New Definitions: What do we follow?

B. Taylor Thompson M.D.

Professor of Medicine,

Harvard Medical School

Sepsis Definitions 2017: Disclosures

NHLBI:

- Medical Director, PETAL CCC
- Co-I, MSCs and Carbon Monoxide for ARDS

Industry: Consultant, DSMB Member/Chair, Author, Editor for:

- ACI Clinical, American Thoracic Society, Asahi Kasei, BioAegis, Bristol Myers Squibb, DaVita, Farron, Ferring, Glaxo Smith Kline InterMune, Ra, Radius Health, Roche/Genentech, UpToDate, Vertex

Outline

- Review of the Sepsis-3 Definition
- Predictive Validity (high event rate) does not necessarily lead to Predictive Enrichment (high ARR and RRR from treatment)

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Developing a New Definition and Assessing New Clinical Criteria for Septic Shock

For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Manu Shankar-Hari, MD, MSc; Gary S. Phillips, MAS; Mitchell L. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPH; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCP; for the Sepsis Definitions Task Force

Literature review, Delphi, 3 Cohorts ~3.2 million pts

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Assessment of Clinical Criteria for Sepsis

For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank M. Brunkhorst, MD; Thomas D. Rea, MD, MPH; André Scherag, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kahn, MD, MSc; Manu Shankar-Hari, MD, MSc; Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

Assess predictive validity in ~1.3 million patients

JAMA February 23, 2016

SEPSIS-3, ICU Definition:

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection

<u>New ICU Definition = Suspected infection and SOFA ≥ 2</u>

Organ dysfunction = 2 point change in total SOFA "consequent to the infection".

Baseline SOFA score assumed to be zero in patients not known to have preexisting organ dysfunction.

A SOFA score = 2 reflects = 10% mortality risk of in a general hospital population with suspected infection.

Singer JAMA 2016

What Happened to SIRS?

Do I really have to memorize the SOFA score to Dx Sepsis in the ICU?

Definition catches up with reality:

"sepsis" requires evidence of organ dysfunction

Old Definition

- **Sepsis** = SIRS + Suspected infection
- **Severe Sepsis** = Sepsis plus organ dysfunction

