

# Updates in Sepsis and Septic Shock

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# Disclosures

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- **Royalties**
  - UpToDate (Procalcitonin chapter)
- **Grant Funding** (related to sepsis surveillance and quality)
  - Centers for Disease Control and Prevention
  - Agency for Healthcare Research and Quality
- **Committee Membership**
  - IDSA Sepsis Task Force
  - CMS Sepsis Outcome Measure Development Technical Advisory Group
- **Consulting**
  - Pfizer (research related to Lyme Disease surveillance)
  - Cytovale (application of early sepsis diagnostics)
- **Editorial**
  - Associate Editor, *Clinical Infectious Diseases*
  - Editorial Board, *Critical Care Medicine* and *Critical Care Explorations*

***No financial conflicts related to this presentation***

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# Outline


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- **Updates in sepsis management**
    - ✓ Highlights from the 2021 Surviving Sepsis Campaign Guidelines
    - ✓ New evidence in 2022 since SSC guideline publication
    - ✓ Overview of time-to-antibiotics controversy
  - **Will not focus on sepsis definitions**
    - Not much new recently (since Sepsis-3 in 2016)
-

## GUIDELINES



# Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

Laura Evans<sup>1\*</sup> , Andrew Rhodes<sup>2</sup>, Waleed Alhazzani<sup>3</sup>, Massimo Antonelli<sup>4</sup>, Craig M. Coopersmith<sup>5</sup>, Craig French<sup>6</sup>, Flávia R. Machado<sup>7</sup>, Lauralyn McIntyre<sup>8</sup>, Marlies Ostermann<sup>9</sup>, Hallie C. Prescott<sup>10</sup>, Christa Schorr<sup>11</sup>, Steven Simpson<sup>12</sup>, W. Joost Wiersinga<sup>13</sup>, Fayez Alshamsi<sup>14</sup>, Derek C. Angus<sup>15</sup>, Yaseen Arabi<sup>16</sup>, Luciano Azevedo<sup>17</sup>, Richard Beale<sup>9</sup>, Gregory Beilman<sup>18</sup>, Emilie Belley-Cote<sup>19</sup>, Lisa Burry<sup>20</sup>, Maurizio Cecconi<sup>21,22</sup>, John Centofanti<sup>23</sup>, Angel Coz Yataco<sup>24</sup>, Jan De Waele<sup>25</sup>, R. Phillip Dellinger<sup>11</sup>, Kent Doi<sup>26</sup>, Bin Du<sup>27</sup>, Elisa Estenssoro<sup>28</sup>, Ricard Ferrer<sup>29</sup>, Charles Gomersall<sup>30</sup>, Carol Hodgson<sup>31</sup>, Morten Hylander Møller<sup>32</sup>, Theodore Iwashyna<sup>33</sup>, Shevin Jacob<sup>34</sup>, Ruth Kleinpell<sup>35</sup>, Michael Klompas<sup>36,37</sup>, Younsuck Koh<sup>38</sup>, Anand Kumar<sup>39</sup>, Arthur Kwizera<sup>40</sup>, Suzana Lobo<sup>41</sup>, Henry Masur<sup>42</sup>, Steven McGloughlin<sup>43</sup>, Sangeeta Mehta<sup>44</sup>, Yatin Mehta<sup>45</sup>, Mervyn Mer<sup>46</sup>, Mark Nunnally<sup>47</sup>, Simon Oczkowski<sup>3</sup>, Tiffany Osborn<sup>48</sup>, Elizabeth Papathanassoglou<sup>49</sup>, Anders Perner<sup>50</sup>, Michael Puskarich<sup>51</sup>, Jason Roberts<sup>52,53,54,55</sup>, William Schweickert<sup>56</sup>, Maureen Seckel<sup>57</sup>, Jonathan Sevransky<sup>5</sup>, Charles L. Sprung<sup>58,59</sup>, Tobias Welte<sup>60</sup>, Janice Zimmerman<sup>61</sup> and Mitchell Levy<sup>62</sup>

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

# Sepsis Screening: The Million Dollar Question

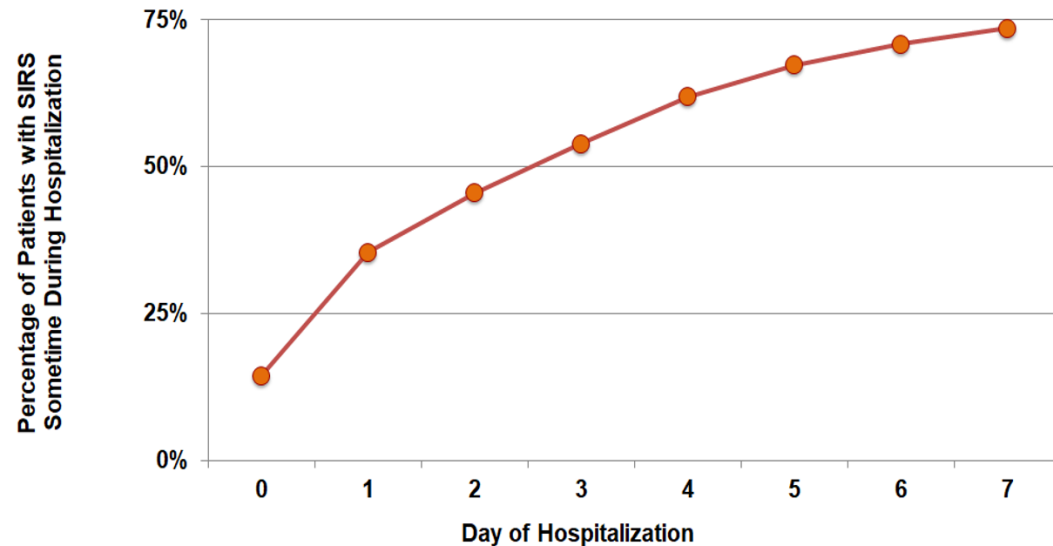
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# Problems with SIRS

## Too Nonspecific

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

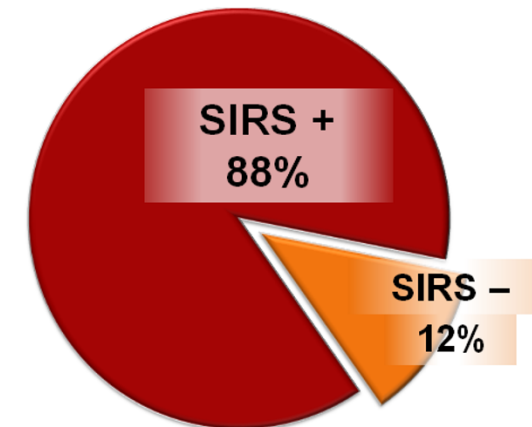


**47% of ward patients met SIRS criteria at least once**

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)

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***“Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection”***

- Eliminated SIRS as part of sepsis definition

**Quick SOFA (qSOFA) proposed for rapid screening 2  
of 3 criteria:**

- **Systolic Blood Pressure  $\leq 100$  mmHg**
  - **Respiratory Rate  $\geq 22$  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

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# How Useful is qSOFA in Undifferentiated Patients?

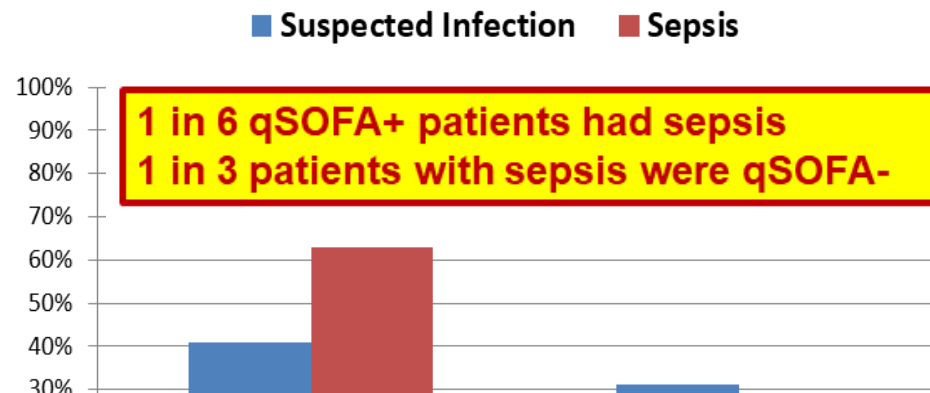
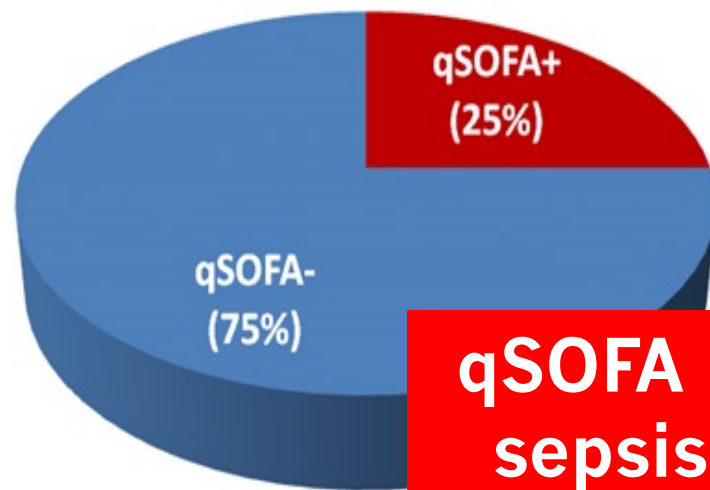
Epidemiology of Quick Sequential Organ Failure Assessment Criteria in Undifferentiated Patients and Associated with Suspected Infection and Sepsis



