THE IMPACT OF ANTIMICROBIAL STEWARDSHIP AND ACCURATE SUSCEPTIBILITY RESULTS ON PATIENTS WITH SEPSIS

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Difficult to Treat MDRO

- 30-year-old male, no significant previous medical history
- Sustained friction burns following flash diesel explosion at industrial plant
- 65% total body surface area burn wounds
- Admitted to the burn unit
- Multiple operations and allografts
- 2 weeks after admission:
  - *K. pneumoniae* in blood cultures

Molecular results (positive blood culture):
bla$_{\text{NDM-5}}$ carbapenemase gene detected

Antimicrobial	*K. pneumoniae*	
Amikacin	≤8	S
Cefazolin	>16	R
Cefepime	>16	R
Cefiderocol	**32**	**R**
Ceftazidime-avibactam	**16**	**R**
Ceftriaxone	>32	R
Ciprofloxacin	>2	R
Ertapenem	**>2**	**R**
Gentamicin	>8	R
Levofloxacin	>4	R
Meropenem	**4**	**R**
Piperacillin-tazobactam	>64/4	R
Tobramycin	>8	R
Trimeth-sulfamethoxazole	>2/38	R

What is happening here?

Laboratory Troubleshooting:

- Confirm there is no mixture
  - pure
- Confirm breakpoints are right
  - Up to date vs. CLSI M100 32nd Edition
- Confirm “R” mechanism testing and MICs
  - NDM-5 detected, same pattern
- Repeat MIC by alternative method
  - MICs confirmed
- Synergy testing with ceftazidime-avibactam and azetreonam was susceptible

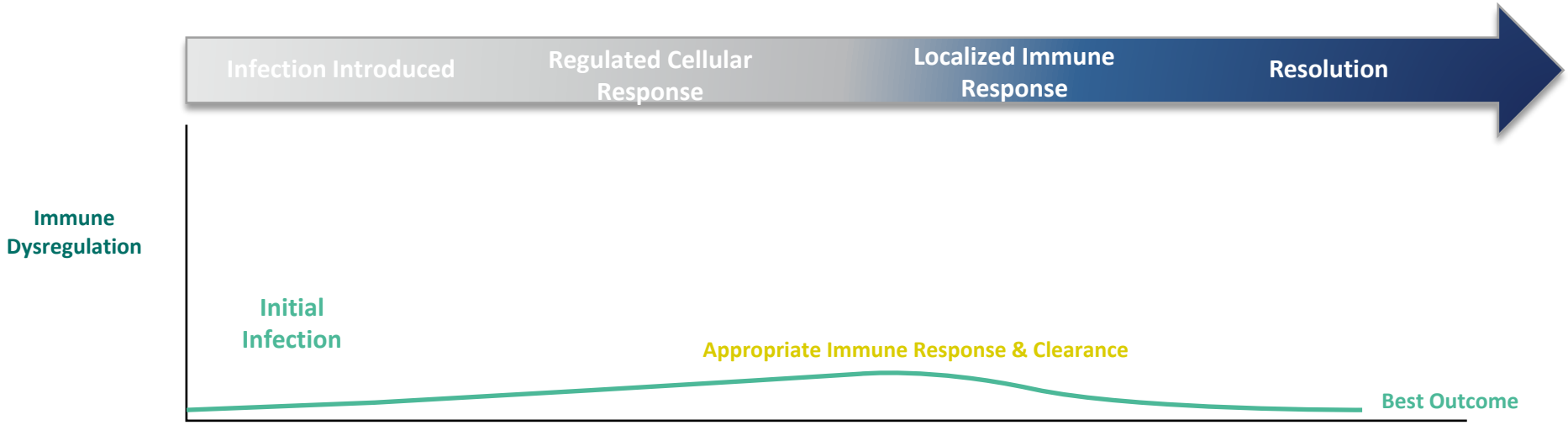
What can we do?

- Synergy Testing
- Novel Agents
  - Cefepime-zidebactam
  - Cefepime-taniborbactam
  - Cefiderocol-xeruborbactam

PMID 34618008

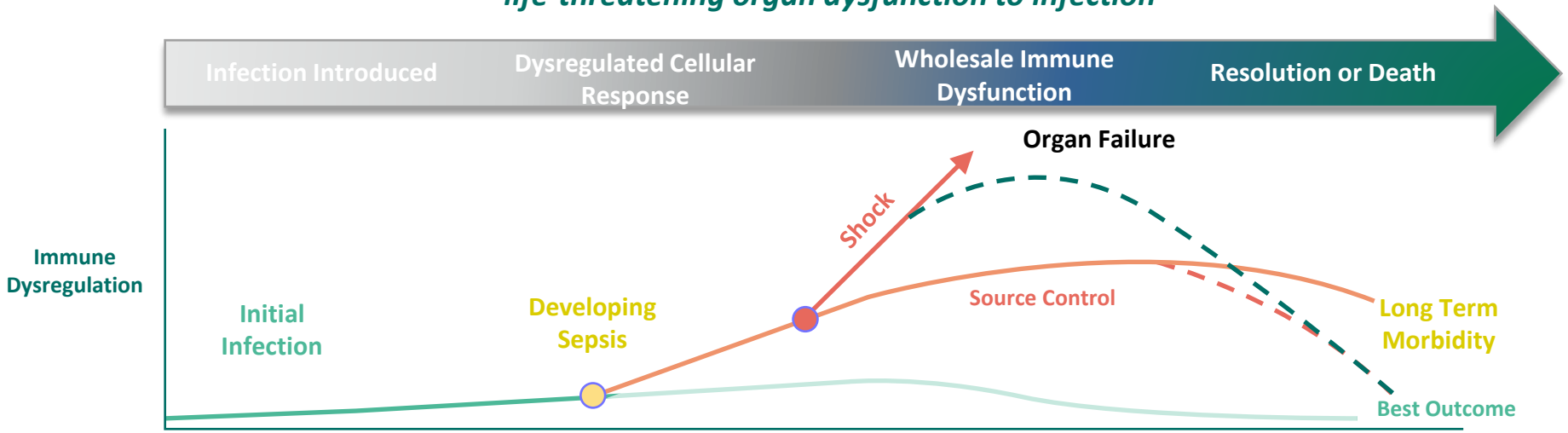
What is Sepsis?

Infection is not synonymous with Sepsis



Sepsis Is A Dysregulated Immune Response To Infection[1]

