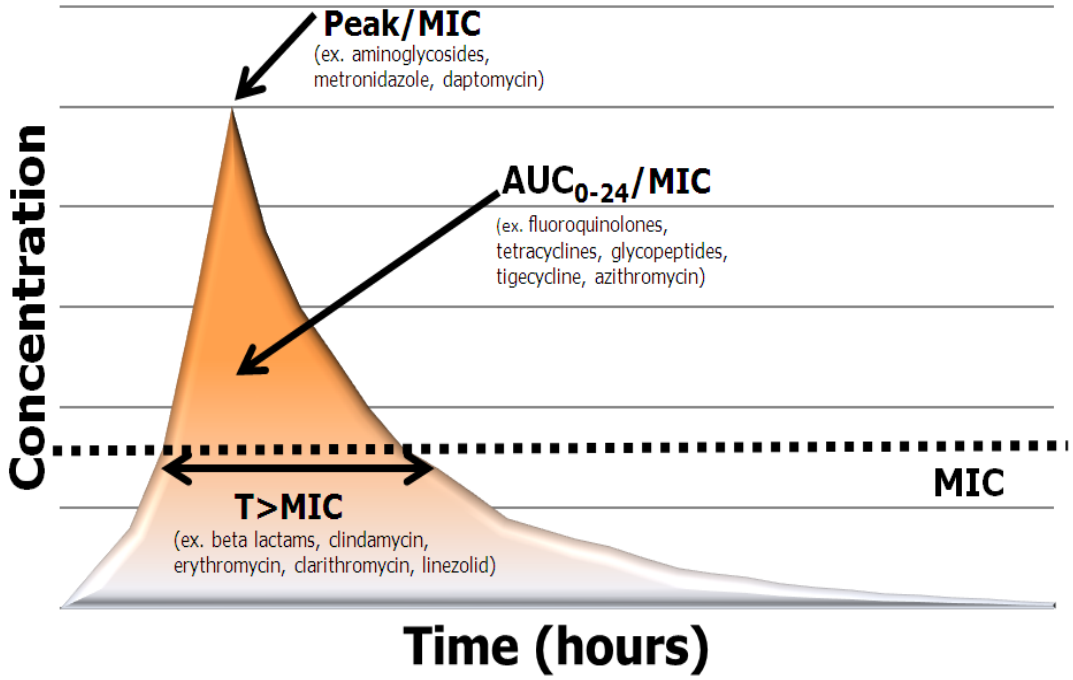
25 For adults with sepsis or septic shock, we **suggest** using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion.

26 For adults with sepsis or septic shock, we **recommend** optimising dosing strategies of antimicrobials based on accepted pharmacokinetic/ pharmacodynamic (PK/PD) principles and specific drug properties.

Dosing Beta-Lactams: Prolonged Infusions

Extended Infusion (3-4 hours) or Continuous Infusion vs Standard Infusion (30 minutes)

- Rationale: More time above MIC leads to:
  - **Greater bactericidal effect**
  - **Higher plasma drug levels**
  - **Potential reduced selection for resistance**
    - More rapid bacterial eradication, less regrowth between doses
- ***Without evidence of higher toxicity risk***



Prolonged infusions most sensible for :

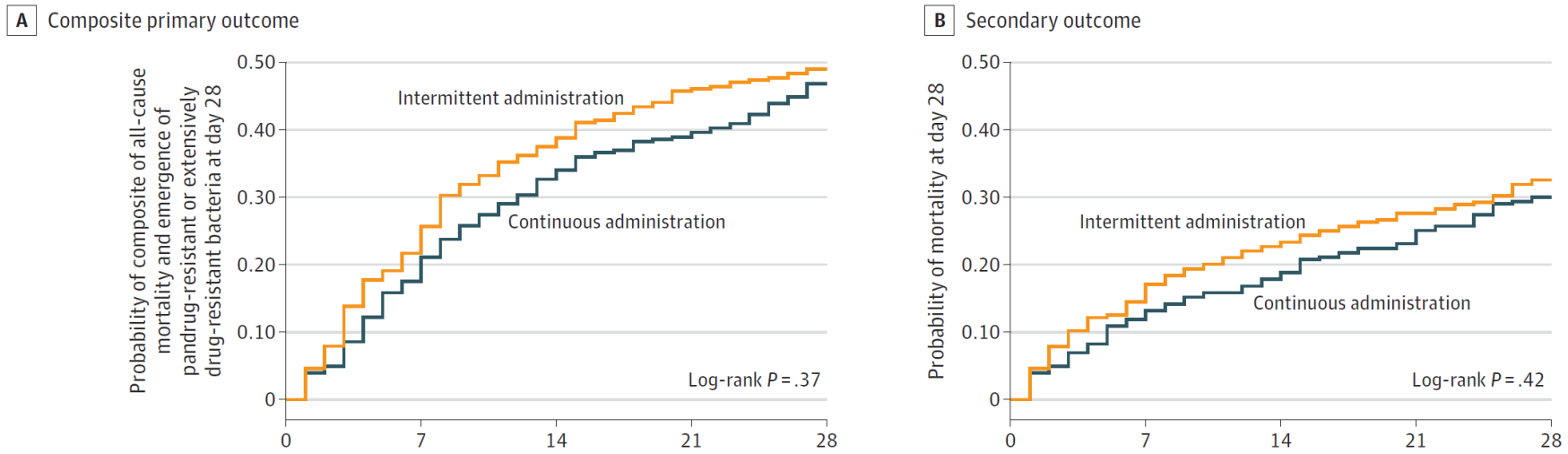
- Severely ill patients with altered pharmacodynamics, and/or
- At risk for drug-resistant gram-negative infections (or with susceptible infections with high MICs)

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Continuous vs Intermittent Meropenem Administration in Critically Ill Patients With Sepsis

The MERCY Randomized Clinical Trial

Multinational RCT of 607 ICU patients with sepsis or septic shock prescribed meropenem by their treating clinicians at 26 hospitals comparing continuous vs intermittent meropenem



