

Life after Sepsis

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Disclosures

Co-Chair of the SCCM Thrive Supporting Survivors after Critical Illness Initiative

Physician advisor, Commonwealth HAP-HIIN “ExSEPSIS (Exiting with Excellence in Sepsis Care)” Initiative

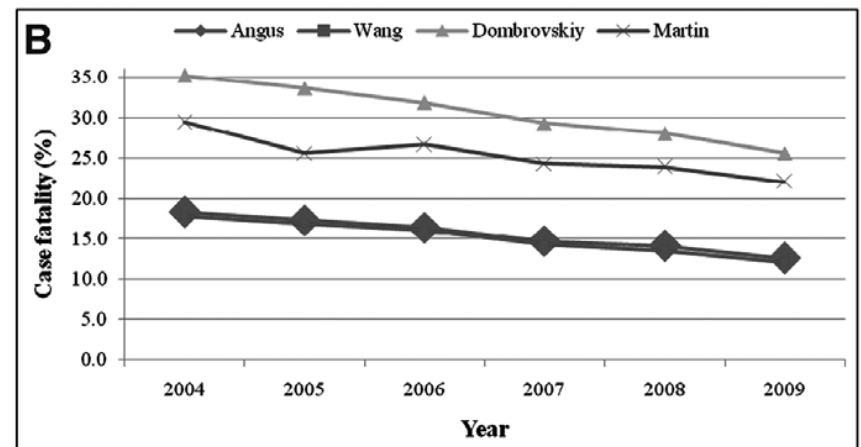
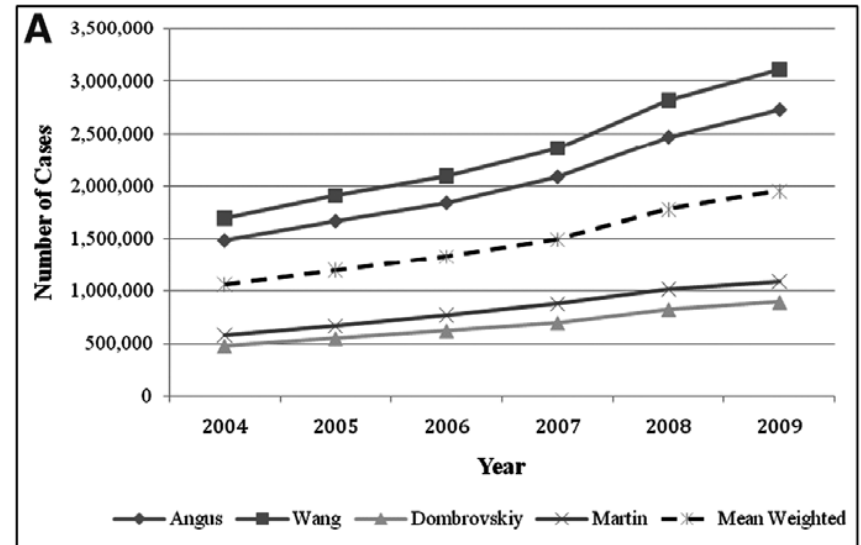
NIH

- NIH Loan Repayment Program Awardee
- NIH NINR R01 Co-investigator to study hospital readmissions after sepsis in patients discharged to home with home health services

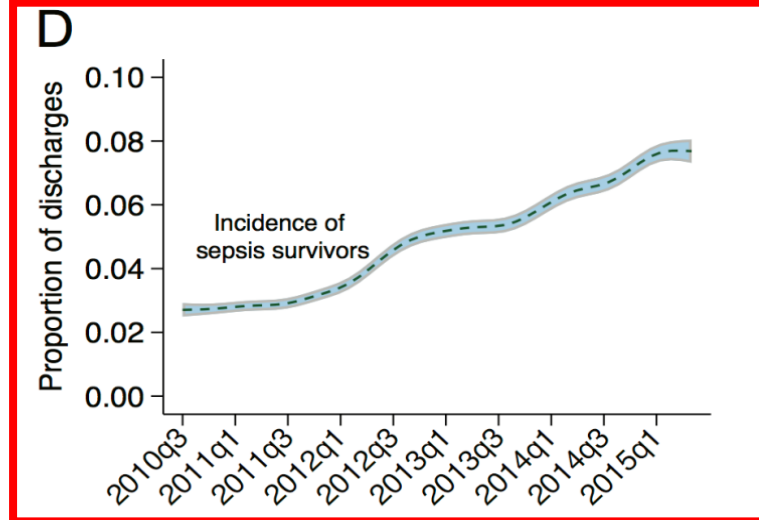
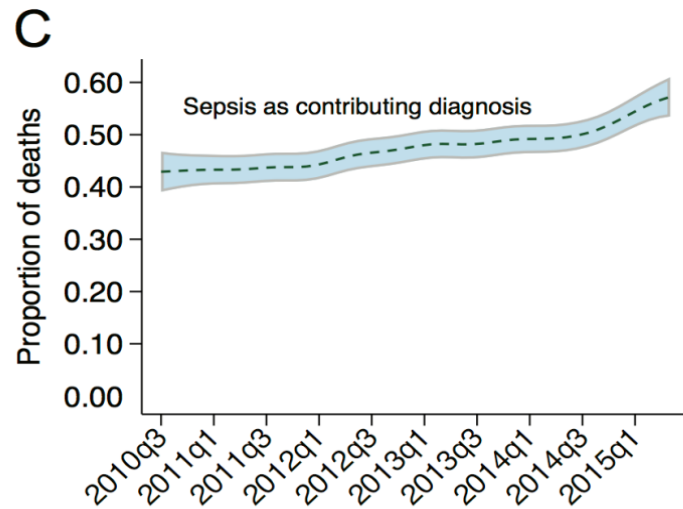
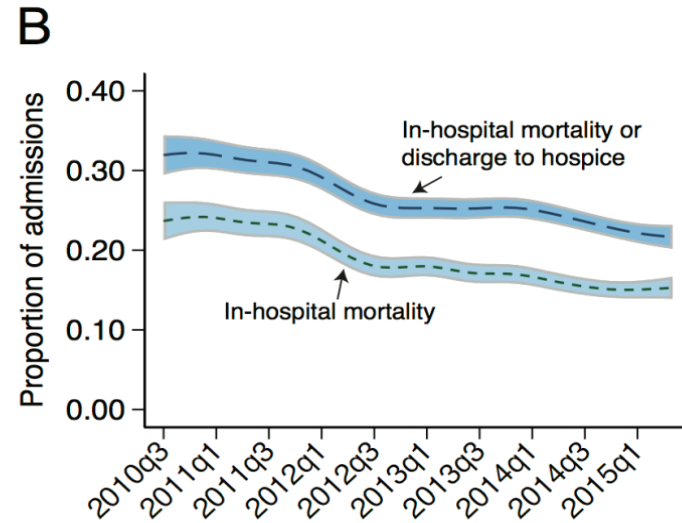
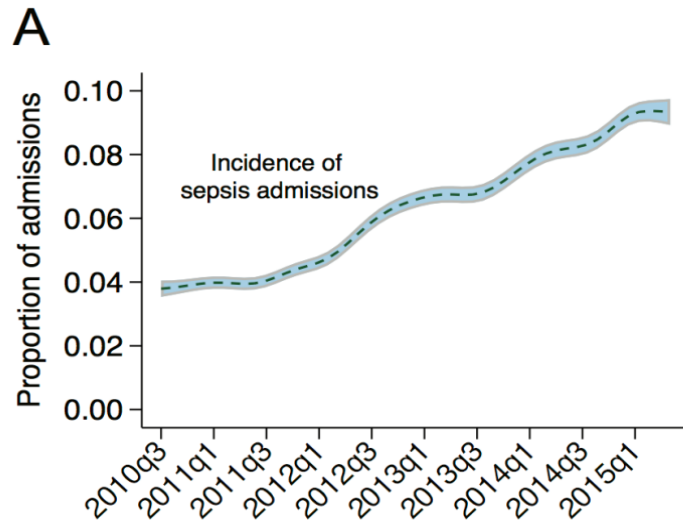
Sepsis Is A Driver of U.S. Health Care

- ◆ Sepsis is common & costly
 - \$ 24 billion
- ◆ Sepsis, driven by improved recognition, is increasing
- ◆ Mortality is decreasing

Gaieski et al Crit Care Med 2013
Lagu et al Critical Care Med 2012
Rhee et al 2017



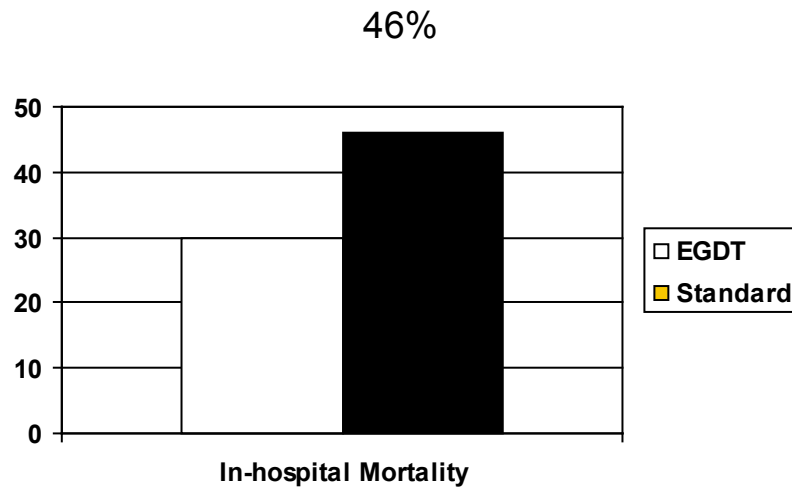
At Penn, the number of sepsis survivors increased from 1,502 in 2010 to 3,900 in 2015



Meyer et al Crit Care Med 2018

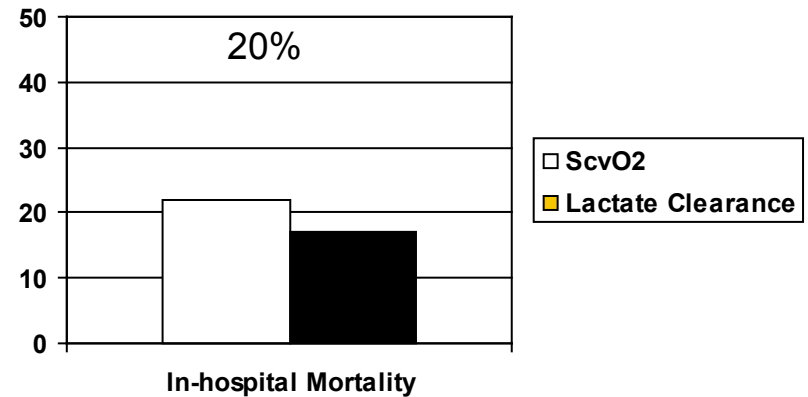
Septic Shock from 2000 - 2015

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



Rivers et al NEJM 2001

Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy A Randomized Clinical Trial

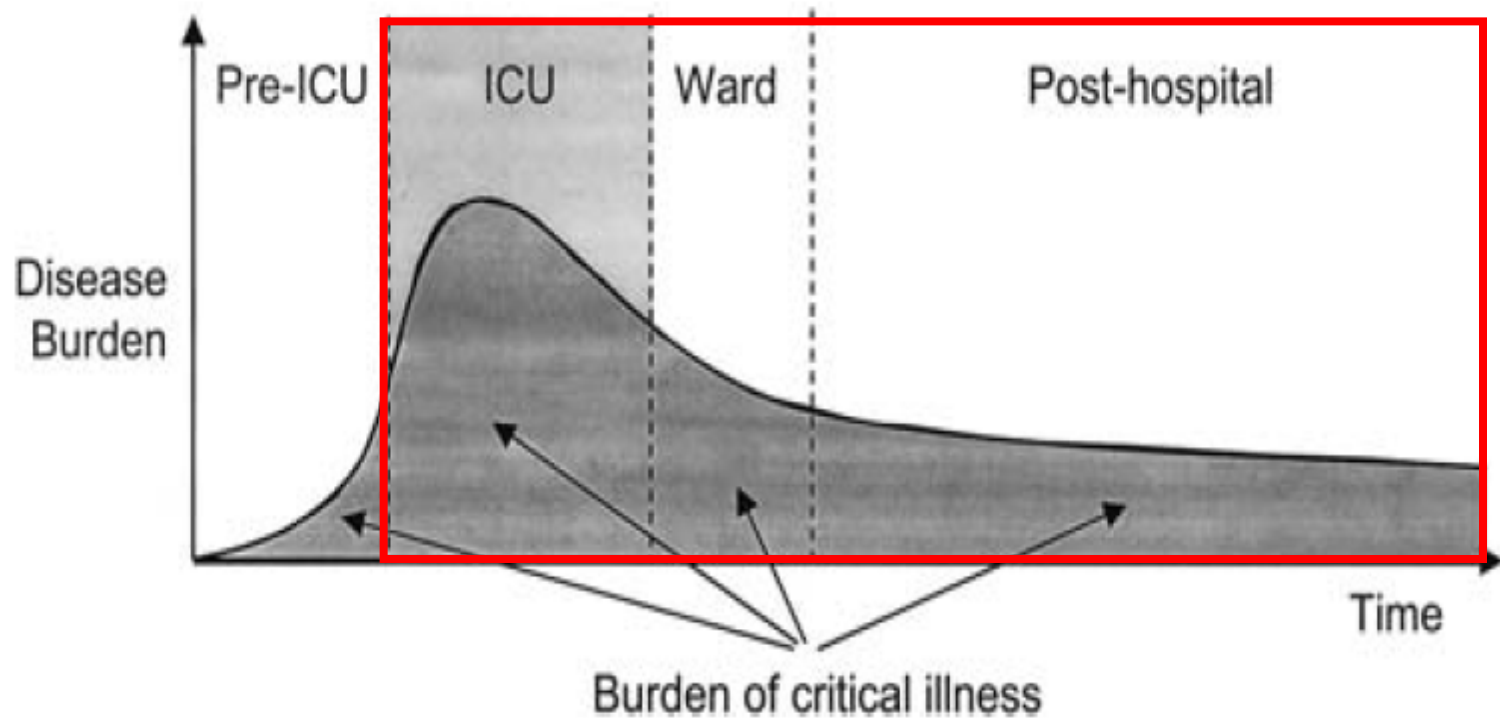


Jones et al JAMA 2010

Process NEJM 2014

Arise NEJM 2014

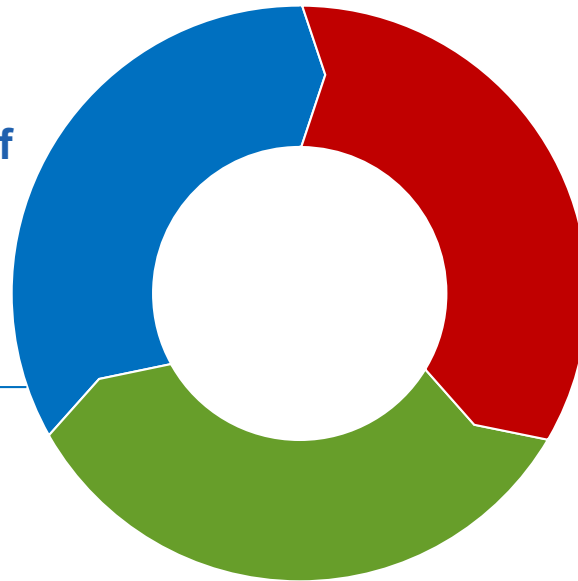
Sepsis: The 21st Century Perspective



Penn Medicine Sepsis Alliance Overview

The Penn Medicine Sepsis Alliance governs health system sepsis care activities with the goal of improving the early identification of sepsis and optimizing care management.

