Sepsis 2025

Evolving insights, Emerging Interventions

SIMCON 2025

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American College of Physicians

Leading Internal Medicine, Improving Lives

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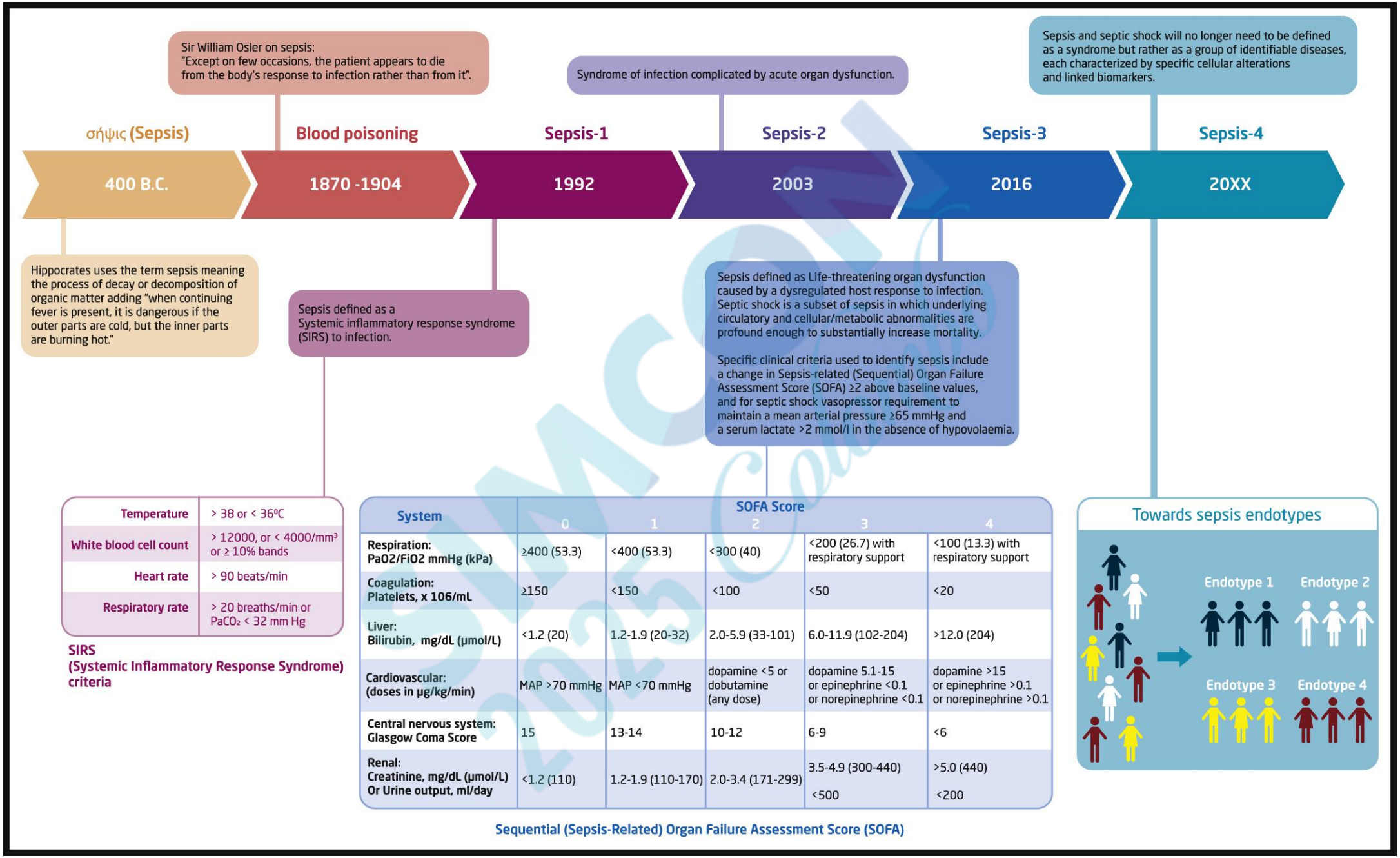
Disclosures: None

Learning Objectives

- Understanding the pathobiology & definition of Sepsis as a syndrome
- Define clinical criteria to diagnose sepsis syndrome
- Key emerging concepts in precision diagnostics, personalized therapies, advanced digital tools in early detection and intervention

Sepsis is a "heterogenous syndrome of acute organ dysfunction caused by a dysregulated host response to infection"

Singer M et al (JAMA 2016;315;801-10): The third International Consensus definitions of Sepsis and Septic Shock (Sepsis 3)



Temperature	> 38 or < 36ºC
White blood cell count	> 12000, or < 4000/mm³ or ≥ 10% bands
Heart rate	> 90 beats/min
Respiratory rate	> 20 breaths/min or $PaCO_2$ < 32 mm Hg

SIRS (Systemic Inflammatory Response Syndrome) criteria

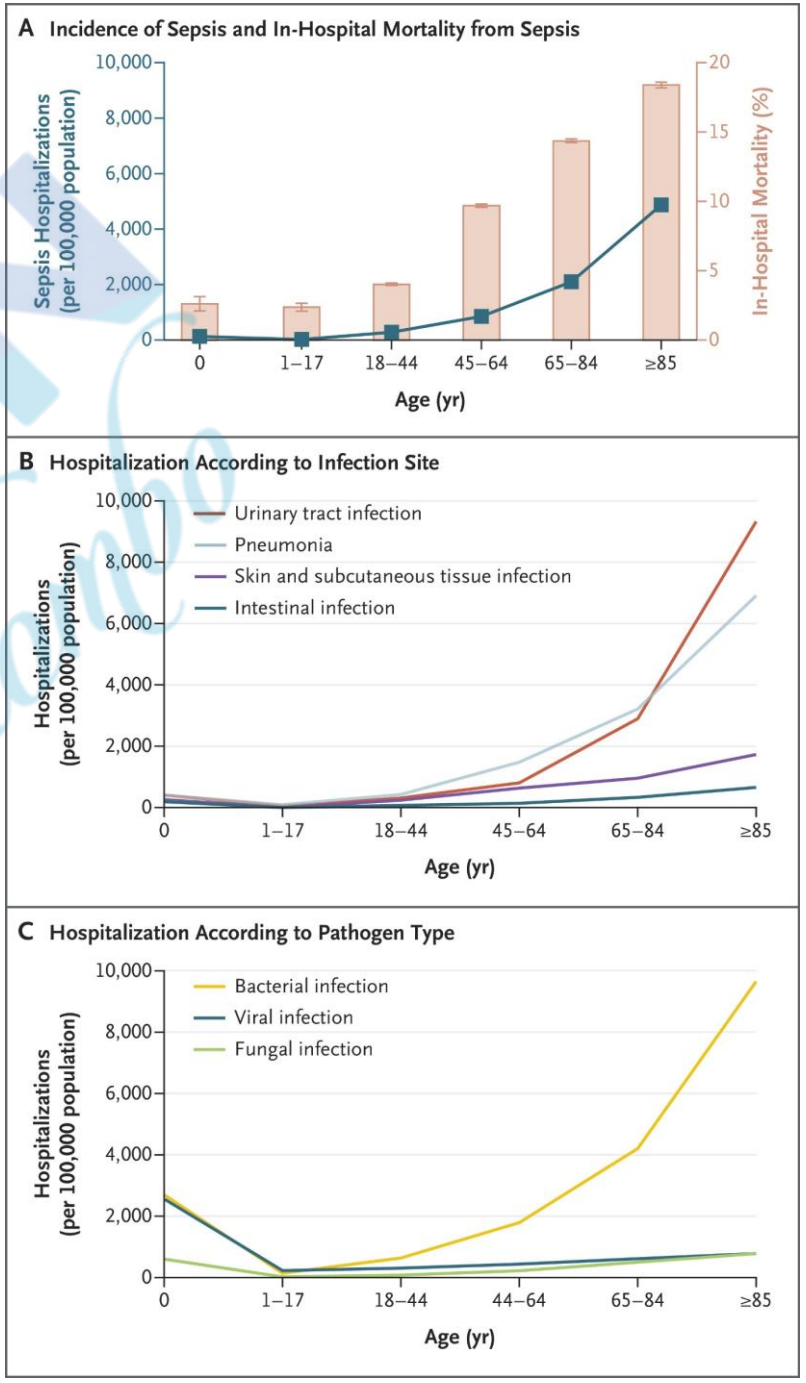
System	SOFA Score 0	1	2	3	4
Respiration: PaO2/FiO2 mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation: Platelets, x 106/mL	≥150	<150	<100	<50	<20
Liver: Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular: (doses in µg/kg/min)	MAP >70 mmHg	MAP <70 mmHg	dopamine <5 or dobutamine (any dose)	dopamine 5.1-15 or epinephrine <0.1 or norepinephrine <0.1	dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system: Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal: Creatinine, mg/dL (µmol/L) Or Urine output, ml/day	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) <500	>5.0 (440) <200

Sequential (Sepsis-Related) Organ Failure Assessment Score (SOFA)

Tom Van der Poll et al (November 2021): Immunology of Sepsis; Immunity 54

Sepsis

- Sepsis remains a **major public health** problem in the US & Globally
- Estimated **50 million cases** with approx. 11 million deaths worldwide annually
- **7.5% of all hospitalizations** and nearly 10% of total hospital days
- **1 in 3 hospital deaths** involves sepsis.
- **$52 billion** in annual hospital costs



Nuala J. Meyer et al ; Sepsis and Septic Shock; N Engl J Med. December 4, 2024

Sepsis Definitions over time:

Category	2001 Definition (Sepsis 2)*	2016 SCCM Definition (Sepsis 3)
Sepsis	≥ 2 of the following with suspected infection: • Temperature > 38C or < 36C - HR > 90 - RR > 20/min or $PaCO_2$ < 32 mmHg - WBC > 12,000/mm^3, < 4000/mm^3, or > 10 % bands/immature forms	Suspected or documented infection and ≥ 2 on qSOFA: - SBP ≤ 100 - Altered mental status - RR ≥ 22/min
Severe sepsis	Sepsis AND: - Sepsis induced hypotension (BP < 90, MAP <65 mmHg, decrease in SBP > 40 mmHg from baseline) - Creatinine >2.0 or urine output <0.5 mL/kg/h for 2 h - Bilirubin >2.0 mg/dL - Platelet count <100,000/mm3 - INR > 1.5 or PTT > 60s - Lactate >2 mmol/L	Not a category
Septic shock	Severe sepsis AND - Persistent hypotension following 30 mL/kg crystalloid fluid resuscitation - Lactate ≥4 mmol/L	Sepsis and vasopressors needed to maintain MAP >65 mmHg and lactate >2 mmol/L

* CMS utilizes criteria similar to Sepsis 2 (2001); BP, blood pressure; HR, heart rate; MAP, mean arterial pressure; qSOFA, quick sequential organ failure assessment; RR, respiratory rate; SBP, systolic blood pressure; WBC, white blood cell count.

B..Long, MD et al; Evaluation and Diagnosis of Sepsis and Septic Shock; American Journal of Emergency Medicine 90 (2025) 169-178

Sequential Organ Failure Assessment Update - SOFA 2

(SOFA 1 was developed in 1996)

	Score				
Organ system	0	1	2	3	4
Brain[c,d]	GCS 15 (or thumbs-up, fist, or peace sign)	GCS 13-14 (or localizing to pain)[d] or need for drugs to treat delirium[e]	GCS 9-12 (or withdrawal to pain)	GCS 6-8 (or flexion to pain)	GCS 3-5 (or extension to pain, no response to pain, generalized myoclonus)
Respiratory[f]	PaO_2:FiO_2 ratio >300 mm Hg (>40 kPa)	PaO_2:FiO_2 ratio ≤300 mm Hg (≤40 kPa)	PaO_2:FiO_2 ratio ≤225 mm Hg (≤30 kPa)	PaO_2:FiO_2 ratio ≤150 mm Hg (≤20 kPa) and advanced ventilatory support[g,h]	PaO_2:FiO_2 ratio ≤75 mm Hg (≤10 kPa) and advanced ventilatory support[g,h] or ECMO[i]
Cardiovascular[j,k,l,m]	MAP ≥70 mm Hg, no vasopressor or inotrope use	MAP <70 mm Hg, no vasopressor or inotrope use	Low-dose vasopressor (sum of norepinephrine and epinephrine ≤0.2 µg/kg/min) or any dose of other vasopressor or inotrope	Medium-dose vasopressor (sum of norepinephrine and epinephrine >0.2 to ≤0.4 µg/kg/min) or low-dose vasopressor (sum norepinephrine and epinephrine ≤0.2 µg/kg/min) with any other vasopressor or inotrope	High-dose vasopressor (sum of norepinephrine and epinephrine >0.4 µg/kg/min) or medium-dose vasopressor (sum of norepinephrine and epinephrine >0.2 to ≤0.4 µg/kg/min) with any other vasopressor or inotrope or mechanical support[i,n]
Liver	Total bilirubin ≤1.20 mg/dL (≤20.6 µmol/L)	Total bilirubin ≤3.0 mg/dL (≤51.3 µmol/L)	Total bilirubin ≤6.0 mg/dL (≤102.6 µmol/L)	Total bilirubin ≤12.0 mg/dL (≤205 µmol/L)	Total bilirubin >12.0 mg/dL(>205 µmol/L)
Kidney	Creatinine ≤1.20 mg/dL (≤110 µmol/L)	Creatinine ≤2.0 mg/dL (≤170 µmol/L) or urine output <0.5 mL/kg/h for 6-12 h	Creatinine ≤3.50 mg/dL (≤300 µmol/L) or urine output <0.5 mL/kg/h for ≥12 h	Creatinine >3.50 mg/dL (>300 µmol/L) or urine output <0.3 mL/kg/h for ≥24 h or anuria (0 mL) for ≥12 h	Receiving or fulfils criteria for RRT[o,p,q] (includes chronic use)
Hemostasis	Platelets >150 × 10^3/µL	Platelets ≤150 × 10^3/µL	Platelets ≤100 × 10^3/µL	Platelets ≤80 × 10^3/µL	Platelets ≤50 × 10^3/µL