New Definition

- **Sepsis** = Suspected infection and organ dysfunction

Suspected infection = History and Physical (SIRS), Labs/images

ORIGINAL ARTICLE

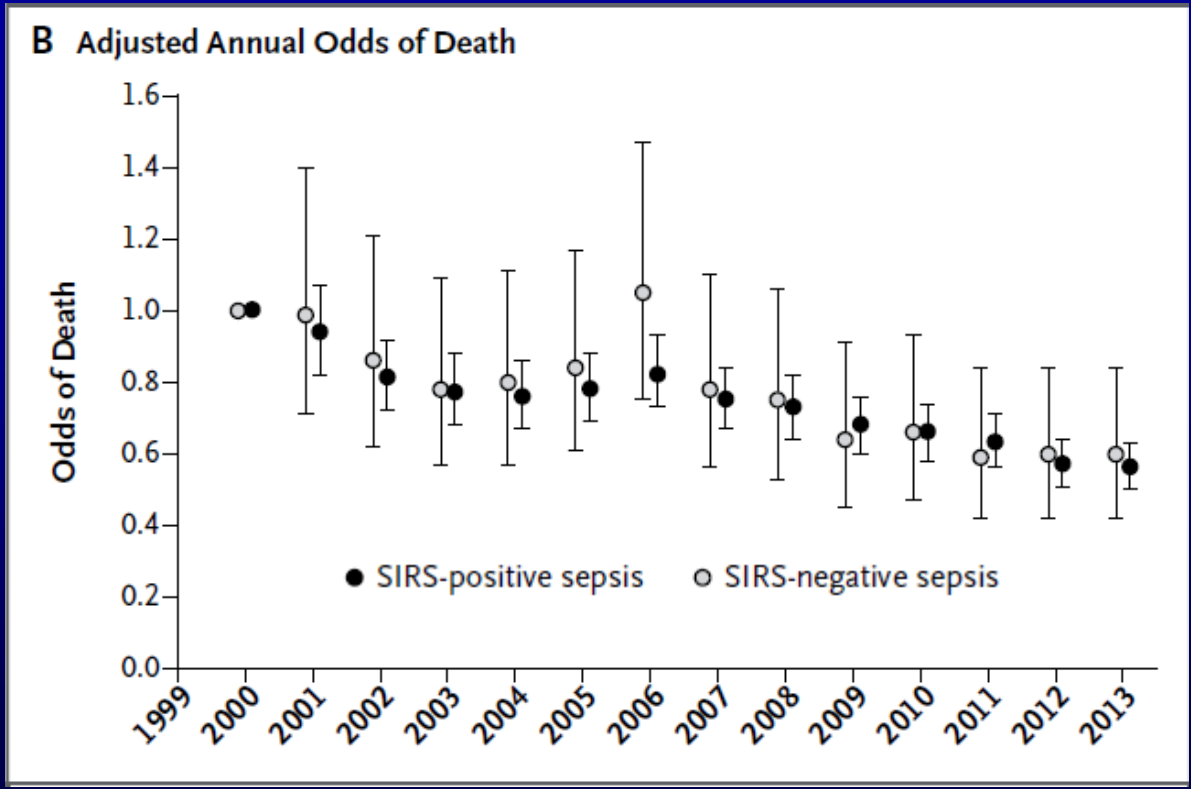
2015

Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

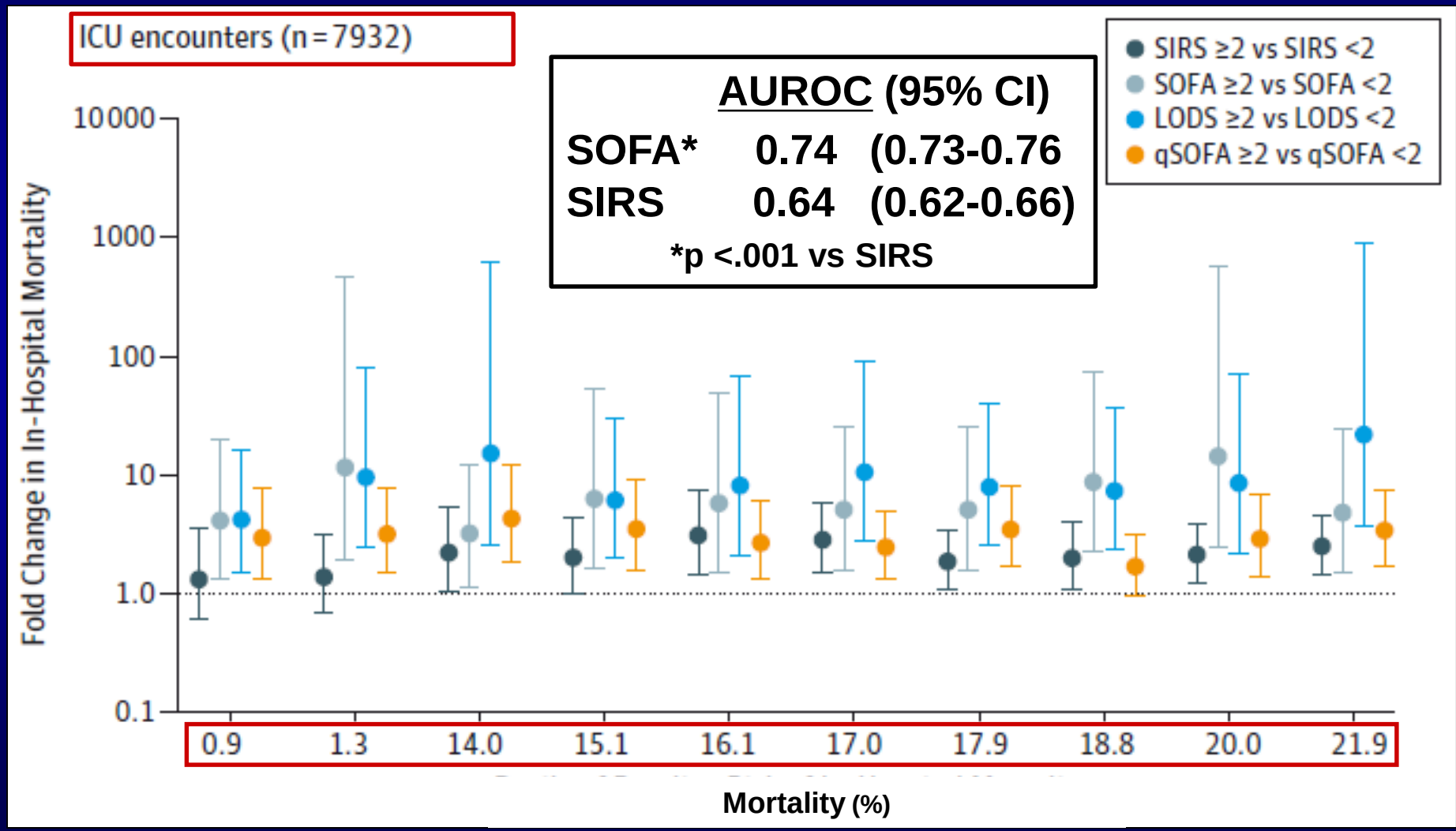
Kirsi-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M.,

Patients with SIRS-Positive Severe Sepsis (N=96,385)

Patients with SIRS-Negative Severe Sepsis (N=13,278)



Fold Change (log scale) in Mortality for Organ Failure Scores: ICU



Seymour JAMA 2016

SOFA Score

System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥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	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Lazy

Supplemental O2	≥ least 1 point* (ARDS =2)
Platelets < 150	1 point + 1 point per Δ 50
Bili or Creat 1.2-1.9	1 point each
MAP < 70	1 point
Not thinking clearly	1 point

* If on 2L NC (FiO2 0.25) and Sp02 = 98; P/F < 400 (391)

SEPSIS-3: Septic Shock

Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality

Septic Shock Definition:

Persisting hypotension requiring vasopressors to maintain MAP > 65 mmHg and having a serum lactate level > 2mmol/L despite “adequate” (NOS) volume resuscitation.

Hospital mortality > 40%.