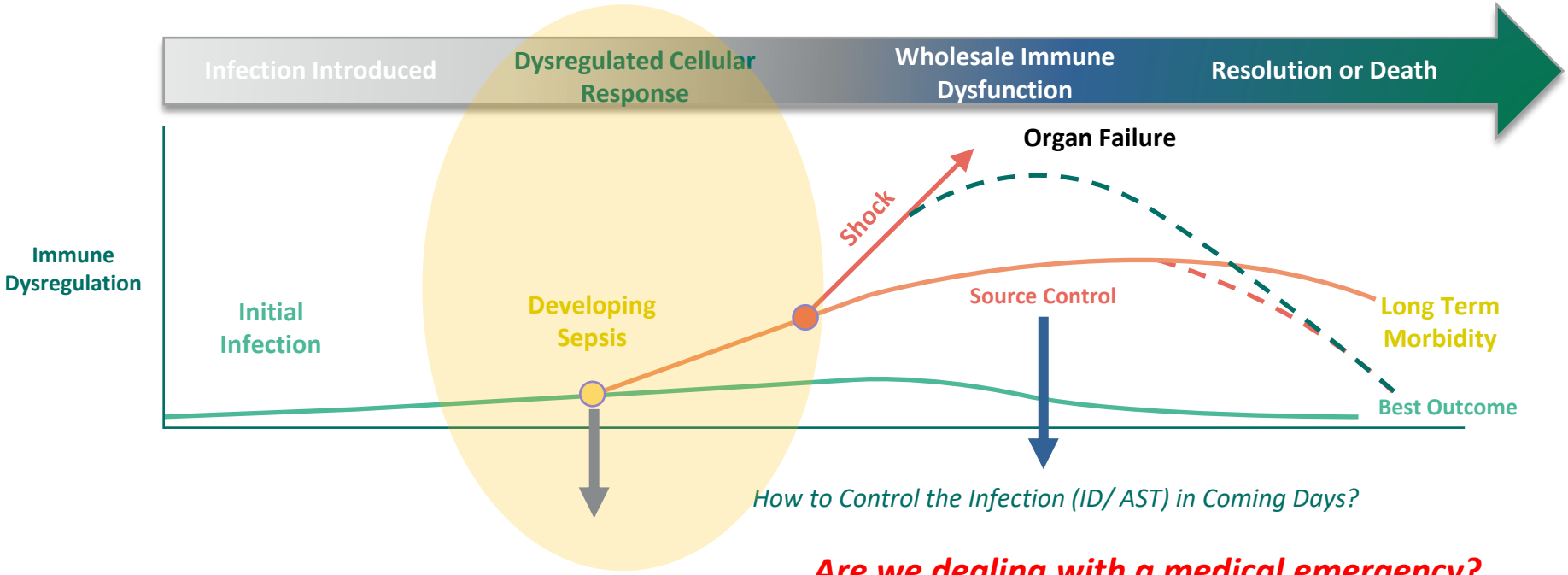
Sepsis is a syndrome and has most recently been defined as life-threatening organ dysfunction to infection[2]



[1]Graphic adapted from Prof. Mervyn Singer, ECCMID 2022
[2]Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801–810. doi:10.1001/jama.2016.0287

Sepsis Poses A Medical Emergency

This dysregulated immune response makes sepsis a medical emergency



Are we dealing with a medical emergency?

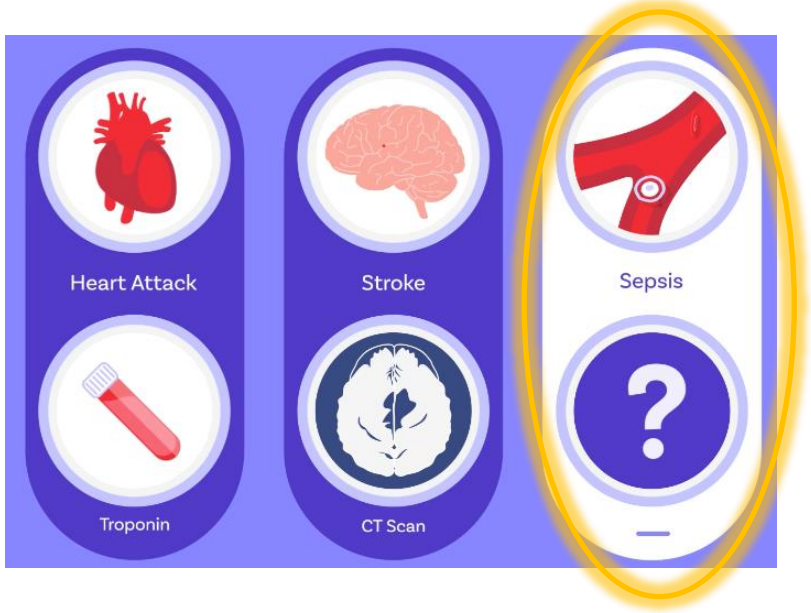
Sepsis Is A Medical Emergency That Needs Actionable Risk Stratification

Sepsis is the leading cause of death in hospitals worldwide

80%
Of sepsis cases present to ED

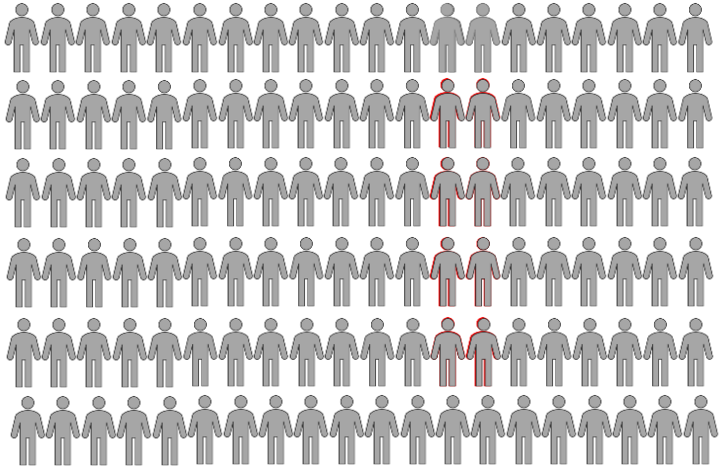
2x
Number of Stroke & Heart Attack cases

1 in 5
Of 150M+ ED patient visits are at risk of sepsis



Challenge of Potentially Infectious Patients in the ED

80% of Sepsis patients present to the ED



Sepsis patients are **masked** by a much larger cohort of suspected infection patients

ED Quandary

Limited Information
(vitals, symptoms, CBC…)

Limited Time
(<3hr to administer ABx per Sep-1 bundle)

No-Win Situation for Emergency Departments

- **Under diagnosis**
  - Rapid clinical deterioration/risks of organ damage
  - Potential for readmission
  - Quality metrics -> reimbursement
- **Over diagnosis**
  - Increased costs/resource utilization
  - ED Throughput
  - Delayed/missed diagnosis
  - IV vs Oral Abx

THERE IS A NEED FOR BETTER MARKERS OF INFECTION STATUS

A Case Study Illustrating the Need

Study Objectives

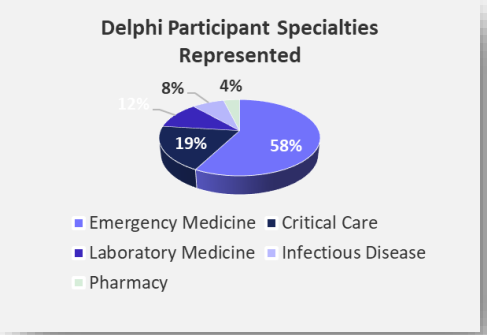
1. **Develop guiding statements** around (1) use of a hypothetical Rapid Sepsis Test (performance characteristics mirror IntelliSep) and (2) direction on clinical use and incorporation into hospital workflow of **IntelliSep**

2. **Gain consensus on statements** with experts across specialties involved in sepsis research and clinical care of sepsis patients

Study Approach

- **Expert Participant Group:**
  - 26 participants – involved in sepsis research and clinical care; majority from academic centers
  - Representative of: Emergency Medicine, Critical Care, Laboratory Medicine, ID, Pharmacy

- **Study Method:**
  - **Modified Delphi approach**, consisting of 2 rounds of questionnaires *(100% participation)*
  - Both questionnaires split into **two sections**: **(1) need statements for a rapid sepsis test** (performance characteristics provided), **(2) clinical action statements based on ISI bands** associated with hypothetical patient cases
  - Participants asked to evaluate majority of statements using a **five-point Likert scale**
  - **Level of agreement for each statement assessed** post-questionnaire



1 Kraus et.al. Manuscript under review

How consistent is the perception of Sepsis Risk?

