Clinical Advancements for the Emergency Department: Sepsis
A Diagnostic Challenge for Clinicians and Laboratories
March 15, 2019

Thomas K. Bane, PhD, PPM
Associate Director
Medical & Scientific Affairs
Sepsis is deadly and costly

Confounding symptoms and comorbidities may delay recognition and treatment

Early identification and treatment improve patient outcomes and reduce mortality*

What is Sepsis?

A life-threatening organ dysfunction caused by a dysregulated host response to infection.
Early Diagnosis and Treatment Reduce Mortality

Each hour delay initiating effective antibiotic administration increases mortality by 7.6%

Adapted from Kumar et al., Crit Care Med 2008; 34 1286.
Comparison with other major diseases

30%-50% of severe sepsis patients die
More than deaths from prostate cancer, breast cancer and AIDS combined

Sepsis: its impact on healthcare

The increasing incidence of sepsis is due to:

› Increased awareness and tracking
› Aging population
› Increased longevity of people with chronic diseases
› Antibiotic-resistant organisms
› Increase in invasive procedures
› Broader use of immunosuppressive and chemotherapeutic agents

Incidence projected to increase by 1.5% per year

CDC - Surviving Sepsis campaign
Clinical Challenges of Sepsis

**Difficult To Diagnose**

- **Sepsis Diagnosis Remains Highly Subjective**
  - Insufficient sensitivity and specificity of tests and risk scores

- **Ambiguous Symptoms In ~30% of Patients**
  - Longer time to antibiotics and higher in-hospital mortality in patients with ambiguous presentations

**Resource-intensive To Treat**

- **Patients Do Not Get Proper Disposition in ER**
  - Higher mortality in patients discharged to general ward or home compared to those in ICU

- **Adherence to Guidelines Remains Inconsistent**
  - Sepsis bundle (SEP-1) compliance is ~50% in U.S., lower in resource-constrained environments

**Time Matters!!!**

- **Delay in Antibiotics Administration Leads To Higher Mortality**
  - Statistically significant increase in hospital mortality/hour for all levels of symptoms severity, from sepsis to septic shock
Clinical Challenges of Sepsis: Presentation

- Non-Septic (MDW-/WBC-)
- Infection (MDW-/WBC+)
- Potentially Septic (MDW+/WBC-)
- Septic (MDW+/WBC+)
Sepsis Symptoms

- Shivering, fever, or very cold
- Extreme pain or general discomfort
- Pale or discolored skin, rash
- Sleepy, difficult to rouse, confused or disoriented
- “I feel like I might die”
- Shortness of breath
- Rapid breathing and heart-rate
Challenges to Identifying Sepsis

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

**Temperature** >38.3° C, or <36° C

**Heart rate** >90 bpm

**Respiratory rate** >20 bpm

**White cell count** <4 or

>12 x 10³/mL

New **altered mental state**

SIRS = systemic inflammatory response syndrome

Source: [www.cdc.gov/vitalsigns/sepsis](http://www.cdc.gov/vitalsigns/sepsis)
A sepsis case study

*People*

**EXCLUSIVE**

How a Simple Cut in Gym Class Led to Fatal Sepsis Infection for Boy, 12 - and the One Mistake That May Have Caused It

POSTED 09/19/2017
Rationale for Early Sepsis Detection in ED:

Presented at SCCM 2019, San Diego, CA

- **Sepsis is #1:**
  - Cause of hospital mortality \(^1\)
  - In terms of costs to the health system \(^2\)

- **Sepsis is most often present on admission:**
  - >70% of sepsis cases are admitted through the Emergency Department. \(^3\)

- **Early sepsis detection is desirable:**
  - **Severe sepsis** (organ failures) –
    - highest per patient mortality \(^4\)
    - early sepsis treatment is protective
  - **Less severe sepsis**
    - more common and when undetected causes more deaths overall \(^4\)
    - early intervention reduces progression to severe sepsis
    - harder to detect, unclear who benefits most from early intervention.

