Outcomes for Critically Ill Sepsis Survivors

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Each year ~ 130,000 Australians are admitted to ICUs at a cost of $3 billion.

Sepsis is a major public health concern

- 1 in 10 patients admitted to an Australian or NZ ICU
- Annual cost of sepsis in the USA is $16.7 billion
- Incidence projected to increase 1.5% annually with increasing comorbidities and organism resistance

Finfer et al, Intensive Care Med, 2004
Kaukonen et al, JAMA, 2014
Angus et al, Crit Care Med, 2001

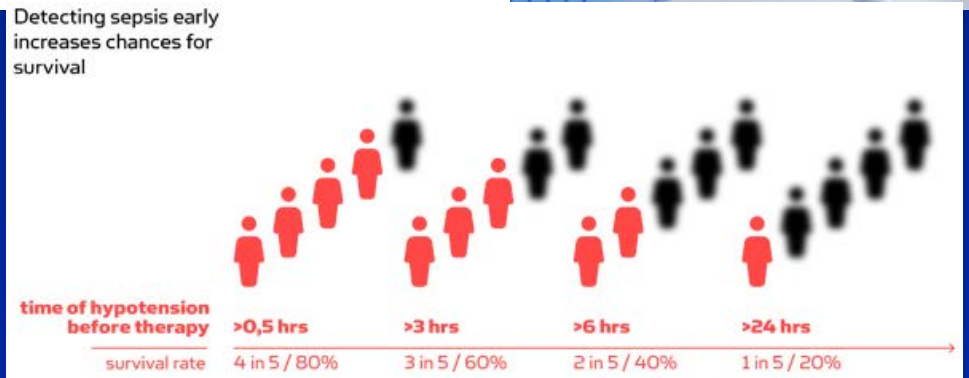
Surviving Sepsis Campaign

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*



Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Kirsi-Maija Kaukonen, MD, PhD, EDIC; Michael Bailey, PhD; Satoshi Suzuki, MD; David Pilcher, FCICM; Rinaldo Bellomo, MD, PhD

IMPORTANCE Severe sepsis and septic shock are major causes of mortality in intensive care unit (ICU) patients. It is unknown whether progress has been made in decreasing their mortality rate.

OBJECTIVE To describe changes in mortality for severe sepsis with and without shock in ICU patients.

DESIGN, SETTING, AND PARTICIPANTS Retrospective, observational study from 2000 to 2012 including 101 064 patients with severe sepsis from 171 ICUs with various patient case mix in Australia and New Zealand.

MAIN OUTCOMES AND MEASURES Hospital outcome (mortality and discharge to home, to other hospital, or to rehabilitation).

RESULTS Absolute mortality in severe sepsis decreased from 35.0% (95% CI, 33.2%-36.8%; 949/2708) to 18.4% (95% CI, 17.8%-19.0%; 2300/12 512; $P < .001$), representing an overall decrease of 16.7% (95% CI, 14.8%-18.6%), an annual rate of absolute decrease of 1.3%, and a relative risk reduction of 47.5% (95% CI, 44.1%-50.8%). After adjusted analysis, mortality decreased throughout the study period with an odds ratio (OR) of 0.49 (95% CI, 0.46-0.52) in 2012, using the year 2000 as the reference ($P < .001$). The annual decline in mortality did not differ significantly between patients with severe sepsis and those with all other diagnoses (OR, 0.94 [95% CI, 0.94-0.95] vs 0.94 [95% CI, 0.94-0.94]; $P = .37$). The annual increase in rates of discharge to home was significantly greater in patients with severe sepsis compared with all other diagnoses (OR, 1.03 [95% CI, 1.02-1.03] vs 1.01 [95% CI, 1.01-1.01]; $P < .001$). Conversely, the annual increase in the rate of patients discharged to rehabilitation facilities was significantly less in severe sepsis compared with all other diagnoses (OR, 1.08 [95% CI, 1.07-1.09] vs 1.09 [95% CI, 1.09-1.10]; $P < .001$). In the absence of comorbidities and older age, mortality was less than 5%.

CONCLUSIONS AND RELEVANCE In critically ill patients in Australia and New Zealand with severe sepsis with and without shock, there was a decrease in mortality from 2000 to 2012. These findings were accompanied by changes in the patterns of discharge to home, rehabilitation, and other hospitals.