Otavio V Ranjani et al (October 29, 2025): Development and Validation of the Sequential Organ Failure Assessment (SOFA)-2 Score; JAMA

Sequential Organ Failure Assessment Update - SOFA 1 ---> 2

The main changes made were:

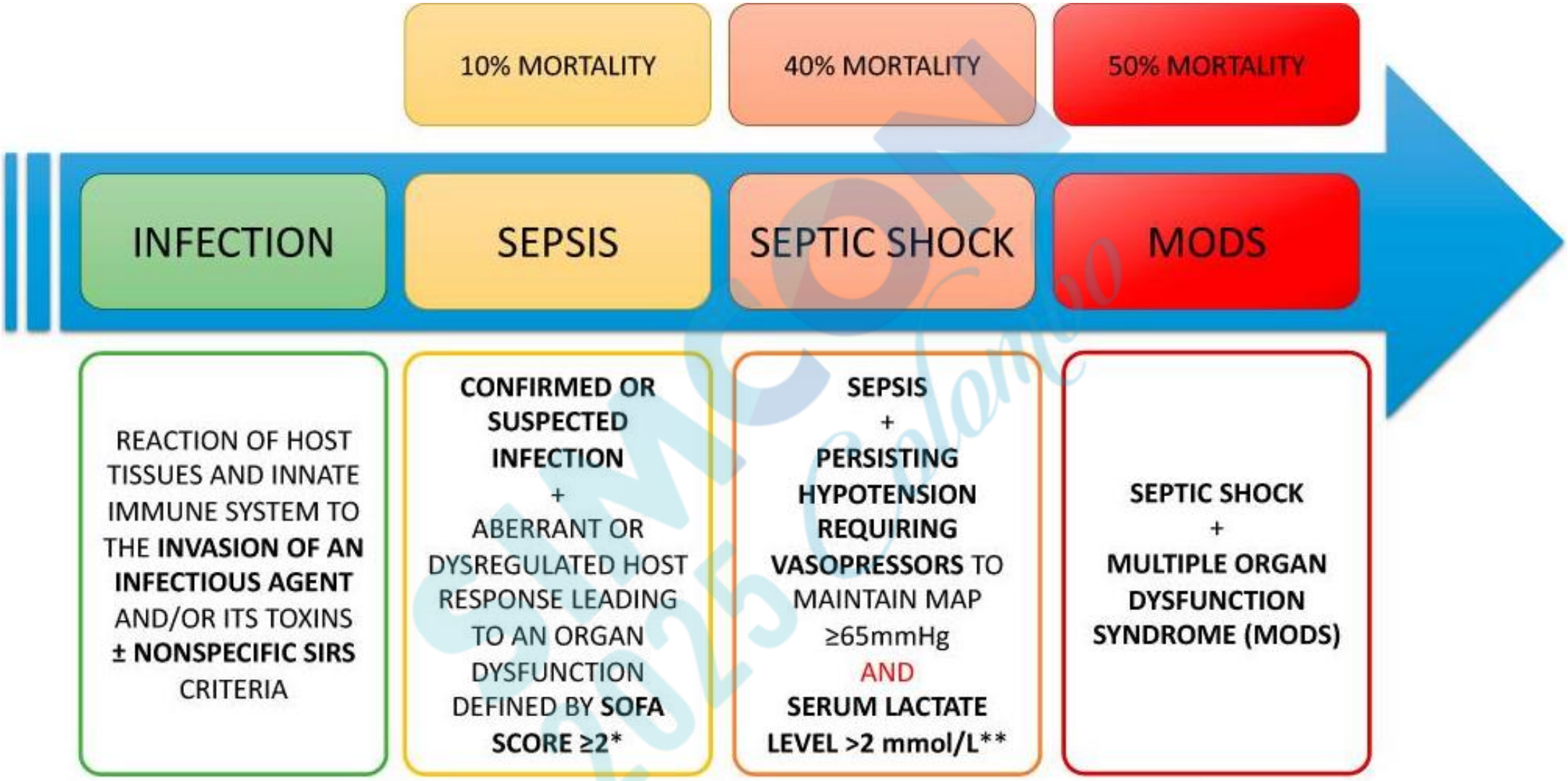
Incorporation of new drugs and devices to support organ systems to reflect current standard management

New score cut offs that aligns with better mortality risk

Alternative variables to be used when primary options are not being used or unavailable (ABG, RRT) or not indicated (e.g, ceiling of treatment)

Organ system	Change from SOFA-1
Brain	• Incorporation of delirium (using specific drug therapy as a surrogate) • Modified point score cutoffs for Glasgow Coma Score • Renamed from central nervous system
Respiratory	• Incorporation of noninvasive respiratory support modalities and ECMO • Modified point score cutoffs for PaO_2:FiO_2 ratio
Cardiovascular	• Summation of doses of catecholaminergic agents • Simple incorporation of all other vasopressor and inotrope agents as well as mechanical support devices
Liver	• Modified point score cutoff for bilirubin level • Renamed from hepatic
Kidney	• Modified point score cutoffs for creatinine level and urine output • Incorporation of renal replacement therapy (or fulfilment of criteria) • Renamed from kidney
Hemostasis	• Modified point score cutoff for platelet count • Renamed from coagulation/hematological
General	• Provision of definitions for dysfunction in each organ system • Provision of alternatives if variables are either not available (eg, arterial blood gas analysis, renal replacement therapy) or not indicated (eg, ceiling of treatment) • Explicit rules for handling scoring of, eg, sedation, chronic organ dysfunction • For missing data on day 1, normal value imputation (rationale: if not measured, likely to be within normal range); for missing data after day 1, carry forward last observation (rationale: if not measured, likely to be stable or irrelevant in a clinical context) • For more detailed discussion of missing data handling, please see the accompanying SOFA-2 article[13]

Otavio V Ranjani et al (October 29, 2025): Development and Validation of the Sequential Organ Failure Assessment (SOFA)-2 Score; JAMA



** or an increase of 2 points compared to the initial value of the SOFA*
*** Despite adequate volume/fluid resuscitation*

Daniel M et al – International Journal of Mol Science: 2022 Aug 17;23(16):9274

Sepsis sources:

Sites:

- Pulmonary (40% – 60%)
- Abdomen (15% - 20%)
- Genitourinary (15% - 20%)
- Bloodstream
- Skin & Soft tissues

Infection:

- Gram Positive/Negative Bacteria
- Fungal or viral

Nuala j. Meyer et al; Sepsis and Septic Shock; December 4, 2024. N Engl J Med 2024;391:2133-2146

Risk Factors

- **ICU admission**
- **Bacteremia**
- **Advanced age (≥65 years)**
- **Immunosuppression** – Comorbidities that depress host-defense (eg, neoplasms, kidney failure, hepatic failure, AIDS, asplenism) and immunosuppressant medications
- **Diabetes and obesity**
- **Cancer** – one of the most common (almost 20%)
- **Community acquired pneumonia**
- **Previous hospitalization** – for infection-related conditions, especially *C.difficile* infection
- **Genetic factors** – genetic polymorphisms

Nuala j. Meyer et al; Sepsis and Septic Shock; December 4, 2024. N Engl J Med 2024;391:2133-2146

Sepsis – Early Warning Scoring Systems

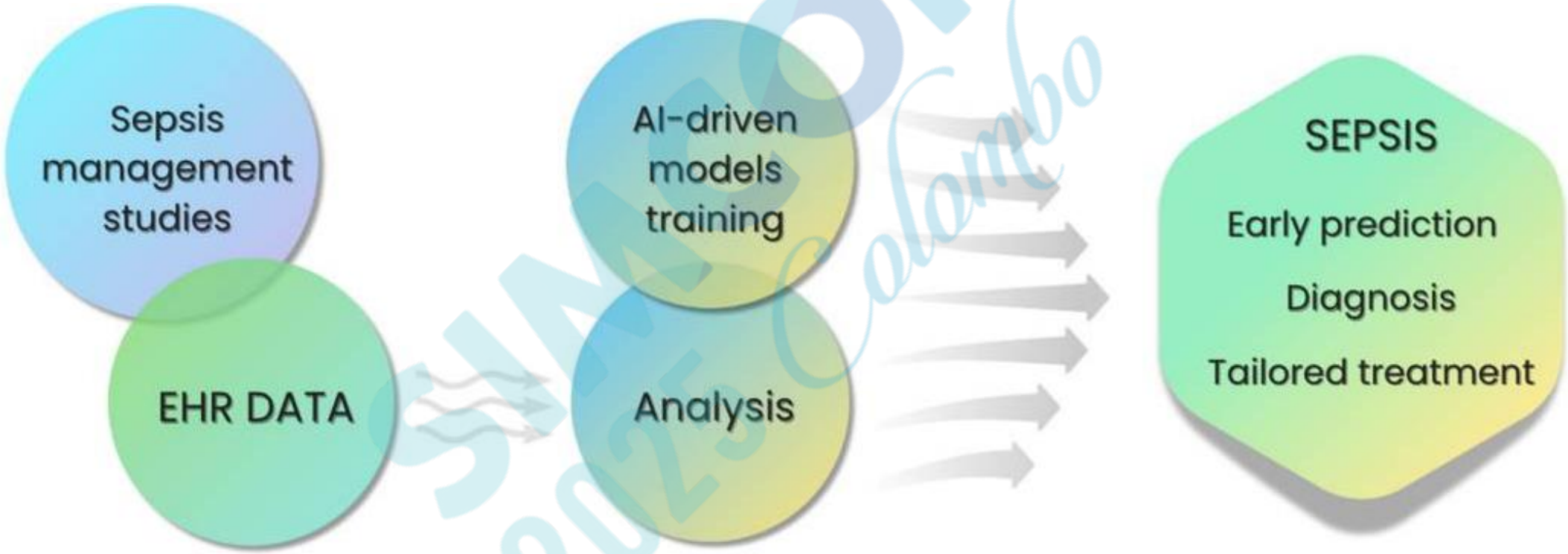
qSOFA	NEWS	MEWS
• Respiratory rate ≥ 22/min • Altered mentation • Systolic blood pressure ≤ 100 mmHg	• Respiration rate • Oxygen saturation • Any supplemental oxygen • Systolic blood pressure • Heart rate • Level of consciousness or new confusion with AVPU score • Temperature	• Systolic blood pressure • Heart rate • Respiration rate • Oxygen saturation • Temperature • AVPU score
Interpretation: 0–1: Not high risk for in-hospital mortality ≥2: High risk for in-hospital mortality	**Interpretation:** 1–4: low score, assessment by registered nurse 5–6: medium score, urgent review by clinician ≥7: high score, emergent assessment by clinical team/critical care outreach team	**Interpretation:** ≥5: increased likelihood of death, admission to intensive care unit

AVPU, alert/verbal/pain/unresponsive.

Criteria	SOFA	mSOFA	qSOFA	Shock Index	Modified Shock Indes
Respiratory	PaO_2/FiO_2 ≤400	SpO_2/FiO_2 ≤400	-	-	-
Coagulation	Platelets <150 × 10^3	Platelets <100 × 10^3	-	-	-
Liver	Bilirubin >1.2	-	-	-	-
Cardiovascular	MAP <70 mmHg	MAP <70 mmHg	-	-	-
CNS	GCS ≤13	GCS ≤13	-	-	-
Renal	Creatine >1.2	-	-	-	-
Shock Index	-	-	-	HR/SBP >0.7	HR/MAP ≥1.0
qSOFA	-	-	Respiratory rate ≥22/minute, AMS, SBP ≤100 mmHg	-	-

B..Long, MD et al; Evaluation and Diagnosis of Sepsis and Septic Shock; American Journal of Emergency Medicine 90 (2025) 169-178

Machine Learning Model



Algorithm based Sepsis Alert System (AI)

- **Targeted Real-Time Early Warning System (TREWS) – Bayesian Health**
  - A bedside EHR integrated tool which combines the patient's medical history symptoms and labs, to alert the clinicians to the risk of sepsis and suggests a treatment protocols, such as fluid therapy and antibiotics
  - 3 percent reduction in sepsis-related mortality when a provider responded
- **Sepsis Prediction and Optimization of Therapy (SPOT) and Sepsis Watch**
  - 10 percent reduction in mortality for patients with severe sepsis
- **The Sepsis ImmunoScore**
  - Prompt identification of patients at high risk of sepsis and adverse outcomes (First FDA approved)
- **Epic Sepsis Prediction Model**
  - can rule out sepsis in many cases (high NPV), it struggles with identifying patients who have sepsis
  - (low sensitivity)

Pathogen and host factors influencing the sepsis sequelae:

Activation of both proinflammatory and anti-inflammatory immune responses occurs promptly after sepsis onset.

The host response to severe sepsis can have four different clinical trajectories:

(1) early MOF leading to death

(2) rapid recovery

(3) late deaths

(4) late sequelae or long-term deaths.