No significant difference in primary or secondary outcomes, including in important pre-specified subgroup analyses

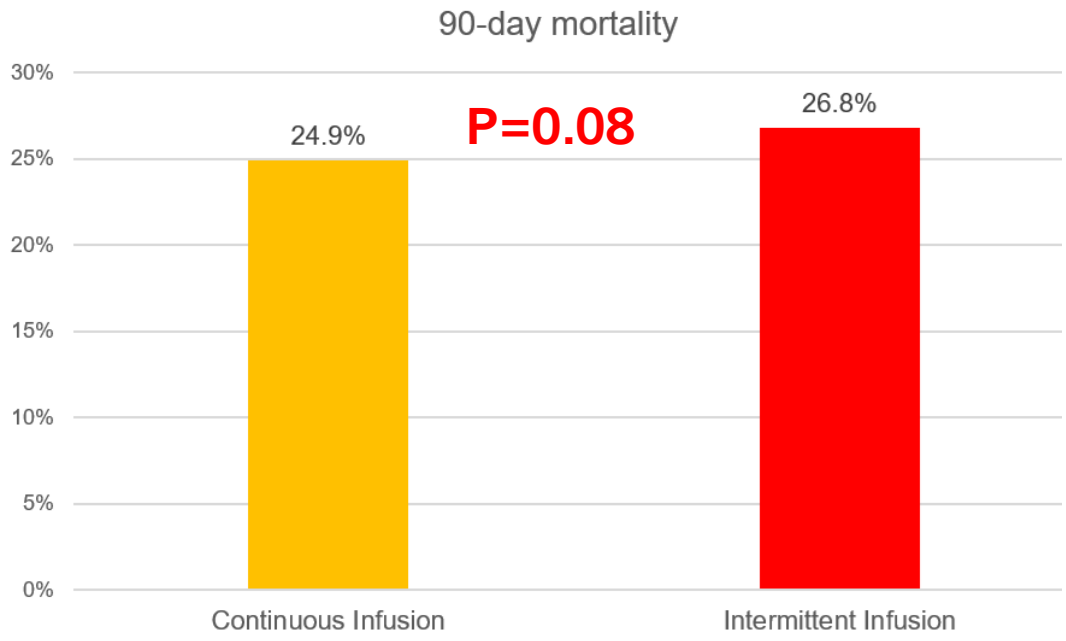
Monti G, *JAMA* 2023; 330:141-151

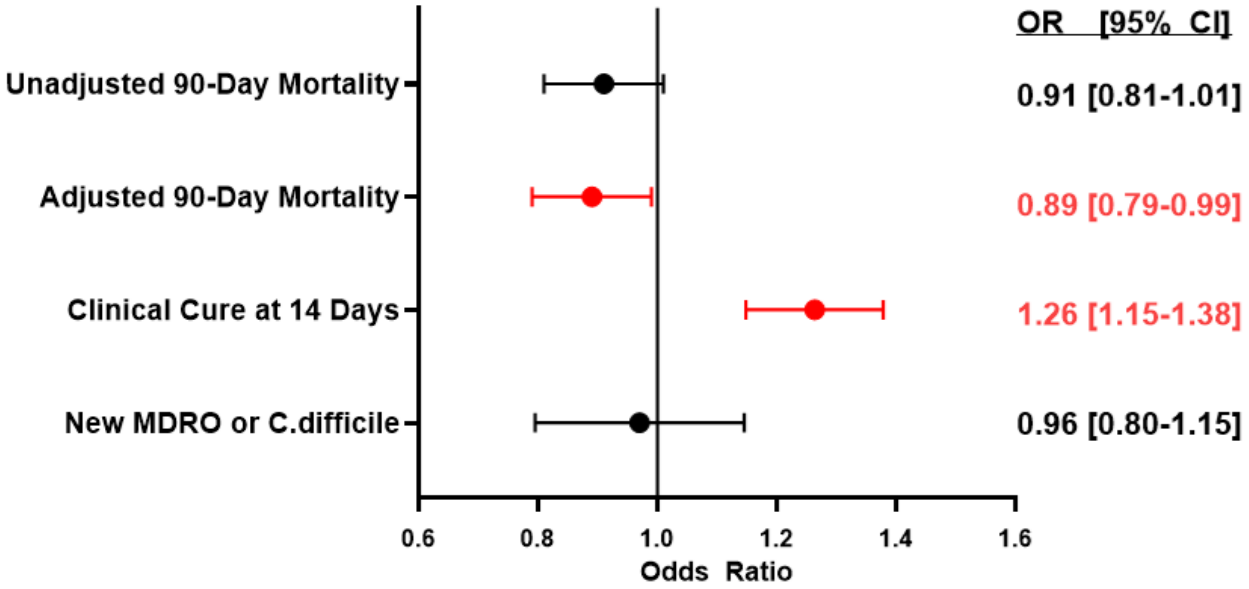
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis

The BLING III Randomized Clinical Trial

RCT of 7,031 critically ill patients with sepsis in 104 ICUs in 7 countries comparing continuous piperacillin-tazobactam or meropenem vs intermittent infusion



