VALIDATION OF A HOST RESPONSE ASSAY, SEPTICYTE® LAB, FOR DISCRIMINATING SEPSIS FROM SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN THE ICU

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Immunexpress

the signature diagnostics for sepsis

RATIONAL AND OBJECTIVES

Rationale: A molecular test to distinguish between sepsis and systemic inflammation of noninfectious etiology (SIRS) could potentially have clinical utility.

Objectives: This study evaluated the diagnostic performance of a molecular host response assay (SeptiCyte® LAB) designed to distinguish between sepsis and SIRS noninfectious systemic inflammation in adults on first day of ICU admission.

METHODS

The study employed a prospective, observational design and recruited a heterogeneous cohort of adult critical care patients from seven sites in the United States (n = 249). An additional group of 198 patients, recruited in the large MARS (Molecular Diagnosis and Risk Stratification of Sepsis) consortium trial in the Netherlands (www.clinicaltrials.gov identifier NCT01905033), was also tested and analyzed, making a grand total of 447 patients in our study. SeptiCyte® LAB generates a quantitative score (SeptiScore®, range 0–10) falling into one of four probability bands defined as follows: band 1 (0.0<SeptiScore®<3.0), band 2 (3.1<SeptiScore® <4.4), band 3 (4.5< SeptiScore® <5.9), and band 4 (6.0< SeptiScore® <10.0). In the absence of a gold standard for diagnosing sepsis, diagnostic performance of SeptiCyte® LAB was compared with retrospective physician diagnosis (RPD) by a panel of three independent expert clinicians. Three different RPD algorithms were used. Diagnosis was designated “consensus” if two panelists agreed or “unanimous” if all three panelists agreed with each other (upper bound estimate of SeptiCyte® LAB performance). If the panelists all disagreed, or if all deemed a subject indeterminate, then the diagnosis was considered indeterminate (37 of 447 [8.3%]). In the third RPD algorithm (“forced” approach), indeterminates underwent a second blinded independent case review and were forced into either the sepsis or SIRS category (lower bound estimate of SeptiCyte® LAB performance).

MEASUREMENTS AND MAIN RESULTS

- In receiver operating characteristic curve analysis, SeptiCyte® LAB had an estimated area under the curve of 0.82–0.89 (depending upon RPD method) for discriminating sepsis from SIRS.
- The relative likelihood of sepsis versus SIRS was found to increase with increasing test score.
- A positive correlation between band number and probability of sepsis was observed.
- In a forward logistic regression analysis, the diagnostic performance of the assay was improved only marginally when used in combination with other clinical and laboratory variables, including procalcitonin.
- The performance of the assay was not significantly affected by demographic variables, including age, gender, or race/ethnicity.
- For blood culture–positive cases (54 of 447 [12%]) that were not suspected of contamination, no SeptiScores® fell in band 1 (assay sensitivity, 1.00; 95% confidence interval, 0.93–1.00), and SeptiScores® were heavily skewed toward bands 3 and 4.
- We have demonstrated that a simplified version of the assay on the near-patient platform (Biocartis Idylla™) performs equally as well.

Figure 1 - SeptiCyte® LAB discriminates sepsis from noninfectious systemic inflammation

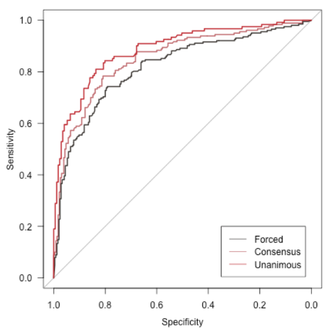


Figure 2 - Higher SeptiScore® = Higher probability of sepsis

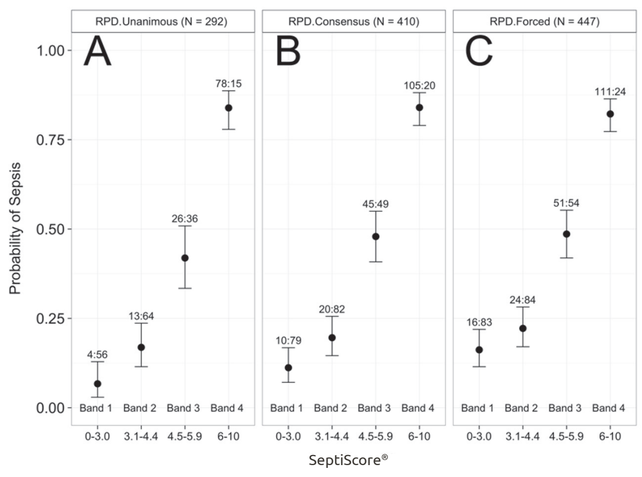


Figure 3 - SeptiCyte® is superior to other clinical variables in SIRS/Sepsis discrimination

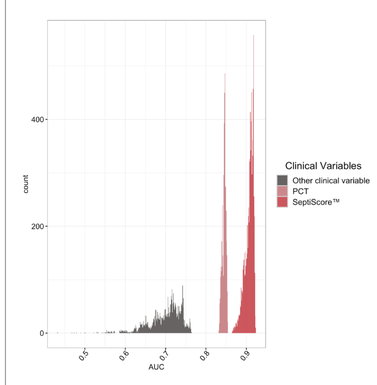
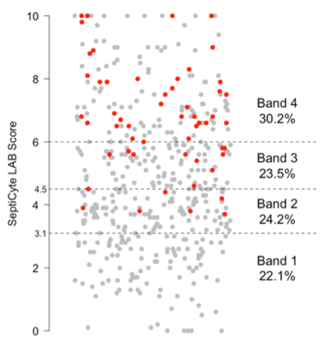