READMISSIONS:
Reduce the number of 7 day and 30 day readmissions after a hospitalization for sepsis.



RECOGNITION: Maximize recognition of sepsis-associated end organ dysfunction.

ADHERENCE: Improve adherence to the 3 hour SEP-1 bundle for inpatients and in the ED.

Long-Term Consequences of Sepsis

Neuropsychological impairment

Physical impairment

Sepsis-induced inflammation and cardiovascular risk

Sepsis-induced immunosuppression

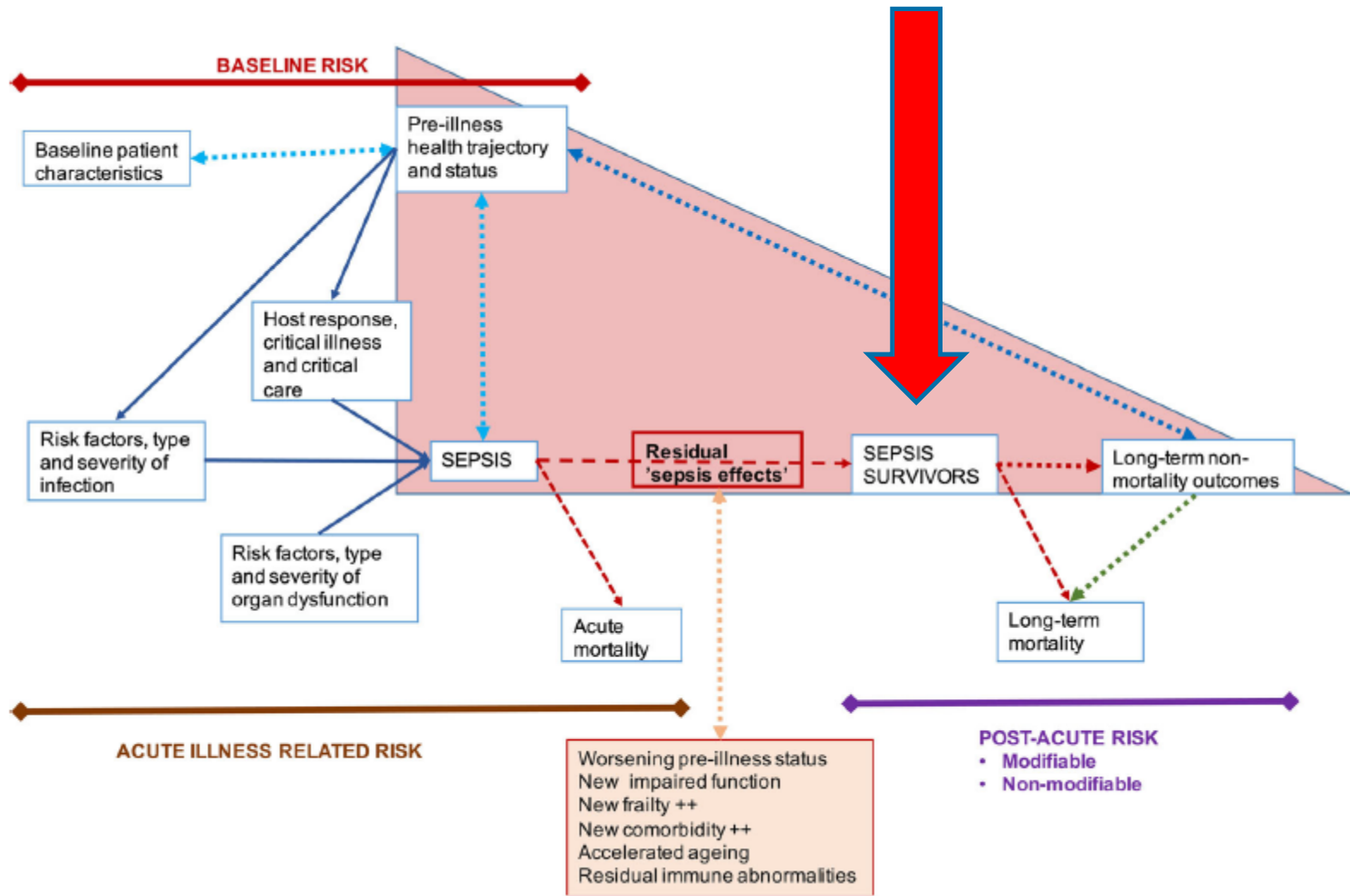
Long-term health-related quality of life

Healthcare resource utilization

Long-term mortality

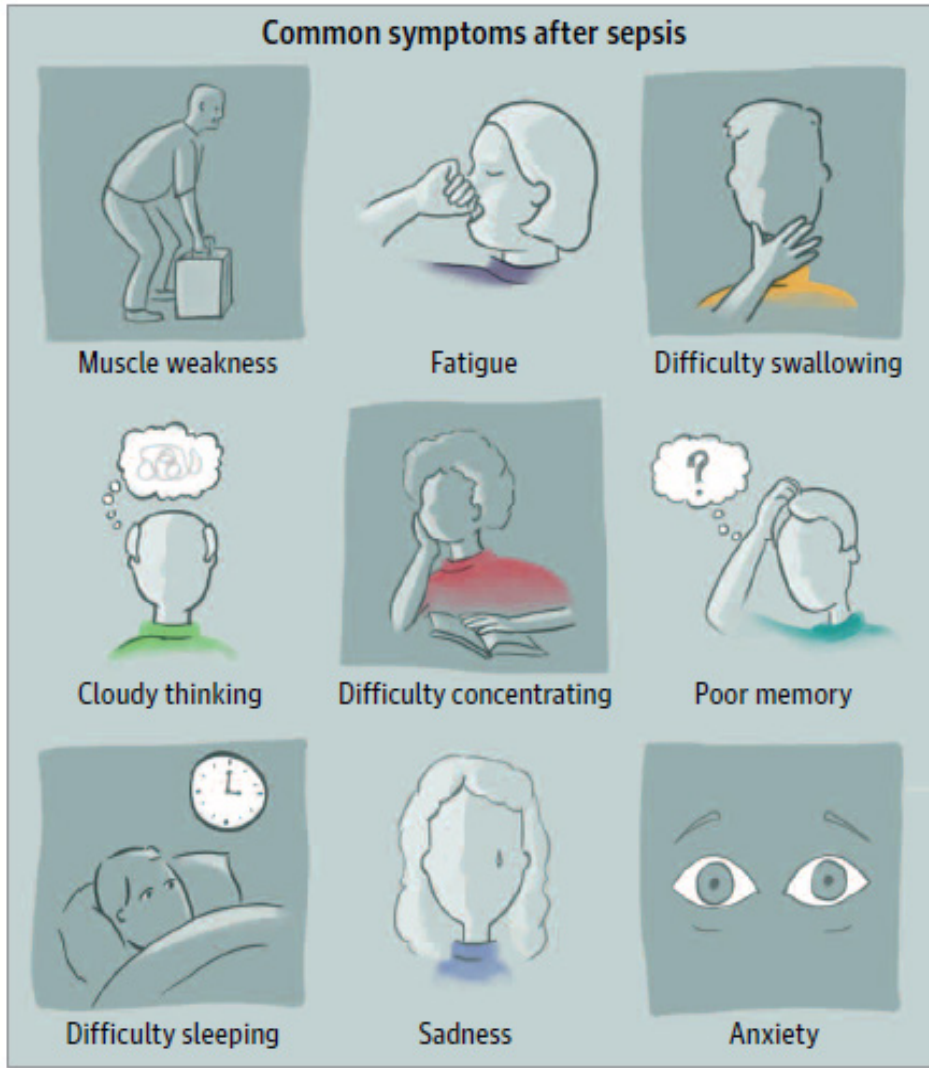
Maley et al Clin Chest Med 2016

Modify What is Modifiable; Manage What is Not



Shankar Hari et al Curr Infect Dis Rep 2016

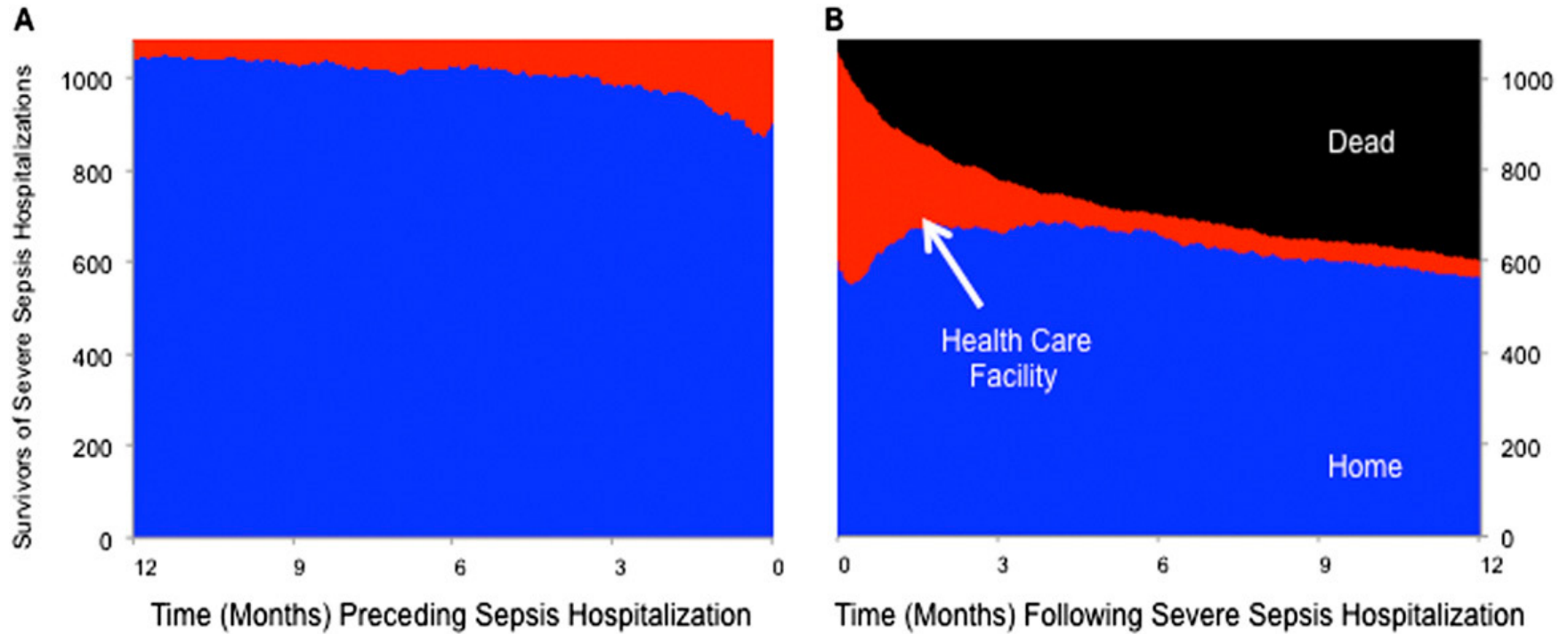
Management & Self-Management



Are these
symptoms
factored into
your discharge
planning?