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Sepsis

Sepsis is a life-threatening medical condition

› **Definition:**
  • The body’s extreme response to an existing infection injuring its own tissues and organs
  • Without timely treatment it can rapidly lead to tissue damage, organ failure and death

› **Typical Infections:**
  • Skin
  • Lungs
  • Urinary tract
  • Gut

www.cdc.gov/sepsis/basic/index.html
Causes of sepsis

Sepsis can be due to:

› Virus
› Fungi
› Bacteria (most common)
   • Staphylococcus aureus
   • Escherichia coli
   • Some types of Streptococcus

https://www.cdc.gov/sepsis/basic/index.html
EFFECT OF SEPSIS: MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS)

› Cardiovascular
  • Hypotension
  • Microvascular injury

› Lung
  › Pulmonary edema
  › Acute respiratory distress syndrome

› GI Tract:
  • Breakdown of normal protective barrier
  • Bacterial overgrowth

› CNS
  • Altered mental state
  • Encephalopathy
  • Neuropathy

› Liver
  • Endotoxins can not be eliminated

› Kidney
  • Decreased urine output
  • Renal failure
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>
</tr>
</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>
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<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>

Image from: https://www.nature.com/articles/s41581-018-0005-7
WHAT IS SEPSIS? AN IMMUNE DYSREGULATION

Evolution of clinical sepsis definitions

› 1991 ACCP/SCCM Consensus: Sepsis-1
  • A combination of a systemic inflammatory response (SIRS) and the presence of an infection.
    – SIRS
      a. Temperature <36°C or >38.3°C, b. HR >90 beats/min
c. RR >20 breaths/min, d. WBC count <4000/mm³ or >12000/mm³
  • Effectively:
    – 2 SIRS criteria + Confirmed or suspected infection

› 2016 Updated Consensus: Sepsis-3
  • A life-threatening organ dysfunction caused by a dysregulated host response to infection
  • qSOFA – adapting Sepsis definition to include organ failure
  • Significant push-back, sporadic adoption

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
- Blood glucose >7.7 mmol/L not diabetic
- New altered mental state

qSOFA

Quick Sepsis-related Organ Failure

- Respiratory Rate >22bpm
- Systolic Blood Pressure <100mmHg
- Altered Mental Status (Glasgow CS)

*Screening for outcomes, not diagnoses

<table>
<thead>
<tr>
<th>Scoring</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>1</td>
<td>2-3%</td>
</tr>
<tr>
<td>&gt;2</td>
<td>&gt;10%</td>
</tr>
</tbody>
</table>

researchgate.net/figure/Criteria-for-Systemic-Inflammatory-Response-Syndrome-SIRS-Adapted-from-McClelland-H_fig2_306927533
intensivecarenetwork.com/sepsis-not-disease
Sepsis: The Intersection of Infection and SIRS

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

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Clinical differentiation & diagnosis

**SIRS**
- Systemic Inflammatory Response Syndrome
- Heart rate >90 bpm
- Respiratory rate >20 breaths/min
- WBC count <4 or >12 g/L
- Blood glucose >7.7 mmol/L – not diabetic
- New altered mental state

**Sepsis**
- Shivering, fever or very cold
- Extreme pain or discomfort
- Clammy or sweaty skin
- Confusion or disorientation
- Short of breath
- High heart rate

**qSOFA**
- Quick Sepsis-related Organ Dysfunction Assessment
- Respiratory rate >22 breaths/min
- sBP <100 mmHg
- Altered GCS
- Screening for outcomes, not diagnosis

https://www.researchgate.net/figure/Criteria-for-Systemic-Inflammatory-Response-Syndrome-SIRS-Adapted-from-McClelland-H_fig2_306927533
https://intensivecarenetwork.com/sepsis-not-disease/
Immune dysregulation in sepsis

Efficient answer against the infection

Excessive pro-inflammatory answer
→ Sepsis

Sepsis-induced immunosuppression
Sepsis severity

- Altered tissue perfusion
- High serum lactate
- Need for vasopressors
- Organ dysfunction
- Fever
- WBC

- SIRS
- Sepsis
- Severe Sepsis
- Septic Shock

Guidelines recommend urgent administration of antibiotics when sepsis is suspected

“The new guidelines recommend that antibiotics should be administered as soon as possible...This recommendation is based on multiple observational studies showing that any delay in antibiotic administration is associated with increased risk of death.”

