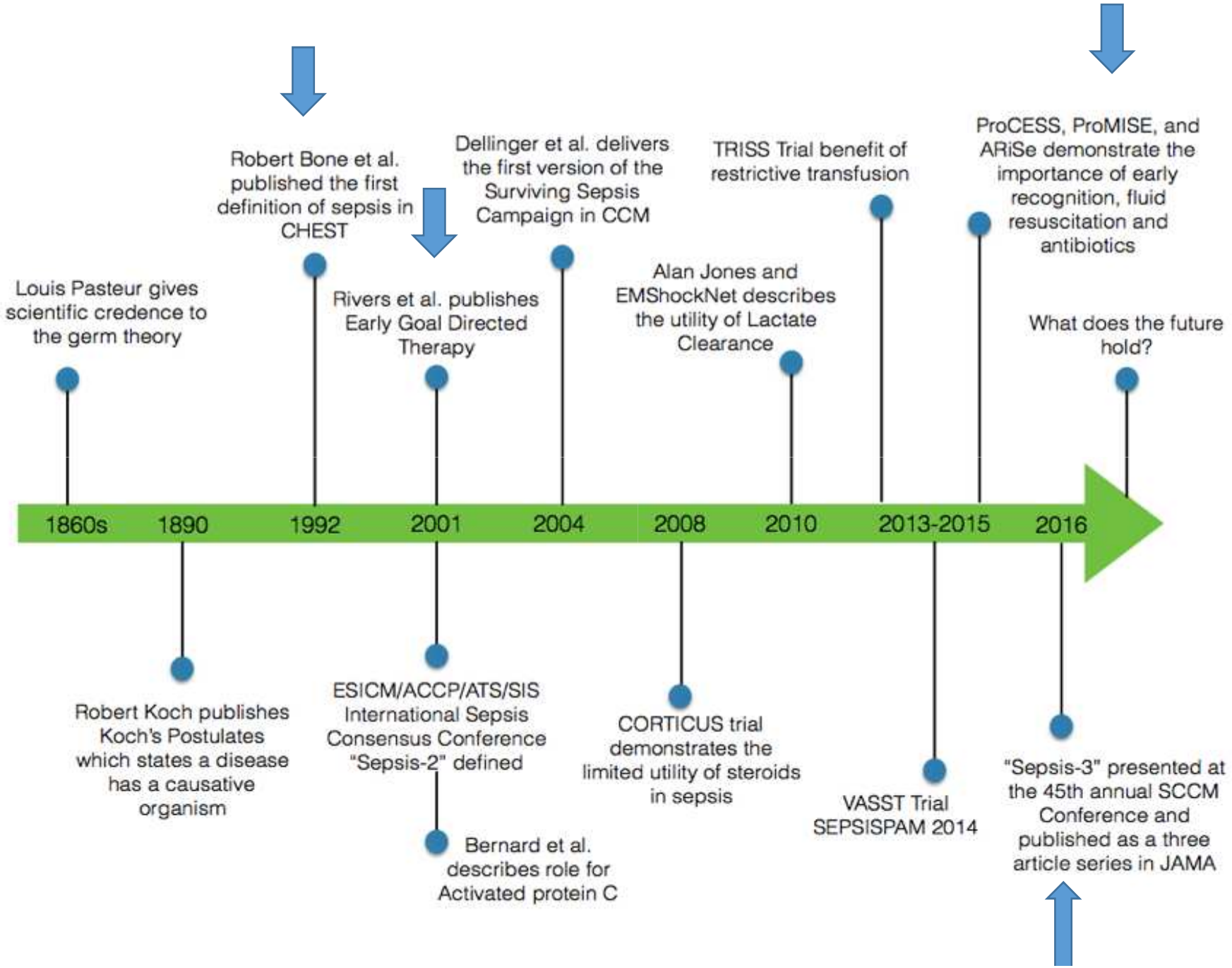
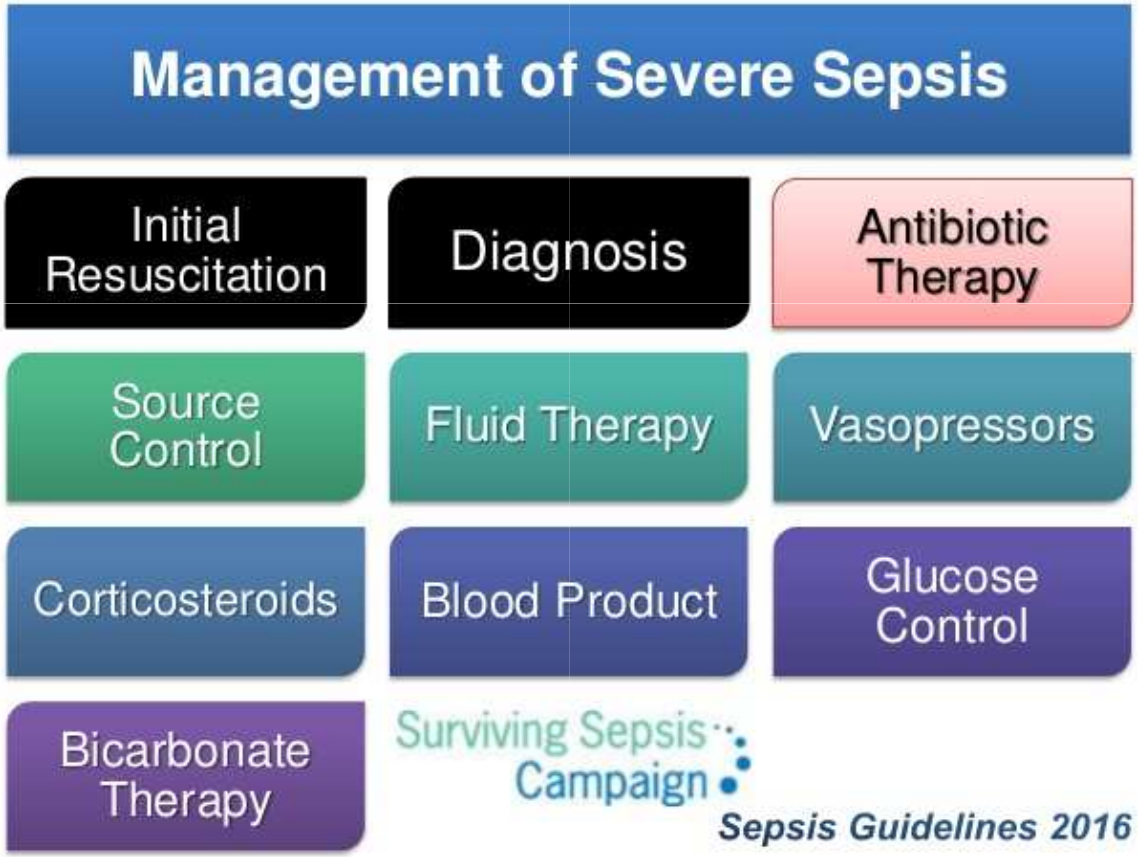

Louis Pasteur gives scientific credence to the germ theory
1860s
Robert Koch publishes Koch's Postulates which states a disease has a causative organism
1890
Robert Bone et al. published the first definition of sepsis in CHEST
1992
Rivers et al. publishes Early Goal Directed Therapy
2001
ESICM/ACCP/ATS/SIS International Sepsis Consensus Conference "Sepsis-2" defined
Bernard et al. describes role for Activated protein C
Dellinger et al. delivers the first version of the Surviving Sepsis Campaign in CCM
2004
Alan Jones and EMShockNet describes the utility of Lactate Clearance
2008
CORTICUS trial demonstrates the limited utility of steroids in sepsis
2010
TRISS Trial benefit of restrictive transfusion
VASST Trial SEPSISPAM 2014
2013-2015
ProCESS, ProMISE, and ARiSe demonstrate the importance of early recognition, fluid resuscitation and antibiotics
What does the future hold?
2016
"Sepsis-3" presented at the 45th annual SCCM Conference and published as a three article series in JAMA

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[25], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

93 Recommendations !
370 over Pages Only To Read !
30 minutes to Present !



Recommendations

- 93 Recommendations
  - 32 **Strong** recommendations: ***"We recommend"***
  - 39 **Weak** recommendations: ***"We suggest"***
  - 18 Best Practice Statements

Determination of Quality of Evidence

Underlying methodology

1. High: RCTs
2. Moderate: Downgraded RCTs or upgraded observational studies
3. Low: Well-done observational studies
4. Very Low: Downgraded controlled studies or expert opinion or other evidence

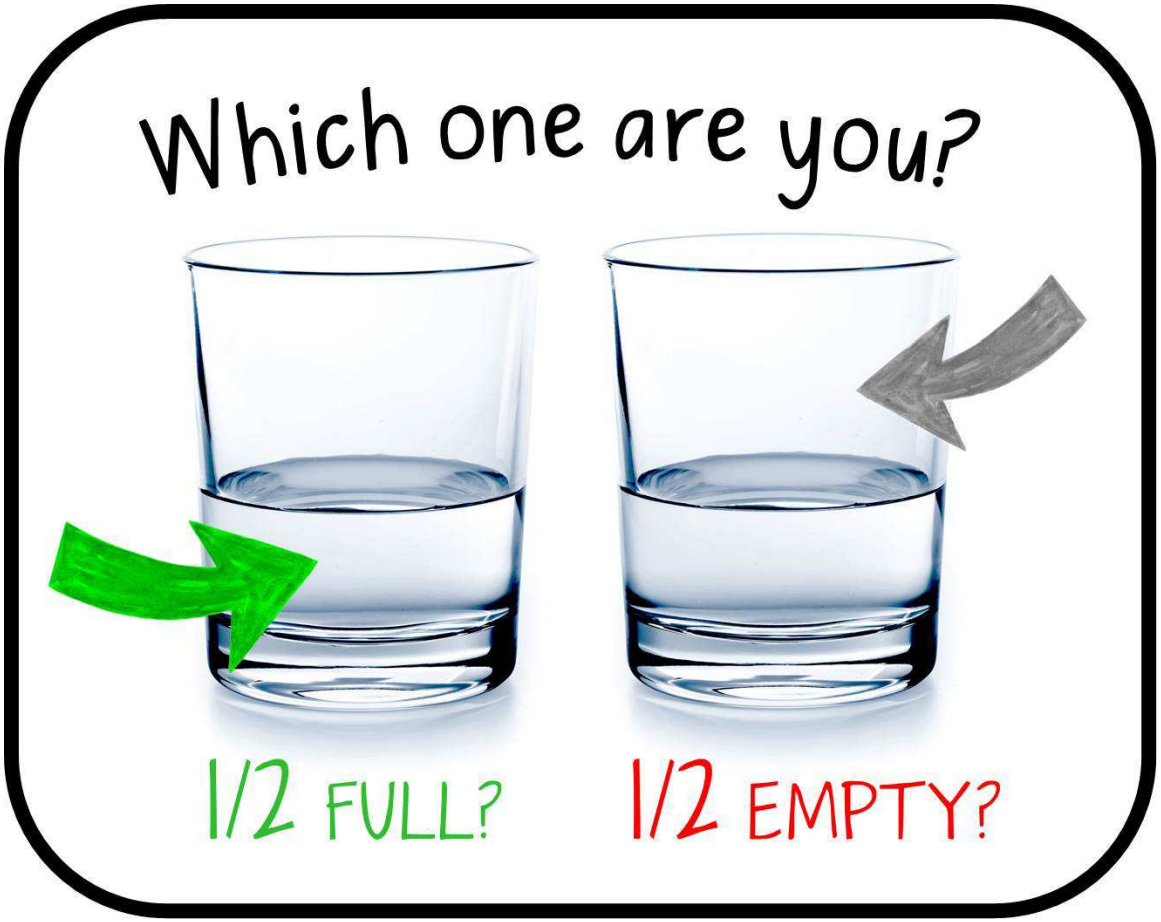
Best Practice Statements

- Strong but ungraded statements
- Use defined criteria

Criteria for Best Practice Statements
Is the statement clear and actionable?
Is the message necessary?
Is the net benefit (or harm) unequivocal?
Is the evidence difficult to collect and summarize?
Is the rationale explicit?
Is the statement better if formally GRADEd?