Prescott et al JAMA 2018

Survival and Healthcare Use After Sepsis



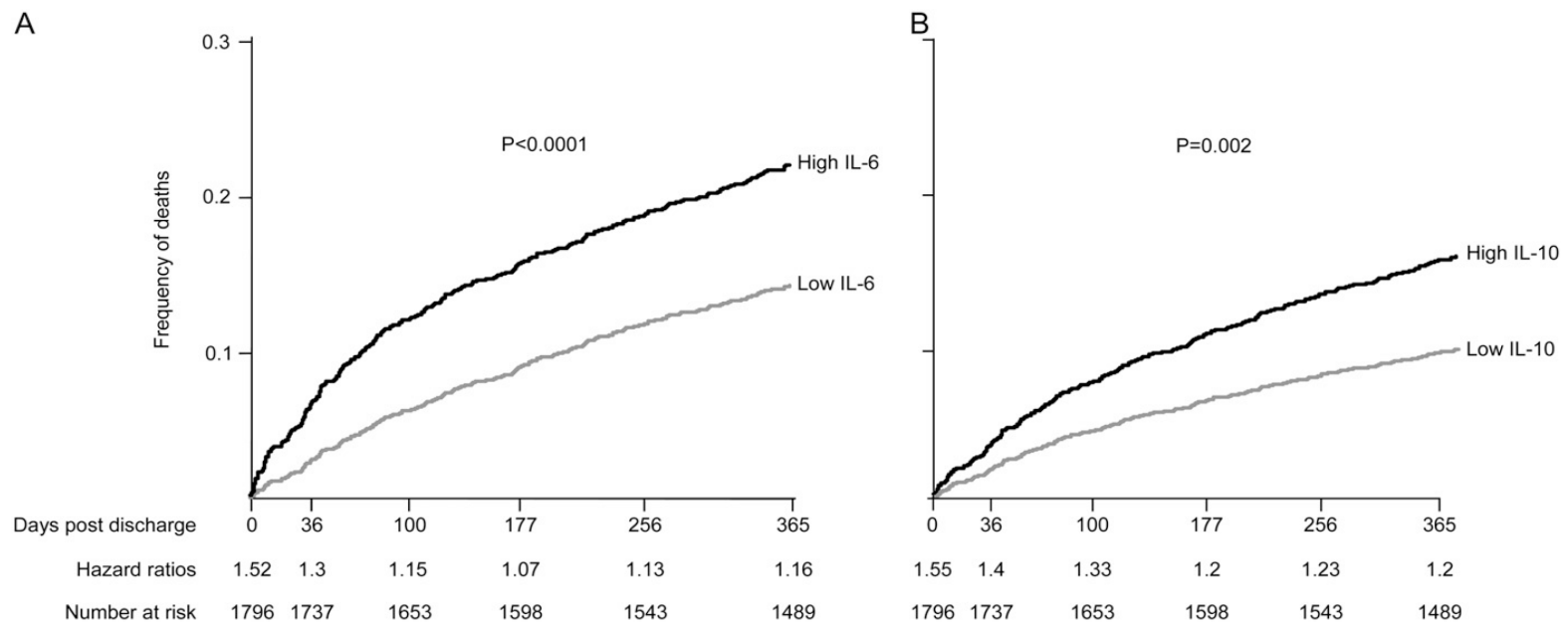
Prescott et al AJRCCM 2014

Mortality after Sepsis

Table 3: Mortality during the Subsequent Year for Patients Hospitalized with Severe Sepsis in the Intensive Care Unit, Matched Intensive Care Unit Control Subjects, Matched Hospitalized with Infection, Matched Hospital Control Subjects, and Matched and Unmatched Population Control Subjects

Variables	Developed Severe Sepsis and Required ICU Care (n = 4,179)	Required ICU Care but Did Not Develop Severe Sepsis (n = 4,179)	Hospitalized with Infection but Did Not Require ICU Care (n = 4,179)	Hospitalized Patients (n = 4,179)	Matched Population Control Subjects (n = 4,179)	Unmatched Population Control Subjects (n = 819,283)
Mortality, %*						
1-yr mortality	40.8	25.4	27.9	20.5	12.8	5.3
2-yr mortality	51.2	36.5	38.9	30.7	21.3	10.3
3-yr mortality	58.9	44.3	48.2	39.1	28.5	15.3
Mortality for those discharged home, %						
1-yr mortality	27.4	17.83	21.4	16.1	—	—
2-yr mortality	40.1	29.2	31.6	25.5	—	—
3-yr mortality	47.2	36.9	40.6	33.7	—	—

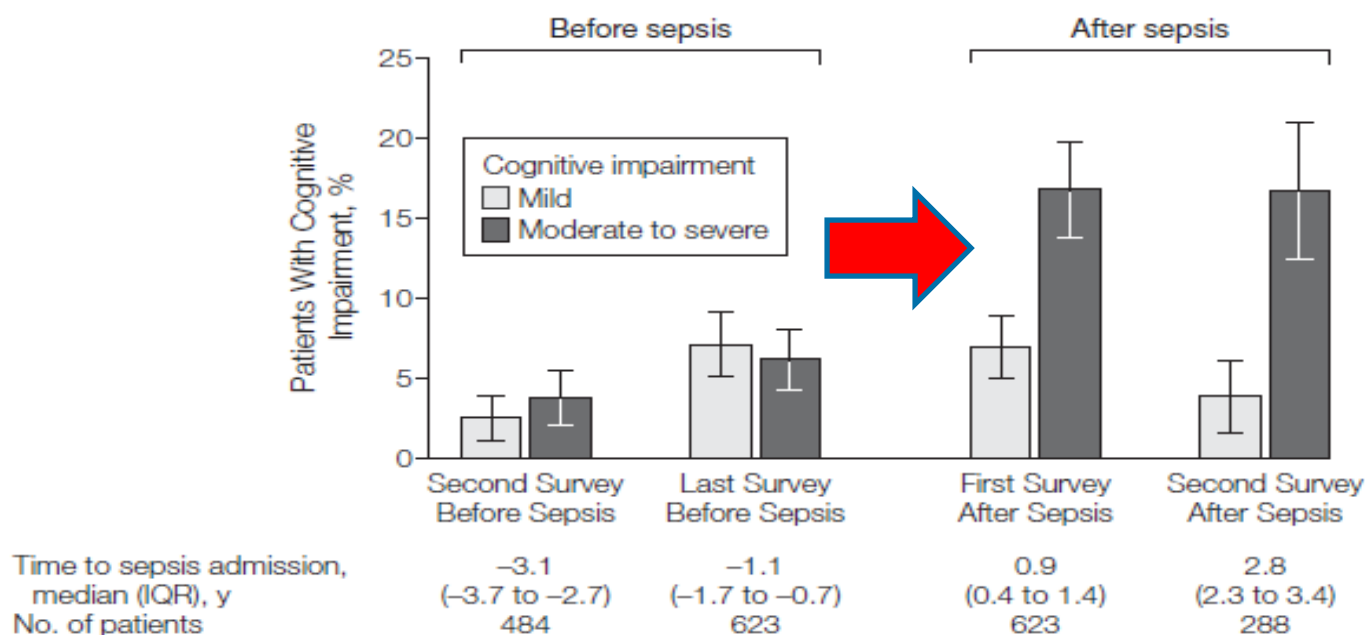
Inflammation (Pro- and Anti-) Persists after Sepsis and is Associated with Mortality



Yende et al AJRCCM 2008

Cognitive Impairment after Sepsis

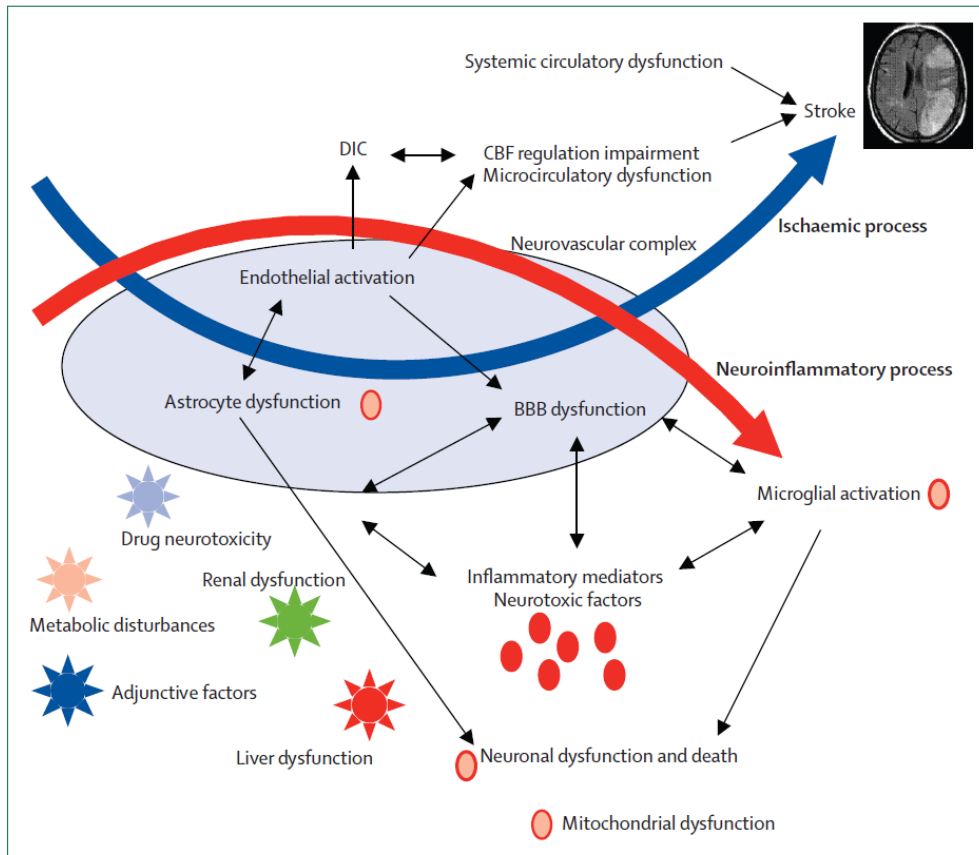
Figure 2. Cognitive Impairment Among Survivors of Severe Sepsis at Each Survey Time Point



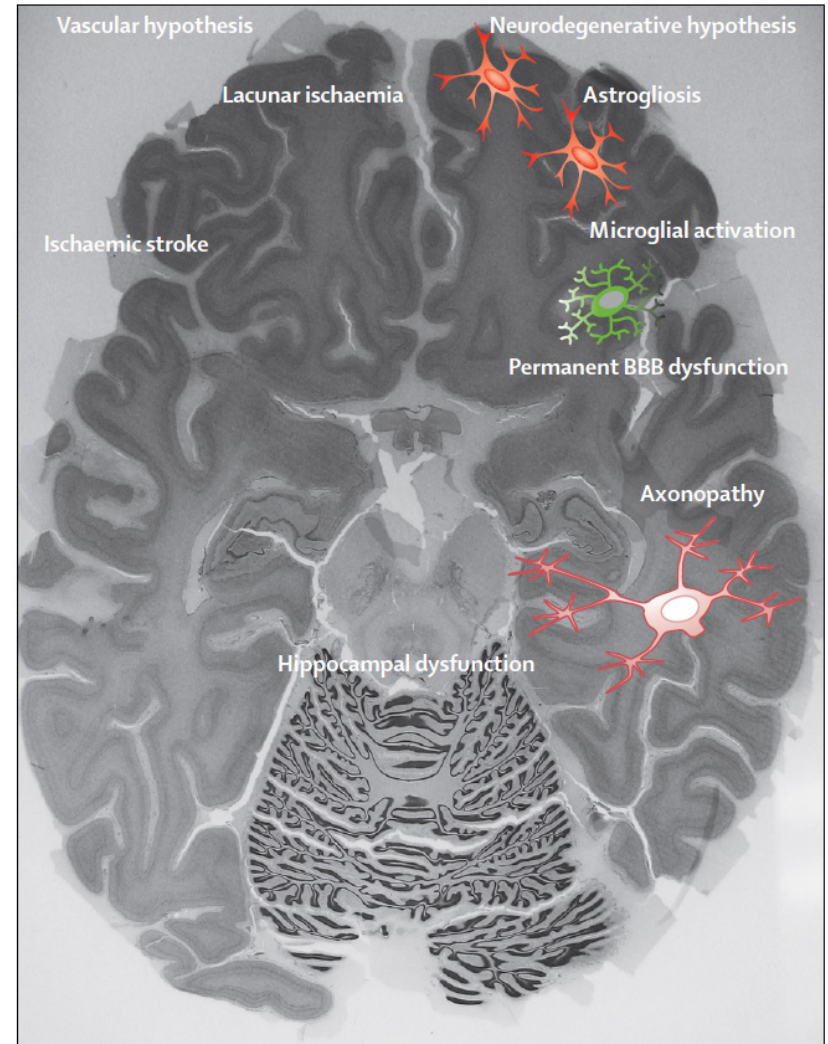
Error bars indicate 95% confidence intervals (CIs); IQR, interquartile range.

Interpretive Example: Compared with stable rates before severe sepsis, the prevalence of moderate to severe cognitive impairment increased from 6.1% (95% CI, 4.2%-8.0%) before severe sepsis to 16.7% (95% CI, 13.8%-19.7%) at the first survey after severe sepsis ($P < .001$ by χ^2 test; Table 2).