Patient Description:

- 72 year-old female nursing home patient
- Past medical history of dementia, hypertension and dyslipidemia
- Presented to the emergency department after nursing home staff noted her to have altered mentation
- Somnolent on the morning evaluation; on repeat evaluation several hours later, the patient remained in bed & very difficult to arouse
- At baseline, able to transfer from bed to bedside commode and wheelchair without difficulty, and is typically bright and communicative. This morning she was arousable only to physical stimulus and spoke incoherently.

On arrival to the Emergency Department:

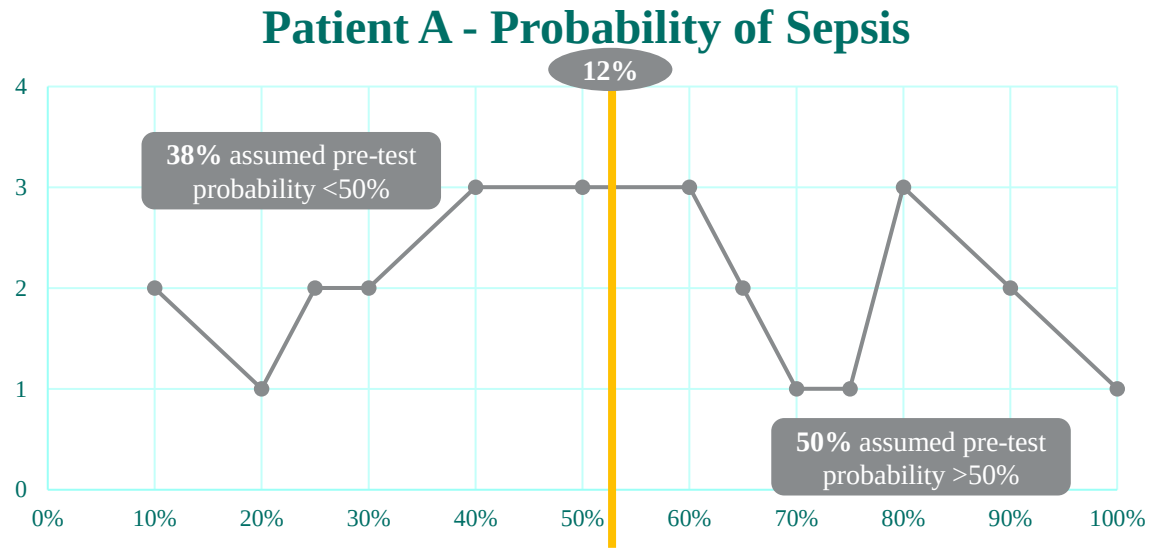
- Temperature: 97.8F, Pulse: 84, Respiratory rate: 16, Blood pressure 98 / 62 mmHg, Oxygen saturation 95% on room air.
- She opened her eyes and moaned incoherently to physical stimulus. An evaluation in the emergency department, including imaging studies, was significant for a:
- WBC of 9.8k, BUN 32, creatinine 1.9 (baseline 0.8), Lactate of 2.8 mmol/L
- Urinalysis (cath specimen) with + nitrites, 6-10 WBC / HPF, 0-5 RBC / HPF and many bacteria on microscopic exam

Little Agreement of Sepsis Risk amongst respondents

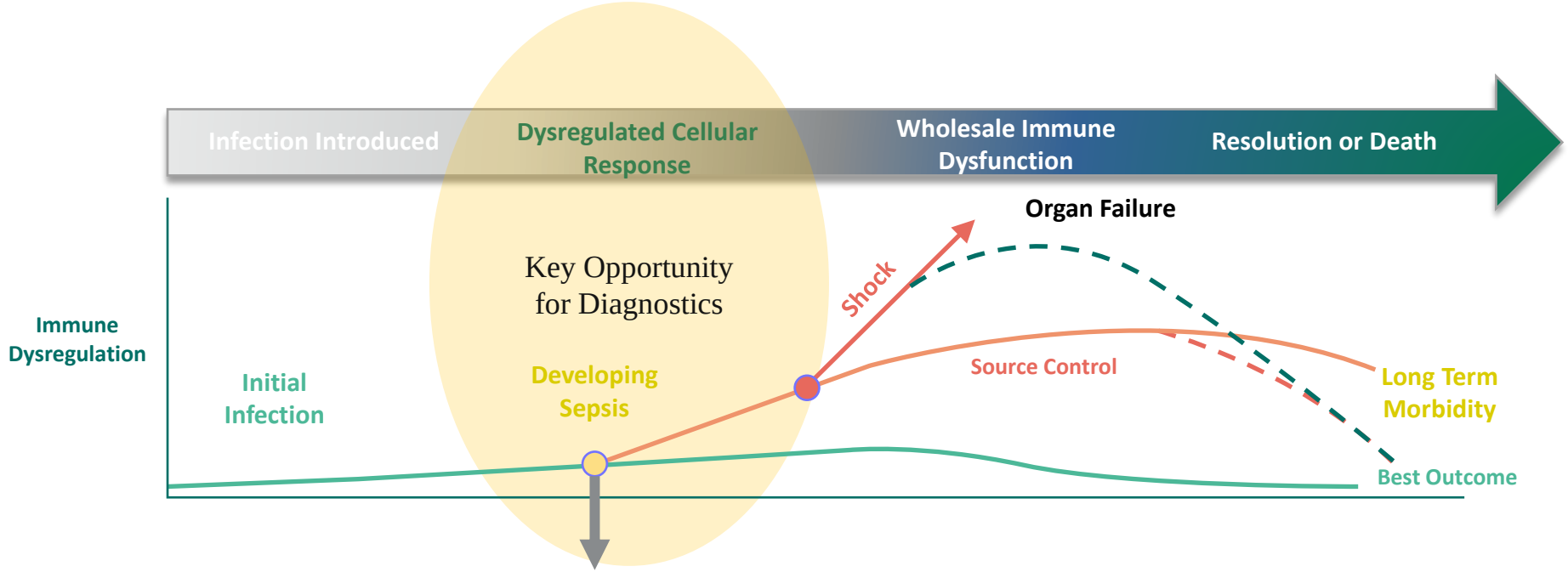
- Provided 2 example cases of potential diagnostic dilemmas and asked about pre-test probability of sepsis for these cases (1 presented here)
- Probability ranged from 10% to 100% for the same case, with little agreement

Providers don't currently "Know sepsis when they see it"

%	Votes
10%	2
20%	1
25%	2
30%	2
40%	3
50%	3
60%	3
65%	2
70%	1
75%	1
80%	3
90%	2
100%	1



HOST RESPONSE CAN PROVIDE CRITICAL INFORMATION WHEN IT IS NEEDED MOST



Are we dealing with a medical emergency?

Limitations Of Current Tools

	EHR Alerts	Bodily Fluid Cultures	Biomarkers & SIRS	Pathogen ID
✓	Clinical impression, vitals and initial testing are often the only information available for early triage	Provide confirmation of infection	Both symptoms and test results available early on in patient triage	Pinpoint the right pathogen type, help guide use of Abx
✗	Dependent on data entry (and limited data) Alert fatigue	Require time	Offer an incomplete picture, non-specific and/or could be a lagging indicator of sepsis	Pathogen Detection is not Sepsis Detection

Above do not answer both questions of

is there a dysregulated host response to infection & is this a medical emergency?