Guyatt GH, Schünemann HJ, Djulbegovic B, et al:
Clin Epidemiol 2015; 68:597–600

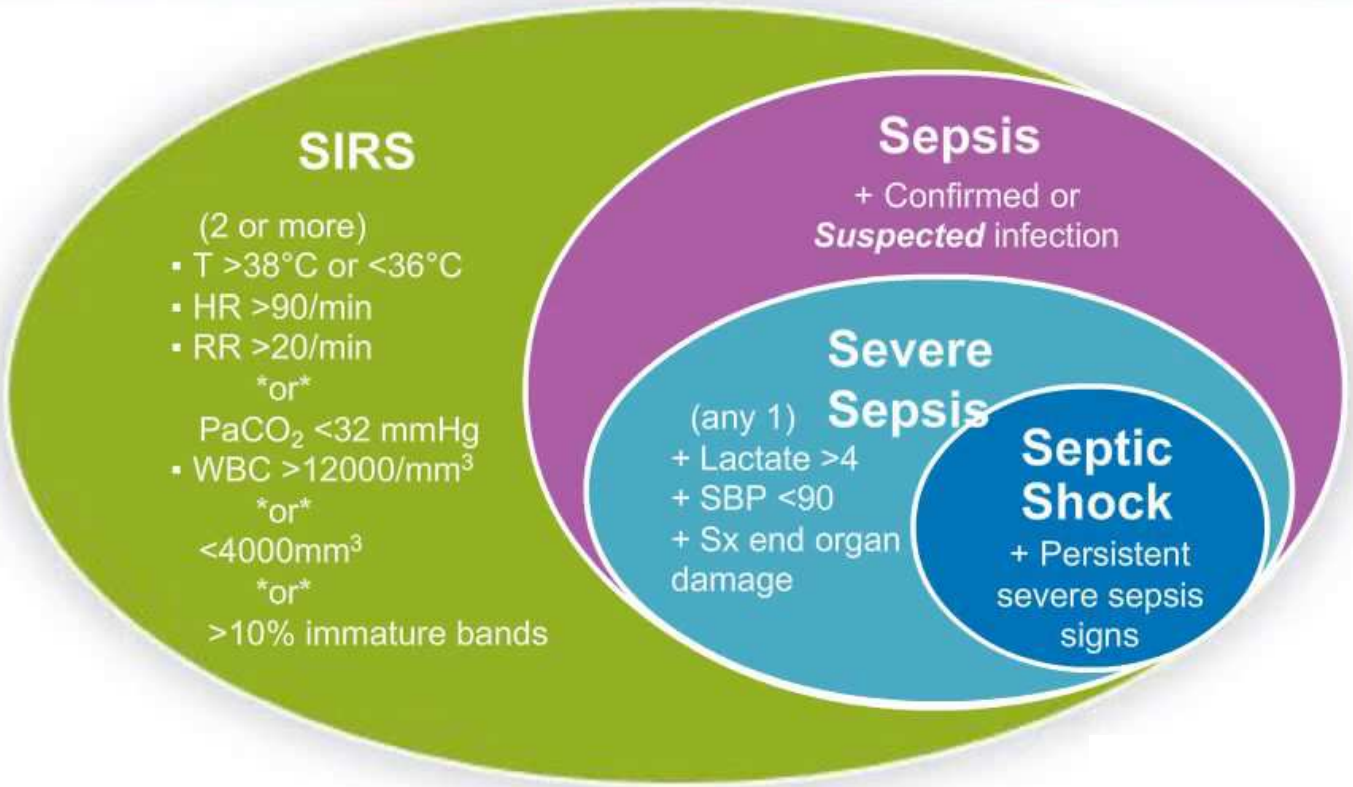
Diagnosis and Definitions ….

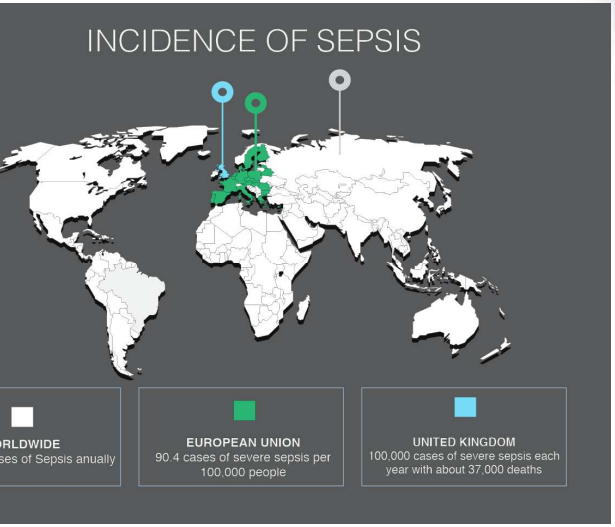


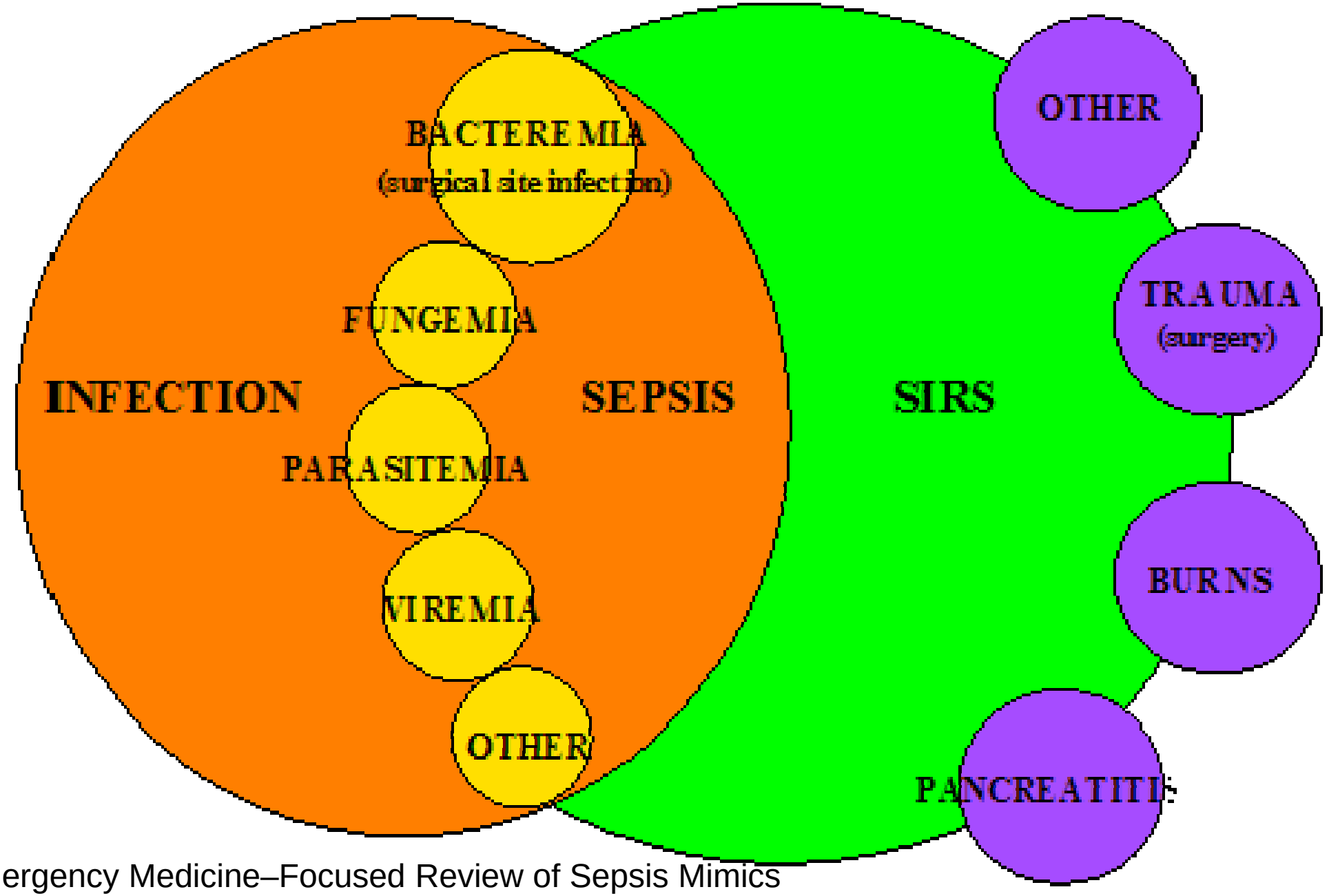
Sepsis is a clinical syndrome caused by a life threatening response to infection[6]

Extremely challenging to diagnose or even define…

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







Anaphylaxis
Aspiration
Adrenal Insufficien
Bowel Obstruction
Diabetic Ketoacidos
Heat Emergency
Hypovolemia
Pulmonary Embolis
Pancreatitis
Intestinal Ischemia
Thyroid Disease
Toxic Ingestion/Overdose
Withdrawal State
Vasculitis
Viral Illness
Spinal Cord Injury

ergency Medicine–Focused Review of Sepsis Mimics

al.J Emerg Med. 2017;52(1):34-42.

Who: A task force organized by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine recognized the need to reexamine the current definitions from the 1991 and 2001 consensus terminology.

How : Retrospective cohort study -12 community and academic hospitals in southwestern Pennsylvania from 2010 to 2012.

Inclusion criteria: > 18 years with suspected infection in ED, (ICU), ward

Onset of suspected infection =positive culture or as antibiotics ordered.

The primary outcome =hospital mortality

Secondary outcome= hospital mortality or ICU length of stay of ≥ 3 days

esults: 148,907 electronic health record data of hospitalized patients with
uspected infection

andomly split

74,453 in the derivation cohort for developing new criteria

74,454 in the validation cohort for assessment of new and existing criteria

The derivation cohort had 7,836 encounters in the ICU and 66,617
encounters outside of the ICU.

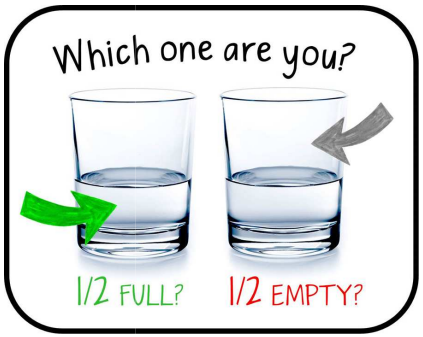
The validation cohort had 7,932 encounters in the ICU and 66,522
encounters outside of the ICU.

- Derived and validated the qSOFA, using SIRS criteria and SOFA score as comparators (2).
- qSOFA performed admirably when utilized in a population outside the ICU setting
- qSOFA score < 2, the in-hospital mortality was only 3%.
- qSOFA of >2 , the in-hospital mortality was 24%.
- When validated in multiple external data sets
- qSOFA's performance remained consistently acceptable

- Seymour CW , et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8): 762-774.

Ability to predict mortality among patients with possible infection outside the ICU

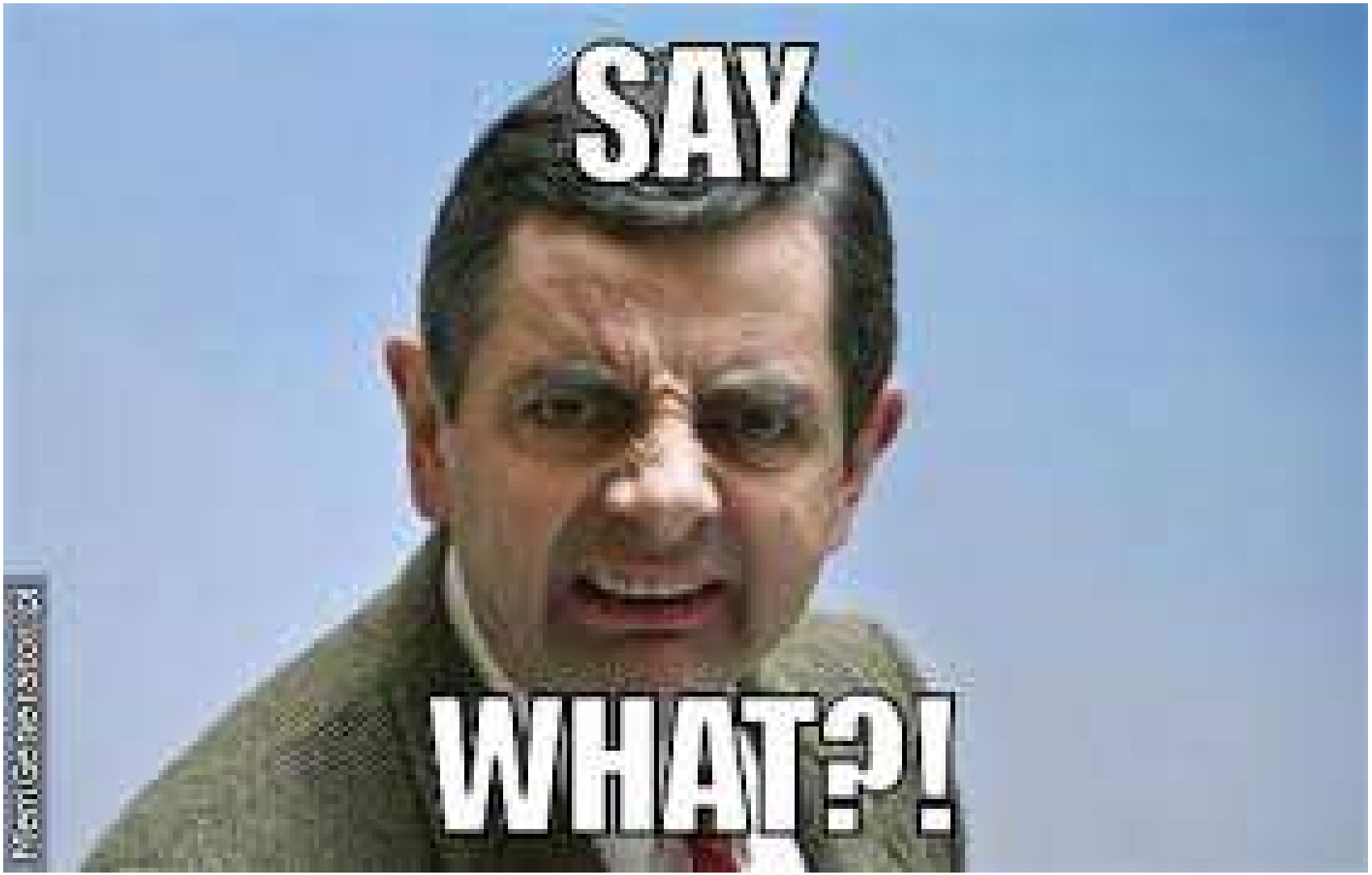
Test	Area under ROC curve	Sensitivity for mortality	Specificity for mortality
SIRS ≥ 2	0.76	64%	65%
SOFA ≥ 2	0.79	68%	67%
qSOFA ≥ 2	0.81	55%	84%