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**

All Hospitalized Patients on Admission



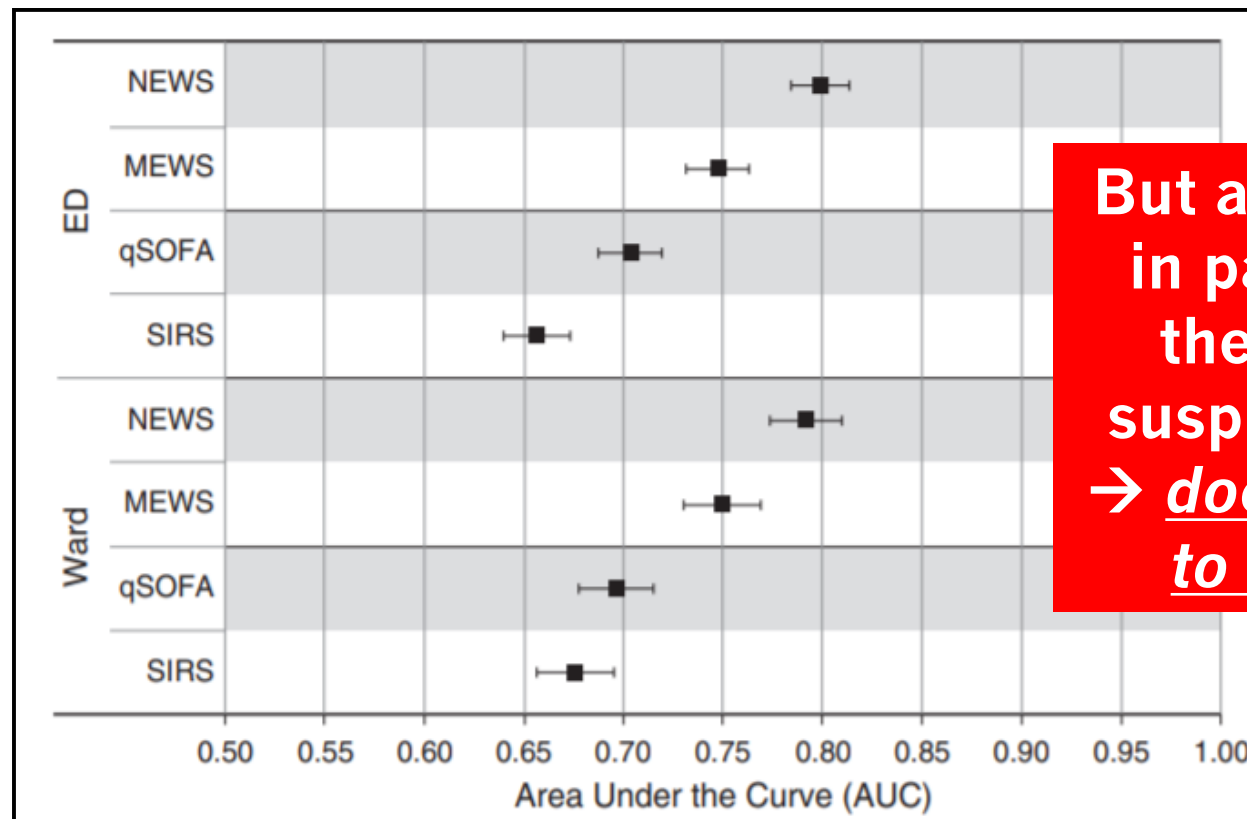
1 in 6 qSOFA+ patients had sepsis  
1 in 3 patients with sepsis were qSOFA-

**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**

# 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**

# Sepsis Screening

## SCREENING FOR PATIENTS WITH SEPSIS AND SEPTIC SHOCK

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



MODERATE

Screening



VERY LOW

Standard operating procedures

### 2016 STATEMENT



*"We **recommend** that hospitals and hospital systems have a performance improvement programme for sepsis including sepsis screening for acutely ill, high risk patients."*

No specific recommendation on what screening tool is best



MODERATE

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

But avoid using qSOFA alone for screening (low sensitivity)







VERY LOW


**3** For adults suspected of having sepsis, we **suggest** measuring blood lactate.



# Initial Fluid Resuscitation



**INITIAL RESUSCITATION**



 **BEST PRACTICE**  **4** Sepsis and septic shock are medical emergencies, and we **recommend** that treatment and resuscitation begin immediately.

  **LOW** **5** For patients with sepsis induced hypoperfusion or septic shock we **suggest** that at least 30 mL/kg of intravenous (IV) crystalloid fluid should be given within the first 3 hours of resuscitation.

**2016 STATEMENT**  
  
"We **recommend** that in the initial resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours."

  **VERY LOW** **6** For adults with sepsis or septic shock, we **suggest** using dynamic measures to guide fluid resuscitation, over physical examination, or static parameters alone.

  **LOW** **7** For adults with sepsis or septic shock, we **suggest** guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate.

  **LOW** **8** For adults with septic shock, we **suggest** using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion.

**30 cc/kg fluid recommendation downgraded**

**Recs informed by ANDROMEDA-SHOCK Trial**

# 30 cc/kg Fluid Bolus

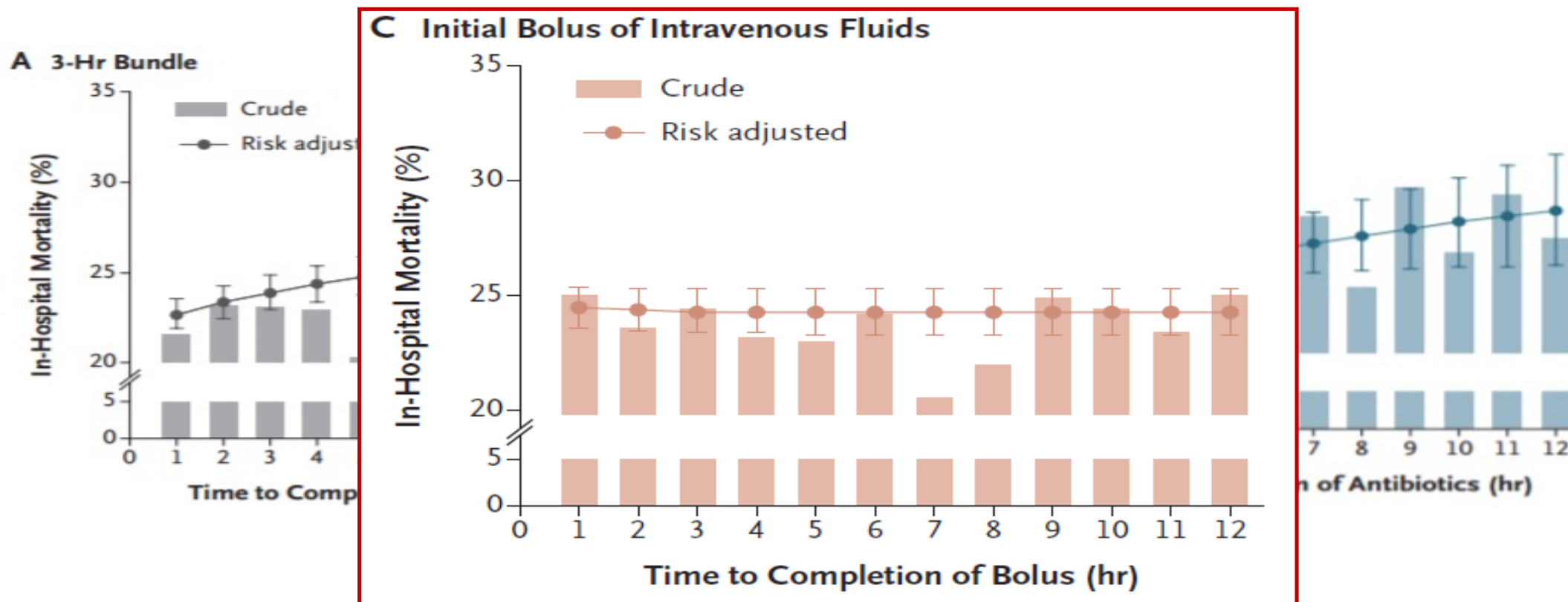
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- 30 cc/kg threshold not rigorously studied in RCTs
- Potential for fluid overload in patients with heart failure, ESRD, respiratory dysfunction
- Increasing evidence about the harmful effects of over-resuscitation and positive fluid balance<sup>1-4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