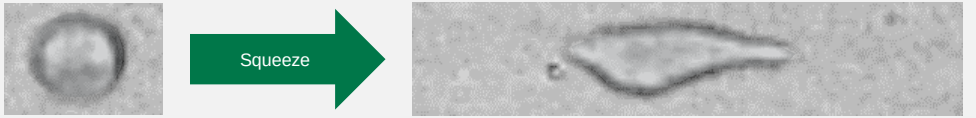
A COUPLE OF HOST RESPONSE SOLUTIONS

PHYSICAL CELL DEFORMATION: AIMING TO PROVIDE A WINDOW INTO DYSREGULATED IMMUNITY AND PHENOTYPIC CELLULAR SHIFTS

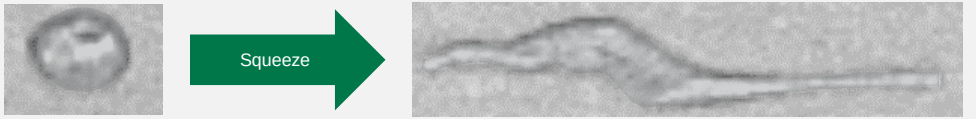
- Interrogates biophysical properties of white blood cells (mainly neutrophils and monocytes) that may signal a **Dysregulated Host Response**
- 10,000 white blood cells are **exposed to a controlled deformation process (squeezed)** and **imaged**
- Squeezing cells **reveals the nuclear architecture** and **level of Immune Activation**
- The cell mechanics are analyzed and interpreted by the Cytovale system's **machine learning algorithm**

Images from Cytovale System

White Blood Cells from a **Healthy Donor**



White Blood Cells from a **Septic Patient**



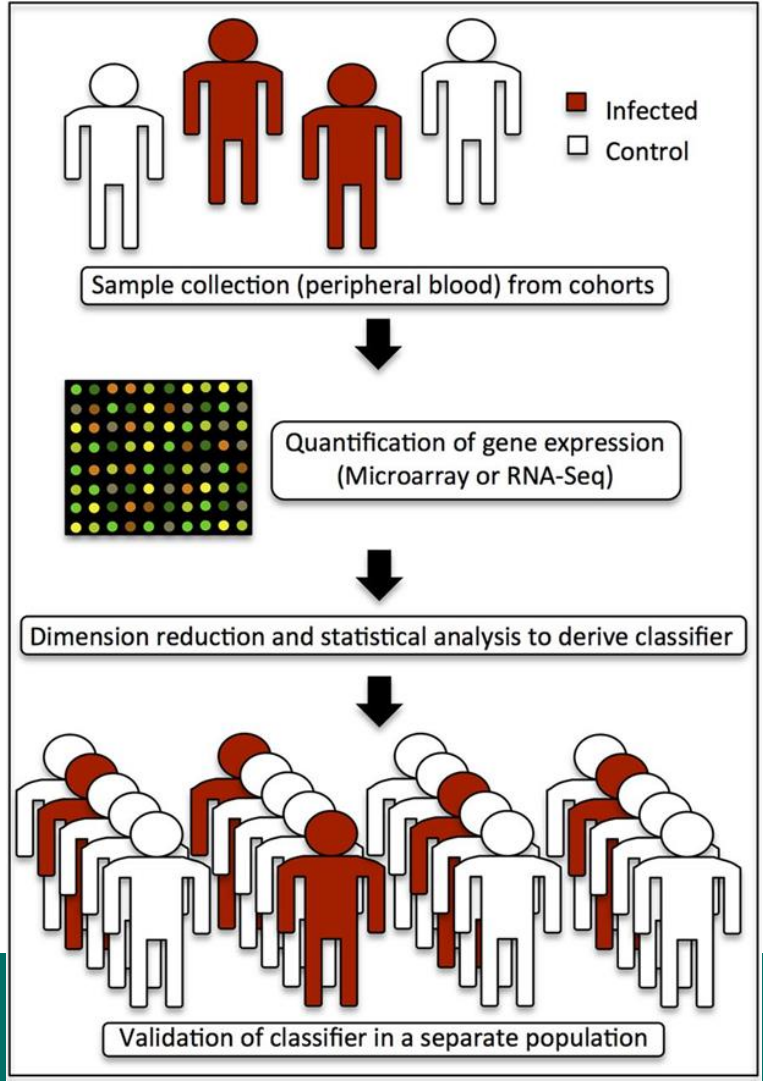
Results are provided on a continuum as an indication of host immune activation

Indicates misclassified patient

Provides a clear and timely indication to the ED provider when it is needed most:

- **Green Band** has very high negative predictive value (NPV) for sepsis, explore other diagnoses or conservative care
- **Yellow Band** slow down, additional workup may be appropriate for this patient
- **Red Band** likely warrants immediate and aggressive management

A BETTER APPROACH TO BIOMARKER DEVELOPMENT



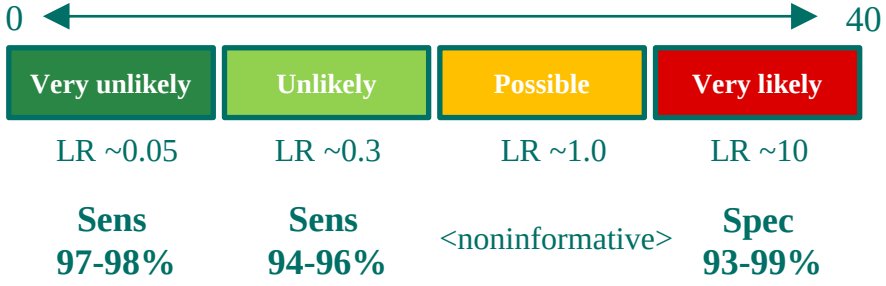
Holcomb ZE et al. J Clin Microbiol. 2017

TRANSCRIPTOMICS APPROACH TO SEPSIS: PRESENCE, TYPE, AND SEVERITY

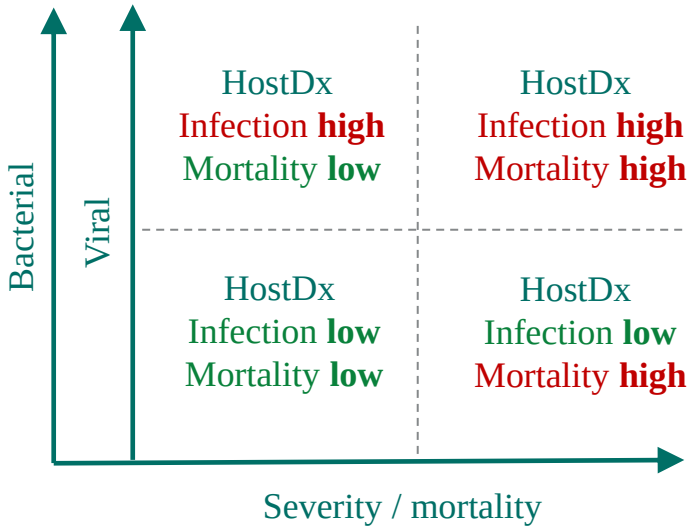
HostDx Sepsis puts out not one but three scores:

1. Bacterial infection,
2. Viral infection, and
3. Severity (30-day Mortality)

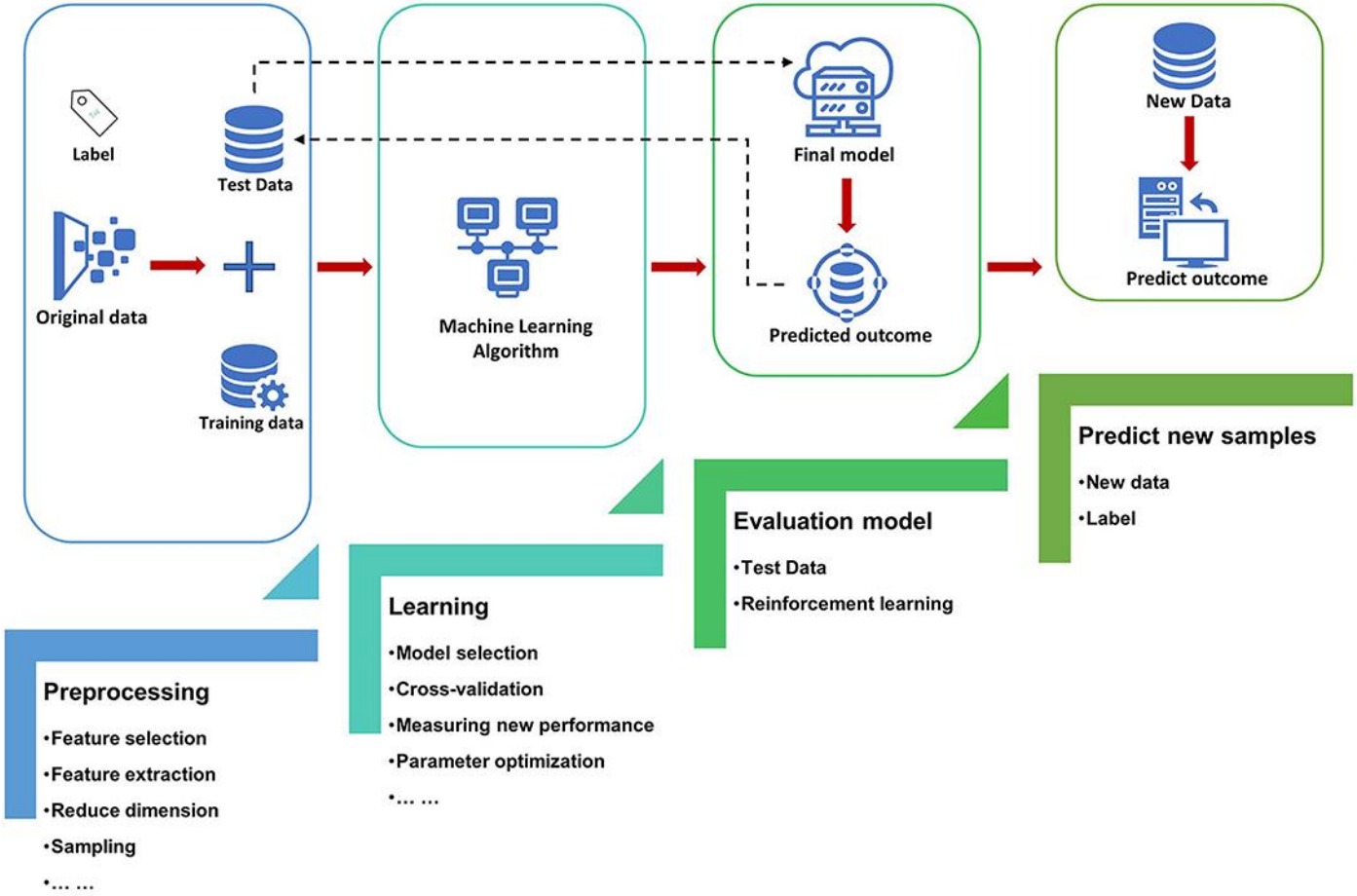
Each score is broken into 4 interpretation bands:



Highly actionable output



AI DRIVEN DECISION SUPPORT



PMID 34055839

HOW DOES HOST-RESPONSE HAVE AN IMPACT ON ANTIMICROBIAL STEWARDSHIP AND PATIENT OUTCOMES?

A TYPICAL NURSE-DRIVEN PROTOCOL FOR SEPSIS EVALUATION IN EPIC

Criteria for Initiating Nurse-Driven Sepsis Evaluation Process (Epic® Electronic Health Record)

Adults Only (Age >= 18 years)

Both of the following are answered 'YES'

1. Is there a suspected infection?
2. Is altered mentation present?

OR

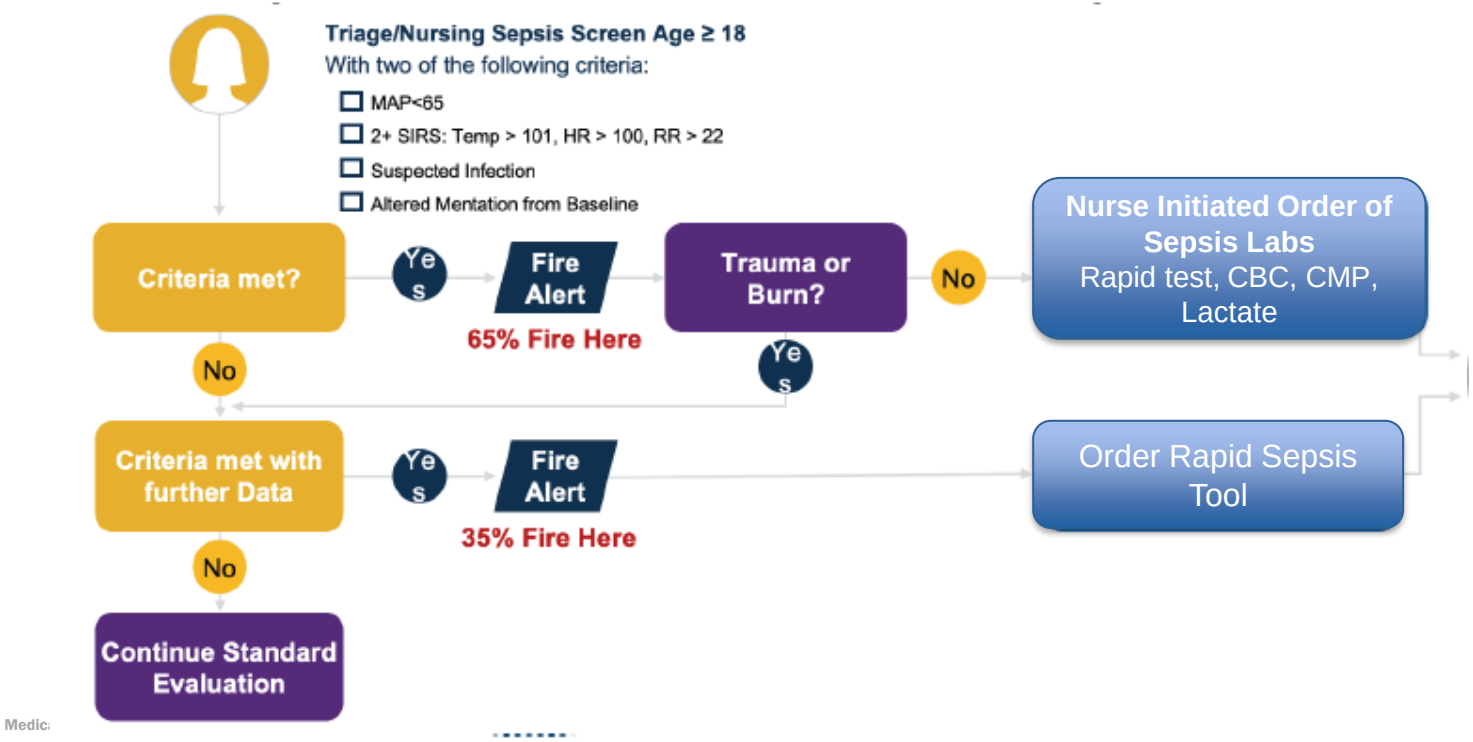
Both of the Following

1. One of the above is answered 'YES'
2. And at least 2 of the Following
   a. Respiratory Rate > 22
   b. Heart Rate > 100
   c. Temperature > 101° F (38.3° C)

