The Evolving Landscape of Sepsis Diagnosis

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REVIEW ARTICLE

C. Corey Hardin, M.D., Ph.D., *Editor*

Sepsis and Septic Shock

Nuala J. Meyer, M.D., and Hallie C. Prescott, M.D.

KEY POINTS

SEPSIS AND SEPTIC SHOCK

- Sepsis is a syndrome of life-threatening acute organ dysfunction due to bacterial, fungal, parasitic, or viral infection.
- Factors that affect the risk of sepsis include age, immune status, pathogen virulence, and pathogen burden.
- Sepsis is associated with long-term complications among survivors.
- Biologic features of sepsis include dysregulated inflammation, immunosuppression, and vascular injury.
- Management of sepsis focuses on prompt infection control and hemodynamic resuscitation.
- Research is ongoing to determine whether and how to modulate the host immune response in order to improve outcomes.

N Engl J Med 2024;391:2133-46.
DOI: 10.1056/NEJMra2403213

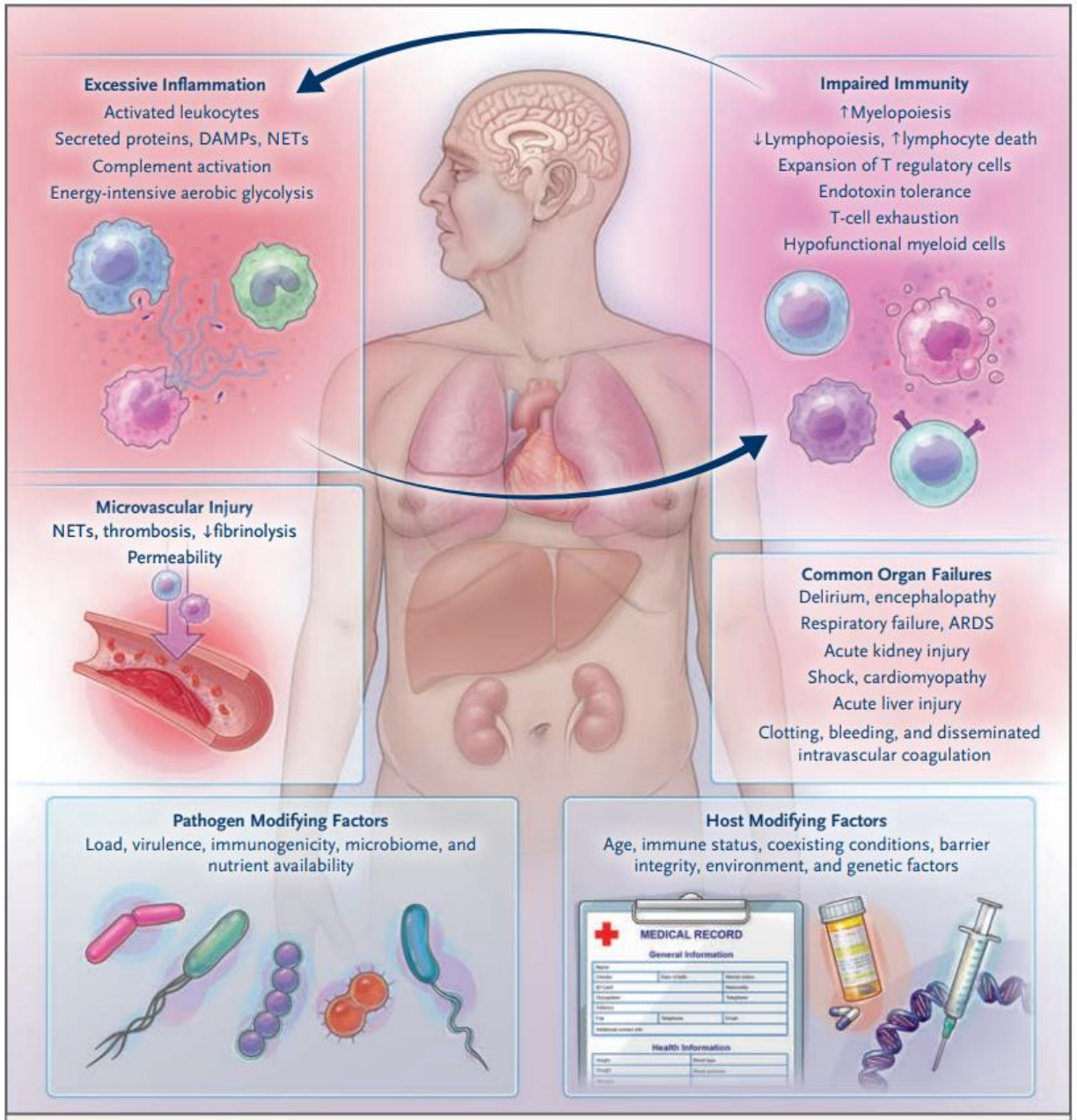
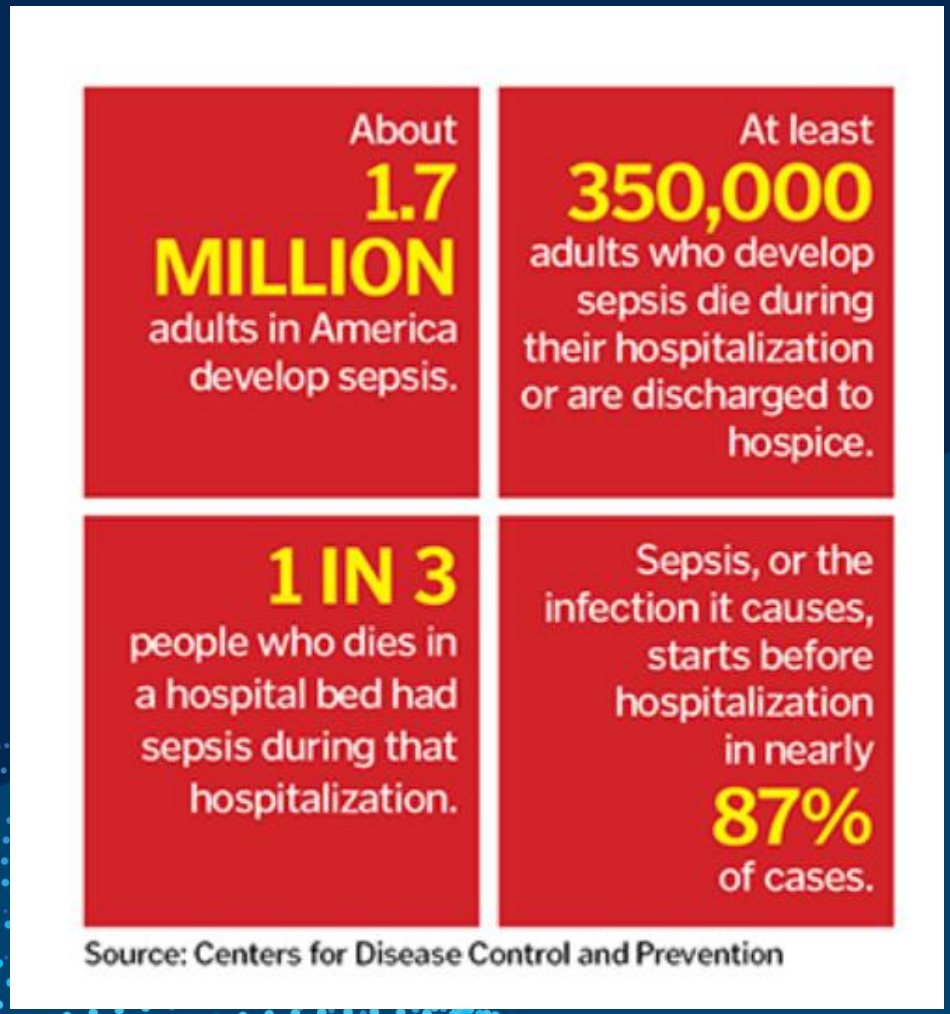


Figure 2. Pathobiology of Sepsis.

Learning Objectives

1. **Identify the key pathophysiologic feature in sepsis diagnosis required to create a successful performance improvement programs**
2. **Evaluate the potential outcomes of elevated diagnostic accuracy in sepsis**
3. **Discuss the neurologic and cardiac complications of sepsis**

Scope of the Problem….



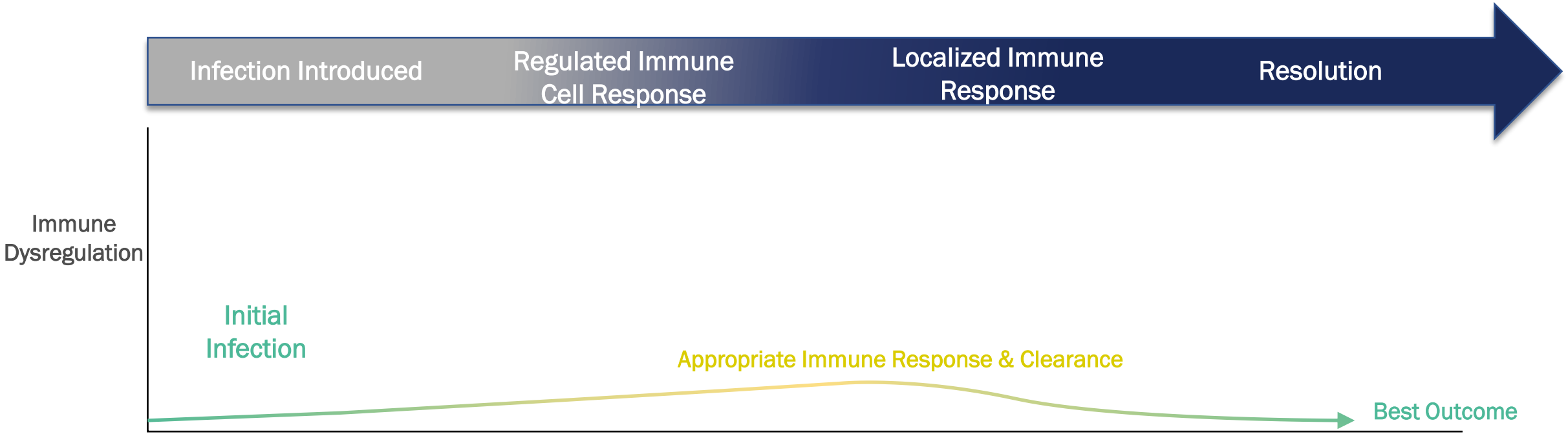
Quality, Patient Safety, and Performance Improvement

Time Sensitive Diseases

- Sepsis
- Cardiac:
  - STEMI and Cardiogenic Shock
- Stroke
- Massive Pulmonary Embolus
- Trauma

Sepsis is Not an Infection

Infections are abundant and are often common, simple nuisances



[1]*Graphic adapted from Prof. Mervyn Singer, ECCMID 2022*

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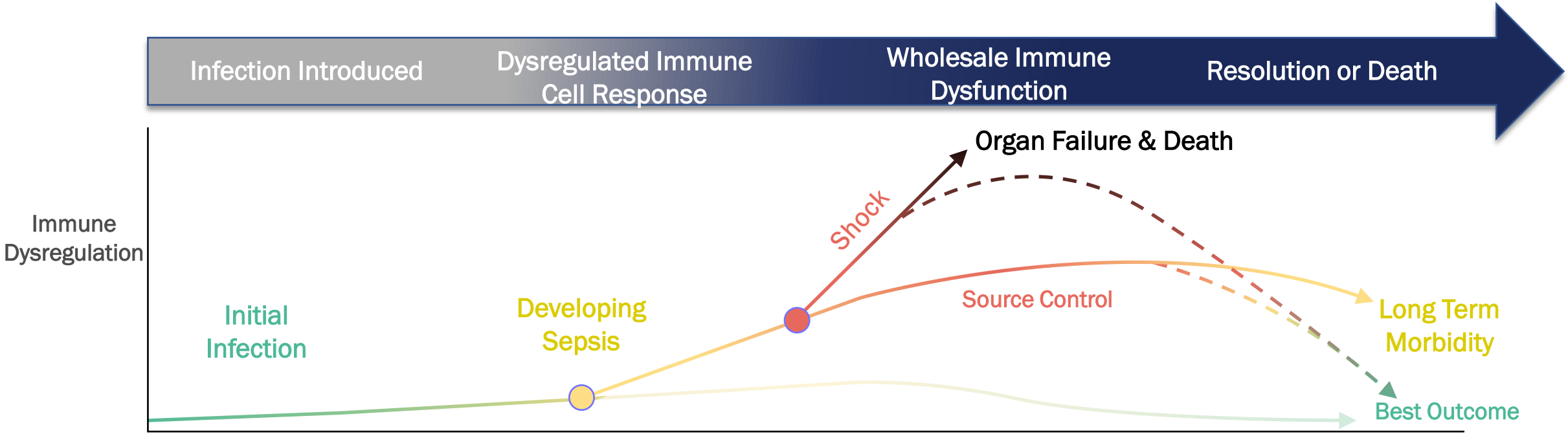
Sepsis is a Dysregulated Immune Response to Infection[1]