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**

# Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock

## The ANDROMEDA-SHOCK Randomized Clinical Trial

- 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!***

# 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

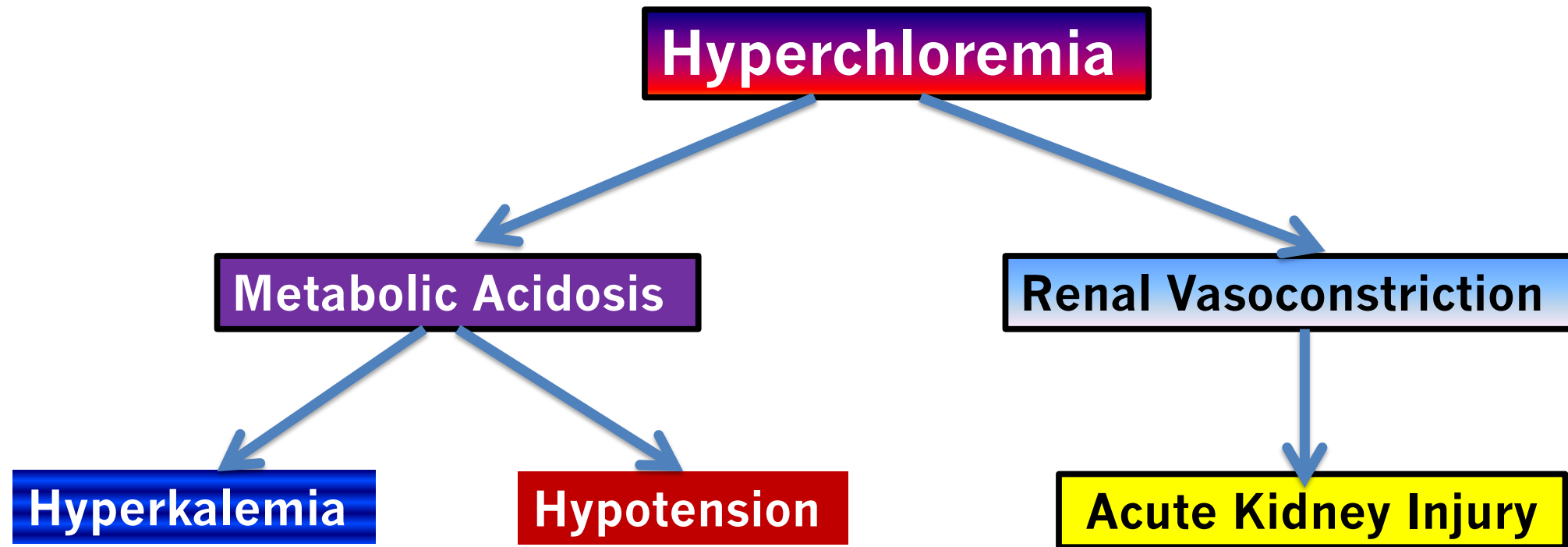


MODERATE

**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

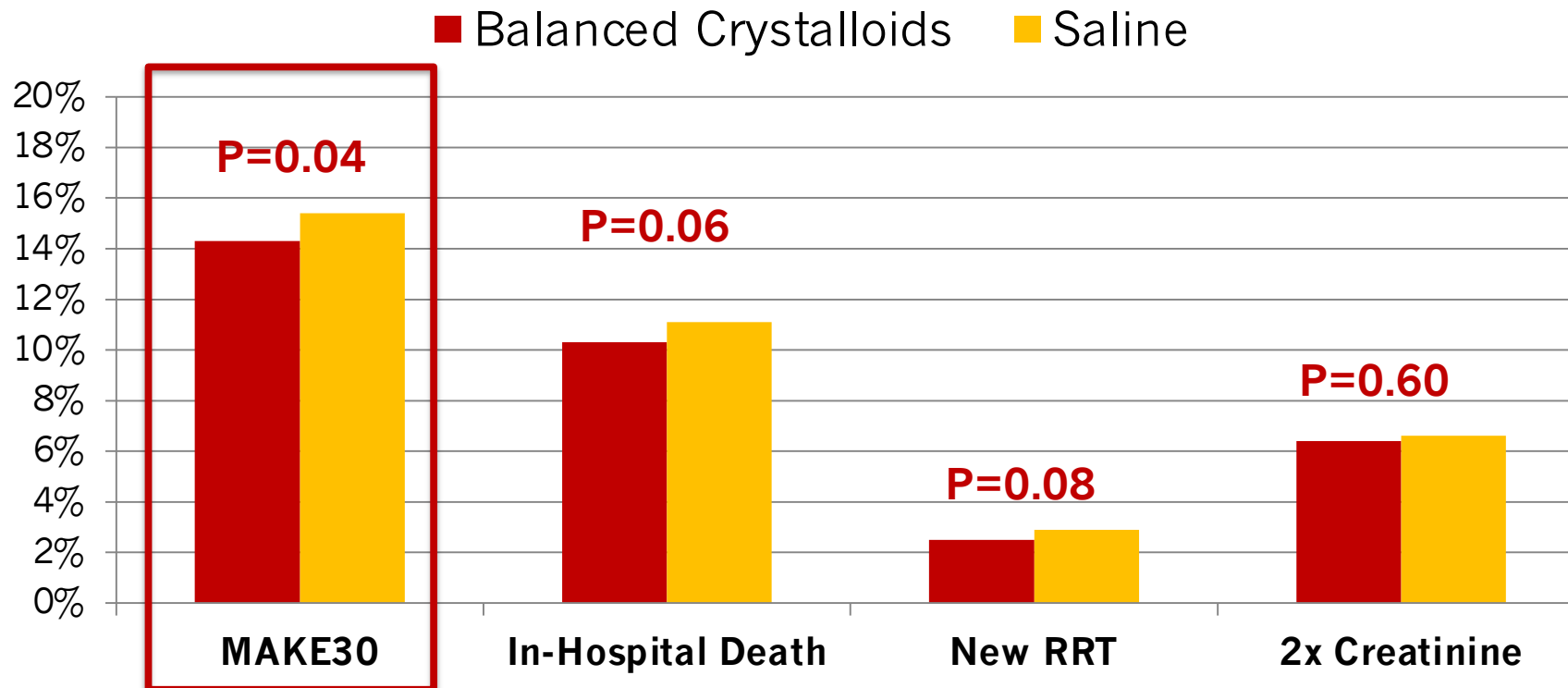
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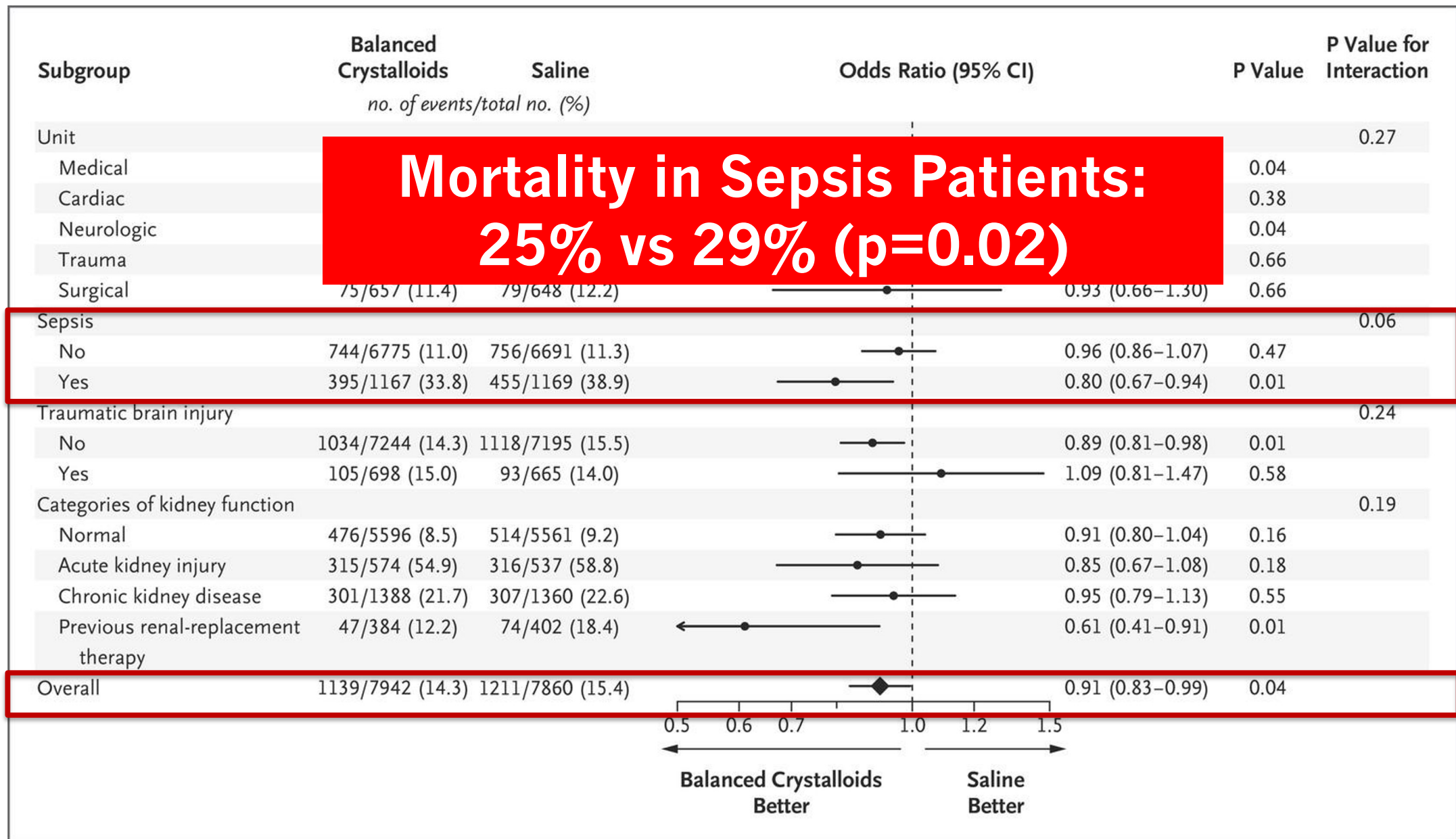
ORIGINAL ARTICLE

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**



# Newer Data: The PLUS Trial

The NEW ENGLAND JOURNAL of MEDICINE

## Balanced Multielectrolyte Solution vs. Saline in Critically Ill Adults

DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

Also no difference in patients with sepsis (~42% of cohort)

Newly initiated renal-replacement therapy

12.7%

Difference, -0.20 percentage points; 95% CI, -2.96 to 2.56

12.9%

Mean maximum increase in serum creatinine

0.41 mg/dl

Difference, 0.01 mg/dl; 95% CI, -0.05 to 0.06

0.41 mg/dl

Use of balanced multielectrolyte solution in critically ill adults did not result in a lower risk of death or acute kidney injury than use of saline.

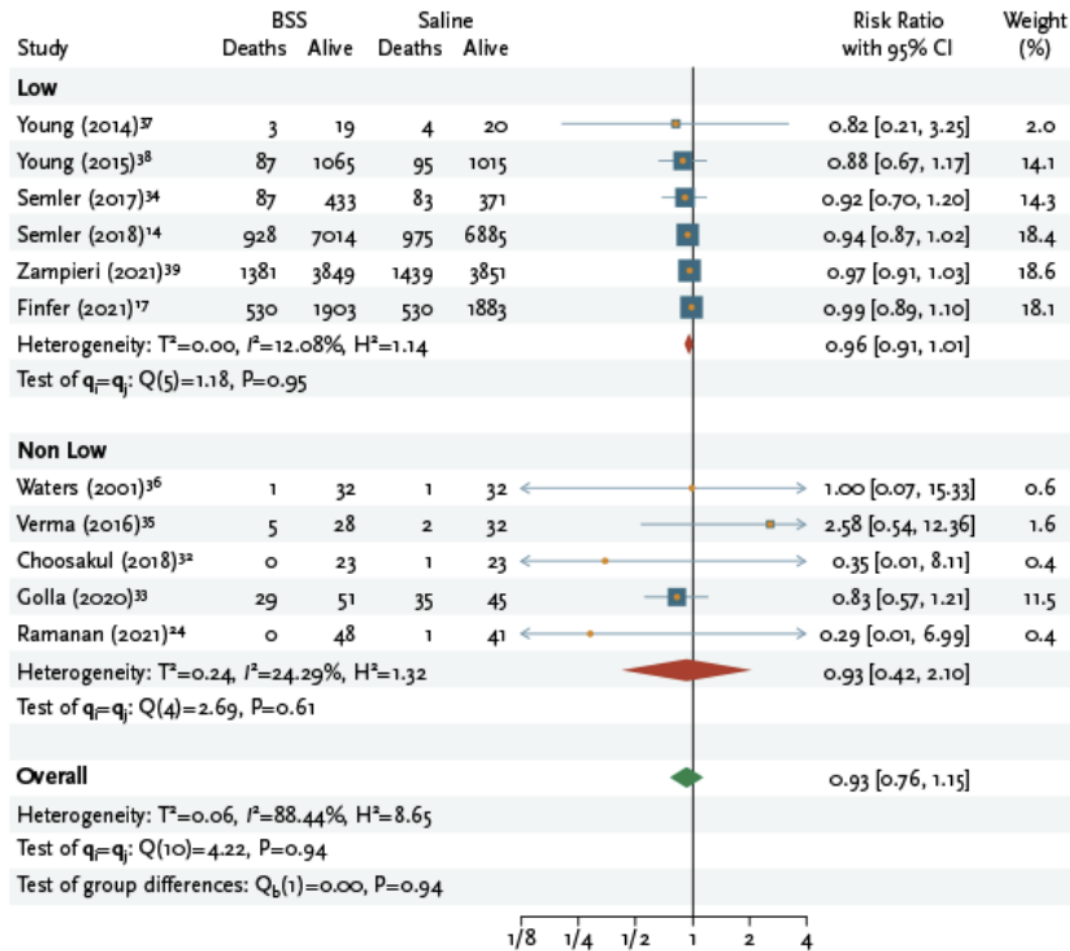
S. Finfer et al. 10.1056/NEJMoa2114464

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

# Updated Meta-Analysis of RCTs

Effect of Balanced Crystalloids Compared with Saline on 90-Day Mortality in Critically Ill Patients by Risk of Bias



**89.5% probability that balanced crystalloids reduce mortality**

➤ **Estimated effect on 90-day mortality ranges from 9% reduction to 1% increase**

**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]**

# MAP Goal and ICU Admission

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## 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)

## ADMISSION TO INTENSIVE CARE



LOW

**10** For adults with sepsis or septic shock who require ICU admission, we **suggest** admitting the patients to the ICU within 6 hours.

# 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

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

➤ **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)**

# Empiric Antimicrobial Therapy

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VERY LOW

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.



VERY LOW

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.



VERY LOW

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.

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# Antibiotic Dosing Strategy

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## NEW EXPLICIT RECOMMENDATION



MODERATE

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.



BEST PRACTICE

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.