Figure 4 - SeptiCyte® LAB Detects 100% of Blood Culture Positive Cases

Band (N=patients per band)	Observed N in Band with sepsis and positive blood culture
Band 1 (N=99)	0
Band 2 (N=108)	6
Band 3 (N=105)	11
Band 4 (N=135)	37



SeptiCyte® LAB – Diagnostic Performance, N = 447

FDA 510(k) clearance pivotal trial → Met all clinical endpoints

0---------- SpetiSCORE® Range (0-10) increases with probability of sepsis ----------10

SIRS | Band 1 | Band 2 | Band 3 | Band 4 | SEPSIS

Band 1 Low risk of sepsis	Performance Estimate** Lower (Forced)	Upper (Unanimous)
Cohort size (N)	447	314
Sensitivity	0.92	0.95
Sepsis probability	16.2%	10.9%
SIRS probability	83.8%	89.1%
Likelihood Ratio	0.23	0.15

Band 4 High risk of sepsis	Performance Estimate** Lower (Forced)	Upper (Unanimous)
Cohort size (N)	447	314
Specificity	.90	0.91
Sepsis probability	82.2%	84.3%
SIRS probability	17.8%	15.7%
Likelihood Ratio	5.61	6.63

** Upper and lower performance estimates are defined as a range based on the confidence in the referenced method (retrospective physician diagnosis). Lower estimates include indeterminate cases. Upper estimates only include cases with a unanimous diagnosis by the physician panel.

Figure 1
Receiver operating characteristic curves for SeptiCyte® LAB, calculated for the Complete Clinical Dataset

Test performance is presented based on three versions of RPD with increasing confidence in patient classification: (Grey) Forced RPD, where the panel must make sepsis/SIRS diagnosis for all patients; (Pink) Consensus RPD, where patients without a consensus panel diagnosis are excluded; (Red) Unanimous RPD, where patients without a unanimous panel diagnosis are excluded.

Dataset. Unanimous RPD (Nsepsis = 121, NSIRS = 171, Nexcluded = 155, AUC 0.89, 95% CI: 0.85-0.93); Consensus RPD (Nsepsis = 180, NSIRS = 230, Nexcluded = 37, AUC 0.85, 95% CI: 0.81-0.89); Forced RPD: Nsepsis = 202, NSIRS = 245, AUC = 0.82, 95% CI: 0.78-0.86).

Figure 2
Positive correlation between SeptiScore® and the probability of sepsis. In each panel the probability of sepsis is plotted against SeptiScore® for four different SeptiScore® ranges (bands). Each box-and-whisker plot indicates the median and the upper and lower 80% confidence interval bounds on sepsis probability for a particular band. The number of sepsis: systemic inflammatory response syndrome (SIRS) subjects in each band is indicated. (A) Unanimous RPD (171 SIRS; 121 sepsis = 121). (B) Consensus RPD (230 SIRS; 180 sepsis; 37 indeterminates excluded). (C) Forced RPD (245 SIRS; 202 sepsis).

Figure 3
Area under the curve (AUC) distributions for logistic models. An exhaustive examination of all 16,383 possible logistic combinations of up to 14 variables was conducted (SeptiScore®, PCT, max glucose concentration, min WBC, max WBC, max MAP, min core T, max core T, min HR, max HR, number of SIRS criteria, age, sex, and race/ethnicity). No imputation of missing values was performed. The comparator was consensus RPD. Red = models containing SeptiScore®; pink = models containing PCT but not SeptiScore®; grey = models without SeptiScore® or PCT.

SUMMARY

1. SeptiCyte® LAB is the first host-response test cleared by the FDA as an aid for diagnosis of sepsis (K163260).
2. SeptiCyte® LAB reliably discriminated sepsis and SIRS in critical care patients.
3. Demonstrated very high assay sensitivity and specificity.
4. SeptiCyte® LAB was able to identify every patient that went on to become blood culture positive.
5. Addition of commonly used clinical and laboratory parameters, including PCT, only marginally improved performance.
6. We have translated this assay to the Biocartis Idylla™ platform and demonstrated similar diagnostic performance. Therefore, SeptiCyte® technology promises reliable sepsis diagnosis in ~1 hour.

CONCLUSIONS

SeptiCyte® technology provides actionable results to aid early recognition and treatment of sepsis patients, independently of the presence of the causative pathogen.

References

*Russell R. Miller III, Bert K. Lopansri, John P. Burke, Mitchell Levy, Steven Opal, Richard E. Rothman, et al.
Validation of a Host Response Assay, SeptiCyte® LAB, for Discriminating Sepsis from Systemic Inflammatory Response Syndrome in the ICU. Am J Respir Crit Care Med. 2018 Oct 1;198(7):903-913.
MARS (Molecular Diagnosis and Risk Stratification of Sepsis) www.clinicaltrials.gov identifier NCT01905033 / VENUS (Validation of Septic Gene Expression Using SeptiCyte) www.clinicaltrials.gov identifier NCT02127502