This dysregulated immune response makes sepsis a medical emergency



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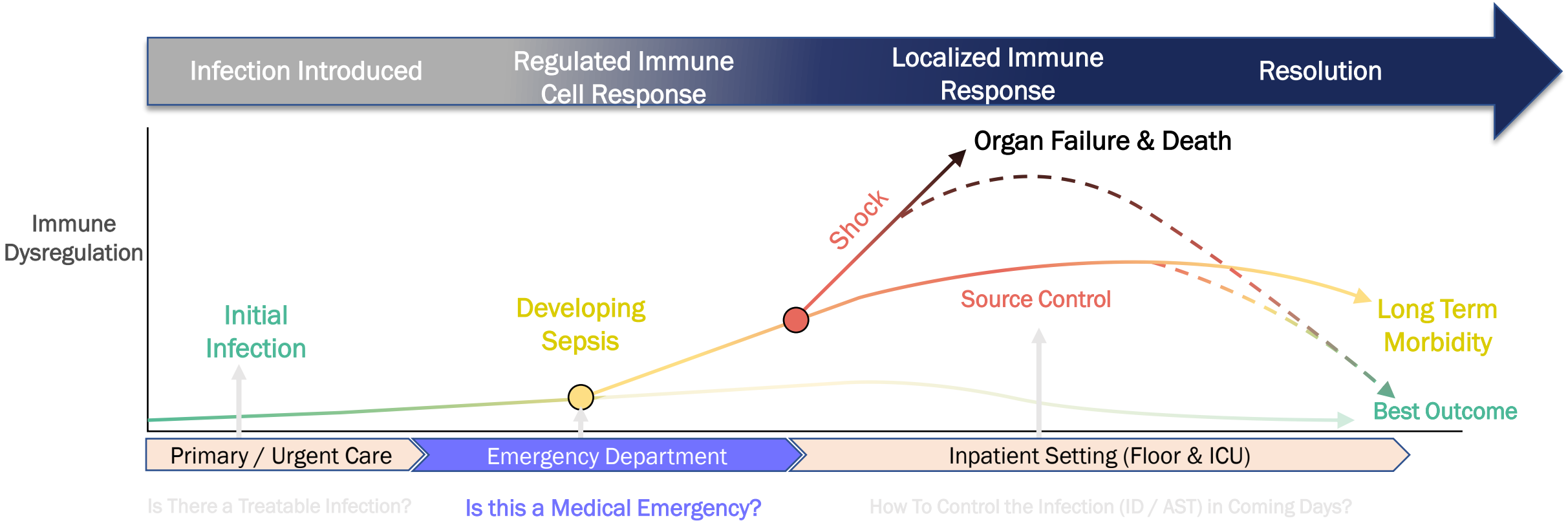

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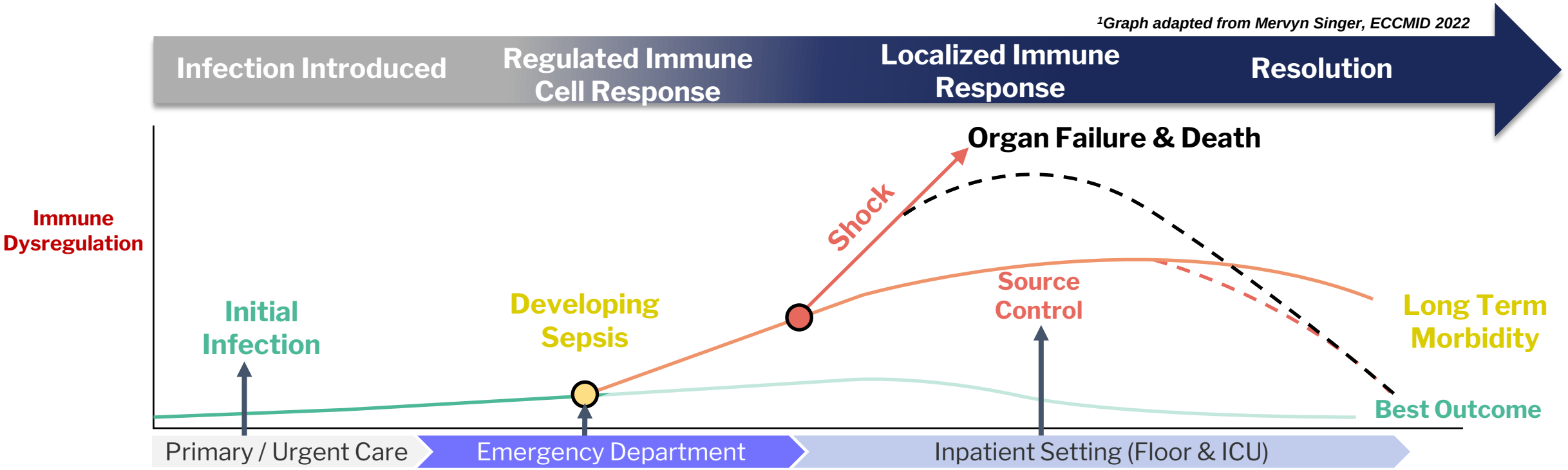
New Technology in the Identification and Treatment of Sepsis

[1]*Graph adapted from Mervyn Singer, ECCMID 2022*



Key Question

Is There a Treatable Infection?

MeMed

Is this a Medical Emergency?

Cytovale

TriVerity™

How To Treat the Infection after admission

T2Biosystems · BIOFIRE · SPECIFIC · KARIUS · ACCELERATE DIAGNOSTICS · BD · BRUKER

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Challenge of Potentially Infected Patients in the ED

>80% of Sepsis Patients Present to the ED

Challenging Situation for ED

However, sepsis patients are masked by a much larger cohort of suspected infection patients

ED Quandary

Limited Information
+
Limited Time

Under Diagnosis & Missed Treatment

- Rapid clinical deterioration/ risks of organ damage
- Potential for readmission
- Quality metrics -> reimbursement

Over Diagnosis & Over Treatment

- Increased costs/resource utilization
- ED Throughput
- Antimicrobial Stewardship

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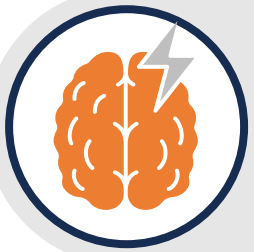
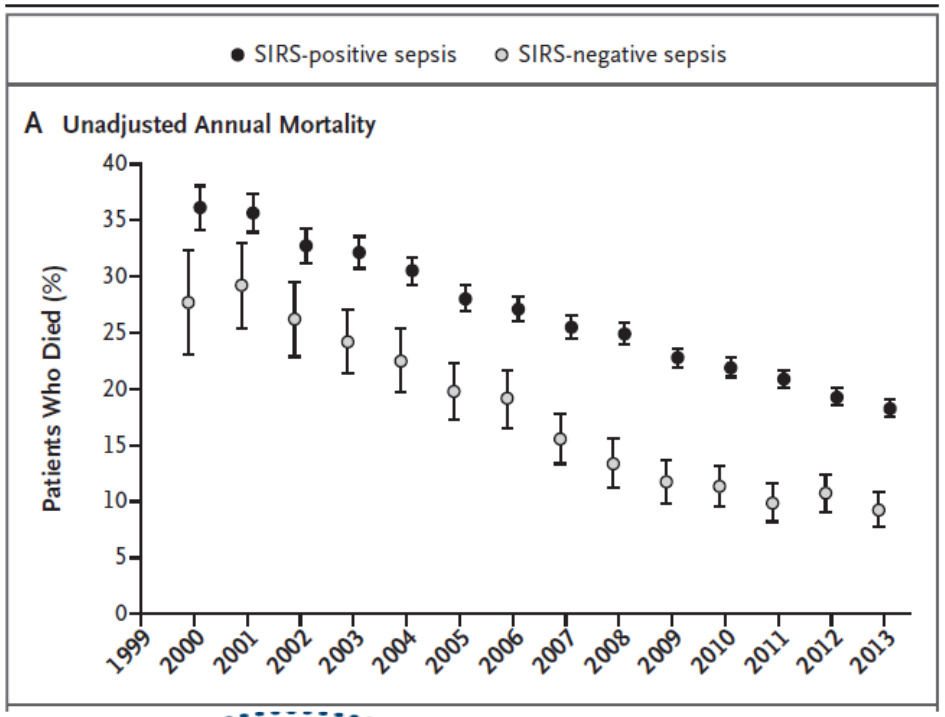
Protocolized Care In Time Sensitive Diseases

TIME SENSITIVE MEDICAL EMERGENCY		Outcome Predictor	Technology Advance Dx	Technology Advance Tx		Benefit	Resources
HEART ATTACK		7.5% Mortality increase for every 30-minute delay	Troponin ECG	Angioplasty	Protocolized Application	↓ Mortality 30% ↓ Costs 35%	Cath Lab On Call Cardi POC ECG/Troponin
STROKE		Significant Morbidity & Mortality beyond 4h	CT Scanning in ED	Clot Retrieval Coils TPA	Protocolized Application	↓ Mortality 10% ↓ LOS 24% ↓ Costs 27%	ED CT Scan Cath Lab On Call INR
SEPSIS		8% Mortality increase for every hour of delay in shock		Rapid Antibiotics & Fluids	SEP-1 Structure	Mortality Resources LOS ED Disposition	

SIRS negative sepsis

All Patients	Patients with SIRS-Positive Sepsis	Patients with SIRS-Negative Sepsis	P Value
no. of patients with data	*no. of patients with data*	*no. of patients with data*	
109,663	96,385	13,278	<0.001



Application of the 2 SIRS criteria to severe sepsis definition will miss 1 in 8 patients

Kaukonen, K. et al. Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis. N Engl J Med 2015;372:1629-1638

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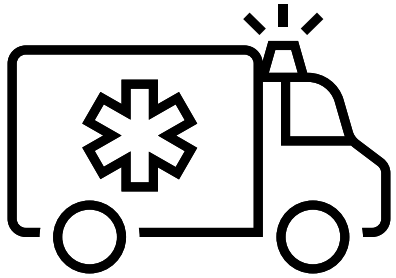
The Potential for Diagnostic Anchoring and Diagnostic Error Driven by Screening without Forced Equipoise



ED Sepsis Screen

SIRS or qSOFA

NEWS2

High Risk

Treatment

Disposition

Metric Police

- -Fluids
- -Antibiotic
- -Arbiter of Mortality in Sepsis

Clinical Assumption: The above process results in efficiency, lives saved, zero harm, and represents best practice.

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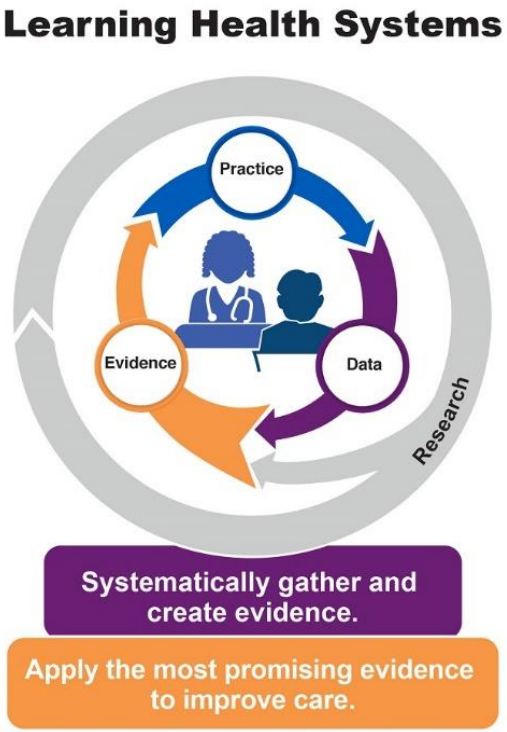
Sepsis Learning Health Initiative

“Be willing to innovate towards doing the right thing” -Sister Helen Cahill

Following the COVID-19 pandemic, FMOLHS developed a sepsis learning health initiative to prepare for the future. The goal of the project was to ensure that patients with potential sepsis received the highest level of care. This goal was achieved through a process of implementation of specific aspects of care, continual evaluation of interventions and outcomes, and modification of process as appropriate. FMOLHS was first system in the United States to broadly adopt early diagnostics into core evaluation of sepsis in 2024 after initial site implementation starting in August 2023