No discussion of “push” dosing for beta-lactams, and no high quality clinical data on clinical outcomes of initial bolus for first dose vs prolonged infusion

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# Dosing Beta-Lactams: Prolonged Infusions

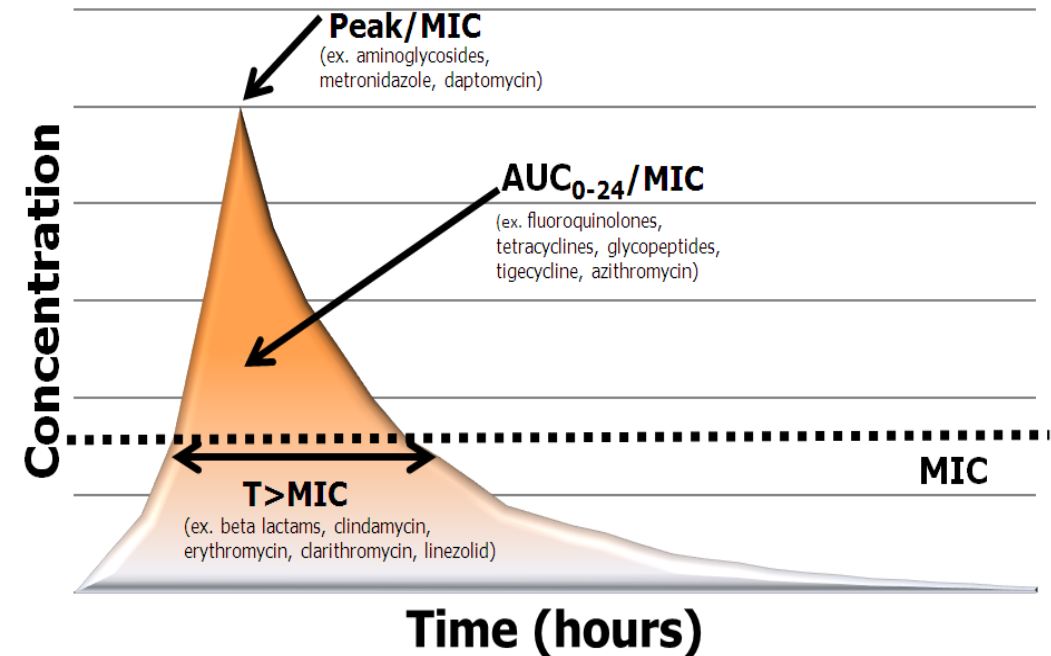
Extended Infusion (3-4 hours) or Continuous Infusion vs Standard Infusion (30 minutes)

➤ 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***



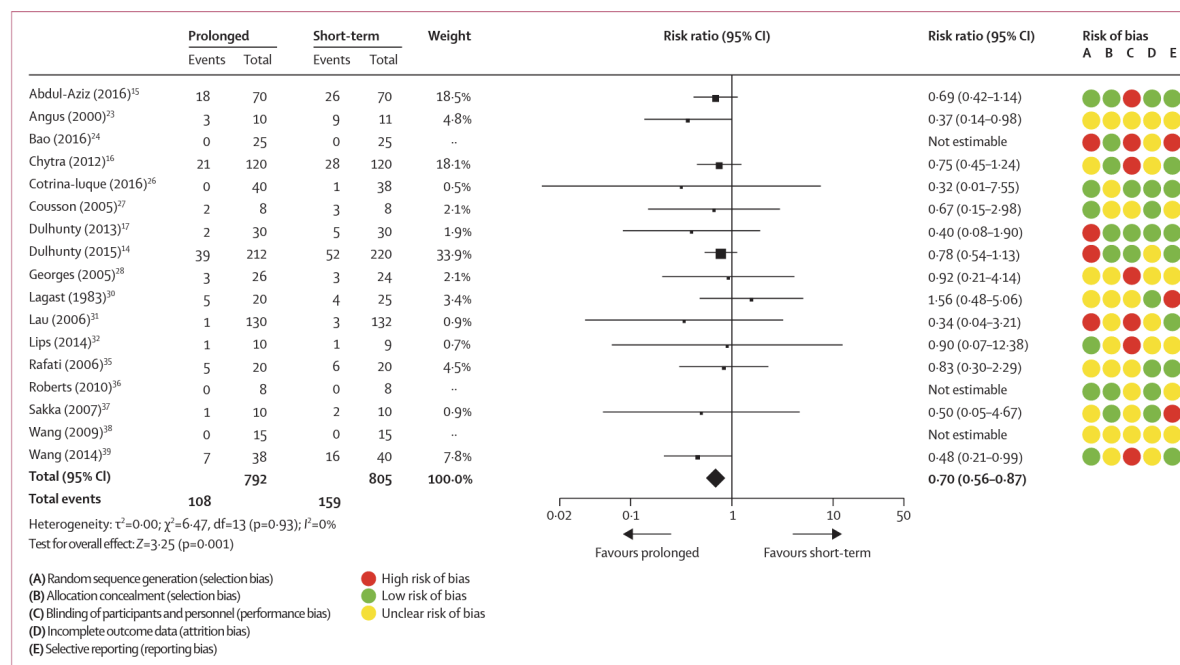
Prolonged infusions most sensible for :

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

# Prolonged versus short-term intravenous infusion of antipseudomonal $\beta$ -lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials

Konstantinos Z Vardakas, Georgios L Voulgaris, Athanasios Maliaros, George Samonis, Matthew E Falagas

## Meta-analysis of 22 RCTs (1876 patients)



**RR for mortality = 0.70  
 [95% CI 0.56-0.87]**

**No heterogeneity or  
 evidence of publication  
 bias**

Figure 2: Forest plot of mortality among patients treated with prolonged versus short-term infusion of antipseudomonal antibiotics. The areas of squares are proportional to the weight given to each study. Risk ratios are the centres of each square. df=degrees of freedom.

# More to Come Soon: The BLING-II Trial

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## Beta-Lactam Infusion Group (BLING) II

Prospective, multinational open phase 3 RCT  
to compare continuous vs intermittent  
infusion in **7,000 critically ill patients with  
sepsis**



# Procalcitonin

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VERY LOW

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.



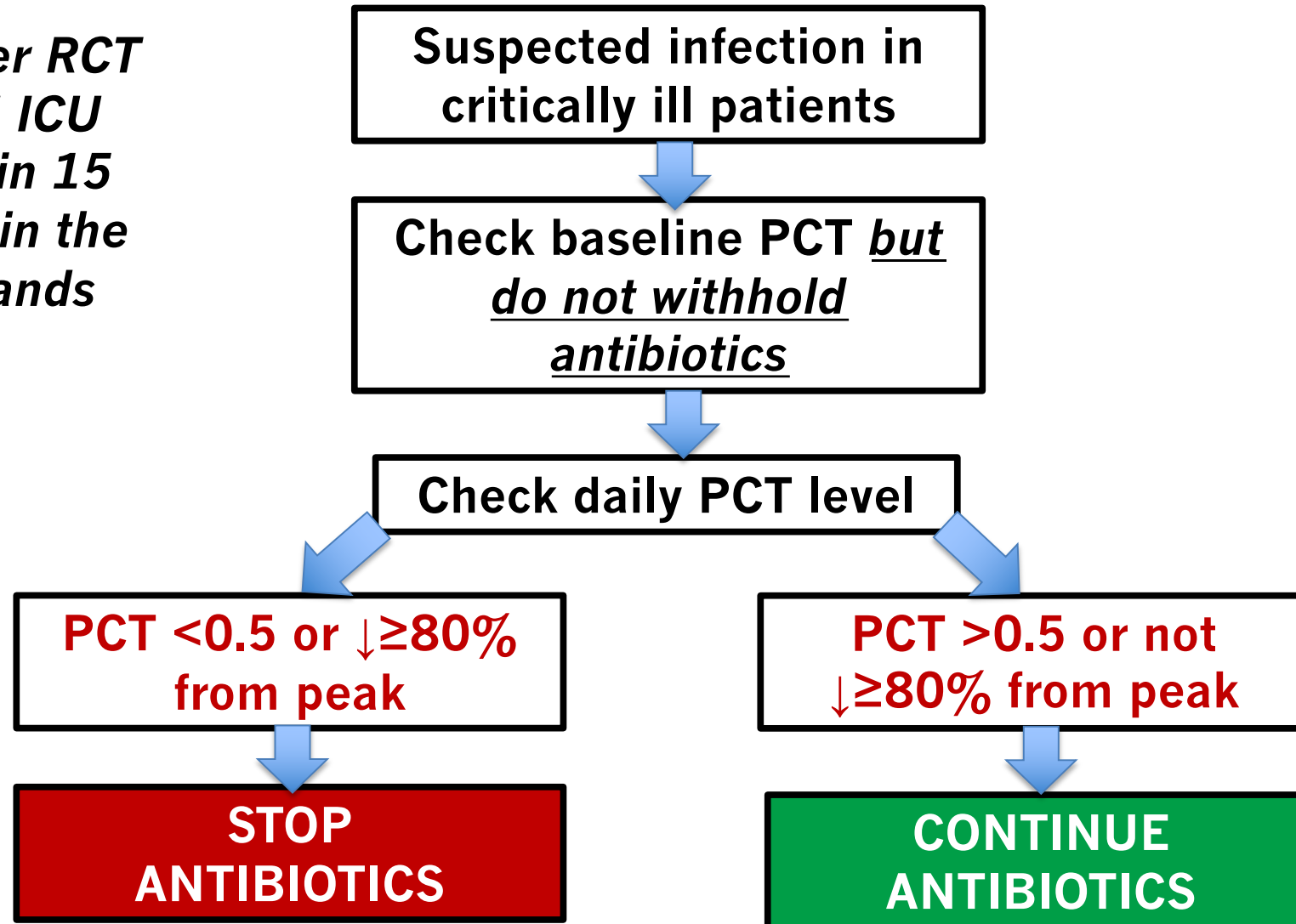
LOW

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.