Editorial page 1295

Supplemental content at jama.com

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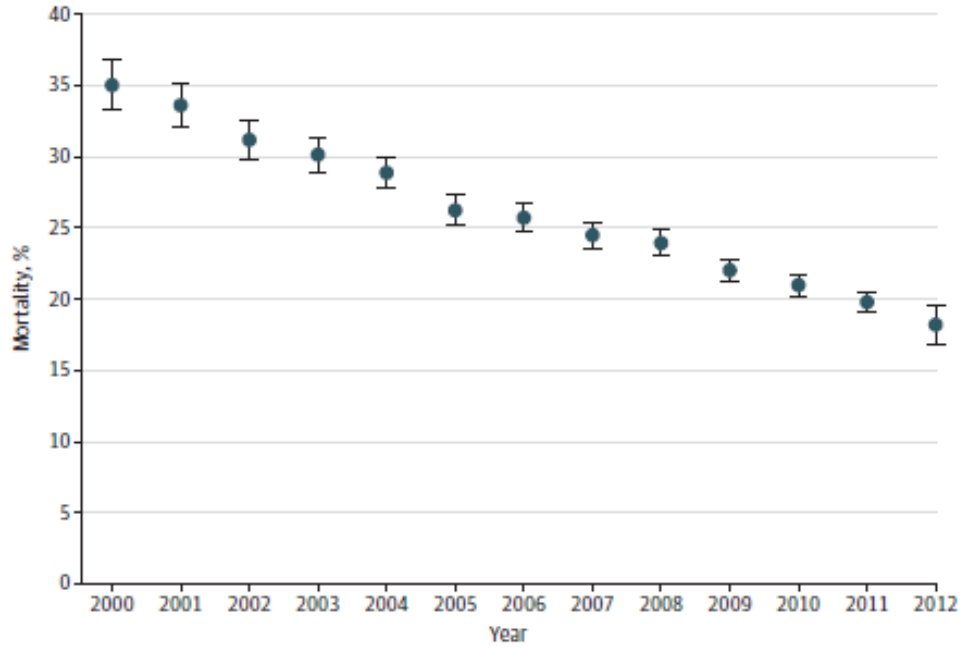
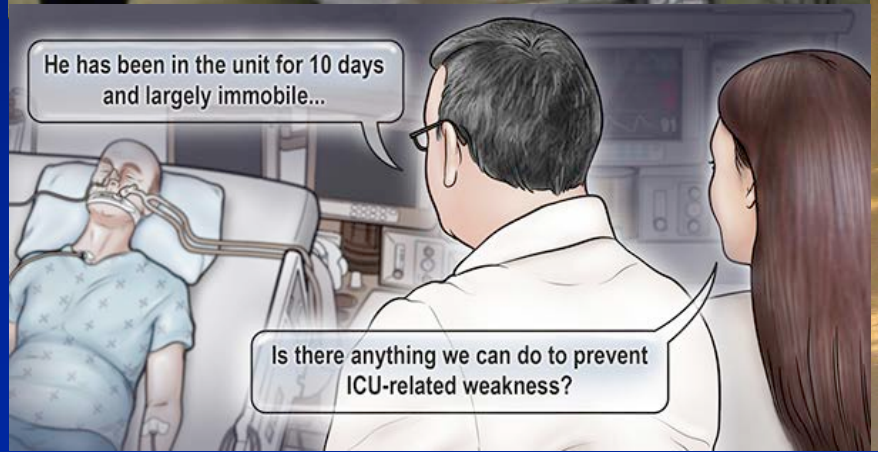
Figure 1. Mean Annual Mortality in Patients With Severe Sepsis



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
No. of patients	2708	3783	4668	5221	6375	6987	7627	8529	8797	10277	11367	12213	12512

Error bars indicate 95% CI.

Kaukonen et al., JAMA, 2014


He has been in the unit for 10 days and largely immobile...
Is there anything we can do to prevent ICU-related weakness?

Burden of sepsis survivorship

- Post-acute mortality
- Readmissions and healthcare use
- Functional disability
- Quality of life
- Cognitive impairment
- Renal outcomes
- Recurrent infections
- ?Interventions

Sepsis is associated with post-acute mortality

Cuthbertson *et al. Critical Care* 2013, **17**:R70
http://ccforum.com/content/17/2/R70

CRITICAL CARE

RESEARCH Open Access

Mortality and quality of life in the five years after severe sepsis

Brian H Cuthbertson[1*], Andrew Elders[2], Sally Hall[3], Jane Taylor[3], Graeme MacLennan[3], Fiona Mackirdy[4] and Simon J Mackenzie[4,5], for
the Scottish Critical Care Trials Group and the Scottish Intensive Care Society Audit Group