In January 2017, the fourth revision of the Surviving Sepsis Guidelines was presented at the 46th annual SCCM meeting and published online jointly in Critical Care Medicine and Intensive Care Medicine. A symposium of the guideline also has been published. The updated guideline was generated by 55 international experts representing 25 international organizations involved in the care of patients with sepsis and providing 55 recommendations on early management of sepsis and septic shock. There are numerous major advances in the revision of the guidelines. Among the various topics covered, initial resuscitation and antibiotic therapy are the domains in which the most important changes and advances were made.

For initial resuscitation, previous guidelines were mainly based on early goal-directed therapy which has been challenged by recent trials, and this approach is no longer recommended. Of note, no harm was demonstrated in those trials, and they are an important case for, example, those with a history of cardiac dysfunction who develop pneumonia, where the nature of circulatory failure is not always obvious.

Another important advance is that the new guidelines recommend the use of dynamic (ie, pulse or stroke volume variations induced by mechanical ventilation or passive leg raise test) over static variables (transcutaneous or pressures or volumes) to predict fluid responsiveness. This is a significant change, as previous guidelines recommended that clinicians should target SV of central venous pressure. Subsequent have shown that central venous pressure has limited value for the prediction of response to fluids. In contrast, the guidelines recommend that if fluid resuscitation is initiated, clinicians should use the invasive techniques to evaluate the effect and safety of fluid administration. When hemodynamic factors fail to improve in response to fluids, further fluid resuscitation can be considered. However, if fluid resuscitation should be discontinued when the response to fluids is not beneficial, a sepsis shock is often induced in clinical practice. This is particularly important because multiple studies have shown that excessive net fluid status is associated with a poorer outcome, including an increase in mortality. Hence, the guidelines moved from a protocollized, quantitative resuscitation strategy to a more patient-centered resuscitation approach guided by hemodynamic assessment including dynamic variables for fluid responsiveness and ongoing reevaluation of the response to treatment.

Infectious source control (eg, retrieval of catheter device suspected to be infected surgical procedure) and early antibiotic therapy remain mainstays of treatment. Sources control should always be obtained as rapidly as possible. The new guidelines recommend that antibiotics should be administered as soon as possible and within 6 hours maximum. This recommendation is based on multiple observational studies showing any delay in antibiotic administration is associated with an increased risk of death. In addition to the timing of antibiotic administration, it is important to ensure the efficacy of the antimicrobial treatment.

“...initiation of resuscitation and treatment, such as...administration of fluids and antibiotics...are all begun immediately.”

The compelling nature of the evidence in the literature, which has demonstrated an association between compliance with bundles and improved survival in patients with sepsis and septic shock, led to the adoption of the Sepsis: Surviving sepsis campaign (SSC) guidelines. Subsequently both by the New York State (NYS) Department of Health [14] and the Centers for Medicare and Medicaid Services (CMS) [15] in the USA for mandated public reporting. The important relationship between the bundles and survival was confirmed in a publication from this NYS initiative [16].

Panel meeting in the management of patients with sepsis is the concept that sepsis is a medical emergency. As with polytrauma, acute myocardial infarction, and stroke, early identification and appropriate immediate management in the initial hours after development of sepsis improves outcomes [7-11, 14, 16-21]. The guidelines state that these patients need urgent assessment and treatment, including initial fluid resuscitation while pursuing source control, obtaining further laboratory results, and attaining more precise measurements of hemodynamic status. A guiding principle is that the complex of initial assessment and then ongoing treatment to restore to the condition consistent with all elements of sepsis (formerly severe sepsis) or septic shock occurred through chart review. Because this new bundle is based on the 2016 Guidelines publication, the guidelines themselves should be referred to for further discussion and evidence related to each element and to sepsis management as a whole.

Hour-1 bundle
The most important change in the revision of the SSC guidelines is that the 3-hour and 6-hour bundles have been combined into a single “hour-1 bundle” with the explicit intention of beginning resuscitation and management immediately. We believe this reflects the clinical reality at the bedside of those seriously ill patients with sepsis and septic shock—that clinicians begin treatment immediately, especially in patients with hypotension, rather than waiting or extending resuscitation measures over a longer period. More than 1 hr may be required for resuscitation to be completed, but initiation of resuscitation and treatment, such as obtaining blood for measuring lactate and blood cultures, administration of fluids and antibiotics, and in the case of life-threatening hypotension, initiation of vasopressor therapy, are all begun immediately.


