Sepsis Overview
Challenges and Solutions from the Clinical Lab

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Global Marketing Manager
For Hematology
Objectives

To Understand:

Basic etiology of Sepsis and its impact on healthcare

The challenges to rapidly diagnose sepsis

The role of the laboratory in the diagnosis and management of sepsis
Sepsis by the Numbers

High Mortality Rate
Sepsis impacts many people and has a high mortality rate

Costly
Sepsis is costly to healthcare organizations

Early Identification
Sepsis is challenging to healthcare organizations
Early Diagnosis and Treatment Reduces Mortality

Each hour delay initiating effective antibiotic administration increases mortality by 7.6%
Typical Sepsis Care Pathway -70%

Patient presents at point of entry

1. Generally Unwell
2. Initial triage indicates possible infection (ED)
3. CBC-Diff BMP UA ordered

Signs & symptoms indicate possible sepsis?
- Systemic inflammatory response syndrome (SIRS)
- Temperature
- Heart Rate
- Respiratory Rate
- White Blood Count

Inpatient admission

4. Sepsis evaluation tests ordered

Empiric antibiotics

4A. Test for Monitoring Lactate, Procalcitonin, CRP, IL6*

4B. Confirmatory Tests

5. Sepsis Diagnosis

SIRS
- Hypotension
- Respiratory failure
- Coagulopathy
- Organ dysfunction
- Mental status

6. Intensive Care Unit

Patient Discharged

Symptoms may only become obvious several hours after presenting to ED
Challenges To Identifying Sepsis

SIRS are not specific to sepsis, making “well looking” patients difficult to identify

- Heart rate >90 bpm
- Respiratory rate >20 breaths/min
- Temperature >38.3°C, or <36°C
- White cell count <4 or >12 x 10^3/mL or bandemia
Sepsis: The Intersection of Infection and SIRS

SIRS = systemic inflammatory response syndrome

Source: http://emedicine.medscape.com/article/168943-overview
https://www.researchgate.net/figure/Criteria-for-Systemic-Inflammatory-Response-Syndrome-SIRS-Adapted-from-McClelland-H_fig2_306927533
Emergency Department Sepsis Assessment

Systemic Inflammatory Response Syndrome (SIRS)

- **Temperature**: >38.3°C, or <36°C
- **Heart rate**: >90 bmp
- **Respiratory rate**: >20 breaths/min
- **White cell count**: <4 or >12 x 10³/mL or bandemia

Quick Sequential Organ Failure Assessment (qSOFA)

- **RR**: >22bpm
- **sBP**: <100mmHg
- **Altered GCS**: 0 = Mortality <1%
  1 = Mortality 2-3%
  >2 = Mortality ≥10%

Screening for outcome rather than diagnosis

https://www.researchgate.net/figure/Criteria-for-Systemic-Inflammatory-Response-Syndrome-SIRS-Adapted-from-McClelland-H_fig2_306927533

- qSOFA
- qSOFA: quick Sequential Organ Failure Assessment
It has been made brutally clear that there is not enough knowledge or awareness out there about sepsis and that needs to change, and I hope to be a part of that change…

“...”

5 Clinician Consults
- Primary Doctor X2
- Urgent Care
- Telemedicine nurse consult
- Emergency Room

5 Diagnoses’/Tests
- Sinus Cold
- Flu test, chest X-ray
- Mononucleosis
- Pneumonia
- Sepsis
  - Mixed Viral and Bacterial

15 Months plus, recovery
Hypothesis Posits That Immunosuppression Occurs Concurrently to the Cytokine Storm

Sepsis Can Affect Major Organs

The more organs affected, the higher the risk of death

### Sources of sepsis

<table>
<thead>
<tr>
<th>Source</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>38%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>21%</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>16.5%</td>
</tr>
<tr>
<td>Others</td>
<td>11.3%</td>
</tr>
<tr>
<td>CRBSI</td>
<td>2.3%</td>
</tr>
<tr>
<td>Device</td>
<td>1.3%</td>
</tr>
<tr>
<td>CNS</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

### Sources of Sepsis

- **Respiratory** 38%
- **Urinary tract** 21%
- **Intra-abdominal** 16.5%
- **Others** 11.3%
- **CRBSI** 2.3%
- **Device** 1.3%
- **CNS** 0.8%