Our Lady of the Lake Health

Our Lady of Lourdes Health

St. Francis Health

St. Dominic's

&

IntelliSep

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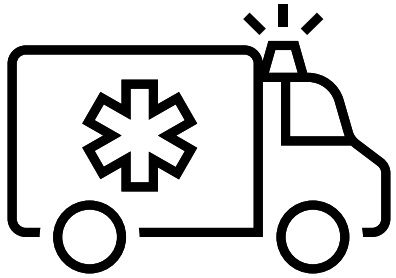
The Potential for Diagnostic Anchoring and Diagnostic Error Driven by Screening without Forced Equipoise



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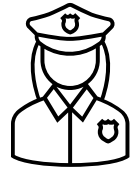

Metric Police

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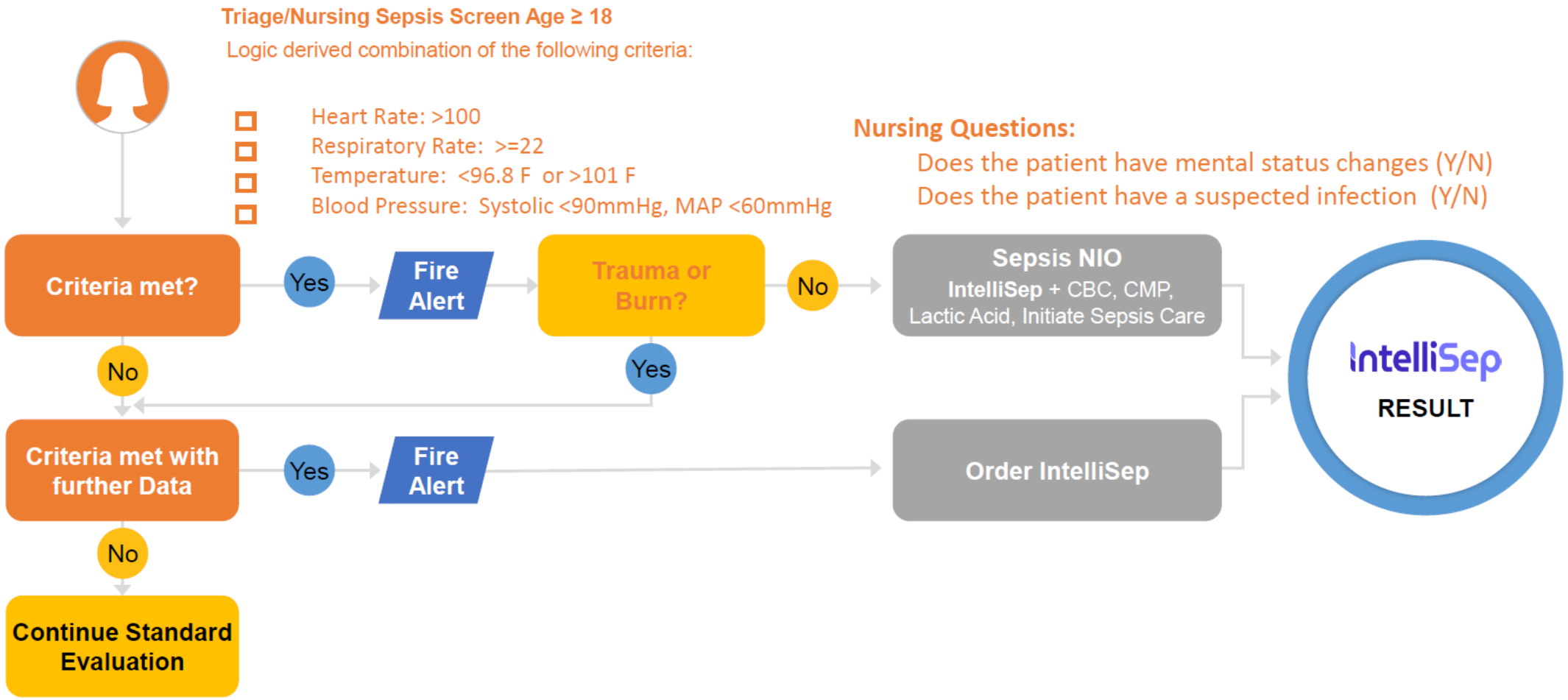
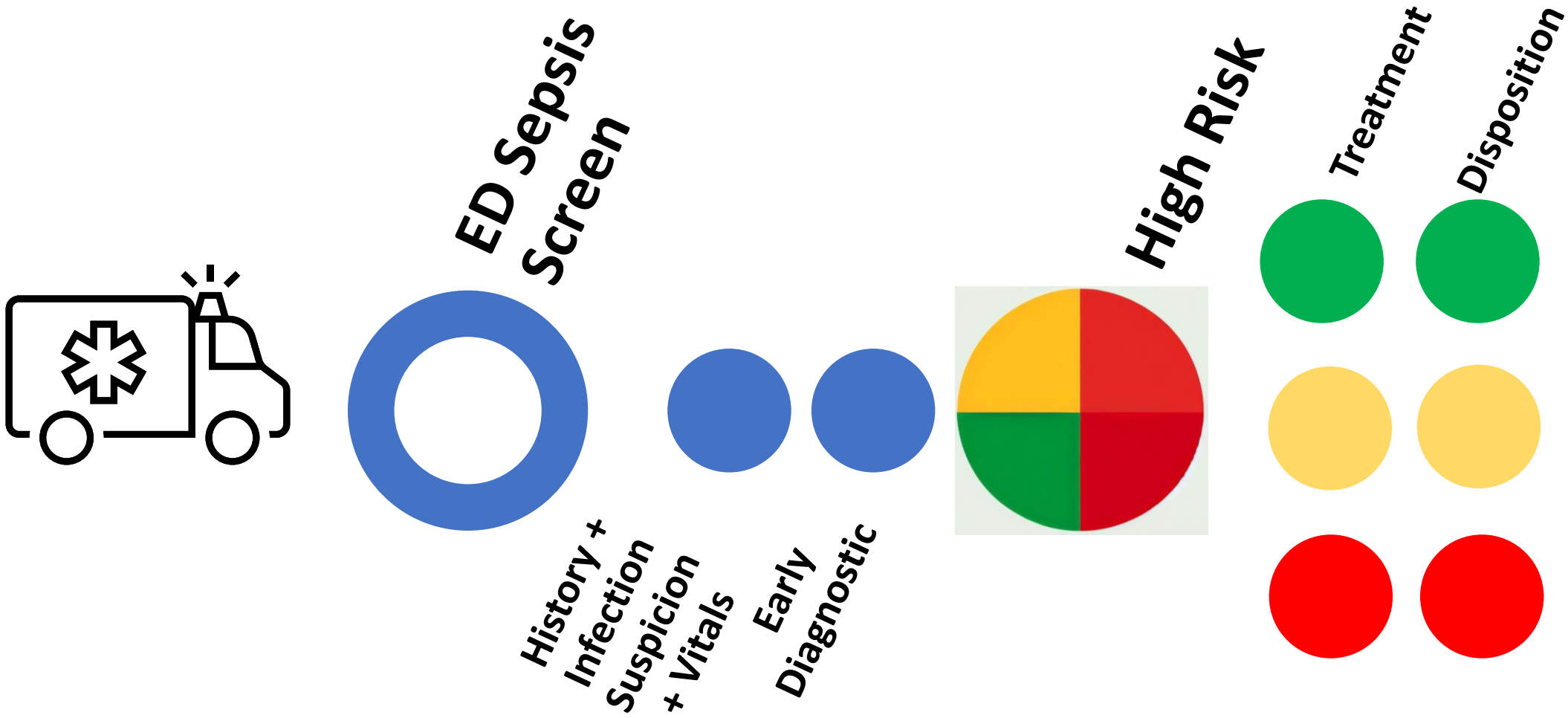
FMOLHS Novel Sepsis Workflow in the Emergency Department



Creating Diagnostic Equipoise based on Objective Evaluation of the Host Response



Equipoise created by an early diagnostic allow for accurate diagnosis and best practice treatment

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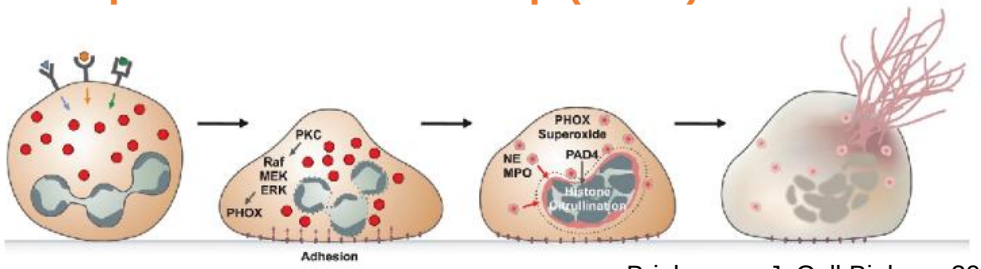
IntelliSep Analyzes White Blood Cells to Assess Immune Activation

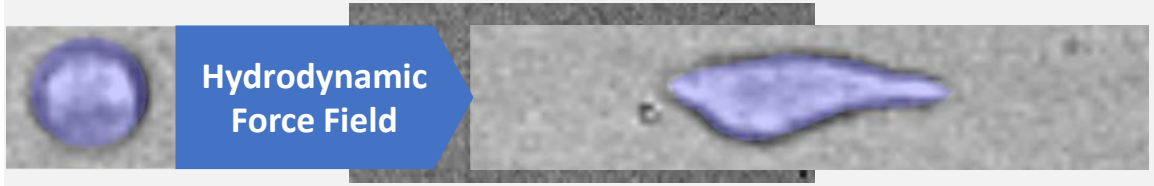
The dysregulated host response in sepsis results in broad activation of circulating leukocytes, upregulated transcriptional activity, and chromatin decondensation

Neutrophil Extracellular Trap (NETs) Formation

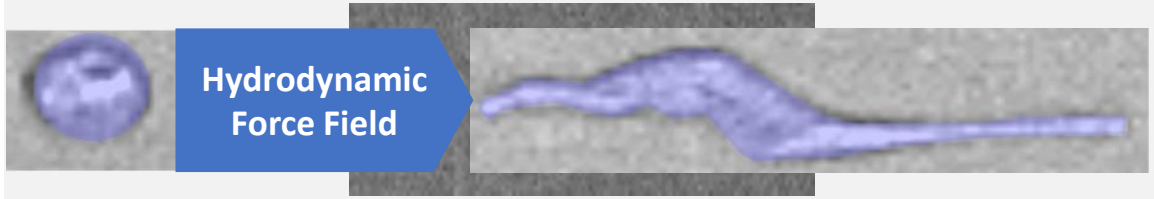


Brinkmann, J. Cell Biology, 2012

White blood cells from a non-septic patient

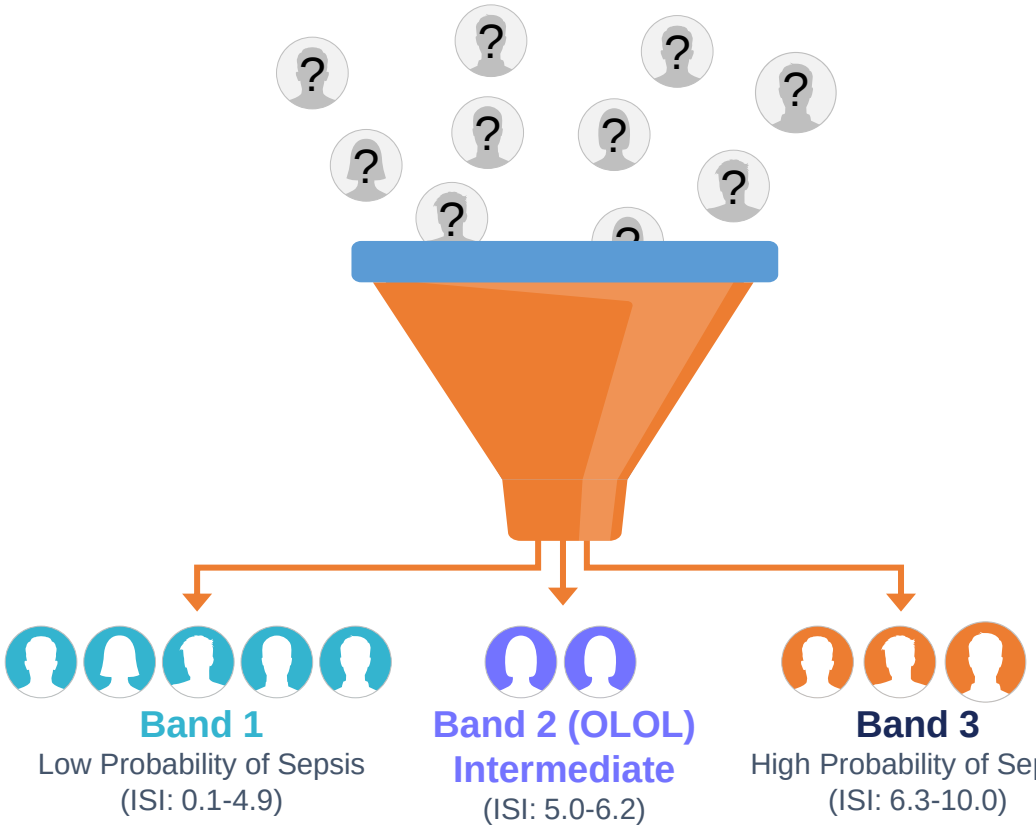


White blood cells from a septic patient



The IntelliSep© Index

Full ISI Range: 0.1-10.0



Band 1
Low Probability of Sepsis
(ISI: 0.1-4.9)