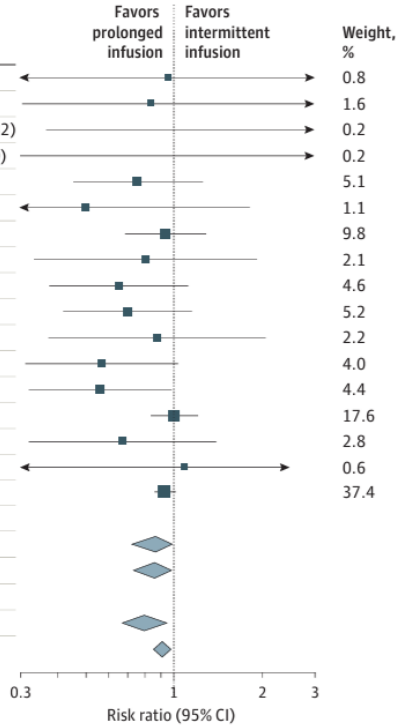


Dulhunty JM, JAMA 2024; 332:629-637

Updated Meta-Analysis of Prolonged β-Lactam Infusions

Meta-analysis of 17 RCTs including 9,014 critically ill adults with sepsis

Study	Dead (prolonged)	Alive (prolonged)	Dead (intermittent)	Alive (intermittent)	Absolute difference (95% CI)	Risk ratio (95% CI)	Weight, %
Georges et al,[33] 2005	3	21	3	20	-0.01 (-0.20 to 0.19)	0.96 (0.21 to 4.27)	0.8
Rafati et al,[34] 2006	5	15	6	14	-0.05 (-0.33 to 0.23)	0.83 (0.30 to 2.29)	1.6
Roberts et al,[35] 2007	3	26	0	28	0.10 (-0.02 to 0.22)	6.77 (0.37 to 125.32)	0.2
Roberts et al,[36] 2009	2	3	0	5	0.33 (-0.12 to 0.79)	5.00 (0.30 to 83.69)	0.2
Chytra et al,[38] 2012	21	99	28	92	-0.06 (-0.16 to 0.04)	0.75 (0.45 to 1.24)	5.1
Dulhunty et al,[39] 2013	3	27	6	24	-0.10 (-0.28 to 0.08)	0.50 (0.14 to 1.82)	1.1
Dulhunty et al,[40] 2015	54	156	60	158	-0.02 (-0.10 to 0.07)	0.93 (0.68 to 1.28)	9.8
Jamal et al,[41] 2015	4	4	5	3	-0.12 (-0.61 to 0.36)	0.80 (0.33 to 1.92)	2.1
Jamal et al,[42] 2015	5	3	8	0	-0.33 (-0.69 to 0.02)	0.65 (0.38 to 1.12)	4.6
Abdul-Aziz et al,[43] 2016	18	52	26	44	-0.11 (-0.27 to 0.04)	0.69 (0.42 to 1.14)	5.2
Zhao et al,[44] 2017	7	18	8	17	-0.04 (-0.29 to 0.21)	0.88 (0.37 to 2.05)	2.2
Khan and Omar,[22] 2023	12	40	20	29	-0.18 (-0.36 to 0.00)	0.57 (0.31 to 1.03)	4.0
Mirjalili et al,[45] 2023	14	54	25	43	-0.16 (-0.31 to -0.01)	0.56 (0.32 to 0.98)	4.4
Monti et al,[14] 2023	127	176	127	177	0.00 (-0.08 to 0.08)	1.00 (0.83 to 1.21)	17.6
Saad et al,[46] 2024	8	22	12	18	-0.13 (-0.37 to 0.10)	0.67 (0.32 to 1.39)	2.8
Álvarez-Moreno et al,[47] 2024	2	10	2	11	0.01 (-0.28 to 0.30)	1.08 (0.18 to 6.53)	0.6
Dulhunty et al,[15] 2024	864	2610	939	2568	-0.02 (-0.04 to 0.00)	0.93 (0.86 to 1.01)	37.4
Bayesian							
Vague priors[a]					-0.03 (-0.08 to 0.00)	0.86 (0.72 to 0.98)	
Semi-informative priors[a]					-0.04 (-0.10 to 0.01)	0.86 (0.73 to 0.98)	
Frequentist							
Hartung-Knapp-Sidik-Jonkman					-0.05 (-0.10 to 0.00)	0.80 (0.67 to 0.94)	
DerSimonian-Laird					-0.03 (-0.07 to 0.00)	0.91 (0.85 to 0.97)	



Pooled RR for 90-day mortality: 0.86 [95% CI 0.72-0.98]

99.1% posterior probability that prolonged infusions lower 90-day mortality

Also: ↓ICU mortality (RR 0.84 [0.70-0.97]) and ↑clinical cure (RR 1.16 [1.07-1.31]