### Neurological system
- Altered mentation
- Confusion
- Disorientation

### Respiratory system
- Hypoxaemia
- $\downarrow$ PaO$_2$:FiO$_2$ ratio

### Cardiovascular system
- Hypotension
- Mottled skin and altered microcirculation
- ↑ Lactate levels (in septic shock)
- Altered echocardiography variables

### Hepatic system
- ↑ Bilirubin levels
- ↑ Liver enzymes

### Renal system
- Oliguria
- ↑ Serum creatinine
- ↑ Blood urea nitrogen
- ↑ Biomarkers

### Haematological system
- Low platelet count
- Disseminated intravascular coagulation
- Petechiae (in some severe cases)
Biomarkers of Sepsis

Infection
- WBC
- CRP
- PCT
- Heart rate
- Respiratory rate
- I/T ratio
- Absolute Neutrophils count
- Sedimentation rate
- Blood culture
- LBP
- Angiopoietin
- ProADM

Inflammation
- WBC
- CRP
- IL6
- IL8
- IL10
- IL12
- CD14
- CD64

Perfusion
- BP
- pH
- Blood gas
- PaO2
- PaCO2
- HCO3

Coagulation
- Platelet count
- Anti-thrombin
- D-dimers
- Fibrin
- PAI-1

Organ failure
- Lactate
- Creatinine
- Bilirubin
- GGT
- ANP

Dysregulated Inflammation

SEPSIS
Current Key Biomarkers for Sepsis

- Lactate
- Procalcitonin
- C-reactive Protein
- WBCs
  - elevated count
  - immature forms
  - leukocyte morphology
- Other: IL-6, IL-10, TNF-α

Lactate

- Lactate is a byproduct of anaerobic metabolism from pyruvate
- With insufficient oxygenation, cells and tissues move from aerobic metabolism to anaerobic metabolism
- Used as a measure of tissue perfusion irrespective of blood pressure
Hour-1 Bundle

“Consistent with previous iterations of the SSC sepsis bundles, ‘time zero’ or ‘time of presentation’ is defined as the time of triage in the emergency department.”
**Lactate**

- Cutoff was reduced to >2 mmol/L from >4 mmol/L
- Mortality is positively correlated in septic patients with lactate >2 mmol/L
Cytokines

IL-6 is produced by monocytes, fibroblasts, endothelial cells, keratinocytes, T-cells, and tumor cells.

- Released into the bloodstream for 4–6 h, decreasing over the next 24–48 h.

IL-8 produced by macrophages and endothelial cells.

IL-10 is an anti-inflammatory cytokine produced by monocytes, macrophages, T and B cells, neutrophils and mesangial cells.
Cytokines

• Measurements of CRP or PCT are more sensitive.
  - Elevated cytokine levels are also seen in SIRS of noninfectious origin.
• No studies prove that the treatment of sepsis based on these markers influences the treatment strategy or improves the clinical result.
• IL-6 and IL-10 can predict higher mortality for septic patients.
C-reactive protein

- Macrophages secrete IL’s which stimulate the liver to initiate the acute-phase response and produce CRP

- Binds to phosphocholine, for uptake by phagocytes

- Bacteria binding to CRP can activate the complement cascade
C-reactive protein

- The concentration of CRP in healthy subjects is <5 mg/L
- Maximum production at 24-38 hours after the onset of inflammation
- Used to distinguish viral and bacterial infections.
- CRP is not a specific parameter for the presence of infectious inflammation

Procalcitonin

- A prohormone of calcitonin
- In physiological conditions, calcitonin is secreted by parafollicular cells of the thyroid
- In sepsis the main producers of PCT are macrophages and monocytic cells of different organs, especially liver

Image from: https://en.wikipedia.org/wiki/Procalcitonin
Procalcitonin

- Minimum elevation of PCT concentration in viral infections
- It is useful to monitor antibiotic effectiveness at ≥0.5 ng/ml
- More specific and more sensitive than CRP, although
  - PCT is not specific for sepsis
  - PCT is not sensitive for patients with abscesses or fungal infections
Procalcitonin

If PCT levels are lower than 0.2 ng/ml, the negative prediction related to bacteremia is higher than 90%.