Band 2 (OLOL)
Intermediate
(ISI: 5.0-6.2)

Band 3
High Probability of Sepsis
(ISI: 6.3-10.0)

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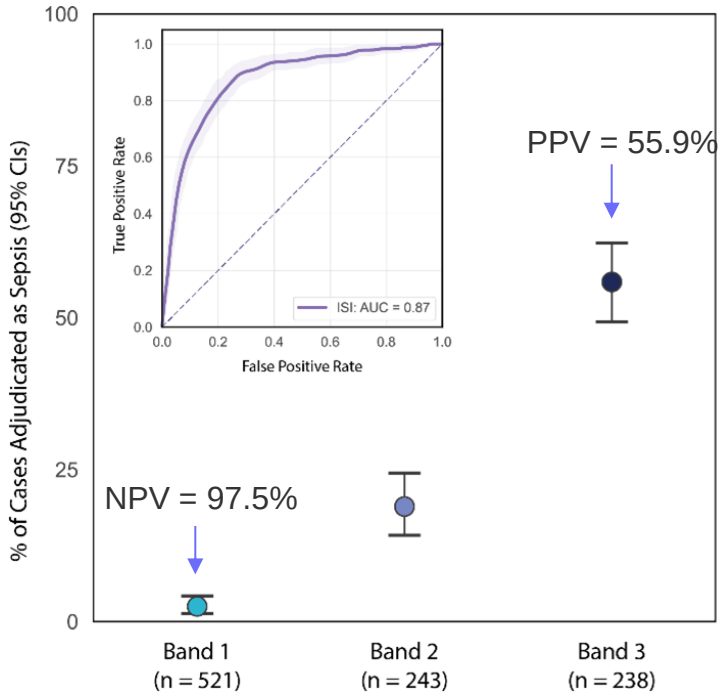
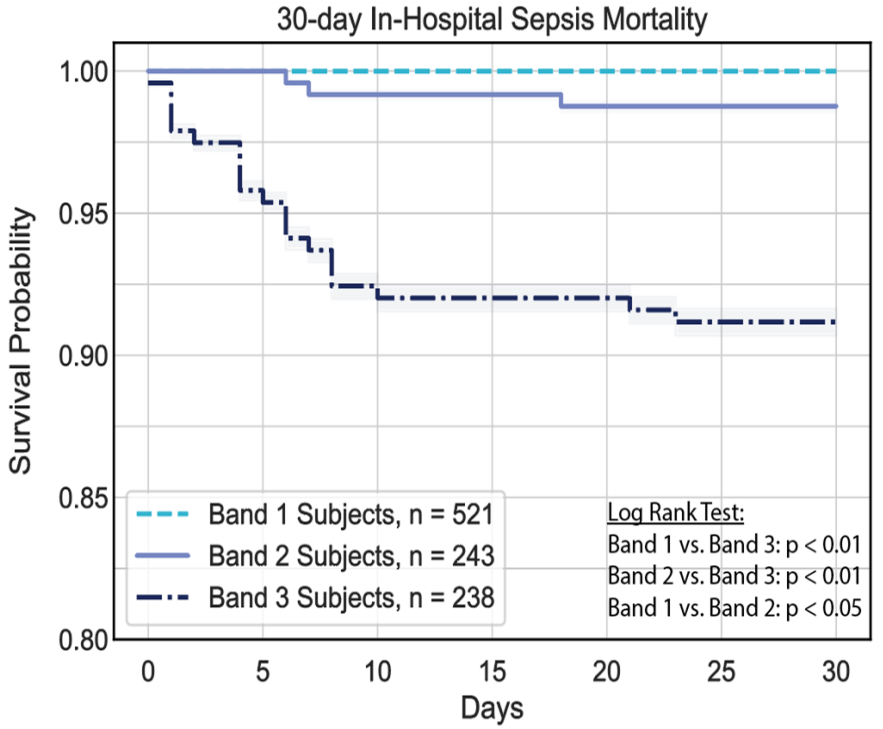
Consolidated Test Performance Across All Studies (n = 1002)[1]





Performance Characteristics - Value (95% CI)	
Population Size	**1002**
Sepsis Prevalence [%]	**19.2%**
AUC	**0.87** (0.84 – 0.90)
Positive Percent Agreement (sensitivity): Band 1 vs. else	**93.2** (88.7 – 96.3)
Negative Percent Agreement (specificity): Band 3 vs. else	**87.0** (81.4 – 91.4)
Negative Predictive Value (NPV): Band 1 vs. else	**97.5** (94.0 – 99.1)
Positive Predictive Value (PPV): Band 3 vs. else	**55.9** (48.4 – 62.9)
LR+	**5.34**
LR- (1/LR-)	**0.11 (9.1)**

Prior clinical study results demonstrated utility of IntelliSep comparable to standard assays for ACS:

Performance Highlights	IntelliSep Test[1] for Sepsis	ECG[2,3] for ACS	Troponin[4,5] for ACS
Negative Predictive Value (NPV) 'Rule Out' Performance	97.5%	94%-98%	98%-100%
Positive Predictive Value (PPV) 'Rule In' Performance	55.9%	46-50%	15%-66%

1. O'Neal HR Jr, et al. "Cellular host response sepsis test for risk stratification of patients in the emergency department: A pooled analysis." *Academic Emergency Medicine*. 2024 doi:10.1111/acem.14923. PMID 38643433

[2] *Fitzpatrick et.al. Am J Em Med 2022.*
[3] *Bjork et.al. BMC 2006*
[4] *Orji et.al. Cureus 2023*
[5] *Lowry et.al EHJ 2023*

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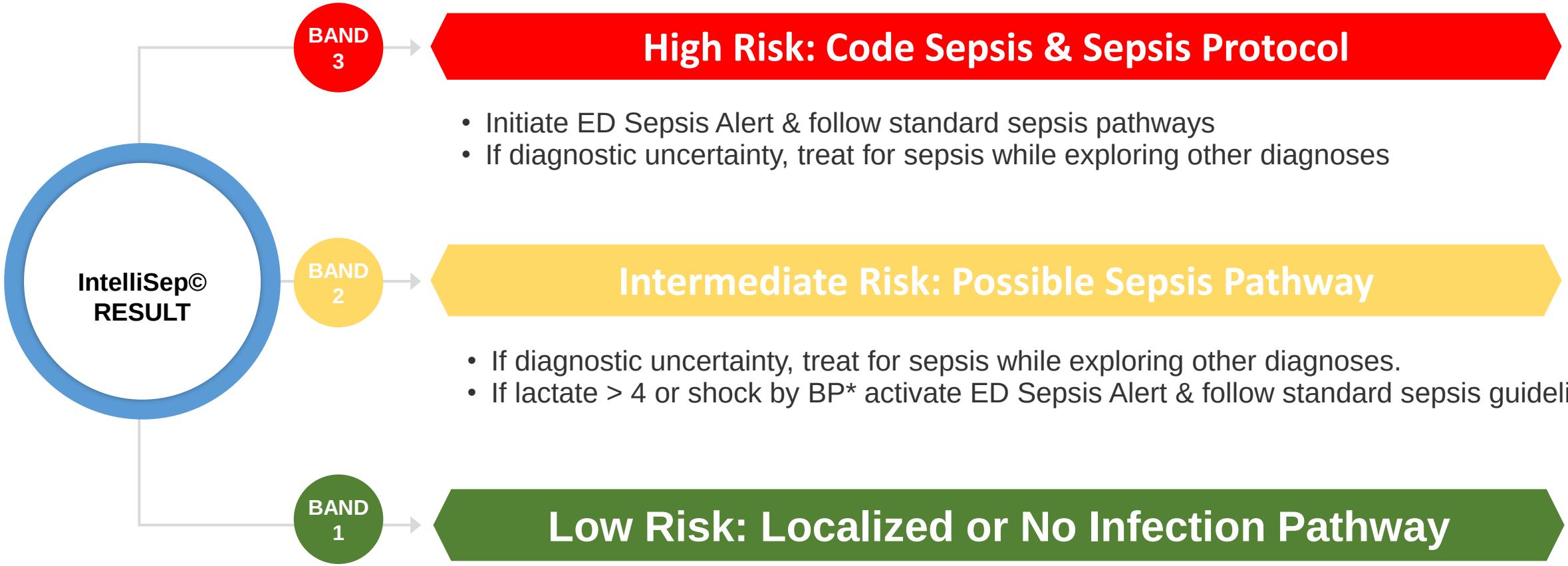
FMOLHS Diagnostic Results & Clinical Interpretation



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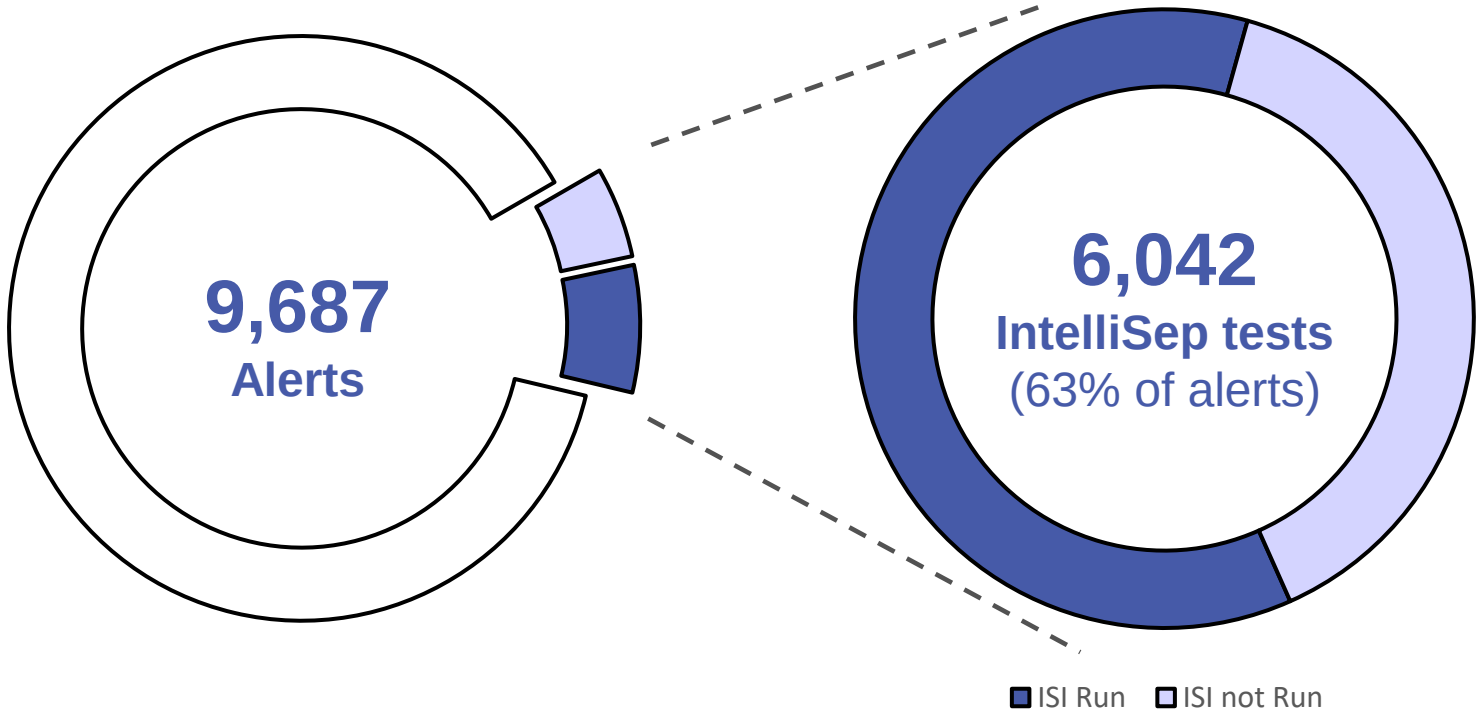
Protocolized Evaluation of at Risk Patients

Between August 2023 and July 2024:

- The alert in-response to the triage nursing sepsis screen fired on **13% of all ER presentations** (9.6K of 76K)
  - 63% of these patients **received an IntelliSep test** (6K tests total)



