

# From Test to Treatment: Clinical Interpretation, Rationale, and Impact of the IntelliSep Sepsis Test

## I. Executive Summary

Sepsis is a dangerous emergent condition, long impeded by challenges in timely diagnosis and treatment. Recognizing these challenges, Our Lady of the Lake Regional Medical Center of Baton Rouge, Louisiana has taken steps to address these issues. The hospital has seen a transformative impact on sepsis patient care following the implementation of a novel diagnostic test for the early identification of this fast-moving condition. Indicated for use in the Emergency Department (ED), the IntelliSep sepsis test has been seamlessly integrated into clinical workflows at the facility, improving triage for patients with suspected sepsis, reducing time to diagnosis, and allowing for more efficient use of antibiotics and blood cultures, thereby optimizing resource utilization. These streamlined processes and care pathways have resulted in substantial clinical benefit as well as cost savings.

The decision to adopt IntelliSep at Our Lady of the Lake Regional Medical Center was based on rigorous clinical validation and observational studies, underscoring the test's potential to set a new standard for sepsis management. This document presents a detailed exploration of Our Lady of the Lake Regional Medical Center's strategy to address sepsis in the ED, improve triage, and develop an effective clinical interpretation and application of the test. It serves as a case study in efforts to improve the approach to sepsis diagnosis and care.

## II. The Great Challenge of Sepsis Detection

Sepsis is characterized by life-threatening organ dysfunction caused by an overwhelmed immune system responding to infection.<sup>1</sup> It strikes 1.7 million Americans annually,<sup>2</sup> and without rapid identification and management, it can quickly escalate to organ failure and death. Every hour that sepsis goes untreated, the risk of mortality increases. Sepsis-related hospitalization costs exceed \$38 billion annually.<sup>3</sup>

Diagnosis and management of sepsis presents significant challenges due to the limitations of biomarkers and the condition's variable symptom presentation. These factors impede the speed at which critical interventions can be taken and complicate antibiotic stewardship efforts. Clinicians are under constant pressure, working against the clock to navigate the complexities of diagnosis and timely treatment. In the ED, sepsis mimickers—conditions with symptoms like systemic inflammation, fever, hypotension, rapid breathing, and altered mental status—often lead to misdiagnosis due to their similarity to sepsis.

Current hospital strategies for managing sepsis are hindered by protocols that may not have been designed to detect early signs of sepsis or may not be consistently applied. Moreover, Centers for Medicare and Medicaid Services (CMS) SEP-1 timelines place pressure on medical teams to implement a standard set of interventions (including antibiotics) quickly in cases of suspected sepsis. This pressure to disposition patients quickly, without missing a sepsis diagnosis, results in considerable diagnostic variability, with under and over diagnosis impacting patient outcomes and costs, as well as antimicrobial stewardship.

Current best practice alerts (BPAs) have their shortcomings, as well. Their efficacy is undermined by the dearth of information available for patients presenting to the ED and their lack of specificity, leading to alarm fatigue. There remains a critical need for improved diagnostics to identify the root cause of sepsis: immune dysregulation.

In response to these considerable challenges, Our Lady of the Lake Regional Medical Center integrated the IntelliSep sepsis test into the clinical workflow of its ED in August 2023. By rapidly evaluating a patient's state of immune activation, IntelliSep provides an index value in around 8 minutes that categorizes, via three discrete bands, the probability of sepsis with organ dysfunction manifesting within the first three days after testing. Our Lady of the Lake Regional Medical Center initiated data collection to evaluate the implementation of IntelliSep over the first 90 days, with data collection ongoing.

