Real sepsis mystery: We all know how to treat sepsis - so why can’t we do it well?

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Multidisciplinary Epidemiology and Translational Research in Intensive Care, Emergency and Perioperative Medicine (METRIC)
Disclosure

- Research support from NIH, CMS, Philips Research North America and Mayo Clinic
- IP rights for critical care related software tools
  - Mayo Clinic and I have Financial Conflict of Interest related to research findings and methods presented
  - This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and is being conducted in compliance with Mayo Clinic Conflict of interest Policies
  - AWARE is licensed to Ambient Clinical Analytics
- No other financial relationships with commercial companies and no other relevant disclosures
Objectives

- Review the challenges for adequate sepsis treatment during golden hours
- Examine the tools to enhance clinical practice in a modern hospital
- Explore the role of novel technologies
## Sepsis

### Immediate considerations

- **Cultures**
  - Cultures should be taken as soon as possible and before antimicrobial therapy

- **Antibiotics**
  - Antibiotics should be initiated as soon as possible according to likely pathogen, site of infection, immune status, and allergy

- **Source control**
  - Remove dead tissue, pus, or infected device for source control

- **Fluid challenge**
  - Start fluid bolus (~30ml/kg), repeat as needed to achieve adequate tissue perfusion taking into consideration fluid responsiveness

- **Vasopressors**
  - Add vasopressors for shock despite fluid resuscitation

- **Steroids**
  - Add steroids for shock despite vasopressors

- **Limit oxygen consumption**
  - Consider mechanical ventilation, use analgesics, sedatives, and neuromuscular blockers as appropriate to limit oxygen consumption

### Management after stabilization

### Cautions
Question

• What is the most important component of Early Goal Directed Therapy for septic shock?

• E
• G
• D
• T
Question

• What is the most important component of Early Goal Directed Therapy for septic shock?

• E
• G
• D
• T
<table>
<thead>
<tr>
<th>Real-Time Variables</th>
<th>Physiologic Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>106 103 106 119 116 124</td>
</tr>
<tr>
<td>NIBP-Systolic</td>
<td>90 91 108 104 95 113</td>
</tr>
<tr>
<td>NIBP-Diastolic</td>
<td>32 39 53 36 28 26</td>
</tr>
<tr>
<td>NIBP-Mean</td>
<td>51 54 71 55 51 54</td>
</tr>
<tr>
<td>Temperature-Manual</td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>25 25 28 28 38 43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fluids IN</th>
<th>Fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystallloid In</td>
<td></td>
</tr>
<tr>
<td>0.9 NaCl 1000 mL at 20 mL/hour</td>
<td>75</td>
</tr>
<tr>
<td>Intermittent Infusions 50 mL</td>
<td>75</td>
</tr>
<tr>
<td>Parameter</td>
<td>09/01</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>17</td>
</tr>
<tr>
<td>Oxygen Device #1</td>
<td></td>
</tr>
<tr>
<td>Oxygen % / LPM #1</td>
<td></td>
</tr>
<tr>
<td>FIO2/O2 %</td>
<td>40.00</td>
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<tr>
<td>Resp. Rate Set - Vent</td>
<td>16</td>
</tr>
<tr>
<td>Resp. Rate Total - Vent</td>
<td>16</td>
</tr>
<tr>
<td>Inspiratory Pressure</td>
<td>410.0</td>
</tr>
<tr>
<td>Expiratory Time</td>
<td></td>
</tr>
<tr>
<td>Tidal Volume Expired</td>
<td>360.0</td>
</tr>
<tr>
<td>PEEP</td>
<td>10.0</td>
</tr>
<tr>
<td>Mean Airway Pressure</td>
<td>14.0</td>
</tr>
<tr>
<td>Insulin 0-10000 unit/hour</td>
<td>3</td>
</tr>
<tr>
<td>Midazolam 0-10000 mcg/hour</td>
<td>1</td>
</tr>
<tr>
<td>Noradrenaline 0-10000 mcg/kg/hr</td>
<td>0.0048</td>
</tr>
<tr>
<td>Vasopressin 0-10000 unit/minute</td>
<td>0.04</td>
</tr>
<tr>
<td>Crystalloid In</td>
<td></td>
</tr>
<tr>
<td>0.9 NaCl 1000 mL at 10 mL/hour</td>
<td>10</td>
</tr>
<tr>
<td>Intermittent Infusions 50 mL</td>
<td></td>
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<tr>
<td>Nutren 1.5 250 mL at 50 mL/hour</td>
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<tr>
<td>Other Tube Feeding 250 mL at.</td>
<td>35</td>
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<tr>
<td>Tube Irrigation</td>
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<tr>
<td>NG/OG Tube 30 mL</td>
<td></td>
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<tr>
<td>Fluids OUT</td>
<td></td>
</tr>
<tr>
<td>Urine out</td>
<td></td>
</tr>
<tr>
<td>Catheter; Indwelling</td>
<td>0</td>
</tr>
<tr>
<td>Fluids out</td>
<td></td>
</tr>
<tr>
<td>CRRT Output</td>
<td>214</td>
</tr>
</tbody>
</table>
Finally…
Critical Importance of Timing