Singer JAMA 2016

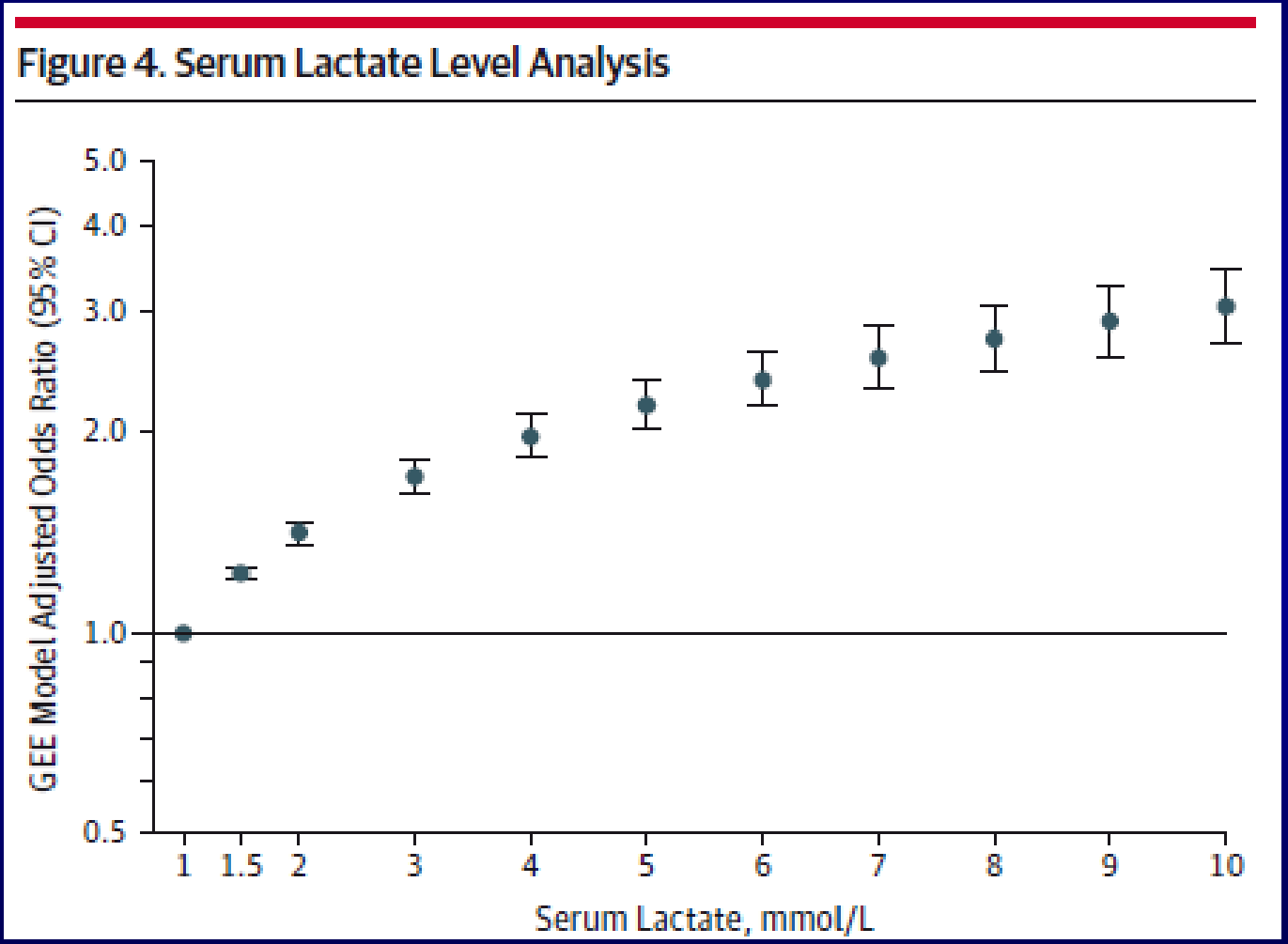
SEPSIS-3 Definition of Shock
Why Vasopressors and Lactate > 2?

Variable	Hypotension after fluids	Vasopressor	Raised Lactate >2 mmol/L
Group 1	Yes	Yes	Yes
Group 2	Yes	Yes	No
Group 3	Yes	No	Yes
Group 4	No	No	Yes
Group 5	No hypotension before fluids	No	Yes
Group 6	Yes	No	No

Variables	**N**	**Hospital mortality, N (%)**
Group		
1 (referent)	8,520	3,602 (42.3)
2	3,985	1,198 (30.1)
3	223	64 (28.7)
4	3,266	839 (25.7)
5	2,696	802 (29.7)
6	150	28 (18.7)

Shankar-Hari JAMA eSuppl 2016

OR for Death by Initial Serum Lactate



Shankar-Hari JAMA 2016

The Septic Shock 3.0 Definition and Trials: A Vasopressin and Septic Shock Trial Experience

James A. Russell, MD[1,2]; Terry Lee, PhD[3]; Joel Singer, PhD[3]; John H. Boyd, MD[1,2]; Keith R. Walley, MD[1,2]; on behalf of the Vasopressin and Septic Shock Trial (VASST) Group

We have a semantics problem. What do we call the patients with septic shock on vasopressors whose lactate is less than or equal to 2 mmol/L (met VASST inclusion criteria with lactate ≦ 2 mmol/L)? They do not meet the Septic Shock 3.0 definition so they are not in "septic shock." There is no "severe sepsis" category so this leaves them categorized as "sepsis." In response to a letter challenging the definitions, the Sepsis 3.0 definition authors recently called this group "pre-shock" (13), a real change in semantics for septic vasopressor-treated patients whom clinicians, investigators, and payers have previously called "septic shock."

Outline

- Review of the Sepsis-3 Definition
- Prognostic Validity (high event rate) does not necessarily lead to Predictive Enrichment (high ARR and RRR from treatment)

Domains of Validity of a Definition

Table 1. Measures of validity

Validity Measure	Explanation
Face validity	Definition appears "on its face" to represent the disease
Content validity	Definition contains all of the elements relevant to the disease
Criterion validity	Definition corresponds to a gold standard
Predictive validity	Definition is able to predict something it theoretically should be able to predict
Concurrent validity	Definition is able to distinguish between groups that it theoretically should be able to distinguish between

Rubenfeld CCM 2003

Domains of Validity of a Definition

Table 1. Measures of validity

Validity Measure	Explanation
Face validity	Definition appears "on its face" to represent the disease
Content validity	Definition contains all of the elements relevant to the disease
Criterion validity	Definition corresponds to a gold standard
Concurrent validity	Definition is able to distinguish between groups that it theoretically should be able to distinguish between

Predictive validity defines criteria that predict patient outcome or response to treatment

Rubenfeld CCM 2003

Enrichment Strategies: FDA 2012

Prognostic enrichment

- Choosing patients with a greater likelihood of having a disease-related endpoint
- Increases the absolute effect difference between groups but will not alter relative effect (eg. simple math)

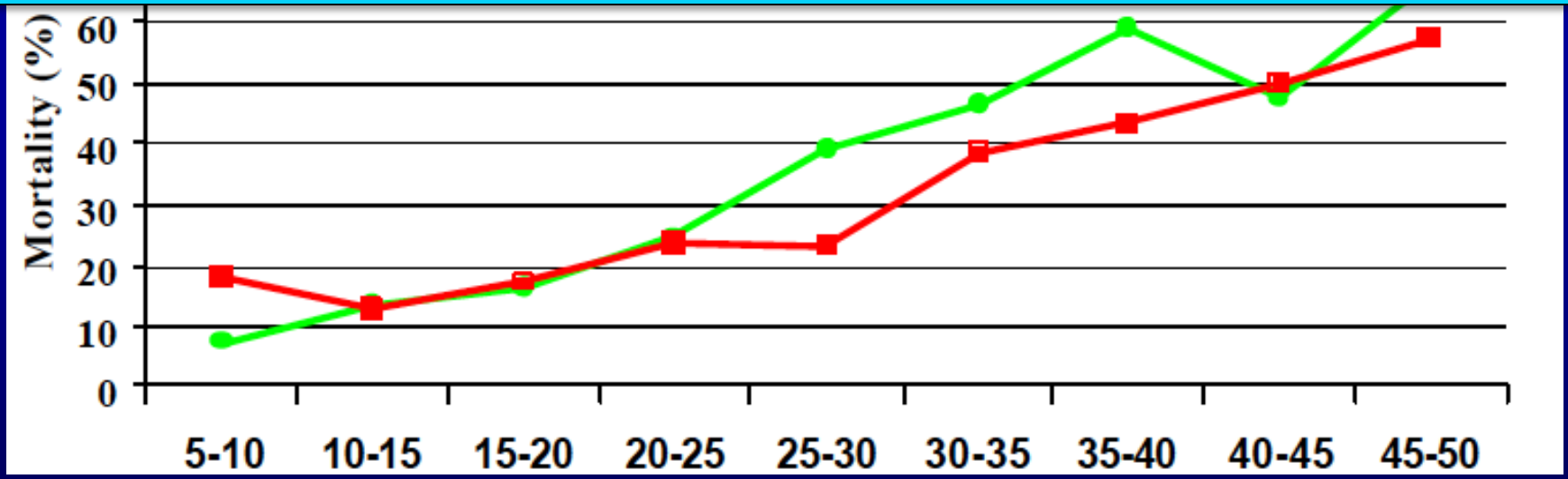
Predictive enrichment

- Choosing patients more likely to respond to the drug treatment (eg. driver mutation for cancer trials).
- Increases both absolute and relative effects *and* reduces sample size

Enrichment Strategies FDA Dec 2012

FDA Approved Xigris for High Risk Severe Sepsis (eg. APACE II > 25)

FDA Approved rhAPC (Xigris) for High Risk Severe Sepsis and suggested an APACE II > 25 be used to estimate high risk. Biology (Predictive enrichment) or simple math (Prognostic Enrichment) or chance?



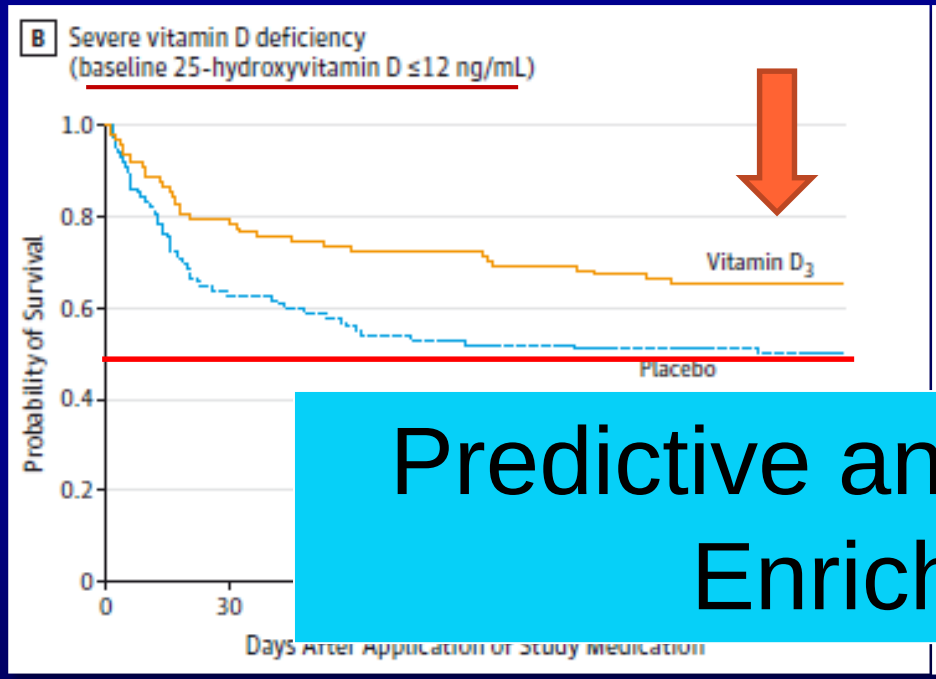
FDA CLINICAL REVIEW

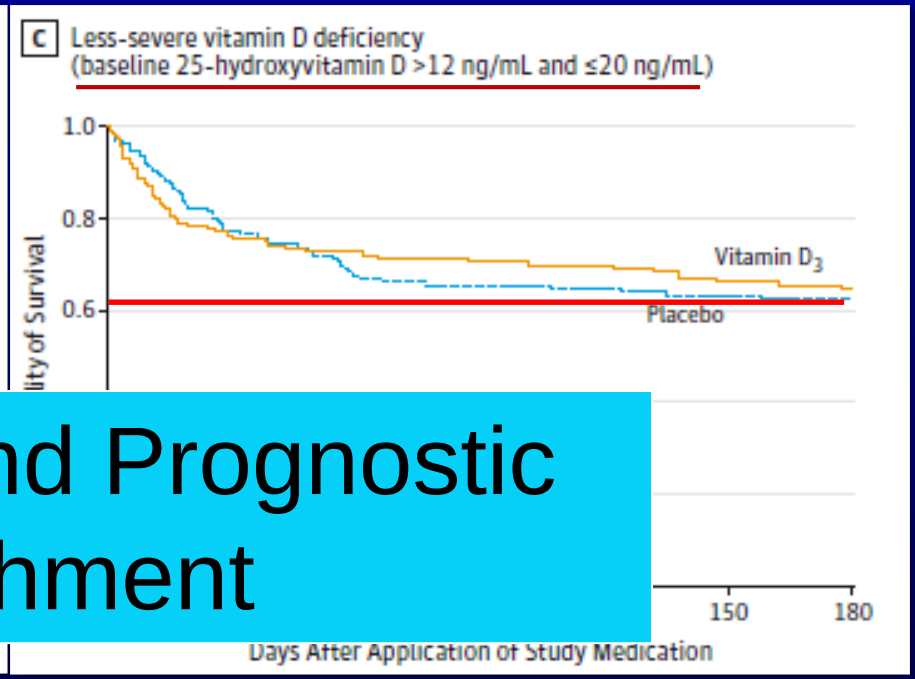
Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of High-Dose Vitamin D_3 on Hospital Length of Stay in Critically Ill Patients With Vitamin D Deficiency

The VITdAL-ICU Randomized Clinical Trial

Karin Amrein, MD, MSc; Christian Schnedl, MD; Alexander Holl, MD; Regina Riedl, MSc; Kenneth B. Christopher, MD; Christoph Pachler, MD;





Predictive and Prognostic Enrichment

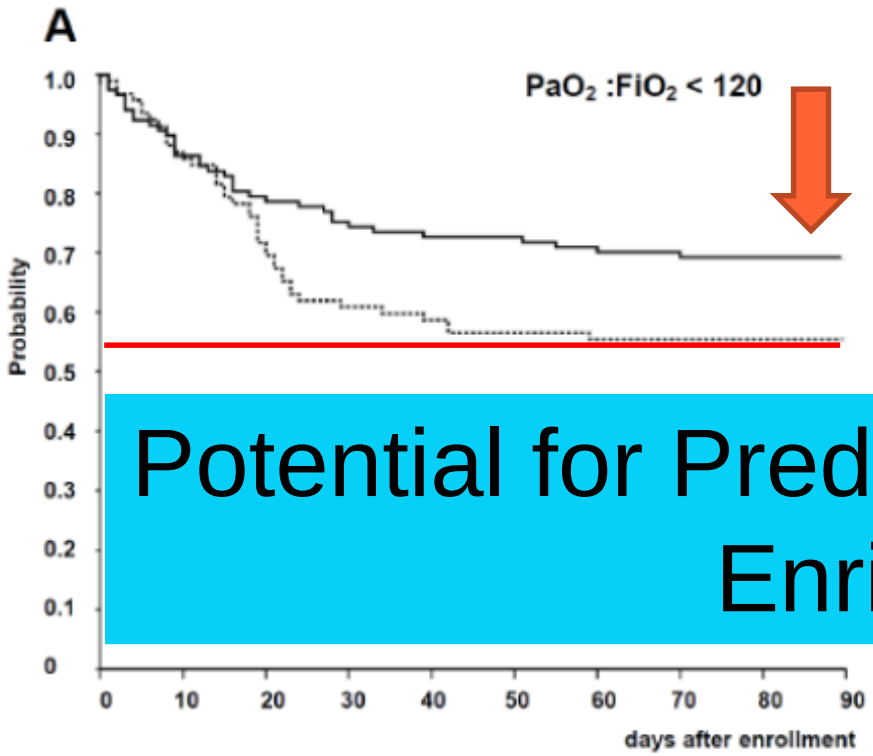
JAMA October 15, 2014

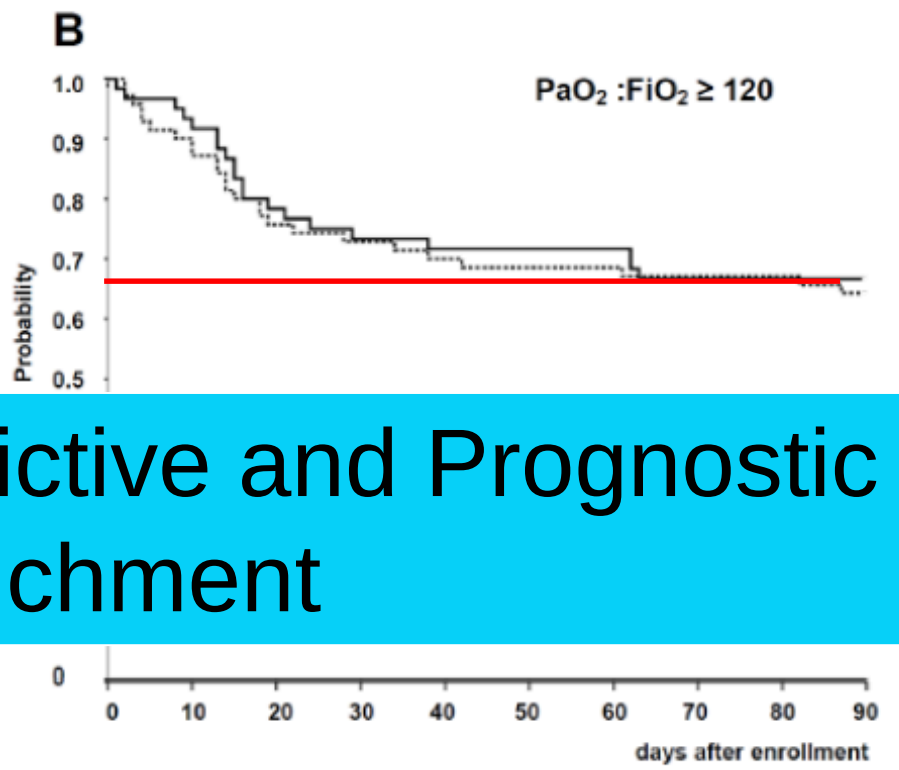
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2010 VOL. 363 NO. 12

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D.,

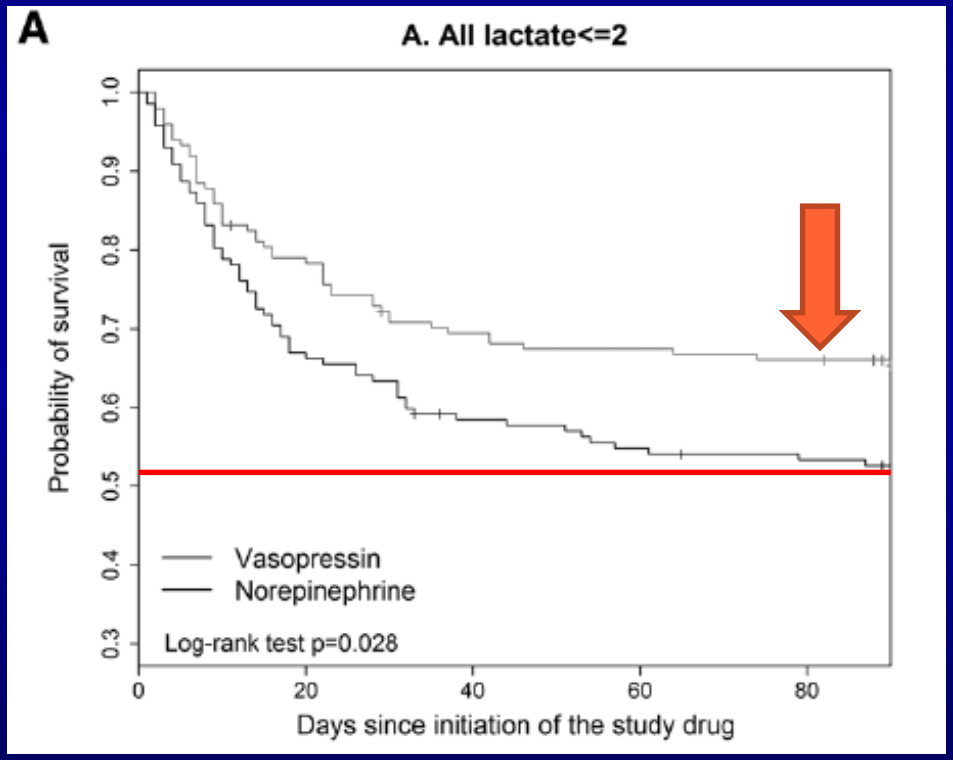


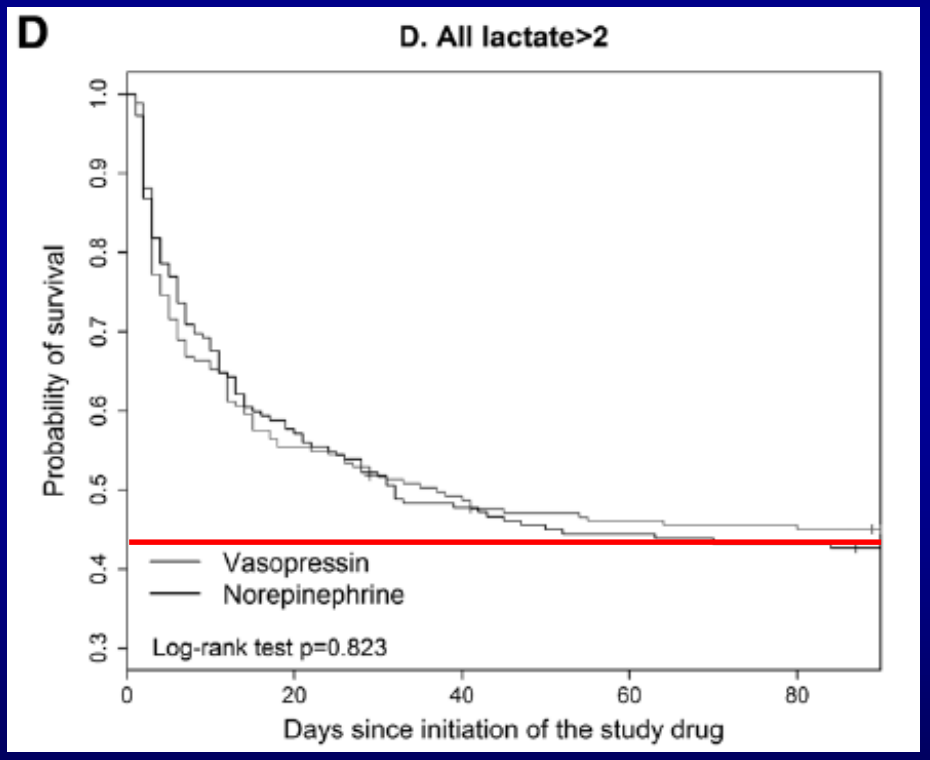


Potential for Predictive and Prognostic Enrichment

The Septic Shock 3.0 Definition and Trials: A Vasopressin and Septic Shock Trial Experience

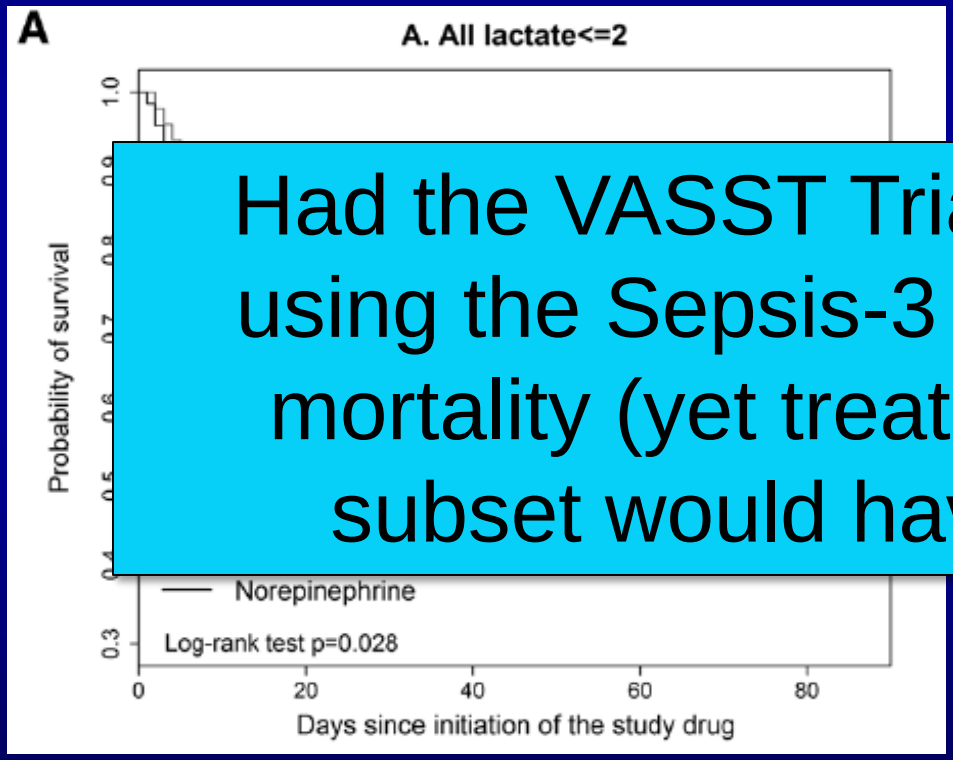
James A. Russell, MD[1,2]; Terry Lee, PhD[3]; Joel Singer, PhD[3]; John H. Boyd, MD[1,2]; Keith R. Walley, MD[1,2]; on behalf of the Vasopressin and Septic Shock Trial (VASST) Group

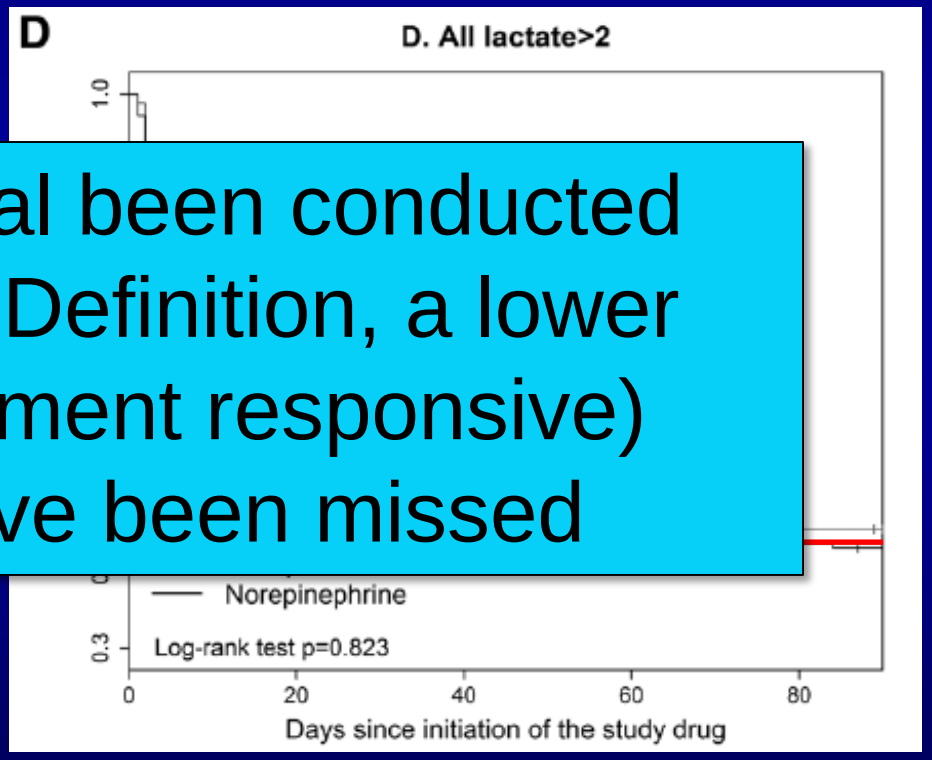




The Septic Shock 3.0 Definition and Trials: A Vasopressin and Septic Shock Trial Experience

James A. Russell, MD[1,2]; Terry Lee, PhD[3]; Joel Singer, PhD[3]; John H. Boyd, MD[1,2]; Keith R. Walley, MD[1,2]; on behalf of the Vasopressin and Septic Shock Trial (VASST) Group





Had the VASST Trial been conducted using the Sepsis-3 Definition, a lower mortality (yet treatment responsive) subset would have been missed

SEPSIS-3 Definition of Shock
Why Vasopressors and Lactate > 2?

Variable	Hypotension after fluids	Vasopressor	Raised Lactate >2 mmol/L
Group 1	Yes	Yes	Yes
Group 2	Yes	Yes	No
Group 3	Yes	No	Yes
Group 4	No	No	Yes
Group 5	No hypotension before fluids	No	Yes
Group 6	Yes	No	No

Variables	**N**	**Hospital mortality, N (%)**
Group		
1 (referent)	8,520	3,602 (42.3)
2	3,985	1,198 (30.1)
3	223	64 (28.7)
4	3,266	839 (25.7)
5	2,696	802 (29.7)
6	150	28 (18.7)

Responsive Subset

Shankar-Hari JAMA eSuppl 2016

Conclusion: What do we follow?

The Sepsis-3 Shock definition identifies patients at high risk of death but not necessarily a subset more likely to respond to treatment

Biological considerations should drive the decision on what definition to use for clinical trials. Preclinical data suggesting potential for Predictive Enrichment should have a higher priority over identification of subsets with high mortality (Prognostic Enrichment)

Extra Slides

SEPSIS-3: Hospital Definition
Suspected infection and qSOFA ≥ 2

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection

RR ≥ 22/min, altered mentation, SBP ≤100mmHg

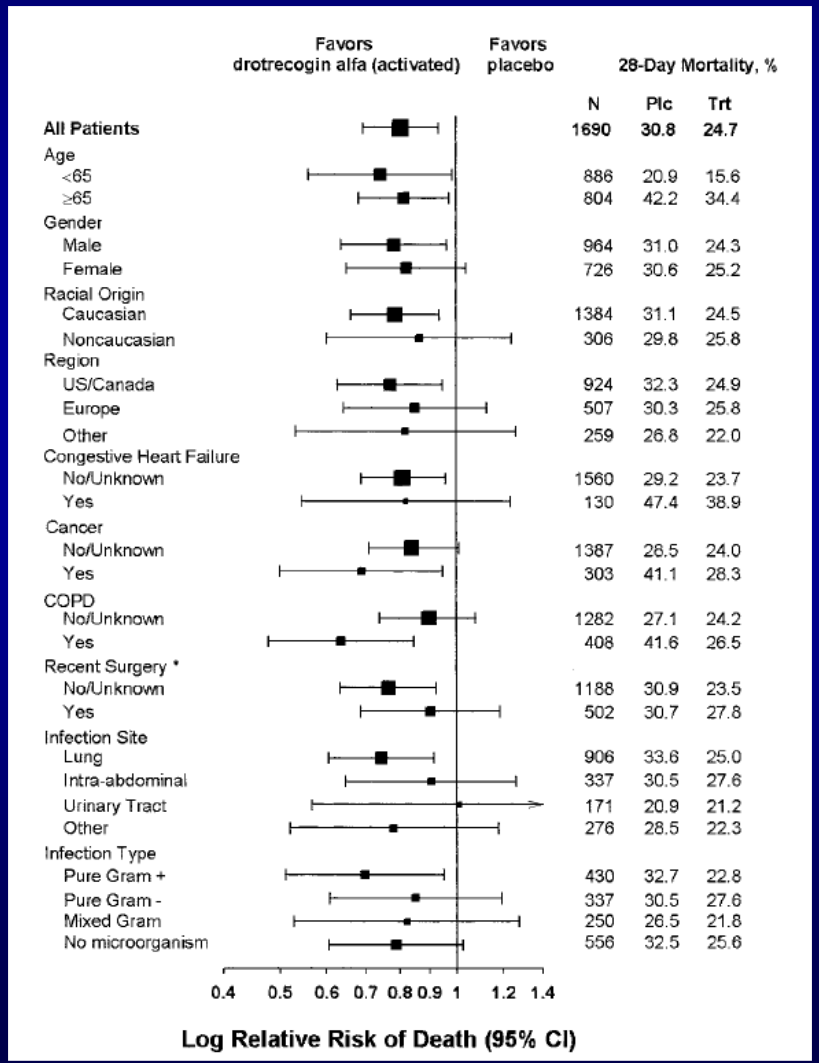
Suspected infection and a qSOFA of 2 or more is associated with prolonged ICU stay or hospital death.

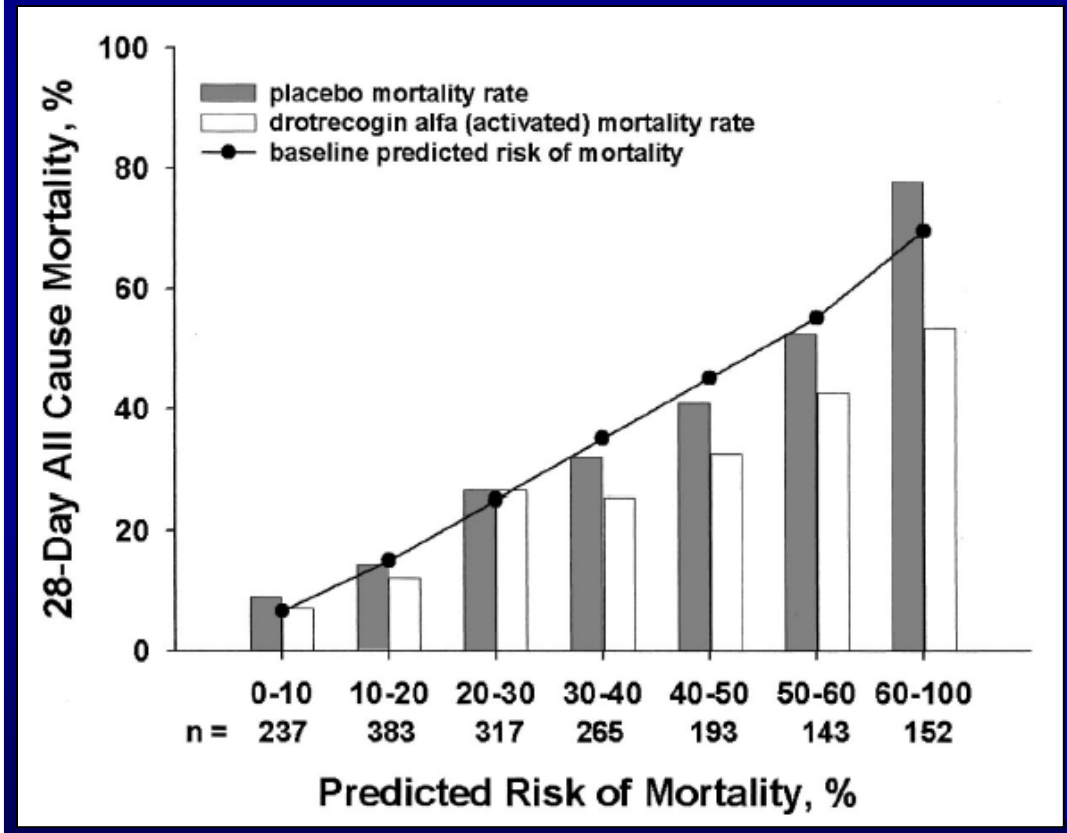
If screen positive by qSOFA, check SOFA

JAMA February 23, 2016

Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis

E. Wesley Ely, MD, MPH; Pierre-François Laterre, MD; Derek C. Angus, MD, MPH; Jeffrey D. Helterbrand, PhD; Howard Levy, MBBCh, PhD; Jean-François Dhainaut, MD, PhD; Jean-Louis Vincent, MD, PhD; William L. Macias, MD, PhD; Gordon R. Bernard, MD; for the PROWESS Investigators





Crit Care Med 2003

What explains heterogeneity of treatment by disease severity?

Higher event rates -> more power to see same relative risk reduction (Prognostic Enrichment, simply math)

More favorable risk benefit for drugs with toxicity (more math)

More “inflammation” in higher risk subset -> more therapeutic opportunity and a higher absolute and relative risk reduction (a biological explanation resulting in Predictive Enrichment)