### III. Our Lady of the Lake Regional Medical Center

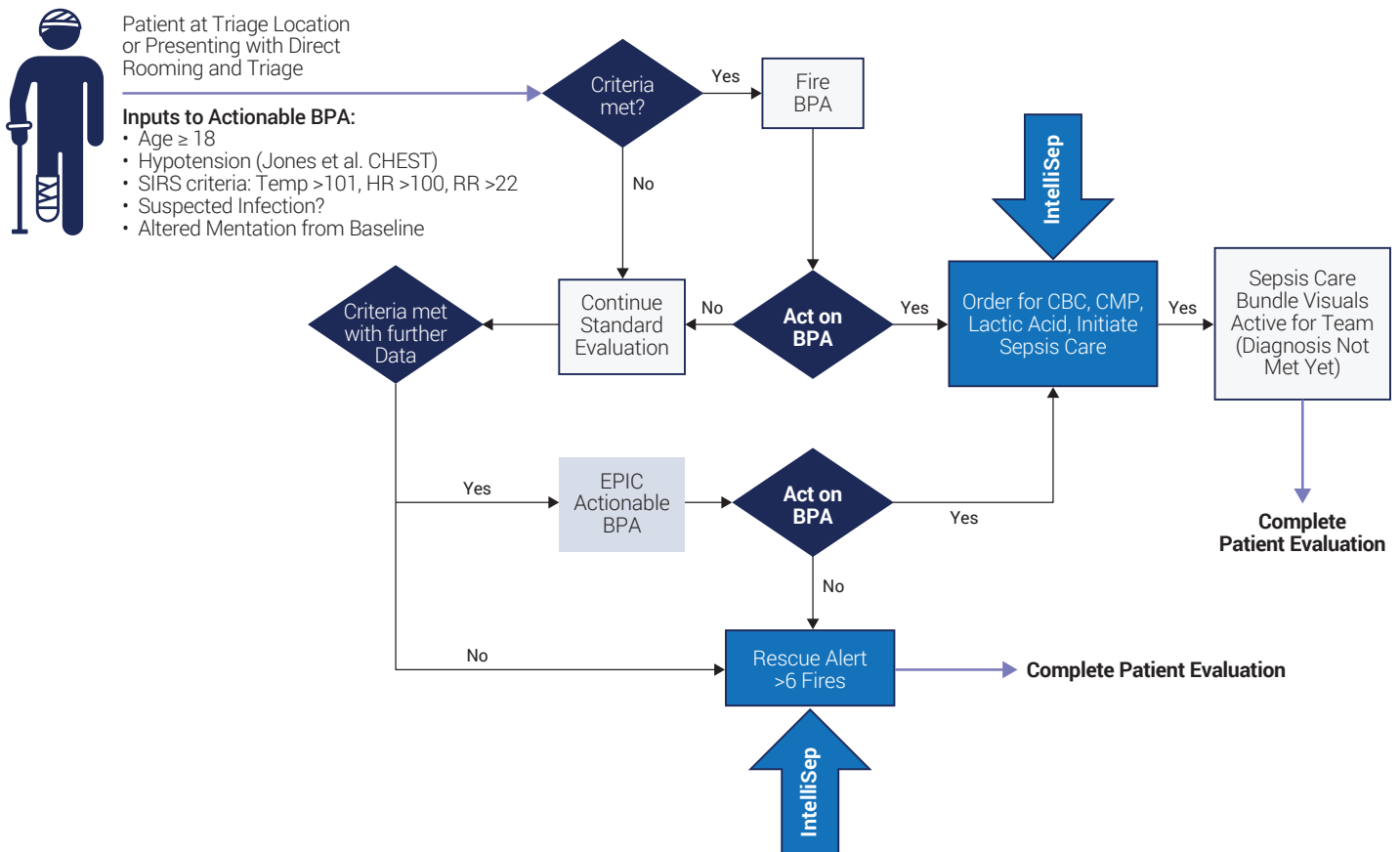
Our Lady of the Lake Regional Medical Center provides about 850 inpatient beds, and its main ED receives around 85,000 visits annually. The site is a level 1 trauma center and a major teaching hospital for the Louisiana State University (LSU)-Baton Rouge based residency programs and the LSU regional campus of the New Orleans medical school. The medical center is part of the Franciscan Missionaries of Our Lady Health System, a Catholic healthcare ministry, and serves as a safety net hospital for the Baton Rouge community.