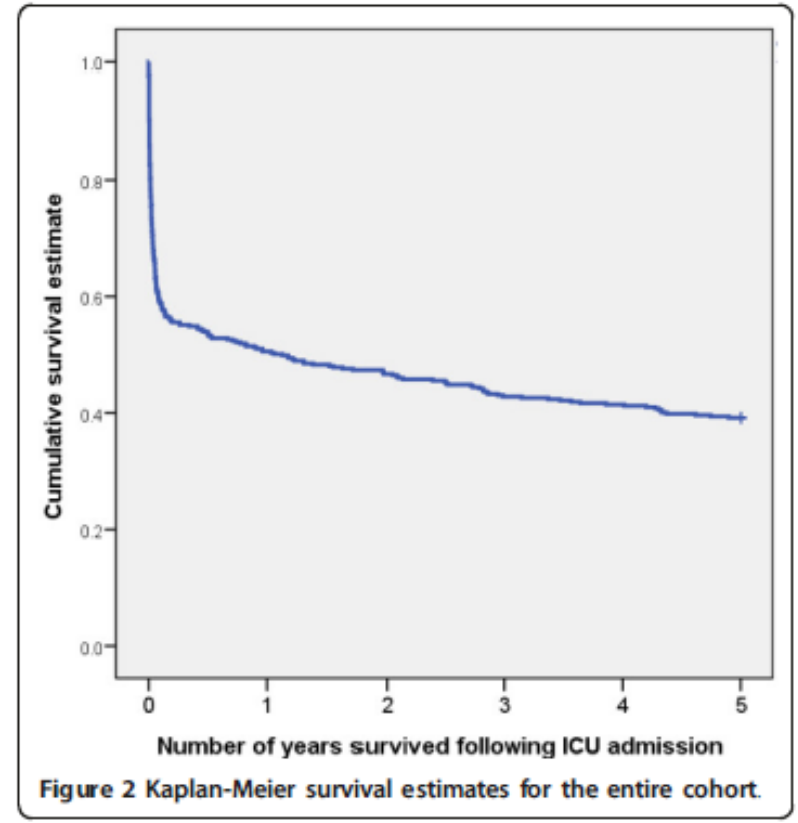
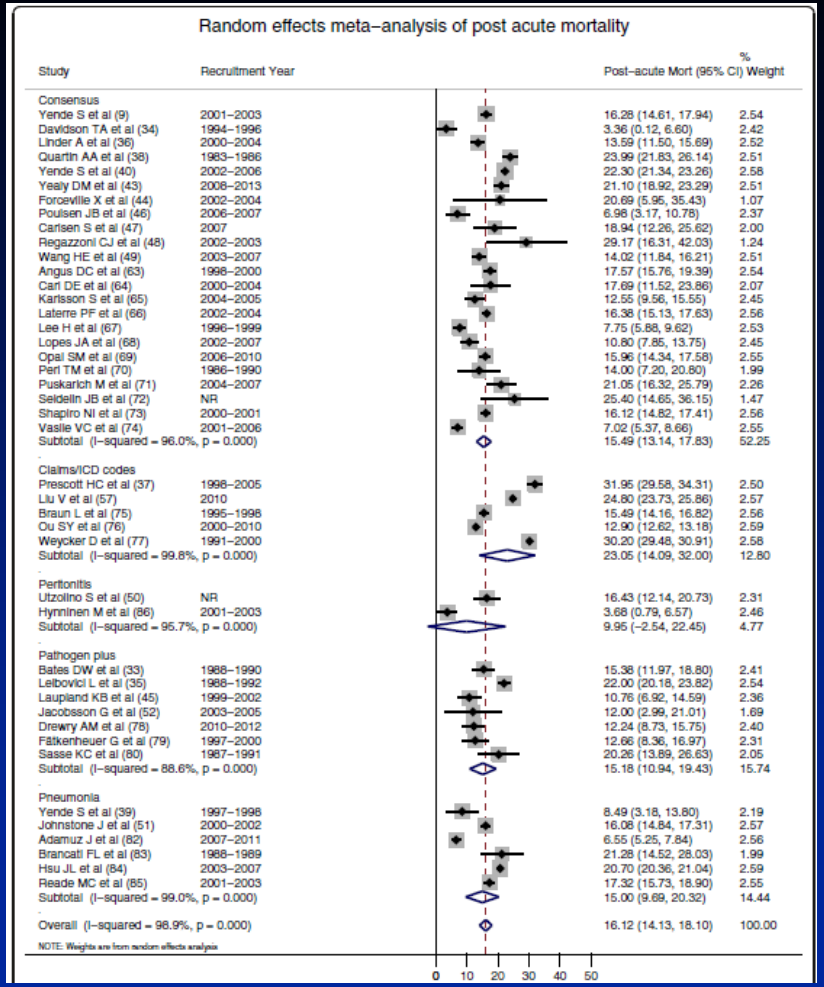


Figure 2 Kaplan-Meier survival estimates for the entire cohort.

Causal link or confounders?

Outcomes are a complex interplay between…

- Patient demographics
- Comorbidities & functional status
- Risk factors for critical illness
- Treatments in ICU
- Critical illness itself



Shankar-Hari et al., Crit Care, 2016

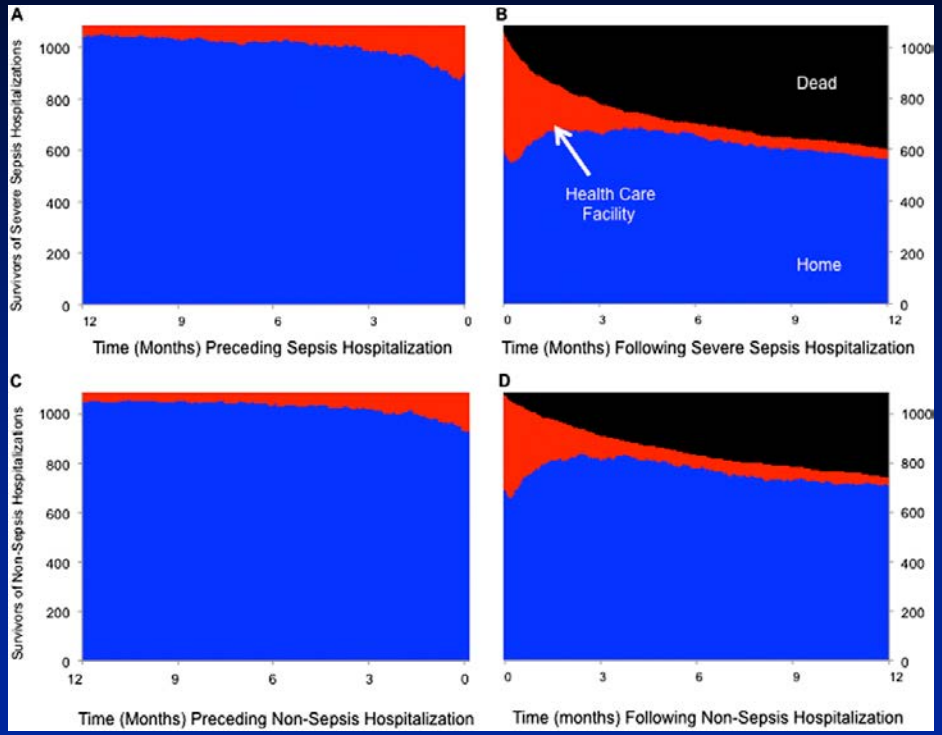
Causal link or confounders?