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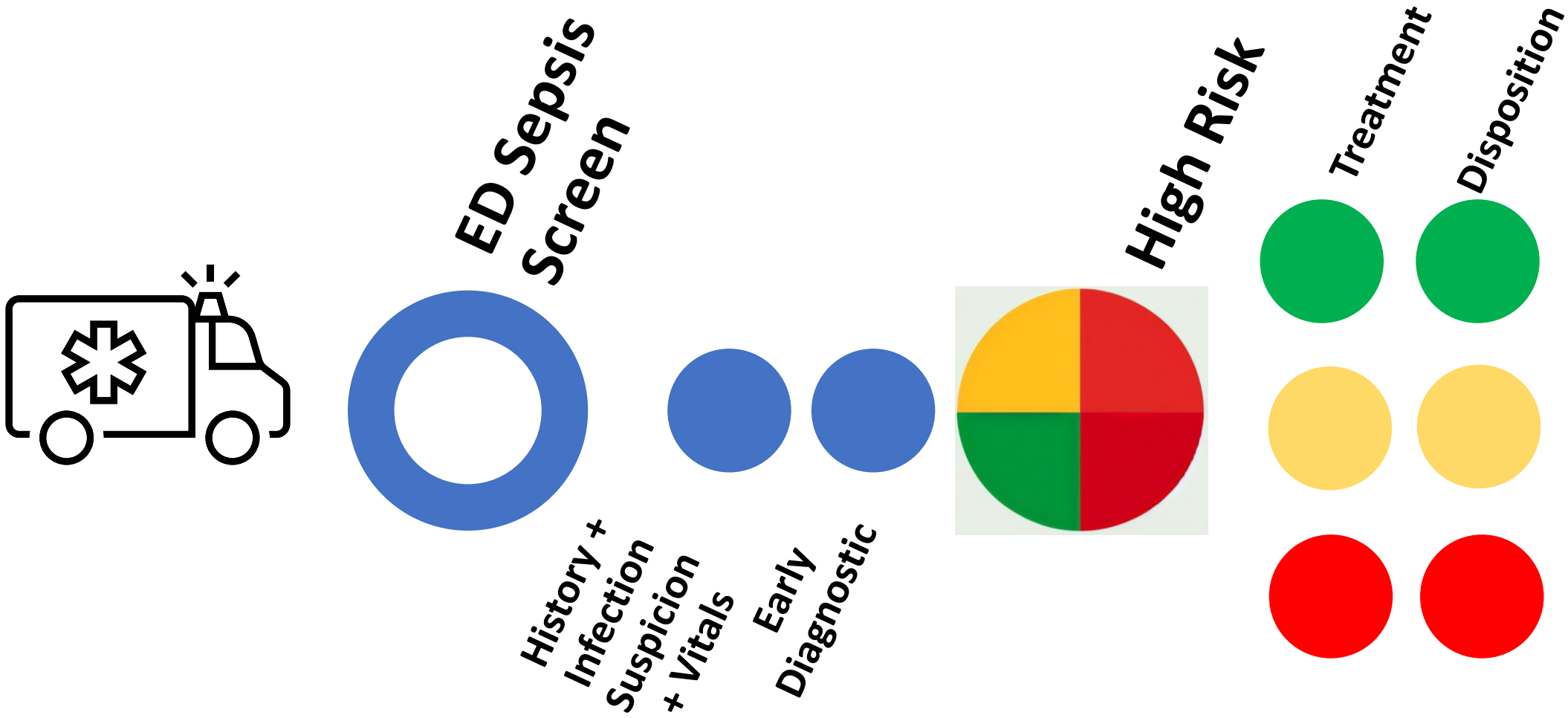
Creating Diagnostic Equipoise based on Objective Evaluation of the Host Response



Equipoise created by an early diagnostic allow for accurate diagnosis and best practice treatment

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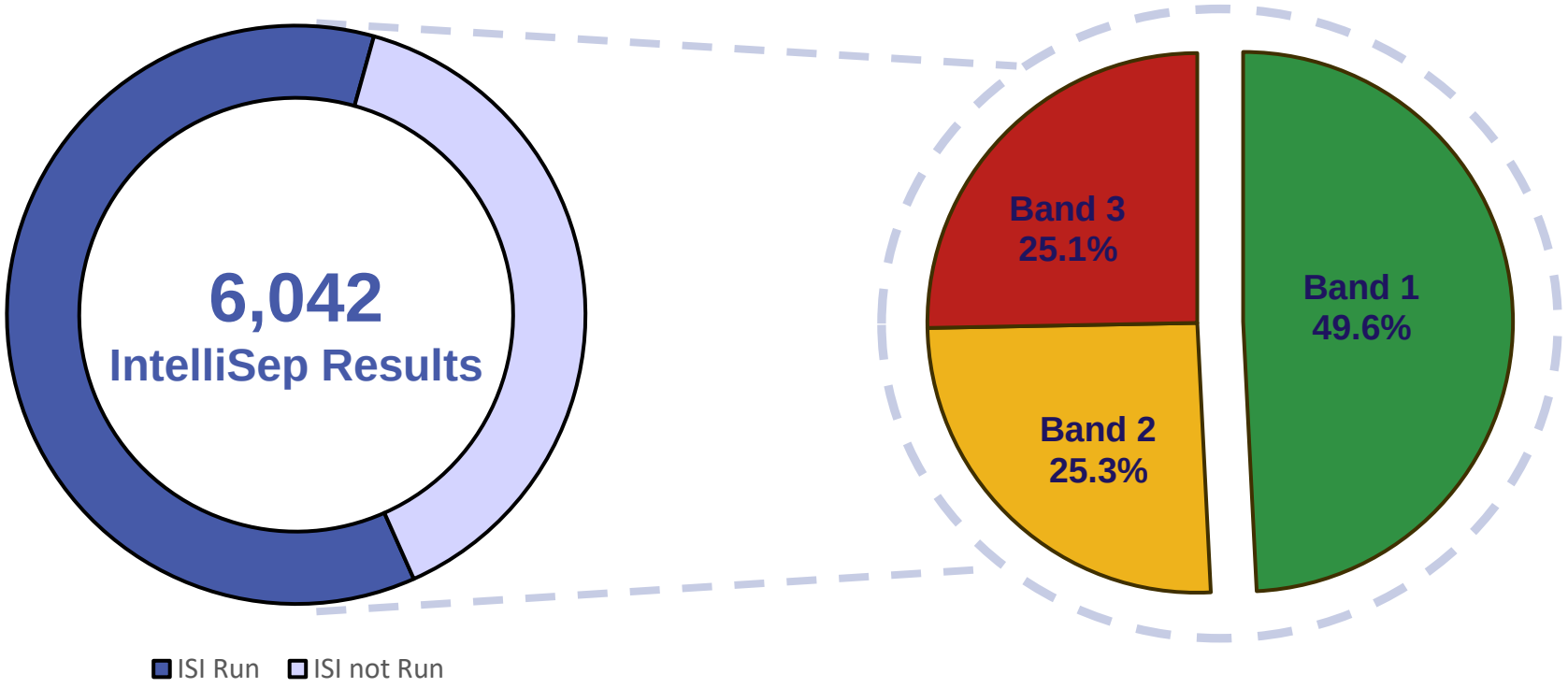
Distribution of Patients Across IntelliSep Interpretation Bands



Orderset compliance increased and stabilized within 3-4 months of implementation

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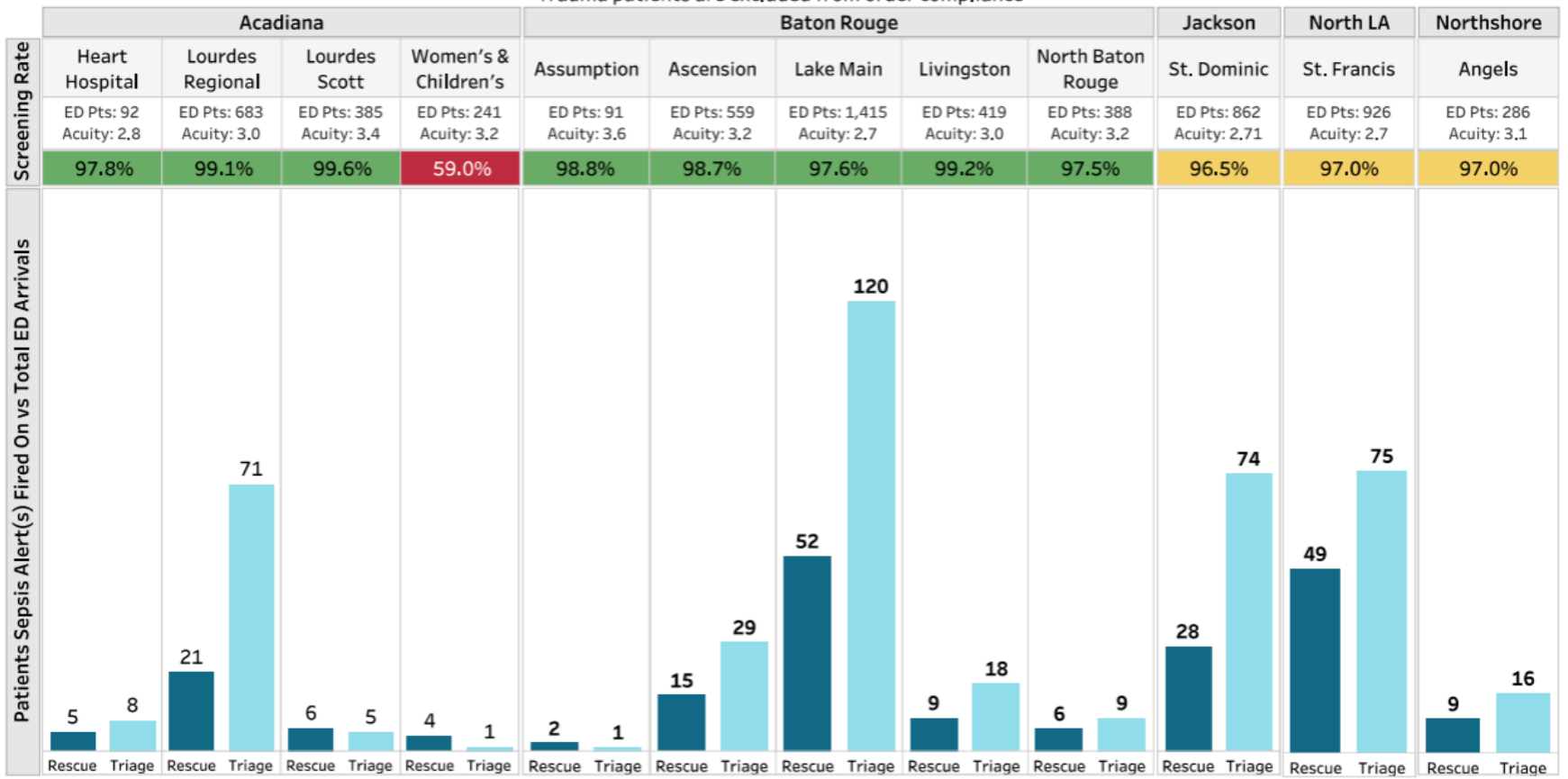
FMOL Health System Emergency Departments - Week of November 24, 2024

Emergency Department Arrivals, Average Patient Acuity, Sepsis Triage Screening Completion and Sepsis Alerts

Trauma patients are excluded from order compliance



The Epic Rescue Alert fires to providers when a patient has an Early Detection of Sepsis Score of 6 or greater, & the order for Initiate Sepsis Care has not been placed. The Sepsis Triage Alert fires to nuring when various criteria (abnormal vital signs, Sepsis Triage Screening, etc.) are met at any point of the patient's ED stay.