- Unadjusted Mortality
- Mortality Observed / Expected Mortality APACHE III
- Median Time to 3 Most Rapid Interventions p<0.001
Chaos Theory of Critical Illness

Window for Early Treatment & Prevention

- Good Outcome
- Bad Outcome

Morning Rounds

<table>
<thead>
<tr>
<th>911</th>
<th>Emergency Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating room</td>
<td>Recovery room</td>
</tr>
<tr>
<td>Hospital ward</td>
<td>Rapid response team</td>
</tr>
</tbody>
</table>

ICU
“The most sophisticated intensive care becomes unnecessarily expensive terminal care…”

Peter Safar
Challenges during golden hour

Factors which may conspire together to make crises challenging

- They may present with opaque, non-specific signs or symptoms.
- They may arise from the interaction of many complex factors.
- The problems may evolve, revealing additional layers of complexity.
- The particular set of circumstances may never have been encountered before.
- Recently introduced processes and equipment may bring new unforeseen problems.
- Skilled assistance may not be available in the necessary time frame.
- They may have to be resolved very rapidly if disaster is to be averted.

Runciman et al. Qual Saf Health Care 2005
Real sepsis “mystery”
“The fundamental problem with the quality of medicine is that we’ve failed to view delivery of clinical practice as a science”

• The tasks of medical science fall into three buckets.
  • understanding disease biology
  • finding effective therapies
  • insuring those therapies are delivered effectively

• That third bucket has been almost totally ignored. It’s viewed as the art of medicine.
  • “That’s a mistake, a huge mistake”
Pioneer of the science of clinical practice in the ICU

Dr Bekele Afessa
1956-2013
Sepsis Workflow Mapping
Sepsis workflow simulation

- Sepsis recognition
  - Source Control
  - Fluid Resuscitation
    - Central Venous Catheterization
    - Vasopressor Administration
    - Transfusion
    - Inotrope Administration
      - Re-assessment
        - Sepsis Resuscitation Goal Reached
Sepsis Checklist + Training = Sepsis Response Team
## Sepsis Response Team: Outcome

<table>
<thead>
<tr>
<th>Institution</th>
<th>Compliance, %</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pre-intervention</td>
<td>5.3</td>
<td>44</td>
</tr>
<tr>
<td>• Post-intervention</td>
<td>10.0</td>
<td>39.7</td>
</tr>
<tr>
<td><strong>Surviving Sepsis Campaign</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pre-intervention</td>
<td>10.9</td>
<td>37</td>
</tr>
<tr>
<td>• Post-intervention</td>
<td>31.3</td>
<td>30</td>
</tr>
<tr>
<td><strong>Mayo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pre-intervention</td>
<td>10.5</td>
<td>31.5</td>
</tr>
<tr>
<td>• Post-intervention</td>
<td>58.4</td>
<td>22.0</td>
</tr>
</tbody>
</table>