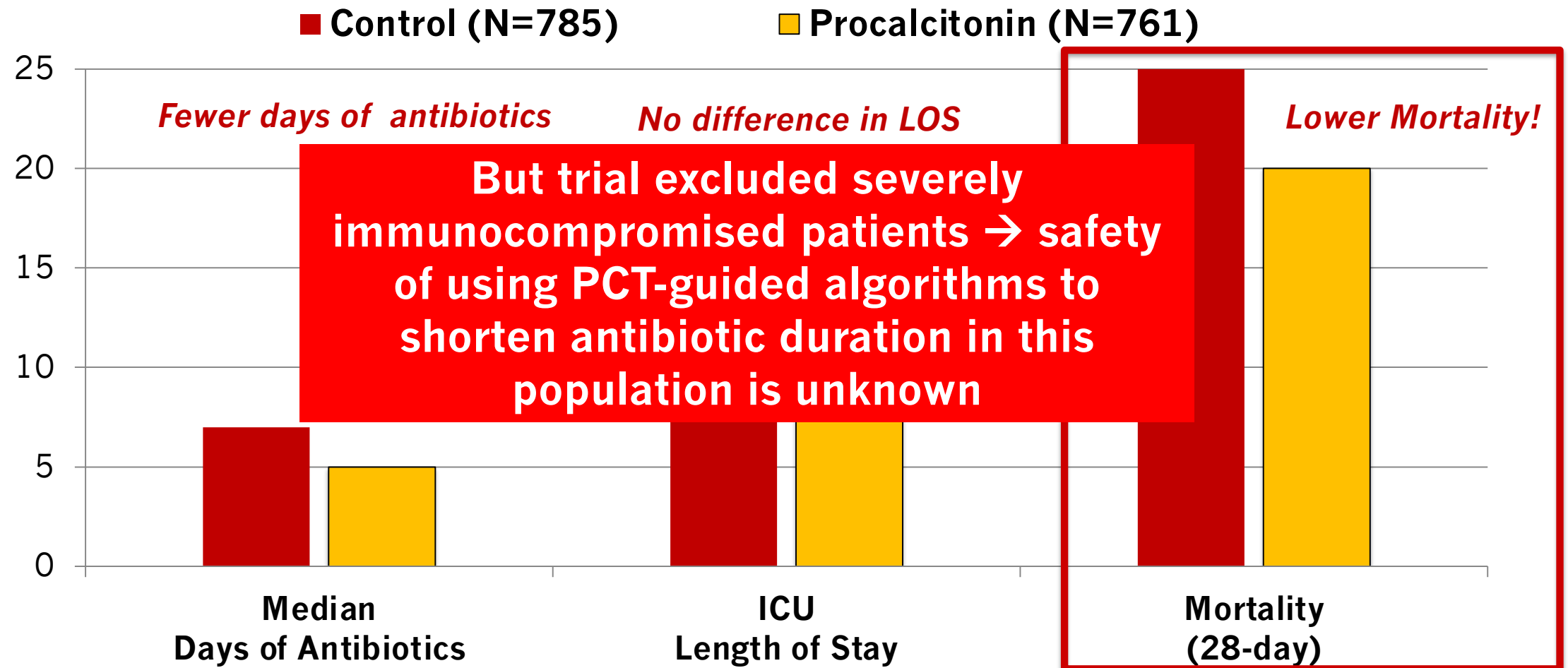
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# SAPS Trial: PCT to Discontinue Antibiotics in the ICU

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



# Procalcitonin in the ICU: SAPS



# Source Control

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**BEST PRACTICE**

**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.



**BEST PRACTICE**

**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**

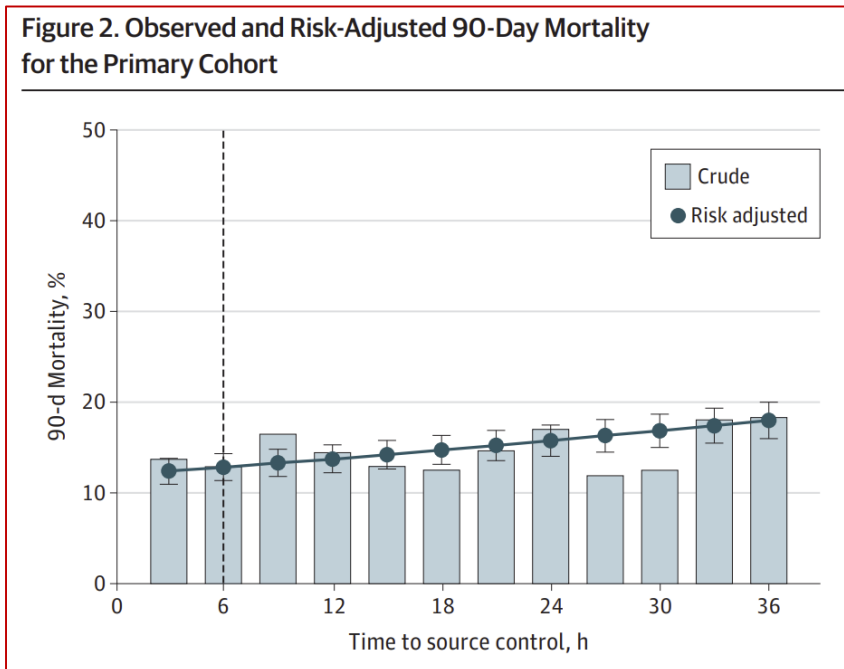
**Limited data on impact of specific time frames of delays**

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# 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**



- **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)**

# Vasopressor Management



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



Dopamine



Vasopressin



Epinephrine



Selepressin



Angiotensin 2

1<sup>st</sup> 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)



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.

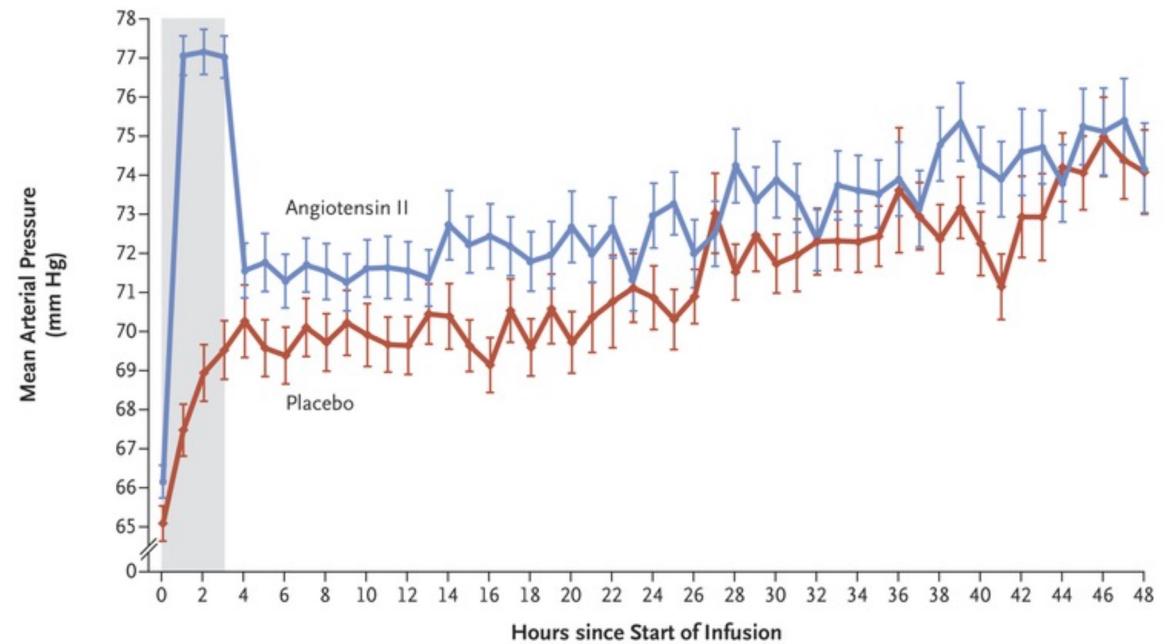


39 For adults with septic shock and inadequate mean arterial pressure levels despite norepinephrine and vasopressin, we **suggest** adding epinephrine.

# 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)

A Mean Arterial Pressure over Time



No. at Risk

Angiotensin II	163	163	159	157	156	152	153	149	150	149	148	149	148	143	140	141	139	139	136	138	136	132	129	128	123
Placebo	158	158	157	153	150	148	145	145	143	143	139	136	136	133	130	131	127	132	125	126	128	122	122	119	112

# Methylene Blue?

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- Inhibits guanylate cyclase (enzyme that produces cGMP) and nitric oxide → inhibits vascular smooth muscle relaxation
- **Most common use: refractory vasodilatory shock following CP bypass**
- **Very limited evidence for septic shock**
  - 2 small RCTs (n=100) demonstrated increased MAPs but no difference in mortality (underpowered)
- Administered as 1-2 mg/kg IV infusion
- Side effects
  - Interfere with O<sub>2</sub> saturation
  - Serotonin syndrome in patients on serotonin agents (partially MAO inhibitor)
  - Potential methemoglobinemia
  - Blue discoloration of skin, mucous membranes, urine (temporary)
  - Contraindicated with G6PD deficiency (hemolytic anemia)

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

# Peripheral Vasopressors and Fluid Resuscitation

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VERY LOW

**44** For adults with septic shock, we **suggest** starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured.

**New SSC recommendation**



**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.

**CLOVERS trial pending at time of guideline publication**

## 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.”*

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# CLOVERS trial design (PETAL Network)

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## What is the Right Balance Between Early Fluids and Early Vasopressors?

**Trial stopped early for futility**

You will receive either:  
**blood pressure** and then  
a **larger amount of fluids**  
medicine to raise

This is assigned by chance (like

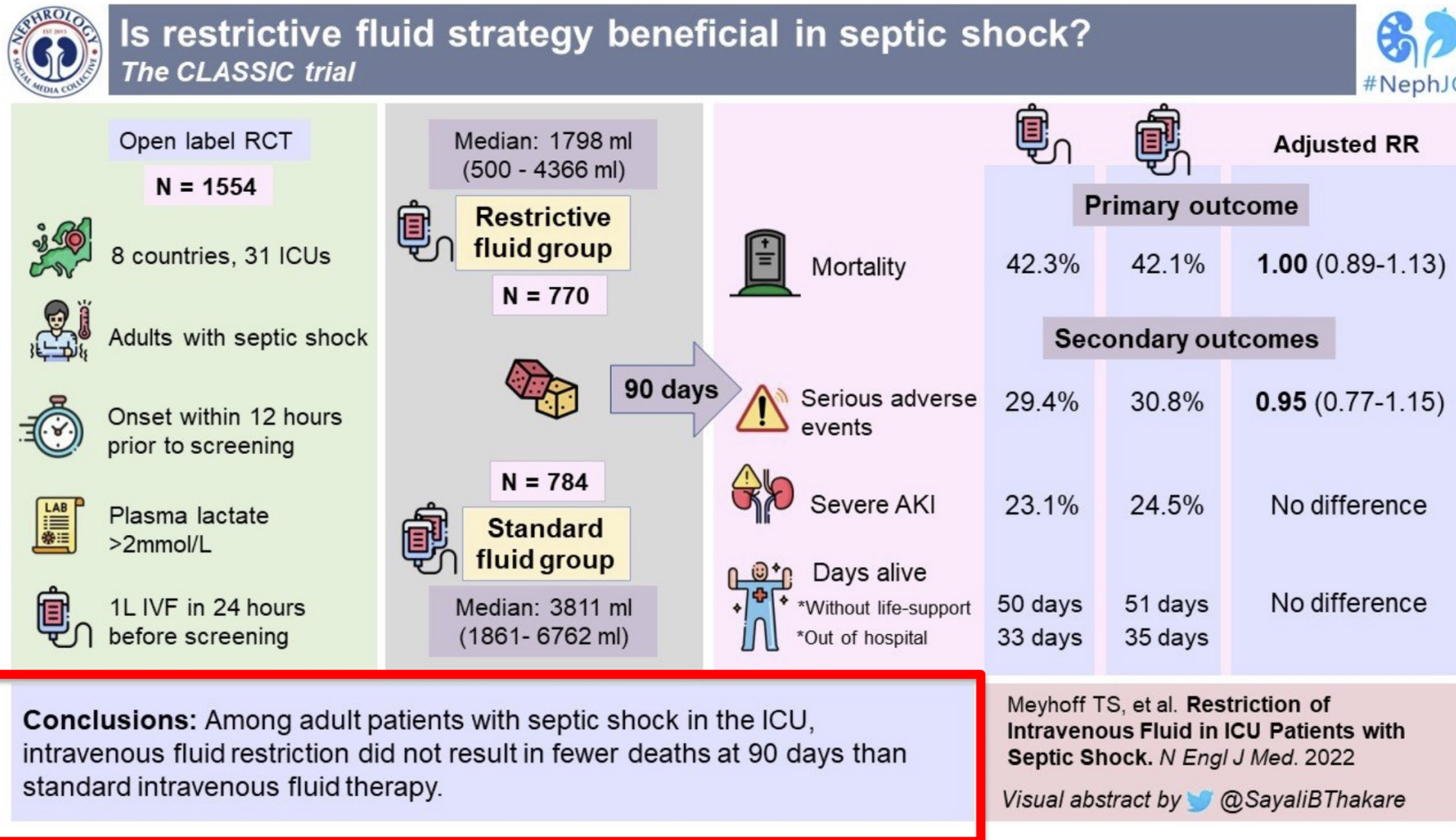
**to Raise Blood Pressure First**

**blood pressure**  
fluids (if needed).  
tube in the vein (IV).

**Fluids First**

group, then **larger amount of fluids FIRST** and  
then medicine to raise **blood pressure** (if needed).  
Both are given through a tube in the vein (IV).