OR

Hypotension (Systolic Blood Pressure < 90 mmHg or Mean Arterial Pressure < 60 mmHg)

NURSE-DRIVEN PROTOCOLS WITH RAPID SEPSIS DIAGNOSTIC



Thomas CB, et al. ISICEM 2024.

IMPACT OF HOST RESPONSE ON LOS AND ABX USE

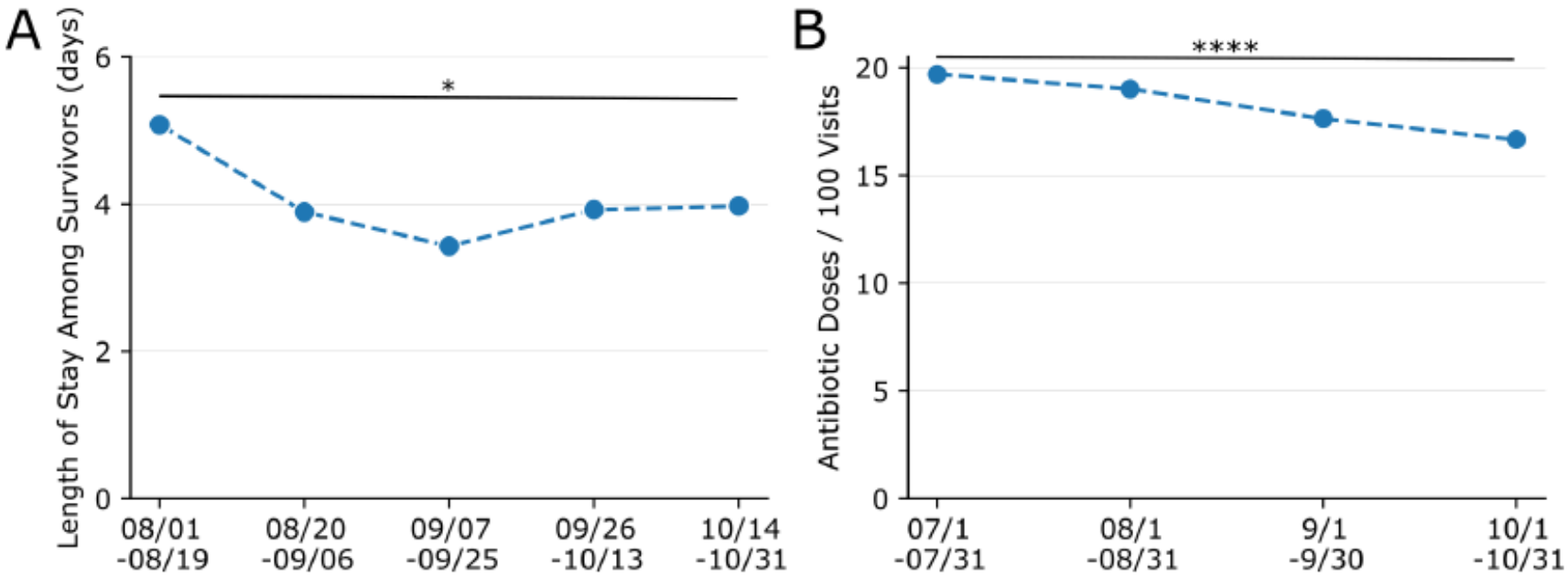


Figure 4: (A) Length of stay among survivors and (B) antibiotic doses per 100 visits for all-comers to the ED (* and **** indicate $p < 0.05$ and $p < 10^{-4}$, respectively).

ARE WE ON A SIMILAR TRAJECTORY TO TROPONIN WITH MI?

TABLE 2 Total Number of MIs and UA in Relation to Method Used for Troponin Measurement in Sweden From 2007 to 2013

	2007	2008	2009	2010	2011	2012	2013
MI							
Total MIs	33,380	31,731	29,712	29,621	28,641	28,123	25,787
Residents >20 yrs old	6,974,057	7,038,351	7,112,622	7,192,356	7,269,107	7,342,808	7,417,271
Incidence per 10,000 py	48	45	42	41	39	38	35
Length of stay, days	8.8 ± 11.5	8.5 ± 11.0	8.2 ± 10.5	8.0 ± 10.3	7.7 ± 10.2	7.4 ± 9.2	7.3 ± 9.1
MI diagnosed with cTn							
Total MIs	N/A	N/A	28,609 (96)	18,986 (64)	10,159 (35)	7,849 (28)	6,732 (26)
Length of stay, days	N/A	N/A	8.2 ± 10.5	7.9 ± 10.2	7.5 ± 10.2	7.2 ± 9.1	7.1 ± 9.4
MI diagnosed with hs-cTnT							
Total MIs	N/A	N/A	439 (1.5)	6,842 (23)	15,120 (53)	18,881 (67)	18,519 (72)
Length of stay, days	N/A	N/A	8.0 ± 8.2	7.8 ± 9.8	7.5 ± 10.1	7.5 ± 9.3	7.4 ± 9.1
MI diagnosed at hospitals with hs-cTnT, higher decision limit*							
Total MIs	N/A	N/A	664 (2.0)	3,793 (13)	3,362 (12)	1,393 (5.0)	536 (2.1)
Length of stay, days	N/A	N/A	10.2 ± 12.8	8.6 ± 11.4	9.2 ± 10.3	8.5 ± 8.7	8.5 ± 8.0