- Not all studies reported non-sepsis control arm comparisons
  - Sepsis not consistently associated with mortality in studies with control arm
- Which control?
  - Non-sepsis ICU vs hospitalised vs general population
- Older age, male sex, comorbidities all independent predictors of mortality in sepsis survivors

"Epidemiological criteria for a causal relationship were not consistently observed."

Shankar-Hari et al., Crit Care, 2016

Readmissions and health care utilisation



- More than double the days in an inpatient facility in the year post-discharge compared to year prior
- Greater mortality than non-sepsis cohort
  - 44% vs 31%
  - Fewer days alive at home

Prescott et al., Am J Respir Crit Care Med, 2014

Readmissions and health care utilisation

TABLE 2. Hospital-Based Acute Care Use in 269 Survivors of Septic Shock

Outcomes	*n* (%)
Hospital readmissions	
30-day hospital readmission	63 (23.4)
60-day hospital readmission	89 (33.1)
90-day hospital readmission	100 (37.2)
ED visits (treat-and-release encounters)	
30-day ED visit[a]	14 (5.2)
Hospital-based acute care postdischarge	
30-day ED visit or readmission	75 (27.9)[b]

TABLE 3. Readmission Diagnoses Following Hospitalization for Septic Shock

Readmission diagnoses potentially related to prior sepsis hospitalization, *n* (%)	
Infection[a]	29 (46.0)
Cardiovascular and thromboembolic[b]	11 (17.5)
Acute kidney injury[c]	4 (6.4)
Complications of devices	2 (3.2)
Other[d]	3 (4.8)
Readmission unrelated to prior hospitalization, *n* (%)	
Related to comorbid condition[e]	14 (22.2)
	Total: *n* = 63

Ortego et al., Crit Care Med, 2015

Functional decline that persists for years

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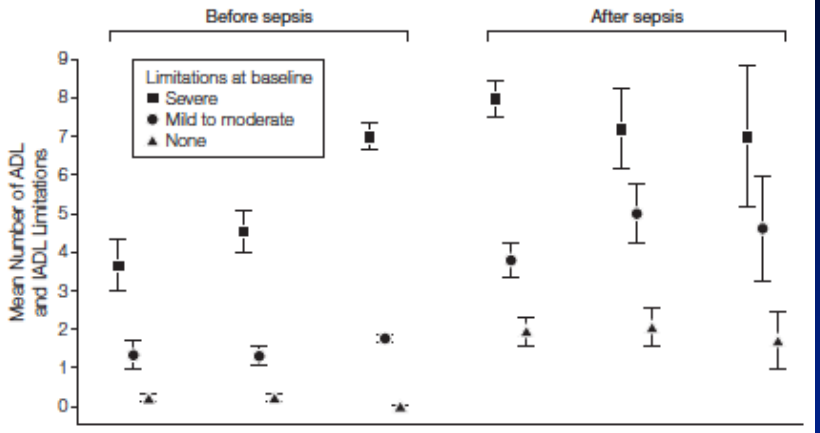
Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