Data Source: Sepsis Performance Improvement Chart Abstraction & Epic Reporting

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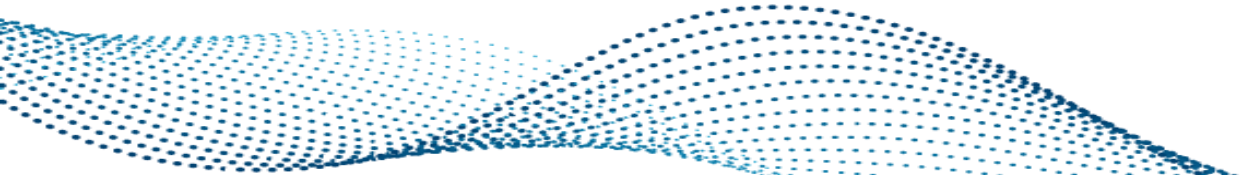
Evaluating the Impact Innovation and Execution



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IntelliSep Financial & LOS Impact

- Pre (n = 196) and post (n=413)implementation comparison conducted
- Average cost of care **reduction of $1429** per patient tested

Early Results

The fiscal impact of a rapid sepsis diagnostic in the Emergency Department (ED)

Authors: Christopher B. Thomas[1, 3], Claude Dantonio[2], Alyse Hollis[2], Kristen Richard[2], Lindsey Booty[2], Tonya Jagneaux[2,3], Mark Laperouse[2,3], LeaAnn Teague[2], Christi Pierce[2], Hollis O'Neal Jr.[1,2.3]

Affiliations:

1. Franciscan Missionaries of Our Lady Health System, Baton Rouge, LA, United States
2. Our Lady of the Lake Regional Medical Center, Baton Rouge, LA, United States
3. LSU Health Science Center: Baton Rouge Campus, Baton Rouge, LA, United States

ISICEM

43rd ISICEM INTERNATIONAL SYMPOSIUM ON INTENSIVE CARE & EMERGENCY MEDICINE

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

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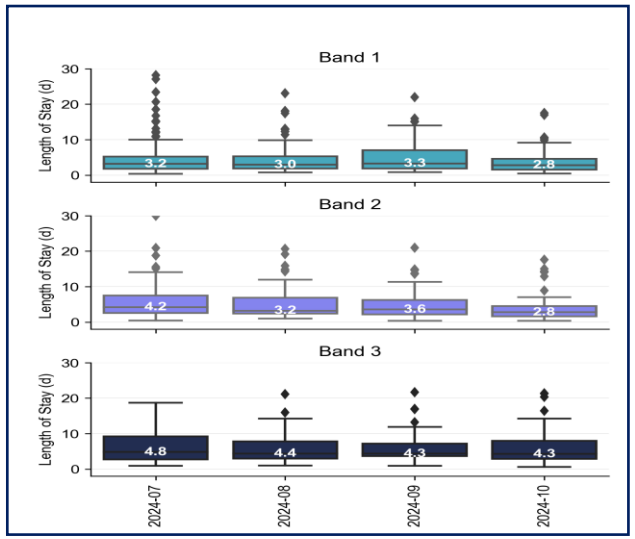
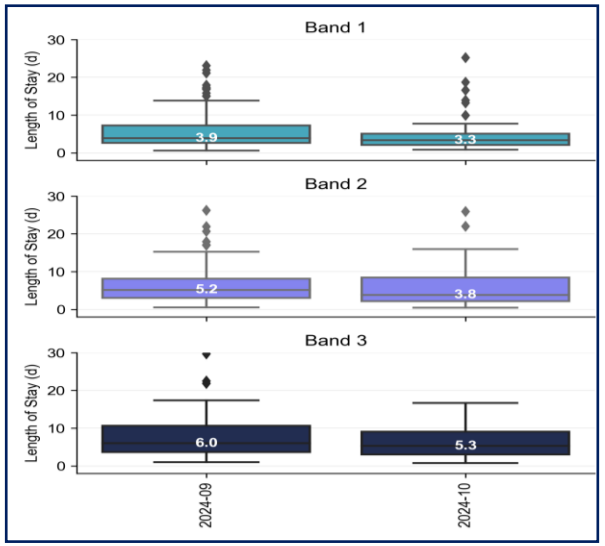
Hospital Length of Stay

Overall Reduction in LOS at 1 year:
Average LOS (1 Day) and Median LOS (1 Day)

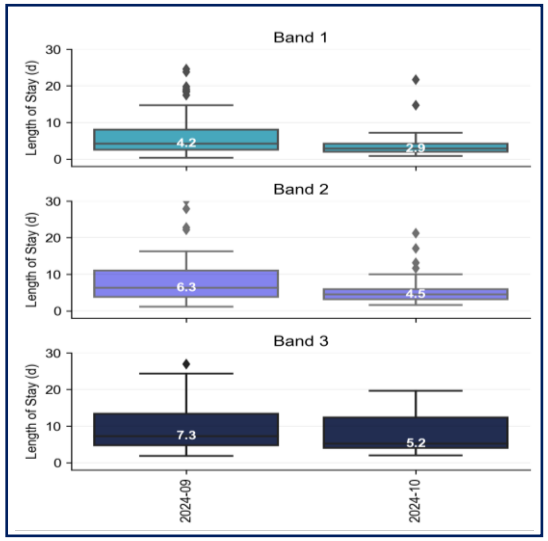
Baton Rouge Market



St. Dominic



St. Francis



Band 1
Band 2
Band 3

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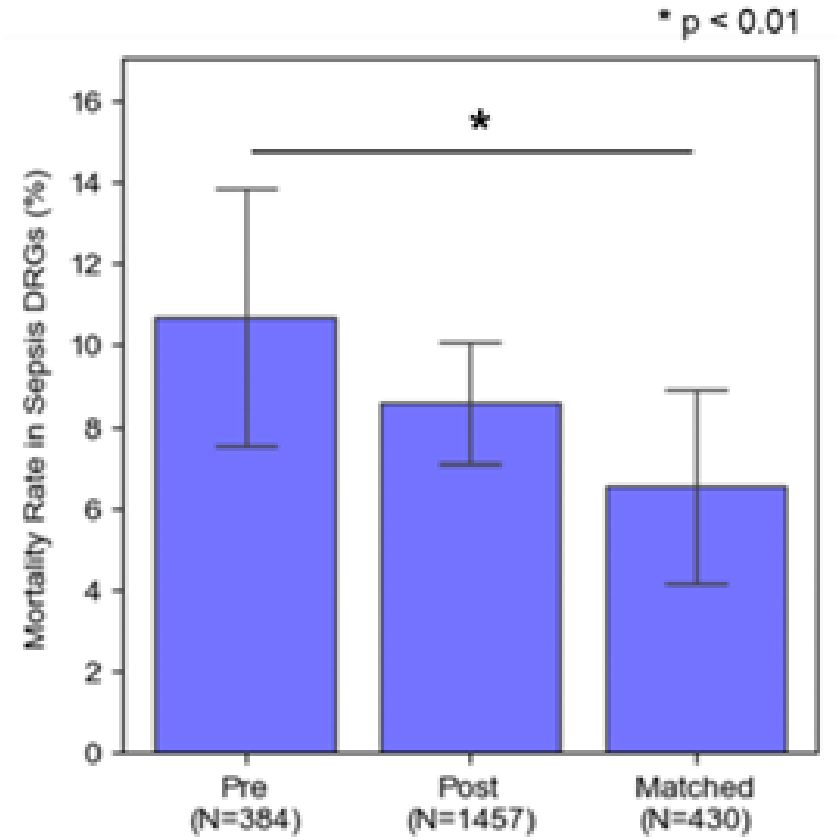
Sepsis Absolute Mortality Reduction



Number Needed to Test: 110

Number Needed to Treat (Post): 43

Number Needed to Treat (Matched): 23

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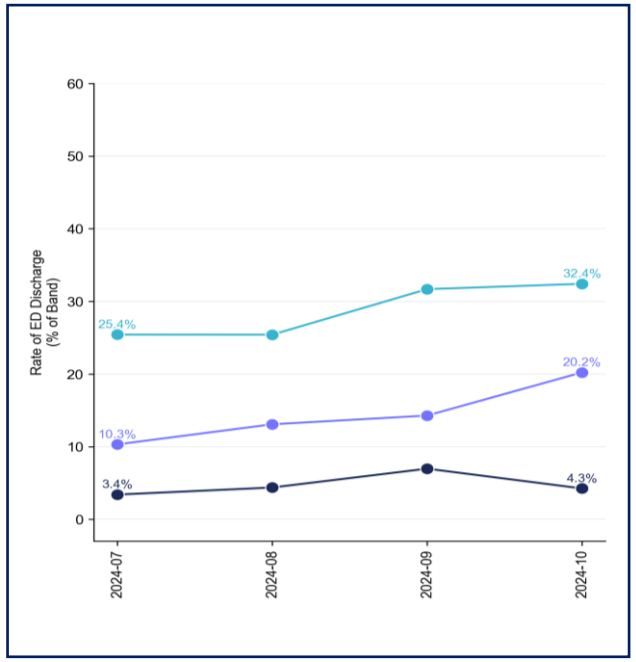
Rate of ED Discharge in Suspected Patients

Baton Rouge Market
Baseline Whole Population
17%



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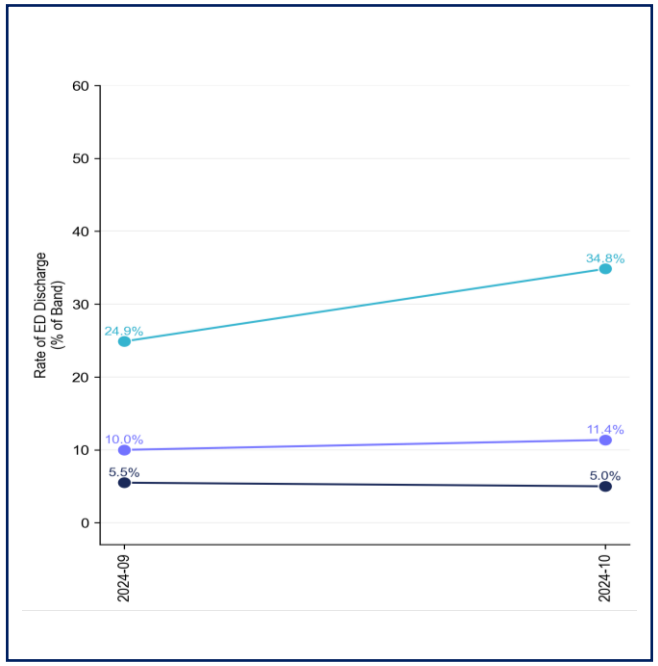

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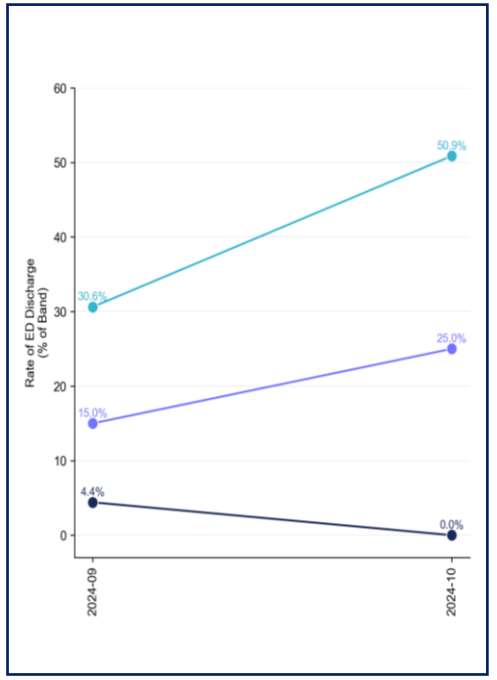

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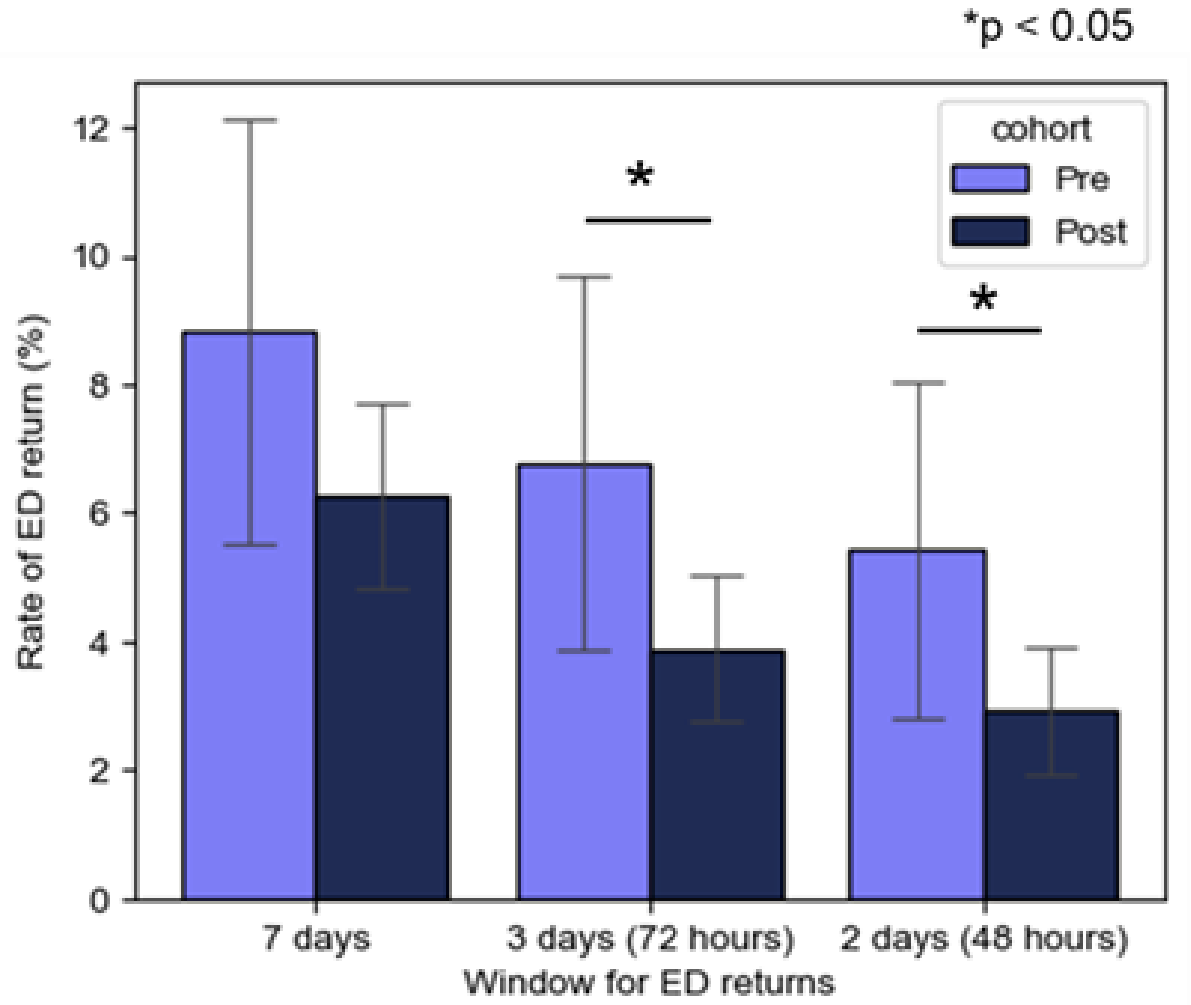
ED Revisits