Abdul-Aziz MH, JAMA 2024; 332:638-648

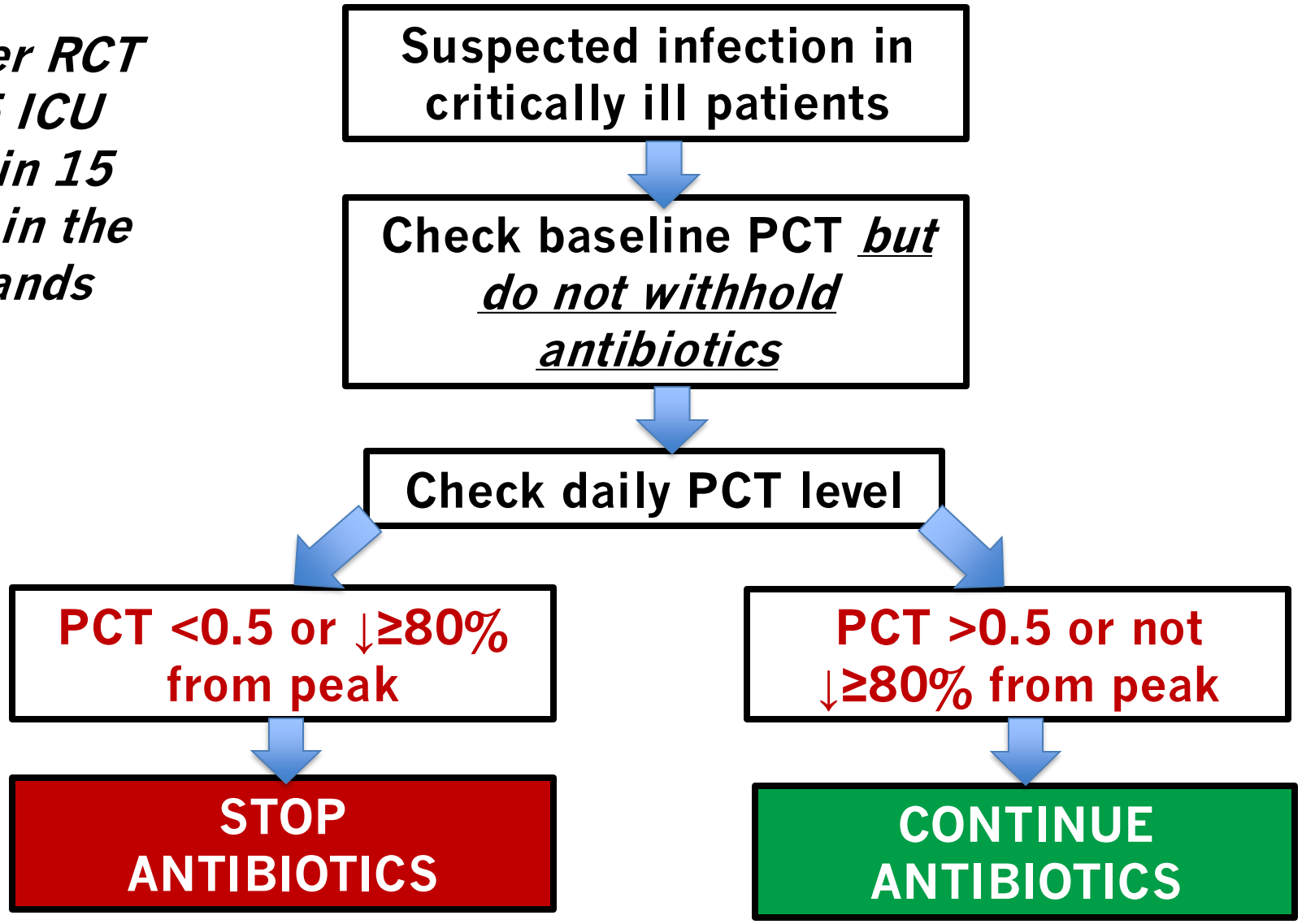
Procalcitonin

16 For adults with suspected sepsis or septic shock, we **suggest against** using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone.

31 For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we **suggest** using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone.

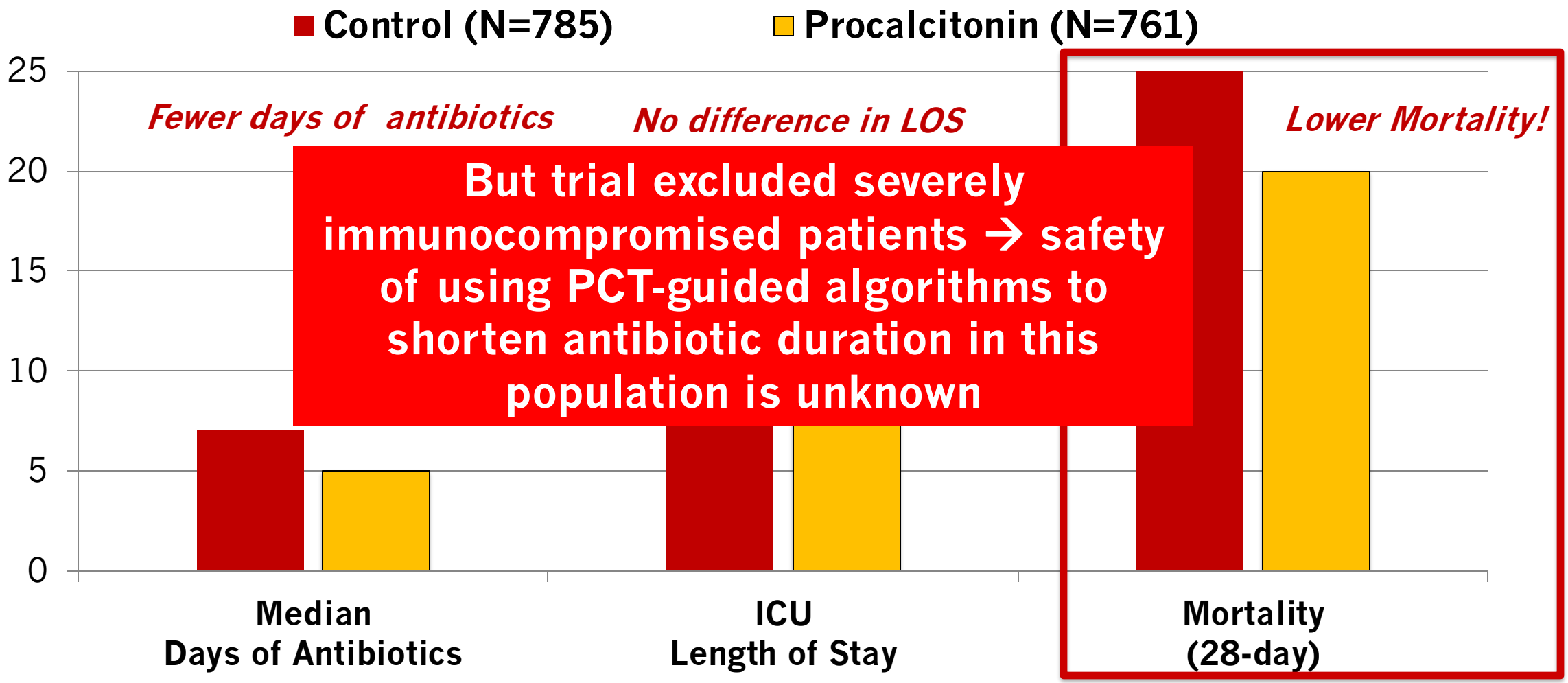
SAPS Trial: PCT to Discontinue Antibiotics in the ICU