Iwashyna et al., JAMA, 2010

Functional decline that persists for years

Figure 3. Functional Trajectories by Baseline Functioning

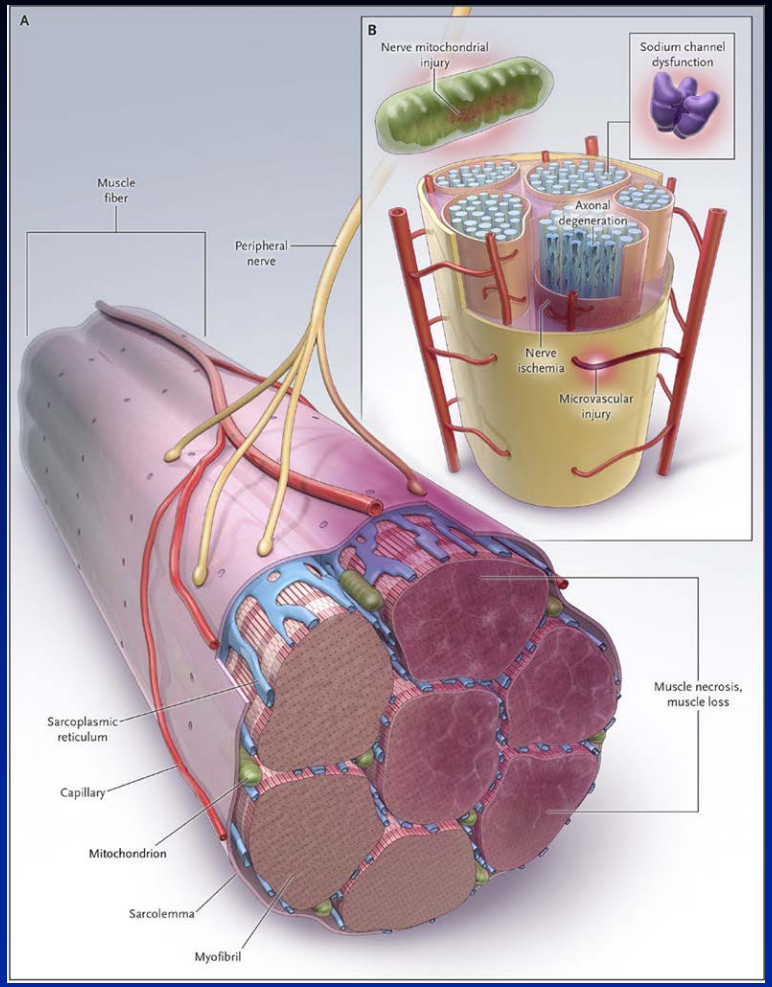


	Third Survey Before Sepsis	Second Survey Before Sepsis	Last Survey Before Sepsis	First Survey After Sepsis	Second Survey After Sepsis	Third Survey After Sepsis
Time to sepsis admission, median (IQR), y	−5.2 (−5.6 to −4.7)	−3.1 (−3.7 to −2.7)	−1.1 (−1.7 to −0.7)	0.9 (0.4 to 1.4)	2.8 (2.3 to 3.4)	5.2 (4.5 to 5.5)
No. of patients, by baseline physical functioning						
Severe limits	87	127	159	159	42	14
Mild to moderate limits	105	151	195	195	93	28
No limits	142	206	269	269	153	56

- Mean 1.5 new functional limitations post-sepsis
  - Worse if no limitations at baseline
- Only 0.5 new limitations in non-sepsis group

Declines persisted for at least 8 years.
Sepsis heralded a more rapid rate of developing limitations.

Iwashyna et al., JAMA, 2010



- Critical illness polyneuropathy affects ~ 50% of ICU survivors
- Axonal degeneration
- Multiple mechanisms
- Sepsis, inflammation & multiorgan failure strongly associated

Kress et al., N Engl J Med, 2014
Zink et al., Nat Rev Neurol, 2009

Peripheral neuropathy is persistent

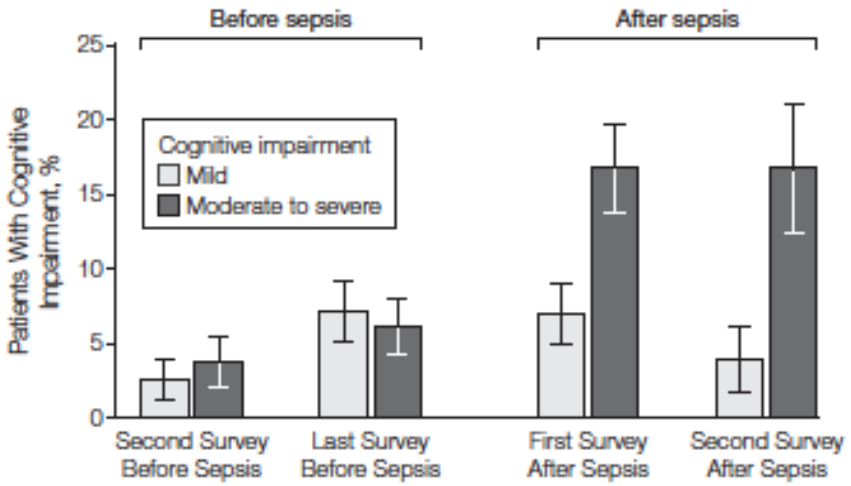
- 1/3 of all patients affected by critical illness polyneuropathy remain so severely limited that they still require assistance with ADLs 12 months later.

- Resolution is slow.

