Title: Protocolized application of a novel host-response assay in standard sepsis treatment workflows at two different emergency departments

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Introduction

Diagnostics to aid the emergency department (ED) in rapid sepsis risk assessment of potentially infected patients are needed[1]. Effective integration into existing workflows will be key for any such test. We evaluated the performance of a host-response test for early sepsis diagnosis implemented in two ED environments as part of the existing protocolized response to suspected infection.

Methods

This study enrolled adults (\geq 18) at 2 sites, (Site-1 (S1): Springfield, MA and Site-2 (S2): Milwaukee, WI; Feb.- Jul. 2023). At both sites, ED triage sepsis best practice alerts fired in response to suspicion of infection and \geq 2 modified SIRS criteria. However, at S1 the test was run on a remnant once the alert fired, whereas at S2, the test was included if ED providers used the sepsis order-set. All blood samples were collected and tested per standard of care within 5 hours. The test generates an Index, stratified into 3 interpretation bands (Bands 1-3) of increasing sepsis likelihood[2]. Sepsis status was determined through blinded retrospective physician adjudication.

Results

At S1, 189 patients (sepsis prevalence: 12.2%), were stratified as 131 (69.3%) in Band 1, 44 (23.3%) in Band 2, and 14 (7.4%) in Band 3. At S2, 120 patients (sepsis prevalence: 35.0%), were stratified as 39 (32.5%) in Band 1, 42 (35.0%) in Band 2, and 39 (32.5%) in Band 3 (Fig 1-A). Differing site sepsis prevalence and operations yielded differences across the Bands. At both sites, the test achieved comparable negative predictive values for Band 1(97.7% & 97.4%) and positive predictive values for Band 3 (71.4% & 59.5%). While the percentage of patients within each Band that received SEP-1 care elements increased across Bands, a similar number of patients received the care metric independent of the Band (Fig 1-B).

Conclusion

Our findings suggest that this host response test may improve risk stratification and resource utilization despite different ED sepsis protocols.

References

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Figure 1 (A) Incidence of adjudicated sepsis (per sepsis-3 definition), and (B) Administration of all SEP-1 elements (order for blood cultures, order for lactate, administration of antibiotics, all within 3-hours), across interpretation bands for the two study sites. Solid bars denote the number of patients in each Band that received the care metric, outlined bars denote the remainder of the patients in each Band that did not receive the care metric.



Protocolized Application of a Novel Host-Response Assay in Standard Sepsis Treatment Workflows at **Two Different Emergency Departments**

Probability of Sepsis

(ISI: 6.3-10.0)



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Introduction

Sepsis, a dysregulated host immune response to infection leading to lifethreatening organ dysfunction¹, is a common, fast-moving condition, with a substantial unmet need for the rapid diagnosis and delivery of precision therapies to prevent resultant morbidity and mortality². Current guidelines stress guick intervention³, yet undifferentiated patients with signs and symptoms of infection present to the Emergency Department (ED) and physicians are tasked with sepsis diagnosis often before adequate, objective diagnostic and prognostic data are available. As such, diagnostics to aid the ED in rapid sepsis risk assessment of potentially infected patients are needed. Effective integration into existing workflows will be key for any such test.

In this study, we evaluated the performance of a host-response test for early sepsis diagnosis implemented in two ED environments as part of the existing protocolized response to suspected infection.

Methods



Figure 1: (A) Photograph of the Cytovale system, a benchtop instrument on which the IntelliSep test is performed (inset) the IntelliSep microfluidic cartridge; (B) The IntelliSep reported result: the IntelliSep Index and Interpretation Bands.

The IntelliSep test

The Cytovale IntelliSep test is an FDA cleared, semi-quantitative test that assesses cellular host response via deformability cytometry of leukocyte biophysical properties and is intended for use in conjunction with clinical assessments and laboratory findings to aid in the early detection of sepsis with organ dysfunction manifesting within the first 3 days after testing . It is indicated for use in adult patients with signs and symptoms of infection who present to the ED. The test is performed on a K2 EDTA anticoagulated whole blood sample.

