Using Predictive Analytics to Improve Sepsis Outcomes

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The Sepsis Problem
Ubiquitous, deadly, and costly

- 20,000 deaths per day worldwide
- 800,000+/year contract sepsis in the U.S.; 250K-300K sepsis deaths/year
- $20+ billion annual cost to U.S healthcare providers
- Mortality rate for septic shock exceeds 50%... and, untreated, grows 7.6% per hour
Early identification is critical and difficult

“Evidence unwaveringly suggests that early administration of appropriate antibiotics reduces mortality...” (Surviving Sepsis Campaign)

"Lack of early recognition is a major obstacle to sepsis bundle initiation." (Surviving Sepsis Campaign, 2012 Guidelines)
Basic Analytics Approaches
EHR triggers may be proposed to aid early sepsis identification.

For example, the traditional 4 SIRS criteria require vitals & labs:
- Heart rate
- Respiratory rate
- Temperature
- White blood cell count, Bands percentage

Benchmark prior to deployment to estimate clinical impact
- Using retrospective EHR data
- Logging results from a live trial implementation
Case Study: SIRS criteria at a 500-bed hospital

- 500-bed U.S. hospital
- Proposed EHR alert requires at least 2 out of 4 SIRS criteria
- Benchmark to estimate alert volume and clinical workload
- Results of running proposed alert on 4 months of real-time data
  - 13142 patients receive the proposed alert
  - Over 100 alerts per day on average
  - Significant burden: alerts require clinical evaluation for infection & sepsis
  - Most alerts are false positives
- Many hospitals end up ignoring or turning off SIRS alerts due to high workload
  - Though it can yield results with continuous training & feedback: UC Davis at HIMSS 2014
Case Study: All 4 SIRS criteria, at a 300-bed hospital

- 300-bed U.S. hospital

- Proposed EHR alert requires all 4 out of 4 SIRS criteria
  - A reaction to the overwhelming volume of alerts from 2 out of 4 criteria

- Benchmark to estimate potential impact on earlier IV antibiotics
  - Look for alert 2+ hours before first standard-of-care antibiotic order
  - For patients who eventually receive a diagnosis of sepsis

- Results of running proposed alert on 6 months of real-time data
  - Only 1 patient in the entire 6 months meets the benchmark criteria
  - The alert is unlikely to help significantly improve early antibiotics
Advanced Analytics Approaches
Obtaining Signal from All Available Data
Knowledge-Based Systems

- Experts
- Guidelines
- Research

Knowledge Base

- Individual Patient Data

Rules Engine

CDS Alerts/Messages
Data Mining / Machine Learning

- Big Patient Data
- Trained Model
- Individual Patient Data
- CDS Alerts/Messages

Offline / Online
Hybrid

Big Patient Data

Knowledge Base

Trained Model

Individual Patient Data

CDS Alerts/Messages

Experts

Guidelines

Research

Offline

Online
CV Sepsis™
Real-time Decision Support

- Clinical decision support software
- Connects to existing hospital information systems and analyzes all patient data 24/7
- Supports early sepsis detection/prediction
- Provides clinical alerts to smartphone/tablet
- Technology:
  - Machine Learning
  - Natural Language Processing
  - Auto-filtering of physiological signals
Clinical Results

- Alerts precede clinician’s standard of care order of antibiotics by > 12 hours for > 45% of alertable sepsis patients, substantially improving upon results already achieved by conventional sepsis initiatives.

- High alerting accuracy (specificity > 99%). Average 1-3 alerts per clinical shift for a 500 bed hospital. Important for avoiding alarm fatigue.
How Does Amara “define” sepsis?

For triggering alerts:
- The CV Sepsis™ predictive model reasons over >100 clinical variables

For machine learning & evaluation:
- Timeliness: To be considered “early” alerts must precede IV antibiotic orders of physicians unassisted by alerts.
- Accuracy: An alert is conservatively considered:
  - True positive only if the patient goes on to receive a coded diagnosis of sepsis.
  - False positive if the patient is never on IV antibiotics.
Research Challenges and Results
Methodological Challenges in Sepsis Research

Previous sepsis studies have faced methodological limitations:
• Interventional trials (e.g. ProCESS) enroll high-acuity patients.
• Chart review studies skew towards high acuity to limit costs.
• Epidemiological studies face accuracy limits of coded data; particularly problematic for low-acuity patients.