Predicted validity for in-hospital mortality

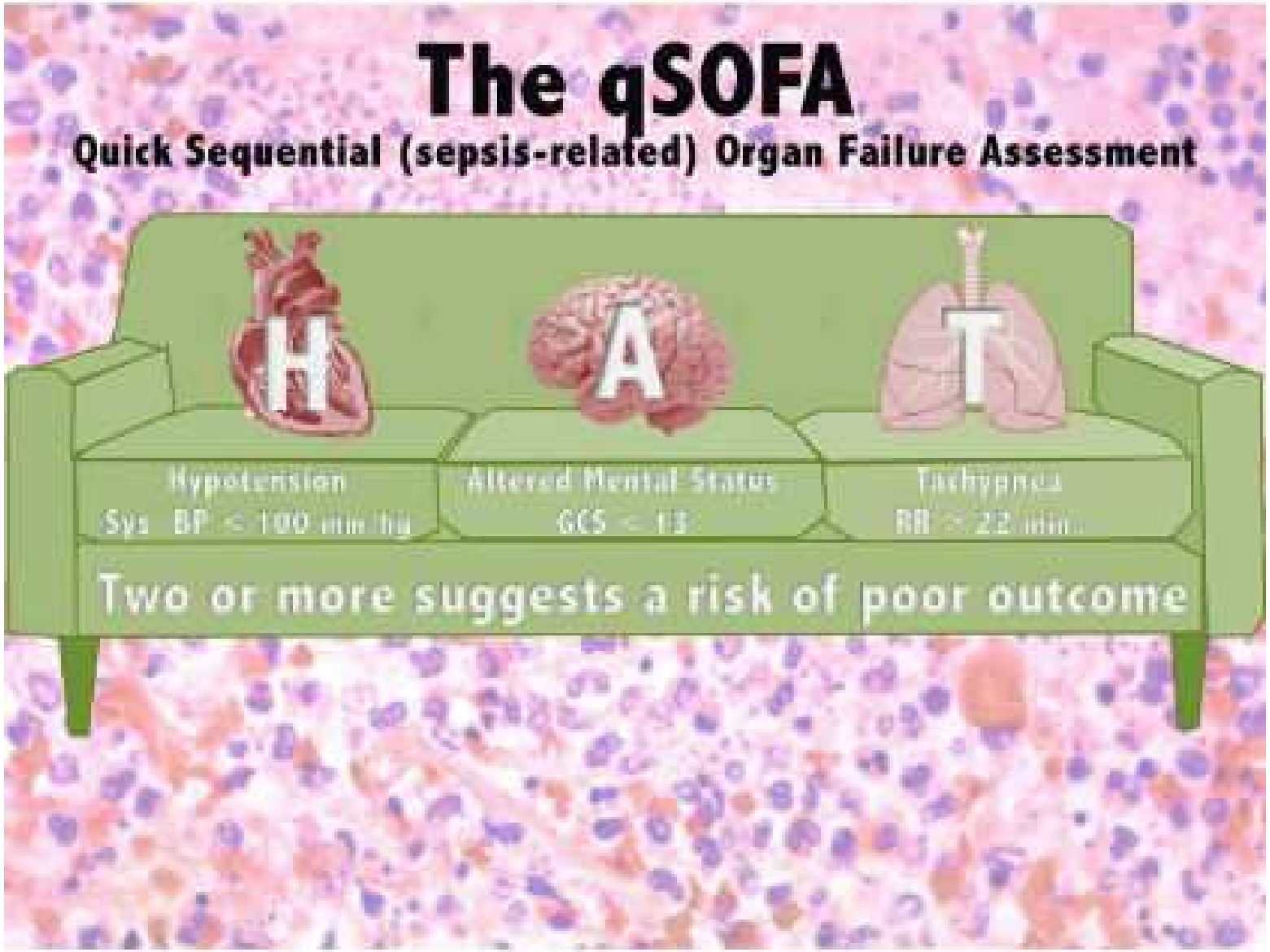
- With ICU encounters - **<** SIRS and (qSOFA) vs. **SOFA**

- With the non-ICU encounters - **>** **qSOFA** vs. SOFA and SIRS


SAY
WHAT?!

The qSOFA

Quick Sequential (sepsis-related) Organ Failure Assessment




qSOFA
BP (systolic <100mmHg
Altered Mental State
Tachypnoea (RR >22)

Call (BAT)man
or
Put on your thinking (HAT)

quick Sepsis-related Organ Failure Assessment score

Altered mentation

Elevated respiratory rate

Systolic hypotension

qSOFA criteria:

Alteration in mental status (GCS < 14)
Hypotension - SBP ≤100 mm Hg
Respiratory rate ≥22/min.


R.I.P.
SIRS
R.I.P.
SEVERE
SEPSIS

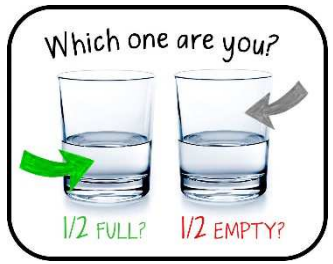

Fashion update :
SIRS is OUT, qSOFA is IN

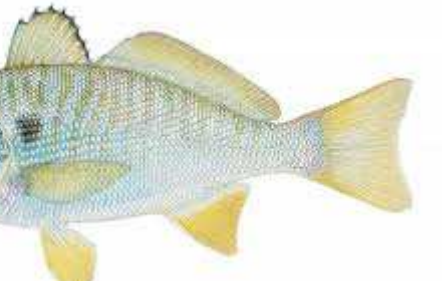
SIRS vs QSOFA

Specificity versus Sensitivity

- **Sensitive Test**
- Let's catch a tuna.
- Use a small mesh net.
- Will catch a lot of fish, and never miss a tuna.
- Definitely will catch a tuna, but will also get mackerel, perch and spot, which will require further sorting.
- False positive results.
- Sensitive but not specific

- **Specific Test**
- Let's catch a tuna.
- Use a big mesh net.
- Everything in net will be tuna.
- Will catch large tuna, but small tuna, mackerel, perch, and spot will not be in net, so no further sorting needed. Will miss some small tuna we would have wanted to keep.
- False negative results.
- Specific but not sensitive





Hello ! Have You Even Tested This ??????

irst Prospective Analysis of the qSOFA score

reund Y et al. Prognostic Accuracy of Sepsis-3 Criteria for **In-Hospital Mortality** Among atients With Suspected Infection Presenting to the Emergency Department. JAMA anuary 17, 2017 Volume 317, Number 3

0 ED across Europe with suspected infection.-879 patients .

-week period -in France, Switzerland, Spain, and Belgium

Multicenter prospective cohort study

hese values were collected -utilized the patient's worst score during their stay.

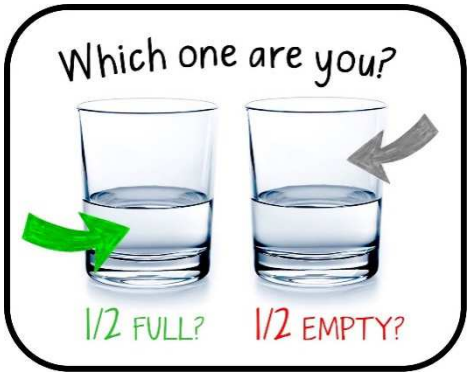
ompare

SOFA score > 2 or greater

SOFA score by 2 points

or more SIRS criteria

evere sepsis=2 or more SIRS criteria and a lactate > 2 mmol/L.



esults

qSOFA score <2 =3% mortality rate , > 2 =24% mortality rate

SOFA outperformed SIRS, SOFA and severe sepsis

SOFA -best diagnostic test characteristics

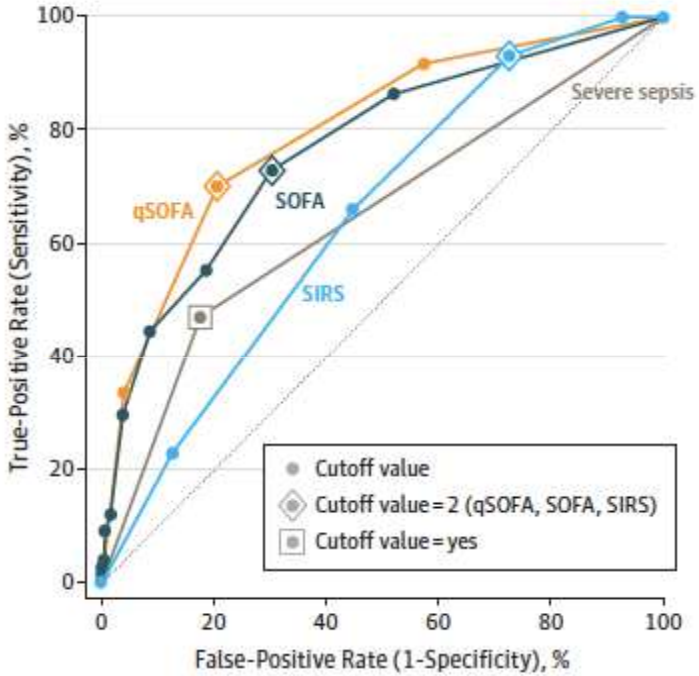
ensitivity -70% for hospital mortality

pecificity of 79%.

SOFA > 2 =associated with in-hospital mortality with a (HR) of 6.2 vs severe sepsis-(HR) of 3.5

	qSOFA	SIRS	Severe Sepsis	SOFA
ensitivity %)	70	93	47	73
pecificity %)	79	27	82	70
-) LR	3.40	1.29	2.70	2.40
) LR	0.37	0.25	0.64	0.39
UROC 95% CI)	0.80 (0.74-0.85)	0.65 (0.59-0.70)	0.65 (0.59-0.70)	0.77 (0.71-0.82)
azard atio 95% CI)	6.2 (3.8 – 10.3)		3.5 (2.2-5.5)	

Figure 2. Receiver Operating Characteristic Curves for In-Hospital Mortality



qSOFA indicates quick Sequential Organ Failure Assessment; SIRS, systemic inflammatory response syndrome; and SOFA, Sequential [Sepsis-related] Organ Failure Assessment. The area under the receiver operating characteristic curves for qSOFA is 0.80 (95% CI, 0.74-0.85); SOFA, 0.77 (95% CI, 0.71-0.82); SIRS, 0.65 (95% CI, 0.59-0.70); and severe sepsis, 0.65 (95% CI, 0.59-0.70).

Thoughts Regarding q sofa

itial assessment due to its **simplicity** for use in the clinical setting.

mple bedside score to rapidly assess patients with suspected infection who are likely to have **poor utcomes.**

linical prompt for sepsis among patients already thought to be infected

larker for severity of illness

uspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly lentified at the bedside

redictor of mortality

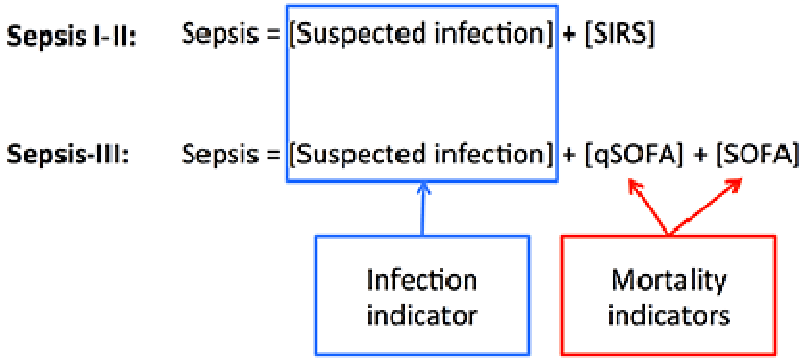
mple, rapid, inexpensive, and valid way to **identify** — among patients with suspected infection — hose at a higher **risk of having or developing sepsis**

ot a diagnostic or immediate prognostic **screening tool**

ot a **standalone indicator for sepsis**

alidated in 1 million encounters

AILORS study in LMICs



NICE
National Institute for
Health and Care Excellence

The Royal College of
Emergency Medicine

THE UK
SEPSIS
TRUST

MEWS & NEWS

Modified Early Warning Score

Score	3	2	1	0	1	2	3
Respiratory rate (min^{-1})		≤ 8		9–14	15–20	21–29	> 29
Heart rate (min^{-1})		≤ 40	41–50	51–100	101–110	111–129	> 129
Systolic BP (mmHg)	≤ 70	71–80	81–100	101–199		≥ 200	
Urine output (ml/kg/h)	Nil	< 0.5					
Temperature (°C)		≤ 35	35.1–36	36.1–38	38.1–38.5	≥ 38.6	
Neurological				Alert	Reacting to voice	Reacting to pain	Unresponsive

Chart 1: National Early Warning Score (NEWS)*

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

*The NEWS initiative flowed from the Royal College of Physicians' NEWSDIG, and was jointly developed and funded in collaboration with the Royal College of Physicians, Royal College of Nursing, National Outreach Forum and NHS Training for Innovation.

Royal College of Physicians

NHS Training for Innovation

NEWS score

Not a test for sepsis.

NEWS is a global risk-stratification tool which identifies patients who ar
critically ill
from *any* disease.

