Sepsis Update 2021: Incidence, Mortality and Bundle Science Update

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ADVANCING NURSING THROUGH KNOWLEDGE & INNOVATION

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DISCLOSURES FOR KATHLEEN VOLLMAN

- Consultant-Michigan Hospital Association Keystone Center
- Subject matter expert HRET: CAUTI, CLABSI, HAPI, Sepsis, Safety culture for HRET
- Consultant and speaker bureau:
  - Stryker Sage
  - Potrero Medical
  - La Jolla Pharmaceutical
  - Baxter Healthcare

Objectives

- Determine the impact sepsis has on mortality, location of disposition in long range economic impact
- Examine any new evidence on the bundles and implementation

Polling Question

- Who is with us today?
  - Quality coordinator
  - Sepsis coordinator
  - CMO, CNO, CEO
  - Unit manager
  - Physicians/APP’s
  - Frontline nurses
  - Nurse educators
  - Clinical nurse specialist

Sepsis is a Public Health Problem

- Affects >1.7 million Americans per year
- 3rd leading cause of death in the US
- 1-week mortality for Medicare beneficiaries with sepsis is 18% vs 4.1% with no sepsis
- Sepsis occurs in just 10% of U.S. hospital patients, but it contributes to as many as half of all hospital deaths
- $41.5 billion spent on sepsis inpatient care and skilled nursing for Medicare beneficiaries in 2018
- 87% of all adult sepsis cases begin outside the hospital

> 700 people die each day from sepsis in the U.S.

Rhee C, et al. *JAMA.* 2017;318(13):1241-1249.
Angus DC, et al.. *Crit Care Med* 2001;29:1303-10.
Buchman TG, et al. Crit Care Med. 2020;48(3):276-288.
Novosad SA, et al. CDC Morbidity and Mortality Weekly Report., 2016;65(33):864-869
Buchman TG, et al. Crit Care Med. 2020;48(3):276-288

Sepsis is the body's response to infection.

Sepsis develops when the immune system fails to limit an infection and vital organ function is compromised.

The rise in inpatient admission rates and counts is proportional across all severities of sepsis. The rate of hospital acquired sepsis ("not present on admission") declined.

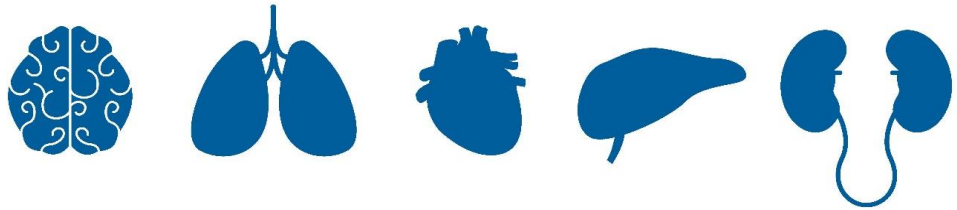
The sepsis event not only predicted higher mortality, but also a poorer quality of life with fewer returning to their family home (57% versus, 80% for non-sepsis admissions) 6 months following a sepsis inpatient admission

The Burdens Of SEPSIS

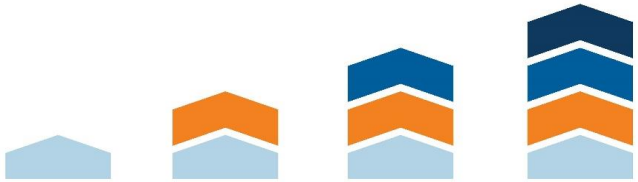
Sepsis is the most costly of inpatient diagnoses.

More than **1.7 million** Americans develop sepsis annually. More than a quarter million die from sepsis.

Source : https://www.cdc.gov/sepsis/datareports/index.html



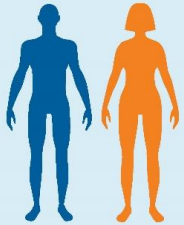
Medicare spent more than $41.5 billion on sepsis inpatient admissions and subsequent skilled nursing facility care in 2018.

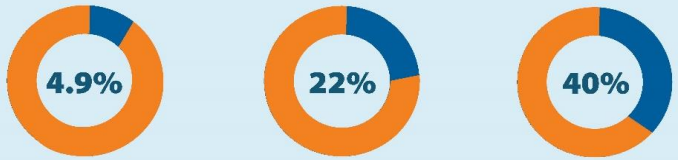


A contemporary rough-order of magnitude estimate of the minimum cost of sepsis in 2019 is in excess of **$62 billion**.

- It does **NOT** include doctor bills.
- It does **NOT** include costs of subsequent outpatient care.
- It does **NOT** include economic losses.
- It does **NOT** include care delivered through federal health systems

Sepsis inpatient admissions rates (per million beneficiaries) rose even faster than the Medicare beneficiary population. In 2018, the count of sepsis inpatient admissions was ~65% greater than it was in 2012





Rate of Growth from 2012 to 2018

The cost of sepsis inpatient admission is steadily declining, and even though the study shows improvement in survival with each passing year, the number of beneficiaries and their rates of sepsis inpatient stays is overwhelming.

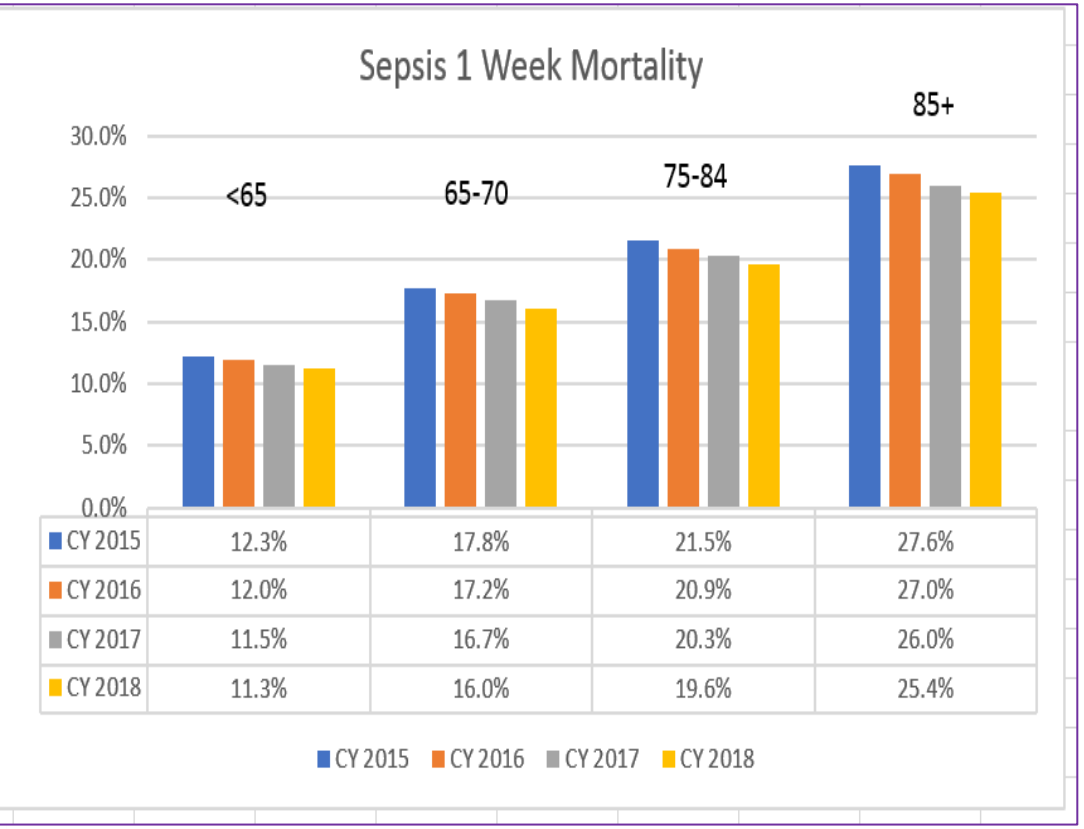
This study presents the most comprehensive analysis of paid Medicare Claims via the Centers for the Medicare & Medicaid Services Data Link Project to provide contemporary estimates of the burden, cost and mortality associated with acute inpatient Medicare beneficiaries admission for sepsis.

Data from Buchman TG, Simpson SQ, Sciarretta KL, et al: *Crit Care Med 2020*

ccmjournal.org
#CritCareMed

Sepsis Admissions and Mortality for Medicare Beneficiaries

Over the 7-year study interval, the rate of sepsis admissions increased by 50%.

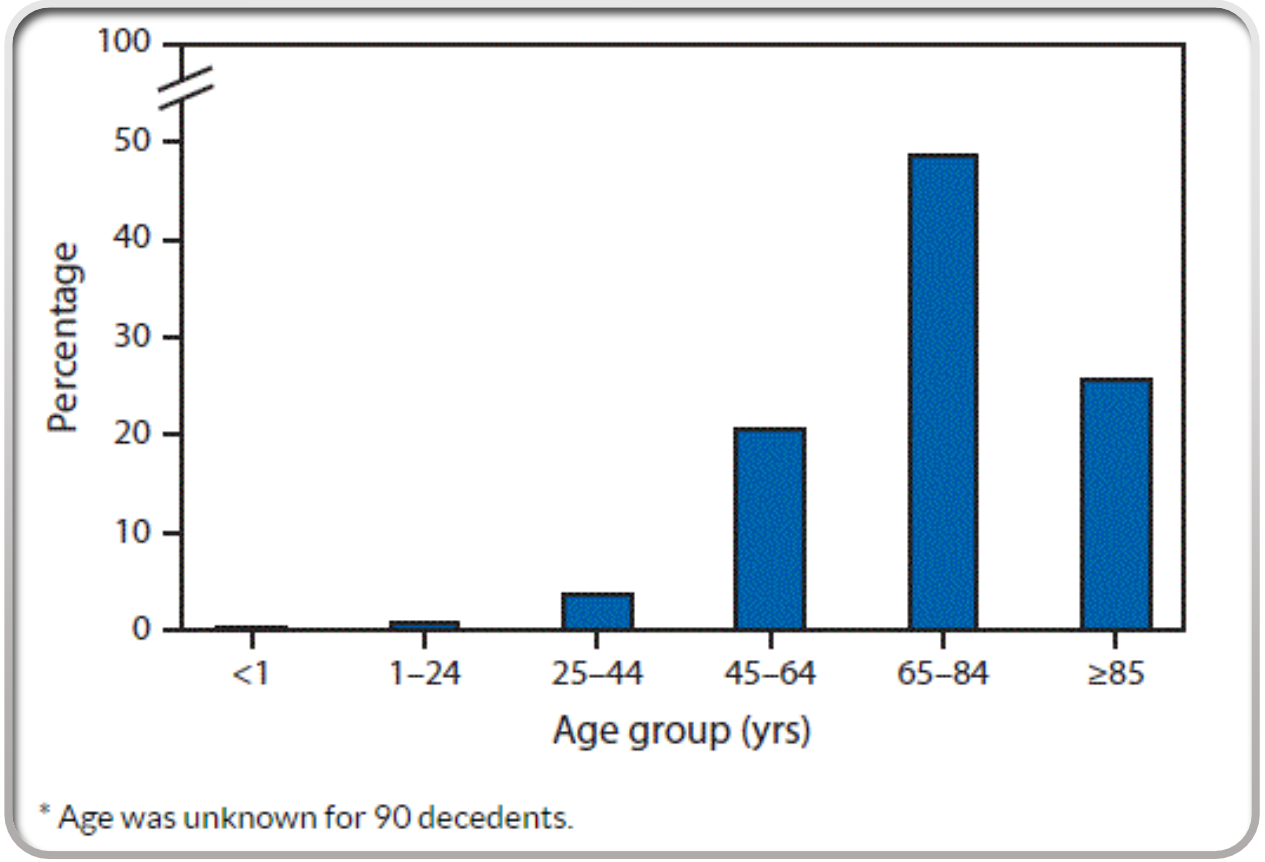


Mortality after hospital discharge is high

- The one-week mortality after discharge among Medicare beneficiaries for
  - Septic shock 40.6%
  - Severe sepsis 15.3%
  - Unspecified sepsis is 11%.
- 6-month after discharge (CY 2018), Medicare beneficiaries mortality rate;
  - septic shock 60%
  - severe sepsis 36%
  - unspecified sepsis 30.9%.
- This high mortality rate continues at 1 and 3 years post initial sepsis hospitalization.