The decision to adopt IntelliSep at Our Lady of the Lake Regional Medical Center was based on rigorous clinical validation. The facility became involved with Cytovale in 2014, and since that time has participated in multiple studies of the IntelliSep test including the 2021 validation study that led to FDA clearance of the IntelliSep test for use as a sepsis diagnostic aid in EDs.

### IV. IntelliSep Implementation at Our Lady of the Lake

Our Lady of the Lake adopted the IntelliSep test into clinical practice in the ED in August of 2023. The facility had already established an approach in the form of a nurse-driven, triage-based, best practice alert, that would fire in response to problematic vital signs, suspected infection, and altered mentation. IntelliSep integrated seamlessly into this existing workflow, with the triage nurse ordering it in conjunction with other standard diagnostic tests. Providers also have the opportunity to order the IntelliSep test in response to a rescue alert issued based on early warning criteria in the EPIC sepsis alert model also employed by the center.

#### IntelliSep & ED Sepsis Workflow

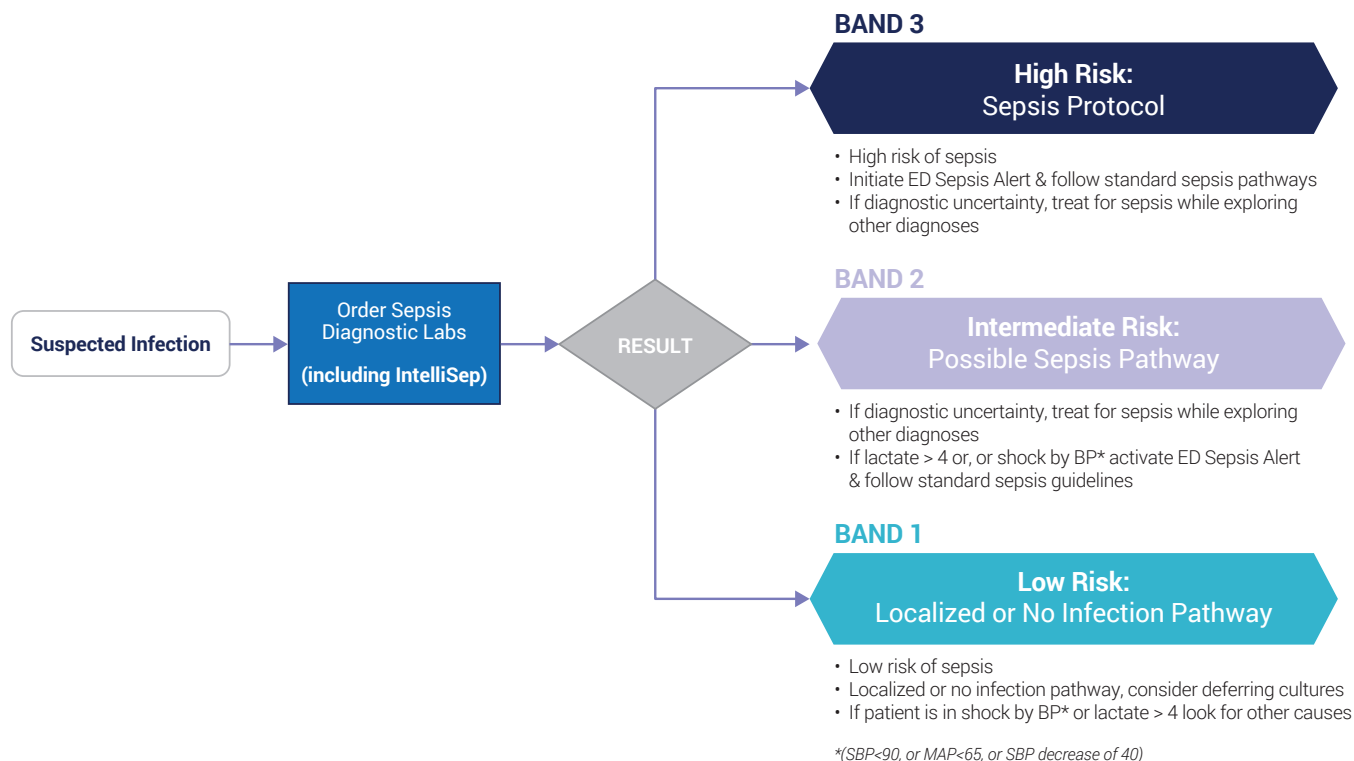


*Our Lady of the Lake Regional Medical Center's ED Sepsis Workflow with IntelliSep*

## V. IntelliSep Clinical Interpretation and Justification

In an ongoing effort to improve patient outcomes and streamline clinical decision-making, a multidisciplinary team at Our Lady of the Lake Regional Medical Center assessed how IntelliSep could inform patient care strategies in the ED. This led to the development of facility-specific risk classifications and treatment pathways that correspond to Band 1, Band 2, and Band 3 results of the IntelliSep test (see image below). The rationale for treatment of the IntelliSep Bands is detailed below, and is based on data from observational studies of the IntelliSep test as well as independent validation work conducted by Our Lady of the Lake Regional Medical Center to determine the effectiveness of the IntelliSep test and related protocols.

### IntelliSep Results & Clinical Interpretation



#### Our Lady of the Lake Regional Medical Center's Clinical Interpretation of IntelliSep Results

### Band 3

#### Results and Clinical Interpretation

Patients with an IntelliSep Index (ISI) score between 6.3 and 10.0 receive a Band 3 result. They are considered by Our Lady of the Lake Regional Medical Center to be at a high risk of having or developing sepsis.