Koch et al., Muscle Nerve, 2014

Cognitive Impairment

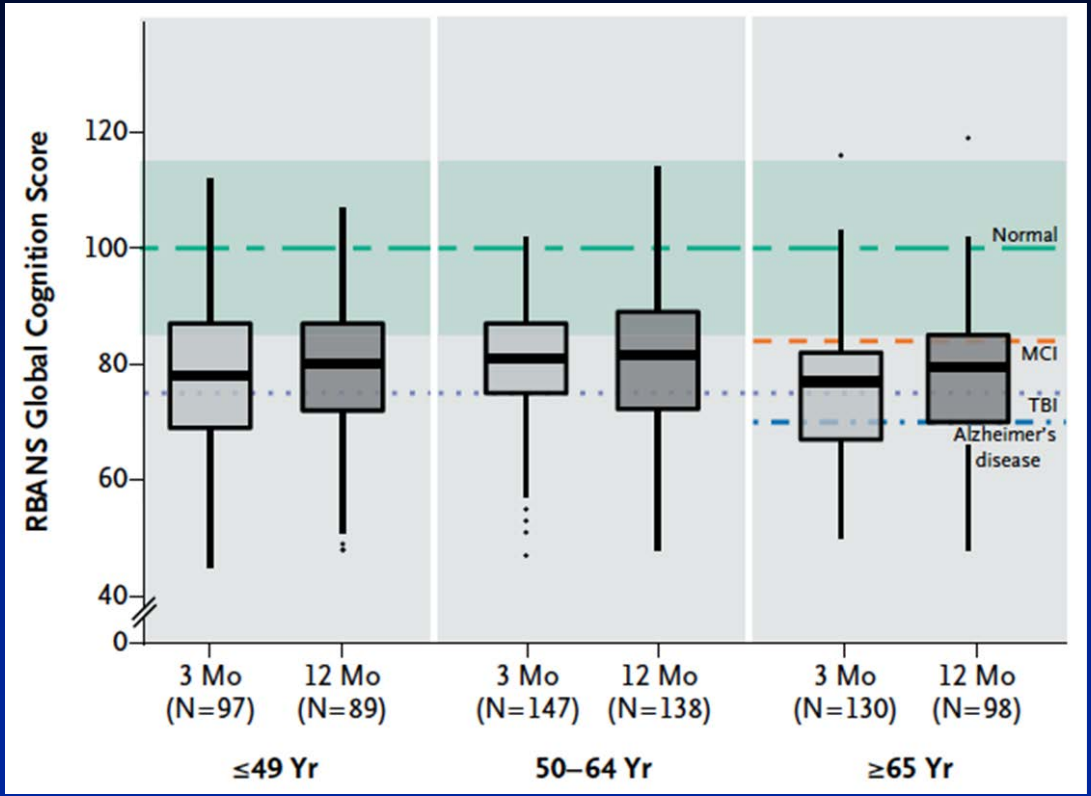
Figure 2. Cognitive Impairment Among Survivors of Severe Sepsis at Each Survey Time Point



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

Iwashyna et al., JAMA, 2010

Cognitive impairment persists



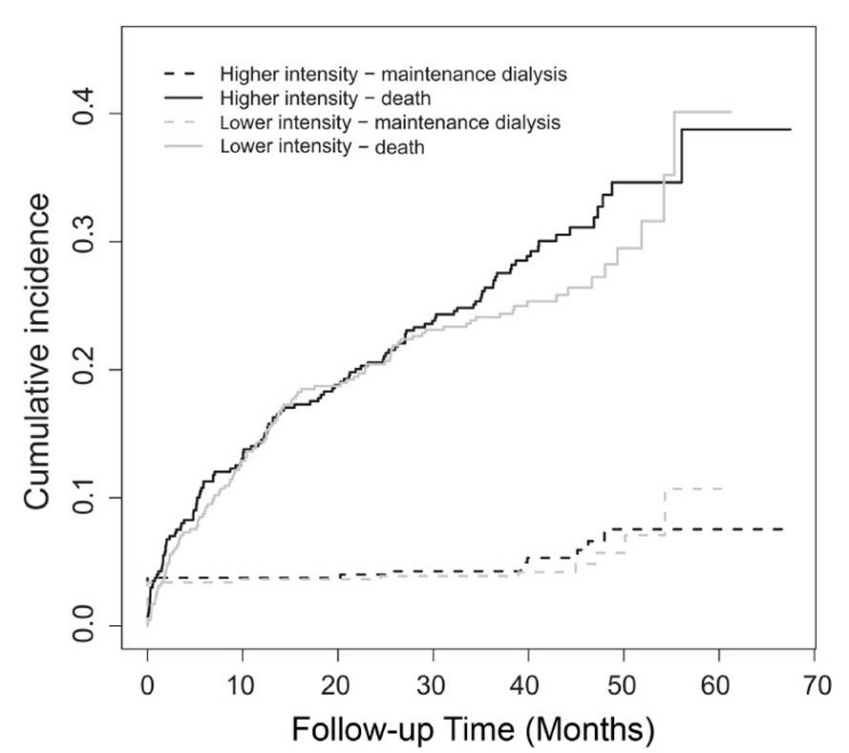
Pandharipande et al., NEJM, 2013

Renal Failure

- Sepsis implicated in 50% of AKI requiring dialysis in ICU.
- Patients with AKI who require renal replacement therapy have high short-term mortality (> 40%).
- Physical impairment & reduced mental health 3 years post-ICU discharge.

Uchino et al., JAMA, 2005
Korkeila et al., Intensive Care Med, 2000
Ahlstrom et al., Intensive Care Med, 2005
Delannoy et al., Intensive Care Med, 2009

Acute renal failure in sepsis is associated with long-term mortality & morbidity



Gallagher et al., PLoS Med, 2014

Acute renal disease in ICU leads to persistent renal disease

- Chronic albuminuria present in almost half of those alive at 4 years.

- Albuminuria is an independent risk factor for:
  - cardiovascular disease
  - later requirement for dialysis
  - death

Gallagher et al., PLoS Med, 2014
Astor et al., Kidney Int, 2011
Klausen et al., Circulation, 2004

Infection risk

- Survivors of sepsis have three-fold greater infection risk compared to survivors admitted to ICU with non-infectious conditions
  - Predominantly pneumonia (vs UTIs in control group)
  - More likely opportunistic pathogens - pseudomonas and candida species

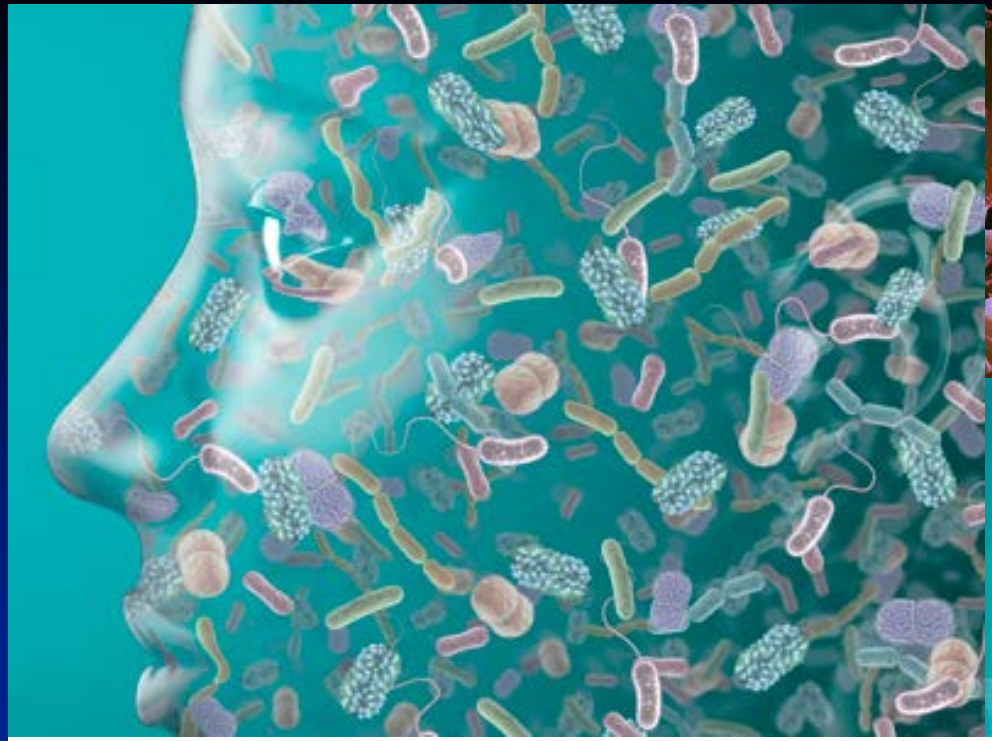
Wang et al., J Intensive Care Med, 2014

Persistent inflammation

- Survivors of community-acquired pneumonia have high levels of IL-6 and IL-10 at hospital discharge.

- Associated with increased 1-year mortality.

Yende et al., Am J Respir Crit Care Med, 2008



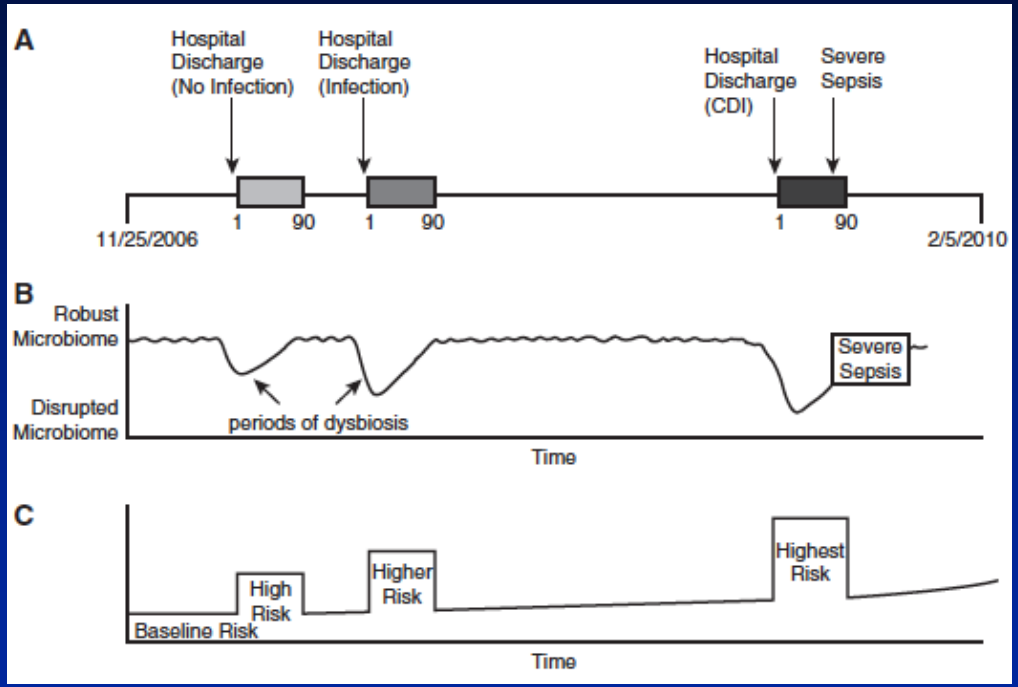
Hospitalization Type and Subsequent Severe Sepsis