Buchman TG, et al. Crit Care Med. 2020;48(3):276-288, Supplement

Sepsis Deaths by Age Group

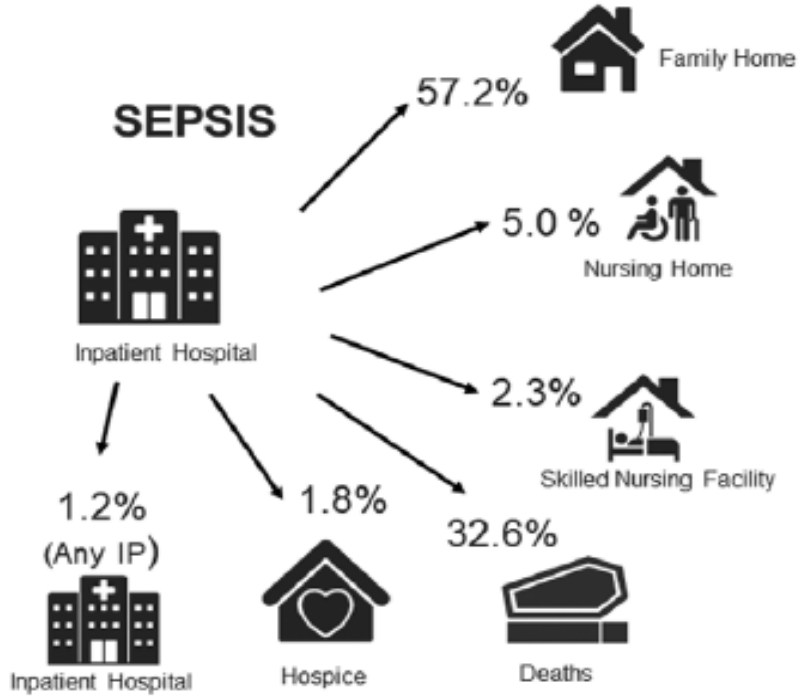


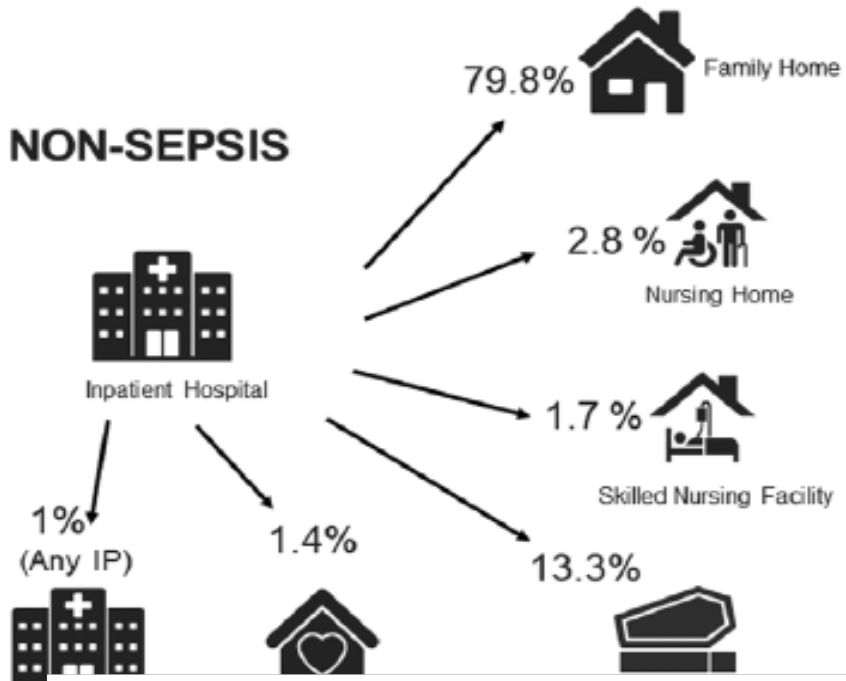
- **Sepsis Deaths by Age Group**

  (N = 2,470,666) based on death certificate data, by age groups* — United States, 1999–2014

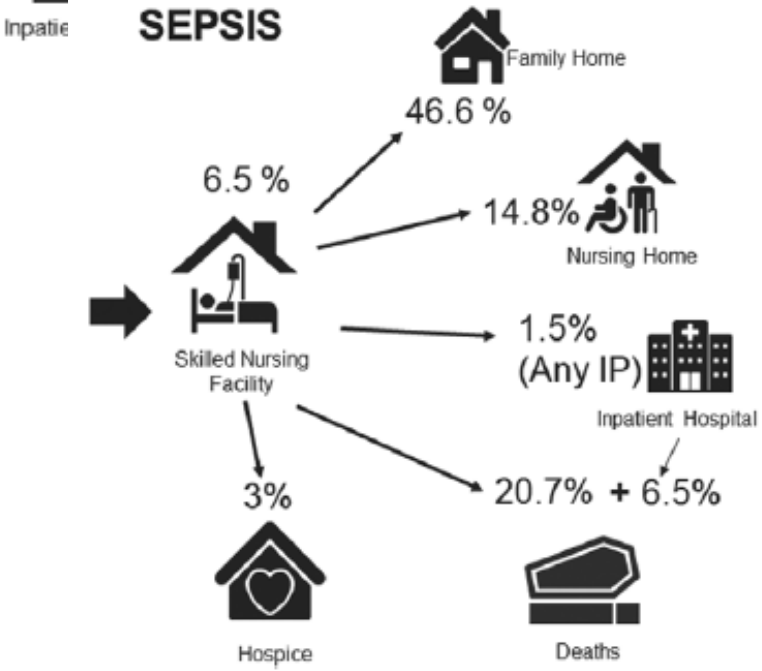
Epstein L, Dantes R, Magill S, Fiore A. Varying Estimates of Sepsis Mortality Using Death Certificates and Administrative Codes — United States, 1999–2014. MMWR Morb Mortal Wkly Rep 2016;65:342–345. DOI: http://dx.doi.org/10.15585/mmwr.mm6513a2

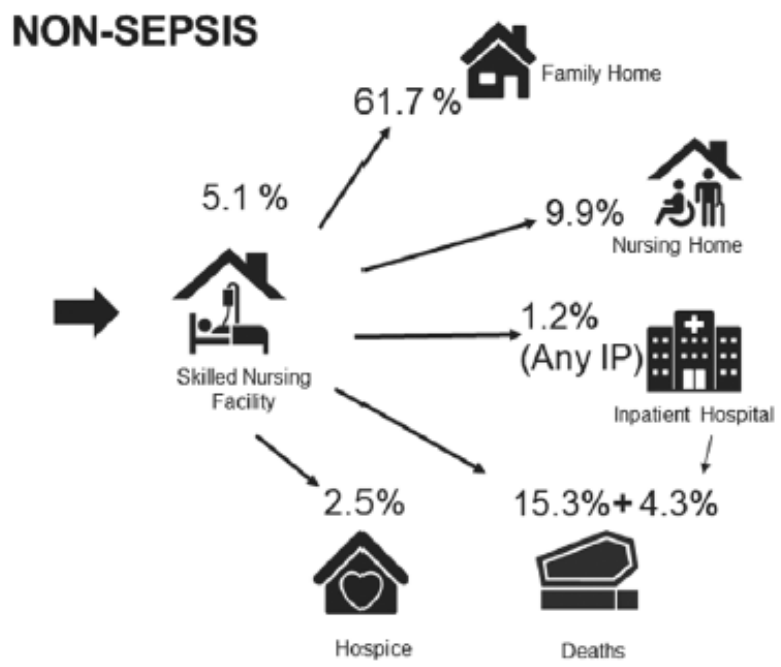
Medicare Beneficences



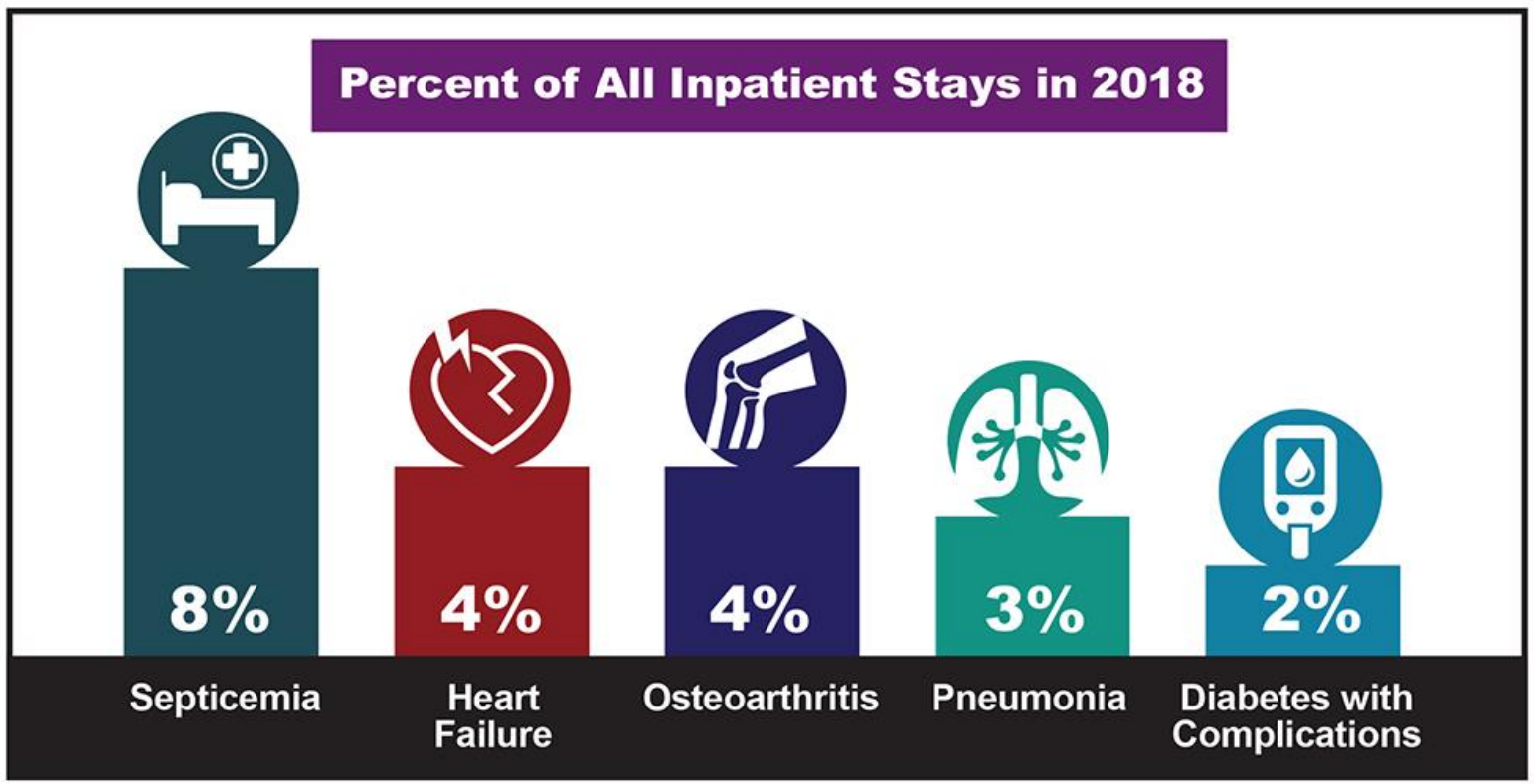


Initial Sepsis sent to Skilled Facility from Hospital





Most Prevalent Conditions Requiring Hospitalization



Source: AHRQ, Healthcare Cost and Utilization Project Statistical Brief #277: *Most Frequent Principal Diagnoses for Inpatient Stays in U.S. Hospitals, 2018.* https://www.hcup-us.ahrq.gov/reports/statbriefs/sb277-Top-Reasons-Hospital-Stays-2018.jsp

HCUP Data Partners can be found at: www.hcup-us.ahrq.gov/partners.jsp

Common Causes of Hospitalization Adults aged 85 and over: U.S.

First-listed diagnosis	2000	2005	2010	Percent change[1] (2000 to 2010)
	Rate of hospitalization per 1,000 population			
Congestive heart failure	48	47	43	−9.5
Pneumonia	51	52	34	−32.8
Urinary tract infection	19	24	30	+55.9
Septicemia	15	18	28	+84.8
Stroke	37	27	28	−25.0
Hip fracture	28	23	21	−25.4

[1]Percent change for each diagnosis is significant from 2000 through 2010 ($p < 0.05$).