The Perfect Storm of Sepsis

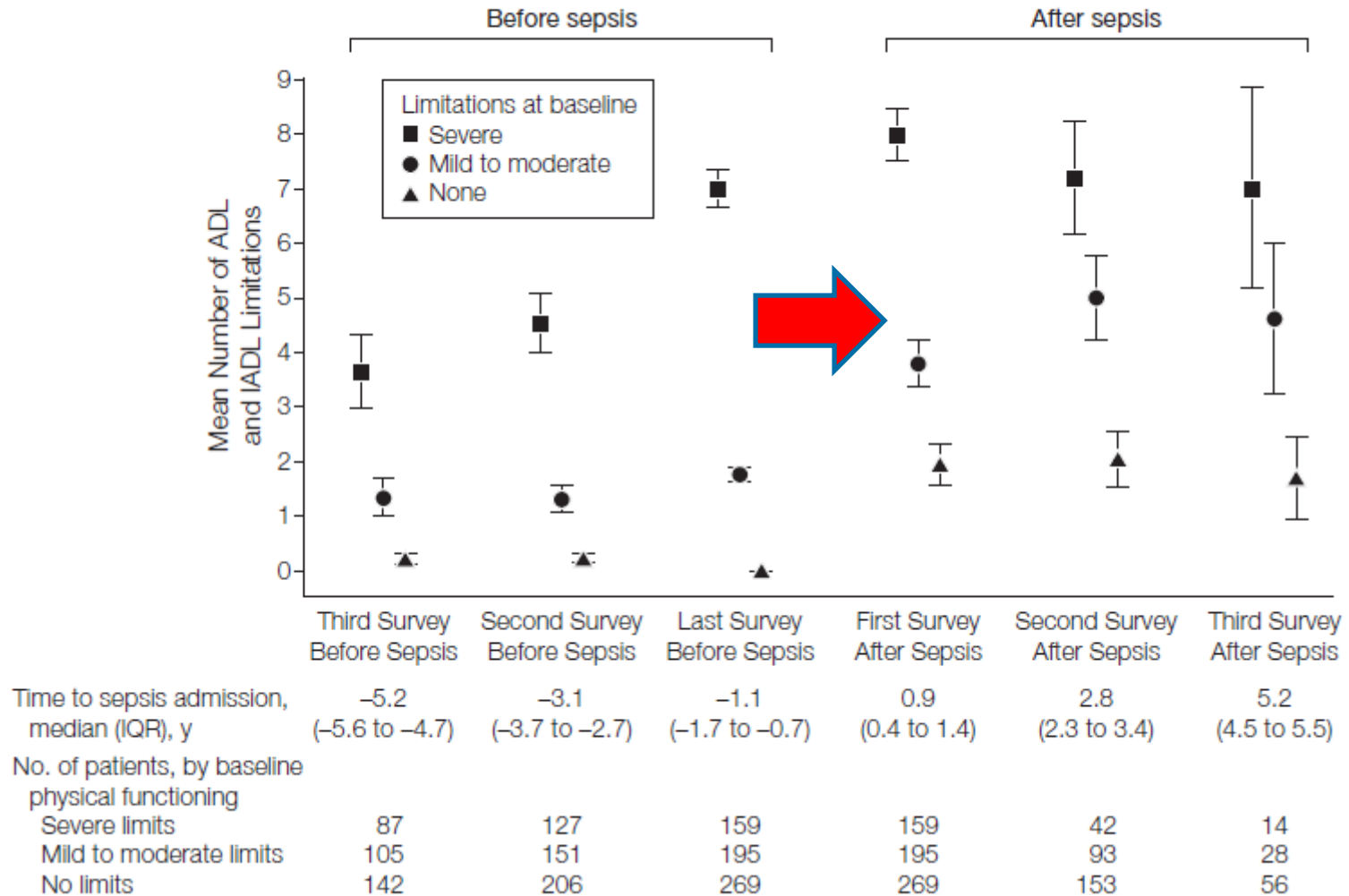


Annane et al Lancet Resp Med 2015

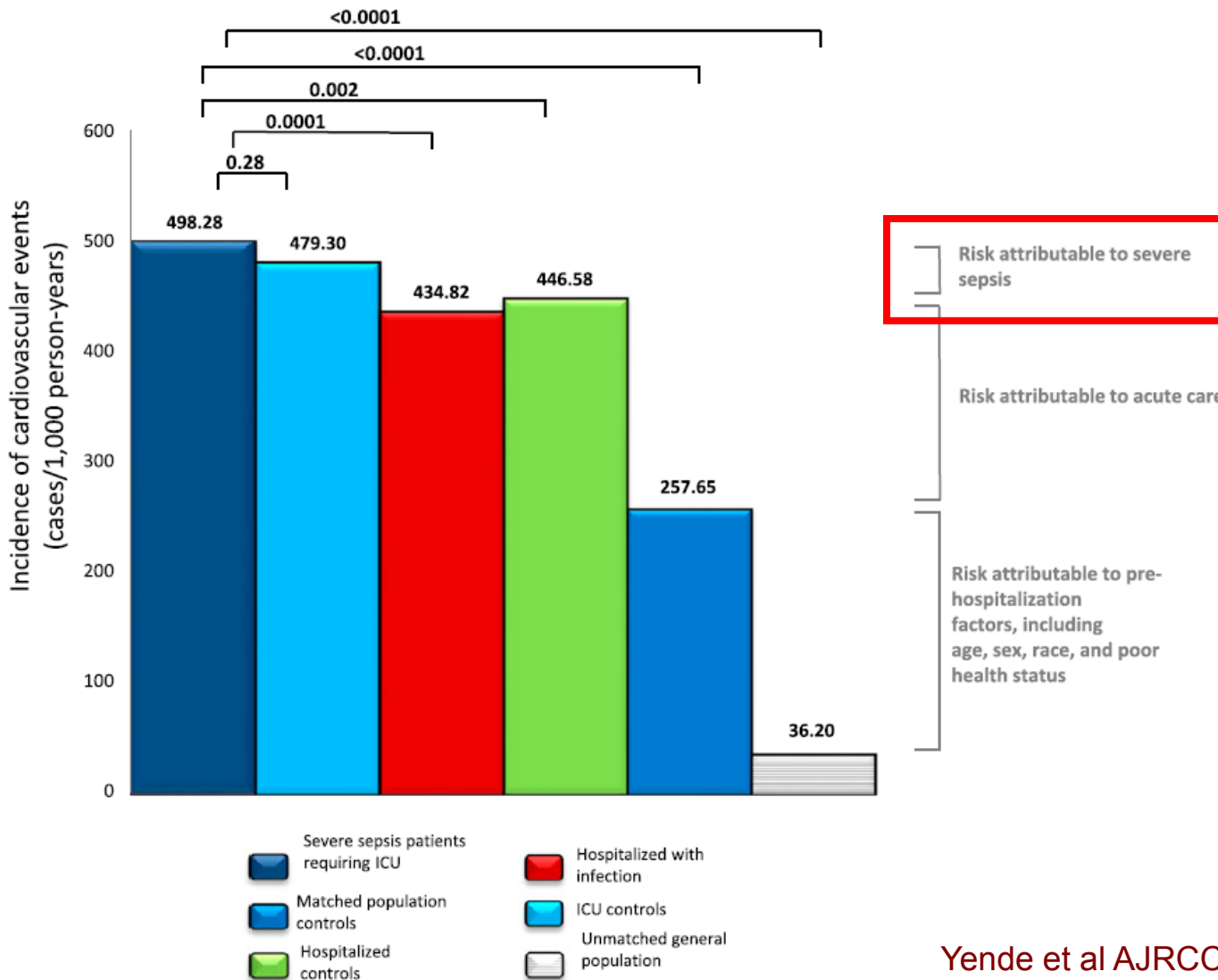


Functional Impairment after Sepsis

Figure 3. Functional Trajectories by Baseline Functioning



Cardiovascular Risk after Sepsis



Yende et al AJRCCM 2014
 Ou et al AJRCCM 2015 (ePub 1.25.16)

Atrial Fibrillation and Sepsis

- ◆ **AF is common during sepsis**
 - 25.5% of Medicare beneficiaries experienced AF
 - New-onset AF accounted for one-quarter of cases
- ◆ **New-onset AF is associated with**
 - In-hospital stroke (4-fold higher)
 - In-hospital mortality (1.5-fold higher)

Walkey et al Am Heart J 2013

Walkey et al JAMA 2011

Atrial Fibrillation after Sepsis

	<u>Rate of AF after Sepsis (N, %)</u>			
Time	<u>No AF (N=95,536)</u>	<u>New-Onset AF (N=9,540)</u>	<u>Prior AF (N=33,646)</u>	<u>P-Value</u>
1 year	7,315 (7.7)	4,193 (44.2)	19,147 (57.2)	<0.001
2 years	9,760 (10.5)	4,651 (49.3)	20,304 (60.9)	<0.001
3 years	11,315 (12.6)	4,874 (52.0)	20,695 (62.3)	<0.001
4 years	12,394 (14.3)	4,987 (53.6)	20,877 (63.1)	<0.001
5 years	13,080 (15.5)	5,074 (54.9)	20,967 (63.5)	<0.001

New-onset AF severe sepsis survivors were more likely to be hospitalized post-discharge for heart failure and ischemic stroke and more likely to die

Walkey et al Chest 2014

Sepsis-Induced Immunosuppression

Viral Reactivation after Sepsis

Virus	Septic	Critically-Ill Non-Septic	Healthy Controls
	<i>No. positive[†]/No. tested (%)</i>		
CMV*	86/356 (24.2)	1/89 (1.1)	0/165 (0)
EBV	287/539 (53.2)	18/149 (12.1)	6/165 (3.6)
HSV	76/538 (14.1)	2/150 (1.3)	0/165 (0)
HHV-6	56/539 (10.4)	1/150 (0.7)	7/165 (4.2)
TTV[‡]	179/231 (77.5)	33/55 (63.6)	98/165 (60.1)
JC**	85/238 (35.7)	10/42 (23.8)	
BK**	35/237 (14.3)	4/42 (9.5)	
Any Virus	432/560 (77.1)	62/161 (38.5)	104/165 (63.0)
>1 Virus	239/560 (42.7)	9/161 (5.6)	9/165 (5.5)

[†]Except where indicated, No. positive reflects the number of patients who tested positive in either whole blood or plasma or both. No. tested represents the total number of patients tested.

*Results are from CMV seropositive patients only.

[‡]Tested in plasma only.

**Tested in urine.

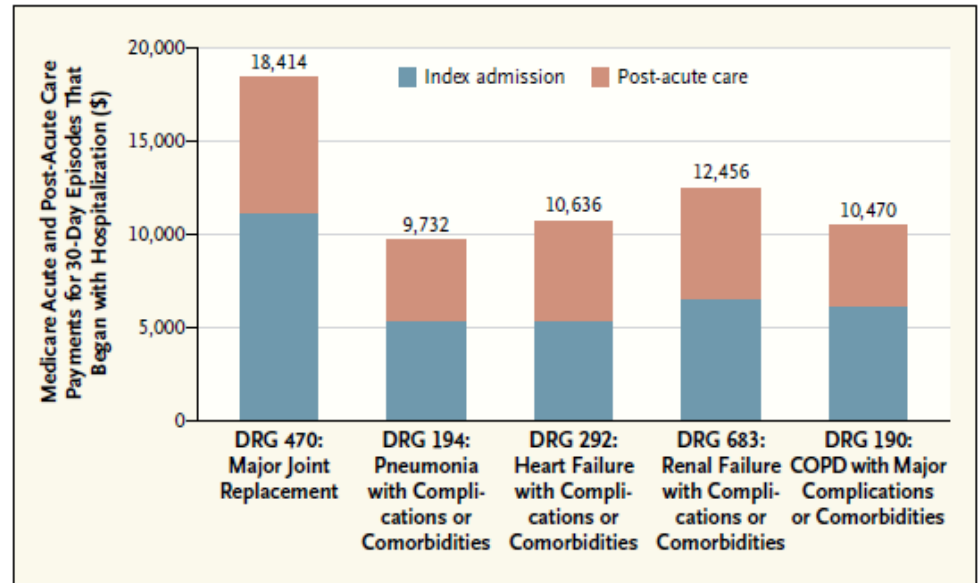
doi:10.1371/journal.pone.0098819.t002

Walton et al 2014



Post-Acute Care Use

- ◆ **Post-acute care costs, including services and placement at discharge and subsequent ED visits and readmissions, are increasing**
- ◆ **The consequences of sepsis may confer an increased risk of post-acute care use**



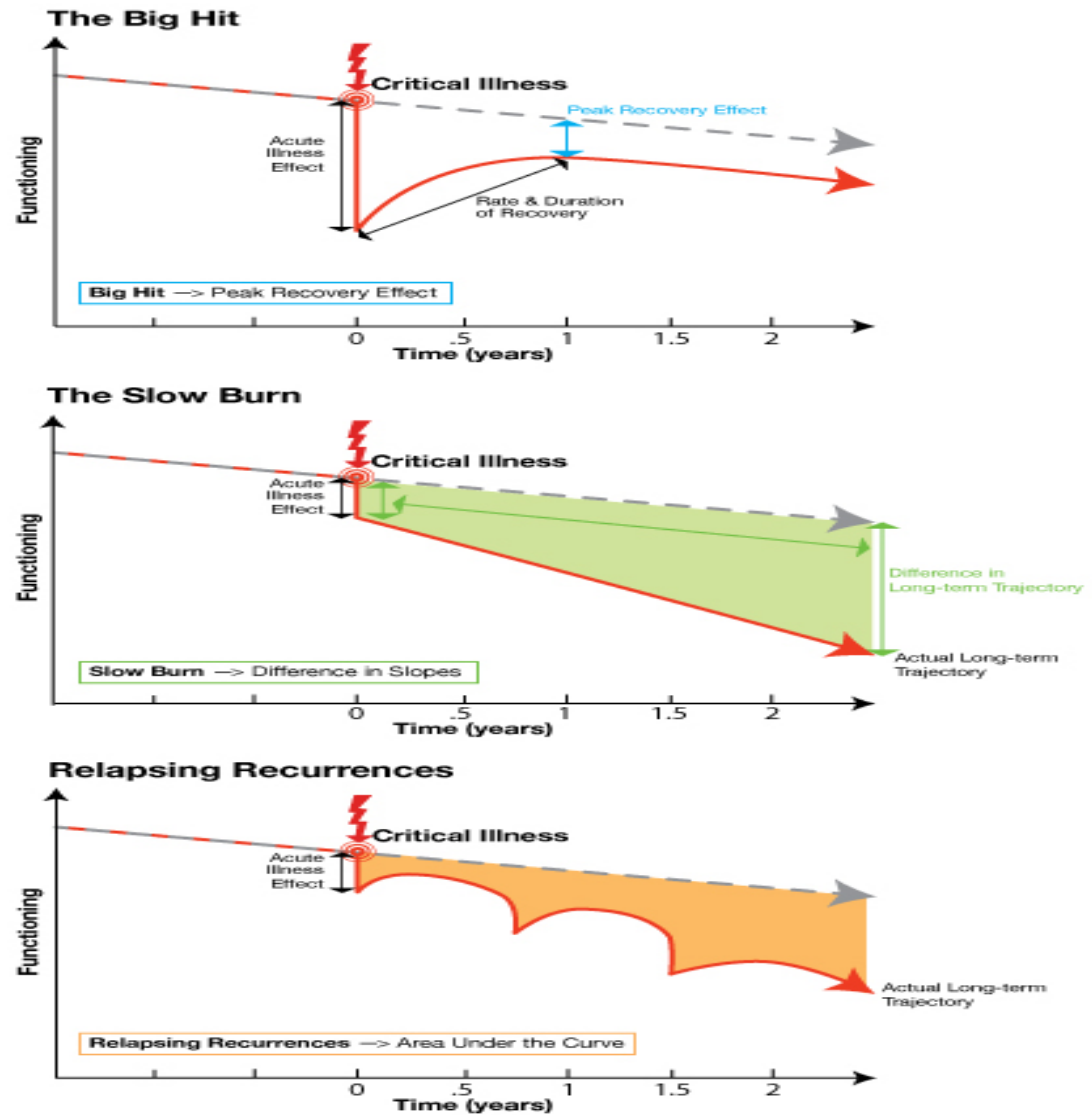
Medicare Acute and Post-Acute Care Payments for 30-Day Episodes That Began with a Hospitalization, 2008.