Table 2
Procalcitonin results in negative and positive blood cultures

<table>
<thead>
<tr>
<th>Procalcitonin at presentation</th>
<th>Blood cultures (n)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td>Total (n)</td>
</tr>
<tr>
<td>&lt;0.5 ng/ml</td>
<td>24</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>0.5 to 2.0 ng/ml</td>
<td>16</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>2.0 to 10.0 ng/ml</td>
<td>13</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>&gt;10.0 ng/ml</td>
<td>12</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>36</td>
<td>101</td>
</tr>
</tbody>
</table>

Koeze J, et al., Critical Care 2011, 15:422
Current Biomarkers Not Sufficient For Less Severe Sepsis

- None of the current biomarkers reach AUC of 0.8 for sepsis of all severities
- Monocyte Distribution Width (MDW) + WBC show increased value over WBC alone

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5519182/
IG: Not An Adequate Biomarker

Table 1

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
<th>AUC (95% CI)</th>
<th>Optimal cut-off</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>1.44 (1.20, 1.73)</td>
<td>&lt; 0.0001</td>
<td>0.63 (0.58, 0.68)</td>
<td>1.3 mmol/L</td>
<td>55.1% (48.7, 61.4)</td>
<td>62.7% (56.8, 68.4)</td>
</tr>
<tr>
<td>Neutrophil #</td>
<td>1.10 (1.06, 1.14)</td>
<td>&lt; 0.0001</td>
<td>0.63 (0.58, 0.68)</td>
<td>7.5 x 10^-9/L</td>
<td>60.7% (54.3, 66.7)</td>
<td>60.7% (54.7, 66.3)</td>
</tr>
<tr>
<td>Neutrophil %</td>
<td>1.05 (1.03, 1.06)</td>
<td>&lt; 0.0001</td>
<td>0.69 (0.64, 0.74)</td>
<td>79%</td>
<td>63.2% (56.9, 69.2)</td>
<td>63.3% (57.4, 68.9)</td>
</tr>
<tr>
<td>IG #</td>
<td>1.45 (0.64, 3.29)</td>
<td>0.37</td>
<td>0.61 (0.56, 0.66)</td>
<td>0.02 x 10^-9/L</td>
<td>49.6% (43.2, 55.9)</td>
<td>67.3% (61.4, 72.7)</td>
</tr>
<tr>
<td>IG %</td>
<td>1.06 (0.96, 1.19)</td>
<td>0.26</td>
<td>0.60 (0.55, 0.64)</td>
<td>0.2%</td>
<td>45.7% (39.5, 52.1)</td>
<td>67.0% (61.2, 72.4)</td>
</tr>
<tr>
<td>WBC</td>
<td>1.04 (1.01, 1.07)</td>
<td>0.004</td>
<td>0.59 (0.54, 0.64)</td>
<td>9.7 x 10^-9/L</td>
<td>57.7% (51.3, 63.8)</td>
<td>57.7% (51.7, 63.5)</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>1.01 (0.99, 1.04)</td>
<td>0.28</td>
<td>0.68 (0.63, 0.72)</td>
<td>0.20 ng/mL</td>
<td>63.0% (56.4, 69.1)</td>
<td>63.0% (56.8, 68.8)</td>
</tr>
</tbody>
</table>

A method for detecting immature granulocytes (promyelocytes, myelocytes, metamyelocytes) compared to peripheral smear review [9]. In this study we evaluated the diagnostic utility of conventional sepsis biomarkers: lactate, PCT, WBC, neutrophil count, and IG; for the prediction of sepsis in ED patients.

were calculated for the AUC, along with 95% CI on the odds ratio [10]. Statistical significance of the odds ratio was defined as p < 0.05. Sensitivity and specificity confidence intervals were calculated using the method of Agresti [11]. AUC analysis was performed with SAS, version 9.4; and recursive partitioning utilized the rpart function and
Stepwise Activation of the Innate Immune Response

Step 1: **Macrophages** phagocytize **BACTERIA** at the infection site

Step 2: Macrophages and monocytes **RELEASE CYTOKINES** into the body (cytokine storm)

Step 3a: Cytokines activate circulating WBC (neutrophils) – **TOXIC GRANULATION**