NOTE: First-listed diagnosis is considered to be the main cause or reason for the hospitalization. The diagnoses were chosen because they were the top six first-listed diagnoses in 2010.

SOURCE: CDC/NCHS, National Hospital Discharge Survey, 2000–2010.

Levant S, Chari K, DeFrances CJ. Hospitalizations for patients aged 85 and over in the United States, 2000–2010. NCHS data brief, no 182. Hyattsville, MD: National Center for Health Statistics. 2015.

Hospital Readmission is Common

Hospital Readmission and Healthcare Utilization Following Sepsis in Community Settings

Vincent Liu, MD, MS[1*], Xingye Lei, PhD, MA[2], Hallie C. Prescott, MD[3], Patricia Kipnis, PhD[1,2], Theodore J. Iwashyna, MD, PhD[3,4], Gabriel J. Escobar, MD[1]

Frequency, Cost, and Risk Factors of Readmissions Among Severe Sepsis Survivors*

Andrew J. Goodwin, MD, MSCR[1]; David A. Rice, MD[1]; Kit N. Simpson, DrPH[2]; Dee W. Ford, MD, MSCR[1]

Post–Acute Care Use and Hospital Readmission after Sepsis

Tiffanie K. Jones[1,2], Barry D. Fuchs[1,2], Dylan S. Small[3,4], Scott D. Halpern[1,2,4,5,6], Asaf Hanish[7], Craig A. Umscheid[1,4,5,7], Charles A. Baillie[5], Meeta Prasad Kerlin[1,2,4,5], David F. Gaieski[8], and Mark E. Mikkelsen[1,2,5]

Unplanned Readmissions After Hospitalization for Severe Sepsis at Academic Medical Center–Affiliated Hospitals

John P. Donnelly, MSPH[1,2,3]; Samuel F. Hohmann, PhD, MS-HSM[4,5]; Henry E. Wang, MD, MS[1]

Rehospitalizations Following Sepsis: Common and Costly*

Dong W. Chang, MD, MS[1]; Chi-Hong Tseng, PhD[2]; Martin F. Shapiro, MD, PhD[2]

All sepsis survivors have an increased risk for readmission (40% within 90 days for Medicare beneficiaries

Liu, et al. *J HospMed*. 2014.
Jones, et al. *AnnalsATS*. 2015.
Donnelly, et al. *CritCare Med*. 2015.
Goodwin, et al. *CritCare Med*. 2015.
Chang, *et al. CritCare Med*. 2015.

Risk for Readmission

Table. Most Frequent Readmission Diagnoses After Hospitalization for Severe Sepsis

Diagnosis[a]	Severe Sepsis (n = 2617)	
	No. of Survivors	% (95% CI)
Sepsis	167	6.4 (5.4-7.3)
Congestive heart failure	144	5.5 (4.6-6.4)
Pneumonia	92	3.5 (2.8-4.2)
Acute renal failure	87	3.3 (2.6-4.0)
Rehabilitation	74	2.8 (2.2-3.5)
Respiratory failure	65	2.5 (1.9-3.1)
Complication of device, implant, or graft	52	2.0 (1.5-2.5)
COPD exacerbation	49	1.9 (1.4-2.4)
Aspiration pneumonitis	47	1.8 (1.3-2.3)
Urinary tract infection	44	1.7 (1.2-2.2)

- Sepsis survivors have an increased risk for readmission (40% within 90 days for Medicare patients) related to
  - infection/sepsis
  - heart failure
  - renal failure.
- Reconciling medications, infection prevention, management of chronic conditions, and cognitive and functional rehabilitation will aid in preventing readmissions.

Prescott, et al. JAMA. 2015;313(10):1055-1057.
Prescott HC and Angus DC. JAMA. 2018;319(1):62-75.

Sepsis and COVID 19

- Sepsis and COVID-19 overlap and are more similar than different
  - There are semantic in real differences between subsystem COVID-19
  - In both the early and later phases of the disease sepsis in COVID-19 are nearly indistinguishable in clinical treatment goals are the same
- Both conditions require timely and accurate diagnosis in order to provide appropriate treatment
  - Phenotyping an endo typing may be valuable for directing therapy
- SSG for COVID:
  - For severe & critical
    - Systemic Corticosteroids
    - Venous thromboprophylaxis
  - Non-ventilated patients/severe
    - Remdesivir
  - For the acute resuscitation of adults with COVID-19 and shock, we suggest using a conservative over a liberal fluid strategy.

Alhazzani W, et al. Critical Care Medicine: March 2021 - Volume 49 - Issue 3

Post-Sepsis Syndrome

- Describes physical and/or long-term effects that affects up to 50% of people who survive sepsis.
- Longer term effects of sepsis include:
  - Sleep disturbance including insomnia
  - Experiencing nightmares, hallucinations, flashbacks and panic attacks
  - Muscle and joint pains which can be severe and disabling
  - Extreme tiredness and fatigue
  - Inability to concentrate
  - Impaired mental (cognitive) functioning
  - Loss of confidence and self-belief

JAMA. Jan. 2, 2018 Patient Page, Postsepsis Morbidity

Polling Question

- What is your current mortality for septic shock
  1. <20%
  2. >20% < 30%
  3. >30% <40%
  4. >40%

Have We Achieved the Mortality Outcomes our Patients Deserve?

- Septic shock mortality is 38-42%
- Severe sepsis mortality is 28-32%
- Sepsis readmissions are 30-35%

Is it Good Enough?

(CMS data)

What is current and what is new!!

Sepsis Management

TO SAVE LIVES.....

Early identification

Early antibiotics

Early fluid resuscitation

SSC Guidelines
Screening

- 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

Evans L, et al. ICM, 2021

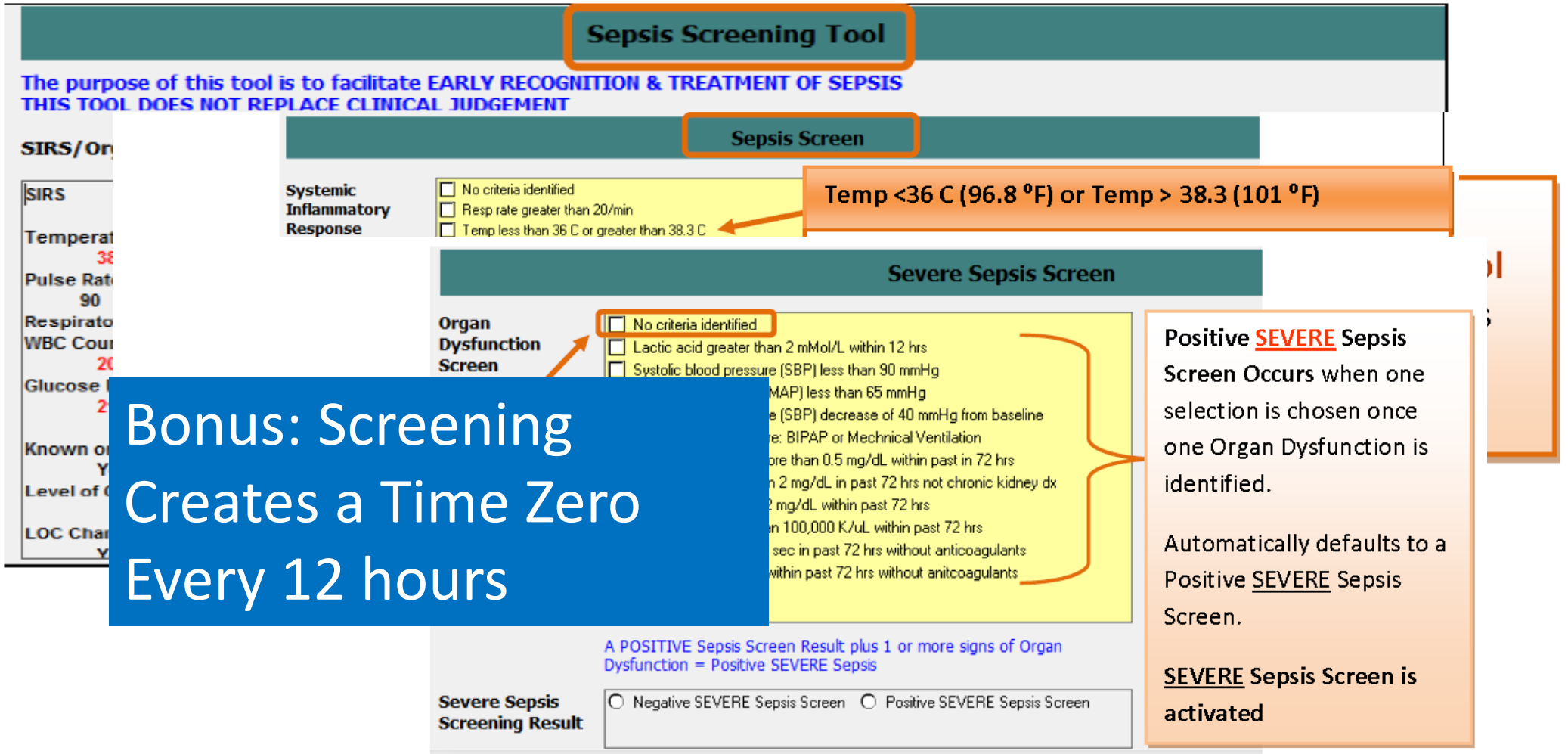
Screening for Severe Sepsis

- **Develop screening process for ED, rapid response team, ICU and house wide** (To screen effectively, it must be part of the nurses' daily routines— i.e., part of admission and shift assessment)
- Education beyond PowerPoint…case studies
- Develop audit process to evaluate compliance and effectiveness
- Ensure screening process has clear "next steps" defined for nursing staff

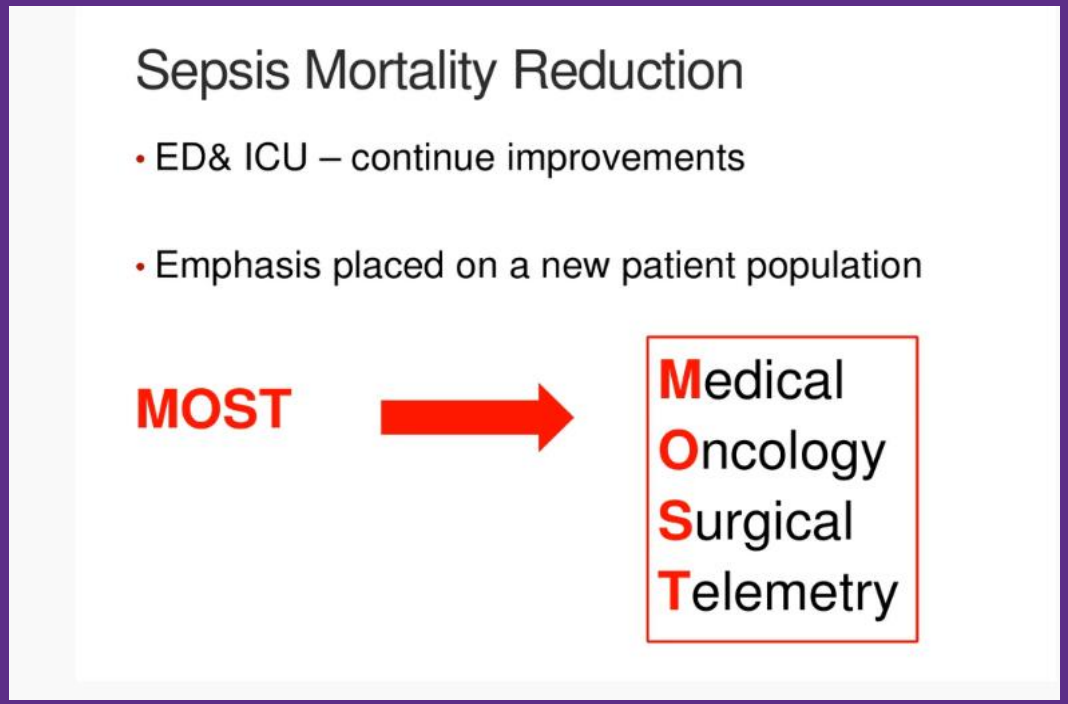
If you don't screen you will miss patients
that may have benefited from the interventions