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Clinical Challenges of Sepsis: Prognostic Slope

› Diagnostic Factors
  • Infection
  • SIRS
  • Test Panel
  • Age
  • Comorbidities
  • ?
Patient presents at point-of-entry

Initial triage indicates possible infection [ED] → CBC-Diff ordered → Provider: Signs and symptoms indicate possible sepsis?

- YES: Sepsis evaluation tests → Empiric antibiotics → Sepsis diagnosis
  - YES: SOFA ≥2* → Patient Discharged
  - NO: Patient Discharged

- NO: Patient Discharged

Symptoms may only become obvious several hours after presenting to ED
THE LABORATORY AND THE DIAGNOSIS OF SEPSIS
The Clinical Laboratory in the Management of Sepsis

Key challenges

• Early diagnosis with better sensitivity than current tests
• Discrimination between infection and other causes of SIRS
• Monitoring antibiotic therapy
• Discriminate bacterial from viral infection

Lab tests for these uses are less likely to impact the current standard of care

• Confirming diagnosis – treatment starts regardless, gold standard for confirmation is the culture
• Prognostication – therapy will be aggressive regardless
LABORATORY TESTS IN THE MANAGEMENT OF SEPSIS

There are various clinical aspects of sepsis care where lab tests may be used:
- Screening emergency department population
- Confirming diagnosis
- Starting therapy
- Monitoring therapy
- Determine prognosis

Additional considerations for new biomarkers of sepsis
- Impact on patient care
- Demonstrate health economic benefit
Biomarkers of Sepsis

Dysregulated Inflammation

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

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

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

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

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

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Current Key Biomarkers for Sepsis

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

References:

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 (oxygenation of tissues) irrespective of blood pressure.
Cutoff was reduced to >2 mmol/L from >4 mmol/L.
Mortality is positively correlated in septic patients with lactate >2 mmol/L.
C-reactive Protein

- Macrophages secrete ILs 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

- Maximum production at 24-38 hours after the onset of inflammation
- The concentration of CRP in healthy subjects is <5mg/l
- Used to distinguish viral and bacterial infections.
- CRP is not a specific parameter for the presence of infectious inflammation
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 which would prove that the treatment of sepsis based on these markers influences the treatment strategy or improves the clinical result.
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.
- Normal value PCT <0.05 ng/mL

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

![Sepsis Biomarker Time Course Following Pathogen Exposure](image-url)


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PCT IN GUIDING ANTIBIOTIC TREATMENT

- **Sepsis Shock**
- **Severe Sepsis**
- **Sepsis**
- **Local Infection**

**PCT Serum Level**
- 10 ng/mL
- 2 ng/mL
- 0.5 ng/mL
- 0.05 ng/mL

- **Antibiotics recommendation**
  - > 0.5 ng/mL: Strongly Encouraged
  - 0.5 – 0.25 ng/mL: Encouraged
  - 0.25 – 0.1 ng/mL: Discouraged
  - > 0.1 ng/mL: Strongly Discouraged

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

<table>
<thead>
<tr>
<th>Procalcitonin at presentation</th>
<th>Negative</th>
<th>Positive</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5 ng/ml</td>
<td>24</td>
<td>8</td>
<td>32</td>
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<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 Great For Less Severe Sepsis

- None of the current biomarkers reach AUC of 0.8 for sepsis of all severities
- MDW + WBC show increased value over WBC alone (current standard of care)—0.85 over 0.75

Table from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5519182/
Innate Immune System Cells

Key Functions In Infection

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

Monocytes
› Phagocytosis
› Ag presentation
› Cytokine production
› Activation of the acquired immune system
Why monocytes matter

Step 1: Macrophages phagocyte bacteria

Step 2: Macrophages RELEASE CYTOKINES

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

Step 4: Cytokines stimulate bone marrow - LEUKOCYTOSIS

Step 5: Released granulocytes must stay in the circulation and reach the site of infection

Step 6: Bone marrow releases more granulocytes in blood, some of which are immature (BANDS - left shift)

Move healthcare forward.
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.