Multicenter RCT of 1,575 ICU patients in 15 hospitals in the Netherlands



De Jong, *Lancet Infect Dis* 2016; 16: 819-27

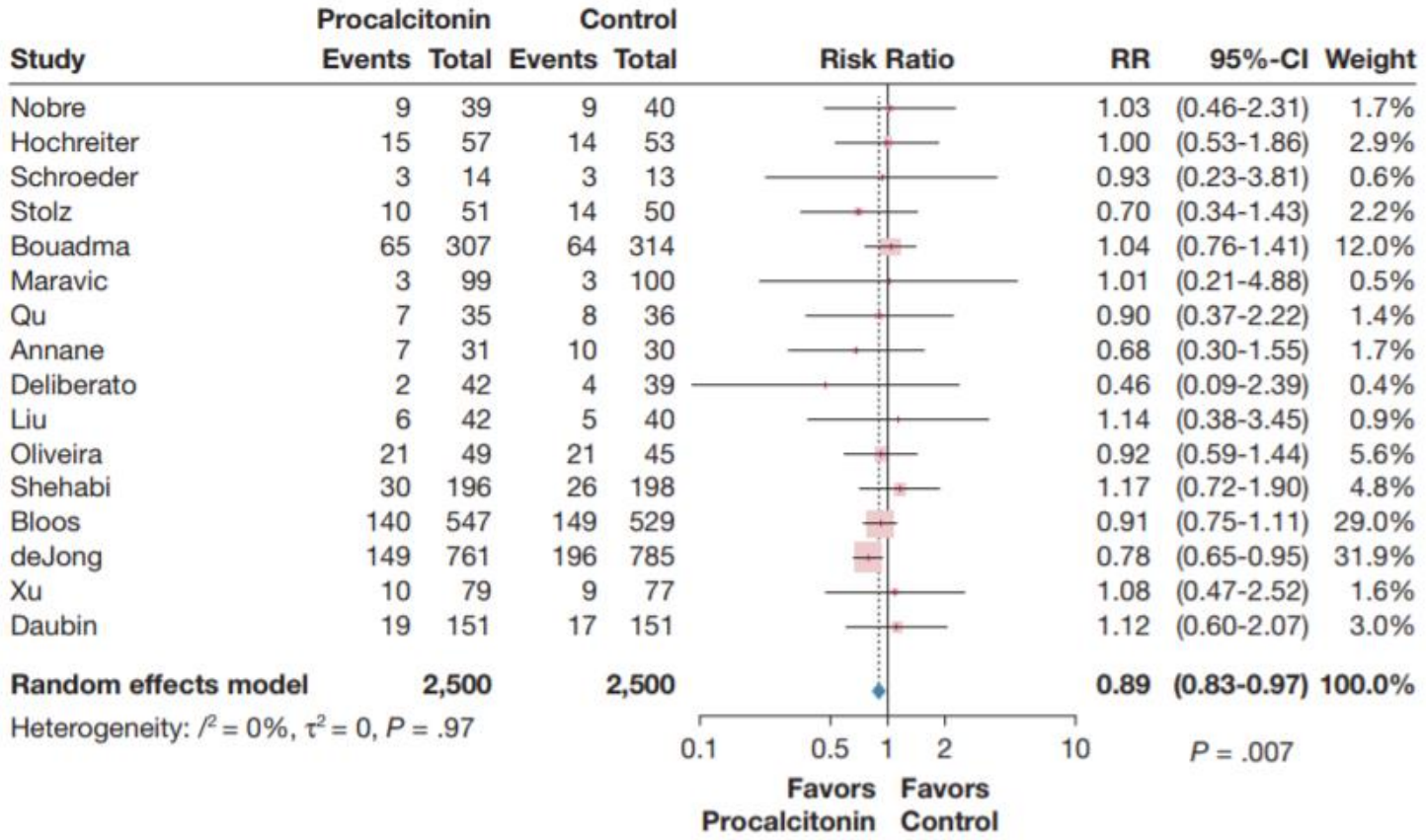
Procalcitonin in the ICU: SAPS



de Jong, *Lancet Infect Dis* 2016;16:819-827

PCT-Guided Antibiotic Discontinuation In ICU Patients and Mortality

Meta-analysis of 5000 ICU patients from 16 RCTs



Study	Procalcitonin Events	Procalcitonin Total	Control Events	Control Total	RR	95%-CI	Weight
Nobre	9	39	9	40	1.03	(0.46-2.31)	1.7%
Hochreiter	15	57	14	53	1.00	(0.53-1.86)	2.9%
Schroeder	3	14	3	13	0.93	(0.23-3.81)	0.6%
Stolz	10	51	14	50	0.70	(0.34-1.43)	2.2%
Bouadma	65	307	64	314	1.04	(0.76-1.41)	12.0%
Maravic	3	99	3	100	1.01	(0.21-4.88)	0.5%
Qu	7	35	8	36	0.90	(0.37-2.22)	1.4%
Annane	7	31	10	30	0.68	(0.30-1.55)	1.7%
Deliberato	2	42	4	39	0.46	(0.09-2.39)	0.4%
Liu	6	42	5	40	1.14	(0.38-3.45)	0.9%
Oliveira	21	49	21	45	0.92	(0.59-1.44)	5.6%
Shehabi	30	196	26	198	1.17	(0.72-1.90)	4.8%
Bloos	140	547	149	529	0.91	(0.75-1.11)	29.0%
deJong	149	761	196	785	0.78	(0.65-0.95)	31.9%
Xu	10	79	9	77	1.08	(0.47-2.52)	1.6%
Daubin	19	151	17	151	1.12	(0.60-2.07)	3.0%
Random effects model		**2,500**		**2,500**	**0.89**	**(0.83-0.97)**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .97$

But results driven mainly by trials with high protocol adherence
→ Low Certainty Evidence (High Risk of Bias)

Pepper D, *Chest* 2019; 155:1109-1118

Source Control

27 For adults with sepsis or septic shock, we **recommend** rapidly identifying or excluding a specific anatomical diagnosis of infection that requires emergent source control and implementing any required source control intervention as soon as medically and logistically practical.