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



# 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,

# Long-Term Outcomes and Goals of Care

## LONG-TERM OUTCOMES AND GOALS OF CARE



BEST PRACTICE

74 For adults with sepsis or septic shock, we **recommend** discussing goals of care and prognosis with patients and families over no such discussion.



LOW

75 For adults with sepsis or septic shock, we **suggest** addressing goals of care early (within 72 hours) over late (72 hours or later).



76 For adults with sepsis or septic shock, there is insufficient evidence to make a recommendation on any specific standardized criterion to trigger goals of care discussion.



BEST PRACTICE

77 For adults with sepsis or septic shock, we **recommend** that the principles of palliative care (which may include palliative care consultation based on clinician judgement) be integrated into the treatment plan, when appropriate, to address patient and family symptoms and suffering.



LOW

78 For adults with sepsis or septic shock, we **suggest against** routine formal palliative care consultation for all patients over palliative care consultation based on clinician judgement.



VERY LOW

79 For adult survivors of sepsis or septic shock and their families, we **suggest** referral to peer support groups over no such referral.



VERY LOW

80 For adults with sepsis or septic shock, we **suggest** using a handoff process of critically important information at transitions of care over no such handoff process.



BEST PRACTICE

82 For adults with sepsis or septic shock and their families, we **recommend** screening for economic and social support (including housing, nutritional, financial, and spiritual support), and make referrals where available to meet these needs.



VERY LOW

83 For adults with sepsis or septic shock and their families, we **suggest** offering written and verbal sepsis education (diagnosis, treatment, and post-ICU/post-sepsis syndrome) prior to hospital discharge and in the follow-up setting.



BEST PRACTICE

84 For adults with sepsis or septic shock and their families, we **recommend** the clinical team provide the opportunity to participate in shared decision making in post-ICU and hospital discharge planning to ensure discharge plans are acceptable and feasible.



VERY LOW

85 For adults with sepsis and septic shock and their families, we **suggest** using a critical care transition programme, compared to usual care, upon transfer to the floor.



BEST PRACTICE

86 For adults with sepsis and septic shock, we **recommend** reconciling medications at both ICU and hospital discharge.



BEST PRACTICE

87 For adult survivors of sepsis and septic shock and their families, we **recommend** including information about the ICU stay, sepsis and related diagnoses, treatments, and common impairments after sepsis in the written and verbal hospital discharge summary.

# Post-Acute Care

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**88** For adults with sepsis or septic shock who developed new impairments, we **recommend** hospital discharge plans include follow-up with clinicians able to support and manage new and long-term sequelae.



**89** For adults with sepsis or septic shock and their families, there is insufficient evidence to make a recommendation on early post-hospital discharge follow-up compared to routine post-hospital discharge follow-up.



**90** For adults with sepsis or septic shock, there is insufficient evidence to make a recommendation for or against early cognitive therapy.



**91** For adult survivors of sepsis or septic shock, we **recommend** assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge.



**92** For adult survivors of sepsis or septic shock, we **suggest** referral to a post-critical illness follow-up programme if available.



**93** For adult survivors of sepsis or septic shock receiving mechanical ventilation for >48hours or an ICU stay of >72 hours, we **suggest** referral to a post-hospital rehabilitation programme.

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# **Time-to-Antibiotics Controversy**

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# 2016 Surviving Sepsis Campaign Guidelines

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- **“We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within one hour for both sepsis and septic shock**
  - *Strong recommendation, moderate quality of evidence*
  - *Grade applies to both conditions*

# SSC 2018 “Hour-1” Bundle Update

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**All elements of the bundle should be initiated  
*within 1 hour* of ED presentation**

Surviving Sepsis Campaign

**BUNDLE**

**HOUR-1 BUNDLE: INITIAL RESUSCITATION FOR SEPSIS AND SEPTIC SHOCK:**

- 1) Measure lactate level.\*
- 2) Obtain blood cultures before administering antibiotics.
- 3) Administer broad-spectrum antibiotics.
- 4) Begin rapid administration of 30mL/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  $\geq 65$  mm Hg.

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

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# Sepsis vs Other Emergent Conditions

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- Easy to recognize: Severe trauma
  - Rapid and accurate biomarker: Myocardial infarction
  - Highly accurate imaging tests: Stroke
- **But none of this is true for sepsis**
- **~1/3<sup>rd</sup> of patients initially treated for sepsis probably do not have bacterial infections**

# Lessons from the Past? The CMS CAP Measure

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- 2002: CMS implemented the **Community-Acquired Pneumonia measure** requiring antibiotic administration **within 4 hours** of ED arrival
  - Based on retrospective analyses showing better outcomes with faster time-to-antibiotics in patients with pneumonia discharge diagnoses
- **But when the rule was applied prospectively and clinicians had to deal with differentiating pneumonia from other syndromes...**

Meehan, *JAMA* 1997; 273:2080-4

Houck, *Arch Intern Med* 2004; 164:637-44

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# Consequences of CAP Antibiotic Mandate

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- **Rise in misdiagnosis and inappropriate antibiotics**
  - 55% of ED physicians admitted they would prescribe antibiotics to patients in order to meet measure
- **No change in mortality rates** for patients with pneumonia
- **Reports of nosocomial *C.difficile* outbreaks** associated with intensive CAP treatment guidelines
  - ***Concern: Sepsis is even more complicated and heterogeneous than pneumonia***

Meterskiy, *Chest* 2006; 130:16–21

Welker, *Arch Intern Med* 2008;168:351-356

Nicks, *Acad Emerg Med* 2009; 16:184–187

Quattromani, *Acad Emerg Med* 2011; 18:496–503

Polgreen, *ICHE* 2007; 28:212-4

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# Increased Antibiotic Use with SEP-1

Impact of SEP-1 on broad-spectrum combination antibiotic therapy in the



*Clinical Infectious Diseases*

MAJOR ARTICLE



Annals of Internal Medicine

ORIGINAL RESEARCH

JAMA  
Network

**...without clear beneficial impact on  
sepsis-associated mortality rates**

Original In

Association Between Implementation of the Severe Sepsis and Septic Shock Early Management Bundle Performance Measure and Outcomes in Patients With Suspected Sepsis in US Hospitals

Chanu Rhee, MD, MPH; Tingting Yu, PhD; Rui Wang, PhD; Sameer S. Kadri, MD, MSc; David Fram, BA; Huai-Chun Chen, PhD; Michael Klompas, MD, MPH; for the CDC Prevention Epicenters Program

Miller, *Am J Emerg Med* 2020; 38:2570-2573

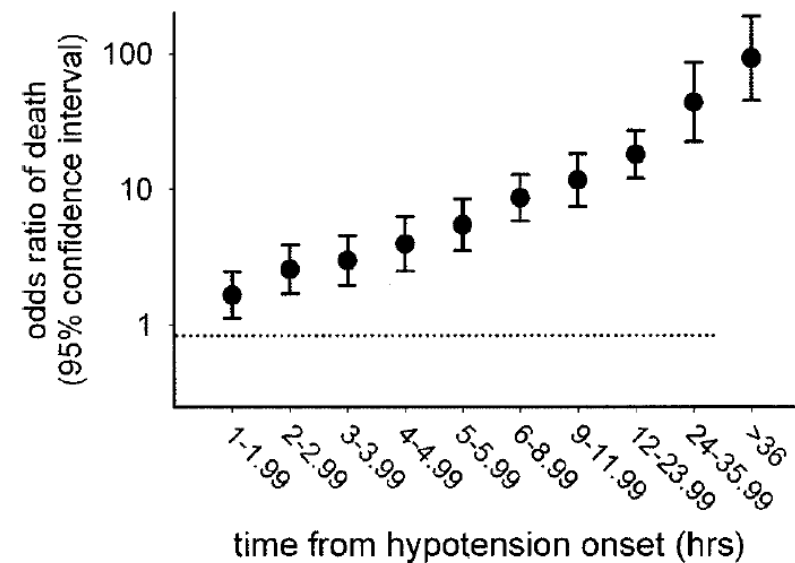
Pakyz, *Clin Infect Dis* 2021; 72:556-565

Barbash, *Ann Intern Med* 2021; 174:927-935

Rhee, *JAMA Netw Open* 2021; 4(12):e2138596

# First Frequency Cited Sepsis Time-to-Antibiotic Study

*Every hour delay in antibiotics associated with an 8% absolute decrease in survival*



**But the cohort included 2,154 patients with septic shock who received antibiotics after the onset of persistent or recurrent hypotension**

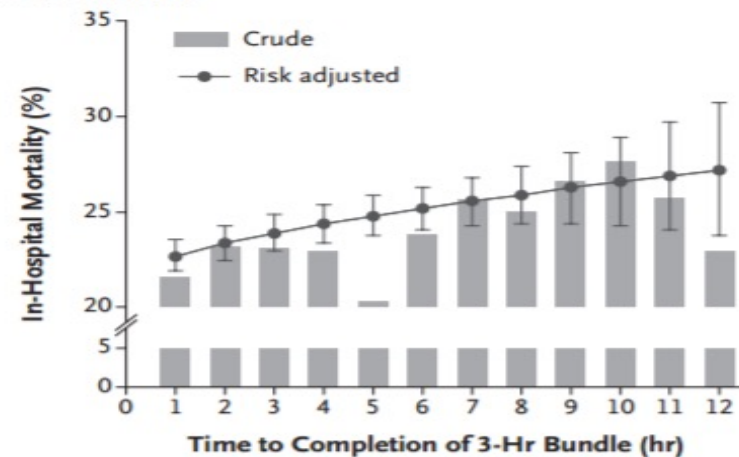
**Does this apply to sepsis without shock?**