Monocyte Distribution Width (MDW)

Sepsis-related Immunosuppression

Pro-inflammatory State
- Cytokine Storm
- Overwhelming Inflammation
- Organ failure

Increased functional heterogeneity of monocytes in sepsis

Morphological variability

Increased MDW
Neutrophils: the most numerous leukocyte population

~60% of all hematopoiesis is committed to leukocyte development, *primarily neutrophils*

Neutrophils reside in three different pools: proliferative, circulating, and marginating pools.

Marginating pool of neutrophils contain metamyelocytes and band neutrophils that can quickly mature and enter the circulation.
What about neutrophils? Immature granulocytes?

Step 1: Macrophages (differentiated from monocytes) phagocytose bacteria

Step 2: Macrophages RELEASE CYTOKINES

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

Step 3b: Cytokines stimulate bone marrow—LEUKOCYTOSIS

Step 4: Bone marrow releases more granulocytes in blood, some of which are immature (IG, BANDS- left shift)

Granule formation and release is sequentially ordered

“Terminal neutrophil maturation is characterized by the sequential formation of the three different neutrophil granules and secretory vesicles as well as nuclear segmentation.”

“Neutrophil granule formation is hierarchical and dependent upon the timing of constituent protein biosynthesis, while exocytosis occurs in the reverse but ordered sequence.”
IG does not correlate well with sepsis

- Over half of all Sepsis patients had negative IG (61.5%)
- 56% of all patients (169/301) had sepsis according to Sepsis-3
- Over half of all Sepsis patients had negative IG (61.5%)
- Performed on XE series

- Over half of culture+ patients had negative IG (56.8%)
- Just under half of culture+/sepsis+ patients had negative IG (46.4%)

Flow Cytometric Digital Morphology

VOLUME (V)

CONDUCTIVITY (C)

LIGHT SCATTER (S)
Sepsis Demonstrates Increased Variability in Monocyte Volume (MDW)

This is a representation of the MDW parameter that is 510(k) cleared by FDA.

MDW is measured by Extended Volume range

- Monocyte volume values are accumulated on an extended volume (EV) range (available internally to the algorithm).
- The extended volume range accurately measures MDW above the standard 5-part differential range.
Sepsis Pivotal Trial Background

Study enrolled a total of 2,158 consecutive adult ED patients
  - Ohio State University, Hackensack University, UPMC

Inclusion criteria
  - Adults, 18-89 years of age
  - CBC-diff ordered within 2 hours of presentation
  - Patient remains in hospital for minimum 12 hours

Sepsis prevalence as defined by the Sepsis-2 Criteria was 17.8%
  Enriched due to >12 hours inclusion criteria
MDW Improves Value of the WBC Results for Sepsis Detection

- Reproduced previous feasibility trial results (Crouser ED et al. *Chest*, 2017 vol. 152, no. 3, pp. 518-526)

- Improvement in AUC is statistically significant (~10%)

Up to 67% of those sepsis patients could have benefited from MDW

**Standard of Care**
- 3.98 hours
  - n = 349
- 100%
  - of Sepsis Patients
  - Identified via Standard of Care

**If MDW had been available**
- 1.34 hours
  - n = 233
- 67%
  - of Sepsis Patients
  - Identified via MDW
Detection of Progression from Infection to Sepsis based on MDW

71% of those who progressed from “infection” at initial presentation to Sepsis-3 within 72 hours were identified by MDW >20.0

- This cohort included 62 patients classified in the study as Infection, but who developed sepsis beyond the 12 hour time point of the study
- 45/62 had MDW >20 on the first CBC-diff in the ED
- These would be classified as false positives at the 12 hour time point

**Added value of MDW modifies the probability of sepsis**

- With MDW>20.0 and abnormal WBC, the probability for sepsis is **~2x higher** than abnormal WBC alone.

- The probability for sepsis with MDW<20.0 and normal WBC is **~2.5x lower** than normal WBC alone.