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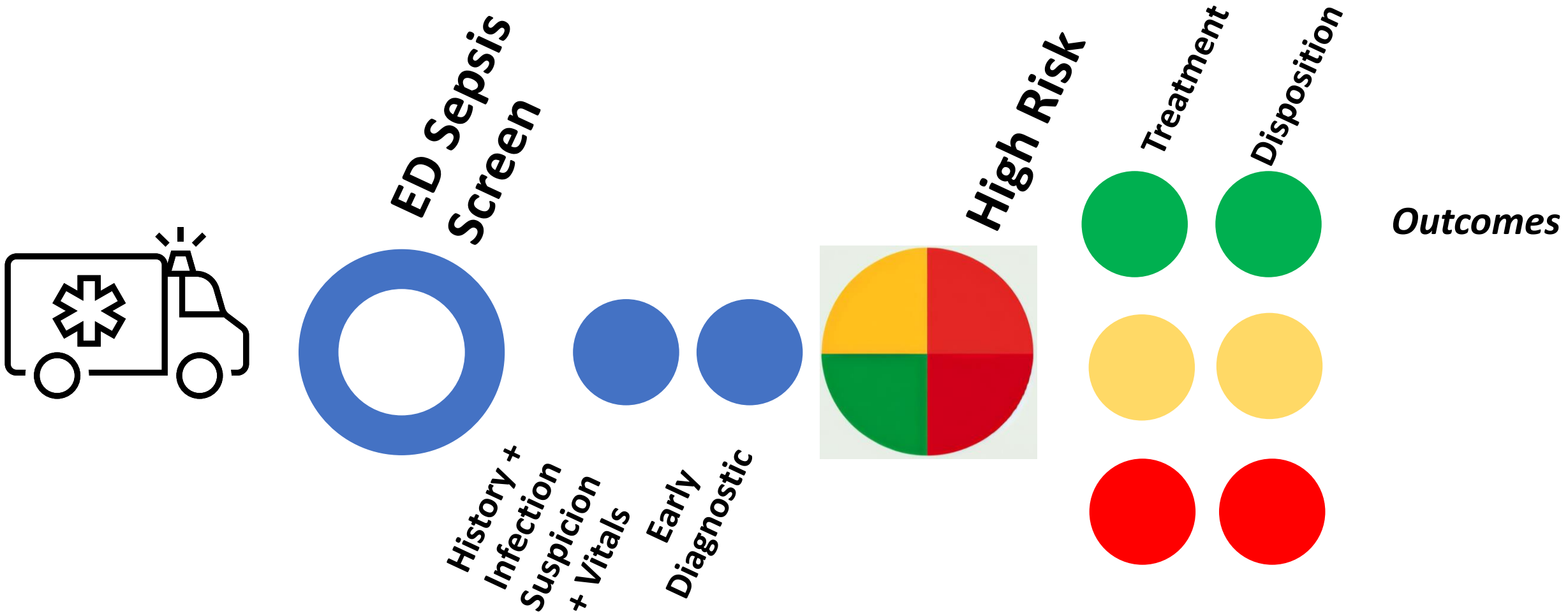
Creating Diagnostic Equipoise based on Objective Evaluation of the Host Response



Equipoise created by an early diagnostic allow for accurate diagnosis and best practice treatment

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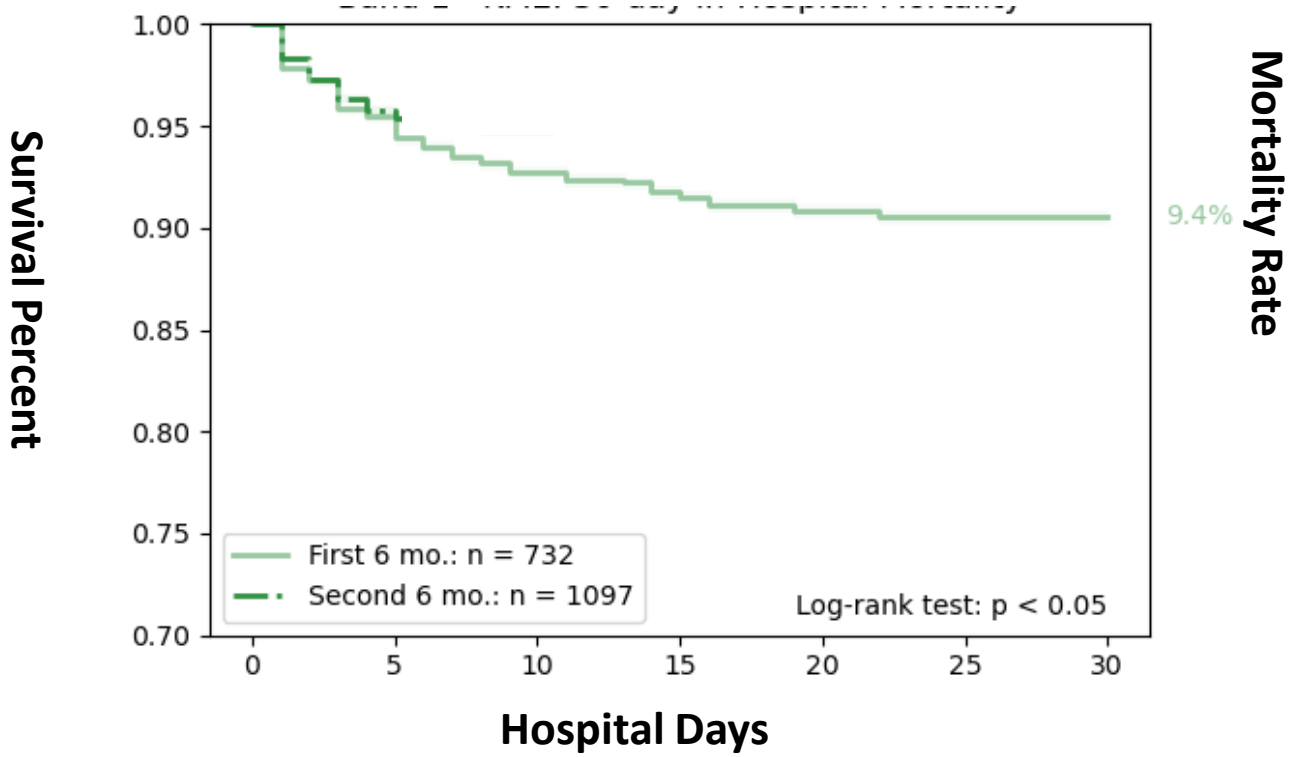
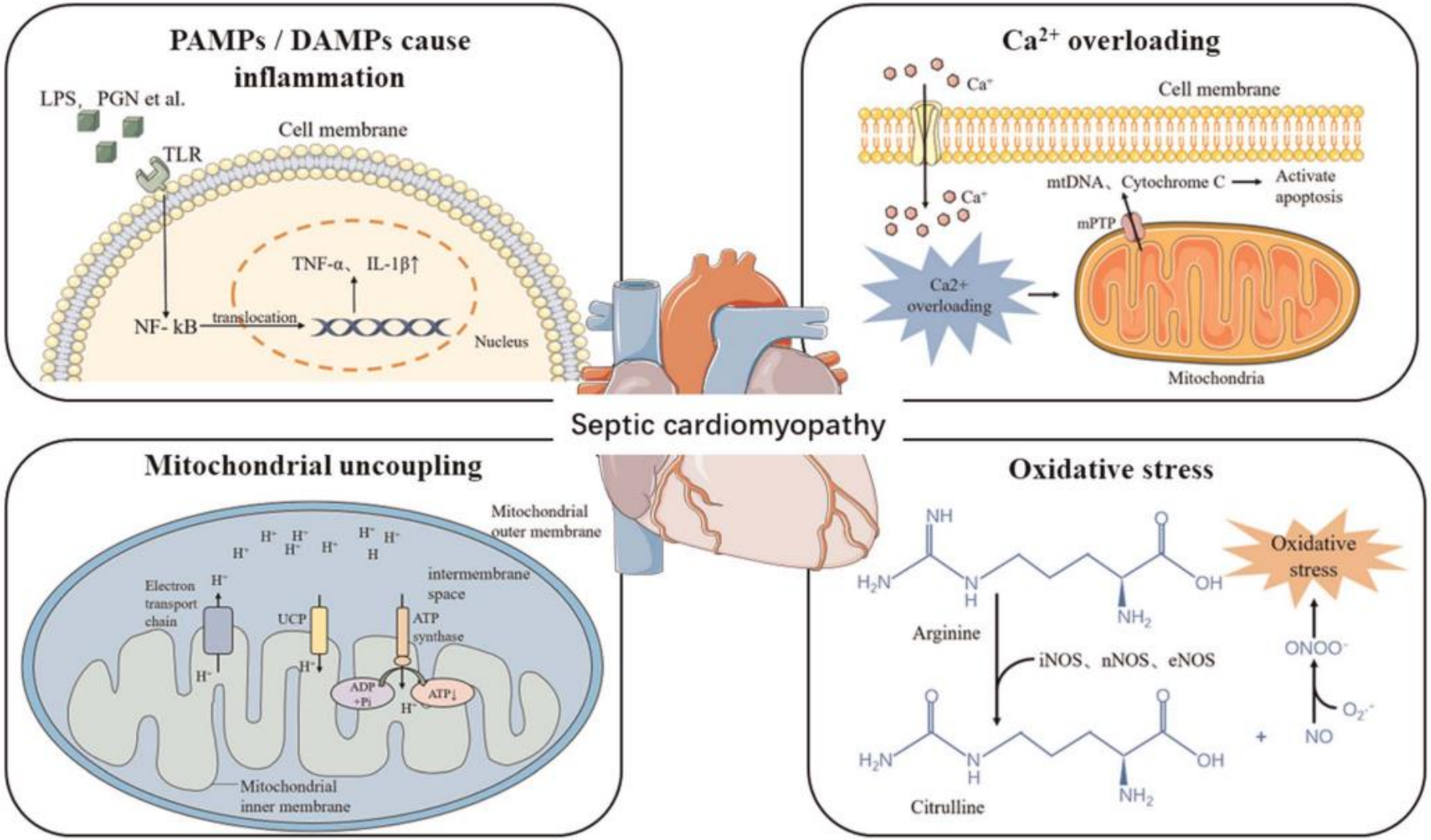
Patients Without Sepsis
30 Day In-Hospital Mortality



The Connection to Cardiology and Neurology Post Accurate Diagnosis

Septic Induced Cardiomyopathy



Xue, W. Septic cardiomyopathy: characteristics, evaluation, and mechanism. *Emergency and Critical Care Medicine* 2(3):p 135-147, September 2022. | *DOI:* 10.1097/EC9.0000000000000006