Dellinger RP, Levy MM, Carlet JM, et al. 2008. Crit Care Med. 2008;36:296-327.
Schorr C. et al Journal of Hospital Medicine, 2016;11:S32-S39

Electronic Routine Screening



7 Hospital Systems: Northern California

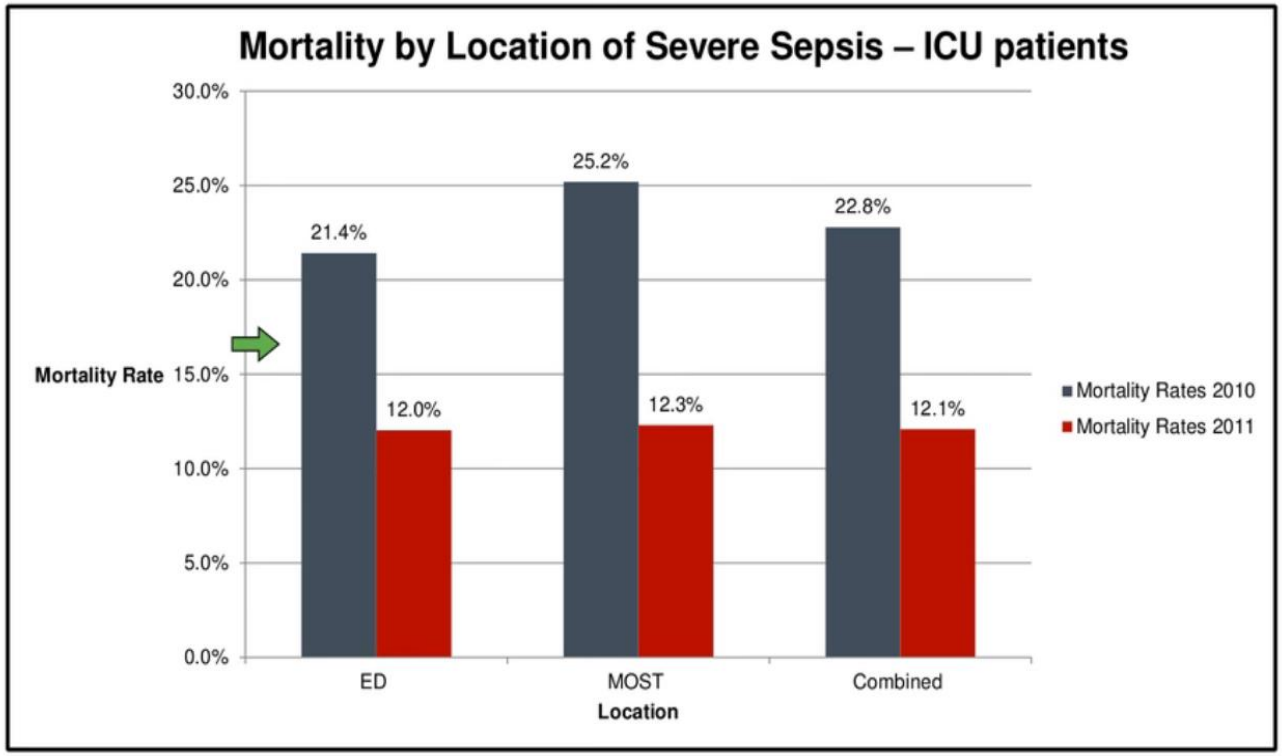


- Introduced screening as part of nurse's shift assessment on the floors
- Already occurring in ED and ICU's
- Started at 1 facility and spread to 6
- Measure impact on bundle compliance and morality

Empowering Nurses for Early Sepsis Recognition accessed on https://www.youtube.com/watch?v=s687VMj6iwo

Outcomes of Screening on the Floors

2010 Baseline and 2011 Outcomes Data



EPIC Sepsis Predication Model: External Validation

- Retrospective cohort study
- 27,697 patients > 18yrs of age who had 38,455 hospitalizations
- ESM (EPCI Sepsis Model) calculated every 15 min
- Evaluate area under the curve at hospital level/prediction horizons of 4, 8, 12, 24hrs

		Time horizons			
Model performance	Hospitalization	24 h	12 h	8 h	4 h
Outcome incidence, %	6.6	0.43	0.29	0.22	0.14
Area under the receiver operating characteristic curve (95% CI)	0.63 (0.62-0.64)	0.72 (0.72-0.72)	0.73 (0.73-0.74)	0.74 (0.74-0.75)	0.76 (0.75-0.76)
Positive predictive value (ESM score ≥6), %	12	2.4	1.7	1.4	0.92
No. needed to evaluate (ESM score ≥6)[a]	15	42	59	73	109

- Alert score ≥6 identified only 7% of patients whose sepsis was missed by the clinician
- EMS did not identify 67% of patients with sepsis despite generating alerts on 18% of all hospitalized patients-causing alarm fatigue

Wong A, et al. JAMA Internal Medicine, 2021; Published online June 2021

Sepsis (Severe Sepsis) and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately

2017 Surviving Sepsis Guidelines Best Practice Statement

Surviving Sepsis Guidelines 2016. Rhodes, A et al. CCM.March 2017 45(3)

SEP-1: Early Management Bundle

To be completed within 3 hours of time of presentation *

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

* *Time of presentation* is defined as the time of earliest chart annotation consistent with all elements of severe sepsis or septic shock, as ascertained through chart review.

Surviving Sepsis Campaign

SEP-1

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to table 1.
7. Re-measure lactate if initial lactate elevated.

SURVIVING SEPSIS CAMPAIGN RECOMMENDATION HIGHLIGHTS

	2012	2016
SEPSIS DEFINITION	Systemic manifestation of infection + suspected infection Severe sepsis: sepsis + organ dysfunction	Life threatening organ dysfunction caused by dysregulated response to infection No severe sepsis category
INITIAL RESUSCITATION	at least 30 cc/kg in first 3 hours Crystalloid fluid (no recommendations on 0.9% NaCl vs balanced solution) Albumin if patients require "substantial" fluids (weak)	
	Protocolized care including CVP ScVO2 Normalize lactate	Use dynamic resuscitation markers (passive leg raise) Target MAP of 65mmHg Reassess hemodynamic status to guide resuscitation Normalize lactate
VASOPRESSORS	target MAP of 65 mmHg 1. Norepinephrine 2. Epinephrine if not at target MAP OR vasopressin to reduce norepinephrine requirement 3. Avoid dopamine in most patinets	
STEROIDS	Only indicated for patients with septic shock refractory to adequate fluids and vasopressors	
ANTIBIOTICS	One or more antibiotics active against presumed pathogen Combination therapy (double coverage) for neutropenic patients and pseudomonas	Initial broad spectrum antibiotics (ex: vancomycin + piperacillin-tazobactam) Against combined therapy (i.e. do not double cover pseudomonas) May use procalcitonin to guide de-escalation
SOURCE CONTROL	Achieve within 12 hours, if feasible	Achieve as soon as medically and logically feasible
VENTILATOR	6 cc/kg tidal volume prone patients with severe ARDS (P/F <150 in 2017 guideliens)	
	no recommendation	Against high frequency oscillatory ventilation (HFOV)
	weak recommendation for noninvasive ventilation in select patients with sepsis induced ARDS	Unable to make recommendation on noninvasive ventilation

Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med [Internet] 2017;1.

Evans L, et al. ICM 2021;

2021
No change from 2016
For patients with sepsis induced hypo perfusion or septic shock **we suggest** that at least 30ML per kilogram of IV crystalloid fluid should be given within the first three hours of resuscitation. **We suggest** using balanced crystalloids instead of normal saline for resuscitation.
No change from 2016 Suggest use of cap refill to assess resuscitation
No change- from 2016 **We suggest** starting vasopressors peripherally to restore MAP rather than delaying initiation till central venous access secured
For adults with septic shock & ongoing requirement for vasopressor **we suggest** using IV corticosteroid
For adults with possible septic shock or high likelihood of sepsis **we recommend** administering antimicrobials immediately, ideally within 1 hr. of recognition. For those with possible sepsis- **we suggest** a time limited course of rapid investigation & if concern for infection persist provided antimicrobials in 3 hrs. For patients at high risk of MRSA **we recommend** empiric antimicrobials with MRSA coverage. We suggest against empiric with MRSA coverage not using if at low risk.
No change from 2016
No change from 2016 No change from 2016 For adults with sepsis induced ARDS **we suggest** using VV ECMO when conventional MV fails in experience centers **We suggest** high flow NC over non-invasive

SEP-1 Updates **(Version 5.10 /Discharges 07/01/21)**

- Broad Spectrum or Other Antibiotic Administration – Documentation of administration of a broad spectrum OR other antibiotic within the specified time frame.
  - △ There are no longer antibiotic selection guidelines – the list of acceptable antibiotics (both broad spectrum & antibiotic combination therapy) has been removed.
  - △ Any antibiotic given in the specified time frame is acceptable for the Broad Spectrum or Other Antibiotic Administration data element. 24hrs before or 3hrs after Severe Sepsis presentation

Antibiotics are Key

ORIGINAL ARTICLE

The Timing of Early Antibiotics and Hospital Mortality in Sepsis

Vincent X. Liu[1], Vikram Fielding-Singh[2], John D. Greene[1], Jennifer M. Baker[1], Theodore J. Iwashyna[3,4], Jay Bhattacharya[5], and Gabriel J. Escobar[1]

[1]Kaiser Permanente Division of Research, Oakland, California; [2]Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California; [3]Center for Clinical Management Research, VA Ann Arbor Health System, Ann Arbor, Michigan; [4]Division of Pulmonary and Critical Care, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; and [5]Primary Care and Outcomes Research, Stanford University, Stanford, California

American Journal of Respiratory and Critical Care Medicine Volume 196 Number 7 | October 1 2017

- Each elapsed hour between presentation and antibiotic administration was associated with a 9% increase in the odds of mortality with sepsis of all severity levels

Increased Time to Initial Antimicrobial Administration Is Associated With Progression to Septic Shock in Severe Sepsis Patients

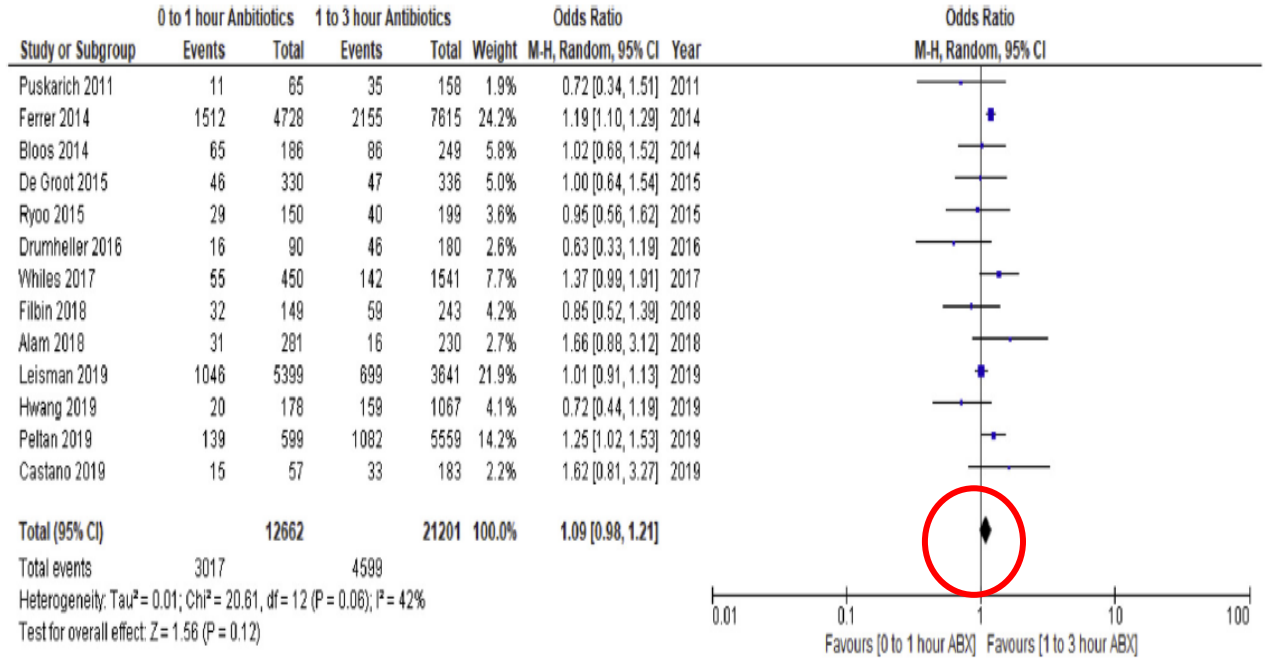
Bristol B. Whiles, BS[1]; Amanda S. Deis, MS[1]; Steven Q. Simpson, MD[2]