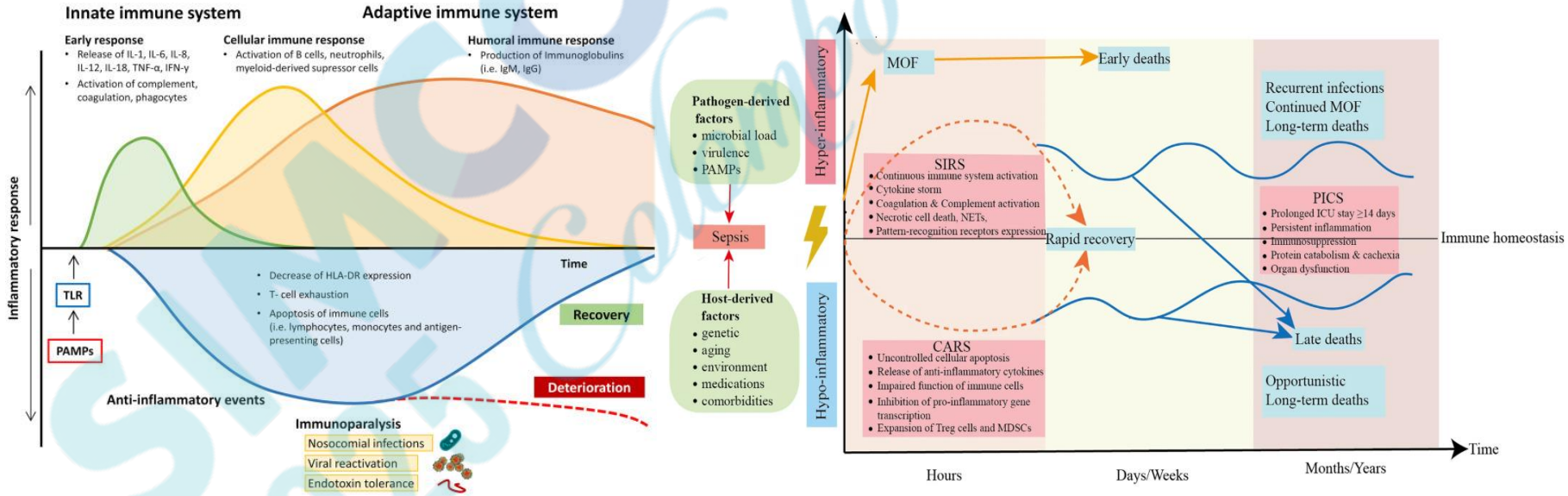
SIRS: systemic inflammatory response syndrome

CARS: compensatory anti-inflammatory response syndrome

MOF: multi-organ failure, NETs Neutrophil extracellular traps

MDSCs: Myeloid-derived suppressor cells

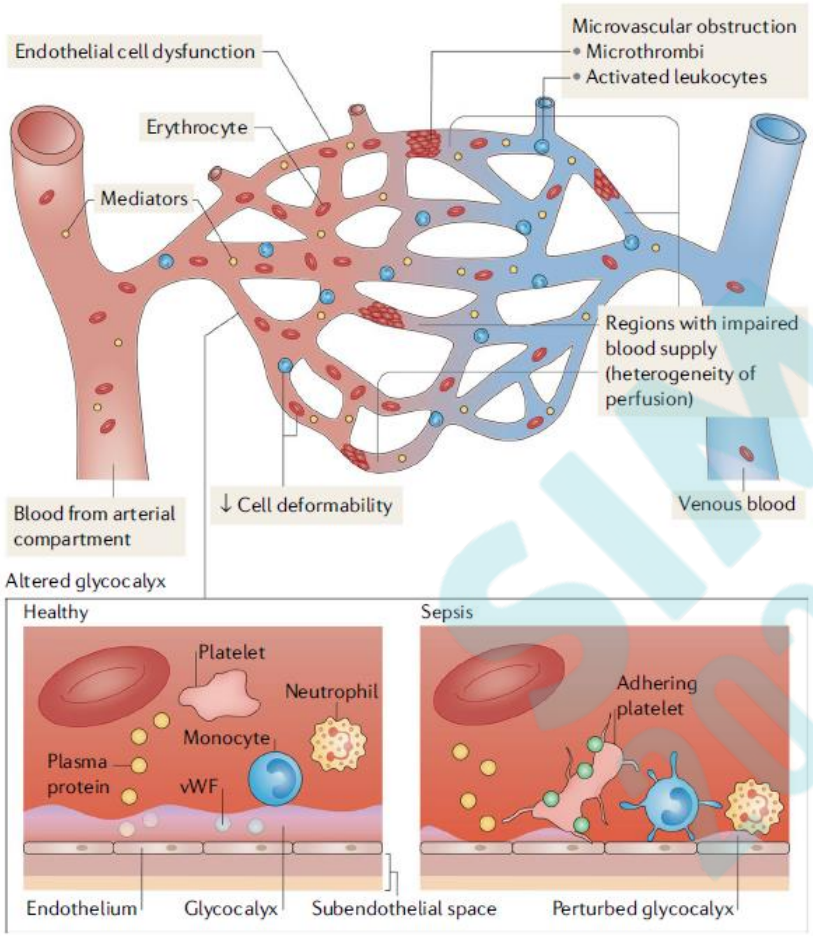
PICS: persistent inflammation, immunosuppression, and catabolism syndrome



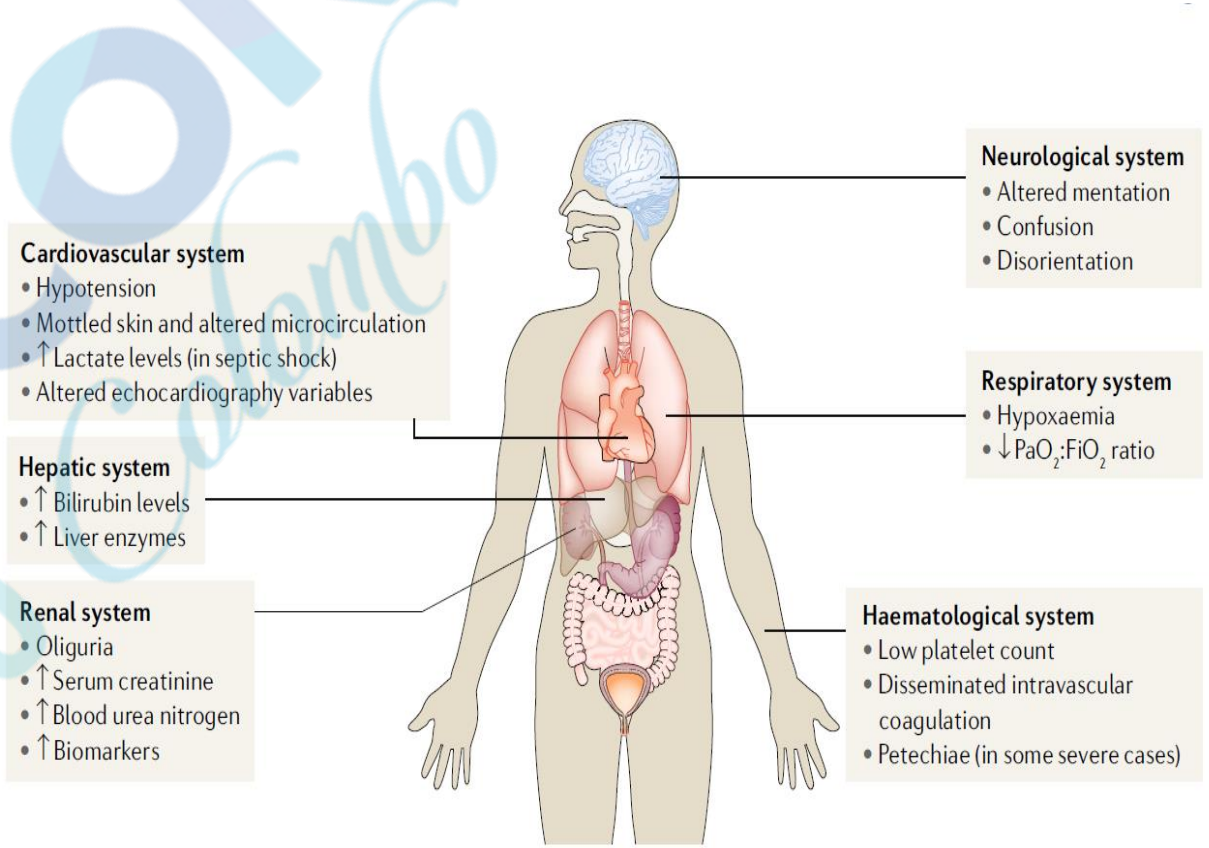
Min Cao et al : 19 December, 2023: Immune dysregulation in sepsis: experiences, lessons and perspectives + other sources

Organ Dysfunction & Clinical Monitoring in Sepsis

- Microvascular & Cellular Alterations:

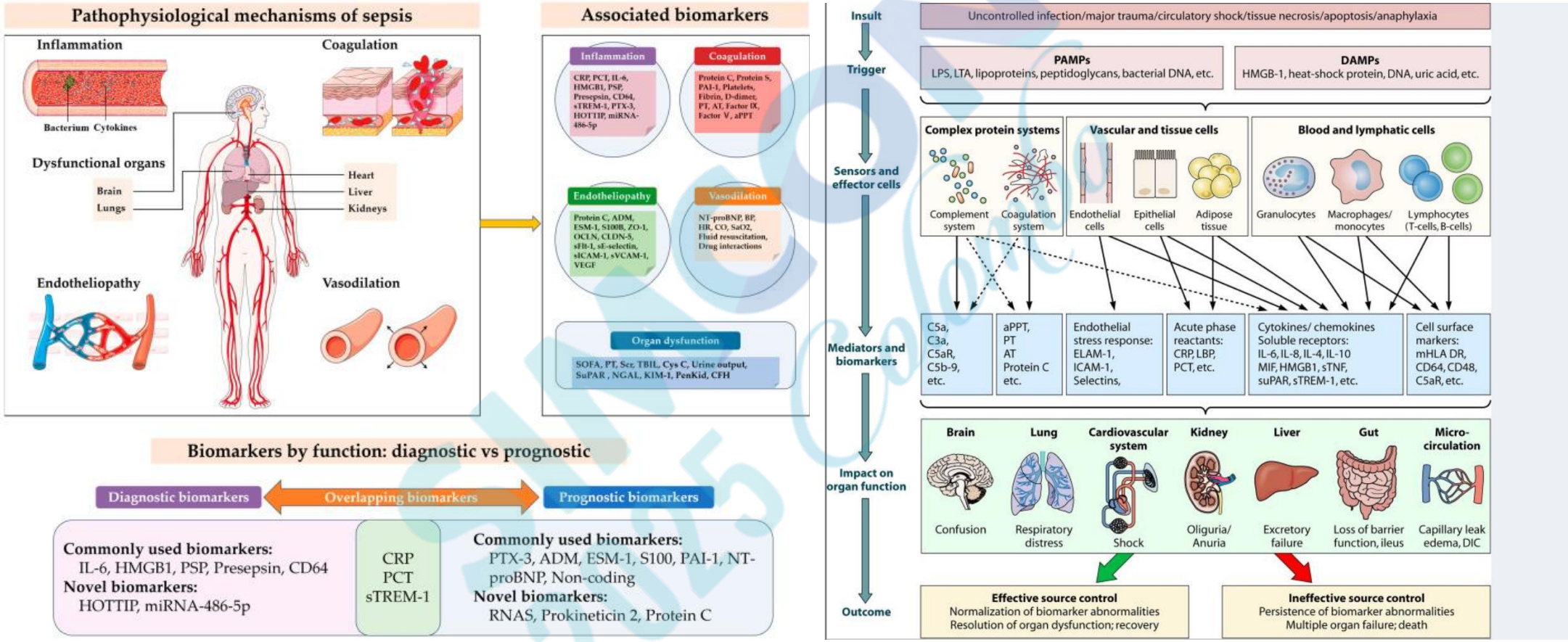


- Major organs that are clinically monitored:



C. Lelubre: Mechanisms and treatment of Organ Failure in Sepsis: Nature Reviews – Nephrology July 2018

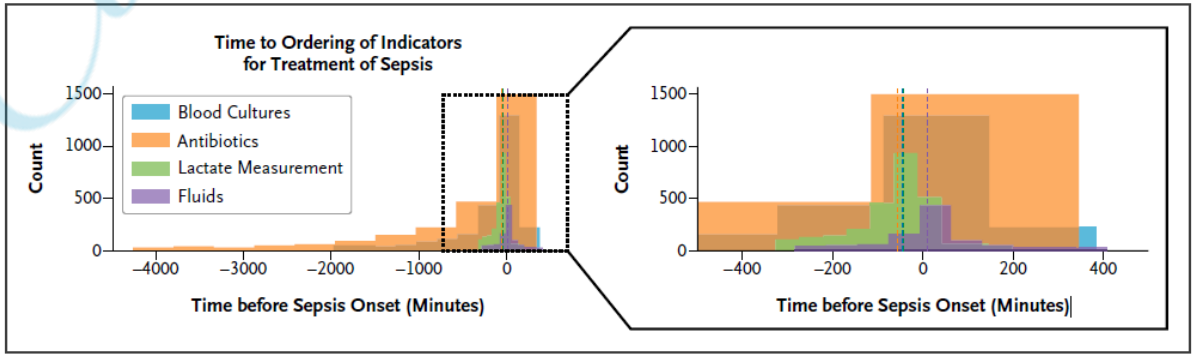
Pathobiology:



Arina Pietro et al: Pathophysiology of Sepsis: Current Opinion in Anesthesiology: April 2021. 2021 Apr 1;34(2):77-84