Step 3b: Cytokines stimulate bone marrow – **LEUKOCYTOSIS** with **ANC** rise

Step 4: BM releases mature granulocytes in blood, including **BANDS**

Step 5: Consumption of neutrophils at the infection may exceed marrow production. The marrow may then respond with a release of **IG** cells

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Abnormal Cell Detection
Morphology and Cytochemical Cell Differentiation
Abnormal Cell Detection
Morphology and Cytochemical Cell Differentiation

1. Mono-Blasts
2. Myelo-Blasts
3. Immature Granulocytes
4. Band Neutrophils
5. Lympho-Blasts
6. Variant Lymphs
7. Low Volume Lymphs
8. Non-White Cells
Early Detection of Sepsis: Feasibility Study

Improved Early Detection of Sepsis in the Emergency Department with a Novel Monocyte Distribution Width Biomarker

Elliott D. Crouser, M.D.1, Joseph E. Parrillo, M.D.2, Christopher Seymour, M.D.3, Derek C. Angus, M.D, M.P.H.3, Keri Bicking, Pharm. D.2, Diana Careaga4, Robert Magari, Ph.D. 4, JoAnna Williams, M.D.5, Douglas R. Closser, M.D. 1, Michael Samoszuk, M.D. 4, Luke Herren1, Emily Robart1, Liliana Tejidor, Ph.D. 4, Fernando Chaves, M.D. 4

1. Department of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH
2. Heart and Vascular Hospital, Hackensack University Medical Center, Hackensack, NJ
3. Department of Critical Care Medicine, University of Pittsburgh School of Medicine Pittsburgh, PA
4. Beckman Coulter, Inc.
5. Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, OH

http://journal.chestnet.org/article/S0012-3692(17)31072-3/fulltext
Innate Immune System Cells

Key Functions in Infection

Neutrophil

- Neutrophils
- Phagocytosis
- Neutrophils contain granules that release enzymes to help kill and digest bacteria

Monocyte

- Phagocytosis
- Ag presentation
- Cytokine production
- Activation of the acquired immune system
Monocytes in Infection and Sepsis: Changes in Morphology

- Functional changes of the monocytes, and, in parallel, changes in cellular morphology, were demonstrated for human THP-1 monocytic cell line, infected with viable C. pneumonia bacteria.

- The differentiation of infected cells into macrophages was accompanied by a change to the amoeboid or diffused morphology.

Measurement of Monocyte Volume Distribution Width
Sepsis Demonstrates Increased Variability In Monocyte Volume (MDW)

MDW = 19.1
WBC cells x10³ = 4.73

MDW = 24.3
WBC cells x10³ = 10.27

Blinded, prospective, observational cohort study was conducted across three sites in the U.S. with 2,158 consecutive adult emergency-departments.

<table>
<thead>
<tr>
<th></th>
<th>MDW</th>
<th>MDW + WBC</th>
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<tbody>
<tr>
<td>Clinical trial AUC</td>
<td>0.75</td>
<td>0.85</td>
</tr>
<tr>
<td>Trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-89 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC-DIFF ordered at presentation</td>
<td></td>
<td>Hospital or ED with a minimal stay ≥12 hours</td>
</tr>
<tr>
<td>K2 EDTA samples tested ≤2 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Multi-center Clinical Trial with Unselected Population

Blinded, prospective, observational cohort study was conducted across three sites in the U.S. with 2,160 consecutive adults entering emergency-departments.

MDW alone

MDW + WBC

AUC = 0.788
Lower = 0.762
Upper = 0.815
**Atypical patient presentation**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Flags</th>
<th>Previous</th>
<th>Days</th>
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<tbody>
<tr>
<td>WBC</td>
<td>6.9</td>
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<tr>
<td>LMRBC</td>
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<tr>
<td>RBC</td>
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<td>HGB</td>
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<tr>
<td>HCT</td>
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<tr>
<td>MCV</td>
<td>92.1</td>
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<tr>
<td>MCH</td>
<td>31.4</td>
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<tr>
<td>MCHC</td>
<td>34.1</td>
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<tr>
<td>RDW</td>
<td>12.9</td>
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<tr>
<td>RDW SD</td>
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<tr>
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<tr>
<td>MPV</td>
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**DIFF**