#### Clinical response

Based on the implementation approach, this result generates an overhead "Code Sepsis" alert, and the care team follows a sepsis pathway. Patients automatically receive broad spectrum antibiotics, and blood cultures are ordered unless there is a very high likelihood of an alternative cause for their immune activation. If these patients are in the waiting room when the IntelliSep Band 3 result comes back, they are immediately brought into the ED for the initiation of care. This pathway intends to expedite care in the highest risk patients.

#### Observational data and care strategy rationale

Observational data generated at Our Lady of the Lake Regional Medical Center indicated that Band 3 patients have a higher risk of sepsis, a higher positivity rate for blood cultures, and are most likely to require ICU-level care. In these studies, in-hospital all-cause mortality for this group has been found to be around 13%, with more than 70% of deaths occurring within 7 days of admission. For this reason, the care team aims to apply immediate, aggressive care to this patient population.

## Band 2

### ***Results and Clinical Interpretation***

Patients that receive a Band 2 result have an ISI score between 5.0 and 6.2. They are considered by Our Lady of the Lake Regional Medical Center to have an intermediate risk for sepsis, and a possible sepsis pathway is encouraged.

### ***Clinical response***

If some degree of diagnostic uncertainty exists, the team will treat the patient for sepsis and infection while exploring other diagnoses. If a lactate result is greater than 4, or shock is determined by a systolic blood pressure reading of less than 90 mmHg, then the patient is determined to be at very high risk for sepsis and the team is directed to activate a "code sepsis". Standard sepsis guidelines are then followed. If staff admits the patient to a medical floor, they are advised to monitor the patient carefully and transfer them to the ICU if necessary. If evidence of pulmonary instability presents in the ED, staff are guided to consider ICU admission as part of their disposition decision making.

### ***Observational data and care strategy rationale***

Data from validation work at Our Lady of the Lake Regional Medical Center indicated that patients in Band 2 are at a higher risk of sepsis compared to those in Band 1. These patients are more likely to require step-up from a non-critical unit to a critical unit following admission and may benefit from closer monitoring to detect clinical changes and hemodynamic instability. Clinical research indicates that Band 2 patients represent the largest proportion of those requiring escalation of care after admission. Prior studies have also shown that all-cause in-hospital mortality for these patients is around 6%, and approximately one in five Band 2 deaths were cases in which the patient had sepsis.