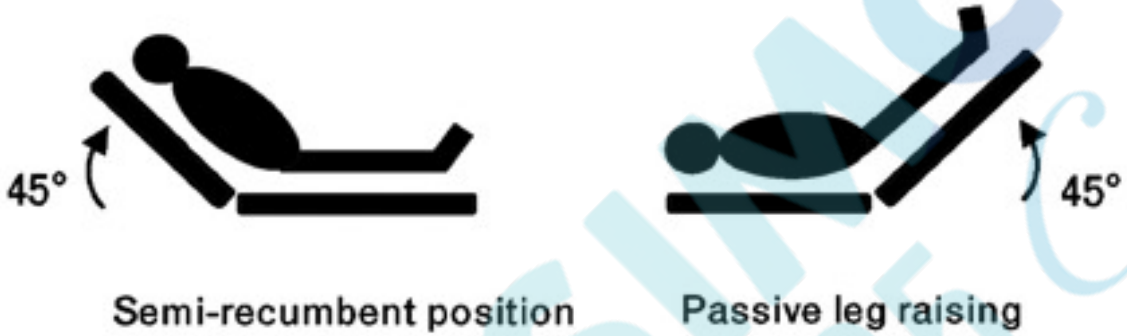
Challenges in diagnosing Sepsis in clinical practice

- Systemic Inflammation can be due to non-infectious causes
- Routine diagnostic tests for infection have low sensitivity
- The transition from infection to sepsis is difficult to recognize
- Co-morbid conditions may mask Sepsis
- qSOFA is not specific for infection

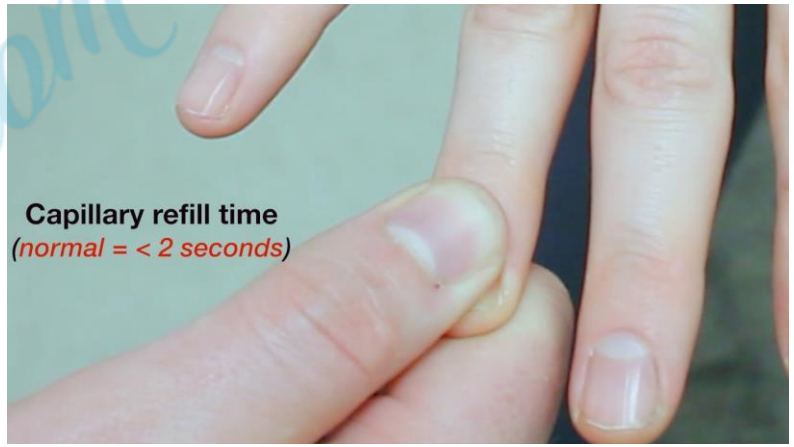


Role of Physical Exams in perfusion assessment:

Passive Leg Raise

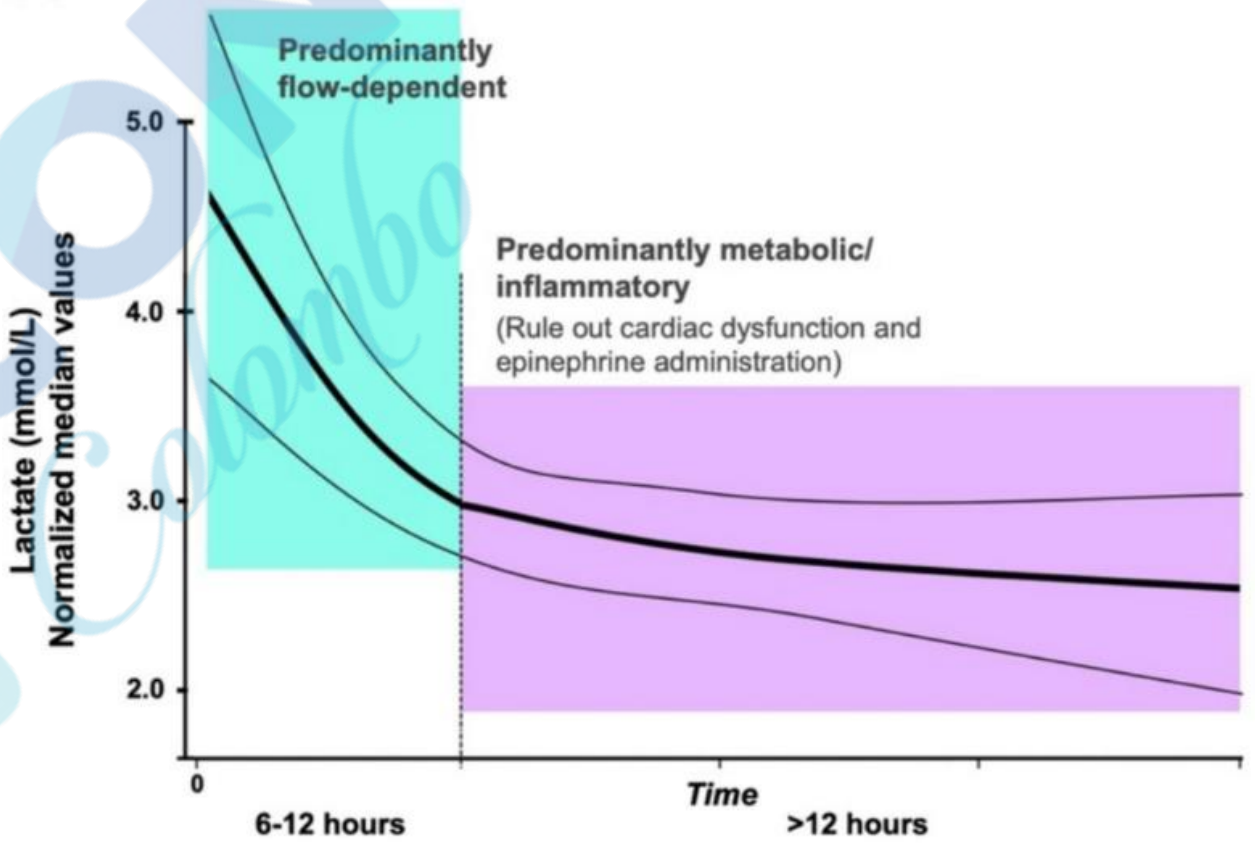


Capillary Refill



Serum Lactate Levels

- **Both hemodynamic and metabolic marker -** now part of Sepsis 3 Definition
- **An indirect marker of tissue hypoperfusion and cellular stress,** not a direct measure of tissue perfusion
- **Prognostic marker in Sepsis** with higher levels and poor clearance associated with increased short-term and 30-day mortality
- Lactic acidosis can occur also in liver diseases, trauma, shock, vigorous exercises, drug intoxication, and cancer



Rong Rong He et al; Sepsis Biomarkers: Advancements and Clinical Applications—A Narrative Review; Int. J. Mol. Sci. **2024**, 25, 9010 plus other sources

C-Reactive Protein (CRP)

- An acute phase reactant - 5 part protein synthesized by the **liver** when exposed to inflammatory markers like IL-6 and IL1B.
- Levels not impacted by Immunosuppression, renal & liver failure or hemodialysis
- It triggers the complement system and encourages platelets, monocytes and endothelial cells to become active.
- Highly Sensitive but less specific.
- Increased levels are seen in localized infections, non-infectious causes – Auto-immune Disorders, Shock, Trauma and Surgery.
- **Estimated CRP velocity (eCRPv)** is a novel marker to differentiate between bacterial and viral infections. eCRPv >4mg/L/h is a strong indicator of bacterial infection.

Rong Rong He et al; Sepsis Biomarkers: Advancements and Clinical Applications—A Narrative Review, Int. J. Mol. Sci. **2024**, 25, 9010 plus other sources

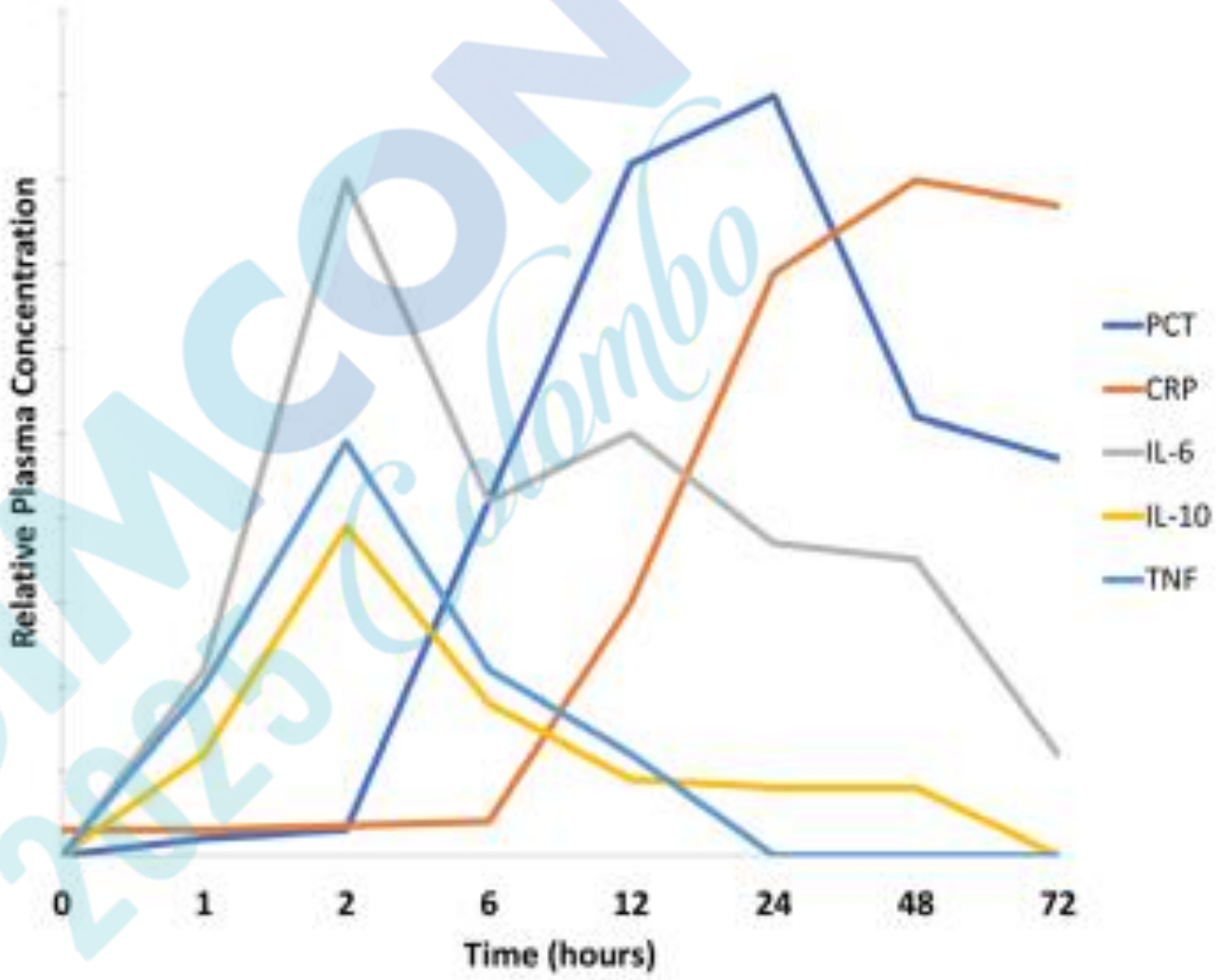
Procalcitonin (PCT)

- Prohormone precursor of Calcitonin produced by almost all organs and macrophages (Source: Thyroid C cells)
- Synthesized from an inactive precursor protein from the liver & other tissues as Pre-Procalcitonin upon triggered by IL-6, IL-1, TNF-A due to a bacterial insult (gm –ve) by activating Macrophages and Monocytes
- In Sepsis - Urinary PCT and CSF PCT can aid UTI & Meningitis as an etiology
- Other causes of increased PCT are – severe Trauma, Shock and Renal Dysfunction
- Some clinical guidelines recommend discontinuing antibiotics when PCT levels falls below 80% from their peak levels. **Hence PCT should be used to reduce antibiotic duration**.
- PCT is more useful in **ruling out than diagnosing** Sepsis

Rong Rong He et al; Sepsis Biomarkers: Advancements and Clinical Applications—A Narrative Review; Int. J. Mol. Sci. **2024**, 25, 9010 plus other sources

Pattern of Procalcitonin as compared to other markers

Procalcitonin increases in Plasma within 2-6 hours, peaks at approximately 12-24 hours and has a half life of about 24 hours



AACC Guidance Document on the Clinical Use of Procalcitonin; May 2023 (598-634)

Novel Laboratory Methods for Sepsis Detection

Cell	• MDW, Intellisep
Gene Expression	• Septicyte Rapid, TriVerity Test
Proteins	• Bacterial Viral Immunoassay (BV) Test

Multiple sources

Monocyte Distribution Width (MDW)

Indication: aids in identifying patients with sepsis or at increased risk within first 12 hours of hospital admission

Upsides of MDW

- Everyone is getting CBC = No physician heuristics needed
- True screening test
- High Positive likelihood ratio

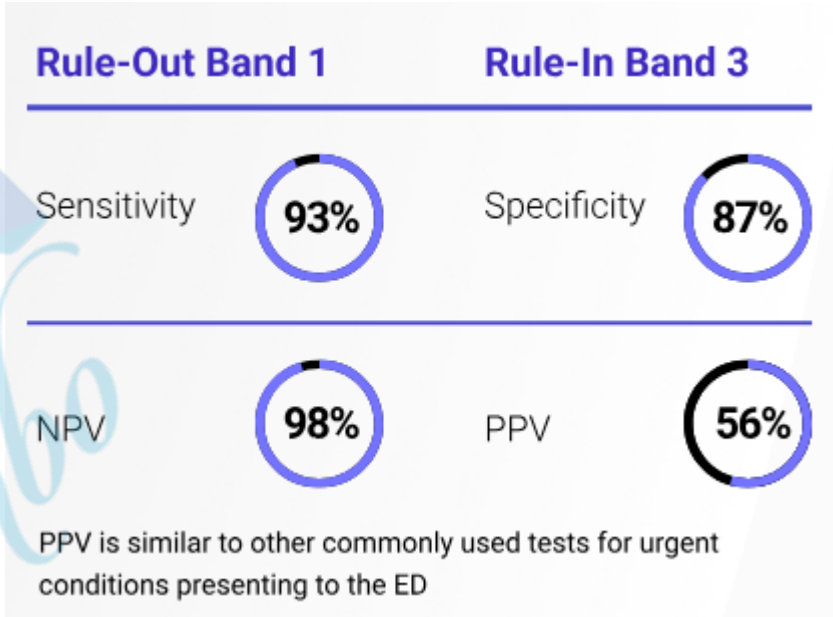
Potential Limitations

- Only available from one hematology manufacturer
- Low Sensitivity & Specificity
- Limited data in pediatrics

The Intellisep Index

Leveraging biochemical properties of WBCs

Aid in the early detection of sepsis with organ dysfunction manifesting within the first 3 days after testing.



