Sepsis Update 2021: Incidence, Mortality and Bundle Science Update
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.

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.

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/datarreports/index.html

1.7 million

The Burdens Of SEPSIS

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

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 rate of inpatient admissions (per million beneficiaries) rose even faster than the Medicare beneficiary population. In 2018, the rate of sepsis inpatient admissions was 40% greater than it was in 2012.

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

Sepsis Deaths by Age Group

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

*Age was unknown for 90 decedents.
Initial Sepsis sent to Skilled Facility from Hospital
**Most Prevalent Conditions Requiring Hospitalization**

**Percent of All Inpatient Stays in 2018**

- **Septicemia**: 8%
- **Heart Failure**: 4%
- **Osteoarthritis**: 4%
- **Pneumonia**: 3%
- **Diabetes with Complications**: 2%

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.

<table>
<thead>
<tr>
<th>First-listed diagnosis</th>
<th>Rate of hospitalization per 1,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>48</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>51</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>19</td>
</tr>
<tr>
<td>Septicemia</td>
<td>15</td>
</tr>
<tr>
<td>Stroke</td>
<td>37</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>28</td>
</tr>
</tbody>
</table>

1Percent 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.

Hospital Readmission is Common

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

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

Andrew J. Goodwin, MD, MSCR; David A. Rice, MD; Kit N. Simpson, DrPH;
Dep W. Ford, MD, MSCR

Post–Acute Care Use and Hospital Readmission after Sepsis

Tiffanie K. Jones1,2, Barry D. Fuchs1,2, Dylan S. Small3,4, Scott D. Halpern1,2,4,5,6, Asaf Hanish7, Craig A. Umscheid1,4,8, Charles A. Balile6, Meeta Prasad Kerlin1,2,4,5, David F. Galeski6, and Mark E. Mikkelsen1,2,8

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

John P. Donnelly, MSPH1,4,5; Samuel F. Hohmann, PhD, MS-HSM1,4,5; Henry E. Wang, MD, MS5

Rehospitalizations Following Sepsis: Common and Costly*

Dong W. Chang, MD, MS5; Chi-Hong Tseng, PhD5; Martin F. Shapiro, MD, PhD3
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.

**Table. Most Frequent Readmission Diagnoses After Hospitalization for Severe Sepsis**

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

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.
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
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%

(CMS data)
Sepsis Management

What is current and what is new!!
Early identification

Early antibiotics

Early fluid resuscitation

TO SAVE LIVES.....
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.
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

Schorr C. et al Journal of Hospital Medicine, 2016;11:S32-S39
Electronic Routine Screening

Bonus: Screening Creates a Time Zero Every 12 hours

Temp <36°C (96.8°F) or Temp > 38.3°C (101°F)

Positive SEVERE Sepsis Screen Occurs when one selection is chosen once one Organ Dysfunction is identified.

Automatically defaults to a Positive SEVERE Sepsis Screen.

SEVERE Sepsis Screen is activated
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

7 Hospital Systems: Northern California

Sepsis Mortality Reduction
- ED & ICU – continue improvements
- Emphasis placed on a new patient population

MOST
- Medical
- Oncology
- Surgical
- Telemetry

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

Mortality by Location of Severe Sepsis – ICU patients

- ED: 21.4%, Mortality Rates 2010
- MOST: 25.2%, Mortality Rates 2010
- Combined: 22.8%, Mortality Rates 2010
- ED: 12.0%, Mortality Rates 2011
- MOST: 12.3%, Mortality Rates 2011
- Combined: 12.1%, Mortality Rates 2011
EPIC Sepsis Prediction 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

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.
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.
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.
<table>
<thead>
<tr>
<th>SURVIVING SEPSIS CAMPAIGN RECOMMENDATION HIGHLIGHTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEPSIS DEFINITION</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>INITIAL RESUSCITATION</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>VASOPRESSORS</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>STEREOS</strong></td>
</tr>
<tr>
<td><strong>ANTIBIOTICS</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>SOURCE CONTROL</strong></td>
</tr>
<tr>
<td><strong>VENTILATOR</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

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

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

• 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

• 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

Early Fluid Resuscitation is Key

• 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

• 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

Application of Fluid Resuscitation in Adult Septic Shock

Sepsis-induced hypotension or lactate ≥ 4 mmol/L
(Based on SSC bundle and CMS threshold)

No high flow oxygen and No ESRD on dialysis or CHF

Rapid infusion of 30 ml/kg Crystalloid

Pneumonia or ALI with high flow oxygen requirements

Not intubated/ mechanically ventilated

Intubated/ mechanically ventilated

Consider Intubation/mechanical ventilation to facilitate 30 ml/kg crystalloid

If no

Total of 30 ml/kg with frequent reassessment of oxygenation

ESRD on hemodialysis or CHF

Total of 30 ml/kg crystalloid with frequent reassessment of oxygenation

*Administer 30 ml/kg crystalloid within first 3 hours

Considerations post 30ml/kg crystalloid infusion
1. Continue to balance fluid resuscitation and vasopressor dose with attention to maintain tissue perfusion and minimize interstitial edema
2. Implement some combination of the list below to aid in further resuscitation choices that may include additional fluid or inotrope therapy
   • blood pressure/heart rate response,
   • urine output,
   • cardiothoracic ultrasound,
   • CVP, Scvo2,
   • pulse pressure variation
   • lactate clearance/normalization or
   • dynamic measurement such as response of flow to fluid bolus or passive leg raising
3. Consider albumin fluid resuscitation, when large volumes of crystalloid are required to maintain intravascular volume.