Whiles BB et al Critical Care Medicine. April 2017. Vol 45 (4) Number 4

- Each hour until initial antimicrobial administration was associated with a 8% increase in progression to septic shock.
- Patients who progressed to shock had significant increase in hospital LOS (18.7 days vs 9.66 days) and mortality (30.1% vs 7%)

1 vs 1-3hr Antibiotics

- 13 studies included
  - 5 prospective longitudinal
  - 8 retrospective cohorts
- 3 studies had high risk of bias
- Quality of evidence low



Study or Subgroup	0 to 1 hour Anbitiotics Events	Total	1 to 3 hour Antibiotics Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Puskarich 2011	11	65	35	158	1.9%	0.72 [0.34, 1.51]	2011
Ferrer 2014	1512	4728	2155	7615	24.2%	1.19 [1.10, 1.29]	2014
Bloos 2014	65	186	86	249	5.8%	1.02 [0.68, 1.52]	2014
De Groot 2015	46	330	47	336	5.0%	1.00 [0.64, 1.54]	2015
Ryoo 2015	29	150	40	199	3.6%	0.95 [0.56, 1.62]	2015
Drumheller 2016	16	90	46	180	2.6%	0.63 [0.33, 1.19]	2016
Whiles 2017	55	450	142	1541	7.7%	1.37 [0.99, 1.91]	2017
Filbin 2018	32	149	59	243	4.2%	0.85 [0.52, 1.39]	2018
Alam 2018	31	281	16	230	2.7%	1.66 [0.88, 3.12]	2018
Leisman 2019	1046	5399	699	3641	21.9%	1.01 [0.91, 1.13]	2019
Hwang 2019	20	178	159	1067	4.1%	0.72 [0.44, 1.19]	2019
Peltan 2019	139	599	1082	5559	14.2%	1.25 [1.02, 1.53]	2019
Castano 2019	15	57	33	183	2.2%	1.62 [0.81, 3.27]	2019
Total (95% CI)		**12662**		**21201**	**100.0%**	**1.09 [0.98, 1.21]**	
Total events	3017		4599				

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 20.61$, df = 12 (P = 0.06); $I^2 = 42\%$

Test for overall effect: Z = 1.56 (P = 0.12)

Rothrock SG, et al. *Ann Emerg Med*. 2020;76(4):427-441.

Early Fluid Resuscitation is Key

Multicenter Implementation of a Treatment Bundle for Patients with Sepsis and Intermediate Lactate Values

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- Decrease in hospital mortality was observed primarily in patients with heart and/or kidney failure ($p<0.04$) who received at least 2 Liters fluid resuscitation for severe sepsis with lactate between 2.1-3.9

Patterns and Outcomes Associated With Timeliness of Initial Crystalloid Resuscitation in a Prospective Sepsis and Septic Shock Cohort*

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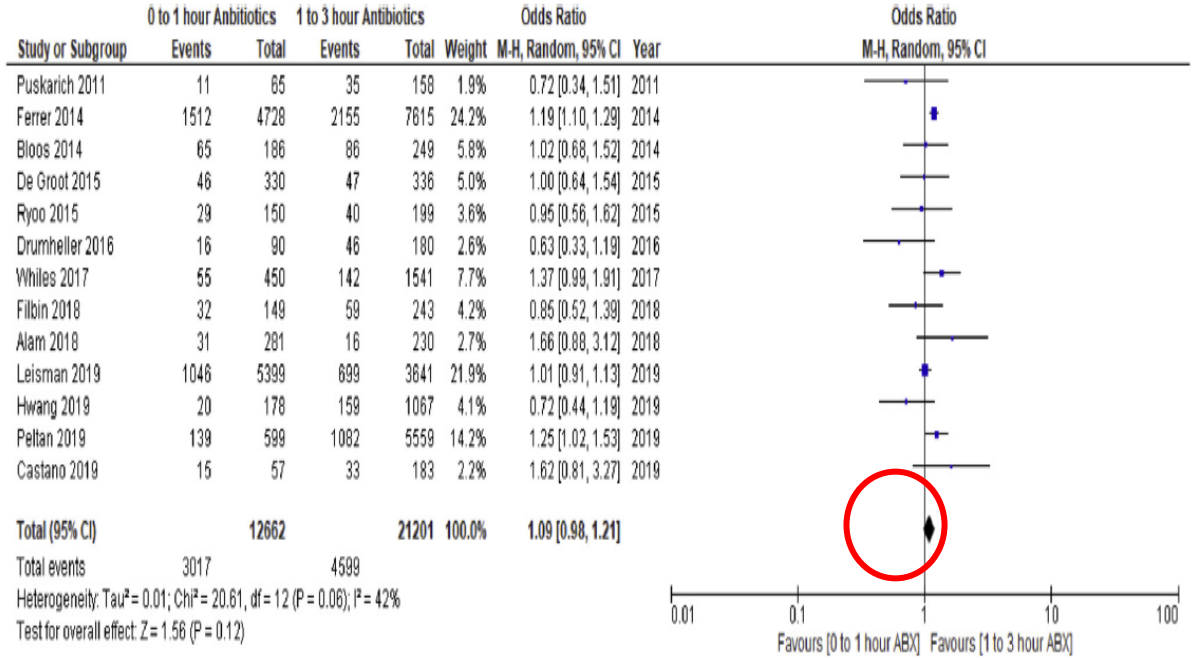
- Early fluid initiation (30-120 minutes) was associated with significantly lower hospital mortality, mechanical ventilation, ICU admission, LOS and ICU days & no harm seen to the patients

1 vs 1-3hr Antibiotics

- 13 studies included
  - 5 prospective longitudinal
  - 8 retrospective cohorts
- 3 studies had high risk of bias
- Quality of evidence low



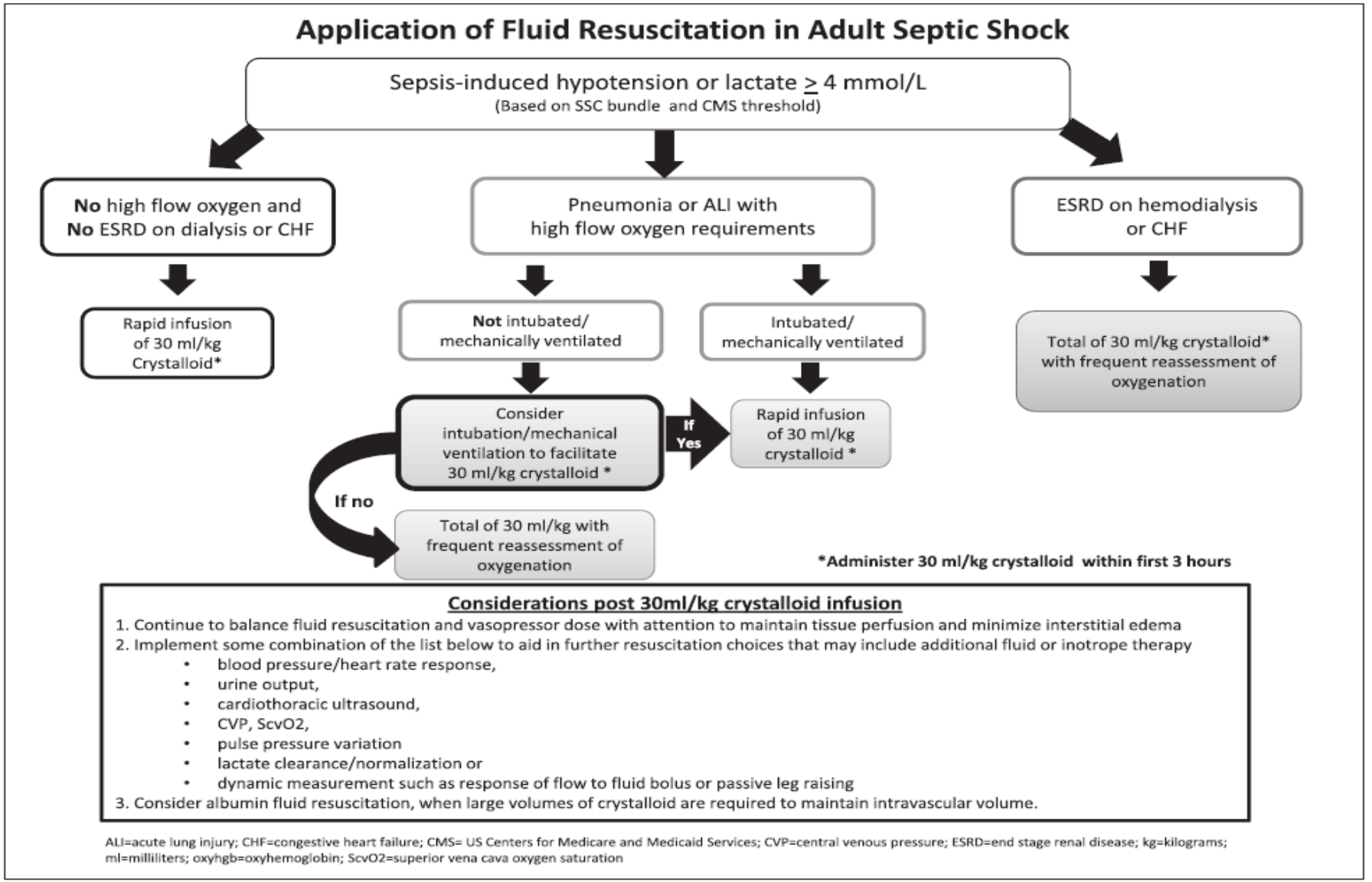
Study or Subgroup	0 to 1 hour Anbitiotics Events	Total	1 to 3 hour Antibiotics Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Puskarich 2011	11	65	35	158	1.9%	0.72 [0.34, 1.51]	2011
Ferrer 2014	1512	4728	2155	7615	24.2%	1.19 [1.10, 1.29]	2014
Bloos 2014	65	186	86	249	5.8%	1.02 [0.68, 1.52]	2014
De Groot 2015	46	330	47	336	5.0%	1.00 [0.64, 1.54]	2015
Ryoo 2015	29	150	40	199	3.6%	0.95 [0.56, 1.62]	2015
Drumheller 2016	16	90	46	180	2.6%	0.63 [0.33, 1.19]	2016
Whiles 2017	55	450	142	1541	7.7%	1.37 [0.99, 1.91]	2017
Filbin 2018	32	149	59	243	4.2%	0.85 [0.52, 1.39]	2018
Alam 2018	31	281	16	230	2.7%	1.66 [0.88, 3.12]	2018
Leisman 2019	1046	5399	699	3641	21.9%	1.01 [0.91, 1.13]	2019
Hwang 2019	20	178	159	1067	4.1%	0.72 [0.44, 1.19]	2019
Peltan 2019	139	599	1082	5559	14.2%	1.25 [1.02, 1.53]	2019
Castano 2019	15	57	33	183	2.2%	1.62 [0.81, 3.27]	2019
Total (95% CI)		**12662**		**21201**	**100.0%**	**1.09 [0.98, 1.21]**	
Total events	3017		4599				

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 20.61$, df = 12 (P = 0.06); $I^2 = 42\%$

Test for overall effect: Z = 1.56 (P = 0.12)

Rothrock SG, et al. *Ann Emerg Med*. 2020;76(4):427-441.