The test results in the IntelliSep Index (ISI), a single score between 0.1-10.0, in < 10 minutes. The score is stratified into three discrete interpretation bands based on the probability of sepsis with organ dysfunction manifesting within the first three days after testing: Band 1 (low), Band 2, and Band 3 (high)^{4,5} (Fig. 1-B).

Scientific Theory of Operation

Biophysical properties such as deformability, density, and size of neutrophils and monocytes are thought to shift with degranulation, neutrophil extracellular trap (NET) formation^{6,7}, or maturity that occurs during the dysregulated immune activation associated with sepsis^{8,9} (Fig. 2-A). As such, these properties differ in cells from septic patients when compared to quiescent white blood cell (Fig. 2-B).

Results & Discussion



- At both sites, the test achieved comparable negative predictive values for Band 1 (97.7% & 97.4%) and positive predictive values for Band 3 (71.4% & 59.5%) despite different ED sepsis protocols (Table 1).
- While the percentage of patients within each Band that received SEP-1 care elements increased across Bands, a similar number of patients received the care metric independent of the Band, indicating the potential for improved resource utilization when using the test.





Table 1: Receiver operator characteristic metrics per site.

| Performance Characteristics – Value (95% CI) | Site 1 | Site 2 |
|--|--------------------|--------------------|
| AUC | 0.87 (0.77 – 0.96) | 0.80 (0.73 – 0.88) |
| Positive Percent Agreement (sensitivity): Band 1 vs. else | 87.0 (66.4 - 97.2) | 97.5 (86.8 - 99.9) |
| Negative Percent Agreement (specificity): Band 3 vs. else | 97.6 (78.1 – 99.9) | 81.2 (64.4 – 90.9) |
| Negative Predictive Value (NPV): Band 1 vs. else | 97.7 (78.1 – 99.9) | 97.4 (83.1 – 99.4) |
| Positive Predictive Value (PPV): Band 3 vs. else | 71.4 (47.1 – 86.8) | 59.5 (40.9 – 73.0) |
| Diagnostic Odds Ratio (LR+/LR-) | 106.7 | 55.7 |
| | | |

SEP-1 Elements Delivered Within 3h of Triage



The IntelliSep test utilizes a microfluidic deformability cytometry technique in combination with technological advances in high-speed imaging and machine learning, to measure the biophysical properties of thousands of individual leukocytes in rapid succession, enabling rapid assessment of immune activation signatures and sepsis risk stratification^{6,10}.



Figure 2: (A) Time series of cell deformation for a representative leukocyte of a septic Band 3 patient (top) and a non-septic Band 1 patient (bottom); (B) Neutrophil extracellular traps (NETs) formation is a rapid active process mediated by NETosis, involving chromatin decondensation and nuclear membrane disintegration¹¹.

Study Design & Setting

- Adults (≥18) were enrolled at 2 sites (Site-1 (S1): Springfield, MA, USA and Site-2 (S2): Milwaukee, WI, USA) from Feb – July 2023.
- At both sites, ED triage sepsis best practice alerts fired in response to suspicion of infection and ≥ 2 modified SIRS criteria. The test was run on a remnant blood specimen: once the alert fired at S1, and if ED providers used the sepsis order-set at S2.
- Blood samples were collected per standard of care and assayed using the IntelliSep test within 5 hours of phlebotomy.
- IntelliSep test result was compared with sepsis status as determined through a combination of blinded objective chart evaluation and retrospective physician adjudication (Sepsis-3 criteria).
- ED nurses and treating clinicians were blinded to IntelliSep results.



Figure 6: SEP-1 care elements delivered within 3-h from triage - (A) lactate measured, (B) blood cultures collected, (C) antibiotics administered, and (D) all elements delivered to a patient (* and ** indicates p < 0.05 & p < 0.01, respectively).

Conclusions

А

Our findings suggest that the IntelliSep test, a cellular host response test, may improve sepsis risk stratification and resource utilization for adults presenting to the ED when incorporated as part of the existing protocolized response to suspected infection, despite different ED sepsis protocols.

References

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