28 For adults with sepsis or septic shock, we **recommend** prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established.

Supported primarily by observational data (no RCT data) and clinical experience

Limited data on impact of specific time frames of delays

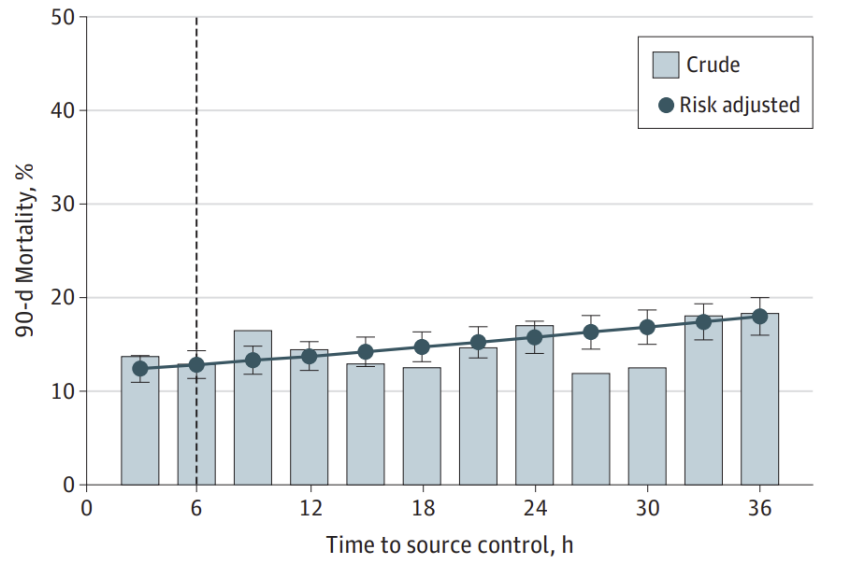
JAMA Surgery | Original Investigation

Association Between Time to Source Control in Sepsis and 90-Day Mortality

Katherine M. Reitz, MD, MSc; Jason Kennedy, MS; Shimena R. Li, MD; Robert Handzel, MD; Daniel A. Tonetti, MD, MSc; Matthew D. Neal, MD; Brian S. Zuckerbraun, MD; Daniel E. Hall, MD, MDiv, MHSc; Jason L. Sperry, MD, MPH; Derek C. Angus, MD, MPH; Edith Tzeng, MD; Christopher W. Seymour, MD, MSc

Retrospective analysis of 4,962 patients with community-onset sepsis who underwent source control procedures

Figure 2. Observed and Risk-Adjusted 90-Day Mortality for the Primary Cohort



- **Early source control (<6 hours) associated with 29% decreased odds of 90-day risk-adjusted mortality vs late source control (6-36 hours)**
- **Strongest association for GI/abdominal and soft tissue interventions (vs orthopedic and cranial interventions)**

Reitz KM, *JAMA Surgery* 2022; July 13;e222761 (ePub)

CORTICOSTEROIDS

Corticosteroids

ADDITIONAL THERAPIES

MODERATE

58 For adults with septic shock and an ongoing requirement for vasopressor therapy we **suggest** using IV corticosteroids.

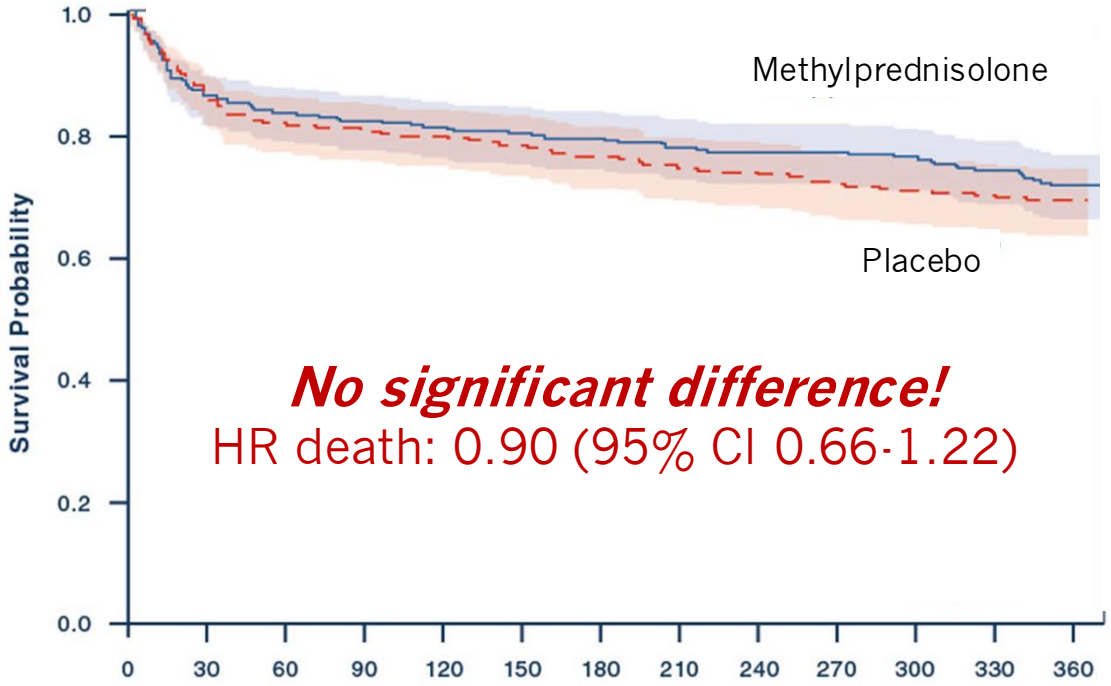
2016 STATEMENT

*"We **suggest against** using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). If this is not achievable, we **suggest** intravenous hydrocortisone at a dose of 200 mg per day."*