Application of Fluid Resuscitation in Adult Septic Shock



User's Guide to the 2016 Surviving Sepsis Guidelines Dellinger, CCM published ahead of print 1-2017

Type of Fluid

SALT-ED and SMART Studies - RCT

SALT-ED

- 13,347 patients
- Saline vs. LR/Plasma-Lyte in non-critically ill
- Median fluids administered 1079 ml

Both demonstrated statistically significant incidence of acute kidney injury (AKI)

SMART

- 15,802 patients
- Saline vs. LR/Plasma-Lyte in critically ill
- Median fluids administered ~ 2.5 L
  - △ ~ 33% mechanical ventilation
  - △ ~ 25% vasopressors

Self et al *NEJM 2018;* 378;9
Semler et al *NEJM 2018;* 378;9

Results: SALT-ED

Table 3. Clinical Outcomes According to Assigned Treatment Group in the Intention-to-Treat Analysis.

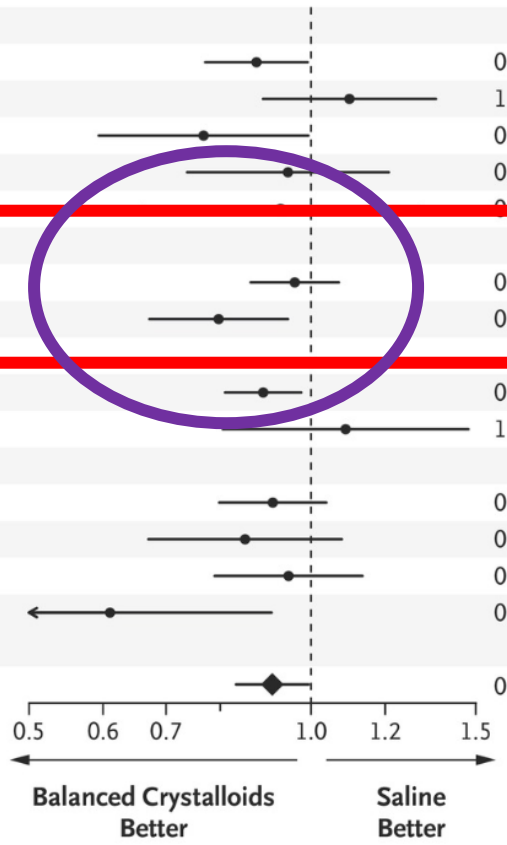
Outcome	Balanced Crystalloids (N=6708)	Saline (N=6639)	Adjusted Odds Ratio (95% CI)*	Adjusted P Value
Median hospital-free days to day 28 (IQR)	25 (22–26)	25 (22–26)	0.98 (0.92–1.04)	0.41
Major adverse kidney event within 30 days — no. (%)	315 (4.7)	370 (5.6)	0.82 (0.70–0.95)	0.01
Death — no. (%)	94 (1.4)	102 (1.5)	0.89	
New renal-replacement therapy — no./total no. (%)†	18/6582 (0.3)	31/6530 (0.5)	0.56	
Final serum creatinine ≥200% of baseline — no./total no. (%)†	253/6582 (3.8)	293/6530 (4.5)	0.84	
Stage 2 or higher acute kidney injury — no./total no. (%)†	528/6582 (8.0)	560/6530 (8.6)	0.91 (0.80–1.03)	0.14
In-hospital death — no. (%)	95 (1.4)	105 (1.6)	0.88 (0.66–1.16)	0.36

KIDNEY Injury Events!

Self et al *NEJM*. 2018:378;9

SMART Trial

Subgroup	Balanced Crystalloids	Saline	Odds Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no. (%)				
Unit					0.27
Medical	615/2735 (22.5)	659/2646 (24.9)	0.87 (0.77–0.99)	0.04	
Cardiac	202/1470 (13.7)	190/1501 (12.7)	1.10 (0.89–1.36)	0.38	
Neurologic	116/1440 (8.1)	141/1377 (10.2)	0.77 (0.59–0.99)	0.04	
Trauma	131/1640 (8.0)	142/1688 (8.4)	0.95 (0.74–1.21)	0.66	
Surgical	[illegible]	[illegible]	[illegible]	[illegible]	
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 et al *NEJM*. 2018;378;9

Secondary Analysis of SMART

- 15,802 patients enrolled in SMART
- 1,641 patients were admitted to the medical intensive care unit with a diagnosis of **sepsis**
- 217 patients **(26.3%)** in the balanced crystalloids group experienced 30-day in-hospital morality, compared with,
- 255 patients **(31.2%)** in the saline group
  - △ (adjusted odds ratio, 0.74; 95% confidence interval, 0.59 – 0.93; p = 0.01)

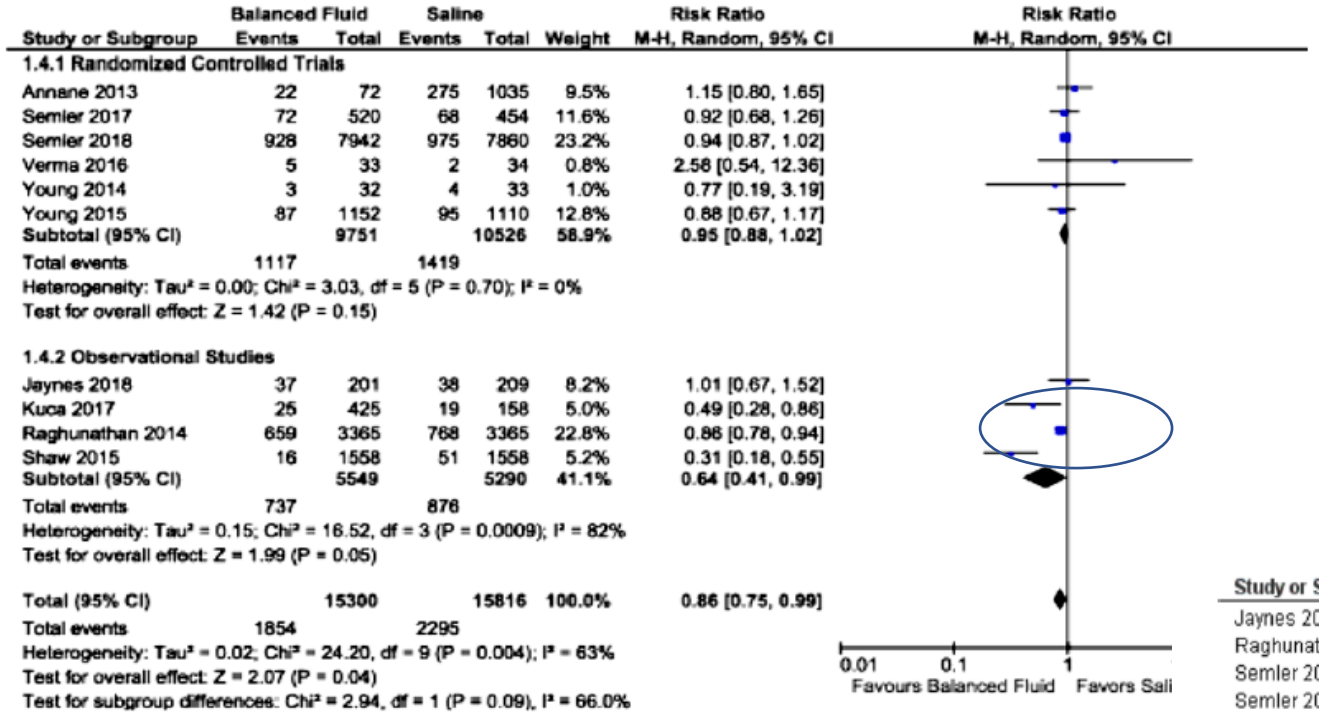
Brown, Wang, Coston et al *Am J Respir Crit Care Med*. 2019;200(12):1487-1495

Secondary Analysis of SMART

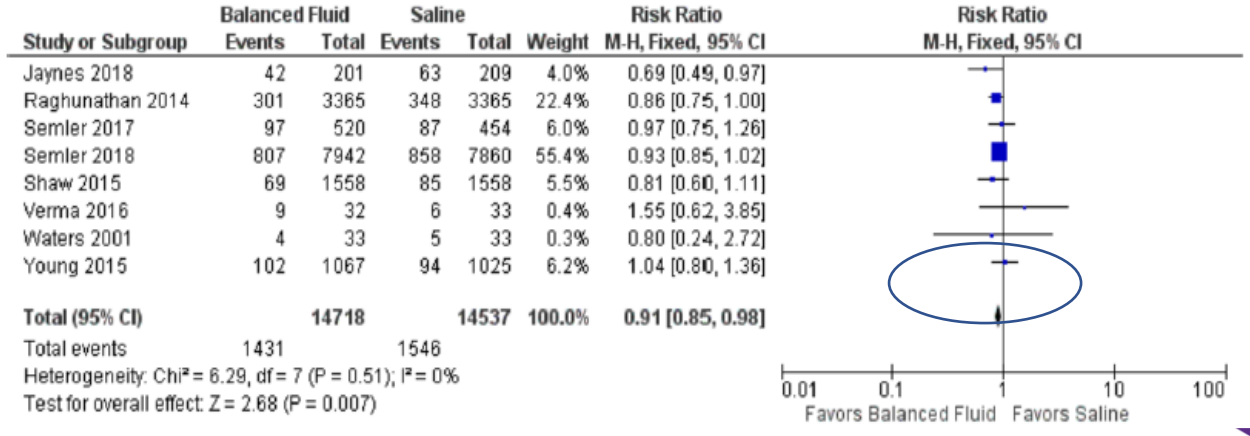
- Patients in the balanced group experienced a lower incidence of major adverse kidney events within 30 days
  - △ (35.4% vs 40.1%; OR 0.78; 95% CI 0.63 – 0.97)
- Greater number of vasopressor-free days
  - △ (20 ± 12 vs 19 ± 13; OR 1.25; 95% CI 1.02 – 1.54)
- Renal replacement therapy-free days
  - △ (20 ± 12 vs 19 ± 13; OR 1.35 [1.08 – 1.69])

Brown, Wang, Coston et al *Am J Respir Crit Care Med.* 2019;200(12):1487-1495

Balanced Crystalloids vs Saline in Critically Ill Adults: A meta-analysis



Study or Subgroup	Balanced Fluid Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Randomized Controlled Trials						
Annane 2013	22	72	275	1035	9.5%	1.15 [0.80, 1.65]
Semler 2017	72	520	68	454	11.6%	0.92 [0.68, 1.26]
Semler 2018	928	7942	975	7860	23.2%	0.94 [0.87, 1.02]
Verma 2016	5	33	2	34	0.8%	2.58 [0.54, 12.36]
Young 2014	3	32	4	33	1.0%	0.77 [0.19, 3.19]
Young 2015	87	1152	95	1110	12.8%	0.88 [0.67, 1.17]
Subtotal (95% CI)		9751		10526	58.9%	0.95 [0.88, 1.02]
Total events	1117		1419			
Heterogeneity: Tau² = 0.00; Chi² = 3.03, df = 5 (P = 0.70); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.15)						
1.4.2 Observational Studies						
Jaynes 2018	37	201	38	209	8.2%	1.01 [0.67, 1.52]
Kuca 2017	25	425	19	158	5.0%	0.49 [0.28, 0.86]
Raghunathan 2014	659	3365	768	3365	22.8%	0.86 [0.78, 0.94]
Shaw 2015	16	1558	51	1558	5.2%	0.31 [0.18, 0.55]
Subtotal (95% CI)		5549		5290	41.1%	0.64 [0.41, 0.99]
Total events	737		876			
Heterogeneity: Tau² = 0.15; Chi² = 16.52, df = 3 (P = 0.0009); I² = 82%						
Test for overall effect: Z = 1.99 (P = 0.05)						
Total (95% CI)		15300		15816	100.0%	0.86 [0.75, 0.99]
Total events	1854		2295			
Heterogeneity: Tau² = 0.02; Chi² = 24.20, df = 9 (P = 0.004); I² = 63%						
Test for overall effect: Z = 2.07 (P = 0.04)						
Test for subgroup differences: Chi² = 2.94, df = 1 (P = 0.09), I² = 66.0%						