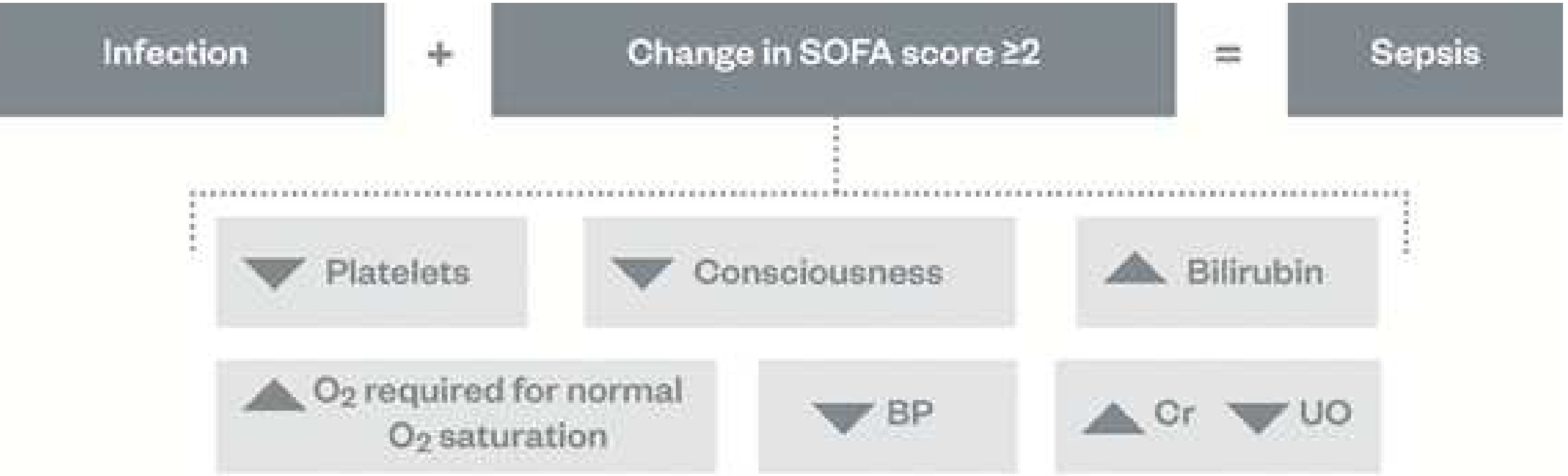
Select cutoffs to predict mortality or ICU transfer

	Sensitivity	Specificity
SIRS ≥ 2	91%	13%
qSOFA ≥ 2	54%	67%
NEWS ≥ 7	77%	53%
NEWS ≥ 8	67%	66%
NEWS ≥ 9	54%	78%

Components of SIRS, qSOFA, MEWS, and NEWS

	SIRS	qSOFA	MEWS	NEWS
Temperature	✓		✓	✓
Heart rate	✓		✓	✓
Blood pressure		✓	✓	✓
Respiratory rate	✓	✓	✓	✓
Oxygen saturation				✓
Use of supplemental oxygen				✓
Mental status		✓	✓	✓
Leukocyte count	✓			
Urine Output			✓	

After qSOFA in the ward and ED
and
In the ICU



SEPSIS CLINICAL CRITERIA

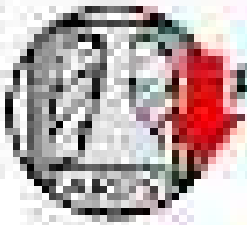
INFECTION

+

CHANGE IN:

SEPSIS-RELATED
ORGAN
FAILURE
ASSESSMENT

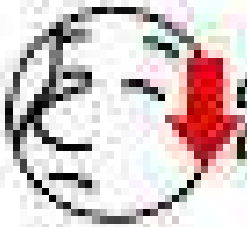
≥2



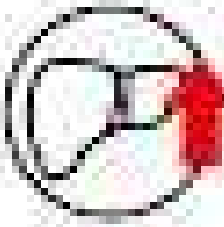
PaO_2/FiO_2

HYPOTENSION OR VASOPRESSORS

PLATELETS



GLASGOW COMA SCALE



BILIRUBIN

CREATININE, OLIGURIA

SOFA

- JL Vincent in Intensive Care Medicine in 1996

A math problem

SOFA score is a bit complicated

- 6 organ systems
- 9 physiologic variables
- Total 24 points

Sequential (Sepsis-Related) Organ Function Assessment (SOFA) Score.[a]

System / Score	0	1	2	3	4
Respiration: PaO_2/FiO_2, 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 $10^3/\mu L$	≥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); 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

Figure 2. Abbreviations: PaO_2/FiO_2, partial pressure of oxygen/fraction of inspired oxygen. a) Adapted from Vincent et al[3]; b) Catecholamine doss in μg/kg/min, >1 hour; c) Glasgow Coma Scale scores range from 3-15 (3 minimum,15 normal).

	OLD	NEW
SEPSIS	SIRS + Suspected Infection	**SUSPECTED/DOCUMENTED INFECTION** + **2 or 3 on qSOFA** (HAT): **H**ypotension (SBP ≤100 mmHg) **A**MS (GCS ≤13) **T**achypnea (≥22/min) OR Rise in SOFA score by 2 or more
SEVERE SEPSIS	Sepsis + SBP <90 mmHg or MAP < 65 mmHg	
	lactate > 2.0 mmol/L INR >1.5 or a PTT >60 s Bilirubin >34 µmol/L Urine output <0.5 mL/kg/h for 2 h Creatinine >177 µmol/L Platelets <100 ×109/L SpO2 <90% on room air	———
SEPTIC SHOCK	SEPSIS + HYPOTENSION after adequate fluid resuscitation	**SEPSIS** + **VASOPRESSORS needed for MAP >65 mmHg** + **LACTATE >2 mmol/L** after adequate fluid resuscitation

Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology[9,10]	Severe sepsis Sepsis-induced hypoperfusion	Septic shock[13]
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[13]

50-year-pneumonia-RR=24,BP : 95/65mmHg
Normal =Urea, GCS: 15

qSOFA-sepsis –Mortality -10%
CURB65 score= 0.6% mortality –home-oral abx

qSOFA	CURB65
Criteria • Abnormal mental status • RR ≥22 • SBP ≤ 100	**Criteria** • Confusion • RR ≥ 30 • SBP <90 *or* diastolic Bp ≤ 60 mm • BUN > 19 mg/dL • Age ≥ 65 YO
Interpretation • >1: sepsis (mortality ~10%)	**Interpretation** • 0: 0.6% mortality • 1: 2.7% mortality • 2: 6.8% mortality • 3: 14% mortality • 4-5: 28% mortality

# of CRB-65 and quick Sepsis-related an Failure Assessment to predict site of e and mortality in pneumonia patients he emergency department: a ospective study

Chen[1], Jun-Yu Wang[1] and Shu-Bin Guo[1,2*]

Chen *et al. Critical Care* (2016) 20:167
DOI 10.1186/s13054-016-1351-0

ct

ound: The quick Sepsis-related Organ Failure Assessment (qSOFA) is a new screening system for sepsis that gnostic performance equal to the full SOFA for patients with suspected infection outside the intensive care U). The predictive value of qSOFA for mortality and site of care in patients with pneumonia is not clear. esent study was designed to investigate the predictive performance of qSOFA, CRB-65 (confusion, respiratory 0/minute, systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg, age ≥65 years) and CRB ion, respiratory rate ≥30/minute, systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg) tality, hospitalisation and ICU admission in patients with pneumonia in the emergency department (ED).

ds: Retrospective analyses of published data on adult patients with pneumonia presenting between January nd May 2014 were undertaken. The prevalence of 28-day mortality, hospitalisation and ICU admission were ed with regard to qSOFA, CRB and CRB-65 scores. The performance of these three systems for predicting es was compared.

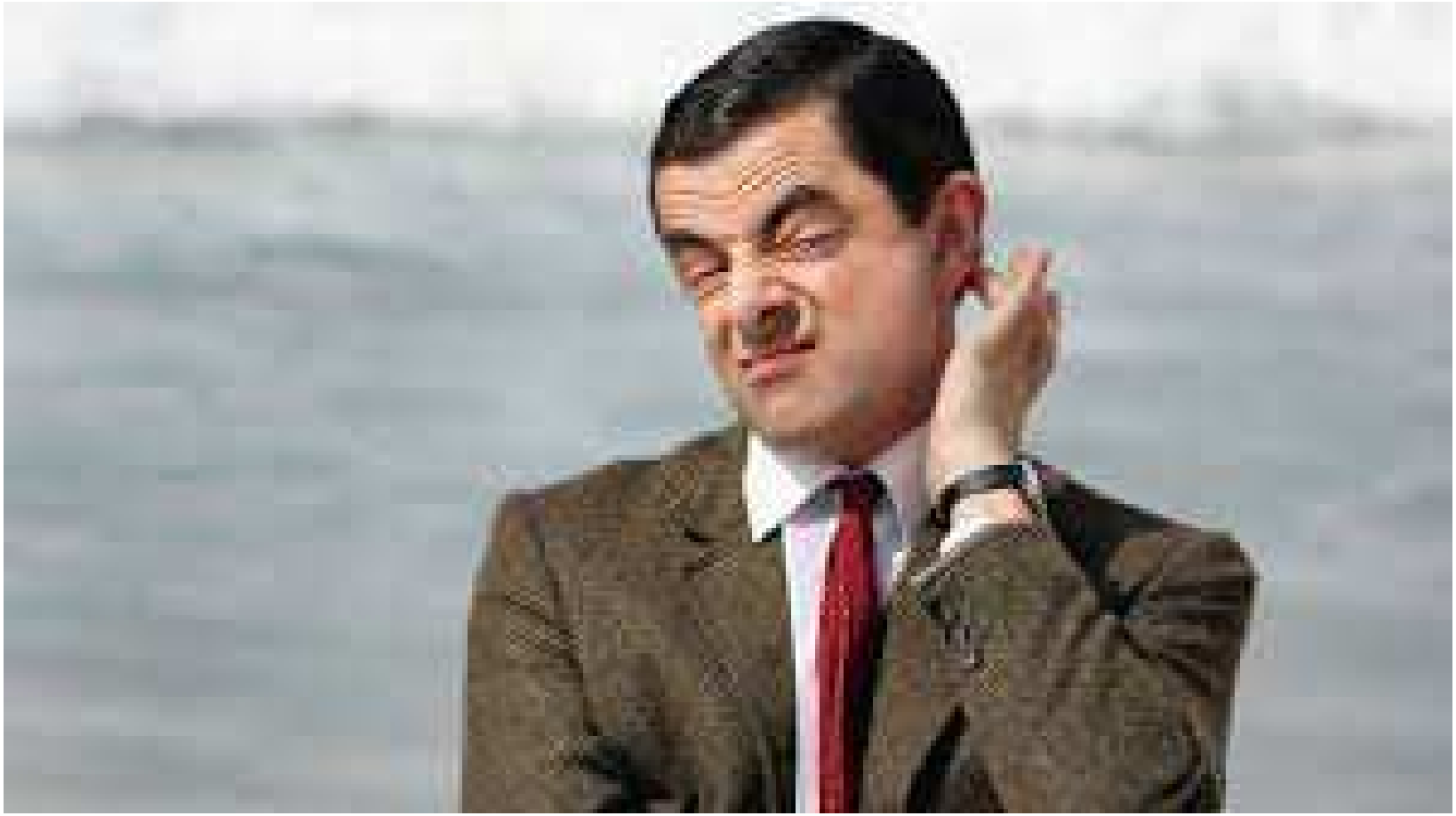
: Of 1641 patients, 861 (53 %) were hospitalised (38 % in a general ward, 15 % in the ICU), and the remaining %) were treated as outpatients or were observed in the ED. Within 28 days, 547 (33 %) of 1641 patients died. CRB and qSOFA scores of patients who died, were hospitalised and admitted to the ICU ose who survived and were not hospitalised or admitted to the ICU ($P < 0.001$). AUC values of qSOFA for on of 28-day mortality, hospitalisation and ICU admission were similar to those for CRB-65 and CRB. Patients OFA scores of 0, 1, 2 and 3 were associated with, respectively, mortality of 16.3 %, 24.4 %, 48.2 % and 68.4 %; nce of hospitalisation of 37.2 %, 47.4 %, 61.6 % and 73.7 %; and prevalence of ICU admission of 9.3 %, 2.4 % and 45.3 %. Patients with qSOFA scores of 2 and 3 had a significantly higher prevalence of mortality and nission than patients with identical CRB-65 scores.

sions: qSOFA is better than CRB-65 for identification of a high risk of mortality and requirement of ICU on.