<table>
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<tr>
<td>MO</td>
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<tr>
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<tr>
<td>LY%</td>
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<tr>
<td>MPV</td>
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</tr>
<tr>
<td>MDW</td>
<td>28.24</td>
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</table>

**Specimen**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>L841270162</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td>Female</td>
</tr>
<tr>
<td>Age:</td>
<td>18 yo</td>
</tr>
</tbody>
</table>

**CBC @ 1.6 Hrs**

- **WBC**: 6.9 x 10^3/mL
- **PLATELET**: 138
- **PCT**: Not performed
- **CRP**: Not performed
- **ESR**: Not performed
- **IL6**: Not performed
- **EAA**: Not performed
- **Lactate**: Not performed
- **Blood Cx**: Not performed
- **SIRS**: 2
- **Initial Dx**: Pneumonia
- **Rx**: Levofloxacin
- **Final Dx @ 7 Hr post CBC**: Sepsis - SIRS + Infection

**MDW**: 28.2*  

*After activation with ESI package.
Beckman Coulter gains FDA 510(k) for Early Sepsis Indicator (ESId)

MDW is included as part of a CBC with differential test, the hematology-based solution is intended to aid detection of patients with or developing sepsis for emergency department clinicians to sepsis or the possibility of sepsis earlier than any other.
Typical Sepsis Care Pathway
ESld included with the CBC/Diff

1. Patient presents at point of entry
   - Initially triage indicates possible infection (ED)

2. CBC/Diff BMP UA ordered
   - DxH Sepsis
     - Available with initial CBC-Diff
     - CBC ordered as part of routine labs

3. Signs & symptoms indicate possible sepsis?
   - Systemic inflammatory response syndrome (SIRS)
     - Temperature
     - Heart Rate
     - Respiratory Rate
     - White Blood Count

4. Inpatient admission
   - Sepsis evaluation tests ordered
     - Test for Monitoring Lactate, Procalcitonin, CRP, IL6*
     - Confirmatory Tests

5. Empiric antibiotics
   - SIRS
     - Hypotension
     - Respiratory failure
     - Coagulopathy
     - Organ dysfunction
     - Mental status

6. Intensive Care Unit
   - YES
   - NO

Patient Discharged

Symptoms may only become obvious several hours after presenting to ED
The results suggest only 68% of sepsis patients may potentially benefit from MDW.

**Standard of Care**
- 100% of Sepsis Patients Identified via Standard of Care
- 4.43 hours
  - n = 412

**If MDW had been available**
- 68% of Sepsis Patients Identified via MDW
- 1.34 hours
  - n = 218
- 3.83 hours
  - n = 132
Early Sepsis Indicator

**Detection Tools**

- **DxH Unicel Instrument**
- **6C Plus QC**
- **Early Sepsis Indicator**

**MDW Parameter included with Differential**

- Decision rules to trigger alerts

**Alerts**

**Lab workflow - 6C Plus controls and Early Sepsis Indicator activation**
Potential Economic VALUE of Early Sepsis Indicator
An economic model was executed from a hospital perspective