Data are from Gage et al.³ Thirty-day fixed episodes include the full amount of all claims incurred within 30 days after discharge, including readmissions. COPD denotes chronic obstructive pulmonary disease, and DRG diagnosis-related group.

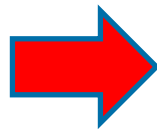
Mechanic et al NEJM 2014

Jencks et al NEJM 2009

Hospital Readmission after Sepsis



The Uncertain Functional Trajectory Post-Sepsis and the Readmission Hypothesis



Rate and Timing of 30-Day Hospital Readmission After Sepsis

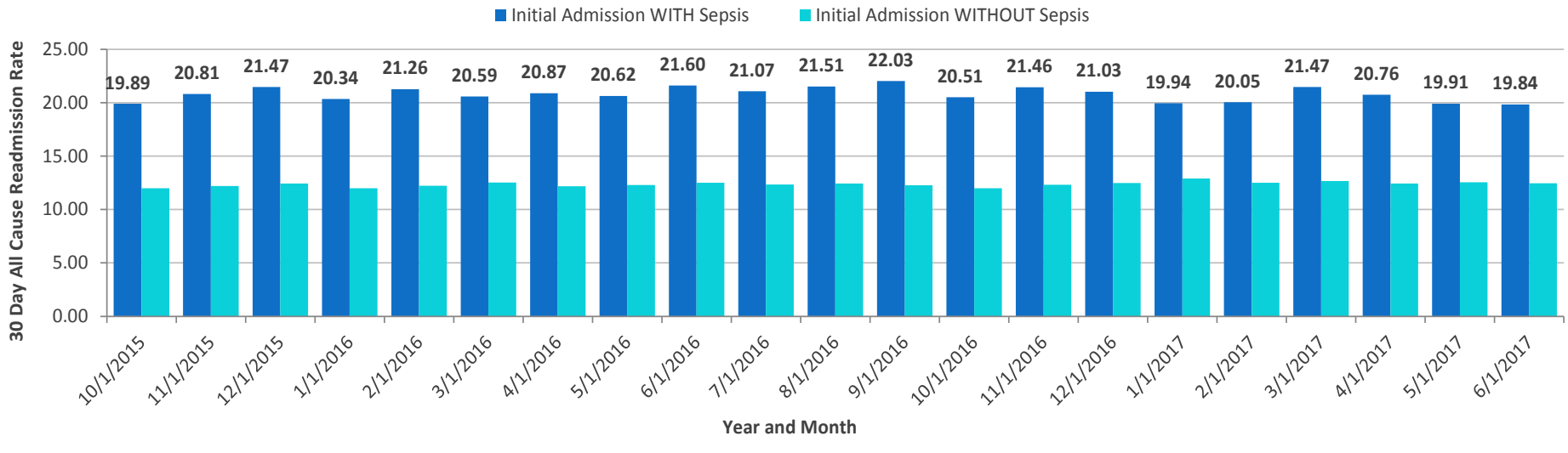
Study	Population	30-day rate	Timing
Elixhauser et al.	<u>Septicemia (N=696,122)</u>	?	--
Liu et al.	<u>Sepsis (N=5479)</u>	?	11 days
Prescott et al.	Elderly <u>severe sepsis</u> survivors (N=1083)	?	--
Ortego et al.	<u>Septic shock (N=269)</u>	?	7 (3 – 15)
Jones et al.	<u>Sepsis (N=1268)</u>	?	13 (6 – 21)
Jones et al.	<u>Severe sepsis (N=2352)</u>	?	11 (5 – 18)
Goodwin et al.	<u>Severe sepsis (43,452)</u>	?	--
Donnelly et al.	<u>Severe sepsis (N=216,328)</u>	?	--
Chang et al.	<u>Sepsis (N=240,198)</u>	?	--

Rate and Timing of 30-Day Hospital Readmission After Sepsis

Study	Population	30-day rate	Timing
Elixhauser et al.	<u>Septicemia (N=696,122)</u>	21.0	--
Liu et al.	<u>Sepsis (N=5479)</u>	17.9	11 days
Prescott et al.	Elderly <u>severe sepsis</u> survivors (N=1083)	26.5	--
Ortego et al. *	<u>Septic shock (N=269)</u>	23.4	7 (3 – 15)
Jones et al. *	<u>Sepsis (N=1268)</u>	27.0	13 (6 – 21)
Jones et al. *	<u>Severe sepsis (N=2352)</u>	26.2	11 (5 – 18)
Goodwin et al.	<u>Severe sepsis (43,452)</u>	25.6	--
Donnelly et al.	<u>Severe sepsis (N=216,328)</u>	19.9	--
Chang et al.	<u>Sepsis (N=240,198)</u>	20.4	--
Norman et al.	<u>Severe sepsis (N=633,407 Medicare) survivors</u>	28.7	--

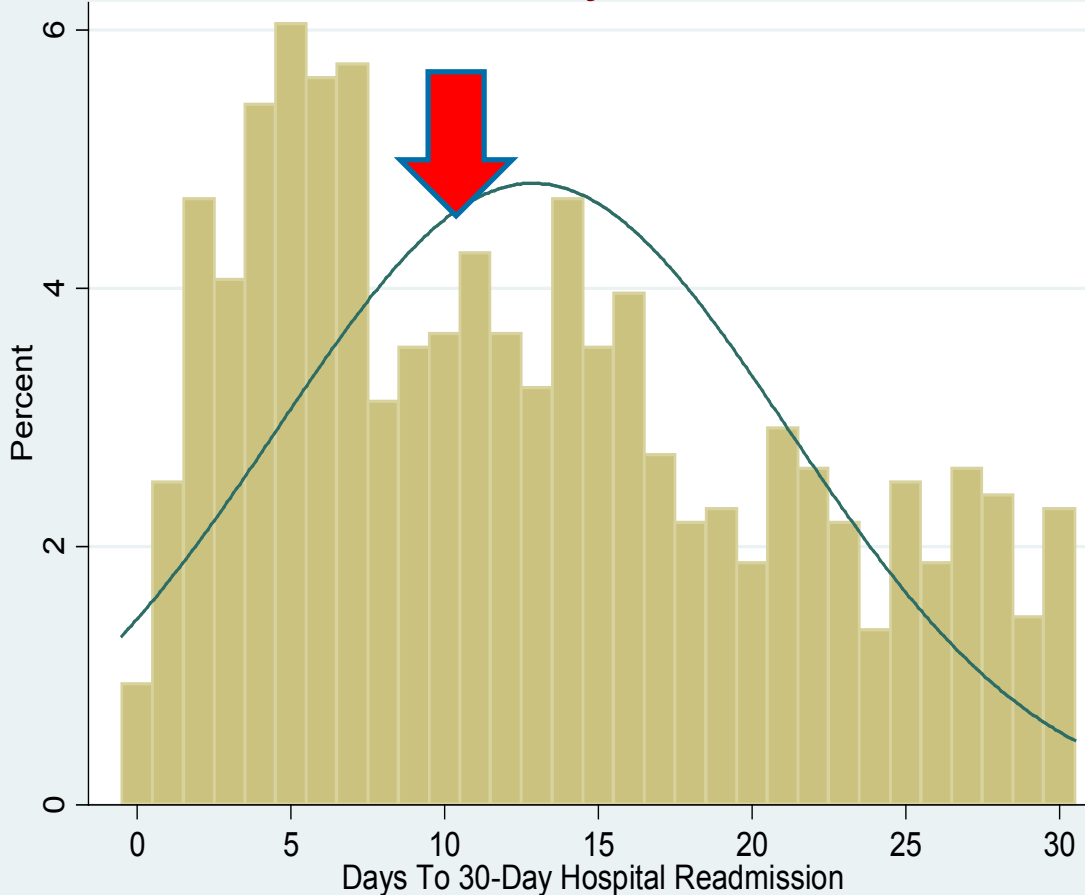
The New York State Situation

30 Day All Cause Readmission Rates by Month



Timing of 30-Day Readmission after Sepsis

New York State Data
Median = 11 days



- Median 12 days, IQR: 6, 19
- No difference between sepsis and non-sepsis index admissions ($p=0.38$)
- Severe sepsis readmissions occurred earlier, compared to sepsis admissions (median 11 days vs. 13 days, $p=0.004$)

Jones et al Annals ATS 2015

Hospital-Based Acute Care Use after Sepsis

<u>Outcomes,</u> <u>n (%)</u>	<u>Non-Sepsis</u> <u>Hospitalization</u> <u>(N=108,958)</u>	<u>Sepsis Hospitalization</u> <u>N=3,620</u>
Readmissions		
7-day	5,657 (5.2)	336 (9.3)*
30-day	16,950 (15.6)	959 (26.5)*
90-day	27,968 (25.7)	1,533 (42.4)*
ED Treat-and-Release Visits		
30-day	4,967 (4.6)	139 (3.8) †

* p < 0.001 for each; † p = 0.04

Jones et al Annals ATS 2015

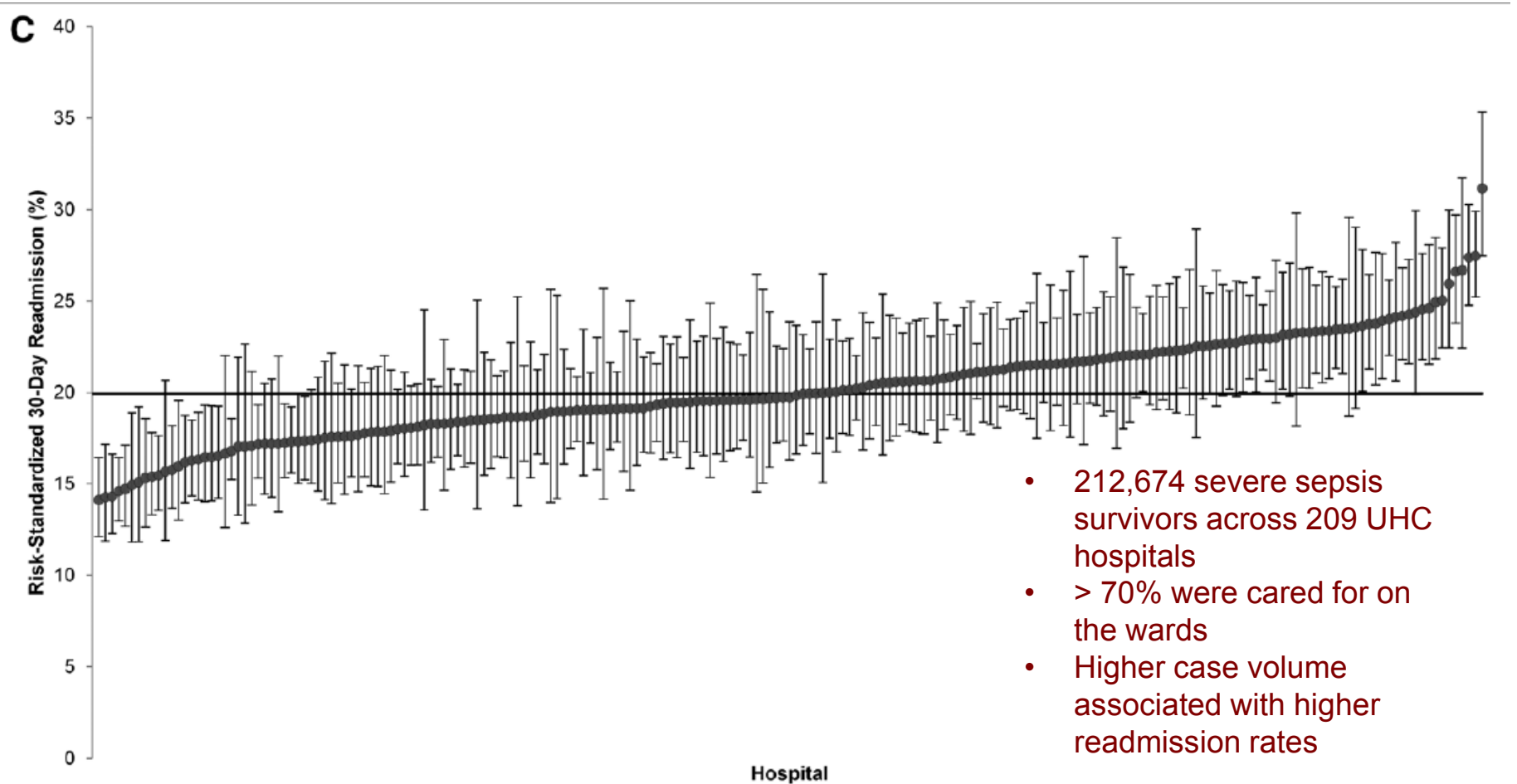
Sepsis Drives Hospital Readmissions

Table 1. High-volume conditions ranked by rate of readmission for all causes within 30 days, 2013