Table 3 Predictive performance of CRB-65, CRB and qSOFA

Outcomes	Predictors	Cut-off value	Sensitivity	Specificity	PPV	NPV	LR^+	LR^-	OR
Mortality	CRB-65	≤1	70 %	57 %	45 %	79 %	1.6	0.5	3.059
	CRB-65	2	30 %	88 %	55 %	72 %	2.5	0.8	3.120
	CRB-65	≥3	7 %	98 %	60 %	68 %	3.5	1.0	3.141
	CRB	≤1	36 %	81 %	51 %	70 %	1.9	0.8	2.442
	CRB	2	9 %	97 %	62 %	66 %	3.0	0.9	3.201
	qSOFA	≤1	53 %	75 %	52 %	76 %	2.1	0.6	3.418
	qSOFA	2	12 %	97 %	68 %	69 %	4.0	0.9	4.783
Hospitalisation	CRB-65	≤1	59 %	56 %	60 %	55 %	1.3	0.7	1.807
	CRB-65	2	22 %	86 %	63 %	50 %	1.6	0.9	1.715
	CRB-65	≥3	5 %	97 %	67 %	48 %	1.7	1.0	1.851
	CRB	≤1	27 %	81 %	62 %	50 %	1.4	0.9	1.630
	CRB	2	6 %	97 %	69 %	48 %	2.0	1.0	2.066
	qSOFA	≤1	42 %	74 %	64 %	53 %	1.6	0.8	2.006
	qSOFA	2	8 %	97 %	74 %	49 %	2.7	1.0	2.673
ICU admission	CRB-65	≤1	76 %	53 %	22 %	93 %	1.6	0.5	3.589
	CRB-65	2	38 %	86 %	32 %	89 %	2.7	0.7	3.611
	CRB-65	≥3	14 %	98 %	57 %	87 %	7.0	0.9	8.444
	CRB	≤1	45 %	81 %	29 %	89 %	2.4	0.7	3.426
	CRB	2	15 %	97 %	49 %	87 %	5.0	0.9	6.352
	qSOFA	≤1	60 %	70 %	26 %	91 %	2.0	0.6	3.554
	qSOFA	2	18 %	96 %	45 %	87 %	4.5	0.9	5.471

Yes that’s all very good…
But what do I do at the bedside !



Management Issues …

etecting sepsis early
creases chances for
rvival

me of hypotension before therapy	>0,5 hrs	>3 hrs	>6 hrs	>24 hrs
survival rate	4 in 5 / 80%	3 in 5 / 60%	2 in 5 / 40%	1 in 5 / 20%

2012 Recommendation for Initial Resuscitation.

We recommend the protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion. During the first 6 hours of resuscitation, the goals of initial resuscitation should include all of the following as a part of a treatment protocol:

a) CVP 8–12 mm Hg
b) MAP ≥ 65 mm Hg
c) Urine output ≥ 0.5 mL/kg/hr
d) **Scvo2 ≥ 70%.**

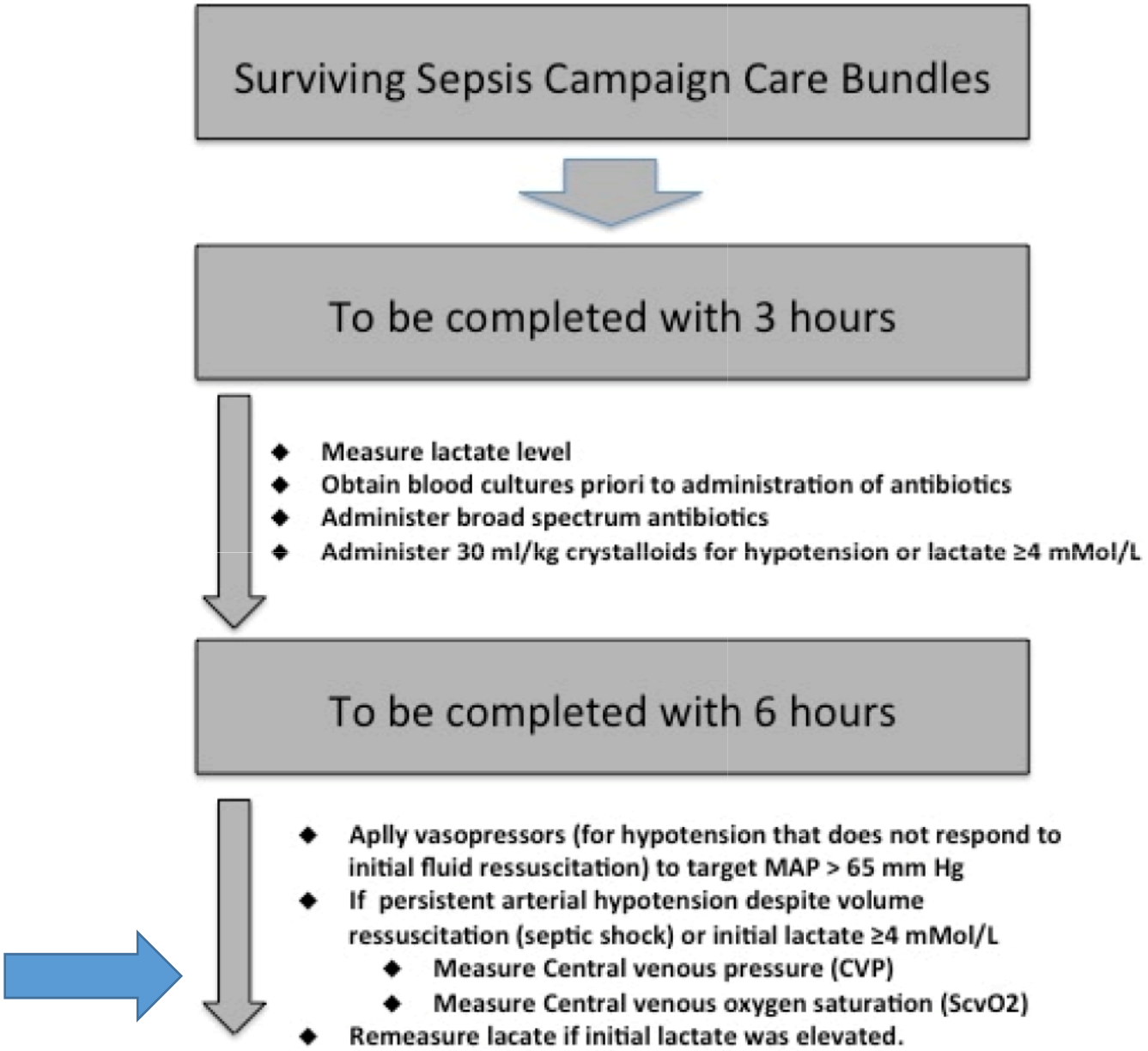
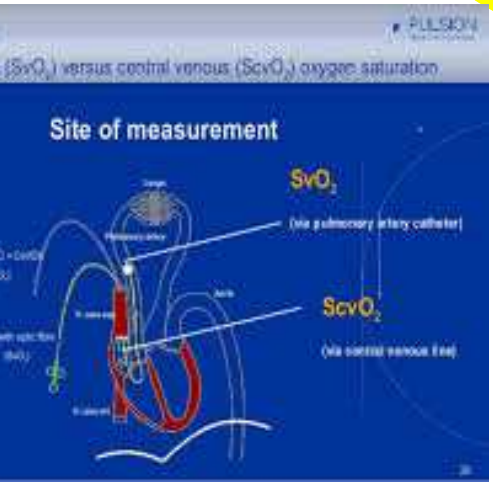
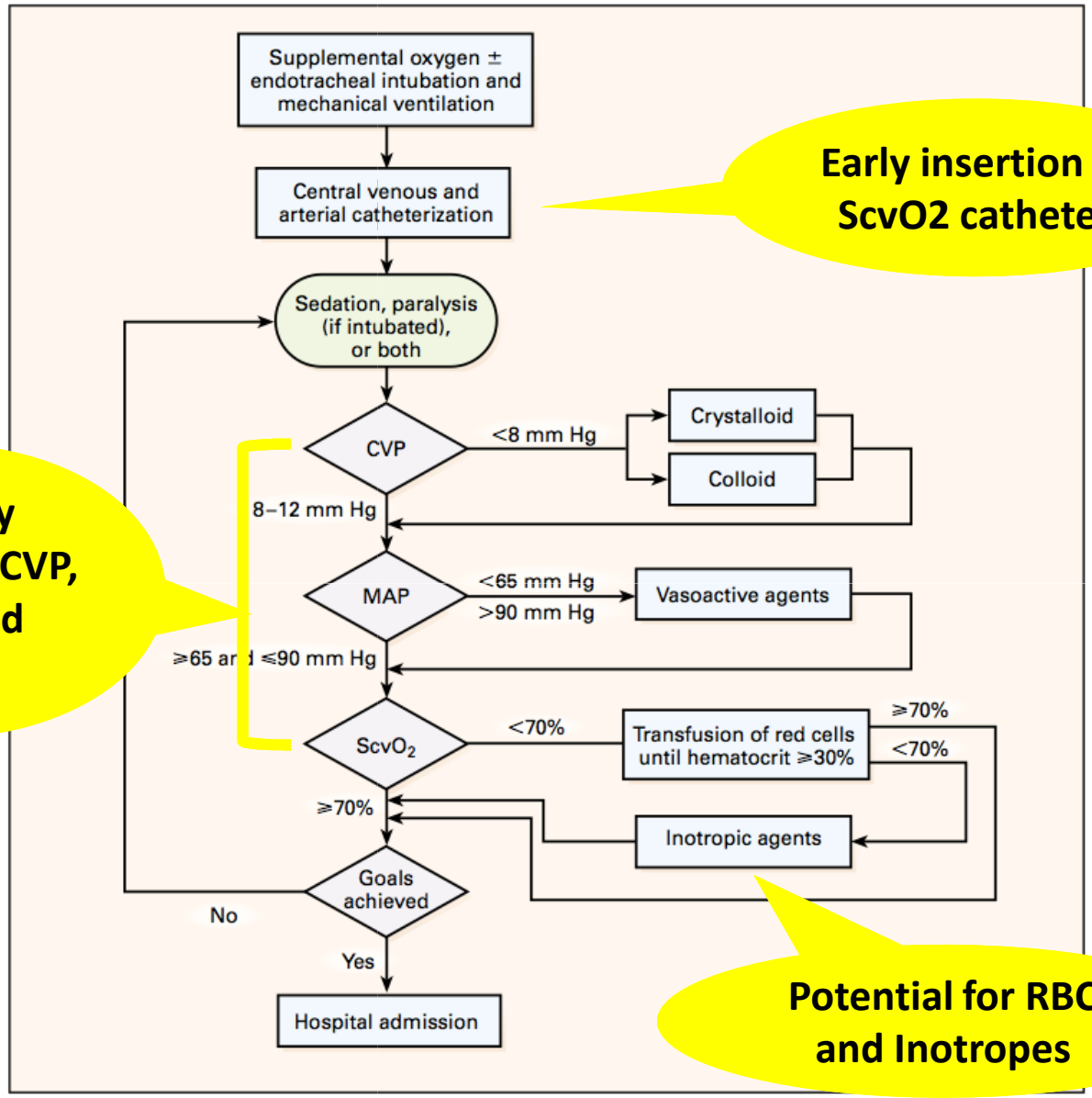


Figure 1: Surviving sepsis campaign care bundles. R.P. Dellinger, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012.

its of mixed venous oxygen saturation	
	Normal extraction O_2 supply >O_2 demand
>50%	Compensatory extraction Increasing O_2 demand or decreasing O_2 supply
>30%	Exhaustion of extraction Beginning of lactic acidosis O_2 supply <O_2 demand
>25%	Severe lactic acidosis Cellular death



