

Introduction

Sepsis, a dysregulated host immune response to infection leading to life-threatening organ dysfunction¹, is a common and fast-moving condition and leading cause of in-hospital death. The majority of cases develop in the community and present to Emergency Departments (ED)², where urgent action is required to prevent resultant morbidity and mortality³. Current guidelines stress ED clinicians to intervene quickly⁴, often before adequate, objective diagnostic and prognostic data are available, resulting in a 'one size fits all' strategy. This causes excessive use of broad-spectrum antibiotics and limited resources^{5, 6}.

Initial investigations demonstrated that immune cell activation is accompanied by changes in biomechanical properties⁷ and Follow-up studies demonstrated the potential for clinically actionable performance characteristics of an investigational test⁸. The objective of this study was to assess the investigational IntelliSep Index (ISI) as a potential aid for risk stratification and resource allocation for the treatment of patients presenting to the emergency department with possible sepsis.



Figure 1: (A) Photograph of the Cytovale system, a benchtop instrument on which the IntelliSep Test is performed; (B) Graphical rendering of blood cell movement through the microfluidic deformation junction, and time series of cell deformation for a representative leukocyte of a septic Red Band patient (top) and a not-septic Green Band patient (bottom); (C) Representative images of the ISI result.

The IntelliSep test

The IntelliSep test, performed on the Cytovale system benchtop instrument (Fig. 1-A) is an investigational in-vitro diagnostic that quantifies the state of immune activation by measuring the biophysical properties of leukocytes from a routine blood specimen. These properties have been shown to differ in the septic patient when compared to those in the quiescent state, enabling rapid assessment of immune activation signatures and the sepsis risk stratification⁷ (Fig. 1-B).

By leveraging microfluidic cell handling techniques in combination with technological advances in high-speed imaging and machine learning, biophysical properties of thousands of leukocytes are analyzed and distilled into the IntelliSep Index (ISI), a single score between 0.1-10.0. The score is stratified into three discrete interpretation bands of increasing probability of disease: Green, Yellow, and Red, developed in prior studies^{8, 9} (Fig. 1-C).

Neutrophil and monocyte structure and biophysical properties such as deformability, density, and size are thought to shift with degranulation, NET formation¹⁰, or maturity that occurs during the dysregulated immune activation associated with sepsis^{12, 13}.

A Rapid, Objective Measure of the Host Response May Help Guide Effi and Judicious ED Care for Sepsis

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- ratio of 20.5 (8.2 36.0, 95% CI) between the Red and Green Bands (Fig 3). Appropriate risk-stratification of subjects was observed independent of demographic groups (age, sex, race) (data not shown). stay among survivors (Fig. 5) Red Band did not receive broad-spectrum antibiotics in the ED, with an average hospital length of stay of 8 days and one fatality. * * * * * 80 academic medical Multiple large * * * * centers in Baton Rouge, LA, and 60 Milwaukee, WI,USA. ≥ ₽ or suspicion of infection prospectively enrolled (Apr. 2019 – Feb. 2020). ă <u>25</u> + • Exclusions consisted of hematologic malignancies, receiving a cytotoxic Band Band Band chemotherapeutic agent in the past 3 (N = 70) (N = 160)(N = 60) months, hematopoietic stem cell or any **Figure 3:** Incidence rate of adjudicated Sepsis-3 across IntelliSep solid organ transplants, transfers from interpretation bands: Green Band 4.4%; Yellow Band 21.4%; Red other acute care facilities. Band 48.3%; (** p < 0.01, **** p < 10⁻⁴, **** p < 10⁻⁵). blood was assayed with the IntelliSep test within 4 * * * * * * * * hours of draw, and patients were * * * * 6.67% followed by retrospective chart review (N = 4)for outcome information. Treating 1.43% 0.62% clinicians did not have access to assay (N = 1)results. Greer Yellow ellow Band Band Band Band Band Band Band (N = 160) (N = 70) (N = 60)(N = 160) (N = 70) (N = 60)(N = 159) (N = 69) (N = 56)Granule protein-
- Adults presenting to the ED with signs
- **Analysis Design & Setting** EDTA-anticoagulated



Figure 2: Neutrophil extracellular traps (NETs) formation is a rapid active process mediated by NETosis, involving chromatin decondensation and nuclear membrane disintegration¹¹.

Scientific Theory of Operation

Results & Discussion

Figure 5: Clinical outcomes across IntelliSep interpretation Bands: all-cause-in-hospital mortality, SOFA maximum of 3-days following presentation, baseline subtracted, and hospital length of stay among survivors (* p < 0.05, ** p < 0.01, **** p < 10⁻⁴, **** p < 10⁻⁵).

Conclusions

- The investigational IntelliSep test has the potential to provide rapid quantification of host-immune response from routine whole blood samples in under 10 minutes.
- The test may have the potential to improve ED decisions for patients with signs or suspicion of infection; aiding in better sepsis risk stratification and resource utilization, and ultimately antibiotic stewardship in the ED.

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• The 290 study patients (sepsis prevalence 17.5%) were stratified by the ISI as 160 (55%) Green, 70 (24%) Yellow, and 60 (21%) Red. Probability of sepsis, as adjudicated per the Sepsis-3 consensus definition significantly increased across the IntelliSep interpretation bands; with a diagnostic odds

• Subjects in the Green Band had significantly lower mortality and severity of illness, as measured by SOFA, ICU admission, and hospital length of

• As depicted in Fig. 4, 16 (10%) subjects in the Green Band received broad-spectrum (antipseudomonal and / or anti-MRSA) antibiotics in the ED; only two of these subjects were septic (both survived without needing ICU care with 0 and 6-day hospital stays). Conversely, 12 septic subjects in the



Acknowledgements

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