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Decision tree</td>
</tr>
<tr>
<td>Intervention</td>
<td>MDW</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard of care (SoC) only</td>
</tr>
<tr>
<td>Target Population</td>
<td>Patients ultimately diagnosed and treated for sepsis</td>
</tr>
<tr>
<td>Perspective</td>
<td>Hospital (actual costs to the hospital)</td>
</tr>
<tr>
<td>Data Sources</td>
<td>MDW pivotal trial, Observational research</td>
</tr>
<tr>
<td>Clinical Inputs</td>
<td>• Mean time to antibiotics for SoC</td>
</tr>
<tr>
<td></td>
<td>• Mean time to antibiotics among patients estimated to benefit from MDW</td>
</tr>
<tr>
<td></td>
<td>• Mean time to antibiotics among patients not estimated to benefit from MDW</td>
</tr>
<tr>
<td></td>
<td>• Proportion of sepsis patients benefiting from MDW</td>
</tr>
<tr>
<td></td>
<td>• Relationship of time to antibiotic and mortality</td>
</tr>
<tr>
<td>Economic Inputs</td>
<td>• Relationship of time to antibiotics and length of stay (overall and ICU)</td>
</tr>
<tr>
<td></td>
<td>• Cost per day</td>
</tr>
<tr>
<td></td>
<td>• Mean number of sepsis hospitalizations per hospital per year (hospital-level analysis only)</td>
</tr>
<tr>
<td></td>
<td>• Cost of MDW (hospital-level analysis only)</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>Patient-level analysis</td>
</tr>
<tr>
<td></td>
<td>• Patient-level cost per hospitalization</td>
</tr>
<tr>
<td></td>
<td>• In-hospital mortality rate</td>
</tr>
<tr>
<td></td>
<td>• Length of stay</td>
</tr>
<tr>
<td></td>
<td>Hospital-level analysis</td>
</tr>
<tr>
<td></td>
<td>• Annual number of sepsis-related hospitalization costs</td>
</tr>
<tr>
<td></td>
<td>• Annual number of in-hospital deaths</td>
</tr>
<tr>
<td></td>
<td>• Annual number of days in the hospital</td>
</tr>
</tbody>
</table>
The model is driven by an improvement in time to antibiotics

Outcomes Evaluated

- Mortality Rate
- Total Costs
- Length of Stay

Sepsis Patients

Standard of Care (SoC) → Identified via SoC

MDW

Identified via MDW → Weighted Mortality Rate
Total Costs
Length of Stay

Not Identified via MDW → Weighted Mortality Rate
Total Costs
Length of Stay
Key limitations and assumptions in the model

1. It was assumed that it would take **30 minutes for the MDW** result to be obtained. This includes the time to **draw** the blood, send the sample to the lab, lab analysis and results reported to physician. This is a reasonable recommendation considering the Surviving Sepsis Campaign\(^1\) goal of antibiotics administration within 1 hour of sepsis detection. However, we realize this turnaround time is aggressive so we also analyzed the data at 45 minutes and 60 minutes in a sensitivity analysis.

2. It was also assumed that clinicians would **act immediately on the MDW** results and promptly order and administer antibiotics to the patients.

3. The base case hospital-level analysis was based on the **2015 national average** number of **sepsis hospitalizations per hospital**. Because hospitals vary in size, we also conducted our analysis for small hospitals (fewer than 100 beds) and large hospitals (more than 500 beds).

The data from the pivotal trial were key inputs to the economic model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Sepsis Patients</td>
</tr>
<tr>
<td>Percent that benefit from MDW</td>
<td>68%</td>
</tr>
<tr>
<td>Time to MDW results</td>
<td>30 minutes*</td>
</tr>
<tr>
<td>Mean time to antibiotics (hours)</td>
<td></td>
</tr>
<tr>
<td>Standard of Care</td>
<td>4.43</td>
</tr>
<tr>
<td>MDW</td>
<td>2.15§</td>
</tr>
<tr>
<td>Relationship between time to antibiotic &amp; outcomes</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>Simple linearization of observational data¹</td>
</tr>
<tr>
<td>Overall Length of Stay</td>
<td></td>
</tr>
<tr>
<td>ICU Length of Stay</td>
<td></td>
</tr>
<tr>
<td>Mean cost per day</td>
<td>$2,154.67²,†</td>
</tr>
</tbody>
</table>

*This input was an assumption. Sensitivity analyses were completed to test the robustness of the results if the time to MDW results was 45 minutes or 60 minutes.

§ The mean time to antibiotic for the MDW arm is a weighted average of those estimated to benefit from ESI (1.34 hours) and those that were not estimated to benefit from MDW (3.83 hours).

† The mean cost per day was calculated using the weighted average of hospitalization costs for the three DRG codes associated with sepsis (870-872).²


The mean number of sepsis hospitalizations per year per hospital was a key input

Average number of sepsis admissions per hospital per year

‡The mean number of sepsis hospitalizations per year per hospital among hospitals with less than 100 beds was calculated first by estimating the number of sepsis hospitalizations among hospital with less than 100 beds. The number of sepsis hospitalizations was then divided by the number of hospitals with less than 100 beds. The same methodology was followed for hospitals with more than 500 beds.\(^1,2\)

§The mean number of sepsis hospitalizations per year per hospital was calculated by dividing the number of sepsis-related hospitalizations in 2015 by the number of hospitals in the US in 2015.\(^1,2\)

Hospitals with fewer than 100 beds: 108\(^1,2,†\)

All hospitals: 205\(^1,2,§\)

Hospitals with more than 500 beds: 1,024\(^1,2,†\)

There are considerable health economic and clinical benefits regardless of the size of the facility.