## Band 1

### ***Results and Clinical Interpretation***

Patients in Band 1 have an ISI score between 0.1 and 4.9, and are considered to have a low risk of developing sepsis.

### ***Clinical response***

The treatment pathway for these patients is based on the observation that an infection, when present, is likely to be localized. ED providers who suspect infection are advised to follow guideline-directed therapy for that specific infection. The collection of blood cultures is not recommended when a patient receives a Band 1 result unless there is high suspicion of bacteremia due to other factors (e.g. IV drug use, indwelling catheter, etc.). If a patient receives a Band 1 IntelliSep result but shows evidence of shock, based on blood pressure or an elevated lactate greater than 4, providers are advised to treat a suspected infection with antibiotics, while also searching for an alternative diagnosis such as cardiac dysfunction.

### ***Observational data and care strategy rationale***

Data from prior clinical studies<sup>4,5</sup> conducted at Our Lady of the Lake Regional Medical Center showed that those in the Band 1 patient population are at a very low risk for sepsis, and are likely to suffer from a localized infection or an alternative disease pathway. The data also demonstrated that the risk of 30-day in-hospital mortality was around 3%. Of the patients who died, zero had sepsis as the cause. It was also observed that when blood cultures were ordered for a Band 1 patient, they were more likely to return a contaminant than a true pathogen. Additionally, it was shown that 80-90% of Band 1 patients that presented with shock (defined by a systolic blood pressure reading of less than 90 mmHg, or lactate >4) were found to not have an infection. Suggesting that, in Band 1 patients, hemodynamic instability may be attributed to a cause other than sepsis.

### Summary of Clinical Study Findings

The table below represents a selection of key findings from a pooled set of data from prior IntelliSep observational studies, that highlights clinical outcomes of patients across IntelliSep interpretation bands.

	Band 1	Band 2	Band 3
Infected	14.4%	34.2%	66.8%
Blood Culture Positive	4%	10.9%	36%
Septic	2.5%	18.5%	55.9%
Admitted to Hospital	57.6%	72%	86.6%
Mortality (In-hospital, 30-day, all-cause)	2.9%	5.8%	12.6%
Sepsis-associated Mortality (30-day)	0%	1.2%	8.8%

As results move from Band 1 to Band 3, there is a significant increase in infection rates (14.4% to 66.8%), blood culture positivity (4% to 36%), diagnosis of sepsis (2.5% to 55.9%), and hospital admission rates (57.6% to 86.6%). In-hospital, 30-day, and all-cause mortality rates climb from Band 1 to Band 3 (2.9%, 5.8%, and 12.6% respectively), while sepsis-associated mortality increases from 0% to 1.2%, to 8.8% across the bands.<sup>6</sup>

