Outcomes for Critically Ill Sepsis Survivors

Yasmine Ali Abdelhamid
Discipline of Acute Care Medicine, University of Adelaide
Intensive Care Unit, Royal Adelaide Hospital
Adelaide, South Australia
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
Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

Detecting sepsis early increases chances for survival

<table>
<thead>
<tr>
<th>time of hypotension before therapy</th>
<th>survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.5 hrs</td>
<td>4 in 5 / 80%</td>
</tr>
<tr>
<td>&gt;3 hrs</td>
<td>3 in 5 / 60%</td>
</tr>
<tr>
<td>&gt;6 hrs</td>
<td>2 in 5 / 40%</td>
</tr>
<tr>
<td>&gt;24 hrs</td>
<td>1 in 5 / 20%</td>
</tr>
</tbody>
</table>
Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Kimi-Maja Kasamon, MD, PhD, EDCF, Michael Bailey, PhD, Satoshi Suzuki, MD, David Alhazzou FCDM, ECFM, RMF

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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% to 36.9%) in 2000 (9467/27061), to 18.8% (95% CI, 17.8% to 19.9%, 23007/12312, P < .001), representing an overall decrease of 46.5% (95% CI, 14.8% to 18.5%), an annual rate of absolute decline of 1.3%, and a relative risk reduction of 47.3% (95% CI, 44.1% to 50.9%). After adjusted analysis, mortality decreased through the study period with an odds ratio (OR) of 0.49 (95% CI, 0.40-0.60) 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, 0.92-0.95]), and for patients with severe sepsis compared with all other diagnoses (OR, 1.03 [95% CI, 1.02-1.05]), OR, 1.03 [95% CI, 1.02-1.05]), (OR, 1.03 [95% CI, 1.02-1.05]), (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, 1.07-1.10]) and 1.09 (95% CI, 1.08-1.10), (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 patients' discharge to home, rehabilitation, and other hospitals.

Author Affiliations: Australian and New Zealand Intensive Care Research Centre/GIACRC, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; Kasamon, Kimi-Maja; Bailey, Michael; Suzuki, Satoshi; Alhazzou, David.

Supplemental content at jama.com
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
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
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**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital readmissions</td>
<td></td>
</tr>
<tr>
<td>30-day hospital readmission</td>
<td>63 (23.4)</td>
</tr>
<tr>
<td>60-day hospital readmission</td>
<td>89 (33.1)</td>
</tr>
<tr>
<td>90-day hospital readmission</td>
<td>100 (37.2)</td>
</tr>
<tr>
<td>ED visits (treat-and-release encounters)</td>
<td></td>
</tr>
<tr>
<td>30-day ED visit</td>
<td>14 (5.2)</td>
</tr>
<tr>
<td>Hospital-based acute care postdischarge</td>
<td></td>
</tr>
<tr>
<td>30-day ED visit or readmission</td>
<td>75 (27.9)</td>
</tr>
</tbody>
</table>

**TABLE 3. Readmission Diagnoses Following Hospitalization for Septic Shock**

<table>
<thead>
<tr>
<th>Readmission diagnoses potentially related to prior sepsis hospitalization, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection(^a)</td>
</tr>
<tr>
<td>Cardiovascular and thromboembolic(^b)</td>
</tr>
<tr>
<td>Acute kidney injury(^c)</td>
</tr>
<tr>
<td>Complications of devices</td>
</tr>
<tr>
<td>Other(^d)</td>
</tr>
<tr>
<td>Readmission unrelated to prior hospitalization, n (%)</td>
</tr>
<tr>
<td>Related to comorbid condition(^e)</td>
</tr>
<tr>
<td>Total: n = 63</td>
</tr>
</tbody>
</table>

*Ortego et al., Crit Care Med, 2015*
Functional decline that persists for years

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

Iwashyna et al., JAMA, 2010
Functional decline that persists for years

- 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

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

- Patients With Cognitive Impairment, %
  - Before sepsis
  - After sepsis

- Cognitive impairment:
  - Mild
  - Moderate to severe

- Time to sepsis admission, median (IQR), y
  - No. of patients

- 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

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

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. Prescott¹,², Robert P. Dickson¹, Mary A. M. Rogers¹,², Kenneth M. Langa¹,²,³,⁴, and Theodore J. Iwashyna¹,²,³,⁴

¹Department of Internal Medicine and ²Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, Michigan; ³VA Center for Clinical Management Research, HSR&D Center of Innovation, Ann Arbor, Michigan; and ⁴Institute for Social Research, Ann Arbor, Michigan
Hospitalisation is associated with microbiome perturbation
Dysbiosis & subsequent sepsis

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