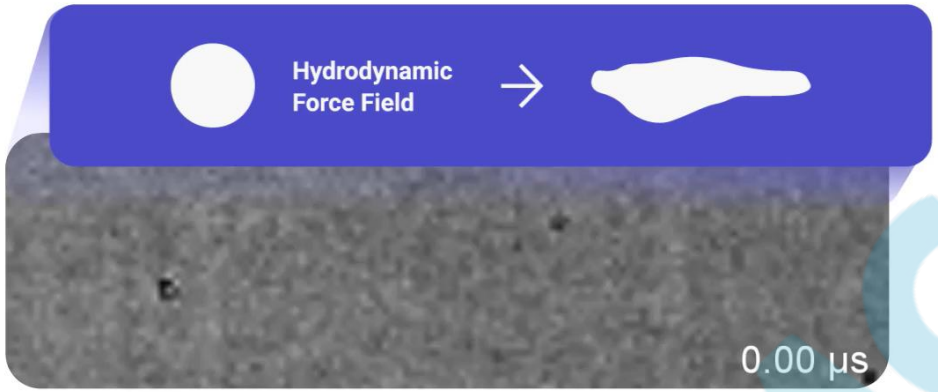
Advantages:

- Good Sensitivity and Specificity in clinical studies
- Observational study associated with reduced mortality and improved resource utilization

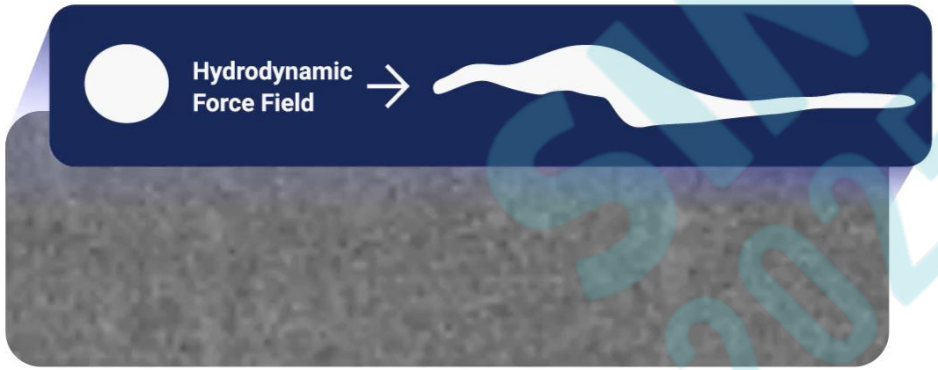
Potential Limitations:

- Requires dedicated instrumentation
- No randomized control trial of implementation impact
- Requires physician heuristics or a specific triage algorithm

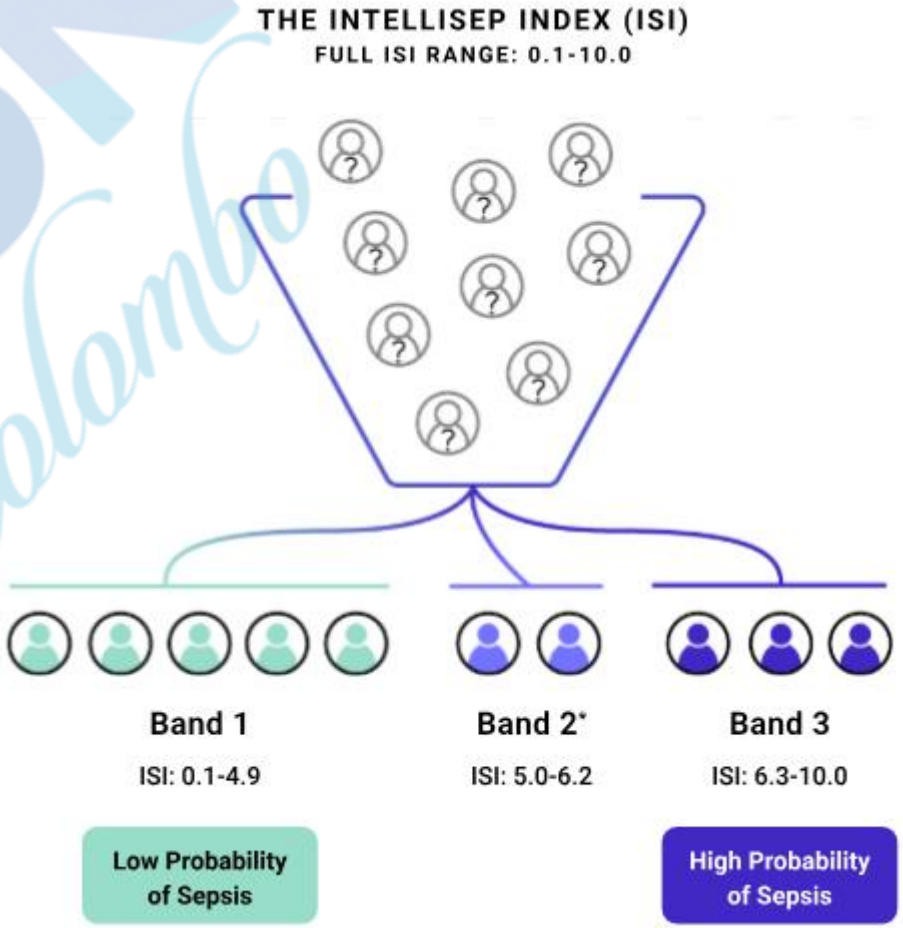
The Intellisep Index:



WHITE BLOOD CELLS FROM A NON-SEPTIC PATIENT

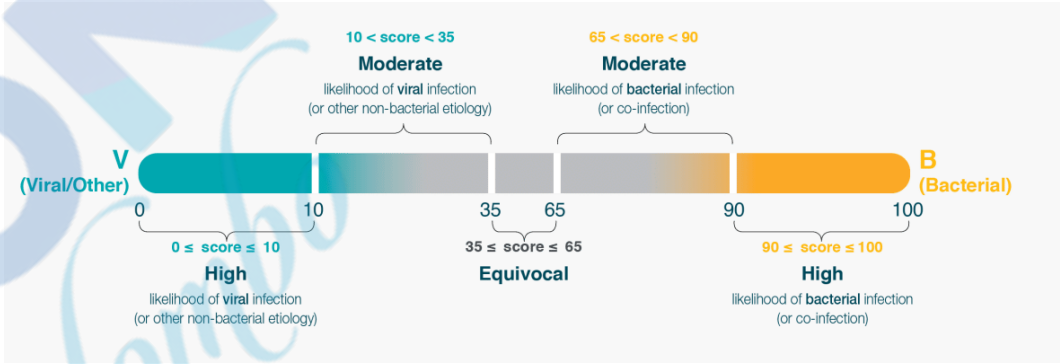


WHITE BLOOD CELLS FROM A SEPTIC PATIENT



Protein based BV assay for Bacterial v/s Viral Infections (MeMed)

- Chemiluminescence immunoassay for host immune proteins: TRAIL, IP-10 and CRP
- Predefined logistics regression model to assign a score 0-100
- Aid to differentiate bacterial from viral infections.
- Patients presenting to ED or Urgent Care with suspected viral or bacterial infection
- Symptoms < 7 days



MeMed BV® Score	FDA indication for use (Etiology)	Recommendation
0 ≤ score ≤10	Viral infection (or other non-bacterial)	Strongly consider **not** prescribing antibiotics
10 < score <35		
35 ≤ score ≤65	Equivocal	Continue with routine care
65 < score <90	Bacterial infection (or co-infection)	Consider prescribing antibiotics
90 ≤ score ≤100		Strongly consider prescribing antibiotics

Protein based BV Assay

Advantages

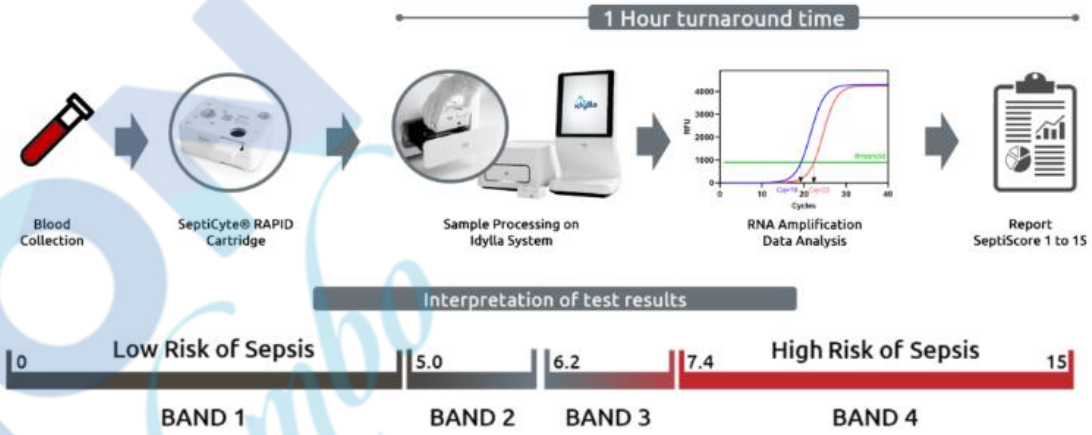
- Good sensitivity and specificity for bacterial infection
- Can be performed at the POC (results within 15-30 mins)
- Also available on a commonly used immunoassay platform

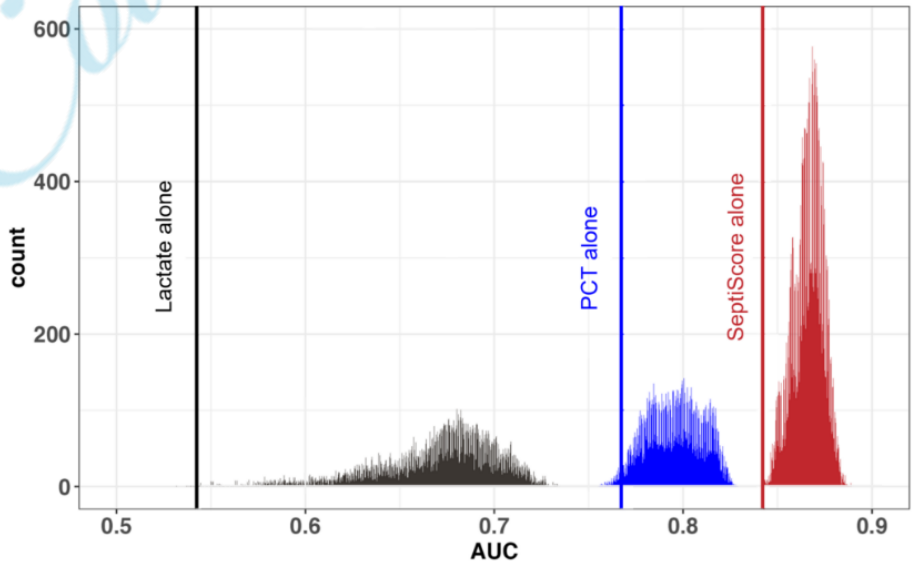
Potential Limitations

- Cannot differentiate between viral and other non-bacterial etiologies
- In some studies, patients with equivocal SOC or BV results were excluded
- Does not predict which patients will become septic (but can used in managing septic patients)

Septicyte Rapid Assay

- PCR based - Detects RNA transcripts PLA2G7 and PLAC8
- Combine to produce “Septiscore” bands
- Aid to differentiate infection positive (sepsis) from infection negative systemic inflammation in patients suspected of sepsis on their first day of ICU admission