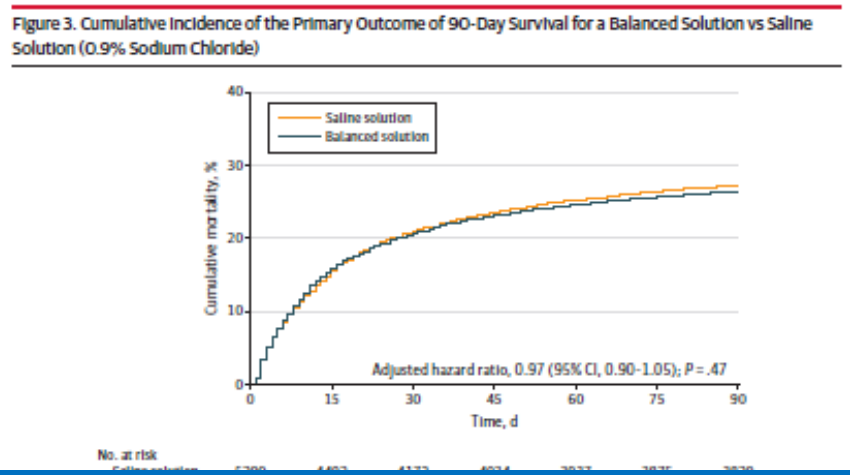


Study or Subgroup	Balanced Fluid Events	Total	Saline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jaynes 2018	42	201	63	209	4.0%	0.69 [0.49, 0.97]
Raghunathan 2014	301	3365	348	3365	22.4%	0.86 [0.75, 1.00]
Semler 2017	97	520	87	454	6.0%	0.97 [0.75, 1.26]
Semler 2018	807	7942	858	7860	55.4%	0.93 [0.85, 1.02]
Shaw 2015	69	1558	85	1558	5.5%	0.81 [0.60, 1.11]
Verma 2016	9	32	6	33	0.4%	1.55 [0.62, 3.85]
Waters 2001	4	33	5	33	0.3%	0.80 [0.24, 2.72]
Young 2015	102	1067	94	1025	6.2%	1.04 [0.80, 1.36]
Total (95% CI)		14718		14537	100.0%	0.91 [0.85, 0.98]
Total events	1431		1546			
Heterogeneity: Chi² = 6.29, df = 7 (P = 0.51); I² = 0%						
Test for overall effect: Z = 2.68 (P = 0.007)						

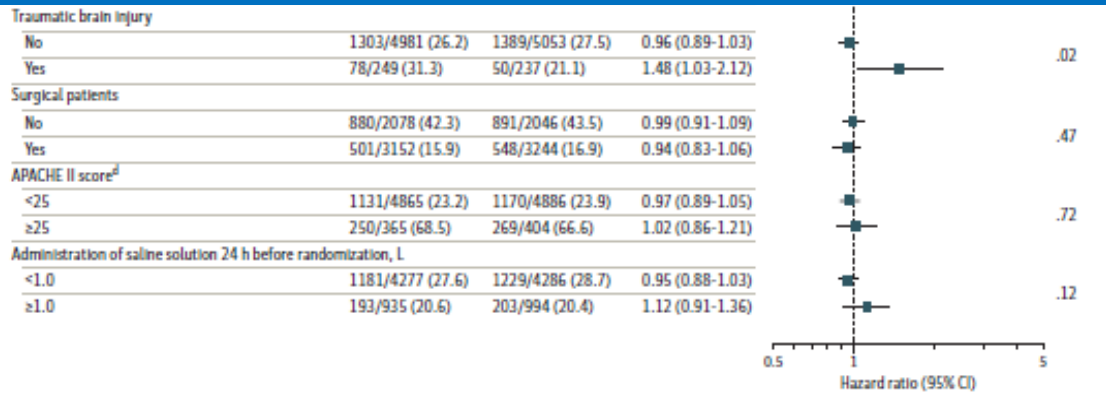
Hammond DA, Lam SW, Rech MA, et al Ann Pharmacother. 2020 Jan;54(1):5-13.

BaSICS Trial: Saline vs Balanced Solution

- 75 ICU's, 11,052 patients
- Double blind factorial RCT
- Admitted to ICU
  - 1 factor for worse outcomes
  - Required 1 bolus
  - Remain in ICU > 24hrs
- Measure difference in mortality & secondary outcomes



For regular bolus of ICU patients, either fluid is likely safe. However we don't have enough data on patients who required a significant amount of volume resuscitation on fluid to use



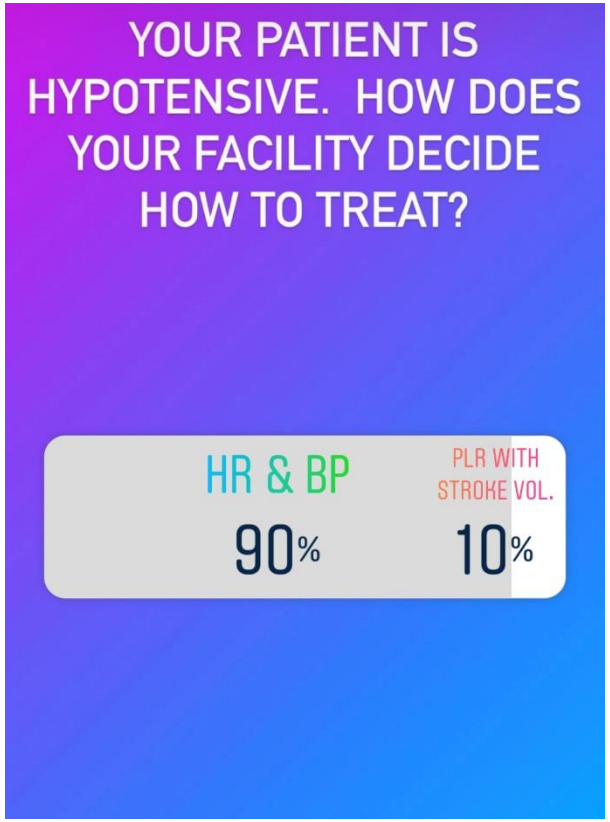
Zampieri FG, et al. *JAMA*. 2021;326(9):1-12.

How do you know if your hypotensive patient is a fluid responder?

OR

Social media poll:

Which measures do you routinely use to determine if the patient needs fluid?



Instagram poll 4/26/2021
6,082 responses

Why B/P is NOT a good predictor of fluid responsiveness?

- The ABP response to intravenous volume expansion is unpredictable
  - Some pts exhibit an increase – others do not
- Fluid administration if aimed to restore and maintain ABP could lead to the following:
  - Unnecessary fluid overload
  - Delayed vasoactive therapy
  - Increased mortality
- BP a late sign of hypovolemia

Medicine Intensiva. 2017;41 (9):546-549

FRESH Trial

- 13 US and UK Hospitals
- Non-blinded RCT
- n = 124 patients
  - 83 treatment vs. 41 Usual Care
  - 2:1 enrollment
- Enrolled in the ER
  - Refractory septic shock
  - < 3L of fluid administered
- PLR with dynamic measure of SV change using Bioreactance
  - Used to guide decision of fluid vs. vasopressors for clinical hypoperfusion
  - Over the next 72 hours of care, or ICU discharge
- Hypoperfusion defined as:
  - MAP < 65
  - Persistent hyperlactemia
  - Cryptic shock – lactate > 4 without hypotension

Douglas I et al, *CHEST* 2020

Primary Endpoint

- **Decreased 72-hour Fluid Balance** (p=0.02)
  - △ Treatment Group: 0.65 L +/- 2.85 L
  - △ Control Group: 2.02 L +/- 3.44 L
- Favoring Treatment Group: -1.37 L

- 43% fluid responsive on initial PLR
- 33% fluid responsive between 48 – 72 hours
- 18% never fluid responsive

Douglas I et al, *CHEST* 2020

Secondary Endpoints

- **Renal Replacement Therapy (RRT)** p = 0.04
  - Treatment Group 5.1%
  - Control Group 17.5 %
- **ICU LOS** p = 0.11
  - Treatment Group 3.31
  - Control Group 6.22
- **Mechanical Ventilation** p = 0.04
  - Treatment Group 17.7%
  - Control Group 34.1%
- **Discharge Home** p = 0.035
  - Treatment Group 63.9%
  - Control Group 43.9 %

Douglas I et al., *CHEST* 2020

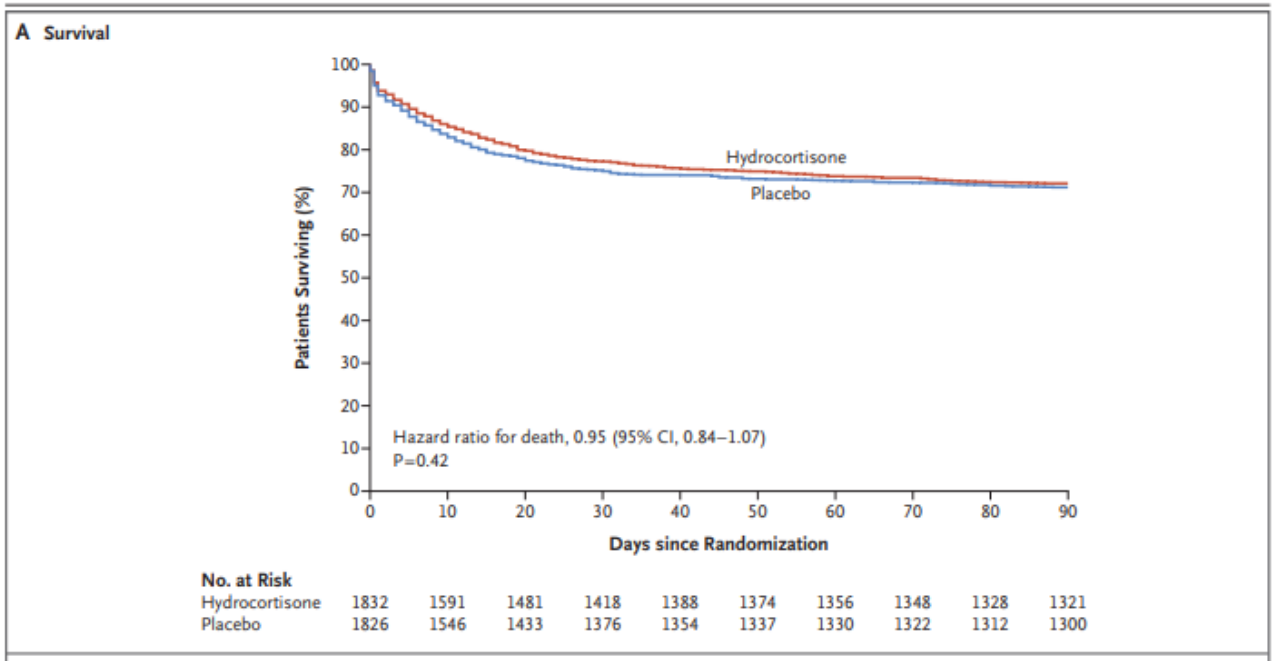
SEP-1 v 5.11 Fluid Volume Requirement Starting 1/1 2022

- Volumes ordered that equals 30mL/kg
- Within 10% less than 30mL/kg is acceptable
- order for less than 30ML per kilogram of crystalloid fluids if the volume is specified in order in one of the following reasons is documented
  - concern for volume overload
  - blood pressure stabilized with lesser volume
  - end stage heart failure
  - end stage renal disease
  - a portion of the crystalloid volume was administered as colloids

Adjunctive Therapies

Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock-ADRENAL Trial

- RCT-3800 patients
  - 5 countries (Australia, NZ, Saudi Arabia, UK & Denmark
  - Tx: 200mg infusion hydrocortisone vs placebo
  - No tapering done/no stim test
- Inclusion:
  - > 18 years
  - Proven or strong suspicion of infection
    - Shock or pressors for a minimum of 4 hours
    - > 2 SIRS criteria
  - Mechanical ventilation
  - Etomidate native