![Graph showing the probability of sepsis with different combinations of MDW and WBC](image-url)
No intervention required by the lab or clinician
MdW Included with each differential*

*After activation with ESI package.
ESId Used With Current Standard Of Care

High Risk
- MDW Cutoff >20
- abnormal WBC

Moderate Risk
- MDW
- normal WBC

Low Risk
- MDW
- abnormal WBC

normal WBC

TYPICAL CARE PATHWAY

Patient presents at point-of-entry → Inpatient admission → ICU

Initial triage indicates possible infection [ED] → CBC-Diff ordered

Provider: Signs and symptoms indicate possible sepsis?

YES → Sepsis evaluation tests → Empiric antibiotics

- Lactate
- Procalcitonin
- CRP
- IL6

Sepsis diagnosis

YES → SOFA ≥2*

NO → Patient Discharged

Confirmatory tests → Patient Discharged

Symptoms may only become obvious several hours after presenting to ED
TYPICAL CARE PATHWAY

Patient presents at point-of-entry → Inpatient admission → ICU

Initial triage indicates possible infection [ED] → CBC-Diff ordered

Provider: Signs and symptoms indicate possible sepsis?

YES → Sepsis evaluation tests

Empiric antibiotics

YES → Sepsis diagnosis

NO → Patient Discharged

DxH Sepsis
• Available with initial CBC-Diff result
• CBC ordered as part of routine labs

Confirmatory tests

• Lactate
• Procalcitonin
• CRP
• IL6

SOFA ≥2*

YES → Sepsis diagnosis

NO → Patient Discharged

Symptoms may only become obvious several hours after presenting to ED
Modulation of Relative Sepsis Risk by MDW

- **MDW+/WBC+** → Higher risk for Sepsis
- **MDW+/WBC-** → Moderate risk for sepsis
- **MDW-/WBC+** → Moderate risk for sepsis
- **MDW-/WBC-** → Lower risk for sepsis

- ~2x higher risk than WBC+ Alone
- ~2.5x lower risk than WBC+ Alone
- ~2.5x higher risk than WBC- Alone
- ~2.5x lower risk than WBC- Alone
Modulation of Relative Sepsis Risk by MDW

- MDW+/WBC+ → Higher risk for Sepsis
- MDW+/WBC- → Moderate risk for sepsis
- MDW-/WBC+ → Moderate risk for sepsis
- MDW-/WBC- → Lower risk for sepsis

40% HIGHER risk than MDW-/WBC+
40% LOWER risk than MDW-/WBC+
Potential Clinical and Economic Value
Simulated Potential economic and clinical benefits of MDW Adoption

<table>
<thead>
<tr>
<th>Base Case Analysis Results</th>
<th>Sensitivity Analysis Results</th>
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<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>$642,583</td>
<td>$3,472,953</td>
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<tr>
<td><strong>Reduction in Annual In-hospital Deaths</strong></td>
<td><strong>Reduction in Annual In-hospital Deaths</strong></td>
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<tr>
<td>10</td>
<td>47</td>
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<tr>
<td><strong>Reduction in Days in Hospital per Year</strong></td>
<td><strong>Reduction in Days in Hospital per Year</strong></td>
</tr>
<tr>
<td>304</td>
<td>1,511</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)
Potential economic & Clinical benefits using different “time-to-MDW” result scenarios

<table>
<thead>
<tr>
<th>Time to MDW Test Result</th>
<th>Reduction in Annual Sepsis Hospital Costs</th>
<th>Reduction in Annual In-Hospital Deaths</th>
<th>Reduction in Annual Hospital LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 minutes</td>
<td>$642,583</td>
<td>10</td>
<td>304</td>
</tr>
<tr>
<td>45 minutes</td>
<td>$582,004</td>
<td>8.7</td>
<td>278</td>
</tr>
<tr>
<td>60 minutes</td>
<td>$524,912</td>
<td>7.9</td>
<td>254</td>
</tr>
</tbody>
</table>

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SUMMARY

• Sepsis is a significant problem here in the United States
  • High-intensity treatment in emergency rooms lead to:
    - High cost
    - Long hospital stays
    - Poor patient outcomes

• Improved biomarkers are needed
  • Procalcitonin:
    - Potentially earlier intervention in suspected sepsis
    - Indication of the effectiveness of the antibiotic treatment over the course
    - Prognosis of the patient under treatment
    - Chemistry & IA
  • Early Sepsis Indicator

• Best foot forward
  • IVD/Biomarker integration into clinical treatment pathway
THANK YOU