Septicyte Summary

Advantage

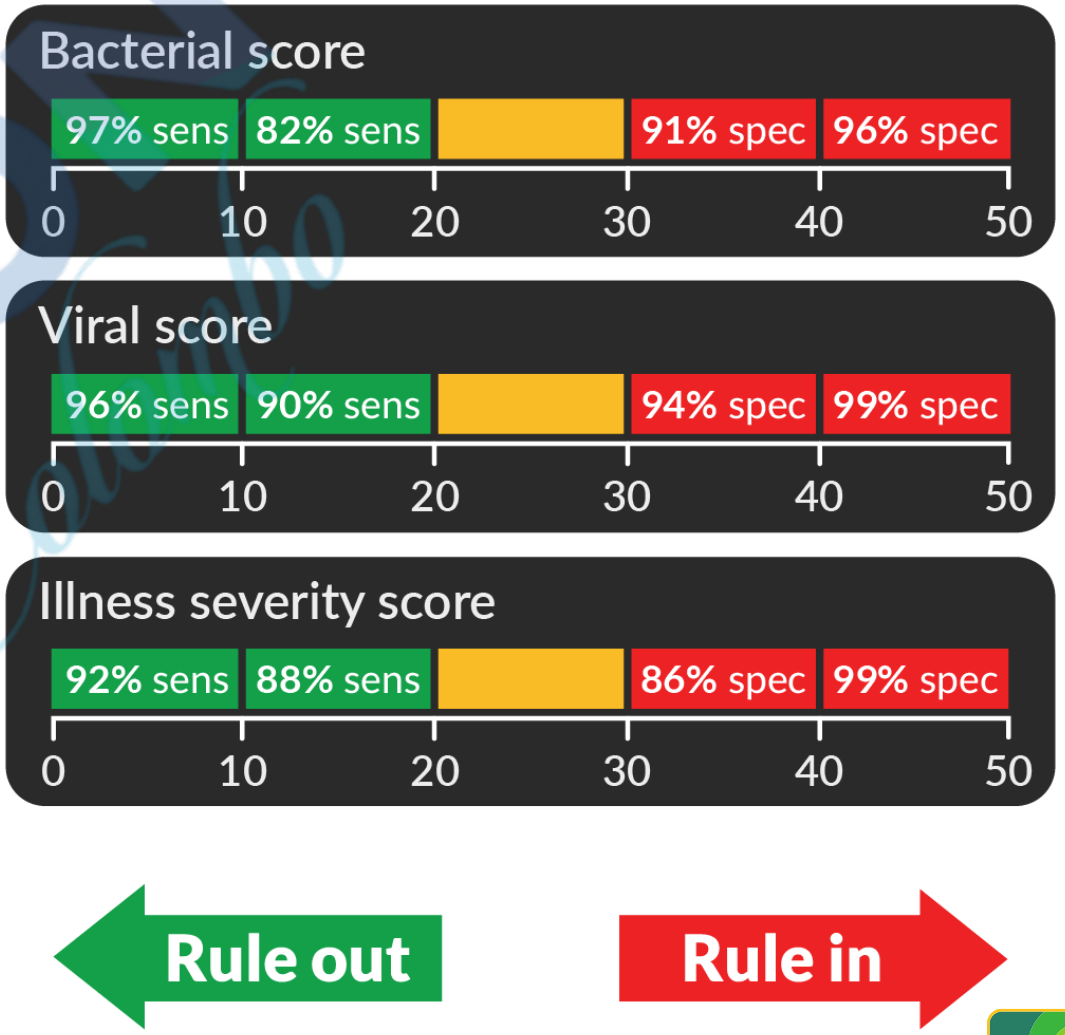
- Rapid results back in 1 hour
- High sensitivity and specificity
- Compares well across sepsis phenotypes

Potential limitations

- If patients are sick enough to be admitted to ICU for sepsis, may already getting antibiotics
- May need higher sensitivity in low risk band to stop antibiotics

Triverity Transcriptomics Assay

- Aid to differentiate bacterial infections, viral infections and non-infectious illness
- Determine the likelihood of 7- day need for mechanical ventilation, vasopressors, and /or renal replacement therapy
- Adults with suspected acute infection or suspected sepsis presenting to the ED
- a transcriptomic-based host response point-of-care test which measures 29 mRNAs

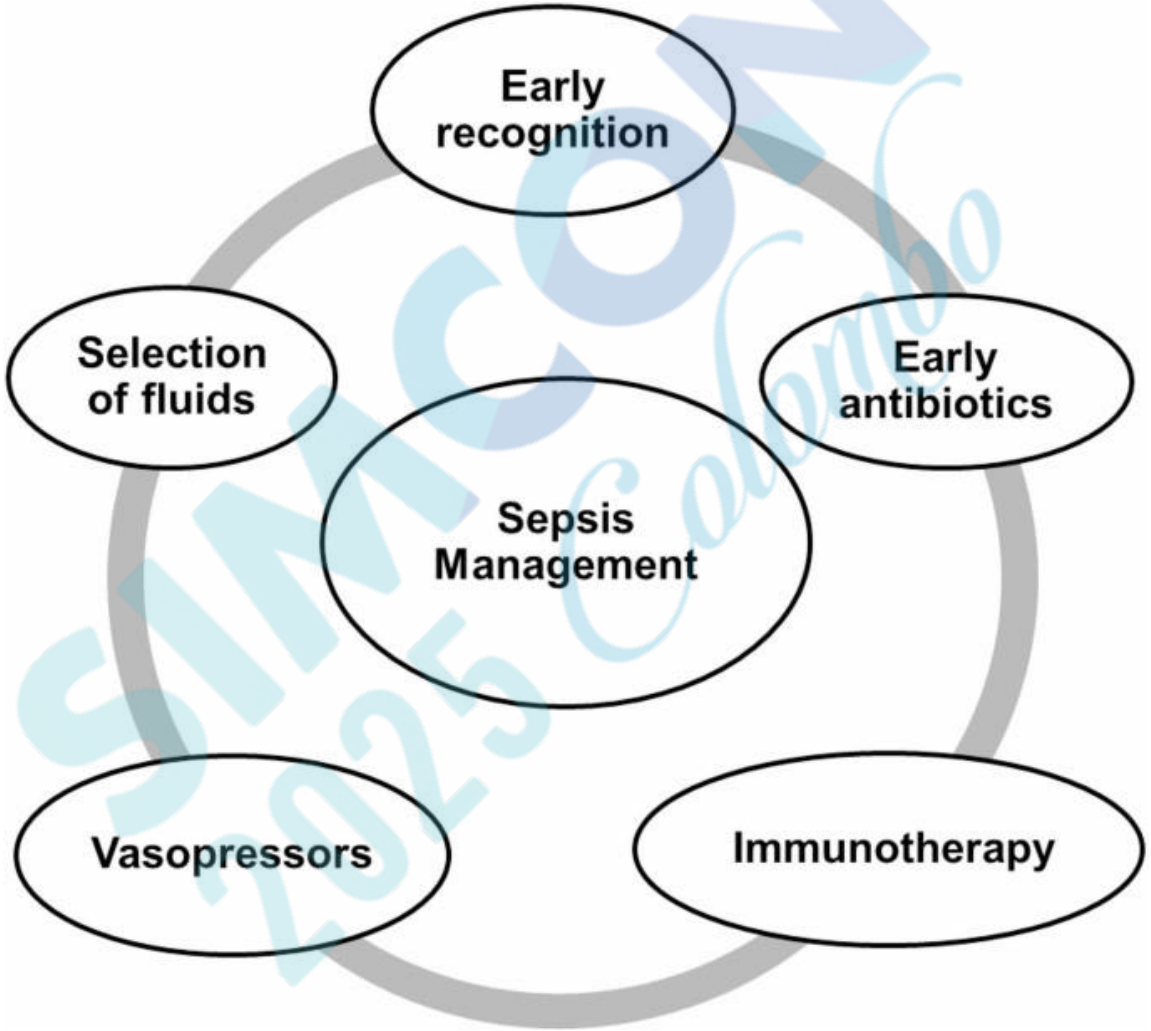


Summary

Test	Indication	What to order on	Population
Cell Based			
MDW	Aid in identifying sepsis within 12h of admissions	All CBC orders from ED	ED
Intellisep	Identifying sepsis within 3 days	Adult, signs and symptoms of infection	ED
Protein Based			
BV	Differentiate bacterial from viral infection	Suspected infection, <7d of symptoms	ED or Urgent Care
Molecular Based			
Septicyte	Differentiate infection positive from infection negative inflammation	Suspected sepsis	ICU, Day 1
Tiverity	Differentiate bacterial, viral and non-infectious. And likelihood of 7d adverse outcomes	Suspected acute infection or sepsis	ED

Multiple sources

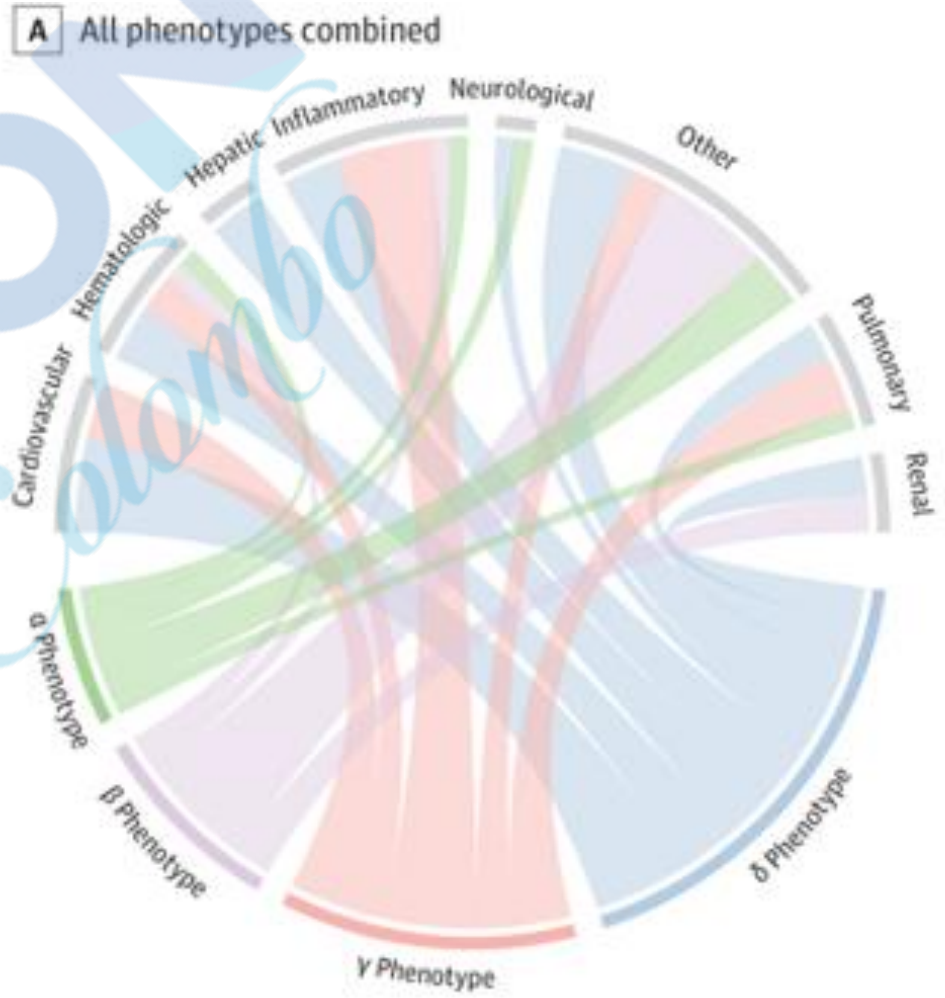
Sepsis Management



Vasiliki Bourika et al; Biomarkers to guide Sepsis Management; Annals of Intensive Care (2025); 15; 103

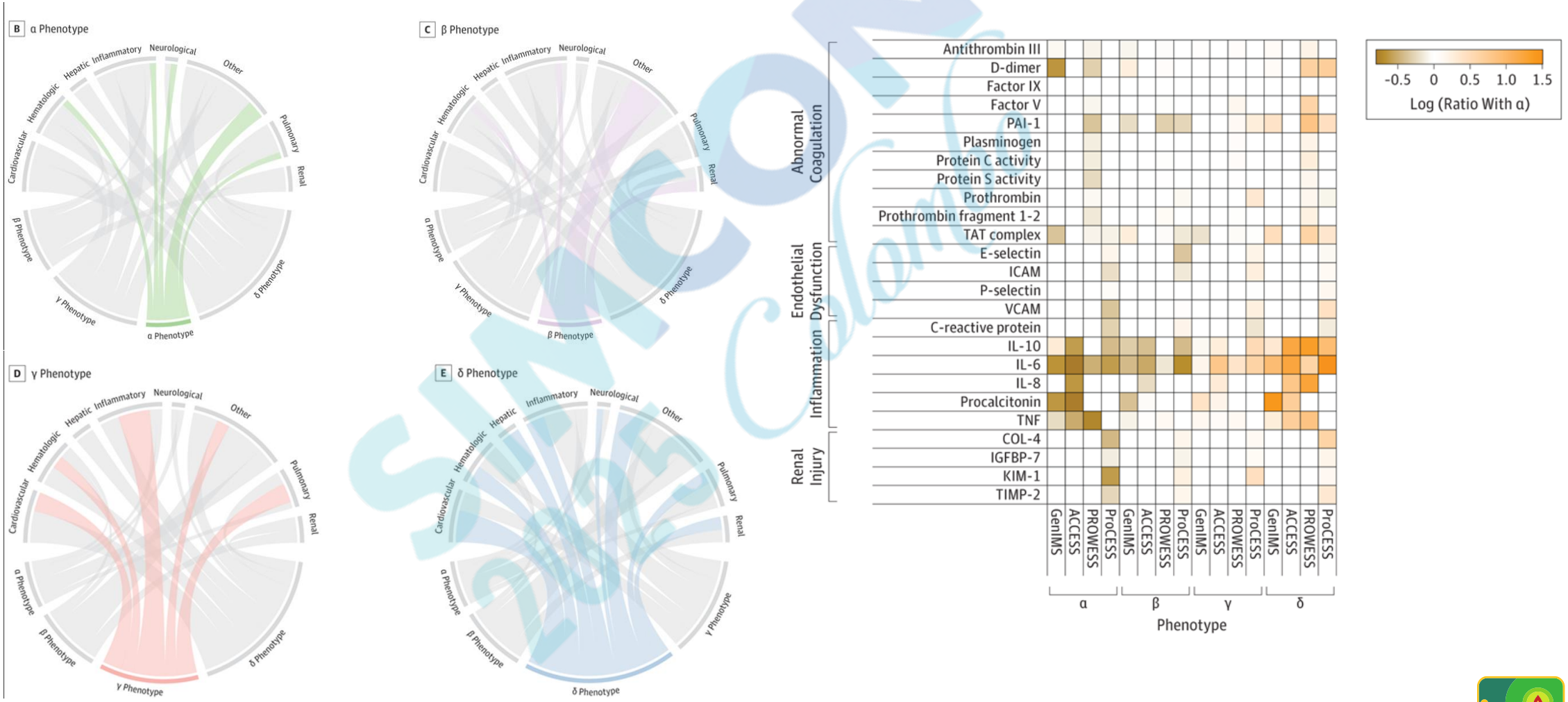
Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