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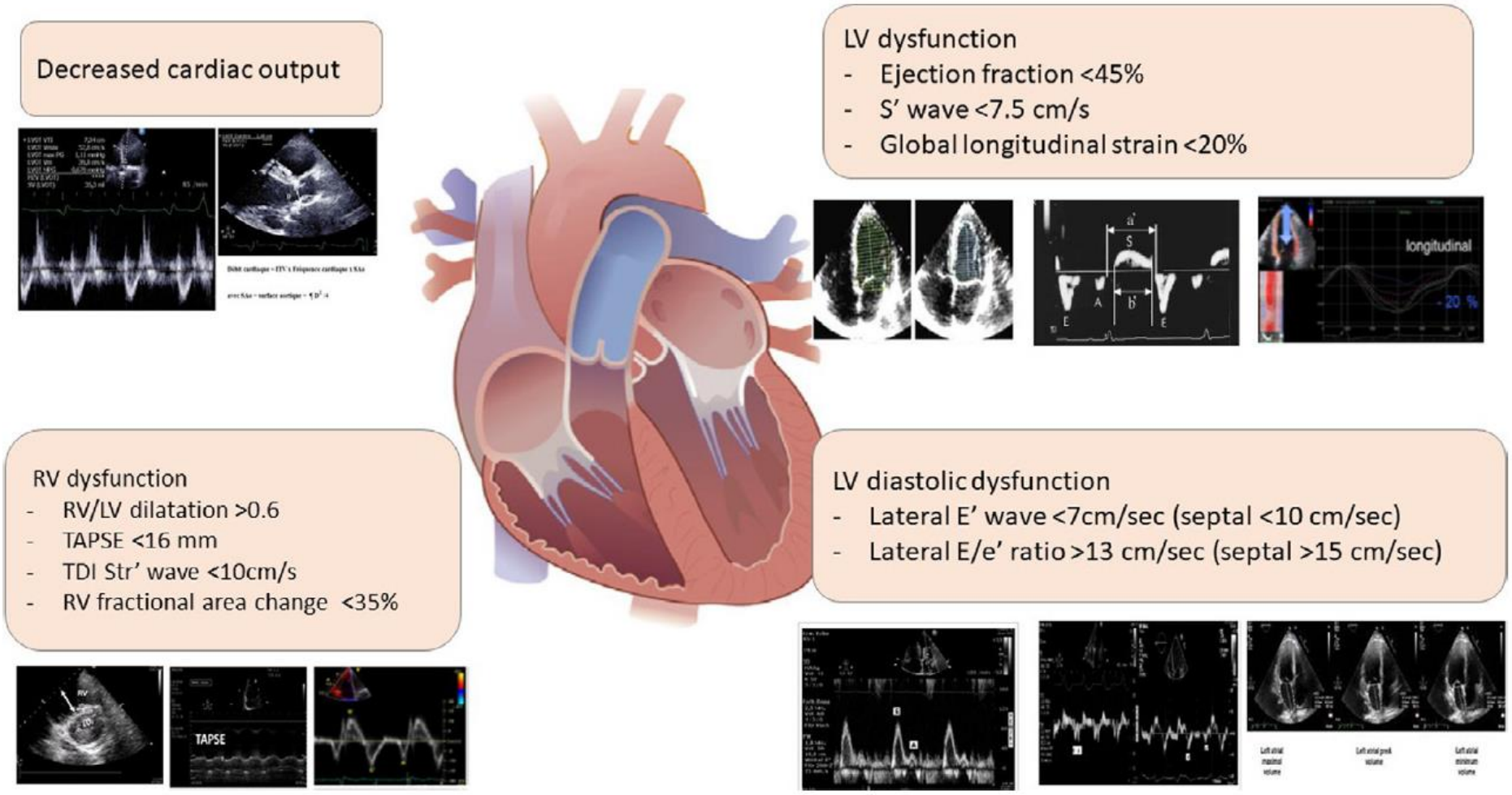


Figure 1. Echo parameters used to diagnose SCM. LV: Left ventricular; RV: Right ventricle; SCM: Septic cardiomyopathy; TDI: Tissue Doppler imaging; TAPSE: Tricuspid annular plane systolic excursion.

The Connection to Cardiology and Neurology Post Accurate Diagnosis

Sepsis-Associated Encephalopathy

Table 1 Risk factors for sepsis-associated encephalopathy

	Medical history	On ICU admission	During ICU stay
Non-modifiable factors	Older age Chronic kidney disease Chronic alcohol abuse History of neurologic disease History of cognitive impairment Long-term use of psychoactive drugs	Medical admission Mechanical ventilation Acute renal failure Bacteremia *Staphylococcus aureus* infection	Bacteremia
Modifiable factors	–	Hypoglycemia < 3 mmol/l Hyperglycemia > 10 mmol/l Hypercapnia > 45 mmHg Hypernatremia > 145 mmol/l	Midazolam Cefepime

Sonneville R, et al. The spectrum of sepsis-associated encephalopathy: a clinical perspective. *Critical Care* (2023) 27:386.

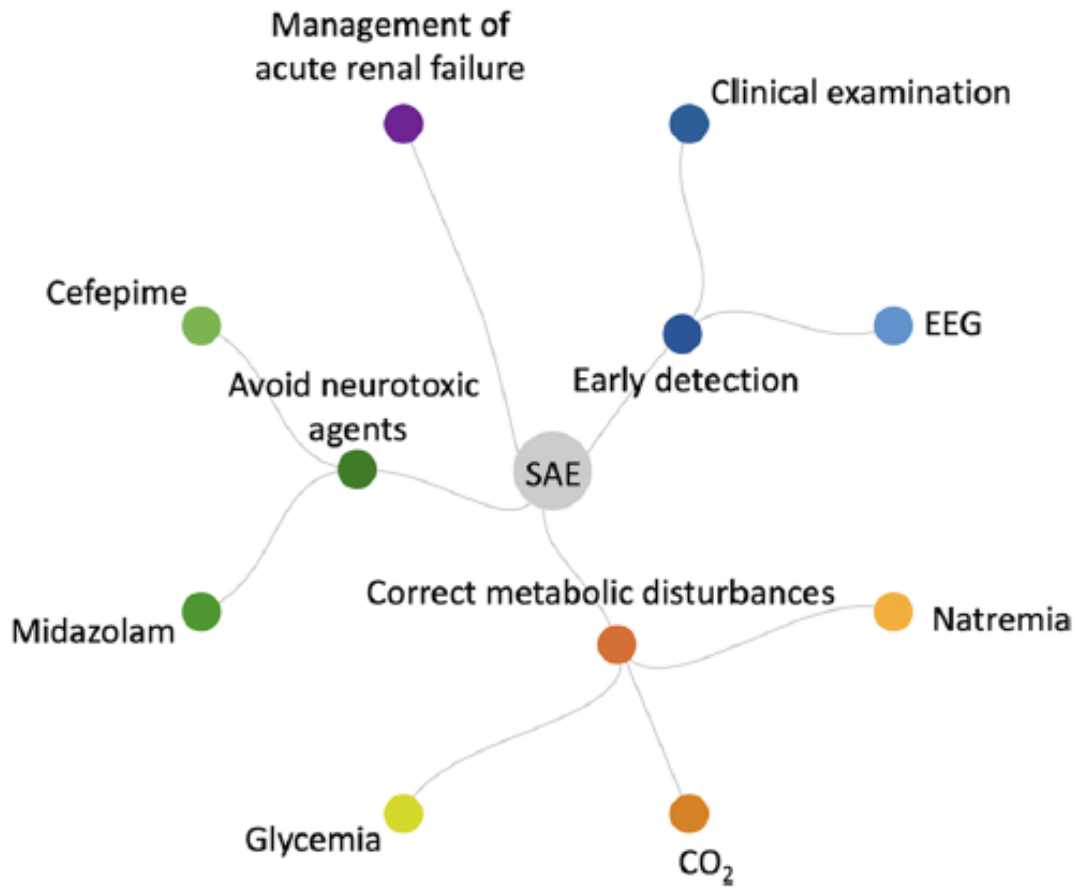
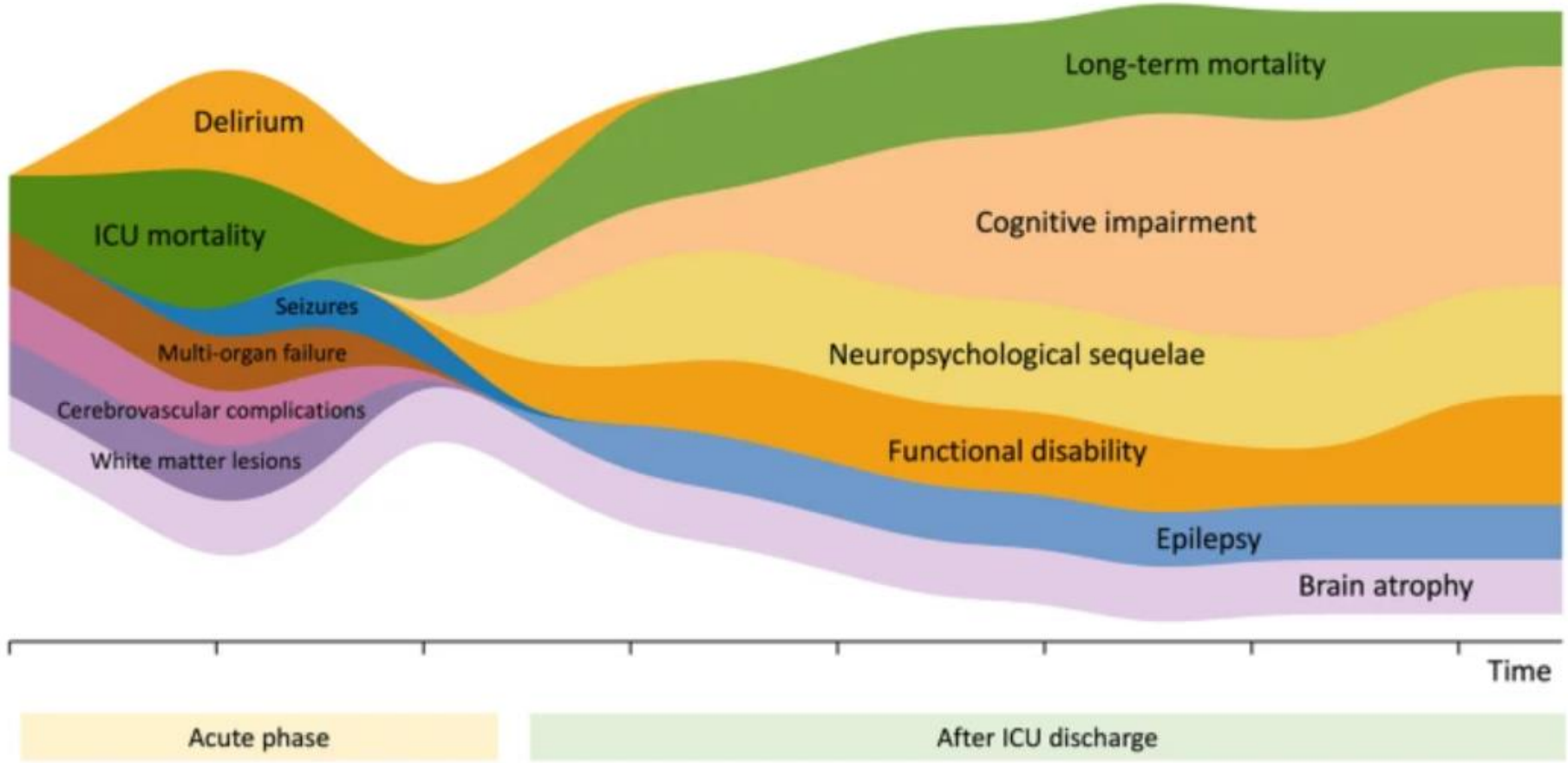


Fig. 3 A multimodal approach for the management of sepsis-associated encephalopathy. EEG Electroencephalography; SAE Sepsis-Associated Encephalopathy

Sonneville et al. Critical Care. The spectrum of sepsis-associated encephalopathy: a clinical perspective. (2023) 27:386.

Fig. 4



Complications associated with sepsis-associated encephalopathy at the acute phase and in the long term

Translating Research into Clinical Quality Via Performance Improvement

“Being willing to challenge *Metric Success* to Achieve Patient Centered Excellence”

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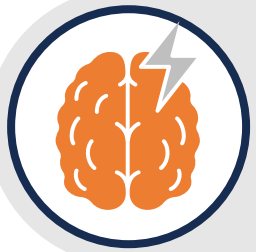
Protocolized Care for Time Sensitive Diseases

TIME SENSITIVE MEDICAL EMERGENCY		Outcome Predictor	Technology Advance Dx	Technology Advance Tx		Benefit	Resoures
HEART ATTACK		7.5% Mortality increase for every 30-minute delay	Troponin ECG	Angioplasty	Protocolized Application	↓ Mortality 30% ↓ Costs 35%	Cath Lab On Call Cardi POC ECG/Troponin
STROKE		Significant Morbidity & Mortality beyond 4h	CT Scanning in ED	Clot Retrieval Coils TPA	Protocolized Application	↓ Mortality 10% ↓ LOS 24% ↓ Costs 27%	ED CT Scan Cath Lab On Call INR
SEPSIS		8% Mortality increase for every hour of delay in shock	IntelliSep®	Rapid Antibiotics & Fluids	Protocolized Application	LOS Detect Time Cost	IntelliSep ® Sepsis Alert

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Questions?