Rank	Principal diagnosis for index hospital stay	Number of index admissions	Number of all-cause readmissions	Aggregate cost of readmissions, \$ millions	Rate of all-cause readmission
Total index admissions for any cause		28,124,869	3,900,556	52,398	13.9
1	Congestive heart failure, non-hypertensive	782,079	183,534	2,728	23.5
2	Schizophrenia and other psychotic disorders	366,256	83,245	772	22.7
3	Respiratory failure, insufficiency, arrest (adult)	290,892	62,684	961	21.5
4	Diabetes mellitus with complications	486,886	99,108	1,204	20.4
5	Acute renal failure	431,452	87,537	1,190	20.3
6	Chronic obstructive pulmonary disease and bronchiectasis	570,077	114,067	1,384	20.0
7	Complication of device, implant or graft	581,289	111,838	1,973	19.2
8	Alcohol-related disorders	261,072	50,081	366	19.2
9	Septicemia	1,011,496	191,156	3,154	18.9
10	Fluid and electrolyte disorders	358,640	65,704	839	18.3

Courtesy of Hallie Prescott

Readmission Risk After Severe Sepsis Varies Dramatically Across Hospitals



Donnelly et al Crit Care Med 2015

WHY? INFECTION

Patient	Initial Hospitalization Infection	Readmission Infection (Chart)	New or Recurrent/ Unresolved
1	C. difficile	Culture negative sepsis	New
2	Intraabdominal abscess and bowel perforation	Pneumonia	New
3	Neutropenic sepsis, c. difficile	Hepatic abscess	New
4	Culture negative sepsis	Urinary tract infection and C. difficile	New
5	MSSA and VRE CLABSI	Klebsiella CLABSI	New

36	C. difficile, hospital-acquired pneumonia	C. difficile	Recurrent/ unresolved
37	Pneumonia	Pneumonia	Recurrent/ unresolved
38	Pneumonia (fungal)	Pneumonia (fungal)	Recurrent/ unresolved
39	Pseudomonal bacteremia	Citrobacter bacteremia (cultures from discharge of initial hospitalization)	Recurrent/ unresolved
40	Pneumonia	Pneumonia	Recurrent/ Unresolved

- 69% of unplanned readmissions attributable to infection via chart review
- 51% of infection-related readmissions were categorized as recurrent/unresolved
- 19% are same site and same organism

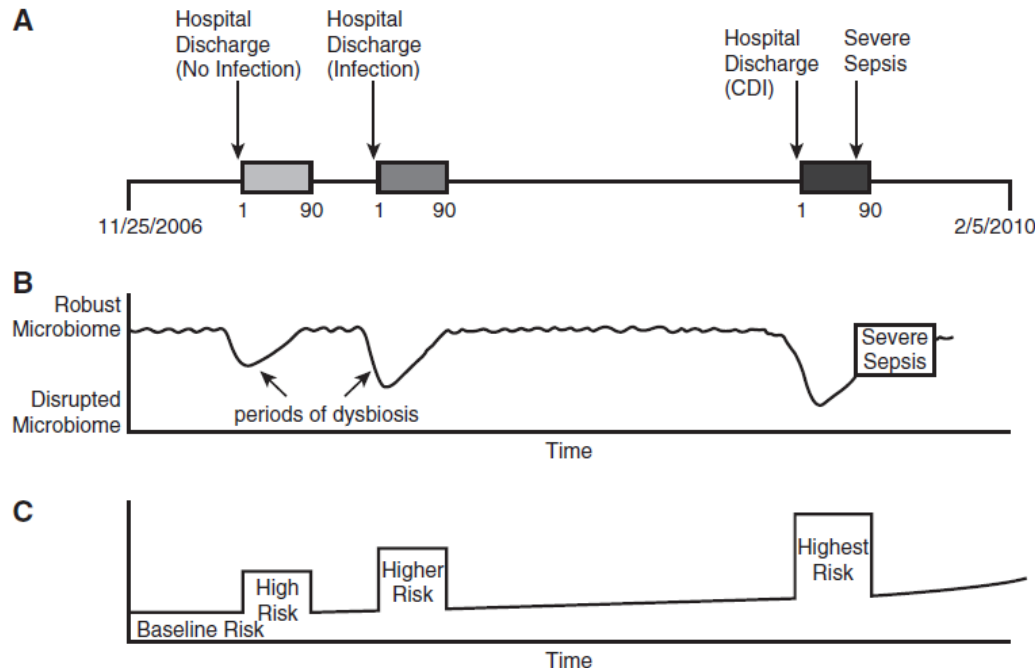
Sun et al CCM 2016
DeMerle et al CCM 2017

Activation-Associated Accelerated Apoptosis of Memory B Cells in Critically Ill Patients With Sepsis

Manu Shankar-Hari, PhD¹⁻³; David Fear, PhD^{2,4}; Paul Lavender, PhD^{2,4}; Tracey Mare, BSc³; Richard Beale, MBBS^{2,3}; Chad Swanson, PhD⁵; Mervyn Singer, FRCP⁶; Jo Spencer, PhD¹

Reduction of Immunocompetent T Cells Followed by Prolonged Lymphopenia in Severe Sepsis in the Elderly*

Shigeaki Inoue, MD, PhD^{1,2}; Kyoko Suzuki-Utsunomiya, PhD¹; Yoshinori Okada, PhD³; Yumi Iida, BS³; Takayuki Taira, MD²; Naoya Miura, MD²; Tomoatsu Tsuji, MD²; Takeshi Yamagiwa, MD²; Seiji Morita, MD²; Tomoki Chiba, PhD⁴; Takehito Sato, PhD⁴; Sadaki Inokuchi, PhD²



Shankar-Hari CCM 2017

Inoue et al CCM 2013

Prescott et al AJRCCM 2015

Most Frequent Readmission Diagnoses After Sepsis

Sepsis

15.0%

Congestive heart failure

12.0%

42% of readmission diagnoses were for Ambulatory Care Sensitive Conditions

**The Big 3:
Infection/Sepsis**

Fluid Balance (Heart failure/Renal failure)

Respiratory (Aspiration pneumonia, COPD)

Aspiration pneumonitis

4.2%

Urinary tract infection

3.9%

What Do Patients Look Like At Readmission?

ED Presentation of Unplanned Hospital Readmissions

Fever upon presentation	25.0%
White blood cell count, initial	10 (7 – 14)
Respiratory rate, initial	18 (16 – 20)
Heart rate, initial	106 (88 – 116)
Sepsis	63.8%

Sun et al CCM 2016

Linking Index Admission with Readmission

Pre-acute illness

Illness severity

Infection-Related

Processes of Care

Discharge

Age

Length of stay

Source (Gastrointestinal)

Procedures

Hemoglobin at discharge

Gender

Microbiology

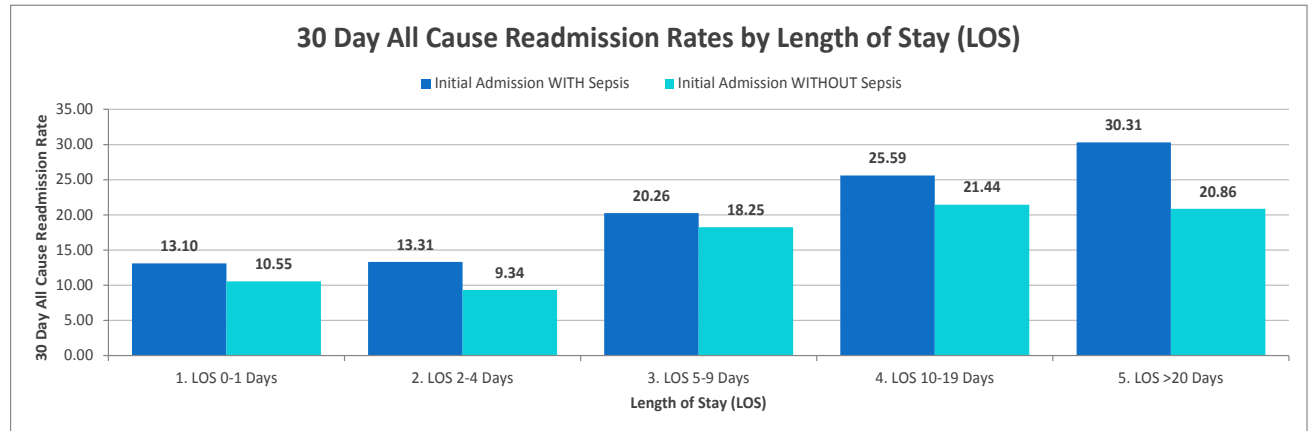
RDW at discharge

Comorbidities

Recent hospitalizations

Insurance status

Lower income, rural

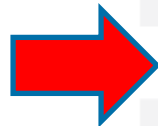


Hospitalization Risk Factors

TABLE 6. Risk Factors Independently Associated With 30-Day Hospital Readmission After Sepsis Hospitalizations

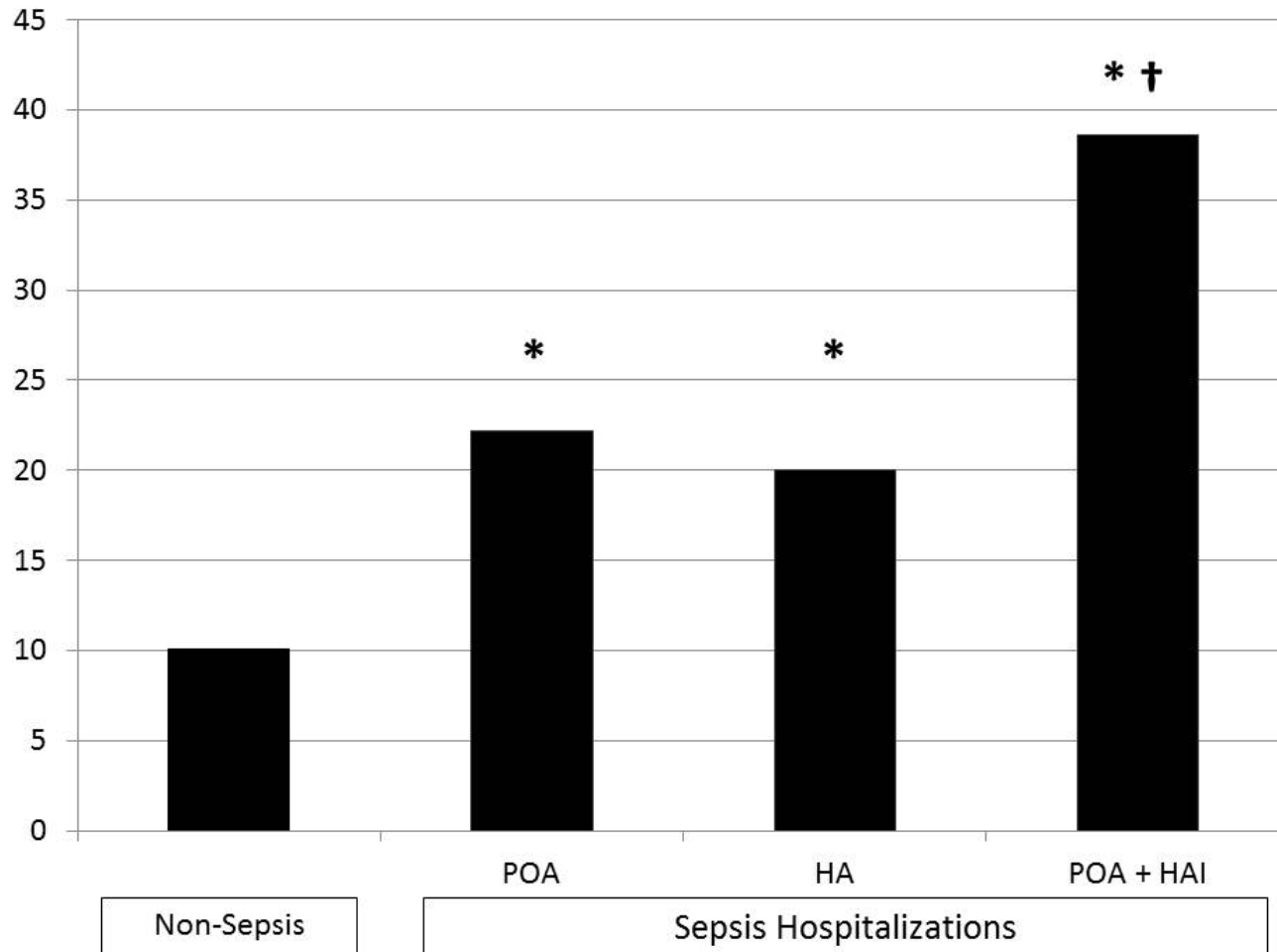
Model (<i>n</i> = 444)	Adjusted OR (95% CI)	<i>p</i>
Use of total parenteral nutrition	2.17 (1.08–4.33)	0.03
Duration of antibiotics, d	1.02 (1.00–1.04)	0.047
Prior hospitalizations		
0	Reference	Reference
1–5	2.12 (1.28–3.53)	0.004
> 5	7.58 (2.81–20.48)	< 0.001
Discharge hemoglobin, g/dL	0.83 (0.70–0.99)	0.04

Duration of antibiotics was the long risk factor associated with infection-related readmission



OR = odds ratio.