ORIGINAL ARTICLE

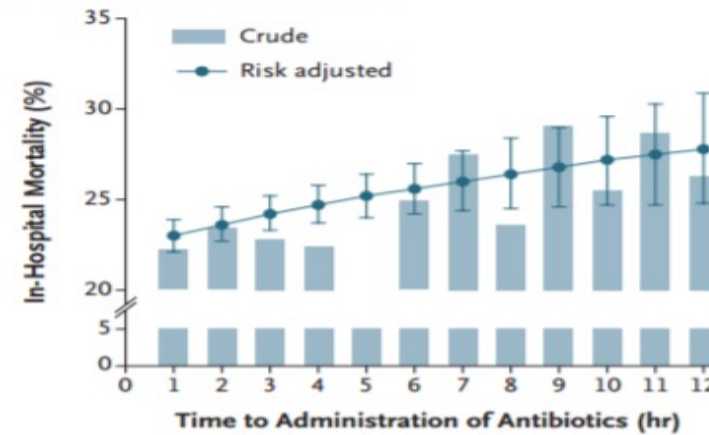
# Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

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

A 3-Hr Bundle



B Administration of Antibiotics

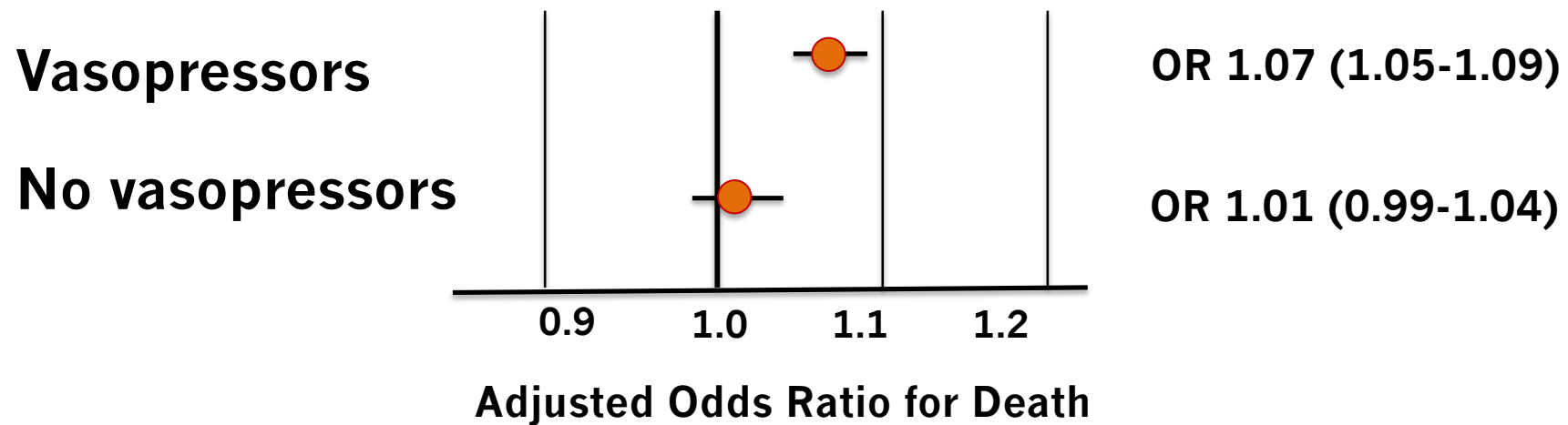


**Each hour delay in bundle completion associated with 4% increase in odds of death (driven by delays in antibiotics)**

# But Mortality Benefit Only Seen in Septic Shock

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## New York State



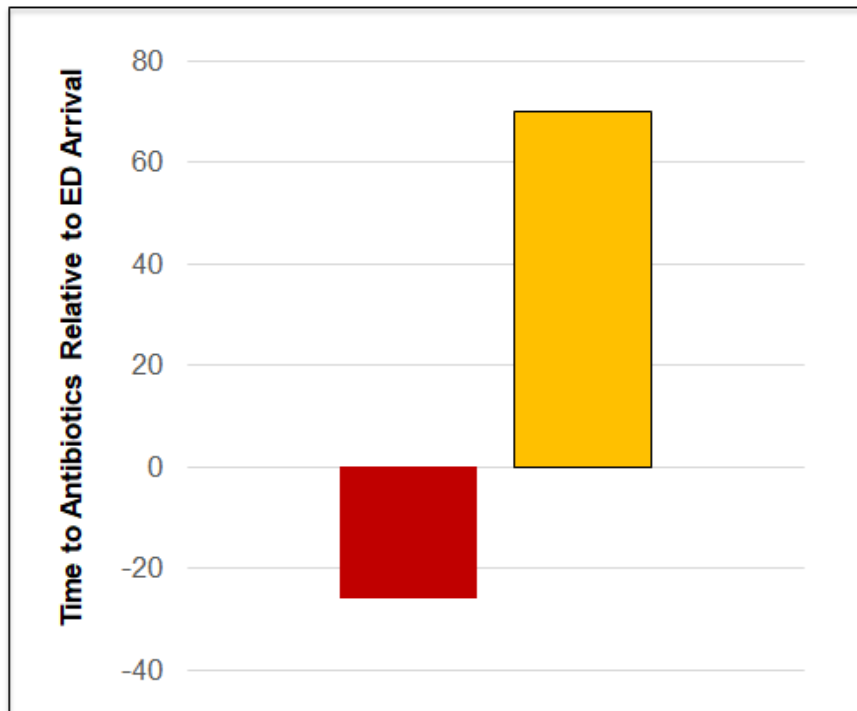
# The PHANTASi Trial: Antibiotics in the Ambulance for Sepsis

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*2,698 patients with sepsis treated in the ambulance (early antibiotics) versus ED (usual care) in the Netherlands*

■ Early Antibiotics      ■ Usual Care

*Antibiotics given ~96mins earlier...*



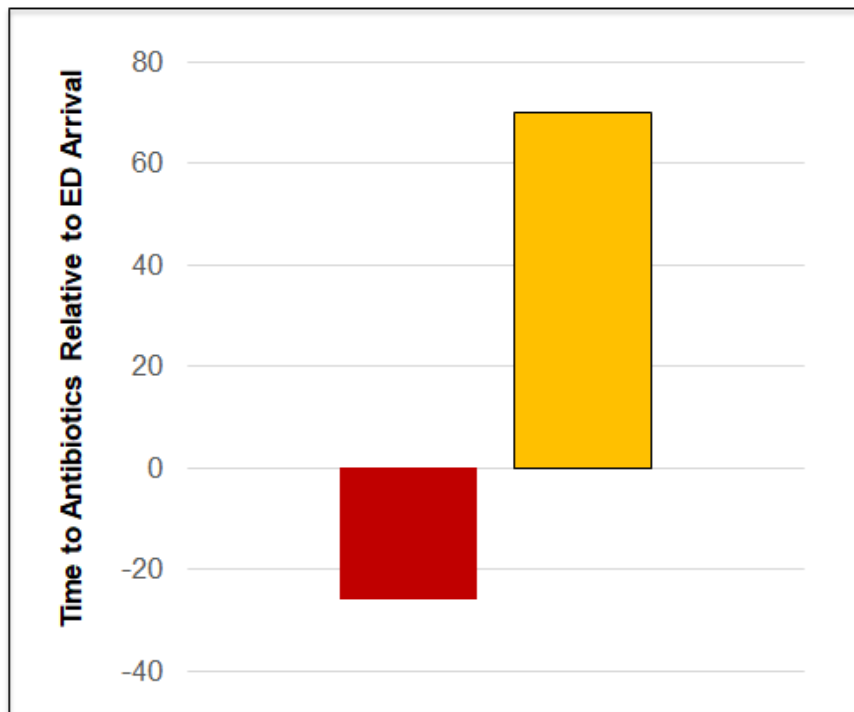
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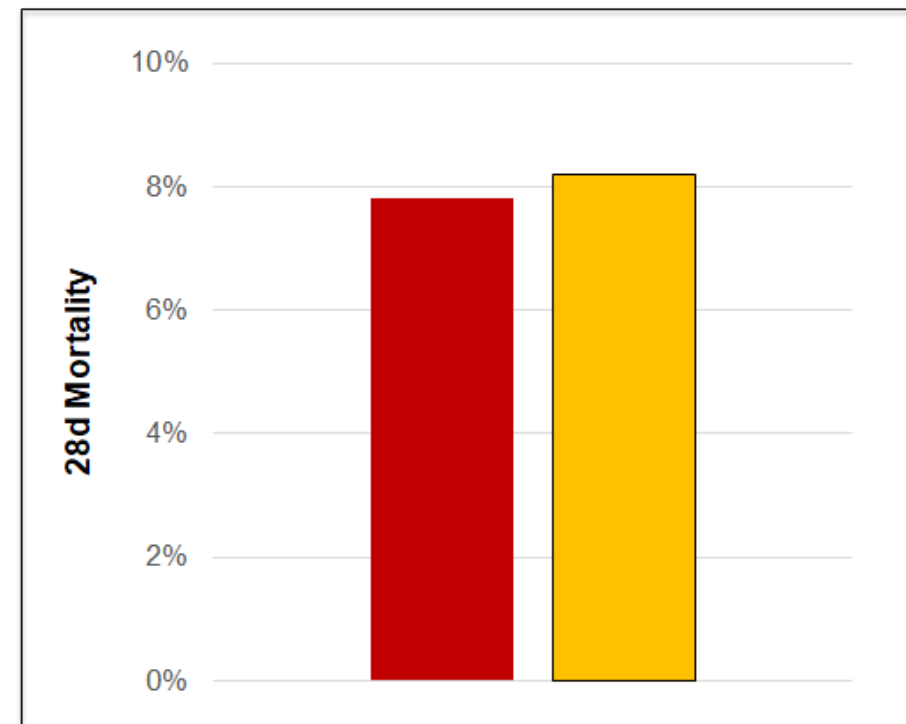
■ Early Antibiotics

■ Usual Care

*Antibiotics given ~96mins earlier...*



*...but no difference in mortality*



# The PHANTASi Trial: Antibiotics in the Ambulance for Sepsis

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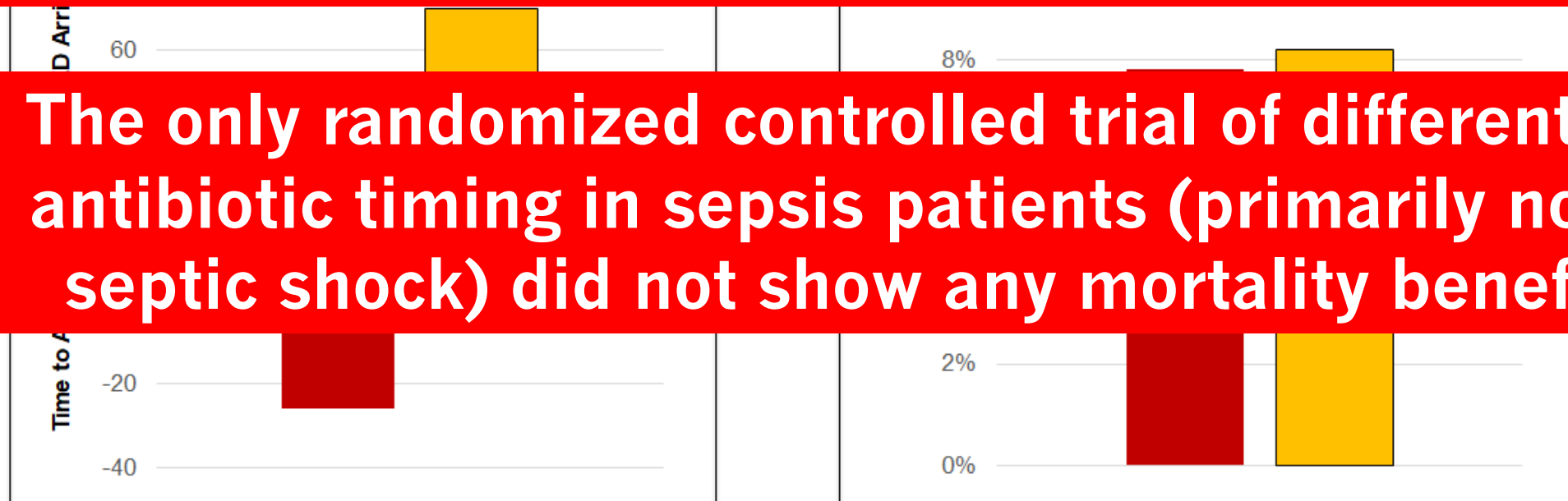
■ Early Antibiotics      ■ Usual Care