## VI. IntelliSep Impact: Data Analysis 90 Days Post-Implementation and Beyond

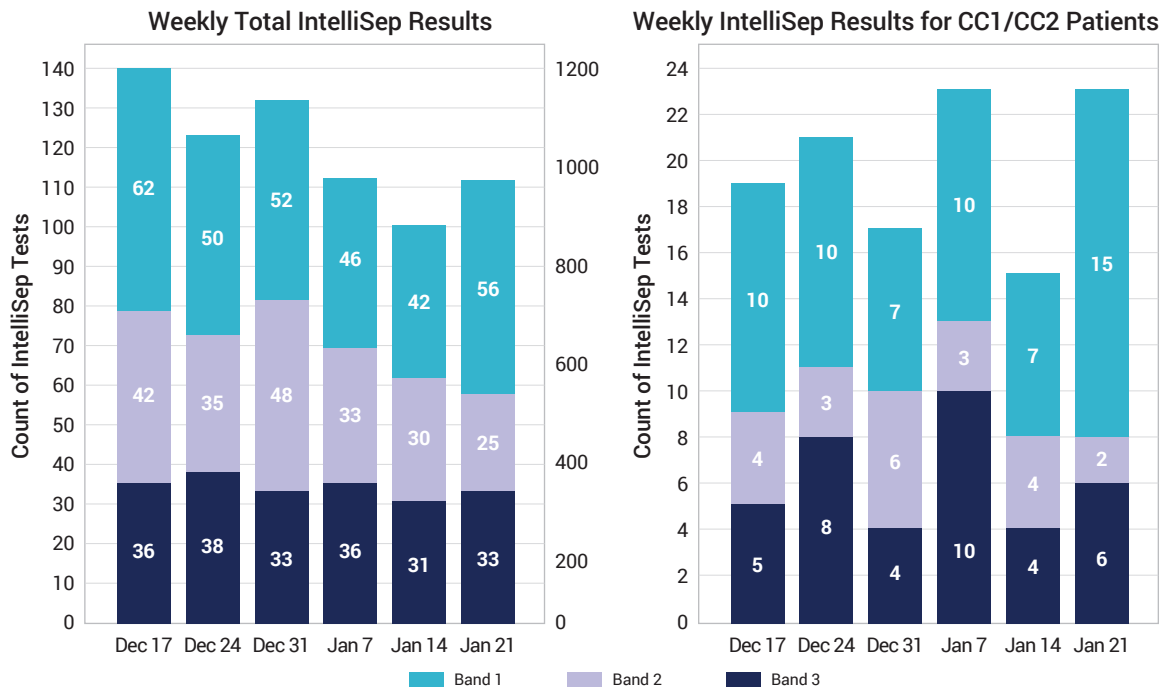
A detailed analysis of real-world outcomes 90 days after implementing the IntelliSep sepsis test at Our Lady of the Lake Regional Medical Center revealed key findings and actionable insights from the data.

### 1. IntelliSep Impact on ED Triage

#### Our Lady of the Lake Regional Medical Center – Main ED

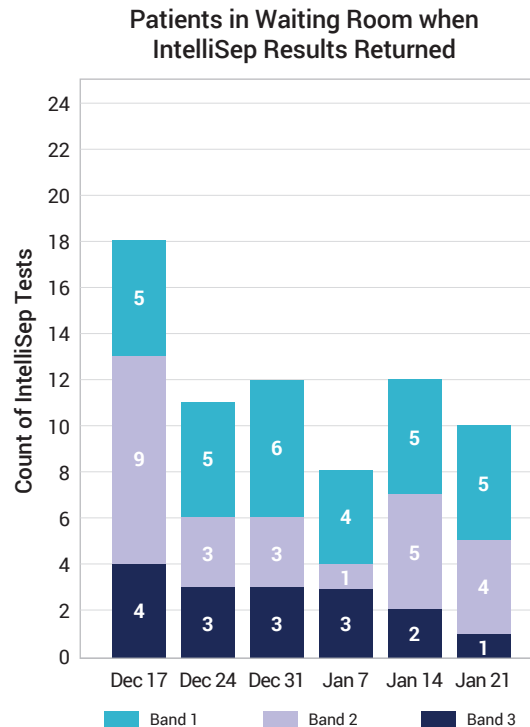
##### IntelliSep Test Results by Band

*IntelliSep can only be ordered through the Sepsis Triage BPA or Rescue Alert*



**Analysis:** In the above graph, generated and shared by Our Lady of the Lake Regional Medical Center, teal, purple, and navy represent Bands 1, 2, and 3 respectively. The left panel represents weekly data for a selected period of time and demonstrates that approximately 50% of results fall into Band 1, while Band 3 constitutes about 20-25% of results, mirroring data from previous studies.