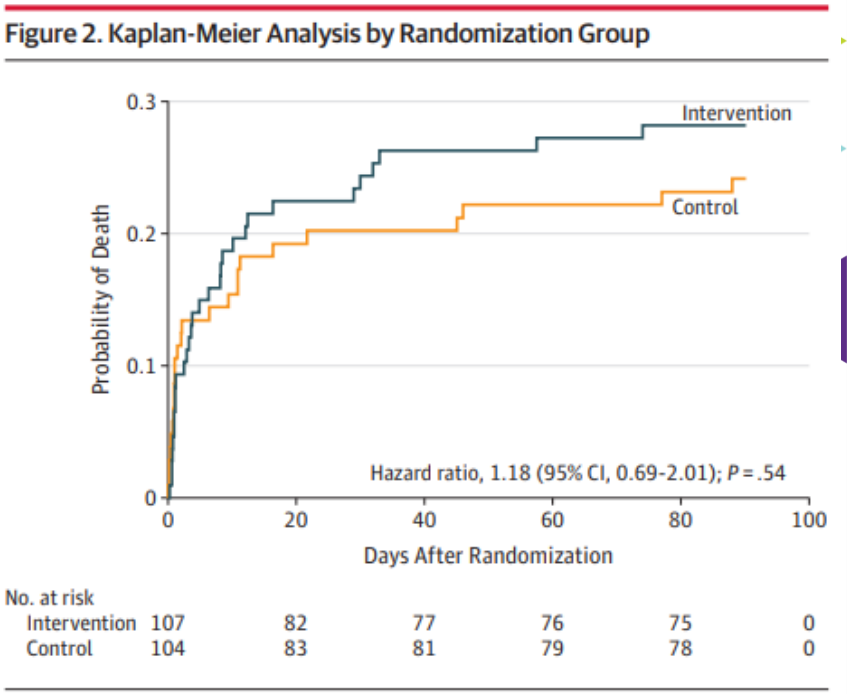
Secondary Benefits

- Faster time to shock reversal
- D/C from ICU faster
- Less PRBC's
- Faster time to extubation

Venkatesh B, et al. N Engl J Med 2018 Mar 1;378(9):797-808

Vitamins RCT: Vitamin C, Hydrocortisone and Thiamine vs. Hydrocortisone Alone

- RCT 10 ICU's in Australia, New Zealand and Brazil
- 216 patients/Sepsis 3 definition for Septic Shock



- Intervention group-109
  - IV vitamin C (1.5g q 6 hrs), IV hydrocortisone (50mg q 6 hrs) & thiamine (200 mg every 12 hrs)
- Control group-107
  - IV hydrocortisone (50 mg q 6 hrs) until shock resolution or 10 days

Results

Time alive and vasopressor free up to day 7

- Intervention group 122.1 hrs
- Control group 124.6 hrs p=.83

No difference in any secondary outcomes

Limitations:

- Open label
- Under powered to detect difference in mortality
- 24 hrs must meet SEP 3 criteria
- **Median time to first dose of Vitamin C was 12.1 hrs from ICU admission**

Fujii T et al. JAMA 2020;323(5):423-431

VICTAS Trial: Vitamin C, Thiamine and Steroid in Treatment of Sepsis

- 43 Hospitals
  - ED or ICU enrollment
  - Patients with sepsis induced cardiac or respiratory dysfunction
  - 500 patients funding withheld (study stopped)/Prior to COVID
  - Vasopressors
    - HFNC, NIV, IMV
  - Vit C 1.5 gm, thiamine (100mg) & steroids (50mg) q 6 vs. placebo
  - Infusion 96hrs, d/c ICU or death
- Outcome Measurements
  - Vasopressor free days
  - Ventilator free days
  - 30-day mortality

Results

- Open label steroids administration 32% in both groups
- No difference in VFD or vasopressor free days
- No difference in 30-day mortality

Sevransky LE, et al. JAMA. 2021;325(8):742-750

Clover Study: Coming Attraction
Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis

Hypothesis

- Restrictive (vs liberal) fluid treatment strategy during the 1st 24hr of resuscitation for sepsis-induced hypotension will reduce 90-day in hospital mortality
  - Conservative (vasopressor first followed by rescue fluids)
  - liberal (fluids followed by rescue vasopressors)

Enrollment to be completed by June 2021

Method

- Multicenter, randomized prospective phase 3 trial
- Intervention: protocolized fluid titration strategies for up to 24 hours
- Sample: 2,320 patients planned to enrollment
- Primary outcome: 90 day inpatient mortality
- 50 Hospitals—acute and critical care (part of Petal Network)

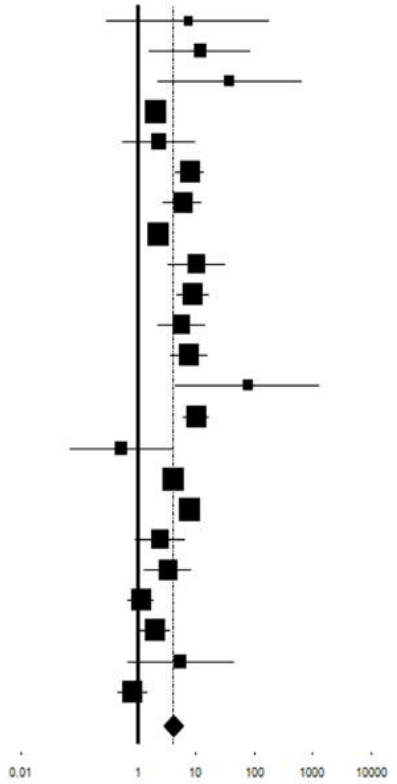
Does Compliance with the Bundle Make a Difference?

Changes in Bundle Compliance & Mortality with a PI Program

6 Hour Bundle Compliance

	ES	95% CI	Sig.
Berg 2013	7.39	0.29 , 185.86	0.224
Castellanos-Ortega 2010	11.98	1.63 , 88.13	0.015
De Miguel-Yanes 2009	38.52	2.22 , 668.17	0.012
Ferrer 2008	2.01	1.42 , 2.83	0.000
Girardis 2009	2.40	0.57 , 10.04	0.231
Jeon 2012	8.14	4.64 , 14.27	0.000
Kuan 2013	6.00	2.79 , 12.91	0.000
Levy 2010	2.23	1.75 , 2.84	0.000
MacRedmond 2010	10.51	3.32 , 33.31	0.000
McKinley 2011	8.95	4.74 , 16.88	0.000
Memon 2012	5.81	2.23 , 15.14	0.000
Na 2012	7.84	3.75 , 16.36	0.000
Nguyen HB 2007	78.66	4.53 , 1366.74	0.003
Noritomi 2014	10.41	6.22 , 17.41	0.000
Plambech 2012	0.54	0.07 , 4.10	0.554
Schramm (a) 2011	4.16	2.70 , 6.41	0.000
Schramm (b) 2011	7.98	5.32 , 11.99	0.000
Shiramizo 2011	2.48	0.93 , 6.61	0.069
Tromp (a) 2010	3.33	1.29 , 8.58	0.013
Tromp (b) 2010	1.17	0.69 , 1.98	0.559
Van Zanten 2014	2.05	1.15 , 3.65	0.015
Wang 2013	5.65	0.69 , 46.11	0.106
Westphal 2011	0.84	0.47 , 1.50	0.559
Overall (random-effects model)	4.15	2.87 , 6.00	0.000

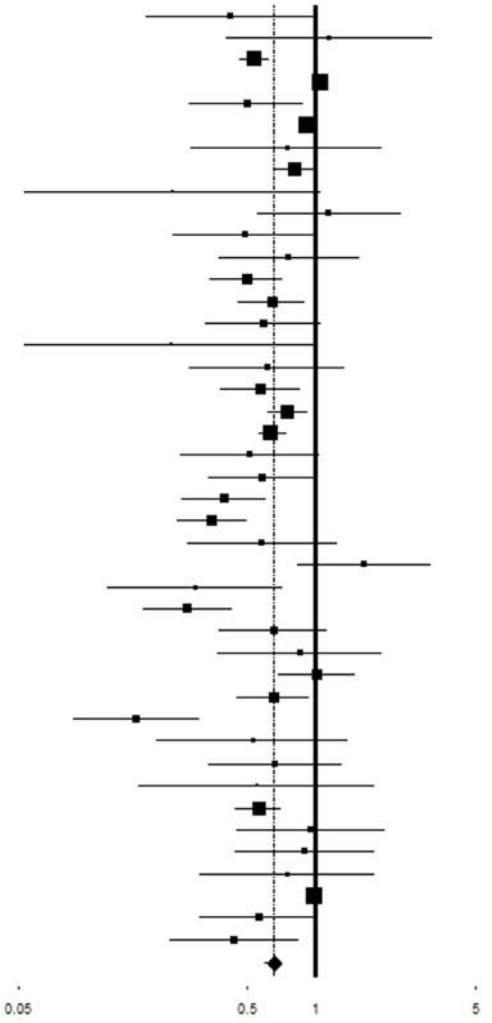
I2 = 84.37%, p=0.000



Mortality

	ES	95% CI	Sig.
Berg 2013	0.43	0.18 , 1.02	0.056
Bond 2013	1.15	0.41 , 3.27	0.791
Cannon 2012	0.54	0.47 , 0.63	0.000
Capuzzo 2012	1.05	1.01 , 1.09	0.006
Castellanos-Ortega 2010	0.50	0.28 , 0.89	0.019
Chen 2013	0.91	0.88 , 0.95	0.000
De Miguel-Yanes 2009	0.75	0.29 , 1.97	0.560
Ferrer 2008	0.81	0.67 , 0.98	0.030
Girardis 2009	0.24	0.05 , 1.07	0.061
Giuliano 2011	1.15	0.56 , 2.38	0.707
Gurnani 2010	0.49	0.24 , 1.03	0.061
Heppner 2012	0.77	0.38 , 1.57	0.469
Hoo 2009	0.50	0.35 , 0.72	0.000
Jacob 2012	0.65	0.46 , 0.91	0.011
Jeon 2012	0.59	0.33 , 1.06	0.080
LaRosa 2012	0.24	0.05 , 1.03	0.055
Laguna-Perez 2012	0.62	0.28 , 1.36	0.232
Lefrant 2010	0.58	0.39 , 0.86	0.007
Levy 2010	0.76	0.62 , 0.93	0.008
MacRedmond 2010	0.64	0.57 , 0.75	0.000
McKinley 2011	0.52	0.26 , 1.05	0.070
Memon 2012	0.59	0.34 , 1.01	0.055
Micek 2006	0.40	0.26 , 0.61	0.000
Miller 2013	0.35	0.25 , 0.50	0.000
Moore 2009	0.59	0.28 , 1.25	0.168
Na 2012	1.65	0.84 , 3.24	0.150
Nguyen HM 2012	0.30	0.12 , 0.72	0.007
Noritomi 2014	0.28	0.18 , 0.44	0.000
Patocka 2014	0.65	0.38 , 1.13	0.127
Sawyer 2011	0.86	0.38 , 1.96	0.714
Schramm (a) 2011	1.01	0.68 , 1.50	0.948
Schramm (b) 2011	0.66	0.46 , 0.94	0.024
Shiramizo 2011	0.17	0.09 , 0.31	0.000
Silverman (a) 2011	0.53	0.20 , 1.40	0.202
Silverman (b) 2011	0.67	0.34 , 1.30	0.238
Sweet 2010	0.56	0.17 , 1.83	0.334
Thiel 2009	0.57	0.45 , 0.71	0.000
Tromp (a) 2010	0.96	0.45 , 2.03	0.910
Tromp (b) 2010	0.90	0.45 , 1.82	0.772
Vallée 2007	0.76	0.31 , 1.83	0.535
Van Zanten 2014	0.99	0.99 , 1.00	0.005
Wang 2013	0.57	0.31 , 1.03	0.061
Westphal 2011	0.44	0.23 , 0.85	0.014
Overall (random-effects model)	0.66	0.61 , 0.72	0.000

I2 = 88.57%, p=0.000



Damiani E, Donati A, Serafini G, et al*LoS One*. 2015;10(5):e0125827. Published 2015 May 6. doi:10.1371/journal.pone.0125827

Effect of Bundle Compliance with SEP-1 on Mortality among Medicare Beneficiaries with Sepsis

- A propensity score matched cohort study
  - Standard & stringent
- 3241 hospitals from 10/01/2015 to 03/31/2017
- Compliance was completion of all SEP-1 elements
- 2 matches completed to evaluate population level effects
  - Standard: 122,870 compliant matched to those care were non-compliant
  - Stringent:107,016 compliant matched with those care were non-compliant
- Outcome Measures:
  - 30-day mortality
  - Changes in LOS

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Demographics Matching

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Adjusted & Unadjusted Impact of Bundle Element Compliance on Mortality

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.

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Compliance with SEP-1 Decrease Mortality

- Compliant Care 30-day Mortality
  - △ 21.81%
- Non-Compliant Care 30-day Mortality
  - △ 27.48%

ARR = 5.67%

(95% CI,5.33-6.0;p < .001)

RR = .794

(95% CI, 0.783- 0.805)

NNT = 17.65

(95% CI, 16.66-18.76)

Compliant care: LOS 5 days vs 6 days (p<.001)

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