*Antibiotics given ~96mins earlier...*

*...but no difference in mortality*

**However, <4% of the patients had septic shock**

➤ **The only randomized controlled trial of differential antibiotic timing in sepsis patients (primarily non-septic shock) did not show any mortality benefit**



# Implications: Urgency of Antibiotics

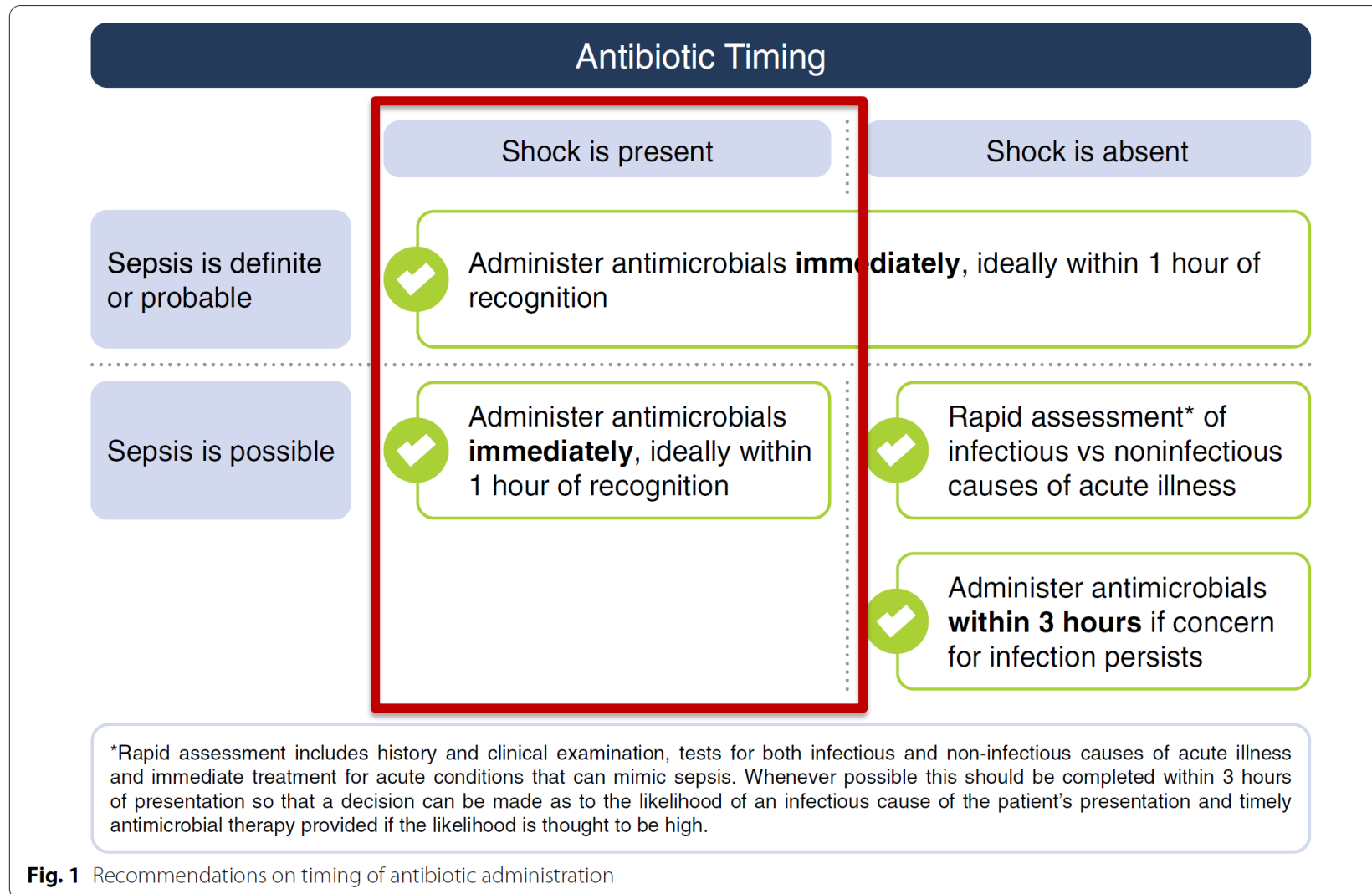
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- If infection is merely one of several potential diagnoses, and the patient is **NOT in shock** or critically ill
  - Clinicians can in many cases take some time to **initiate a workup**
  - Even a **few short hours** can often provide more diagnostic clarity
    - And potentially **more thoughtful choice of antibiotics**
- **Antibiotics should given promptly if:**
  - Infection is clear-cut or probable, OR
  - Patient is in shock with **possible** infection
    - **All agree there is no margin for error in patients with shock**

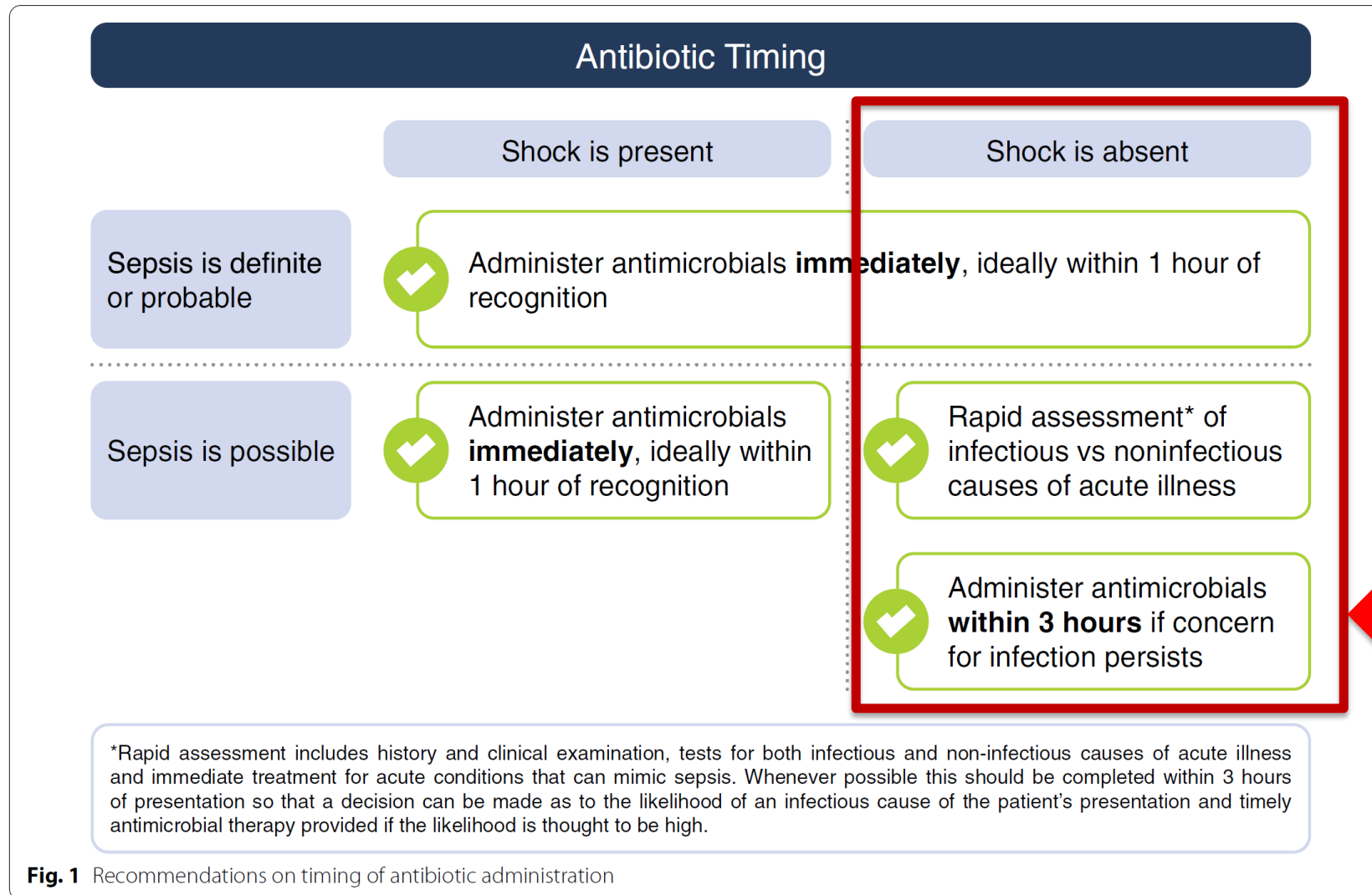
**Margin for error is also lower in patients who are immunocompromised or have other severe comorbidities**

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# 2021 Surviving Sepsis Campaign Guidelines



# 2021 Surviving Sepsis Campaign Guidelines



# Summary and Take-Home Points

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- **Updates from 2021 vs 2016 SSC guidelines**
    - qSOFA as a stand-alone sepsis screening tool discouraged
    - 30 cc/kg fluid recommendation downgraded
    - Limitations of lactate-guided resuscitation acknowledged (equivalent to capillary refill time)
    - Preference for balanced crystalloids over normal saline
    - Preference for peripheral vasopressors over delaying care for CVC
    - Similar recommendations on MAP targets (65 mmHg), vasopressor choices (NE → vasopressin), procalcitonin use (mainly to de-escalate/stop antibiotics on the back end), corticosteroids (refractory shock)
    - Recommendation for extended infusion beta-lactams after initial dose
    - New focus on goals of care and post-acute management
    - **More nuance in time-to-antibiotic recommendations → stratify by presence of shock and level of suspicion of infection (1 vs 3 hours)**
      - **Informed by ongoing controversies and reappraisal of strength of evidence supporting time-to-antibiotics in sepsis vs septic shock**
-



# Thank You!

## For all the lives we touch

Clean hands protect our patients.

Always perform hand hygiene  
and help others do the same.



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