## Sepsis Response Team (SRT)

<table>
<thead>
<tr>
<th>Bundle element</th>
<th>Study Periods</th>
<th></th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline N = 268</td>
<td>Weekly feedback N = 284</td>
<td>SRT activation N = 432</td>
<td></td>
</tr>
<tr>
<td>Lactate measured</td>
<td>202 (75.4%)</td>
<td>259 (91.2%)</td>
<td>419 (97.0%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood culture before antibiotics</td>
<td>235 (87.7%)</td>
<td>264 (93.0%)</td>
<td>422 (97.7%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Timely antibiotics</td>
<td>207 (77.2%)</td>
<td>238 (83.8%)</td>
<td>393 (91.0%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adequate fluid</td>
<td>153 (57.1%)</td>
<td>184 (64.8%)</td>
<td>333 (77.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Appropriate vasopressor</td>
<td>264 (93.0%)</td>
<td>252 (94.0%)</td>
<td>385 (89.1%)</td>
<td>0.046</td>
</tr>
<tr>
<td>All or None</td>
<td>34 (12.7%)</td>
<td>107 (37.7%)</td>
<td>232 (53.7%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Schramm at al Crit Care Med 2011
Multicenter Implementation of a Severe Sepsis and Septic Shock Treatment Bundle

Russell R. Miller III\textsuperscript{1,2}, Li Dong\textsuperscript{3}, Nancy C. Nelson\textsuperscript{3}, Samuel M. Brown\textsuperscript{1,2}, Kathryn G. Kuttler\textsuperscript{3,4}, Daniel R. Probst\textsuperscript{3}, Todd L. Allen\textsuperscript{3}, and Terry P. Clemmer\textsuperscript{1,2}; for the Intermountain Healthcare Intensive Medicine Clinical Program

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Figure Caption}
\end{figure}

\section*{AT A GLANCE COMMENTARY}

\subsection*{Scientific Knowledge on the Subject}
Severe sepsis and septic shock are leading causes of intensive care unit admission, morbidity, and mortality. The effect of compliance with bundled elements of sepsis management guidelines on outcomes is unclear.

\subsection*{What This Study Adds to the Field}
Total severe sepsis and septic shock bundle compliances increased substantially and were associated with a marked reduction in hospital mortality after adjustment for age, severity of illness, and comorbidities over 7 years in a multicenter intensive care unit cohort. Early resuscitation bundle element compliance predicted ineligibility, through lower subsequent severity of illness, for later bundle elements.
Surviving Sepsis Campaign (SSC)

- In 2002, the SSC declared goal to reduce the relative mortality of sepsis by **25% in five years**
  - Developed Sepsis Bundles
  - Created Education Materials
  - Recruited Sites and Local Champions
  - Local and National Launch of Campaign
  - Distributed Secure Database for Data Collection and Transfer
  - Developed Interface for Practice Audit and Local Feedback

- From 2004 to 2009, **12.1% to 35.2% decrease** in in-hospital mortality

SurvivingSepsis.org; Gaieski DF et al, 2013
State of the affairs

- Great strides have led to improvements in sepsis care and mortality world-wide
- Still, even the best efforts did not achieve better than 50% success in timely delivery of intended best practices
### Probability of Performing Perfectly

1) **Reduce steps**
2) **Improve reliability**

Need for Ambient Intelligence

REVIEW

The hospital of the future: building intelligent environments to facilitate safe and effective acute care delivery

Brian W Pickering1, John M Litell2, Vitaly Herasevich1,2 and Ognjen Gajic2,3
AWARE – Ambient Warning and Response Evaluation

Reduced cognitive load (happy clinicians)
Reduced errors (happy patients)
Reduced time (happy administrators)

Perfecting sepsis care in the hospital

1. Existing detection algorithm
2. Existing failure to rescue algorithm
3. To Develop: Detection algorithm adjusted for low monitoring setting

Focus on detection prior to ICU admission and "failure to rescue" in ICU
### Sepsis “sniffer”