Advanced clinical analytics enables new kinds of sepsis studies:
• Comprehensive data on a large scale with no chart review costs
  • Across the entire sepsis acuity spectrum
• Including detailed real-time clinical data
• Including events identified using natural language processing
Assessing the True Sepsis Burden
[from data presented at ISICEM 2014]

• Total of 216,550 patients over 36 months from 2 hospitals
• 34,465 patients got IV antibiotics (suspected infection; sepsis)
• This minority of patients (16%) has a majority (63%) of in-hospital deaths

Outcome Occurrence among All Sepsis Patients
Automatically Compute Complex Severity Scores

PIRO sepsis staging: Predisposition, Infection, Response, Organ failure


Mortality vs PIRO score, manually abstracted [Howell et al.]:

Mortality vs PIRO score, computed automatically [our data]:
CV Sepsis™ Alert [preliminary data]

- CV Sepsis screened all patients
- Alerts logged in the background (non-interventional)
- Alert triggered on 3986 of 30479 patients who received IV antibiotics (13%)
- IV Antibiotic patients with CV Sepsis alert notification had increased mortality and hospital length of stay.

![Bar chart showing mortality comparison between patients with and without CV Sepsis alert]

![Bar chart showing median length of stay comparison between patients with and without CV Sepsis alert]
Antibiotic Timing and Mortality

- Surviving Sepsis, NY Sepsis Regulations, etc. prioritize early antibiotics.
- Mortality & LOS for varying delay from CV Sepsis™ alert to IV antibiotics

For 2217 patients with moderate initial severity (PIRO score 5-14)

Earlier antibiotics after CV Sepsis alert are associated with better outcomes.
Lactate Timing and Mortality
[from data presented at ISICEM 2014]

• **3-hour sepsis bundle** includes: “Measure lactate level”
• Compare mortality for:
  • **Early Lactate** (measured 0-3 hours after CV Sepsis alert)
  • **Delayed Lactate** (more than 3 hours after CV Sepsis alert)

<table>
<thead>
<tr>
<th></th>
<th>Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Lactate (n=4151)</td>
<td></td>
</tr>
<tr>
<td>Delayed Lactate (n=922)</td>
<td></td>
</tr>
</tbody>
</table>

• The timing of the assessment, *independent of lactate level*, was prognostic of outcome.
Serial Lactate
[from data presented at ISICEM 2014]

• Surviving Sepsis Bundles & NY Sepsis Regulations Guidance include: “Remeasure lactate if initial lactate was elevated.”
• For patients with initial lactate>4, compare mortality based on serial lactate measurement.

![Graph showing mortality rates for different lactate categories](image)

- Serial Lactate <4 (n=279)
- Serial Lactate ≥4 (n=211)
- No serial lactate (n=89)

• Unmeasured serial lactate, and serial lactate ≥ 4, are associated with large mortality burden.
APPENDIX
Competitive Analysis

Response
Percentage of CV Sepsis™ Performance

- CV:Sepsis
- SIRS
- Vanderbilt
- Michigan
- BJH
- Epic
- Cerner
- Truven
- CSC

0% 20% 40% 60% 80% 100%
Hospital Value: Better Outcome & Lower Costs

- Significantly lower mortality and higher quality of life for survivors

- Example estimated impact at a 500-bed community hospital:
  - 750 fewer sepsis bed-days per year and lower mortality
  - Correspondingly shorter ICU stays
  - **Projected direct savings of >$2.5M per year**

- **>10X annual ROI** on purchase of *CV Sepsis™*
Internal System Architecture

- Disease Modeling
- Patient Timeline
- Feature Extraction
- Data Acquisition

Data Mining & Machine Learning

Clinical NLP
Medical Ontologies
Multisource Integration
Time Series Processing

Sepsis Model
Reasoning Engine

ADT Labs EHR CPOE Admin Devices
Patient Timeline Data for Research & Reporting
Clinical Results: *Sepsis 2012* data

*R.C. Arnold, S.M. Hollenberg, R.P. Dellinger. Sepsis 2012*

Data from a 300-bed community hospital

<table>
<thead>
<tr>
<th></th>
<th>Median LOS (days)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no alert</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>abx order 24-0 hrs</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>hrs prior to alert</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abx order 0-12 hrs</td>
<td>6</td>
<td>8.9</td>
</tr>
<tr>
<td>hrs after alert</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abx order &gt;12 hrs</td>
<td>8</td>
<td>9.6</td>
</tr>
<tr>
<td>after alert</td>
<td></td>
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Patients experienced better outcomes when treatment was initiated sooner, compared to the time of the *CV Sepsis™* alert.