ALI=acute lung injury; CHF=congestive heart failure; CMS=US Centers for Medicare and Medicaid Services; CVP=central venous pressure; ESRD=end stage renal disease; kg=kilograms;
mL=milliliters; oxyc=oxigen saturations; Scvo2=superior vena cava oxygen saturation

Type of Fluid
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Fluid Regimen</th>
<th>Fluids Administered Median</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALT-ED</td>
<td>13,347</td>
<td>Saline vs. LR/Plasma-Lyte in non-critically ill</td>
<td>1079 ml</td>
<td>~ 33% mechanical ventilation ~ 25% vasopressors</td>
</tr>
<tr>
<td>SMART</td>
<td>15,802</td>
<td>Saline vs. LR/Plasma-Lyte in critically ill</td>
<td>~ 2.5 L</td>
<td>Both demonstrated statistically significant incidence of acute kidney injury (AKI)</td>
</tr>
</tbody>
</table>

Both studies by Self et al. NEJM 2018; 378:9 and Semler et al. NEJM 2018; 378:9
Results: SALT-ED

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

**KIDNEY Injury Events!**

Self et al NEJM. 2018:378;9
### SMART Trial

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Balanced Crystalloids</th>
<th>Saline</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>615/2735 (22.5)</td>
<td>659/2646 (24.9)</td>
<td>0.87 (0.77–0.99)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>202/1470 (13.7)</td>
<td>190/1501 (12.7)</td>
<td>1.10 (0.89–1.36)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>116/1440 (8.1)</td>
<td>141/1377 (10.2)</td>
<td>0.77 (0.59–0.99)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>131/1640 (8.0)</td>
<td>142/1688 (8.4)</td>
<td>0.95 (0.74–1.21)</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>75/667 (11.4)</td>
<td>76/640 (11.6)</td>
<td>0.92 (0.66–1.29)</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>744/6775 (11.0)</td>
<td>756/6691 (11.3)</td>
<td>0.96 (0.86–1.07)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>395/1167 (33.8)</td>
<td>455/1169 (38.9)</td>
<td>0.80 (0.67–0.94)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Traumatic brain injury</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1034/7244 (14.3)</td>
<td>1118/7195 (15.5)</td>
<td>0.89 (0.81–0.98)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>105/698 (15.0)</td>
<td>93/665 (14.0)</td>
<td>1.09 (0.81–1.47)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td><strong>Categories of kidney function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>476/5596 (8.5)</td>
<td>514/5561 (9.2)</td>
<td>0.91 (0.80–1.04)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>315/574 (54.9)</td>
<td>316/537 (58.8)</td>
<td>0.85 (0.67–1.08)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>301/1388 (21.7)</td>
<td>307/1360 (22.6)</td>
<td>0.95 (0.79–1.13)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Previous renal-replacement therapy</td>
<td>47/384 (12.2)</td>
<td>74/402 (18.4)</td>
<td>0.61 (0.41–0.91)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1139/7942 (14.3)</td>
<td>1211/7860 (15.4)</td>
<td>0.91 (0.83–0.99)</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>
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 mortality, 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)
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])
Balanced Crystalloids vs Saline in Critically Ill Adults: A meta-analysis

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.

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
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
Secondary Endpoints

**Renal Replacement Therapy (RRT)** $p = 0.04$
- Treatment Group 5.1%
- Control Group 17.5%

**Mechanical Ventilation** $p = 0.04$
- Treatment Group 17.7%
- Control Group 34.1%

**ICU LOS** $p = 0.11$
- Treatment Group 3.31
- Control Group 6.22

**Discharge Home** $p = 0.035$
- Treatment Group 63.9%
- Control Group 43.9%

Douglas I et al., CHEST 2020
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

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)

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)

Enrollment to be completed by June 2021
Does Compliance with the Bundle Make a Difference?
Changes in Bundle Compliance & Mortality with a PI Program

6 Hour Bundle Compliance

Mortality

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

Demographics Matching
Adjusted & Unadjusted Impact of Bundle Element Compliance on Mortality

| 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*              | 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 6 h bundle: Repeat lactate level | 159,646           | 68.5          | 25.3                        | 30.8                        | 0.863                  | 0.779-0.828                  | < .001 |  
| Shock 3-h bundle: Crystalloid fluid administration | 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: Vaspressors              | 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: Vaspressors 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   |  

*Data inclusive from quarter 4, 2015, to quarter 1, 2017; data in all other rows represent quarter 4, 2015, to quarter 2, 2016.

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)