<table>
<thead>
<tr>
<th>Physiological Concept</th>
<th>EMR Representation</th>
<th>Rule</th>
<th>Additional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspicion of Infection</td>
<td>Any Culture Order</td>
<td>Blood or Lavage or Stool or Urine or Fluid or Sputum</td>
<td>≥ 1 event, including 72 past hours</td>
</tr>
<tr>
<td>Systemic Inflammatory Response</td>
<td>WBC</td>
<td>&lt; 4.0 or &gt; 12.0</td>
<td>≥ 1 (WBC or Body Temperature) event and ≥ 1 additional event from any of three remaining categories, within a 6 hour window</td>
</tr>
<tr>
<td></td>
<td>Body Temperature</td>
<td>&gt; 38.0 or &lt; 36.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory Rate</td>
<td>&gt; 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart Rate</td>
<td>&gt; 90</td>
<td></td>
</tr>
<tr>
<td>Organ Hypoperfusion and Dysfunction</td>
<td>Lactate</td>
<td>≥ 4.0</td>
<td>≥ 1 event</td>
</tr>
<tr>
<td></td>
<td>Systolic Blood Pressure (SBP)</td>
<td>&lt; 90</td>
<td>≥ 1 event</td>
</tr>
<tr>
<td>Shock</td>
<td>Vasopressors</td>
<td>Norepinephrine or Epinephrine or Dopamine or Vasopressin or Phenylephrine</td>
<td>≥ 1 event</td>
</tr>
<tr>
<td></td>
<td>Fluid Resistant Hypotension</td>
<td>SBP &lt; 90 despite ≥ 30 mL/kg Crystalloid and/or 18 mL/kg Colloid Fluid Bolus</td>
<td>Within a 3 hour window</td>
</tr>
</tbody>
</table>
Emergency department
Process of care/QI dashboard
Sepsis surveillance system
CERTAIN: Checklist for Early Recognition and Treatment of Acute Illness

• Simple solution scalable to variable settings
  – Including low resource
CERTAIN: Checklist for Early Recognition and Treatment of Acute Illness

**Problem list**
- Sepsis

**Background**
- Shortness of breath
- History: Chronic liver failure
- Meds: Insulin
- Allergies: None

**Findings**
- B-line
- Collapsing IVC
- Hyperdynamic

**Sepsis**

**Immediate considerations**
- Cultures
  - Cultures should be taken as soon as possible and before antimicrobial therapy
- Antibiotics
  - Antibiotics should be initiated as soon as possible according to likely pathogen, site of infection, immune status, and allergy
- Source control
  - Remove dead tissue, pus, or infected device for source control
- Fluid challenge
  - Start fluid bolus (~30ml/kg), repeat as needed to achieve adequate tissue perfusion taking into consideration fluid responsiveness
- Vasopressors
  - Add vasopressors for shock despite fluid resuscitation
- Steroids
  - Add steroids for shock despite vasopressors
**Management after stabilization**
- Limit oxygen consumption
  - Consider mechanical ventilation, use analgesics, sedatives, and neuromuscular blockers as appropriate to limit oxygen consumption

**Cautions**

**Suggested medications**
- Antibiotic
- Fluid bolus
- Vasopressor
- Steroid

**Suggested interventions**
- Cultures
- Source control
- Intubation
Keeping track of interventions

Ordered
- Consult - Infectious disease 02:59
- X-ray - Chest 02:57
- Normal saline 1000 ml Inf 02:56
- Levofoxacin 750 mg IV 02:54

Completed
- Normal saline 1000 ml Inf 02:56
- Cefepime 1 gr IV 02:56
- Culture - Blood 02:55
- Culture - Urine 02:55
- Culture - BAL 02:55
- Albuterol 2 puffs Inh 02:55
- 12-lead ECG 02:54
- Laboratory 02:45
- Vascular access 02:45
- Oxygen 02:45
We need to be AWARE & CERTAIN

Special thanks to AWARE and CERTAIN teams

...to prevent DEATH

(Diagnostic Errors and Therapeutic Harm)

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http://www.icertain.org/
Multidisciplinary Epidemiology and Translational Research in Intensive Care

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“Failure to rescue” concept
“Failure to rescue” concept
Surviving Sepsis Campaign: Association Between Performance Metrics and Outcomes in a 7.5-Year Study

Mitchell M. Levy, MD, FCCM; Andrew Rhodes, MB BS, MD (Res); Gary S. Phillips, MAS; Sean R. Townsend, MD; Christa A. Schorr, RN, MSN; Richard Beale, MB BS; Tiffany Osborn, MD, MPH; Stanley Lemeshow, PhD; Jean-Daniel Chiche, MD; Antonio Artigas MD, PhD; R. Phillip Dellinger, MD, FCCM
Multicenter Implementation of a Severe Sepsis and Septic Shock Treatment Bundle


B

Mortality (%)  


0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80

Total Bundle Compliance (%)