<table>
<thead>
<tr>
<th>Base Case Analysis Results</th>
<th>Sensitivity Analysis Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction in Annual Sepsis Hospital Costs</strong></td>
<td><strong>Reduction in Annual Sepsis Hospital Costs</strong></td>
</tr>
<tr>
<td><strong>$725,710</strong></td>
<td><strong>$357,815</strong> Hospitals with fewer than 100 beds†</td>
</tr>
<tr>
<td><strong>11</strong> Reduction in Annual In-hospital Deaths</td>
<td><strong>6</strong> Hospitals with fewer than 100 beds†</td>
</tr>
<tr>
<td><strong>361</strong> Reduction in Days in Hospital per Year</td>
<td><strong>190</strong> Hospitals with fewer than 100 beds†</td>
</tr>
<tr>
<td><strong>56</strong> Reduction in Annual In-hospital Deaths</td>
<td><strong>56</strong> Hospitals with more than 500 beds‡</td>
</tr>
<tr>
<td><strong>3,381,957</strong> Reduction in Annual Sepsis Hospital Costs</td>
<td><strong>1,803</strong> Hospitals with more than 500 beds‡</td>
</tr>
</tbody>
</table>

†Result based on the average number of sepsis hospitalizations at hospitals with less than 100 beds (base case based on the overall average number of sepsis hospitalizations per hospital)
‡Result based on the average number of sepsis hospitalizations at hospitals with more than 500 beds (base case based on the overall average number of sepsis hospitalizations per hospital)
The impact of the timing of the ESI test result was also tested

**Base Case Analysis**
It was assumed that it would take 30 minutes for the MDW result to be obtained.

**Sensitivity Analysis**
A sensitivity analysis was completed by testing the robustness of the results assuming the time it would take for the MDW result was longer.

- 45 minutes to MDW test result
- 60 minutes to MDW test result
There are considerable health economic benefit regardless of the time to ESI test result

<table>
<thead>
<tr>
<th>Base Case Analysis Results</th>
<th>Sensitivity Analysis Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in Annual Sepsis Hospital Costs</td>
<td>Reduction in Annual Sepsis Hospital Costs</td>
</tr>
<tr>
<td><strong>$725,710</strong></td>
<td><strong>$669,983</strong></td>
</tr>
<tr>
<td>30 minutes</td>
<td>45 minutes‡</td>
</tr>
<tr>
<td>Reduction in Annual In-hospital Deaths</td>
<td><strong>$617,370</strong></td>
</tr>
<tr>
<td>11</td>
<td>9.7</td>
</tr>
<tr>
<td>30 minutes</td>
<td>60 minutes‡</td>
</tr>
<tr>
<td>Reduction in Days in Hospital per Year</td>
<td>Reduction in Days in Hospital per Year</td>
</tr>
<tr>
<td><strong>361</strong></td>
<td><strong>335</strong></td>
</tr>
<tr>
<td>30 minutes</td>
<td>45 minutes‡</td>
</tr>
</tbody>
</table>

†Result based on assuming 45 minutes to MDW test result (base case assumes 30 minutes to MDW test result)
‡Result based on assuming 60 minutes to MDW test result (base case assumes 30 minutes to MDW test result)
Sepsis is a Global Healthcare Problem

- 30 million people worldwide each year
- More common than heart attacks
- Claims more lives than any cancer
- $17 billion (average of $50,000 per case) / year
- Primary cause of death from infection despite advances in modern medicine, vaccines, antibiotics and advanced acute care

* World Sepsis Day, September 13, 2016 Fact Sheet
Time = Life

- Delay is the critical determinant of survival

- Broad spectrum IV antibiotics should be administered within 1-HOUR of symptom onset

The Lab Plays a Major Role
Beckmancoulter.com/earlysepsis
Thank you
references: sepsis by the numbers

References:


