Importance of Early Sepsis Diagnosis for Clinical Care and Patient Outcomes

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Henry Ford Hospital
Clinical Professor, Wayne State University
Detroit, Michigan

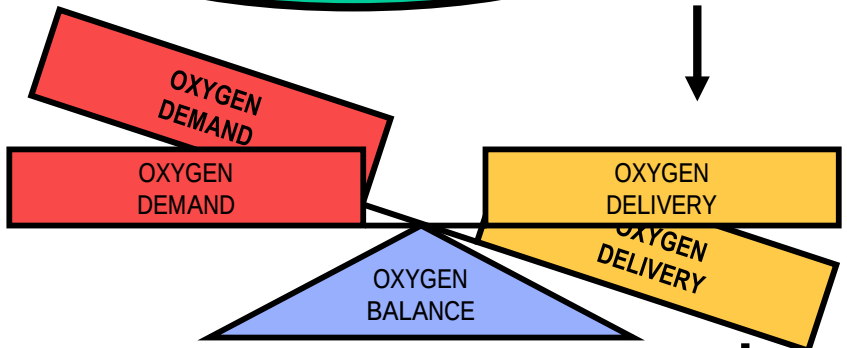
- No competing interests
- Thank you:
  - National Academies
  - Gordon and Betty Moore Foundation
  - Planning Committee

The Early Pathogenesis of Sepsis

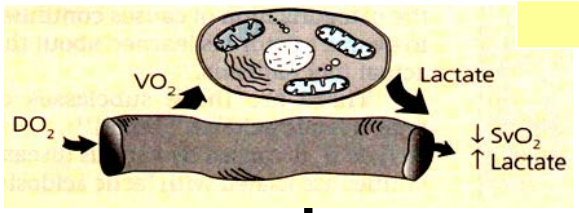
Infectious Insult

Increased Metabolic Demands: Fever, Tachypnea

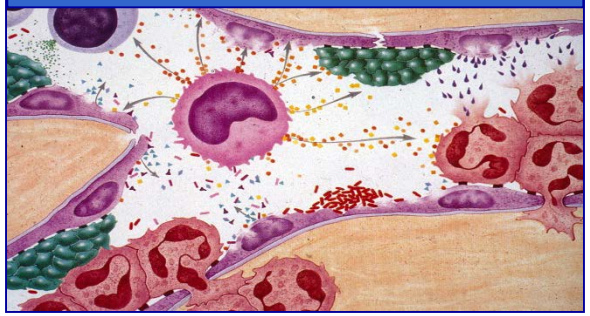
Hypovolemia,Vasodilation & Myocardial Depression



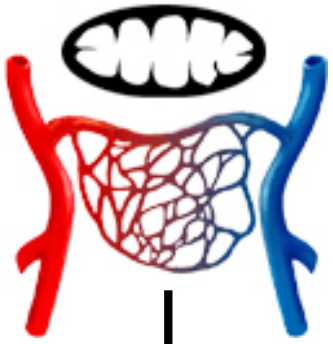
Global Tissue Hypoxia



Generalized Inflammation



Microvascular Alterations: Impaired Tissue Oxygen Utilization



Organ Dysfunction and Increased Mortality

Generalized Inflammation

Systemic … y syndrome: An alternati … syndrome”

ERNEST BENJAM … N OROPELLO, MD; THOMAS J. IBER …

Karimova A, Intensive Care Med, 2001

Hemodynamic and Inflammatory Phenotypes

SHOCK, Vol. 45, No. 1, pp. 4–9, 2016

COMPREHENSIVE INTERPRETATION OF CENTRAL VENOUS OXYGEN SATURATION AND BLOOD LACTATE LEVELS DURING RESUSCITATION OF PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK IN THE EMERGENCY DEPARTMENT

Tae Gun Shin,* Ik Joon Jo,* Sung Yeon Hwang,* Kyeongman Jeon,† Gee Young Suh,† Euna Choe,* Young Kun Lee,* Tae Rim Lee,* Won Chul Cha,* and Min Seob Sim*

*Department of Emergency Medicine; and †Department of Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Lactate Measurements in Sepsis-Induced Tissue Hypoperfusion: Results From the Surviving Sepsis Campaign Database

Brian Casserly, MD[1,3,4]; Gary S. Phillips, MAS[5]; Christa Schorr, RN, MSN[6]; R. Phillip Dellinger, MD[6]; Sean R. Townsend, MD[7]; Tiffany M. Osborn, MD, MPH[8]; Konrad Reinhart, MD[9]; Narendran Selvakumar, MD[4]; Mitchell M. Levy, MD[2,3]

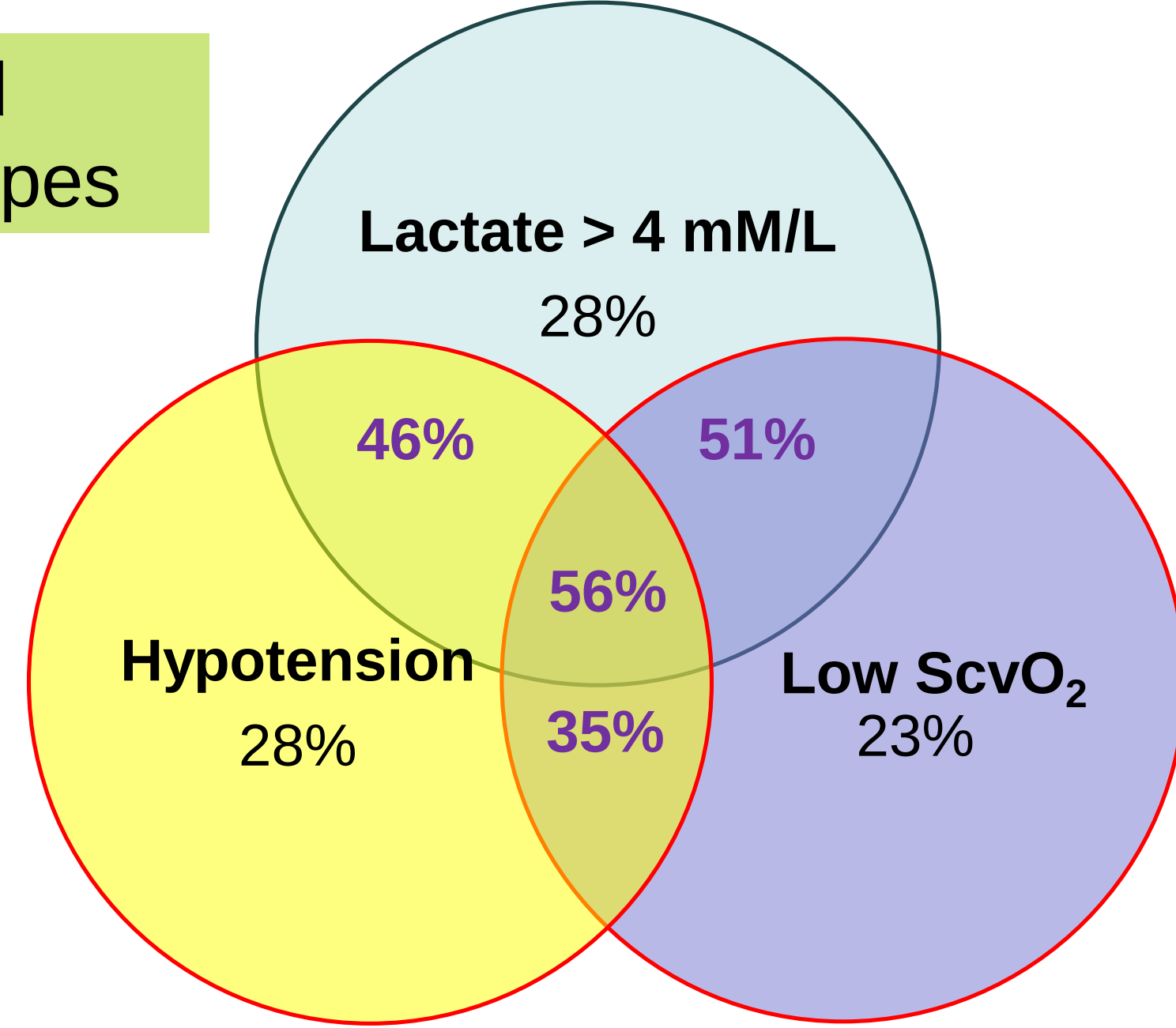
Crit Care Med, 2014

CURRENT OPINION

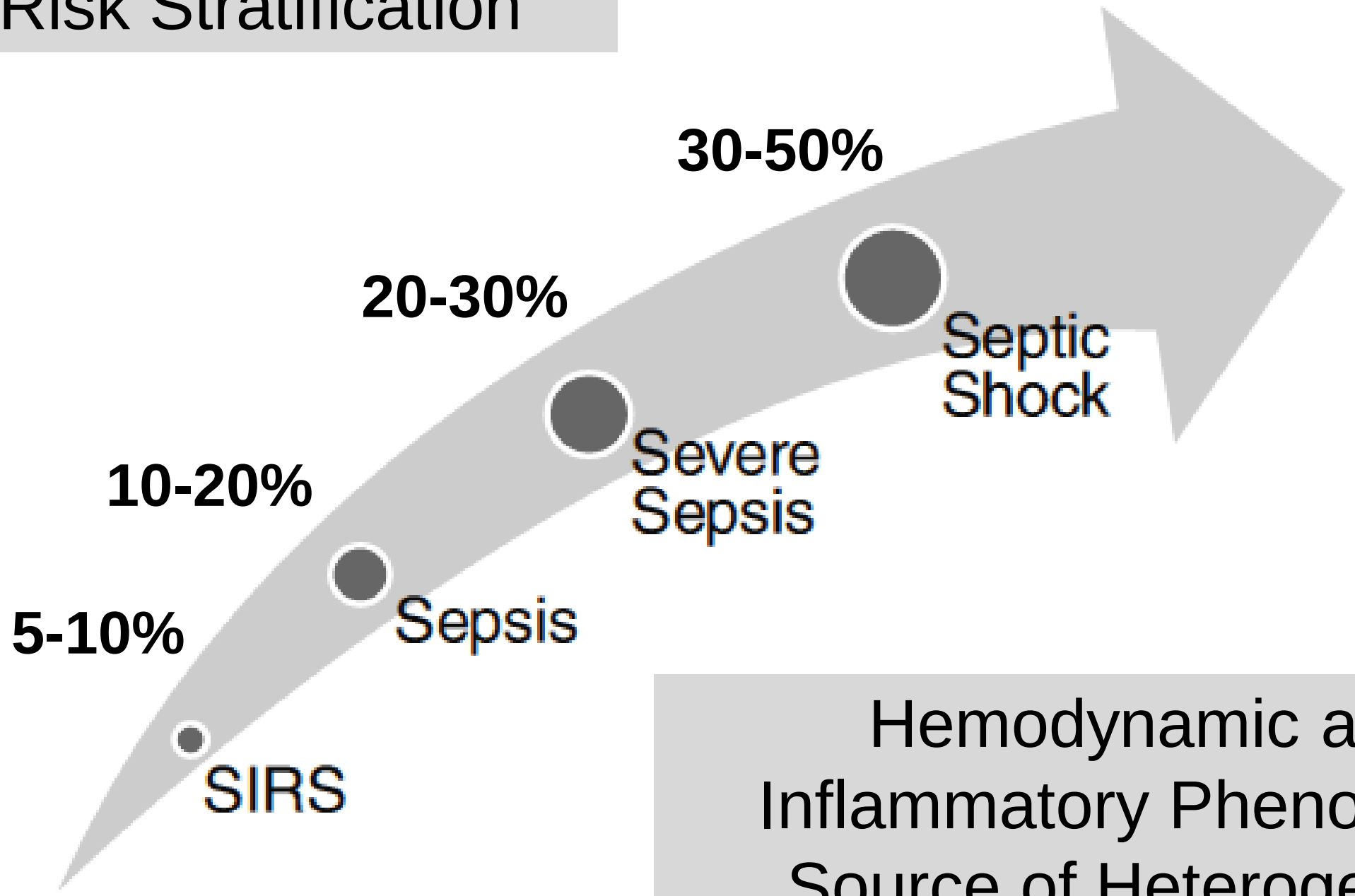
Oxygen extraction and perfusion markers in severe sepsis and septic shock: diagnostic, therapeutic and outcome implications

Emanuel P. Rivers[a], Angel Coz Yataco[b], Anja Kathrina Jaehne[a], Jasreen Gill[a], and Margaret Disselkamp[b]

Volume 21 • Number 5 • October 2015



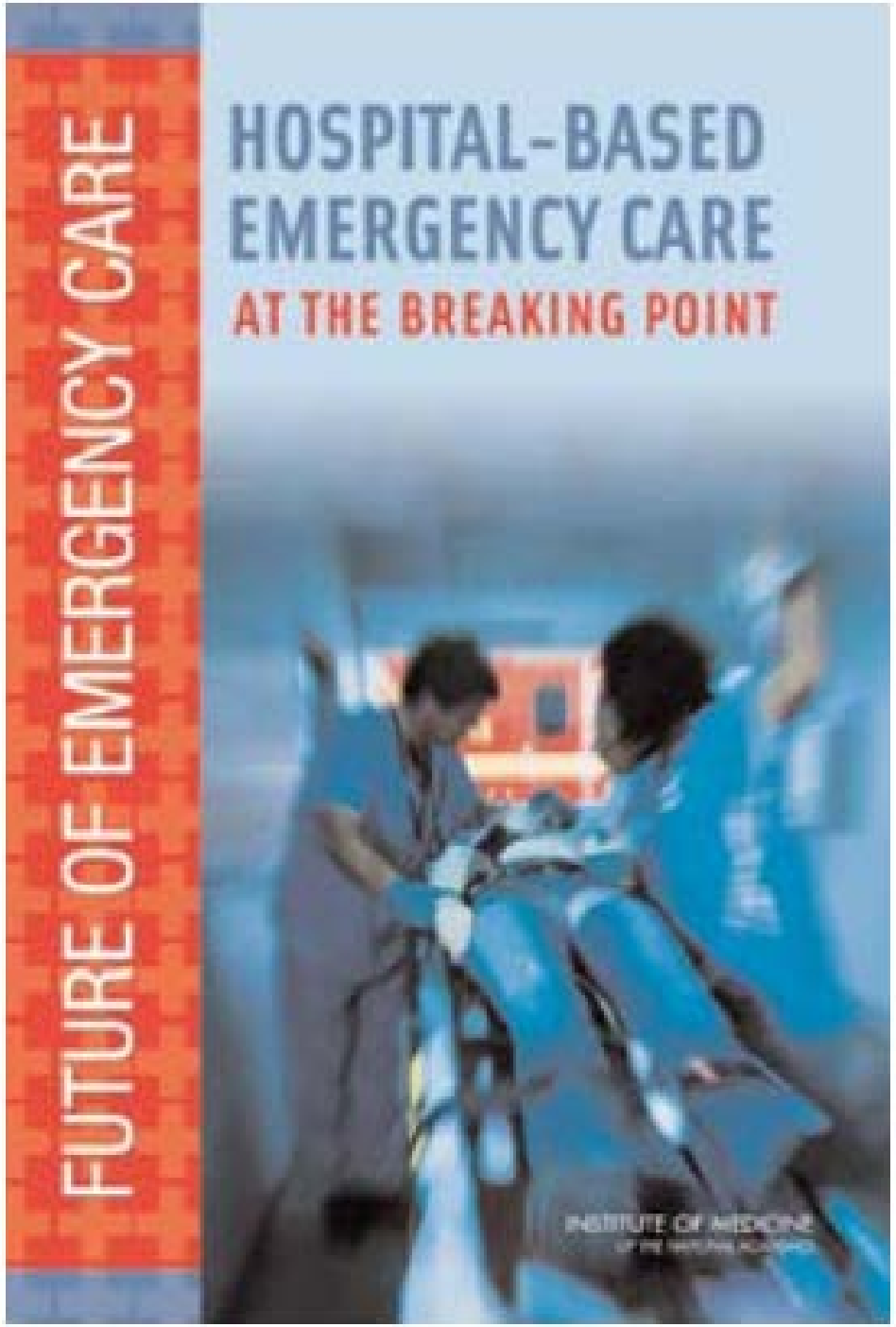
Risk Stratification



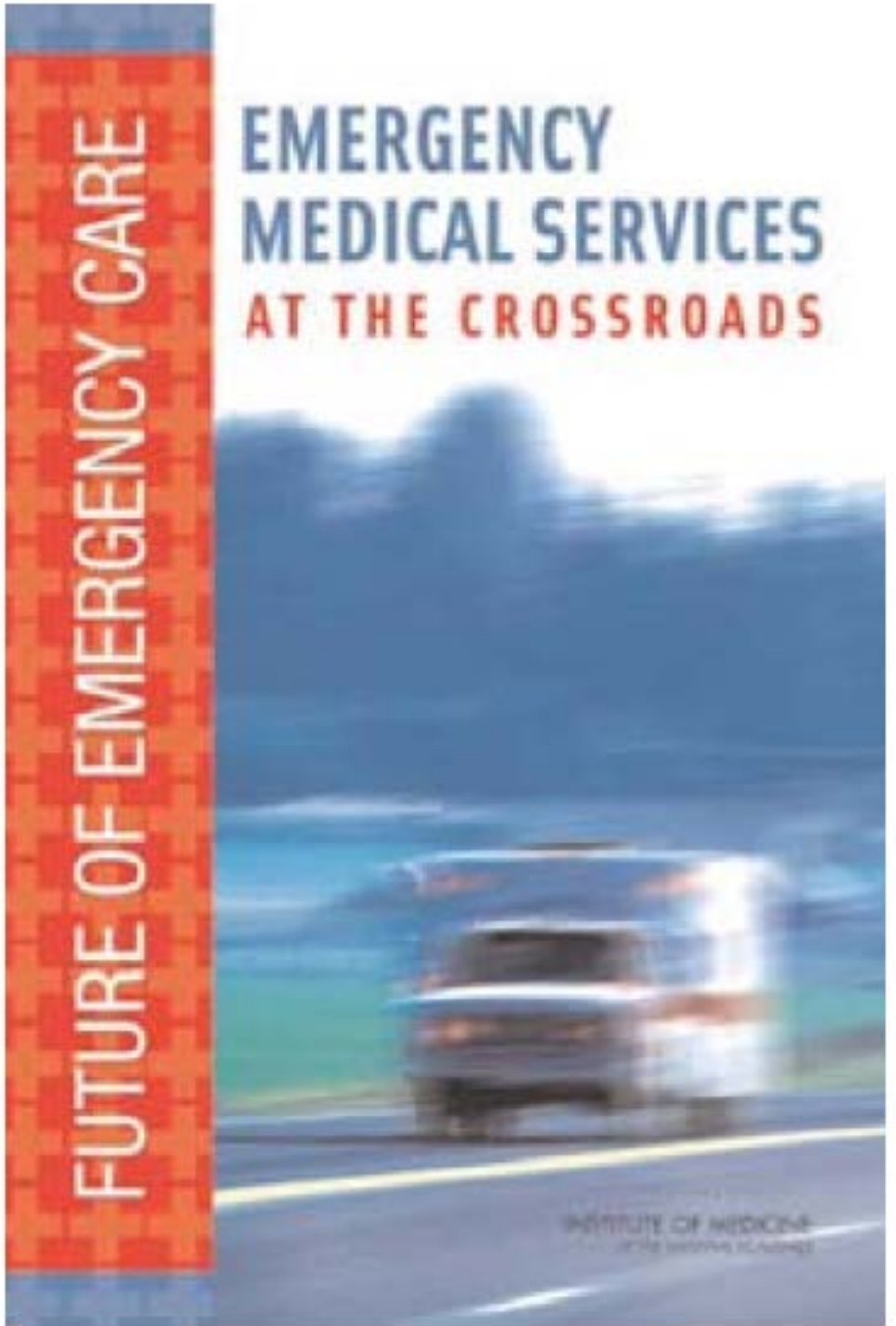
Hemodynamic and Inflammatory Phenotypes: Source of Heterogeneity

Why Expand The Diagnostic and Therapeutic Landscape of Sepsis Care?

Going to the disease instead of waiting for it to come to you



IOM Reports
1990's

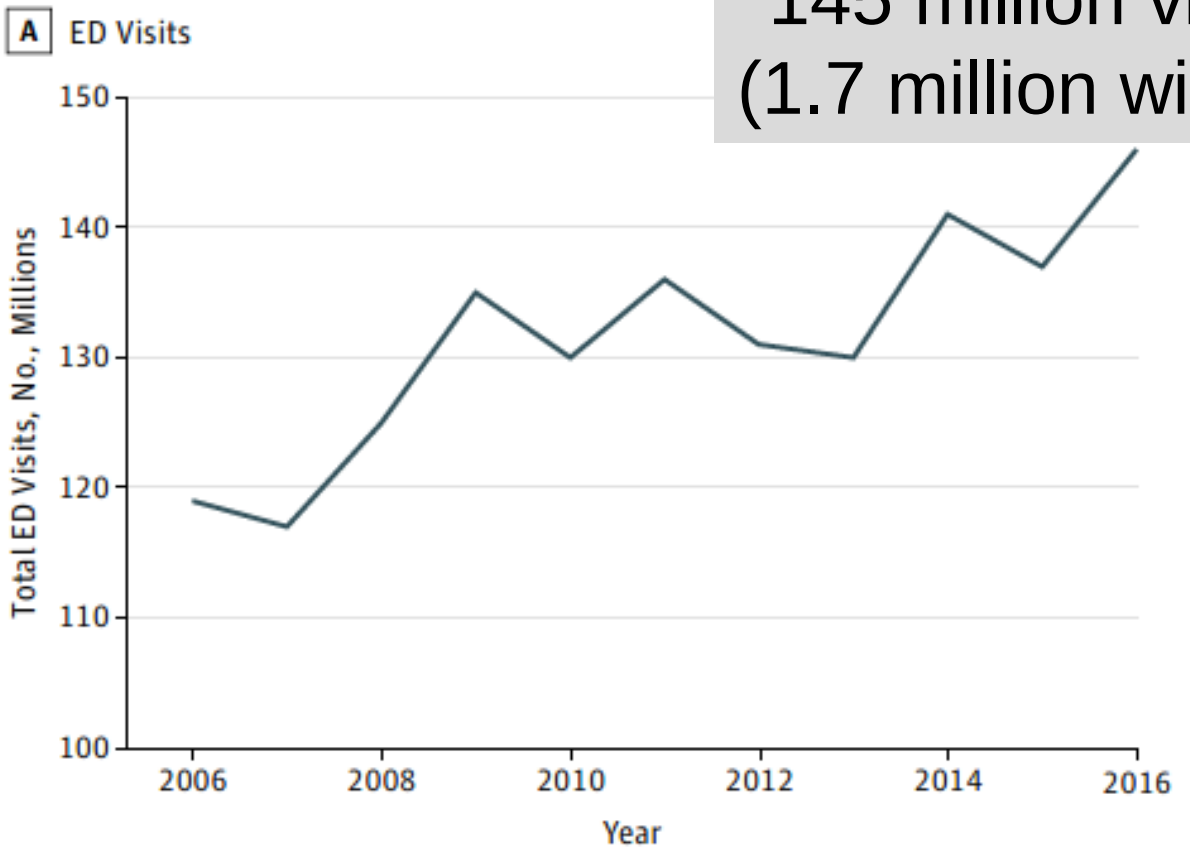


Original Investigation | Emergency Medicine

US Emergency Department Visits and Hospital Discharges Among Uninsured Patients Before and After Implementation of the Affordable Care Act

Adam J. Singer, MD; Henry C. Thode Jr, PhD; Jesse M. Pines, MD

145 million visits/year
(1.7 million with sepsis)



The number of ED visits between 2013 and 2016 increased 2.3 million per year

AMA Network Open, April 19, 2019

The Reality of Early Sepsis Care: Location Matters

Pre-Hospital or Transfers

ED

General IPD Floors and Post Op

ICU

50%

Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study

Mitchell M Levy, Antonio Artigas, Gary S Phillips, Andrew Rhodes, Richard Beale, Tiffany Osborn, Jean-Louis Vincent, Sean Townsend, Stanley Lemeshow, R Phillip Dellinger

Lancet Infect Dis 2012; 12: 919–24

	USA	Europe	p value*
Hospital mortality if origin is emergency department	3008 (24·6%)	736 (34·1%)	<0·0001
Hospital mortality if origin is ward	1661 (34·9%)	1481 (43·5%)	<0·0001
Hospital mortality if origin is ICU	644 (36·1%)	502 (48·0%)	<0·0001

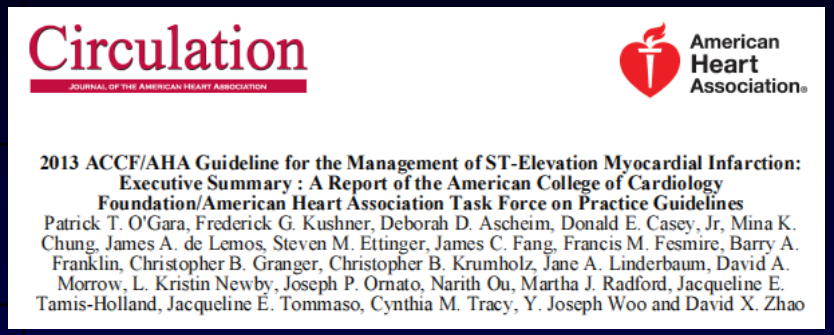
The Landscape of Early Sepsis Care in 1997

The Landscape of Early Sepsis Care -1997

- No SIRS criteria
- No risk stratification
  - No Lactate
- No antibiotic recommendations
- No quality assurance measures
- No Surviving Sepsis Campaign
- No CMS measure

- No resuscitation standards:
  - No fluid therapy recommendations
  - No MAP endpoints
  - No recognition of myocardial dysfunction
  - No reassessment standards

	Cases/year	Mortality (%)
Stroke	591,996	6-7
AMI	540,891	10
Trauma	697,025	5-16
Sepsis	859,858	15-20
Severe Sepsis	791,000	27-40
Septic Shock	200,000	36-47
Pneumonia	1,187,180	5-9


Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Patrick T. O'Gara, Frederick G. Kushner, Deborah D. Ascheim, Donald E. Casey, Jr, Mina K. Chung, James A. de Lemos, Steven M. Ettinger, James C. Fang, Francis M. Fesmire, Barry A. Franklin, Christopher B. Granger, Christopher B. Krumholz, Jane A. Linderbaum, David A. Morrow, L. Kristin Newby, Joseph P. Ornato, Narith Ou, Martha J. Radford, Jacqueline E. Tamis-Holland, Jacqueline E. Tommaso, Cynthia M. Tracy, Y. Joseph Woo and David X. Zhao


Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live℠

Part 11: Adult Stroke : 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Edward C. Jauch, Brett Cucchiara, Opeolu Adeoye, William Meurer, Jane Brice, Yvonne (Yu-Feng) Chan, Nina Gentile and Mary Fran Hazinski

Right Care Right Now

Fundamentals of Disaster Management
fccs FDM
Fundamental Critical Care Support

Critical Care is not a location, it is a process. It takes place not only in the ICU but everywhere."

Dr. Peter Safar, 1974

Society of Critical Care Medicine
The Intensive Care Professionals

Task Force of the American College of Critical Care Medicine

Practice parameters for hemodynamic support of sepsis in adult patients in

Crit Care Med 1999 ;27:639-60

- Fluids
- Vasopressors
- Inotropes
- Lactate
- Hematocrit of 30%
- SvO_2

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

November 8, 2001

Changing the Landscape

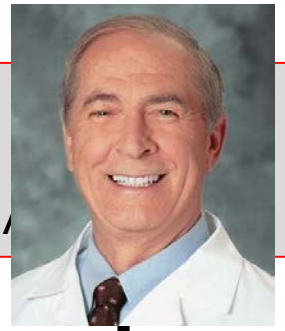
Systems Approach To Poor Sepsis Care

A Composite of Multiple Studies

The Sepsis Policy Landscape

SSC originated

The Sepsis Alliance Dr. Flatly



NQF Approval #2 with ProCESS, ARISE and ProMISE results

Gabby's Law, Ill

NQF Approval #3

2003	2004	2007	2008	2008	2012	2013	2014	2015	2016	2016	2017

SSC #1

SSC #2

SSC #3

NY state Rory Rules and 1st US Senate Hearing

CMS IQR and Specifications SEP-1

SSC #4 and CDC

CMS 1st 2-years

CDC Centers for Disease Control and Prevention

Saving patients from sepsis is a race against time CDC calls sepsis a medical emergency; encourages prompt action for prevention, early recognition

Tuesday, August 23, 2016, 1:00 p.m. ET

https://www.youtube.com/watch?v=pRtwfsTIR9s

VOLUME 345 NOVEMBER 8, 2001 NUMBER 19

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAYSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

Improved
Usual-Standard Care

SIRS
Cultures
Antibiotics
Lactate Screening
Fluid Challenge
Re-assesment
Early ICU Admission

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

NEJM, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

NEJM, 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

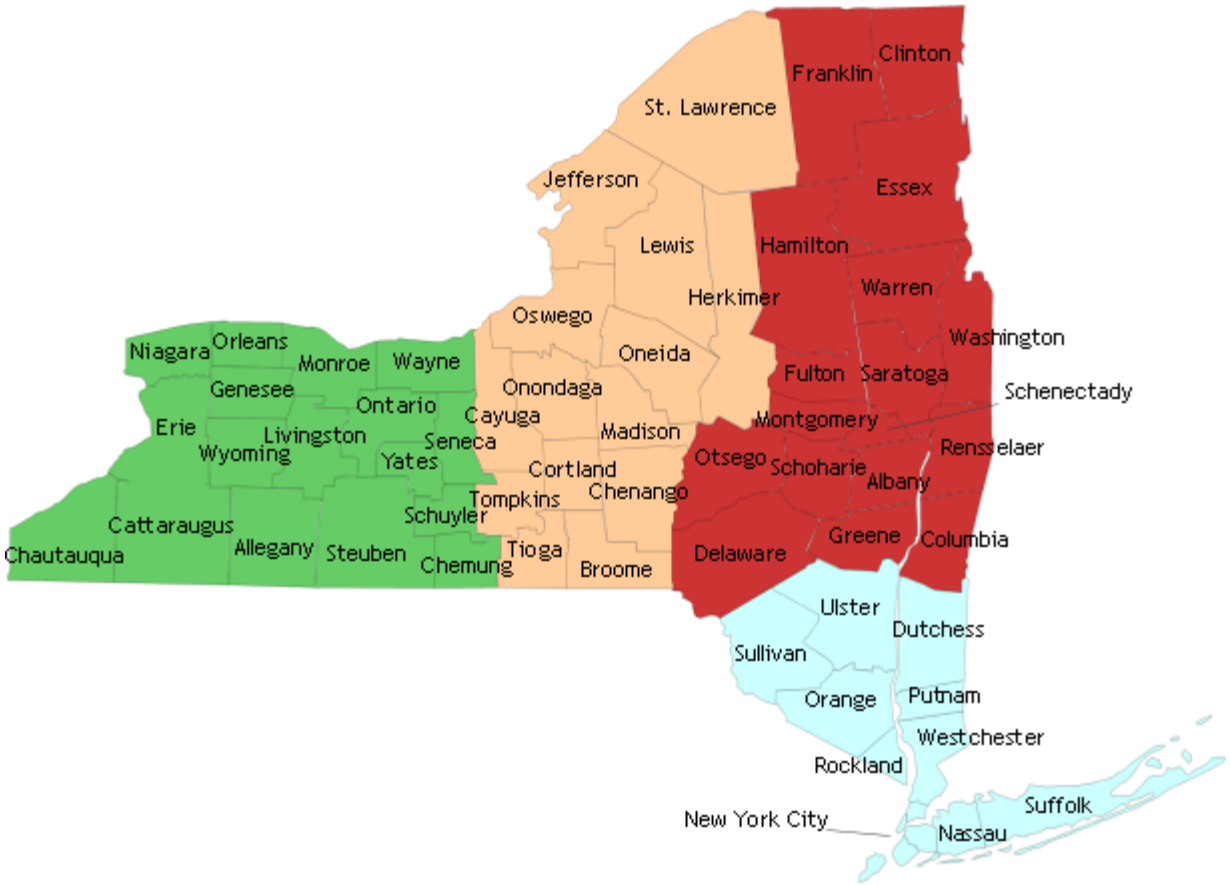
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

NEJM, 2014

The Outcome Evidence of Early Sepsis Care

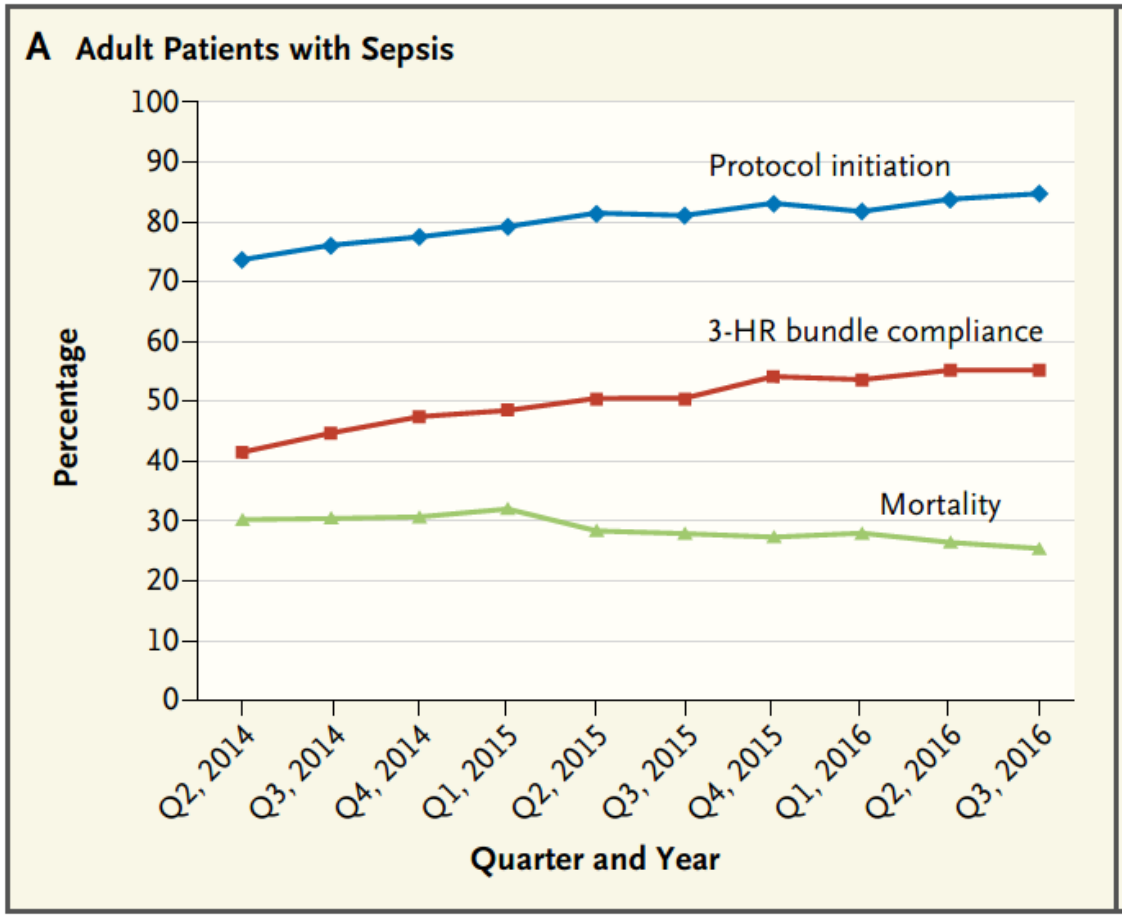
Results From State to National Health Care Policy



GREATER NEW YORK HOSPITAL ASSOCIATION
GNYHA

CMS
CENTERS for MEDICARE & MEDICAID SERVICES

The NEW ENGLAND JOURNAL of MEDICINE



Rates of Initiation of Sepsis Protocol, Compliance with Protocol Bundle, Patients with Sepsis in New York State, 2014–2016.

Data are from the New York State Department of Health.[2]

ORIGINAL ARTICLE

June, 2017

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

- Nearly 50,000 patients with sepsis treated at 149 New York hospitals.
- Compliance with early intravenous, fluids, antibiotics, and other elements of the early-resuscitation bundle increased from 41.5% to 55.2%.
- Mortality fell from 30.2% to 25.4%.
- Decreased hospital LOS, Levy, 2018.

Appendix Table 8: Probabilities and odds ratios of in-hospital mortality based on separate logistic regression models containing the compliance risk factor along with each of the variables in the risk adjusted model for hospital mortality developed through collaboration with the State of New York.

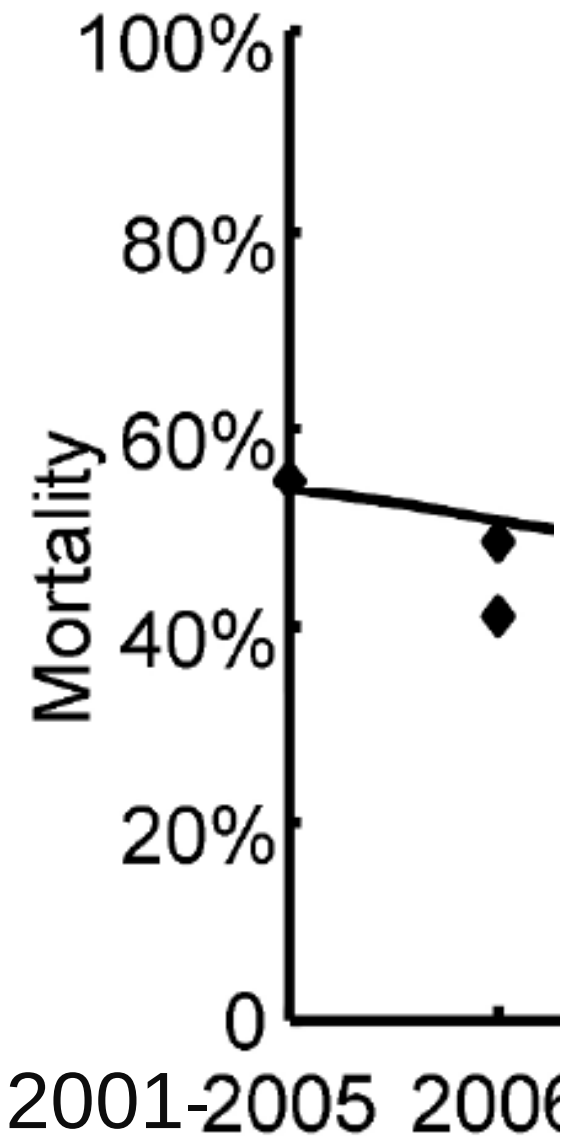
Compliance risk factor	N	Probability of in-hospital mortality %	95% CI	OR for In-hospital mortality	95% CI	*p*-value	
3-hour bundle							5.1%
No	29,134	29.3	28.8 – 29.8	0.73	0.70 – 0.76	< 0.001	
Yes	44,996	24.2	23.9 – 24.6				
6-hour bundle							4.5%
No	46,390	27.4	27.1 – 27.8	0.74	0.71 – 0.77	< 0.001	
Yes	27,361	22.8	22.3 – 23.3				
Lactate reported in 3 hours							4.4%
No	7,721	30.2	29.3 – 31.1	0.76	0.72 – 0.81	< 0.001	
Yes	66,409	25.8	25.5 – 26.1				
Blood cultures obtained prior to antibiotics							4.3%
No	18,179	30.2	29.6 – 30.8	0.72	0.69 – 0.75	< 0.001	
Yes	55,951	24.9	24.6 – 25.3				
Antibiotics started in 3 hours							4.0%
No	11,448	29.7	28.9 – 30.4	0.78	0.74 – 0.82	< 0.001	
Yes	62,682	25.7	25.3 – 26.0				
Adequate fluids in hypotensive or elevated lactate							4.0%
No	24,052	32.1	31.6 – 32.7	0.79	0.76 – 0.83	< 0.001	
Yes	27,855	28.1	27.6 – 28.6				
Vasopressors if refractory hypotension							0.6%
No	12,449	38.2	37.4 – 39.0	1.03	0.97 – 1.10	0.32	
Yes	12,145	38.8	38.0 – 39.6				
Lactate re-ordered if missing or elevated							5.0%
No	9,893	40.0	39.1 – 40.9	0.77	0.72 – 0.82	< 0.001	
Yes	12,979	35.0	34.3 – 35.8				

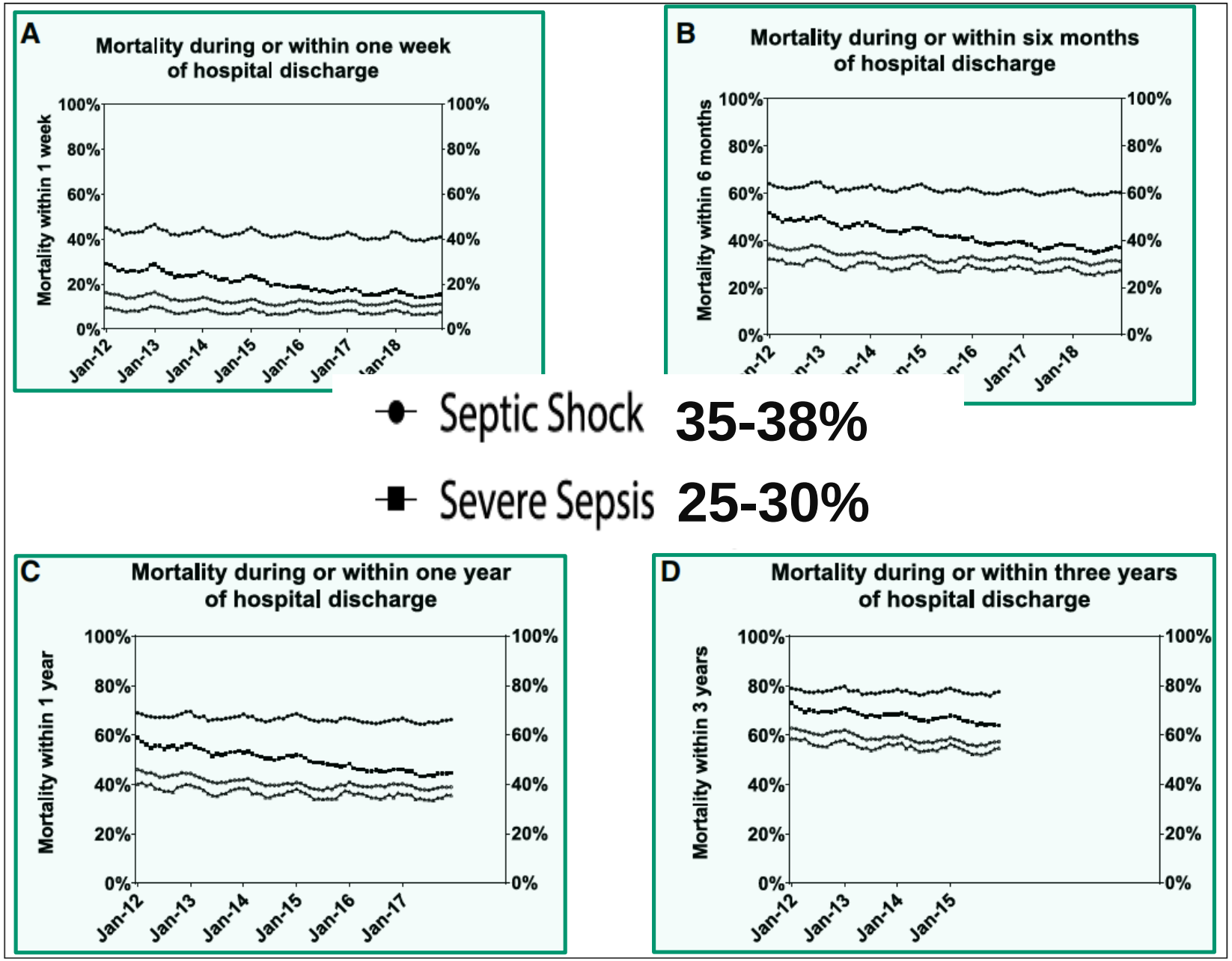
"A SINGLE ARROW IS EASILY BROKEN, BUT NOT TEN IN A BUNDLE."

CHINESE PROVERB

Individual Bundle Elements Make Up the Concept

There is still much work to do!


100%
80%
60%
40%
20%
0
Mortality
2001-2005
2006


A
Mortality during or within one week of hospital discharge
Mortality within 1 week
B
Mortality during or within six months of hospital discharge
Mortality within 6 months
Septic Shock 35-38%
Severe Sepsis 25-30%
C
Mortality during or within one year of hospital discharge
Mortality within 1 year
D
Mortality during or within three years of hospital discharge
Mortality within 3 years
Jan-12
Jan-13
Jan-14
Jan-15
Jan-16
Jan-17
Jan-18


4 2015

Inflammatory Phenotypes Guiding Therapy: Revisiting Previous Therapies

Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: A phase III, randomized, double-blind, placebo-controlled, multicenter trial

Steven M. Opal, MD; Charles J. Fisher, Jr, MD, FCCM; Jean-François A. Dhainaut, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCM; Rainer Brase, MD; Stephen F. Lowry, MD; Jerald C. Sadoff, MD; Gus J. Slotman, MD, FCCM; Howard Levy, MD; Robert A. Balk, MD, FCCM; Maire P. Shelly, FRCA; John P. Pribble, PharmD; John F. LaBrecque, PhD; Janice Lookabaugh, MPH; Hugh Donovan, BS; Howard Dubin, MD, FCCM; Robert Baughman, MD; James Norman, MD; Eric DeMaria, MD; Klaus Matzel, MD; Edward Abraham, MD, FCCM; Michael Seneff, MD; The Interleukin-1 Receptor Antagonist Sepsis Investigator Group*

Conclusions: A 72-hr, continuous intravenous infusion of rhIL-1ra failed to demonstrate a statistically significant reduction in mortality when compared with standard therapy in this multicenter clinical trial. If rhIL-1ra treatment has any therapeutic activity in severe sepsis, the incremental benefits are small and will be difficult to demonstrate in a patient population as defined by this clinical trial. (Crit Care Med 1997; 25:1115–1124)

Table 1. Inclusion criteria for the interleukin-1 receptor antagonist trial in severe sepsis

1. Clinical evidence of infection, as suggested by, but not limited to, the presence of one or more of the following signs within the previous 72 hrs
   a. Presence of polymorphonuclear cells in a normally sterile body fluid
   b. Culture or Gram stain of blood, sputum, urine, or normally sterile body fluid is positive for a pathogenic microorganism
   c. Chest radiograph is consistent with a diagnosis of pneumonia
   d. Focus of infection is identified by visual inspection (e.g., ruptured bowel with the presence of free air or bowel contents in the abdomen found at the time of surgery; wound with purulent drainage; radiographic or computed tomography evidence of an abscess or osteomyelitis; etc.)
   e. Patient has an underlying disease or condition that is likely to be associated with infection (e.g., ascending cholangitis, ischemic bowel, etc.)

2. Evidence of a systemic response to infection, as defined by the presence of all of the following signs within the previous 24 hrs
   a. Fever or hypothermia (core temperature of ≥38.0°C [≥100.4°F] or ≤36.0°C [≤96.8°F])
   b. Tachycardia (HR of ≥90 beats/min), except in patients receiving a β-adrenergic receptor blocking agent or with a rate control pacemaker
   c. Tachypnea (RR of ≥20 breaths/min while spontaneously breathing) or patient requires mechanical ventilation

It is also possible that this cytokine inhibitor has significant therapeutic actions, but that this activity cannot be convincingly demonstrated with this clinical trial design. Human sepsis is a complex, dynamic, and heterogeneous clinical syndrome that is difficult to accurately recognize in its early stages (21–28). The inability to define accurately a discriminatory patient population for sepsis trials remains the principal impediment to further progress in the field of sepsis research. The ideal patient population would be those patients with reversible physiologic derangements at the early phases of the cytokine-mediated, systemic inflammatory response syndrome (13). Patients who have potential major morbidity or mortality primarily attributable to sepsis would be the optimal study population for sepsis trials (22).

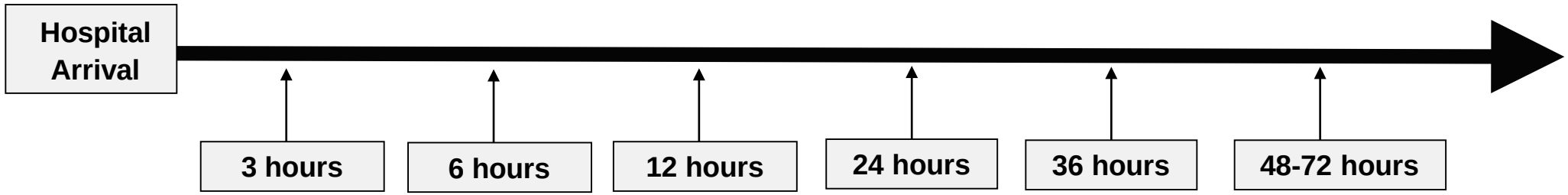
SHOCK, Vol. 39, No. 2, pp. 127–137, 2013

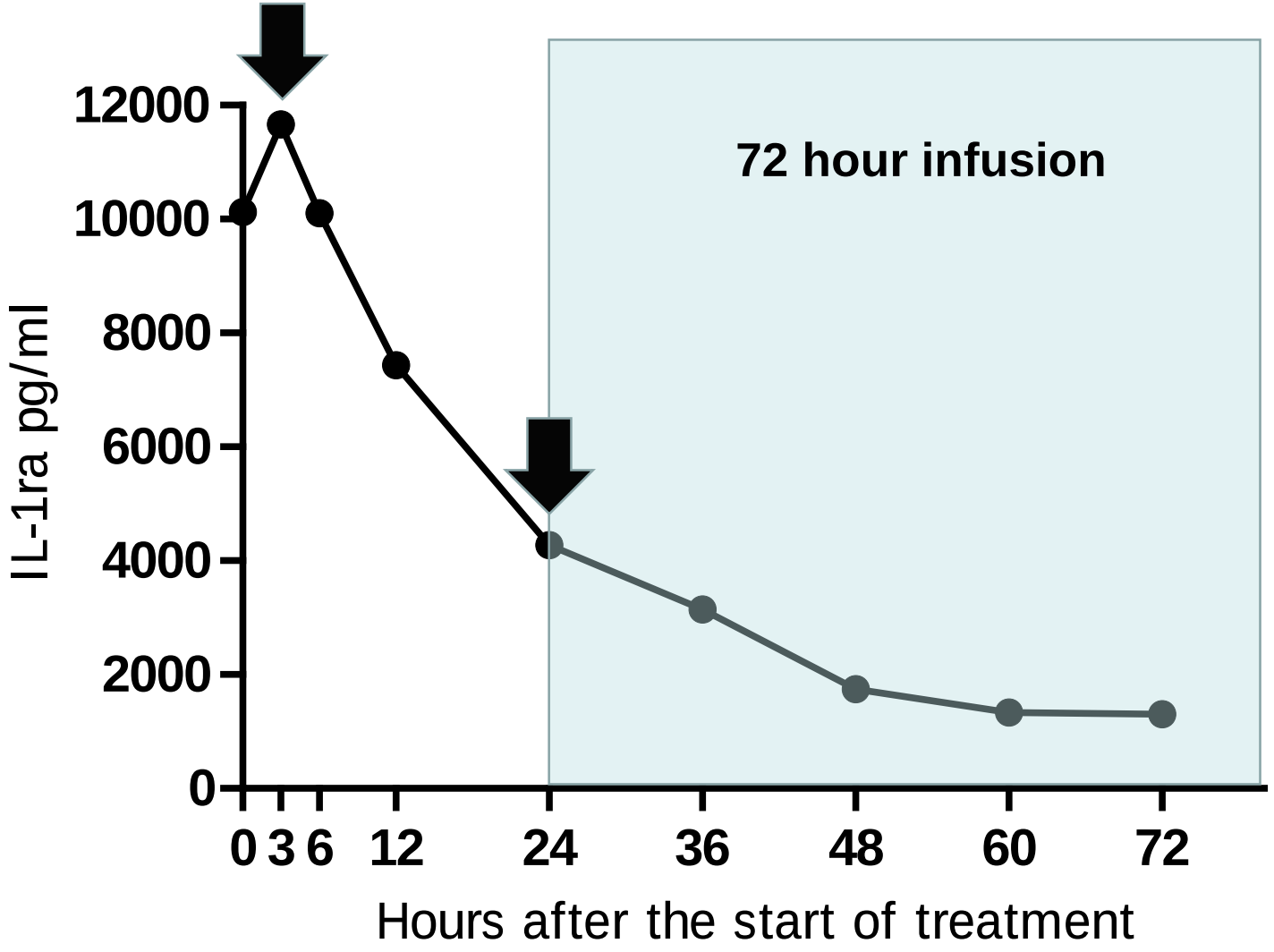
Review Article

EARLY BIOMARKER ACTIVITY IN SEVERE SEPSIS AND SEPTIC SHOCK AND A CONTEMPORARY REVIEW OF IMMUNOTHERAPY TRIALS: NOT A TIME TO GIVE UP, BUT TO GIVE IT EARLIER

Emanuel P. Rivers,* Anja Kathrin Jaehne,* H. Bryant Nguyen,† Demosthenes G. Papamatheakis,‡ Daniel Singer,§ James J. Yang,‖ Samantha Brown,* and Howard Klausner*

**Department of Emergency Medicine and Surgery, Henry Ford Hospital, Detroit, MI; †Departments of Emergency Medicine and Medicine, Critical Care, Loma Linda University, Loma Linda; and ‡Division of Pulmonary and Critical Care, University of California, San Diego, CA; §Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY; and ‖Department of Biostatistics and Epidemiology, Henry Ford Hospital, Detroit, Michigan*

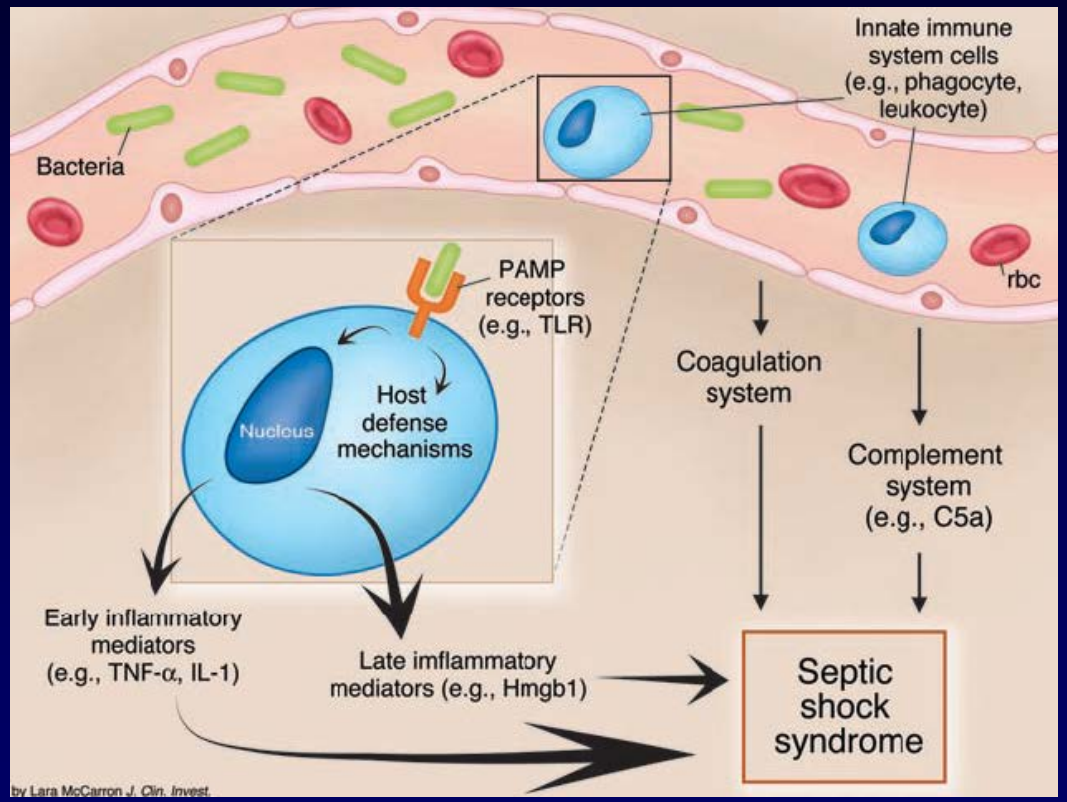




- Peak concentration at 3 hours.
- Enrollment window up to 24 hours after onset.
- Drug be g infusion after the window of maximal biomarker activity.

Opal SM, Crit Care Med 1997;25:1115-24.
Fisher CJ, JAMA 1994;271:1836-43.
Fisher CJ, Crit Care Med 1994;22:12-21.
Boermeester MA, Arch Surg 1995;130:739-48.

The Futures of Diagnostics



- **Multiple markers define disease and transitions more comprehensively.**
- **Multi-marker panels can aid in differential diagnosis and better define therapy.**

Importance of Early Diagnosis and Clinical Care