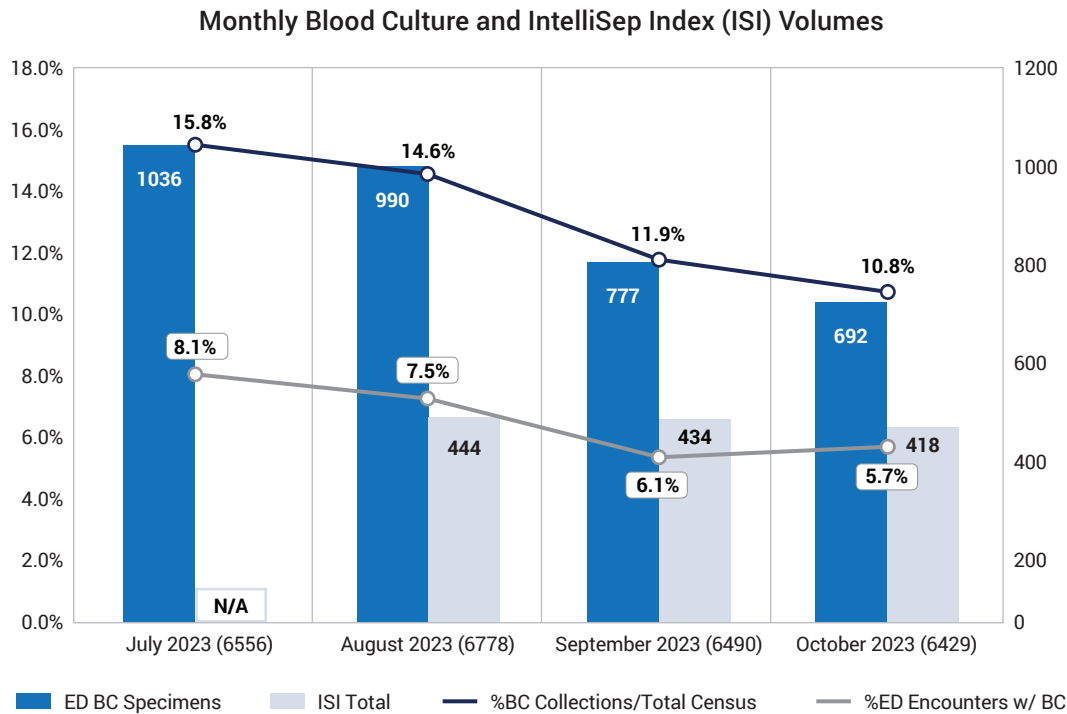
The right panel, which largely trends with the left panel, represents medically ill patients in the ED's critical care beds. Among them, an unexpectedly higher number received a Band 1 result, indicating that about 50% of these patients appear critically ill, but have a low likelihood of sepsis. For patients with lactate >4 and a Band 1 IntelliSep result, only 1 in 6 has an infection. This suggests that there is a high probability that Band 1 patients admitted to these critical care beds have a different condition and encourages the care team to explore alternate diagnoses.



The graph above represents a subset of total IntelliSep results for a particular week, and focuses on the group of patients that are in the ED waiting room after triage, further depicted by their band color. An unexpected number of patients were found to be in Band 2 or Band 3. Patients with a Band 3 result are pulled from the waiting room and placed in a bed immediately, ahead of all other patients. By doing so, IntelliSep results have enabled Our Lady of the Lake Regional Medical Center to advance the care of these Band 3 patients by more than an hour relative to Band 1 patients in the waiting room. Since risk of mortality from sepsis can increase by up to 8% per hour of treatment delay<sup>7</sup>, this may lead to improved patient care. Upon subsequent investigation, 90% of these Band 3 patients are admitted, and around 50% ultimately receive a sepsis diagnosis.

**Key insight:** Critically ill patients, even those whose condition is unclear upon presentation, are evaluated with the IntelliSep test, resulting in an improved triage process. These data also suggest that sepsis may be missed in triage, as a number of patients placed in the waiting room were later discovered to have a Band 3 IntelliSep result. In these scenarios, IntelliSep results allow physicians to expedite care and reallocate resources effectively. Moreover, when Band 3 results are identified, a streamlined response is initiated, adhering to the sepsis treatment pathway.