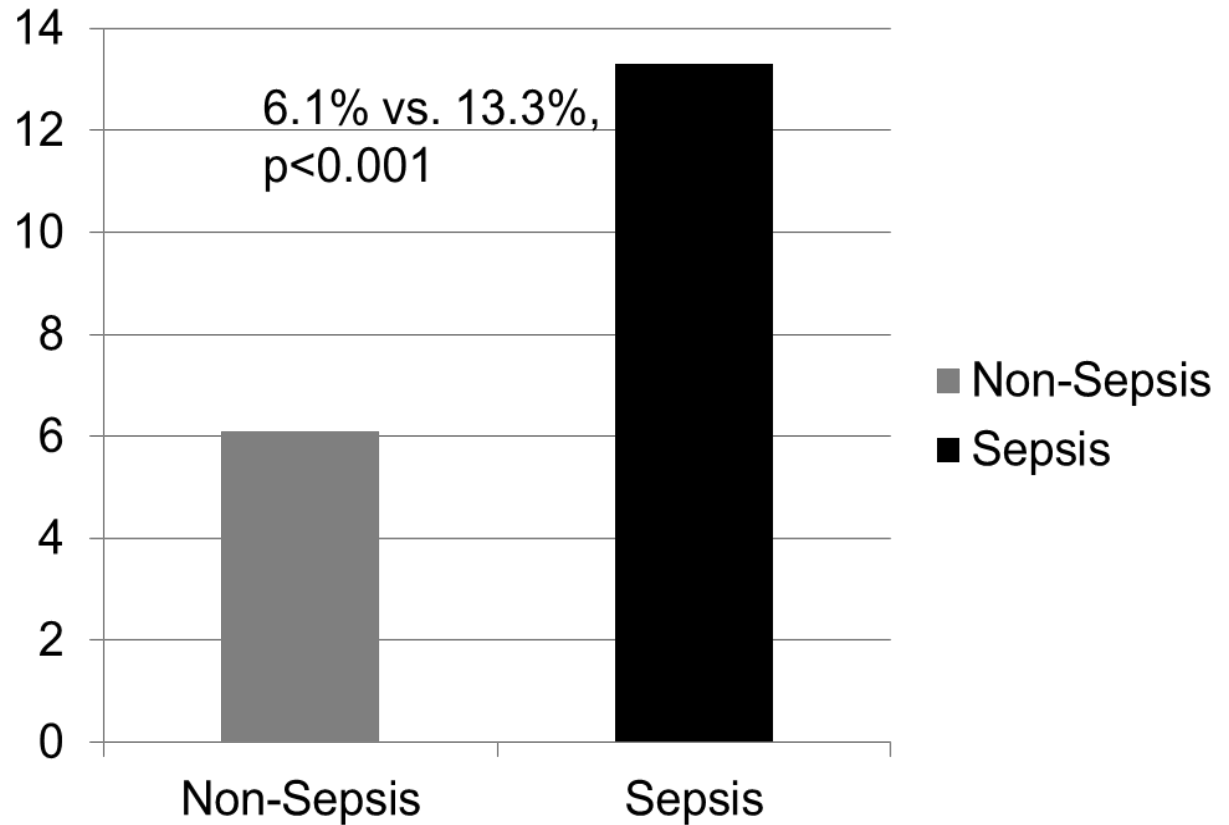
The Timing of the Infection Matters



Readmission Outcomes Are Worse After Sepsis

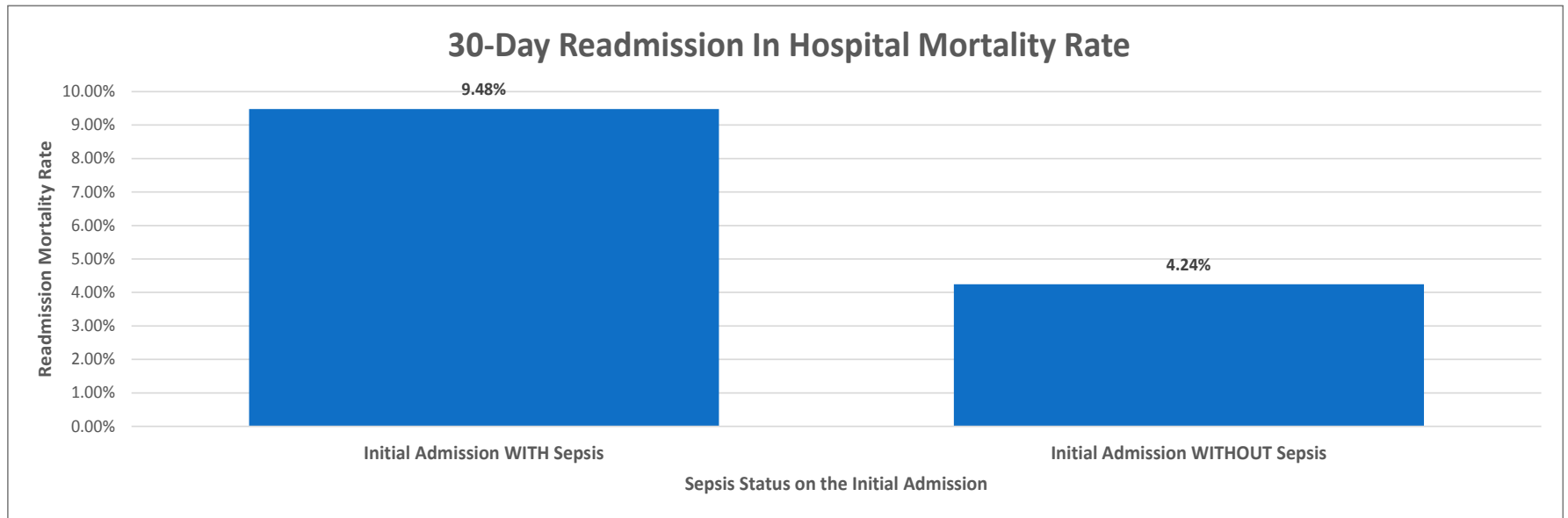
13-16% of readmissions after sepsis result in death or transition to hospice
- Maley et al Clin Chest Med 2016

Highlight the potential role of **targeted early palliative care**

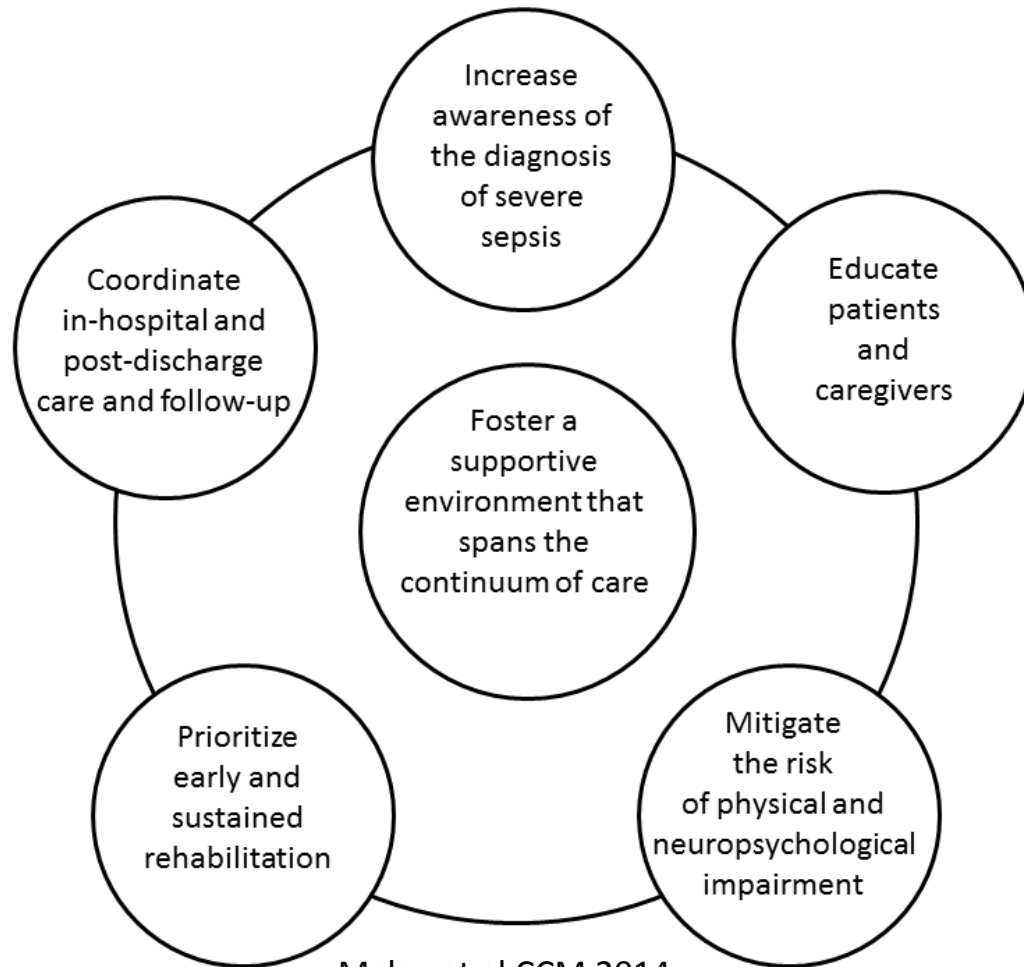


Jones et al Annals ATS 2015

Readmission Mortality after Sepsis: NYS Data



Moving Forward: Forge The Alliance

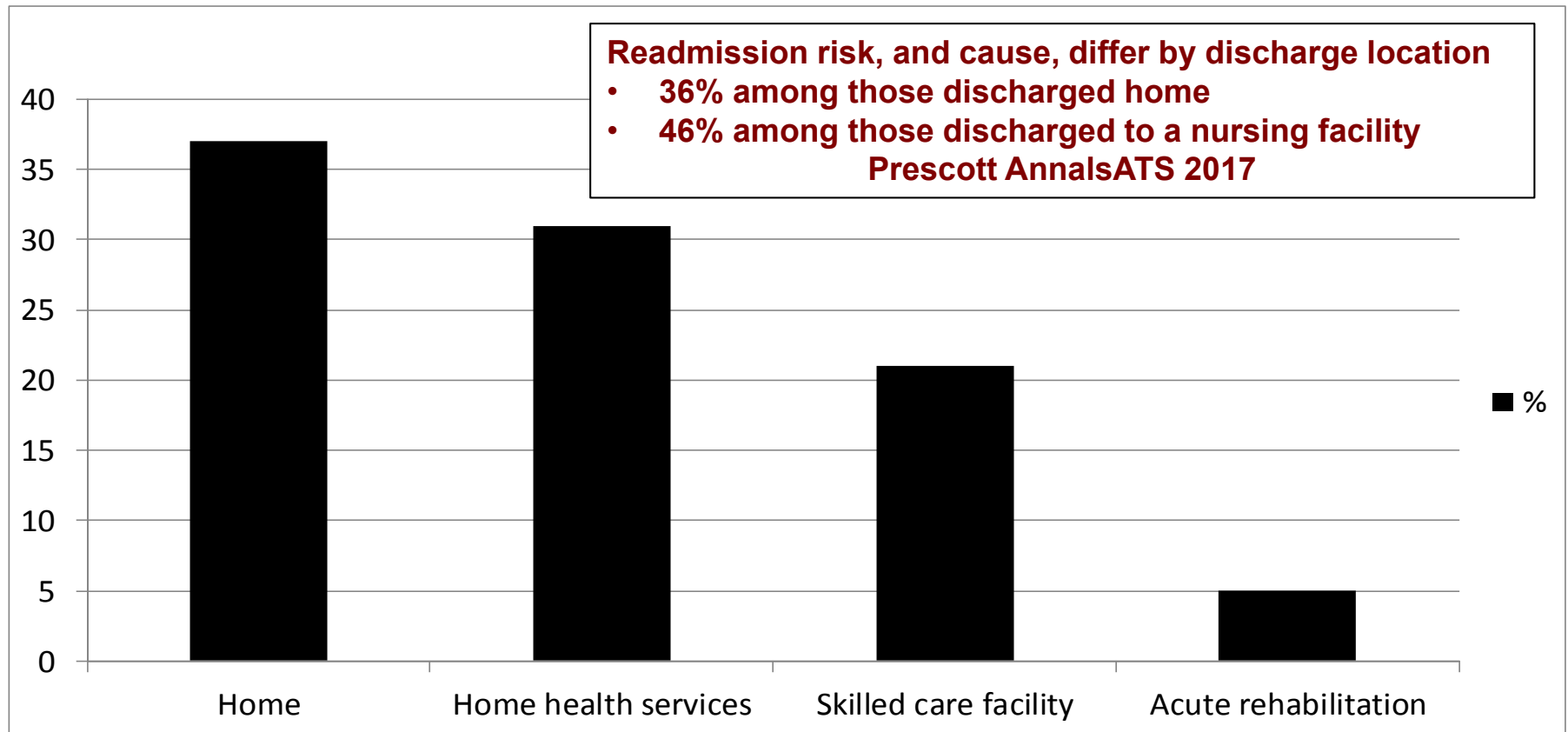


- ◆ Empower survivors, their caregivers, and their providers
- ◆ Start by calling it what it is: sepsis

Moving Forward: Optimize Care Coordination

Coordination of follow-up was absent or too late in **two-thirds** of UPHS septic shock survivors who were readmitted within 30 days

- Ortego et al Crit Care Med 2014



UPHS Data 2010 – 2015 for Sepsis Survivors

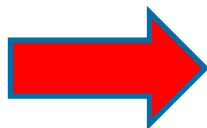
Discharge Planning: Room for Improvement

- **Sepsis was rarely listed on the hospital discharge summary**
- **76% of patients/caregivers were not provided instructions about what to do should the patient's condition worsens**
- **90% of sepsis survivors readmitted within 30 days had no follow-up appointment scheduled or follow-up was scheduled > 10 days post-discharge**
- **96% of patients/caregivers were not provided specific contact information to call if problems arose after hospital discharge**

Qutulqutub Lumpkin BSN,CCRN, Julie Rogan MSN, CNS
Chart review at Penn Presbyterian Medical Center

A Sepsis-Specific Approach at Discharge

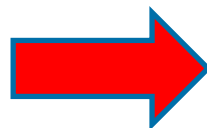
Raise Awareness



As a sepsis survivor, @NAME@ is at high risk for the following:

- Physical and cognitive impairment post-sepsis
- 30-day-all cause hospital readmission, with general risk in the 20-25% range at Penn.