- Retrospective analysis of data sets from 64K patients with sepsis
- 4 clinical phenotypes were identified
- Correlated with host-response patterns and clinical outcomes
- Simulations in 3 RCTS (5K patients) suggested these phenotypes may help in understanding heterogeneity of treatment effects



C.Seymour et al; JAMA; 2019;321;(20):2003-2017

Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis



C.Seymour et al; JAMA; 2019;321;(20):2003-2017

Sepsis Management:

Infection / Antimicrobial Agents

Source Control

Restoration of Adequate Perfusion
30 ml/kg (serial boluses)

Balanced Solutions – RL or PlasmaLyte followed by NS, Albumin

Severe or Persistent Hypotension

- Vasopressor – Norepinephrine, second choice Vasopressin (MAP >/= 65mm hg)
- Decreased CO – Dobutamine or Epinephrine

Adjunctive therapies

Corticosteroids

- Hydrocortisone (200mg/day) with Fludrocortisone combination

Restrictive Blood Product Transfusions

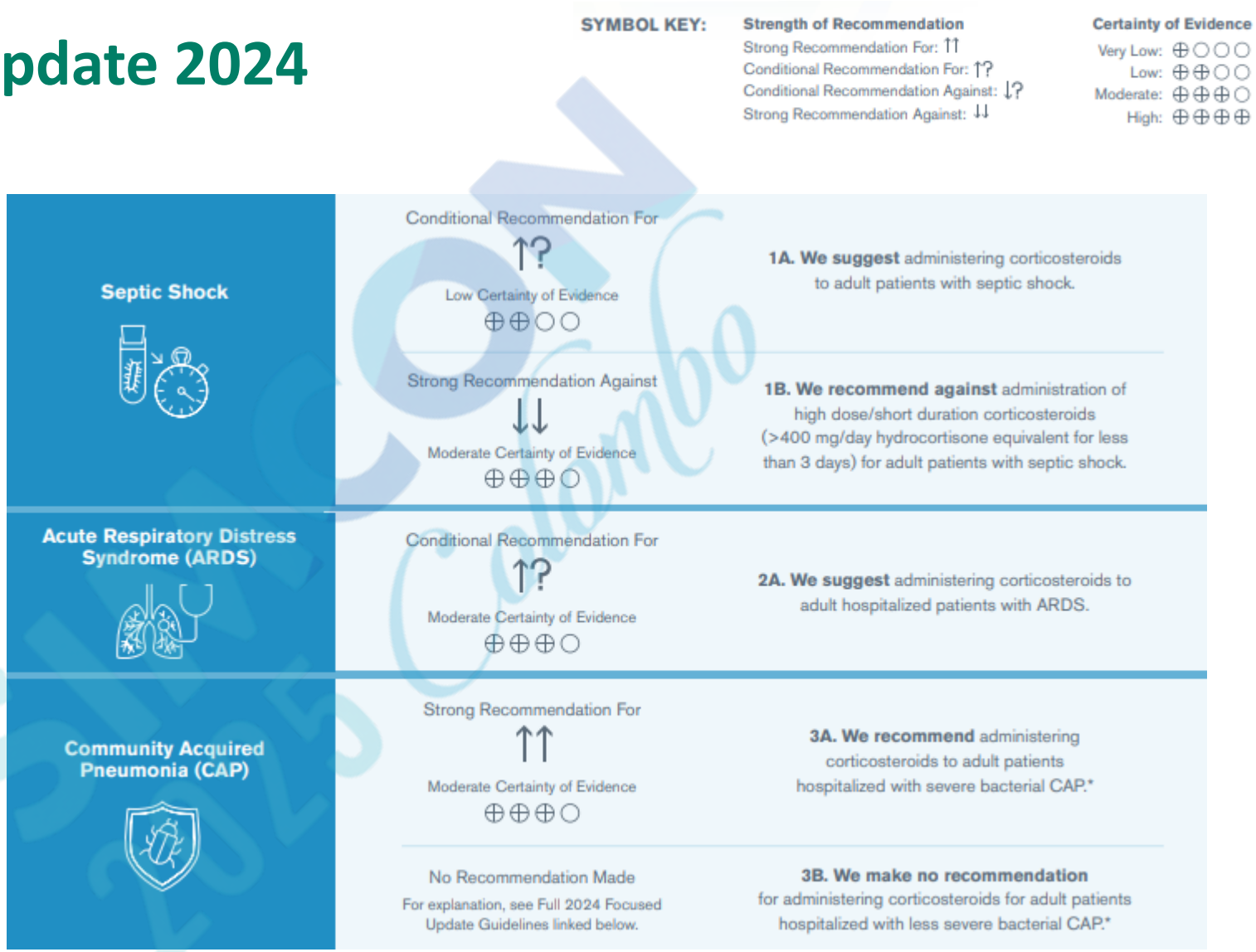
Sodium Bicarbonate (? AKI and pH </= 7.2)

? Methylene Blue

Nuala j. Meyer et al; Sepsis and Septic Shock; December 4, 2024. N Engl J Med 2024;391:2133-2146

SCCM Focused Update 2024

Guidelines on Use of Corticosteroids in Sepsis, ARDS & CAP

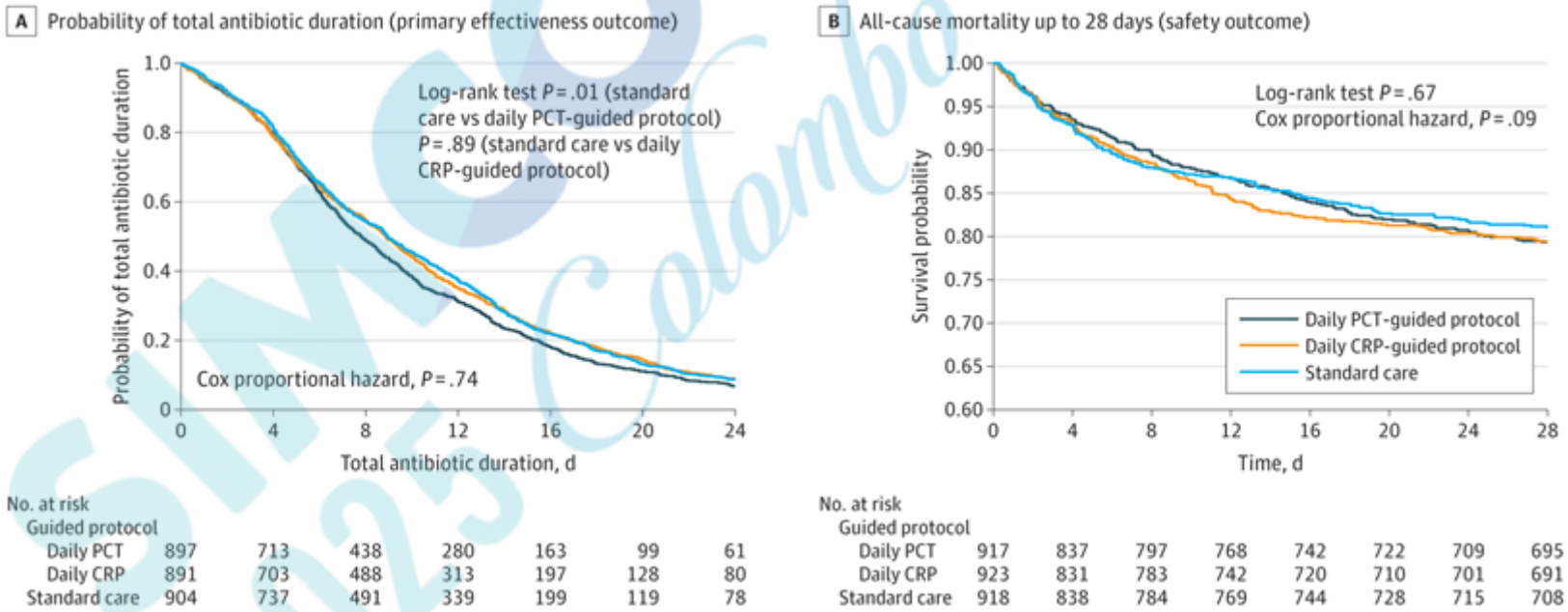


Society of Critical Care Medicine - 2024

The ADAPT-Sepsis Randomized Clinical Trial

In critically ill hospitalized adults with sepsis, there is a significant safe reduction in the total antibiotic days when a daily PCT-guided protocol is administered compared with standard care.

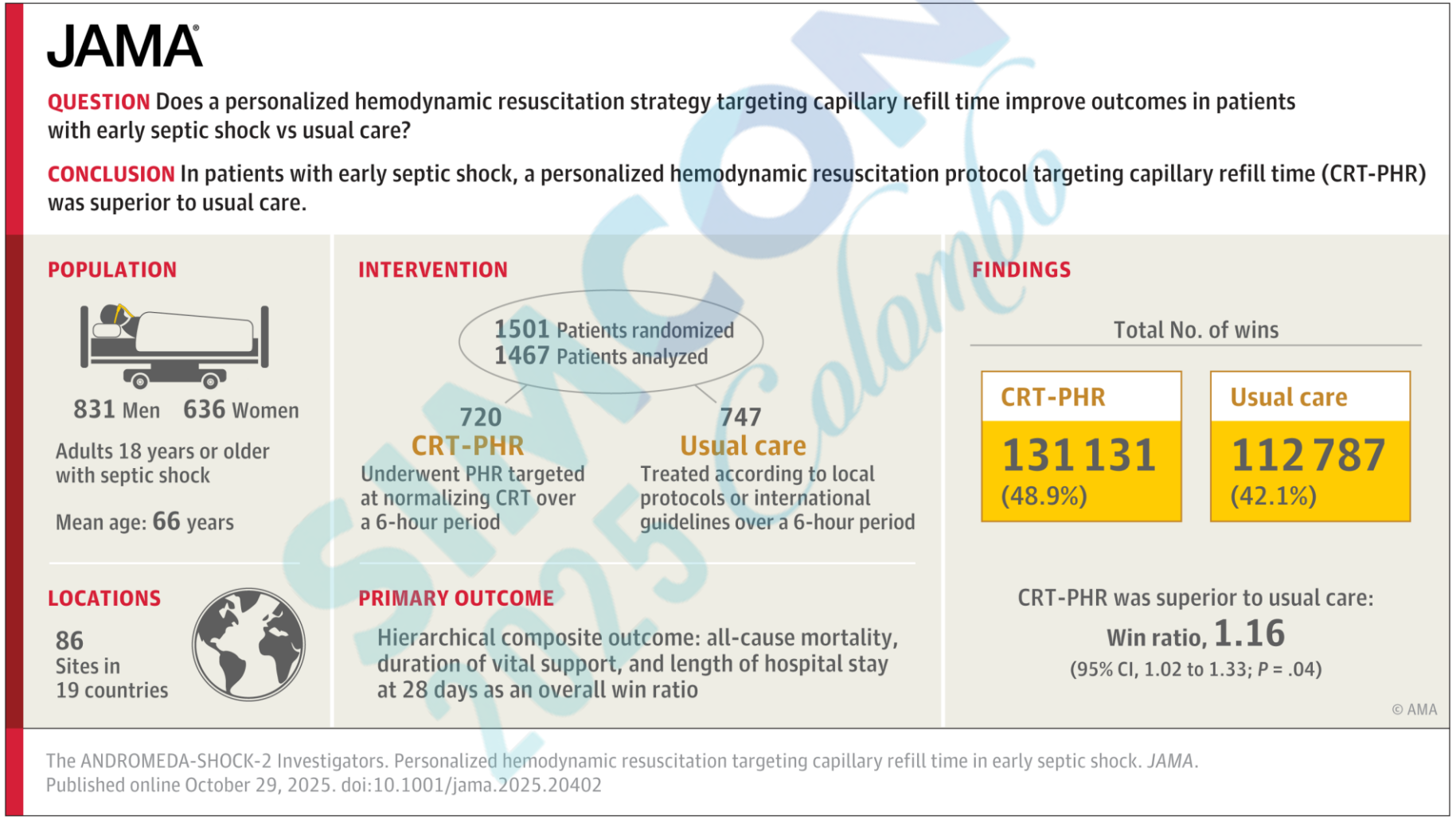
A daily CRP-guided protocol does not reduce the total duration of antibiotics



Paul Dark et al; Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis: JAMA 2025;333;(8):682-693.