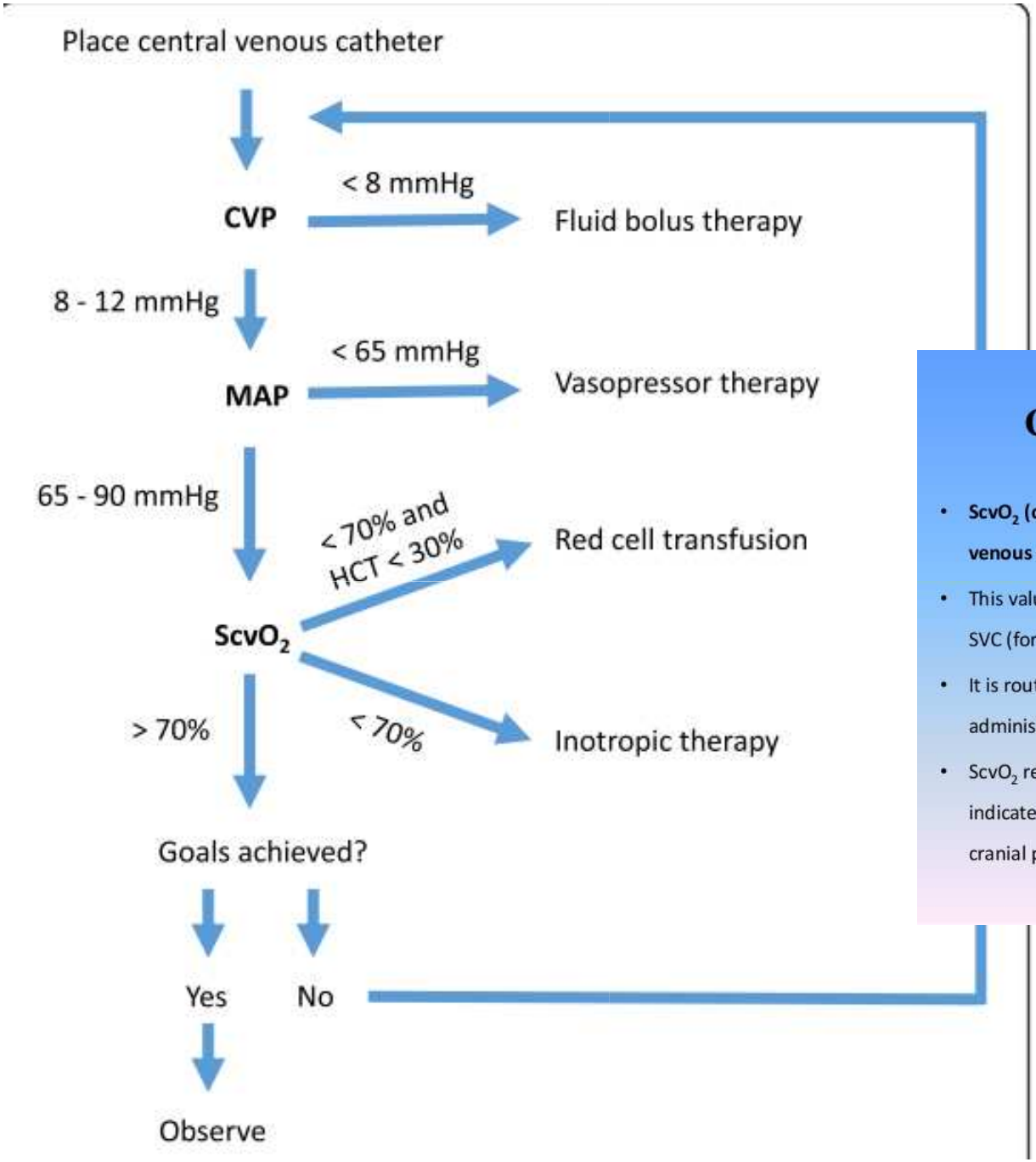


Early insertion of ScvO2 catheter

Therapy titrated to CVP, MAP and ScvO2

Potential for RBC and Inotropes

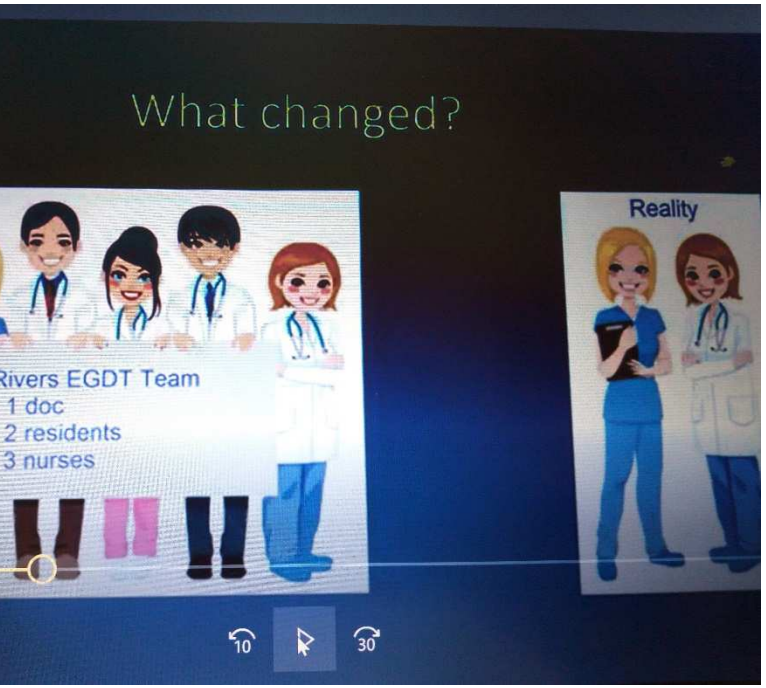
N Engl J Med, Vol. 345, No. 19 · November 8, 2001



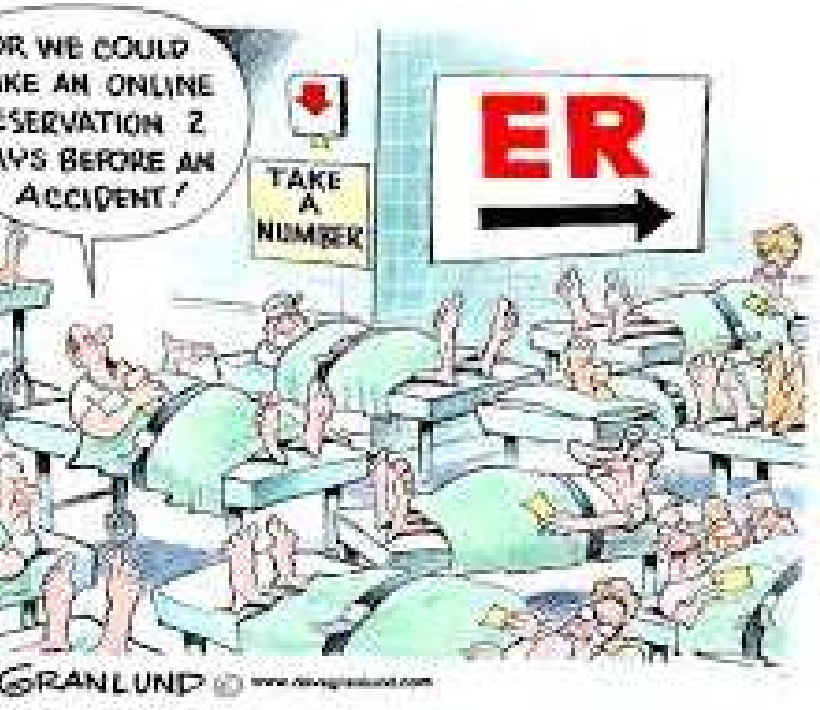
Central venous saturation /ScvO

- **$ScvO_2$ (central venous oxygen saturation) is the oxygen saturation o**
  venous blood.
- This value is obtained by placing a fiberoptic central venous catheter
  SVC (for continuous) or a simple catheter.
- It is routinely inserted in critically ill patients for monitoring of CVP ar
  administration of inotropes/vasopressors and TPN.
- $ScvO_2$ reflects oxygen saturation of blood returning from the upper b
  indicates the balance between oxygen delivery and oxygen consumpt
  cranial portion of the body, including the brain.

Variable	Standard Therapy (N=133)	Early Goal-Directed Therapy (N=130)	Relative Risk (95% CI)	P Value
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27


What changed?
Rivers EGDT Team
1 doc
2 residents
3 nurses
Reality
10
30


HURRY UP!
CAN I SEE?
200 WATT OK, DOC?
HEY! I'M NEXT!
YES, JUST HURRY!
HEY!
MAINTENANCE
CHOO!
BONES AND STUFF
BAM
BATHROOM IN HERE?
EMT
E.R. (GOOD LUCK)


OR WE COULD
KE AN ONLINE
SERVATION 2
AYS BEFORE AN
ACCIDENT!
TAKE A NUMBER
ER
GRANLUND

- 2014-2015

- Protocolized Care for Early Septic Shock (**ProCESS**)
- 31 ED in the United States

- Australasian Resuscitation in Sepsis Evaluation (**ARISE**)
- 51 ED in Australia, New Zealand, Finland, Hong Kong,Ireland

- The Protocolised Management in Sepsis (**ProMISe**)
- 56 ED in the United Kingdom

Name	**ProMISe**	**ProCESS**	**ARISE**
Full title	Protocolised Management In Sepsis	Protocolized Care for Early Septic Shock	Australasian Resuscitation In Sepsis Evaluation
Location	UK	USA	Australasia
Population	1260 adult severe sepsis patients presenting to ED	1935 adult sepsis patients with fluid refractory hypotension or lactate ≥ 4 mmol/l	1600 adult sepsis patients with fluid refractory hypotension or lactate ≥ 4 mmol/l
Intervention	early, goal-directed, protocolised resuscitation (targeting specific, measured haemodynamic goals)	Early goal-directed therapy using CVP and ScvO2	6 hours early goal-directed therapy using CVP and ScvO2
Control	usual resuscitation	(1) protocolised standard care (no CVC) (2) usual care	Standard non-protocolised care
Primary outcome	90 day mortality	60 day hospital mortality	90 day mortality

Characteristics of included randomised controlled trials

	Number of patients (EGDT/ control)	Design	Clinical setting	Study population	Goals in EGDT group	Goals in control group	Timing of EGDT	Morta end p
et al 2001	263 (130/133)	P-R-NB-SC	ED	Adult patients with severe sepsis, septic shock or sepsis syndrome	SvO_2 ≥70% CVP:8–12 mm Hg MAP:65–90 mm Hg UO ≥0.5 mL/kg/h	Standard therapy: CVP:8–12 mm Hg MAP:65–90 mm Hg UO ≥0.5 mL/kg/h	Within the first 6 h	Hospit 28-day 60-day
al 2010	303 (157/146)	P-R-NB-MC	ICU	Adult patients with severe sepsis or septic shock	$ScvO_2$ ≥70% CVP:8–12 mm Hg SBP >90 mm Hg MAP ≥65 mm Hg UO ≥0.5 mL/kg/h	Standard therapy: CVP:8–12 mm Hg SBP >90 mm Hg MAP ≥65 mm Hg UO ≥0.5 mL/kg/h	Within the first 6 h	ICU 28
SS 2014	895 (439/456) 885 (439/446)	P-R-NB-MC	ED/ICU	Adult patients with septic shock	$ScvO_2$ ≥70% CVP:8–12 mm Hg MAP:65–90 mm Hg UO ≥0.5 mL/kg/h	Usual care Standard therapy: SBP ≥100 mm Hg	Within the first 6 h	30-day 60-day 90-day
2014	1591 (793/798)	P-R-NB-MC	ED/ICU	Adult patients with septic shock	$ScvO_2$ ≥70% CVP:8–12 mm Hg MAP:65–90 mm Hg UO ≥0.5 mL/kg/h	Usual care	Within the first 6 h	ICU H 28-day 60-day 90-day
e 2015	1251 (625/626)	P-R-MB-MC	ED/ICU	Adult patients with septic shock	$ScvO_2$ ≥70% CVP ≥8 mm Hg MAP >60 mm Hg SBP >90 mm Hg	Usual care	Within the first 6 h	Hospit discha 28-day 60-day 90-day

Table 2 The source of bias in terms of patient population and methodology of included trials

	Rivers *et al*	ProCESS, ARISE and ProMISe
Illness severity heterogeneity*		
Fluid challenge before enrolment	20 to 30 mL/kg	1000 mL
Blood lactate levels at baseline, mmol/L	6.9	4.2–5.1
APACHE II score at baseline	20.4	15.8–20.7
$ScvO_2$, at baseline, %	49.2	NR
$ScvO_2$, 0–6 h, %	66	75.9†
Mechanical ventilation 0–6 h, %	53.8	19.0–22.4
28-day mortality	49.2%	15.9–24.5%
Methodological differences		
CVC, %‡	100	50.9–61.9
Corticosteroid use	None	8–37%
Antibiotics treatment	After enrolment	Before enrolment
Treatment in control group	Well-defined	Vague
Blinding	Double blinded	Unblinded to the ICU clinicians
Time of conduction	1997–2000	2008–2014 (EGDT recommendatio SSC Guidelines and the sepsis six

Rivers Study 1999

	EGDT	Usual
IVF	4.9L	3.5L
Pressors	27.4%	30.3%
CVC	Mandatory	Mandatory
PRBC	64.1%	18.5%

ProCESS

	EGDT	Protocol	Usual
IVF	5.0L	5.5L	4.4L
Pressors	54%	52%	44%
CVC	93%	86%	87%
PRBC	14.4%	8.3%	7.5%

ARISE

	EGDT	Pragmatic
IVF	1.96L	1.71L
Pressors	66.6%	57.8%
A-Lines	91%	76%
CVC	90%	61.9%
PRBC	13.6%	7.0%

ProMISE

	EGDT	Usual
IVF	2.23L	2.02L
Pressors	53.3%	46.6%
A-Lines	74.2%	62.2%
CVC	92.1%	50.9%
PRBC	8.8%	3.8%

1 Comparison of some features of the Rivers, ProCESS, ARISE, and ProMISe studies

	Rivers et al. [1]	ProCESS [6]	ARISE [7]	ProMISe [8]
tion year	2001	2014	2014	2015
n years	1997–2000	2008–2013	2008–2014	2011–2014
r of patients in control/ groups	133/130	902/439	796/792	620/623
r of patients screened/ r/month	8	3.9	1.6	2.6
r of patient included/ r/month	7.4	0.9	0.5	0.5
% (EGDT group)	49	71	73	70
at inclusion (mEq/l)	7	5	4	5
m arrival at ED to mization (min)	Median 55/mean 80	Mean 190	Median 168	Median 162
dministered before mization	20–30 ml/kg in 30 min (received NA)	≥20 ml/kg in 30 min later >1000 ml (received 2200)	>1000 ml (received 2500)	>1000 ml (received 1600)
tics within 6 h (%)	89	97	100	100
ate antibiotics (%)	95	NA	90	NA
ement of resuscitation in EGDT (%)	99.2	88.1	80 ($ScvO_2$ at 6 h)	85
ty control/EGDT (%)	50/33	19/21	19/19	29/29

Comparison of EGDT studies				
	Rivers et al	**ProMISe**	**ProCESS**	**ARISE**
Location	US	UK	US	Australasia
Population	263	1260	1351	1600
Sepsis Definition				
Suspected / Actual Infection	Yes	Yes	Yes	Yes
SIRS criteria ≥ 2	Yes	Yes	Yes	Yes
Refractory ↓BP or lactate ≥ 4 mmol/l	Yes	Yes	Yes	Yes
Protocol				
Fluid before randomisation	20–30 ml/kg	1000 ml	~20–30 ml/kg Changed during study	1000 ml
Recruitment	not specified	<5h from ED arrival & <2h from shock criteria	<12h from ED arrival & <2h from shock criteria	<5h from ED arrival & <2h from shock criteria
Intervention	EGDT 6 hours	EGDT 6 hours	EGDT 6 hours	EGDT 6 hours
Control	Usual therapy	Usual therapy	1) Protocol usual therapy 2) Usual therapy	Usual therapy
Primary outcome	In-hospital mortality	90-day mortality	60-day mortality	90-day mortality
Primary Outcome				
Intervention	30.5%	n/a	21.0%	18.8%
Control	46.5%	n/a	1) 18.2% 2) 18.9%	18.8%

A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

Angus, D.C.. et al. Intensive Care Med (2015) 41: 1549. doi:10.1007/s00134-015-3822-1

To determine whether early goal-directed therapy (EGDT) reduces **mortality** compared with other resuscitation strategies for patients presenting to the emergency department **(ED)** with septic shock.