19.9% 60.0% 12.2% 7.0%

Control
Figure 1. Mean Annual Mortality in Patients With Severe Sepsis

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

![Graph showing annual mortality rates from 2000 to 2012 with data points and error bars indicating variability.](Graph.png)

- Mortality, %: 30, 27, 25, 23, 21, 20, 19, 18, 17, 16, 15, 14, 13
- No. of patients: 2708, 3783, 4668, 5221, 6375, 6987, 7627, 8529, 8797, 10277, 11367, 12213, 12512

JAMA April 2, 2014 Volume 311, Number 13
| Initial Care Bundle  
(First 6 hr of presentation) | Participation in SSC, yr | Hospital Mortality OR<sup>a</sup> | 95% CI       | p    |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Measured lactate</td>
<td>&lt; 2</td>
<td>0.80</td>
<td>0.73–0.89</td>
<td>&lt; 0.001</td>
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<tr>
<td></td>
<td>2 to &lt; 3</td>
<td>0.67</td>
<td>0.59–0.76</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
<td>0.69</td>
<td>0.63–0.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood cultures before antibiotics</td>
<td>Not applicable&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.82</td>
<td>0.77–0.87</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Broad-spectrum antibiotics</td>
<td>Not applicable&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.85</td>
<td>0.81–0.90</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fluids and vasopressors</td>
<td>&lt; 2</td>
<td>0.86</td>
<td>0.73–1.01</td>
<td>0.074</td>
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<tr>
<td></td>
<td>2 to &lt; 3</td>
<td>0.63</td>
<td>0.48–0.81</td>
<td>&lt; 0.001</td>
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<tr>
<td></td>
<td>≥ 3</td>
<td>0.74</td>
<td>0.62–0.88</td>
<td>0.001</td>
</tr>
<tr>
<td>CVP &gt; 8 mm Hg</td>
<td>Not applicable&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.84</td>
<td>0.78–0.91</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Scvo&lt;sub&gt;2&lt;/sub&gt; &gt; 70%</td>
<td>Not applicable&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.83</td>
<td>0.76–0.90</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>All resuscitation measures</td>
<td>Not applicable&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.79</td>
<td>0.73–0.85</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

| Management Bundle  
(First 24 hr after presentation) | | |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid policy</td>
<td>&lt; 2</td>
<td>0.96</td>
<td>0.84–1.09</td>
<td>0.527</td>
</tr>
<tr>
<td></td>
<td>2 to &lt; 3</td>
<td>0.76</td>
<td>0.64–0.89</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
<td>0.88</td>
<td>0.79–0.99</td>
<td>0.031</td>
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<tr>
<td>rhAPC policy</td>
<td>Not applicable&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.93</td>
<td>0.87–1.00</td>
<td>0.061</td>
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<tr>
<td>Glucose policy</td>
<td>Not applicable&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.71</td>
<td>0.68–0.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Plateau pressure control</td>
<td>Not applicable&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.81</td>
<td>0.74–0.89</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>All management measures</td>
<td>Not applicable&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.74</td>
<td>0.69–0.79</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

SSC = Surviving Sepsis Campaign; OR = odds ratio; CVP = central venous pressure; Scvo<sub>2</sub> = central venous oxygen saturation; rhAPC = recombinant human activated protein C.
Yue Dong,
Other Industry
In Conclusion

• Knowledge alone does not translate into better patient outcomes

• Investment in infrastructure which facilitates knowledge translation is essential for Mayo Clinic and out patients

• The AWARE platform is being built to facilitate the reliable application of knowledge at the bedside of critically ill patients and beyond
AWARE components

- **Resuscitation module**
  - Addresses time sensitive clinical interventions

- **Multipatient viewer**
  - Group level population management

- **Single patient viewer**
  - Pertinent clinical information

- **Administrative dashboard**
  - Resource planning, Quality improvement

---

**Hand over**
- Essential information at a glance
- Focused on patient problems

**Claim patient**
- Links provider and patients
- One stop communication

**Task list**
- Shared list of tasks
- Outside of clinical note

**Rounding tool (Checklist)**
- Structured clinical assessment
- Generates clinical note
Surviving Sepsis Campaign: Association Between Performance Metrics and Outcomes in a 7.5-Year Study

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![Graph showing a linear trend with a slope of 0.7% drop in mortality per quarter and a p-value < 0.001.](image-url)