ANDROMEDA-SHOCK-2 trial:

Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock



The ANDROMEDA-SHOCK-2 Investigators. Personalized hemodynamic resuscitation targeting capillary refill time in early septic shock. *JAMA*. Published online October 29, 2025. doi:10.1001/jama.2025.20402

Emerging Bio-markers

Heparin-binding protein (HBP):	•Indicates neutrophil activation and guides diagnosis and severity prediction.
Monocyte distribution width (MDW):	•Assesses monocyte activation for early sepsis detection and prognosis.
Interleukin-6 (IL-6) and Interleukin-10 (IL-10):	•Markers for assessing immune activation, cytokine storm, and candidate selection for immunomodulatory agents.
Presepsin:	•Used for distinguishing bacterial sepsis and guiding early intervention.
Ferritin:	•Elevated levels point toward hyperinflammatory states or macrophage activation syndrome, guiding therapy intensity.
sTREM-1 and bioADM:	•Endothelial injury and vascular dysregulation indicators, utilized to personalize vasopressor and organ support strategies.
HLA-DR (Monocyte):	•Low expression signals immunosuppression and suitability for immune-stimulatory therapies.
DPP-3 (Dipeptidyl peptidase 3):	•Linked to organ failure progression; guides use of targeted monoclonal antibody interventions.
Gene-based panels (e.g., CKAP4, FCAR, RNF4, NONO):	•AI-driven panels for rapid stratification and prediction of responsiveness to different immunotherapies.
CBC-derived parameters:	•AI models using complete blood count with differentials and advanced neutrophil phenotype have shown promise for risk scoring and early identification.

Multiple Sources

Traditional v/s Emerging Biomarkers

Feature/Role	Traditional Markers (CRP, PCT, Lactate)	Emerging Biomarkers (HBP, MDW, circRNAs, ncRNAs, gene panels, cell morphology)
Diagnostic Sensitivity	Moderate	Higher
Specificity for Sepsis	Moderate	Higher for stratifying sepsis vs non-infectious SIRS, bacterial vs viral
Speed of Results	Minutes to hours	Minutes for cell morphology tests; hours for gene panels
Mechanistic Insights	Limited (general inflammation or perfusion)	Directly reflect immune activation, cell death, organ injury, gene expression
Prognosis/Severity Stratification	Limited	Accurate risk stratification and identification of endotypes

Investigational Therapies:

Immune Checkpoint Inhibitors (ICIs): Therapies such as nivolumab (anti-PD-1), BMS-936559 (anti-PD-L1), and TIGIT antibodies are being studied to reverse sepsis-induced immunosuppression and restore T-cell function.

Cytokine-Based Immunomodulation: Agents like interferon-gamma (rhIFN-γ), anakinra (IL-1 receptor antagonist), granulocyte-macrophage colony stimulating factor (GM-CSF), and thymosin α1 (Tα1) are employed based on the patient's immune activation state. These therapies aim to either dampen hyperinflammation (e.g., anakinra, tocilizumab) or stimulate immunity when immuno-paralysis is detected (e.g., IFN-γ, GM-CSF, Tα1).

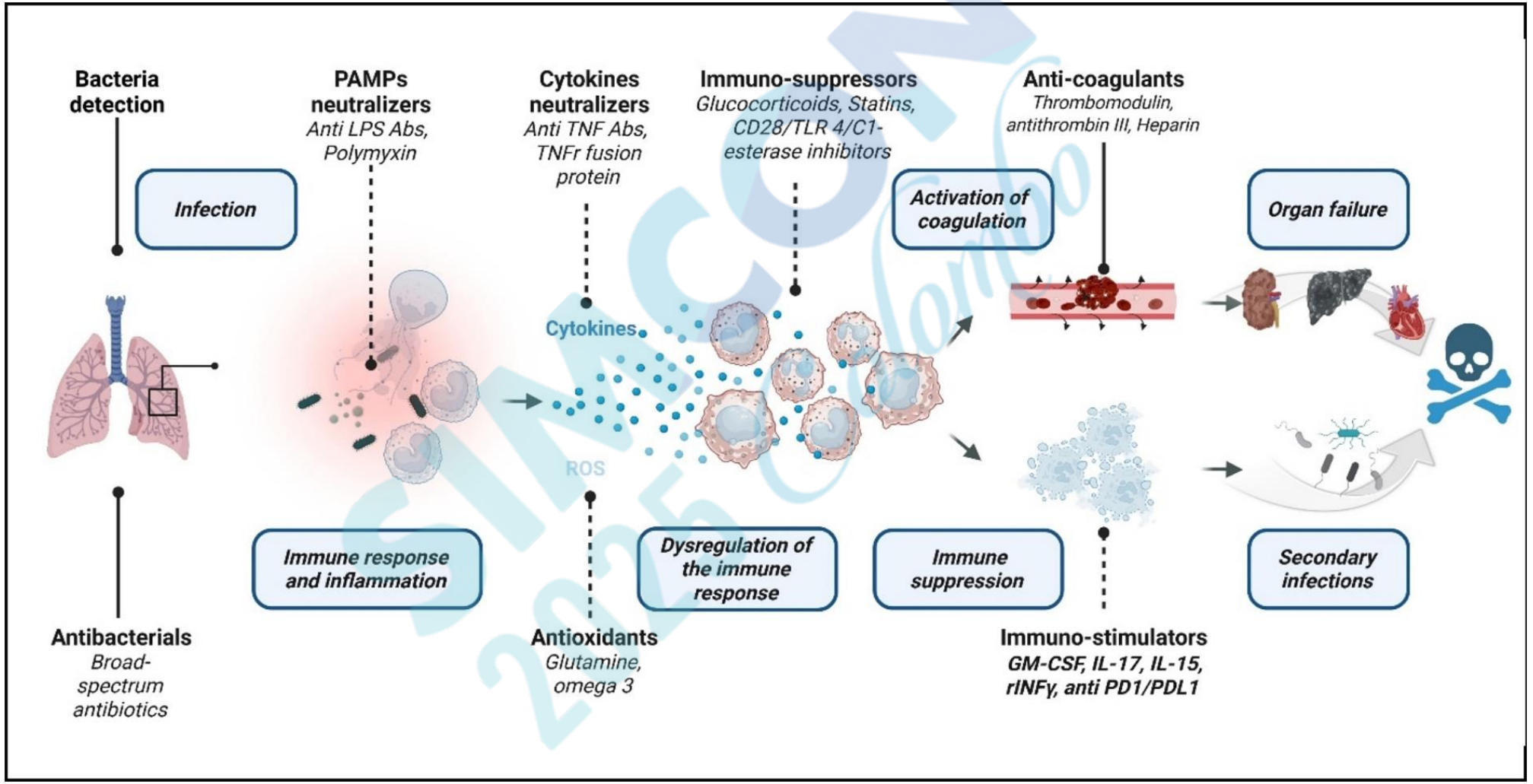
Monoclonal Antibodies: Novel monoclonal antibodies such as procizumab (targeting DPP3) and adrecizumab (targeting bio-adrenomedullin) are used to restore vascular tone and counteract organ failure in septic shock.

IgM-Enriched Immunoglobulin Preparations: Pentaglobin and IgGAM, rich in IgM and IgA, are administered to sepsis patients with low immunoglobulin levels, based on serum titers, to enhance infection clearance.

Cellular Therapies: Mesenchymal stem cells (MSCs) are being evaluated for their ability to reduce organ injury and modulate immune responses through anti-inflammatory and antimicrobial mechanisms.

Precision Medicine Initiatives: Clinical trials such as ImmunoSep stratify sepsis patients based on immune signatures (hyperinflammatory vs. immunosuppressed) and deliver targeted immunotherapy, resulting in better outcomes.

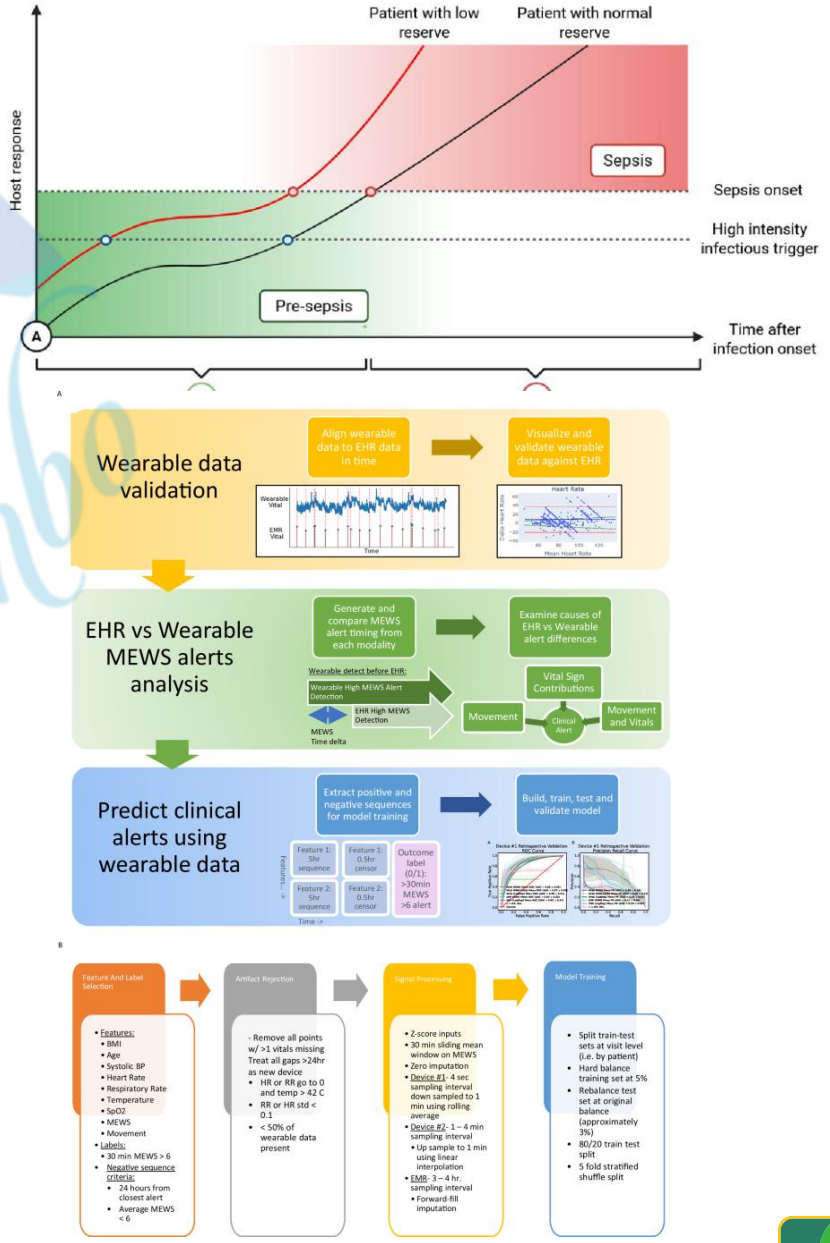
Targeted Therapies:



Younes Louaguenouni et al: Nano-particles-based approaches for Sepsis treatment: Current trends and practices. Journal of Controlled Release: 386 (2025) 114139

Pre-Sepsis

- The current Sepsis – 3 definition may be too late for effective intervention
- Pre-Sepsis phase refers to host's initial response to infection (trigger)
- Early Immune dysregulation before organ damage
- Early detection and intervention may lead to better outcomes
- ? Wearables



R. Gerard. July 31, 2025; Is "pre-sepsis" the new sepsis? A narrative review
M.Scheid et al : Development and validation of a clinical wearable deep learning based continuous in-hospital deterioration prediction model; 16, 9513 (Nov 3, 2025)

Emerging Concepts in Sepsis Management & Research

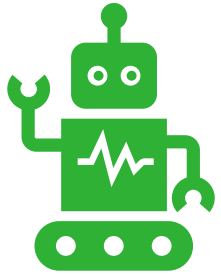
Precision diagnostics

Newer biomarkers like heparin-binding protein (HBP), monocyte distribution width (MDW), **Interleukin-6 (IL-6),** interleukin-10 (IL-10), and gene-based panels (e.g., CKAP4, FCAR, RNF4, NONO) are offering higher sensitivity and specificity.

Personalized therapies

Machine learning techniques are now being used to identify and classify sepsis sub-phenotypes (**personalized medicine**), allowing for more precise risk classification and targeted therapy, moving away from the "one-size-fits-all" approach

Emerging Concepts in Sepsis Management & Research



Advanced Digital Tools:

AI and ML now assist in early sepsis recognition, patient risk stratification, outcome prediction, and treatment personalization by analyzing large clinical and molecular datasets.

Innovative Immunotherapies:

To correct immunosuppression and restore balance, research interests has grown in therapies that address the immune dysfunctions of sepsis, notably **immune checkpoint inhibitors (ICIs) and cytokine-based immunomodulation**.

Summary

Sepsis is the **most common diagnosis requiring hospitalization** and is associated with **substantial mortality and healthcare costs**.

The definition of Sepsis has evolved to more accurately identify patients with infection who suffer **organ dysfunction** due to a **dysregulated immune response**

Challenges to accurate diagnosis of Sepsis include **heterogeneity of clinical presentation, non-infectious mimics of disease, difficulty in identifying infections and co-morbid conditions** that may mask sepsis onset.

Emerging concepts focuses on **precision medicine, early detection using advanced technologies and integrated, multi-modal approaches** to diagnosis and management.

Thank you !

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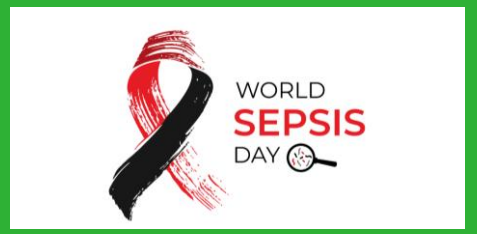

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