January 2000 to January 2015.

3 randomised clinical trials (*n* = 4735 patients)

No effect on the primary mortality outcome (EGDT: 23.2 % [495/2134] versus control: 22.4 % [582/2601]

Pooled estimate of **90-day mortality** from the 3 multicentre studies (*n* = 4063) =**No difference**

EGDT increased vasopressor use (OR 1.25)and **ICU admission** [OR 2.19)

EGDT is not superior to usual care for ED patients with septic shock but is associated with increased utilisation of ICU resources.

Yu H, Chi D,
et al. Effect of early
ected therapy on
in patients with
epsis or septic
meta-analysis
mised controlled
MJ Open 2016;**6**:
. doi:10.1136/
-2015-008330

BMJ Open

Effect of early goal-directed therapy on mortality in patients with severe sepsis or septic shock: a meta-analysis of randomised controlled trials

Results: 5 studies that enrolled 4303 patients with 2144 in the EGDT group and 2159 in the control group were included in this meta-analysis. Overall, there were slight decreases of mortality within 28 days, 60 days and 90 days in the random-effect model in patients with severe sepsis or septic shock receiving EGDT resuscitation. However, none of the differences reached statistical significance

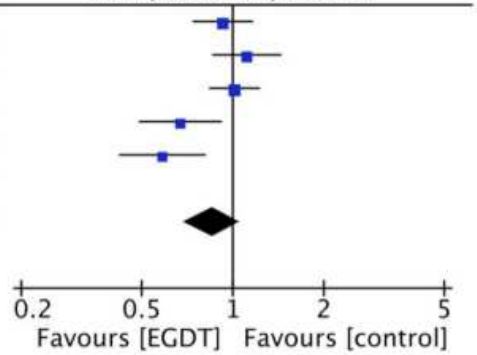
Conclusions: The current meta-analysis pooled data from five RCTs and found no survival benefit of EGDT in patients with sepsis.

28-day mortality

Study or Subgroup	EGDT Events	EGDT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISE2014	117	792	127	797	21.6%	0.93 [0.74, 1.17]
ProCESS2014	91	439	85	456	20.1%	1.11 [0.85, 1.45]
ProMISe2015	155	625	152	621	23.3%	1.01 [0.83, 1.23]
Rivers2001	40	130	61	133	17.8%	0.67 [0.49, 0.92]
Yan2010	39	157	62	146	17.2%	0.58 [0.42, 0.81]
Total (95% CI)		**2143**		**2153**	**100.0%**	**0.86 [0.69, 1.06]**
Total events	442		487			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 13.78$, df = 4 (P = 0.008); $I^2 = 71\%$

Test for overall effect: Z = 1.41 (P = 0.16)

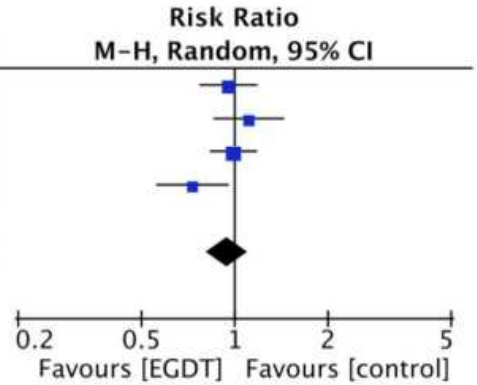


60-day mortality

Study or Subgroup	EGDT Events	EGDT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISE2014	132	792	139	796	26.4%	0.95 [0.77, 1.19]
ProCESS2014	92	439	86	456	20.9%	1.11 [0.85, 1.45]
ProMISe2015	176	625	178	626	32.5%	0.99 [0.83, 1.18]
Rivers2001	50	130	70	133	20.2%	0.73 [0.56, 0.96]
Total (95% CI)		**1986**		**2011**	**100.0%**	**0.94 [0.81, 1.10]**
Total events	450		473			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.23$, df = 3 (P = 0.16); $I^2 = 43\%$

Test for overall effect: Z = 0.74 (P = 0.46)

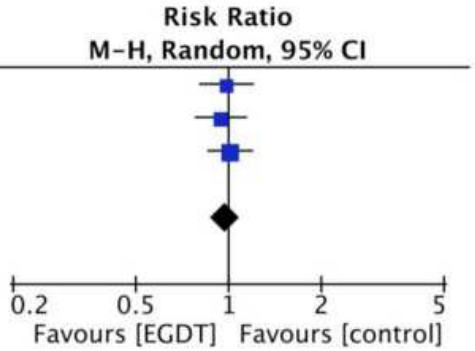


90-day mortality

Study or Subgroup	EGDT Events	EGDT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISE2014	147	792	150	796	28.5%	0.98 [0.80, 1.21]
ProCESS2014	129	405	139	412	31.1%	0.94 [0.78, 1.15]
ProMISe2015	184	623	181	620	40.4%	1.01 [0.85, 1.20]
Total (95% CI)		**1820**		**1828**	**100.0%**	**0.98 [0.88, 1.10]**
Total events	460		470			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.27$, df = 2 (P = 0.87); $I^2 = 0\%$

Test for overall effect: Z = 0.31 (P = 0.75)



The River's work was useful….

- As it provided us a construct on how to understand resuscitation:
  - Start early- (give antibiotics)
  - Correct hypovolaemia
  - Restore perfusion pressure
  - And in some cases a little more may be required..!

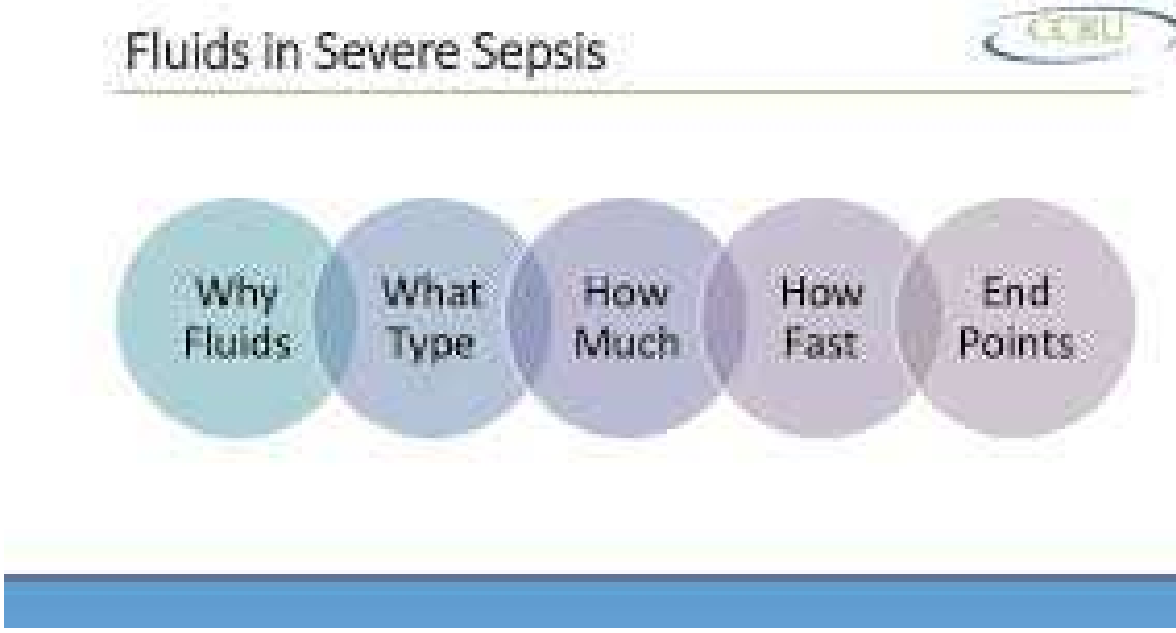
- These concepts are as important today as they ever were.

Recommendations

- 93 Recommendations
  - 32 **Strong** recommendations: ***"We recommend"***
  - 39 **Weak** recommendations: ***"We suggest"***
  - 18 Best Practice Statements

Fluids


Intravenous Fluids
3 – 4.5 L
in
1st 6 Hours


Fluids in Severe Sepsis
Why Fluids
What Type
How Much
How Fast
End Points

Initial Resuscitation

30ml/kg of intravenous crystalloid fluid be given within the **first 3 hours.**

(**Strong** recommendation; low quality of evidence)

Type of Fluids

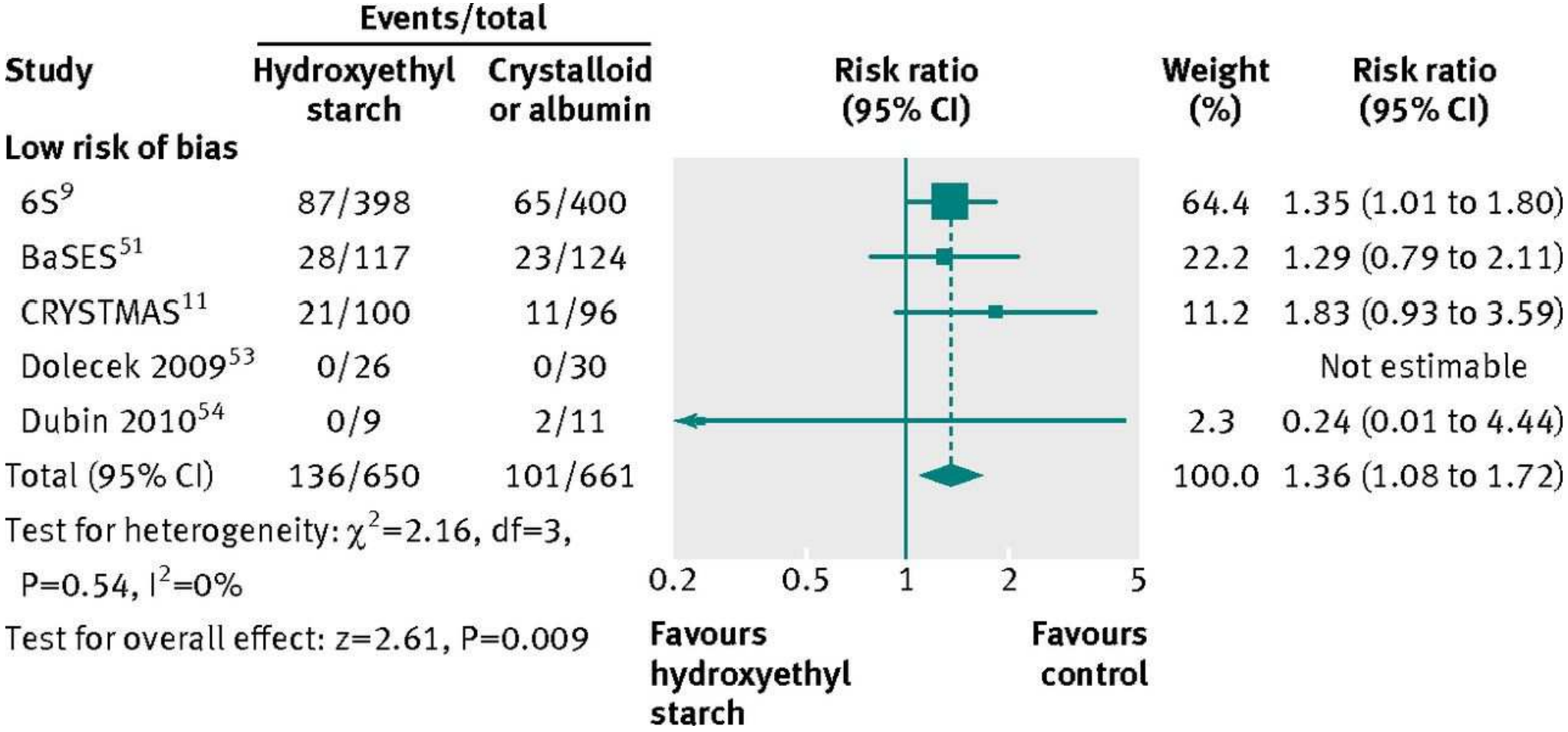
Fluid Therapy

- **Crystalloids** as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement

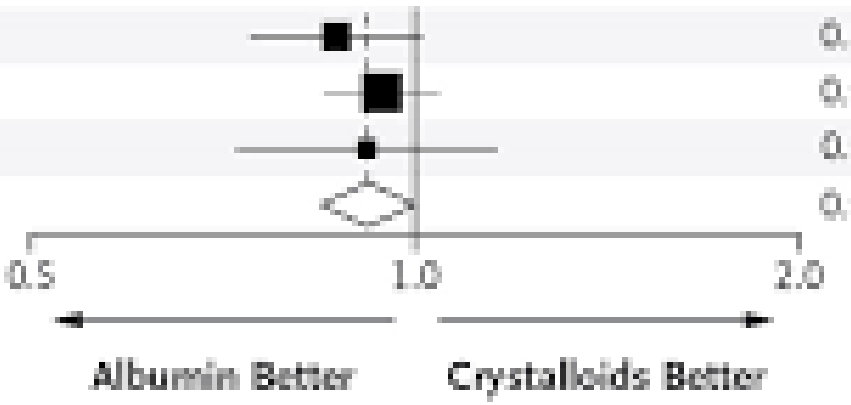
(**Strong** recommendation, moderate quality of evidence).