PMID 29880121

IMPACT OF HOST RESPONSE AND LAB STEWARDSHIP

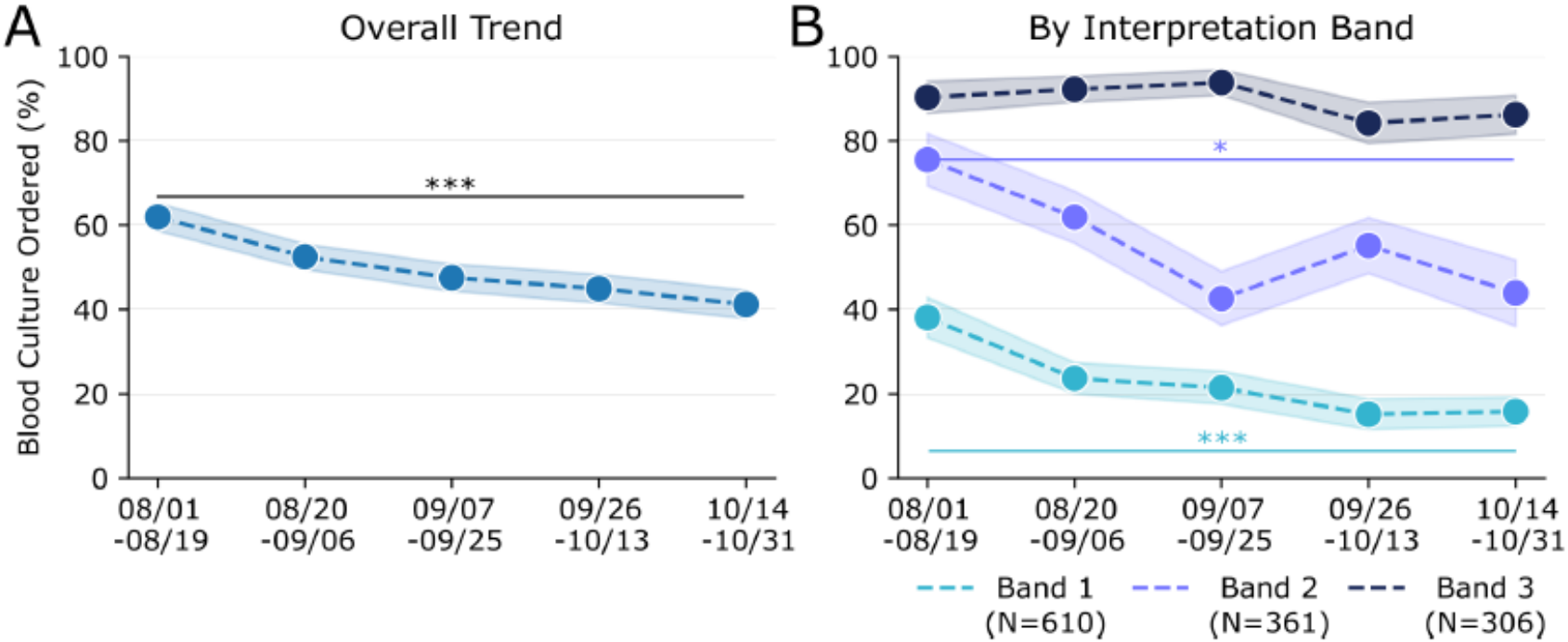


Figure 5: Rate of blood cultures ordered across time for (A) all patients with an ISI ordered and (B) across interpretation band. (* and *** indicate $p < 0.05$ and $p < 0.001$, respectively)

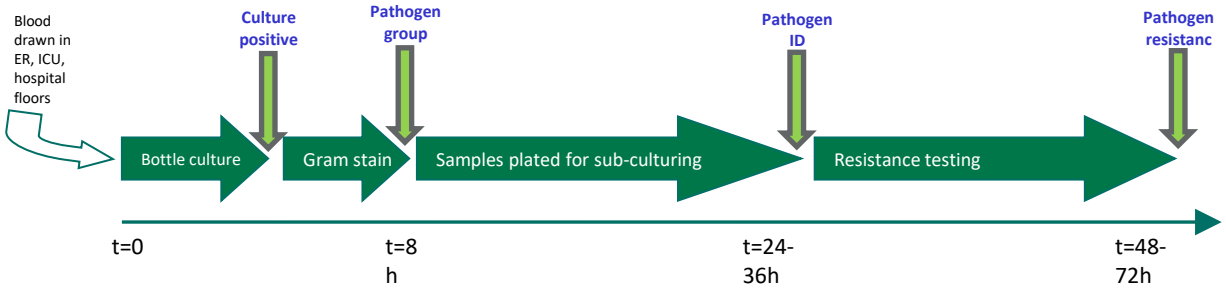
FINANCIAL IMPACT OF EARLY HOST RESPONSE IN SEPSIS

Disposition	Cost Reduction	LOS Reduction
Overall	**$1429**	
Observation	$243	
Inpatient	$1930	1.28 Days
ICU	$3624	2.42 Days

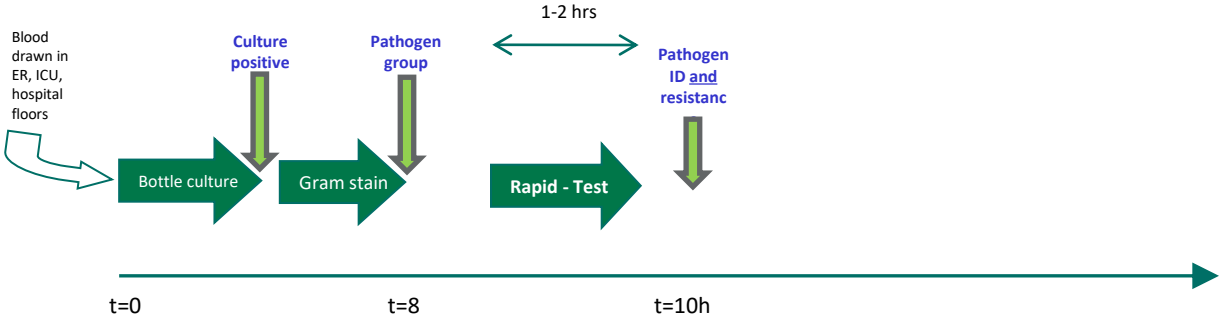
Thomas CB, et al. ISICEM 2024.

IS THE MICROBIOLOGY LAB EVER GOING TO BE ENGAGED IN THE FUTURE OF SEPSIS CARE?

Current Blood Culture Workflow

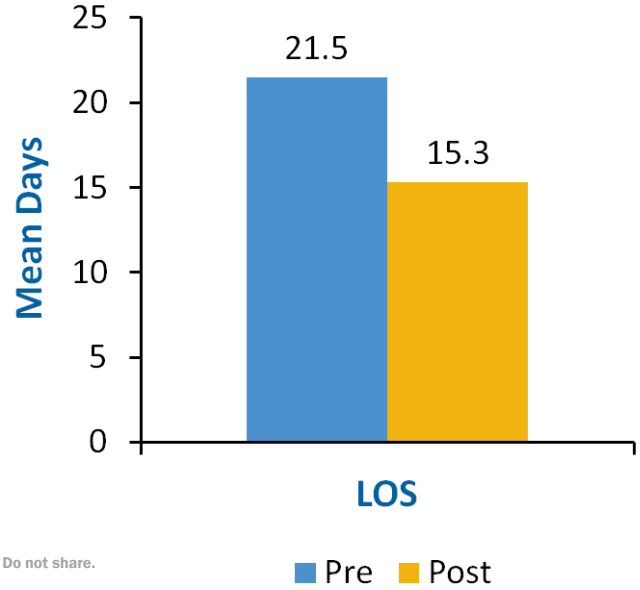


Workflow with Rapid Tests



OUTCOMES: LENGTH OF STAY (LOS)

- Mean LOS was reduced by 6.2 days in the post-rapid diagnostic group. (21.5 versus 15.3, *P* = 0.07)



[1] Bauer KA, West JE, Balada-Llasat JM et al. *Clin Infect Dis*. 2010;51:1074-80.