Reflects 3 NEJM RCTs published since 2016 SSC guidelines; meta-analysis suggests faster resolution of shock, increase in neuromuscular weakness, and unclear benefit on mortality

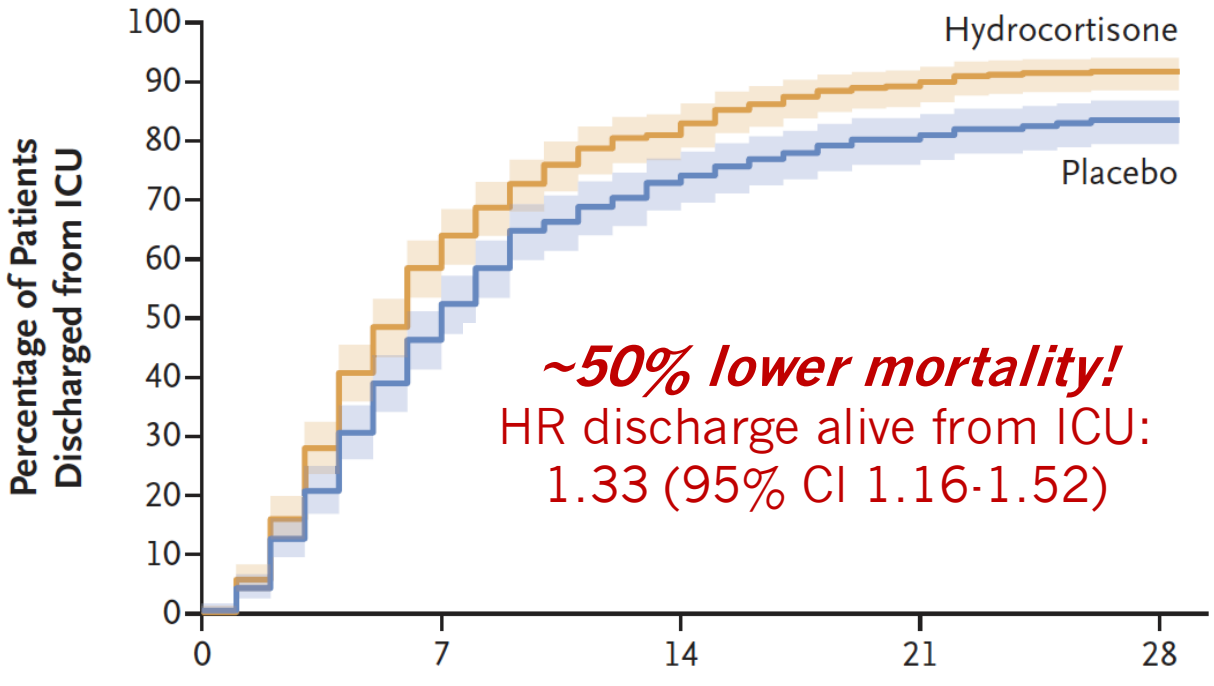
Steroids for Severe CAP

584 ICU & intermediate care patients with CAP at 42 VA hospitals randomized to methylprednisolone 40mg/day x7d then 13d taper



Meduri GU, *Intensive Care Med* 2022;48:1009–1023

CAPE-COD Trial: 795 ICU patients with severe CAP (without septic shock) randomized to hydrocortisone 200mg/day x 4-8d then taper



Dequin P, *NEJM* 2023;288:1931-1941

Differences in Meduri vs CAPE-COD Trials

Meduri Trial

- Treatment started up to 96h after admission
- 96% of participants were male
- ~10% of patients had influenza

CAPE-COD Trial

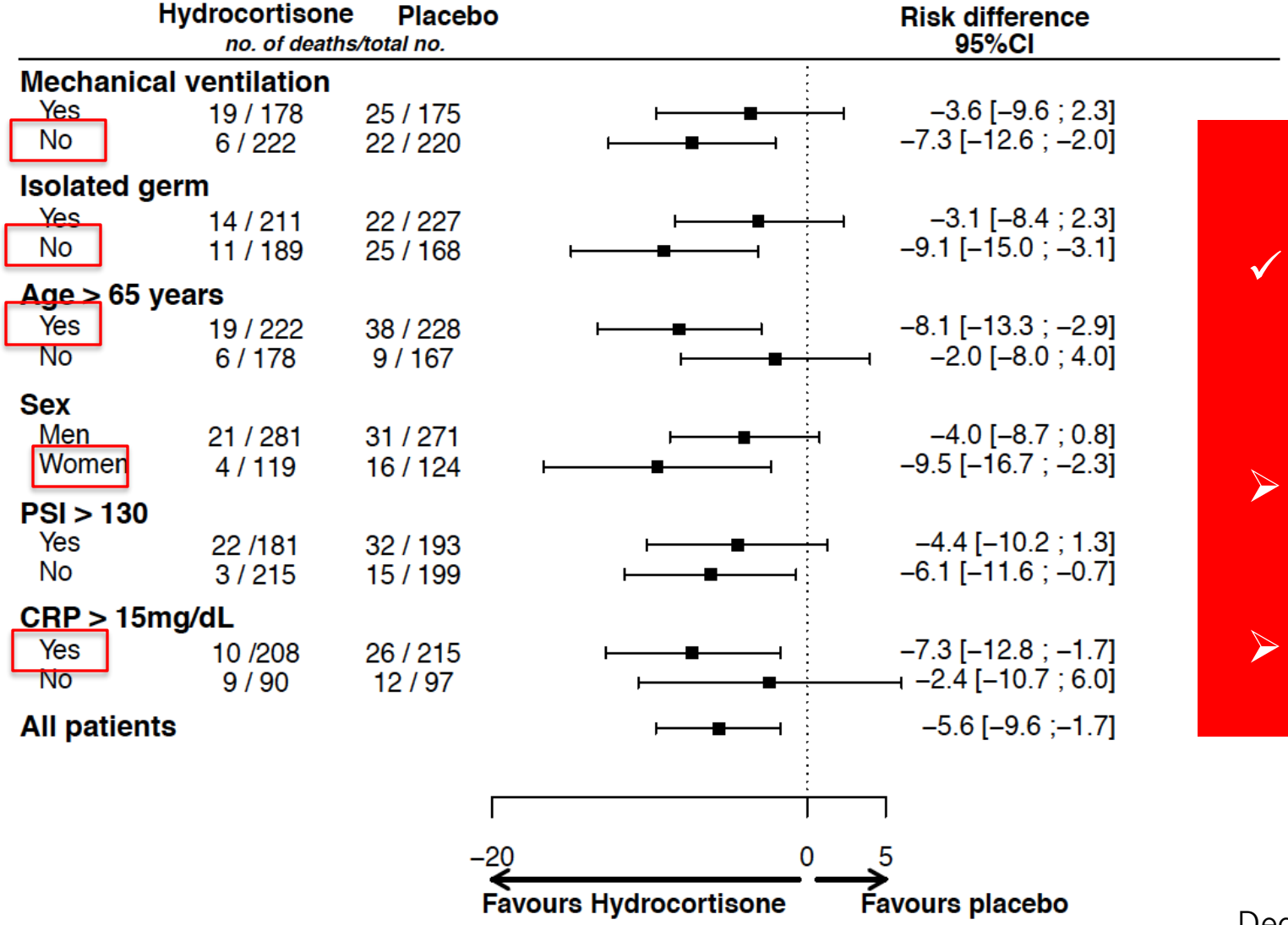
- Treatment started up to 24h after admission
- 31% of participants were female
- Excluded patients with influenza