Hallie C. Prescott[1,2], Robert P. Dickson[1], Mary A. M. Rogers[1,2], Kenneth M. Langa[1,2,3,4], and Theodore J. Iwashyna[1,2,3,4]

[1]Department of Internal Medicine and [2]Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, Michigan; [3]VA Center for Clinical Management Research, HSR&D Center of Innovation, Ann Arbor, Michigan; and [4]Institute for Social Research, Ann Arbor, Michigan

Dysbiosis & subsequent sepsis

- Hospitalisation is associated with microbiome perturbation



Prescott et al., Am J Respir Crit Care Med, 2014

Dysbiosis & subsequent sepsis

- Rate of sepsis increased 90 days after hospital discharge
- Degree of increased risk correlates with type of hospitalisation

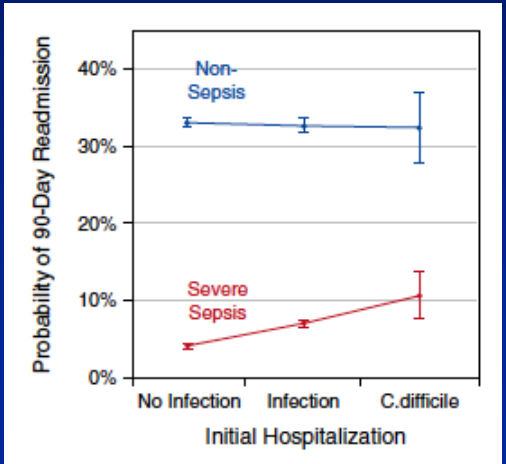


Table 2. Probabilities of 90-Day Readmissions for Severe Sepsis and Nonsepsis Diagnoses

	Readmissions for Severe Sepsis		Readmissions for Nonsepsis Diagnoses	
Index Hospitalization	Unadjusted Probability (95% CI)	Adjusted* Probability (95% CI)†	Unadjusted Probability (95% CI)	Adjusted* Probability (95% CI)‡
Noninfection-related hospitalization	3.7% (3.6–3.9%)	4.1% (3.8–4.4%)	31.7% (31.0–32.5%)	33.1% (32.4–33.7%)
Infection-related hospitalization	8.4% (7.7–9.1%)	7.1% (6.6–7.6%)	34.7% (33.7–35.7%)	32.7% (31.9–33.6%)
Hospitalization with CDI	16.8% (12.2–21.4%)	10.7% (7.7–13.8%)	37.9% (32.7–43.3%)	32.4% (27.8–37.0%)

Prescott et al., Am J Respir Crit Care Med, 2014

Psychological consequences are common

- Depression
- Anxiety
- Post-traumatic stress
- Family effects

Angus et al., Intensive Care Med, 2003
Davydow et al., Int Rev Psychiatry, 2009
Herridge et al., N Engl J Med, 2011

Potential interventions

BMJ Open

IMPOSE (IMProving Outcomes after Sepsis)—the effect of a multidisciplinary follow-up service on health-related quality of life in patients postsepsis syndromes—a double-blinded randomised controlled trial: protocol

Jennifer D Paratz,[1,2,3,4] Justin Kenardy,[5] Geoffrey Mitchell,[6] Tracy Comans,[7] Fiona Coyer,[8] Peter Thomas,[1,2,4] Sunil Singh,[9] Louise Luparia,[1,3] Robert J Boots[1,2]

Long-Term Patient Outcomes After Prolonged Mechanical Ventilation: The Towards Recover Study

M. S. Herridge[1], L. M. Chu[2], A. L. Matte[2], L. Chan[3], G. Tomlinson[2], N. D. Ferguson[4], S. Mehta[5], J. Friedrich[4], N. Adhikari[6], R. Fowler[7], F. Lamontagne[8], J. C. Rudkowski[9], H. Meggison[10], N. Ayas[11], Y. Skrobik[12], J. Batt[13], C. Dos Santos[13], J. Flannery[14], S. Abbey[2], G. D. Rubenfeld[15], D. C. Scales[16], T. Sinuff[7], B. Cuthbertson[17], E. Fan[18], A. S. Slutsky[19], G. Leung[20], A. Moody[17], M. Levasseur[21], M. Bayley[14], C. Lee[18], V. Lo[2], S. Mathur[3], A. Tan[2], C. Tansey[4], M. E. Wilcox[22], J. C. Marshall[23], D. J. Cook[24], J. I. Cameron[3], Canadian Critical Care Trials Group

Further Research

- Mechanisms leading to cognitive impairment and functional disability
- Interventions
- Studying elderly and young cohorts separately
- Using longer term survival and functional outcomes in studies rather than the traditional 28-day mortality

Conclusions

- Intensive care treatment saves lives in sepsis but…

- Significant burden of survivorship
- Sepsis may be a sentinel event
- Under recognised public health problem with major implications for patients, families and the healthcare system
- Emerging data can inform discussions about goals of care
- Interventions to improve outcomes in this group are urgently needed

Questions?