CLINICAL AND TREATMENT-RELATED OUTCOMES

Outcome	Total		
	Pre-intervention (n = 256)	Intervention (n = 245)	*P* Value
Clinical outcomes			
30-day all-cause mortality	52 (20.3)	31 (12.7)	0.021
Time to microbiological clearance, d	3.3 ± 4.8	3.3 ± 5.7	0.928
Length of hospitalization, d	14.2 ± 20.6	11.4 ± 12.9	0.066
Length of ICU stay, d	14.9 ± 24.2	8.3 ± 9.0	0.014
Recurrence of same BSI	15 (5.9)	5 (2.0)	0.038
30-day readmission with same BSI	9 (3.5)	4 (1.6)	0.262
Treatment-related outcomes			
Time to effective therapy, h	30.1 ± 67.7	20.4 ± 20.7	0.021
Time to optimal therapy, h	90.3 ± 75.4	47.3 ± 121.5	<0.001

Huang AM, et al. Clin Infect Dis 2013; 57:1237–45

ANTIMICROBIAL STEWARDSHIP IS CRITICAL

Organism	Mean time to optimal antibiotic therapy, h (range)		Difference, h (95% CI)	*P Value*
	Pre-PCR	Post-PCR		
S. aureus	23.8 (0.20–74.70)	25.0 (0.50–91.30)	+1.2 (−5.1, 9.8)	>0.1
MRSA	10.7 (0.22–24.72)	14.4 (0.67–36.88)	+3.7 (−1.8, 9.1)	>0.1
MSSA	32.8 (0.27–96.10)	35.1 (0.52–98.48)	+2.3 (−10.5, 15.2)	>0.1
MSSA isolates initially treated with vancomycin monotherapy				
All	55.3 (24.8–74.7)	62.3 (39.2–98.5)	+7.0 (−20.9, 24.9)	>0.1
No PCR performed		57.3 (55.4,59.3)	+2.0	>0.1
Antibiotics optimized after PCR, before C & S		48.4 (39.2–55.8)	−6.9 (−21.6, 7.7)	>0.1
Antibiotics optimized after PCR and C & S		73.7 (44.7–98.5)	+21.4 (3.0, 33.7)	0.02

Frye AM, et al. JCM 2012; 50: 127–33

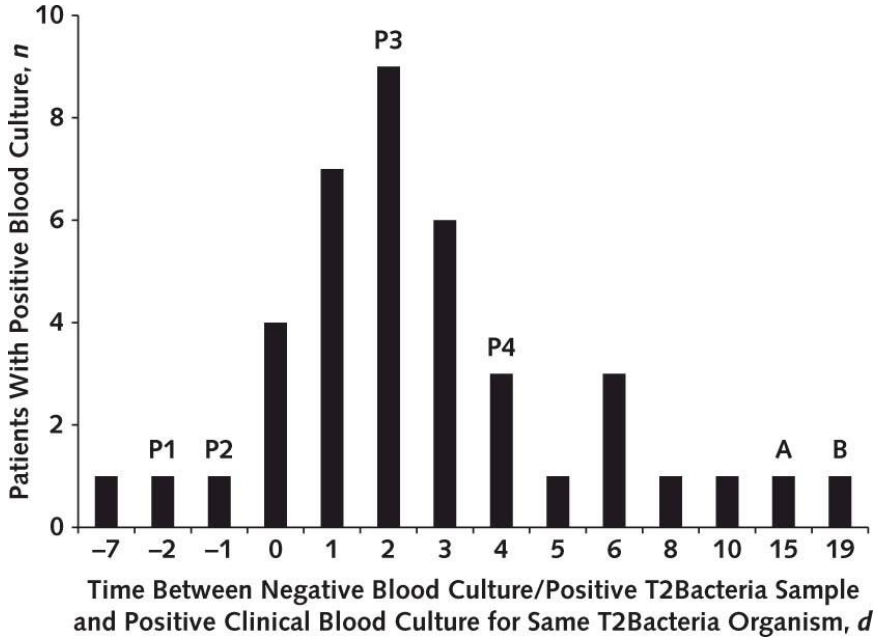
RANDOMIZED CONTROL STUDY

- Single Center
- Used antimicrobial stewardship intervention
- No differences in:
  - Mortality
  - Time to discharge
  - ICU duration of stay
  - Blood culture clearance

Outcome	Control	Rapid Multiplex PCR	Rapid Multiplex PCR + Stewardship	*P* Value Comparing 3 Groups
Duration of therapy[a], h				
Vancomycin				
All patients (n = 357)	44 (22–72)	42 (21–93)	42 (19–90)	.92
Organisms not requiring vancomycin[b] (n = 169)	8.2 (0–26)	0 (0–16)	0 (0–3)[c]	.032
Vancomycin-susceptible enterococci (n = 32)	20 (1–59)	70 (48–88)[c]	82 (40–96)[c]	.037
Methicillin-susceptible *Staphylococcus aureus* (n = 42)	23 (20–53)	11 (0–26)	8 (0–44)	.2
Nafcillin, oxacillin, or cefazolin (n = 50)	42 (24–57)	71 (51–79)[c]	85 (42–92)[c]	.035
Piperacillin-tazobactam (n = 214)	56 (39–82)	44 (27–74)[c]	45 (19–78)[c]	.012
Cefepime (n = 181)	55 (28–96)	71 (43–96)	58 (32–96)	.56
Antibiotic modifications				
Time to first appropriate de-escalation[d] (n = 344)	34 (21–55)	38 (22–66)	21 (7–37)[c,e]	<.0001
Time to first appropriate escalation[f] (n = 122)	24 (3–67)	6 (2–36)	5 (2–22)[c]	.04
Time to administration of active antibiotics (n = 123)[g]	11 (2–51)	6 (2–31)	4 (2–20)	.55
Contaminated blood cultures not treated or treated for <24 h, No. (%)[h]	47 (75)	49 (89)[c]	57 (92)[c]	.015

Banerjee R, et al. Clin Infect Dis 2015; 61.

IMPORTANT TAKE HOME FOR DIRECT DETECTION ASSAYS



Nguyen MH et al. Ann Intern Med. 2019.

SUSCEPTIBILITY TESTING MATTERS!

- Among patients with any infectious & parasitic disease diagnosis

  - Those who had isolates tested for antimicrobial susceptibility had 30% lower probability of death

  - 26% lower mean length of stay (-1.8 days)

  - 36% lower cost than those who did not, $7,524 lower cost per discharge

HOW DOES THE MIC PLAY A ROLE?

- Most laboratories and automated AST systems only perform break point testing
  - Only test dilutions near breakpoint, which does not give a true representation of the MIC and possible treatment regimens
  - MIC data are most useful when considering antibiotic pharmacodynamics because drug exposure is always referenced to the MIC when deciding how much and over what dosing interval to administer an antibiotic.
- The use of broth microdilution or Etest is preferred to collect data on MIC distributions locally (by hospital or by unit) and can also be used for individual patients with MDR infections to help optimize antibiotic therapy, as both of these methodologies will provide for a larger MIC range to be tested.
  - The local MIC distribution can be used to support interventions like increased dosing or prolonged infusion

SUMMARY - WHY IS HOST RESPONSE SO IMPACTFUL?

- Patients at high risk of sepsis are immediately started on appropriate anti-infectives and appropriate resuscitation is initiated
- Patients at moderate risk can use clinical exam plus other lab data to further evaluate risk of sepsis
- Patients at low risk of sepsis
  - Evaluate for other causes of shock (ie cardiogenic, hypovolemic, or obstructive)
  - May be able to defer microbiology testing
- Could be a key screen to improve utility of direct pathogen detection tests
  - No longer concerned about cost of new pathogen detection or AST approach due to low positivity