## 2. IntelliSep Impact on Blood Cultures



**Analysis:** This graph shows a marked decrease in blood cultures, indicated in blue. The top line reflects culture collections which is approximately double the percentage of encounters due to the standard practice of ordering blood cultures in pairs. The middle line indicates the percentage of ED visits leading to blood cultures. A notable decline in blood cultures was observed following the education and implementation phase, with sustained reductions through October.

**Key insight:** Blood culture utilization was reduced by approximately 30% post implementation of IntelliSep, decreasing monthly blood culture counts by 200-300. In addition to laboratory time and materials, this saved 23-30 hours of nursing time per month (around 7 minutes per culture) which can be reallocated to bedside patient care, reflecting the initiative's success.

*July 2023 data is presented to show a baseline prior to implementation of IntelliSep in August 2023; data collection methodologies were identical both pre- and post-IntelliSep implementation.*

## 3. Financial Implications of the IntelliSep Implementation

**Key insight:** The IntelliSep implementation resulted in substantial improvements to patient care and financial cost, achieving an average cost-of-care reduction of around \$1400 per patient tested<sup>8</sup>.

## VII. Conclusion

The implementation of IntelliSep at Our Lady of the Lake Regional Medical Center demonstrated effectiveness in the early diagnosis of sepsis, leading to notable operational improvements in ED patient care. These advancements facilitated more accurate triage, more timely diagnosis of sepsis, and resulted in shorter hospital stays and improved recovery. The economic impact of these resource utilization and healthcare cost improvements cannot be understated.

These favorable results, along with the ease of integrating IntelliSep into the existing clinical workflow, signal great potential to improve patient outcomes on a wider scale at additional sites.

## VIII. References

- <sup>1</sup> Singer M, Deutschman CS, Seymour CW. Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810. doi:10.1001/jama.2016.0287.
- <sup>2</sup> What is Sepsis? | Sepsis | CDC. Centers for Disease Control and Prevention. <https://www.cdc.gov/sepsis/what-is-sepsis.html>. Accessed March 4, 2024.
- <sup>3</sup> Hollenbeak CS, Henning DJ, Geeting GK, et al. Costs and Consequences of a Novel Emergency Department Sepsis Diagnostic Test: The IntelliSep Index. *Crit Care Explor*. 2023;5(7):e0942. doi:10.1097/CCE.0000000000000942.
- <sup>4</sup> O’Neal HR, Jr., et. al., Assessment of a Cellular Host Response Test as a Sepsis Diagnostic for Those With Suspected Infection in the Emergency Department. *Crit Care Explor* 2021; 371 3: e0460.
- <sup>5</sup> O’Neal HR, Jr., et. al., Assessment of a cellular host response test to risk-stratify suspected COVID-19 patients in the Emergency Department setting. *PLoS One* 2022; 17(3): e0264220.
- <sup>6</sup> O’Neal et.al. Academic Emergency Medicine – Publication Pending.
- <sup>7</sup> Kumar A, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006 Jun;34(6):1589-96. doi: 10.1097/01.CCM.0000217961.75225.E9.
- <sup>8</sup> Thomas CT, Dantonio C, Hollis A, et al. Fiscal Impact of a Rapid Sepsis Diagnostic in the ED. Poster presented at: 43rd International Symposium on Intensive Care and Emergency Medicine (ISICEM); March 19, 2024; Brussels, Belgium. Presented by Hollis O’Neal Jr., MD, MSc.

## IX. Contact

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*The above data regarding IntelliSep were provided by a Cytovale commercial partner. IntelliSep data generated is based on their institutional practices and site validation of IntelliSep.*

*See the IntelliSep Test Instructions for Use for all cleared claims, performance data, and limitations.*