Meduri GU, *Intensive Care Med* 2022;48:1009–1023

Dequin P, *NEJM* 2023;288:1931-1941

CAPE-COD: Subgroup Analyses

795 patients ICU patients with severe CAP comparing hydrocortisone 200mg/day x 4-8d vs placebo



Bottom Line

- ✓ **Consider steroids for Severe CAP requiring ICU care**
- ➢ ***Ideally within 24h of admission***
- ➢ ***Especially if ↑CRP***

Dequin P, *NEJM* 2023;288:1931-1941

2024 FOCUSED UPDATE

Society of Critical Care Medicine
The | ntensive Care Professiona s

Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community Acquired Pneumonia

SYMBOL KEY:

Strength of Recommendation
Strong Recommendation For: ↑↑
Conditional Recommendation For: ↑?
Conditional Recommendation Against: ↓?
Strong Recommendation Against: ↓↓

Certainty of Evidence
Very Low: ⊕◯◯◯
Low: ⊕⊕◯◯
Moderate: ⊕⊕⊕◯
High: ⊕⊕⊕⊕

This infographic visualizes results of a focused update to guidelines previously issued in 2008 and 2017 by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.

Scan or click the QR code to access the 2024 Focused Update Guidelines Executive Summary.

POPULATION: **Acutely Ill Adult Patients Requiring Hospitalization**
(Specific recommendations for pediatric patients are not made.)

Septic Shock

Conditional Recommendation For
↑?
Low Certainty of Evidence
⊕⊕◯◯

1A. We suggest administering corticosteroids to adult patients with septic shock.

Strong Recommendation Against
↓↓
Moderate Certainty of Evidence
⊕⊕⊕◯

1B. We recommend against administration of high dose/short duration corticosteroids (>400 mg/day hydrocortisone equivalent for less than 3 days) for adult patients with septic shock.

Acute Respiratory Distress Syndrome (ARDS)

Conditional Recommendation For
↑?
Moderate Certainty of Evidence
⊕⊕⊕◯

2A. We suggest administering corticosteroids to adult hospitalized patients with ARDS.

Community Acquired Pneumonia (CAP)

Strong Recommendation For
↑↑
Moderate Certainty of Evidence
⊕⊕⊕◯

3A. We recommend administering corticosteroids to adult patients hospitalized with severe bacterial CAP.*

No Recommendation Made
For explanation, see Full 2024 Focused Update Guidelines linked below.

3B. We make no recommendation for administering corticosteroids for adult patients hospitalized with less severe bacterial CAP.*

Crit Care Med 2024; 52:e219-e233

Summary and Take-Home Points, 1/2

- **Screening:**
  - ✓ Electronic sepsis alerts *may* help improve bundle compliance and outcomes
  - ✓ Best set of criteria remains unknown, but avoid using qSOFA alone

- **Fluid Resuscitation:**
  - ✓ Initial 30 cc/kg target for fluid resuscitation is controversial and not evidence-based
  - ✓ Balanced crystalloids preferred over saline (may have mortality and renal benefit)
  - ✓ Lactate-guided resuscitation no better (and potentially worse) than perfusion-guided resuscitation
  - ✓ No difference in early liberal fluid strategy vs early vasopressors (CLOVERS)
  - ✓ No difference in late restrictive vs standard fluid strategy (CLASSIC)

- **Vasopressors/Hemodynamic Management:**
  - ✓ Norepinephrine remains first-line, vasopressin as adjunct
  - ✓ Methylene blue might help if administered early but needs further study
  - ✓ Avoid beta-blockers
  - ✓ MAP target default is still 65 mmHg, but can potentially lower in elderly patients

Summary and Take-Home Points, 2/2

- **Antibiotics:**
  - ✓ Time-to-antibiotics most urgent in suspected septic shock (1 hour target, vs 3 hours for sepsis without shock)
  - ✓ There may be other phenotypes that benefit from immediate antibiotics (e.g., metastatic cancer, multiorgan failure without shock)
  - ✓ Prolonged β-lactam infusions likely improve outcomes
  - ✓ Procalcitonin use can help de-escalate/stop antibiotics and may improve mortality
  - ✓ Timely source control associated with improved outcomes
- **Adjunctive:**
  - ✓ Corticosteroids indicated for refractory shock and likely benefits patients with severe CAP (even without shock)

Thank You!

crhee@bwh.harvard.edu