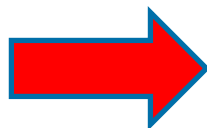
Schedule timely follow-up and inform care providers



Recommend:

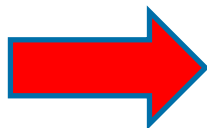
1. Follow-up within 7-10 days of discharge with primary care physician, including information re: patient's sepsis course, source, and antibiotic needs included in the discharge summary

Mitigate and manage new or worsening impairments



2. Assessment by physical and occupational therapy for home physical therapy or acute rehabilitation prior to discharge

Be vigilant for new or recurrent infections, as 2 out of 3 survivors who present to the ED present with sepsis again



3. Assessment of ability to manage medication list prior to discharge, given risk of cognitive impairment after sepsis, with recommendation to engage caregivers in healthcare needs if patient deemed high-risk for inability to manage medications and engage home health services

4. Timely evaluation of signs and symptoms suggestive of a recurrent or new infection, as the majority of 30-day hospital readmissions are due to a new or recurrent infection

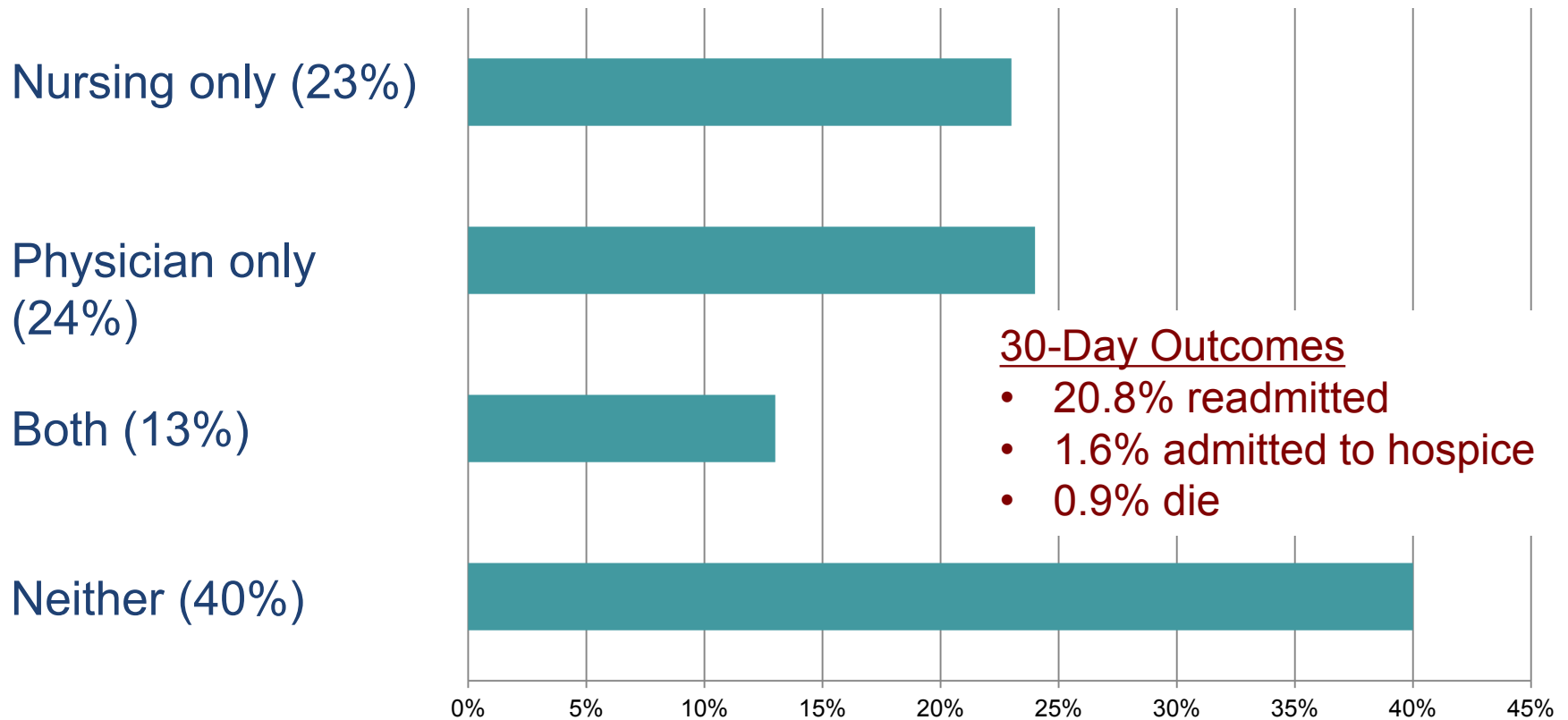
Show the Life After Sepsis video with patients and their family at discharge

Surveillance: The Potential Benefit of Early and Intense Home Health Services

- ◆ **Home health care is common and costly**
 - 3.5 million beneficiaries received home health services
 - 30% of sepsis survivors discharged to home health care
 - \$17.9 billion

- ◆ **Early and intensive home health nursing visits and early physician follow-up for sepsis survivors may reduce 30-day all-cause readmission rates**

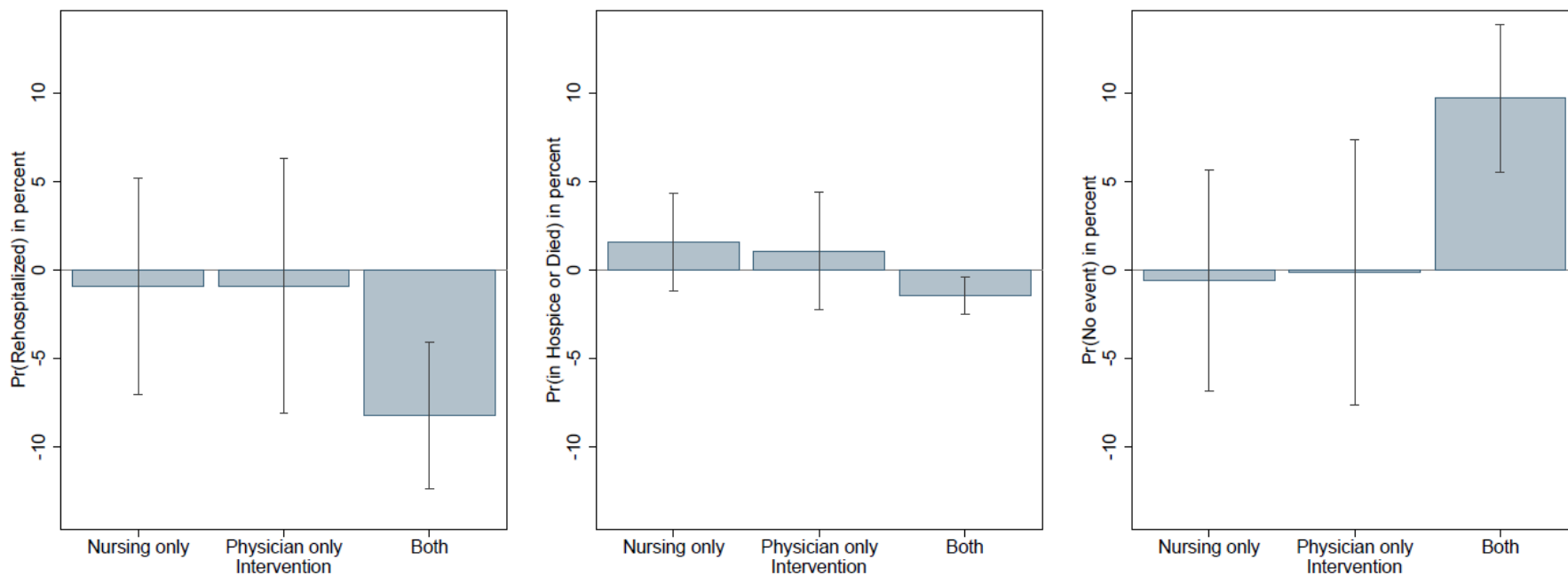
Heart Failure Study: Percent Receiving Each Treatment



Courtesy of Christopher Murtaugh

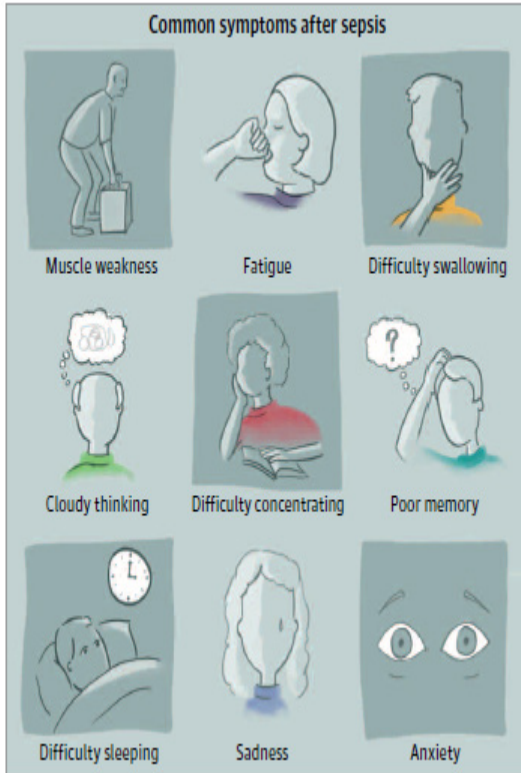
Frontloading Improves Outcomes in Heart Failure: Might It In Sepsis?

Figure 2. Treatment effects with 95% confidence intervals on 30-day rehospitalizations and other events



Note: Estimates from a multinomial logit model with control function adjustment for endogenous treatment.

Penn Home Health Program Design



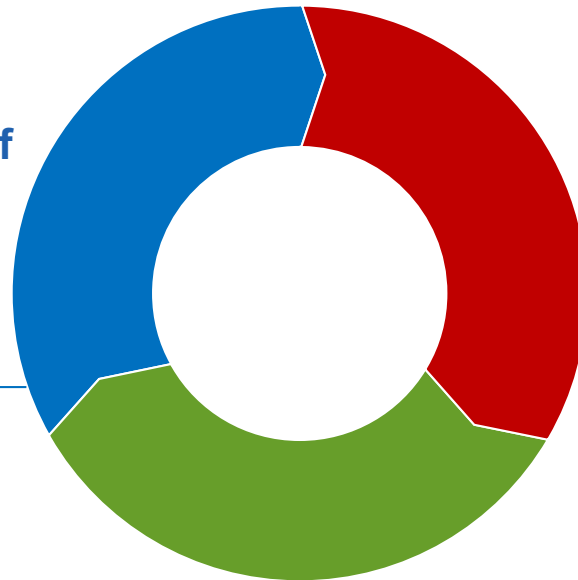
Physical Therapy	Occupational Therapy	Speech and Language	Skilled nursing
2-4 times per week 2 weeks	2-4 times per week 2 weeks	2-4 times per week 2 weeks	2-3 times per week 2 weeks
<ul style="list-style-type: none"> a) Mobility program b) Daily exercise program c) Time spent out of bed daily 	<ul style="list-style-type: none"> a) Sleep hygiene b) Daily ADL participation c) Cognitive assessment and retraining 	<ul style="list-style-type: none"> a) Aspiration screening b) Cognitive linguistic training 	<ul style="list-style-type: none"> a) Education for patient and family- Fact Sheet on Life after Sepsis b) Surveillance training c) Medication education / reconciliation d) Anxiety & Depression Screening Tool

Prescott JAMA 2018

Penn Medicine Sepsis Alliance: The Circle of Sepsis

The Penn Medicine Sepsis Alliance governs health system sepsis care activities with the goal of improving the early identification of sepsis and optimizing care management.

READMISSIONS:
Reduce the number of 7 day and 30 day readmissions after a hospitalization for sepsis.



RECOGNITION: Maximize recognition of sepsis-associated end organ dysfunction.

ADHERENCE: Improve adherence to the 3 hour SEP-1 bundle for inpatients and in the ED.

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- ◆ Samuel Jackson

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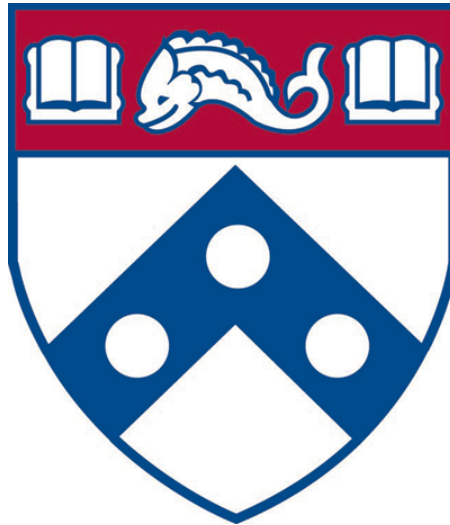
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- ◆ Adair Andrews
- ◆ And many others

Questions?

Please feel free to contact me at mark.mikkelsen@uphs.upenn.edu



Lessons Learned from SMOOTH

- SMOOTH tested whether, compared to usual care, patient training and case management could improve health-related quality of life
- The intervention, designed before readmission risk was known, focused on post-sepsis PICS-like symptoms

<u>Outcome</u>	<u>Intervention</u>	<u>Control</u>
SF-36 MCS	48.8 (12.5)	49.2 (12.6)
SF-36 PCS	25.9 (9.4)	24.7 (8.0)
Depression	36 (24.8)	32 (23.5)
PTSD	15.2%	14.0%
Cognition (TICS-M)	33.7 (3.4)	33.1 (3.9)

Schmidt et al JAMA 2016