- **Albumin** in addition to crystalloids when patients require substantial amounts of crystalloids

(**Weak** recommendation, low quality of evidence).


Events/total
Study
Hydroxyethyl starch
Crystalloid or albumin
Risk ratio (95% CI)
Weight (%)
Risk ratio (95% CI)
Low risk of bias
6S[9] 87/398 65/400 64.4 1.35 (1.01 to 1.80)
BaSES[51] 28/117 23/124 22.2 1.29 (0.79 to 2.11)
CRYSTMAS[11] 21/100 11/96 11.2 1.83 (0.93 to 3.59)
Dolecek 2009[53] 0/26 0/30 Not estimable
Dubin 2010[54] 0/9 2/11 2.3 0.24 (0.01 to 4.44)
Total (95% CI) 136/650 101/661 100.0 1.36 (1.08 to 1.72)
Test for heterogeneity: χ^2=2.16, df=3, P=0.54, I^2=0%
Test for overall effect: z=2.61, P=0.009
0.2
0.5
1
2
5
Favours hydroxyethyl starch
Favours control

Trial	Albumin	Crystalloids	Relative Weight	Relative Risk (95% CI)	P Value
	no. of patients who died/total no.		%		
SAFE[2]	185/603	217/615	30.41	0.87 (0.74–1.02)	
ALBIOS[1]	365/888	389/893	54.90	0.94 (0.85–1.05)	
EARSS[3]	96/399	103/393	14.69	0.92 (0.72–1.17)	
All trials	646/1890	709/1901	100.00	0.92 (0.84–1.00)	0.046

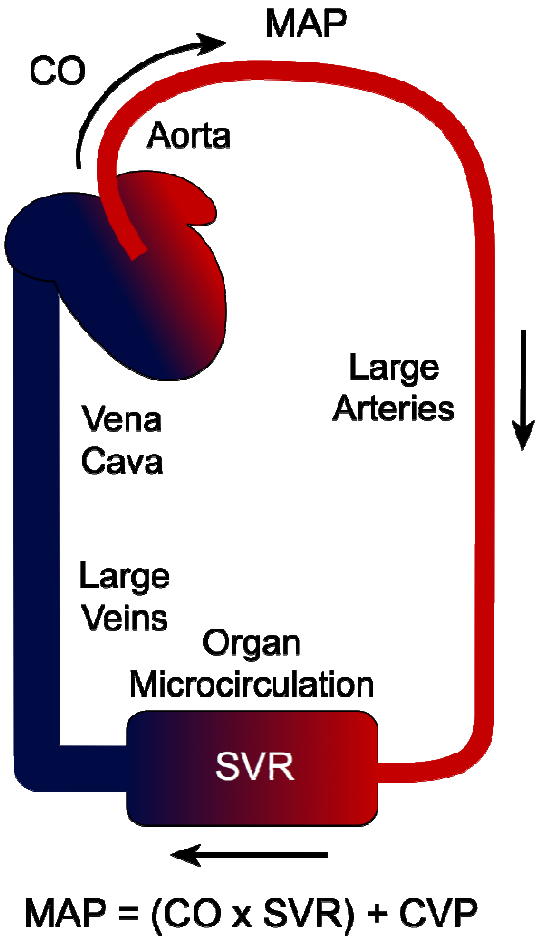


Albumin Replacement for Patients with Septic Shock

ALBIOS Trial

1135 patients with septic shock, in 100 ICUs Aug 2008 to Feb 2012			
	20% Albumin	Crystalloids	
# of Patients	565	570	
28 Day Mortality	35%	37%	X
90 Day Mortality	43.6%	49.9%	↓

MAP



Mean Arterial Pressure

- Average pressure driving blood forward into tissues throughout cardiac cycle
- Formula for approximating mean arterial pressure

$$MAP = \frac{SBP + (2 \times DBP)}{3}$$

MAP = mean arterial pressure

SBP = systolic blood pressure

DBP = diastolic blood pressure

High versus Low Blood-Pressure Target in Patients with Septic Shock

Initial target mean arterial pressure of **65 mmHg** in patients with septic shock requiring vasopressors.
(Strong recommendation; moderate quality of evidence)

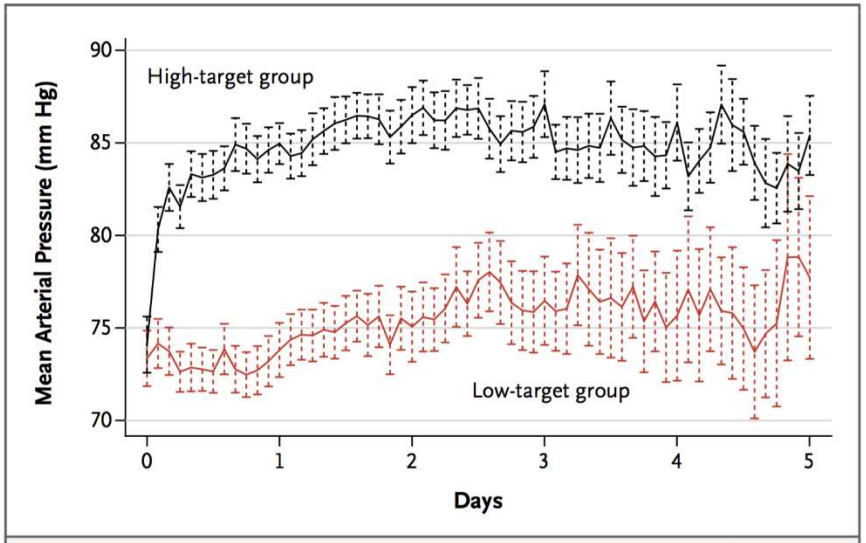


Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

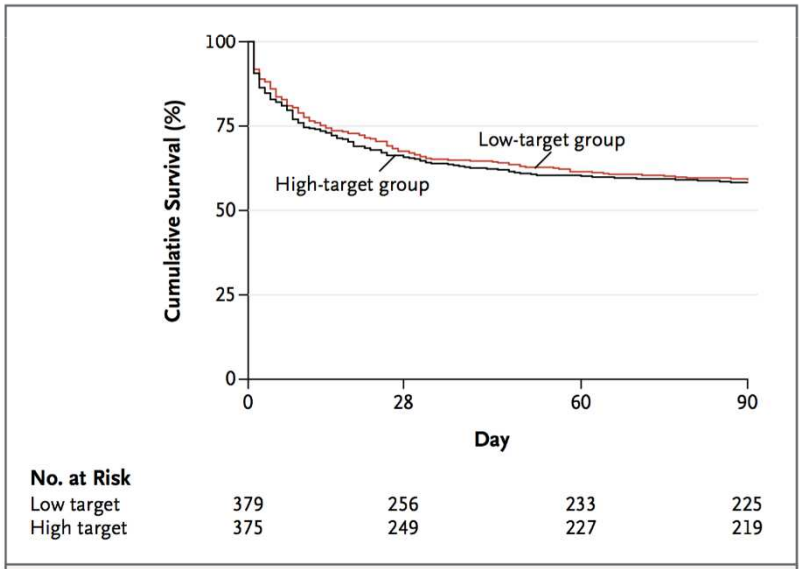
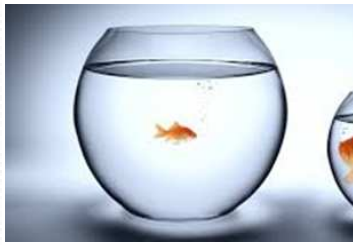


Figure 3. Kaplan–Meier Curves for Cumulative Survival.

DOI: 10.1056/NEJMoa1312173

SEPSISPAM Trial was published along side ProCESS (Protocol-Based Care for Early Septic Shock)
trial April 2014

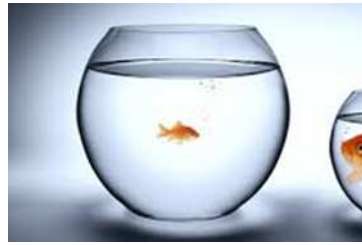


- Multicenter, open label trial of 776 patients with septic shock from 29 hospitals in France
- Septic Shock = Sepsis with Refractory Hypotension after 30cc/kg bolus of IVF
- Primary Outcome: 28 day mortality
- Also looked to see if higher MAP beneficial in patients with chronic HTN

High versus Low Blood-Pressure Target in Patients with Septic Shock

SEPSISPAM Trial

776 patients with septic shock, 29 centers Mar 2010 to Dec 2011	Low MAP 65 to 70 mm Hg	High MAP 80 to 85 mm Hg	
Doubling of S-Cr (ALL)	41.6%	38.6%	X 0.42
No Chronic HTN	33%	38.5%	X 0.32
Chronic HTN	52.3%	38.6%	∫ 0.02
Renal Replacement Therapy (ALL)	35.8%	33.5%	X 0.05
No Chronic HTN	30.7%	34.8%	X 0.36
Chronic HTN	42.2%	31.7%	∫ 0.046



Vasopressor

VASOACTIVE MEDICATIONS

2012	2016
Choice of vasopressors: Norepinephrine > epinephrine > Vasopressin	Norepinephrine > Vasopressin > Epinephrine

Vasoactive agents

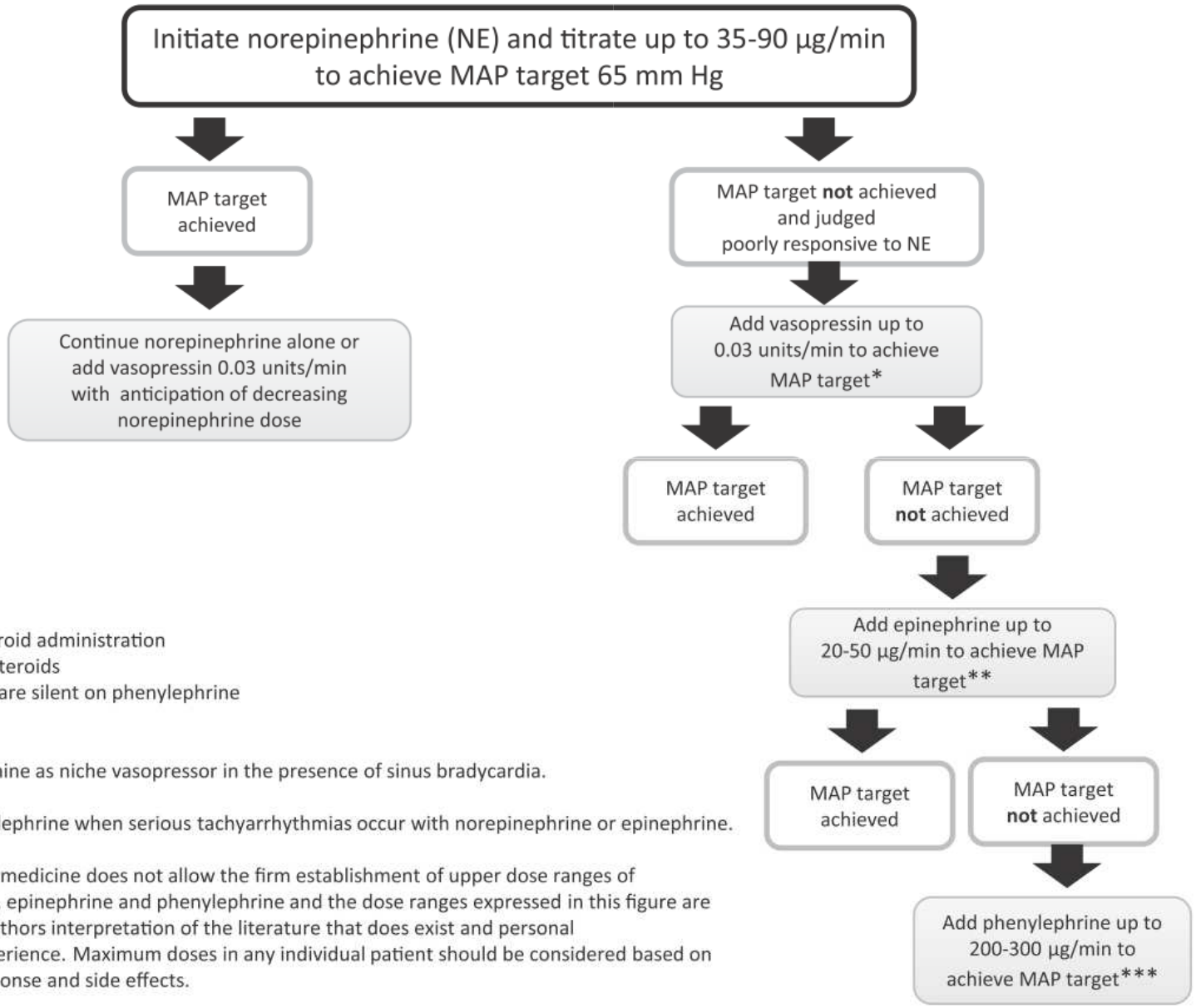
- **Norepinephrine** as the first choice vasopressor

(**Strong** recommendation, moderate quality of evidence).

- Adding either **Vasopressin** (up to 0.03 U/min**) or Epinephrine** to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage.

(**Weak** recommendation, low quality of evidence)

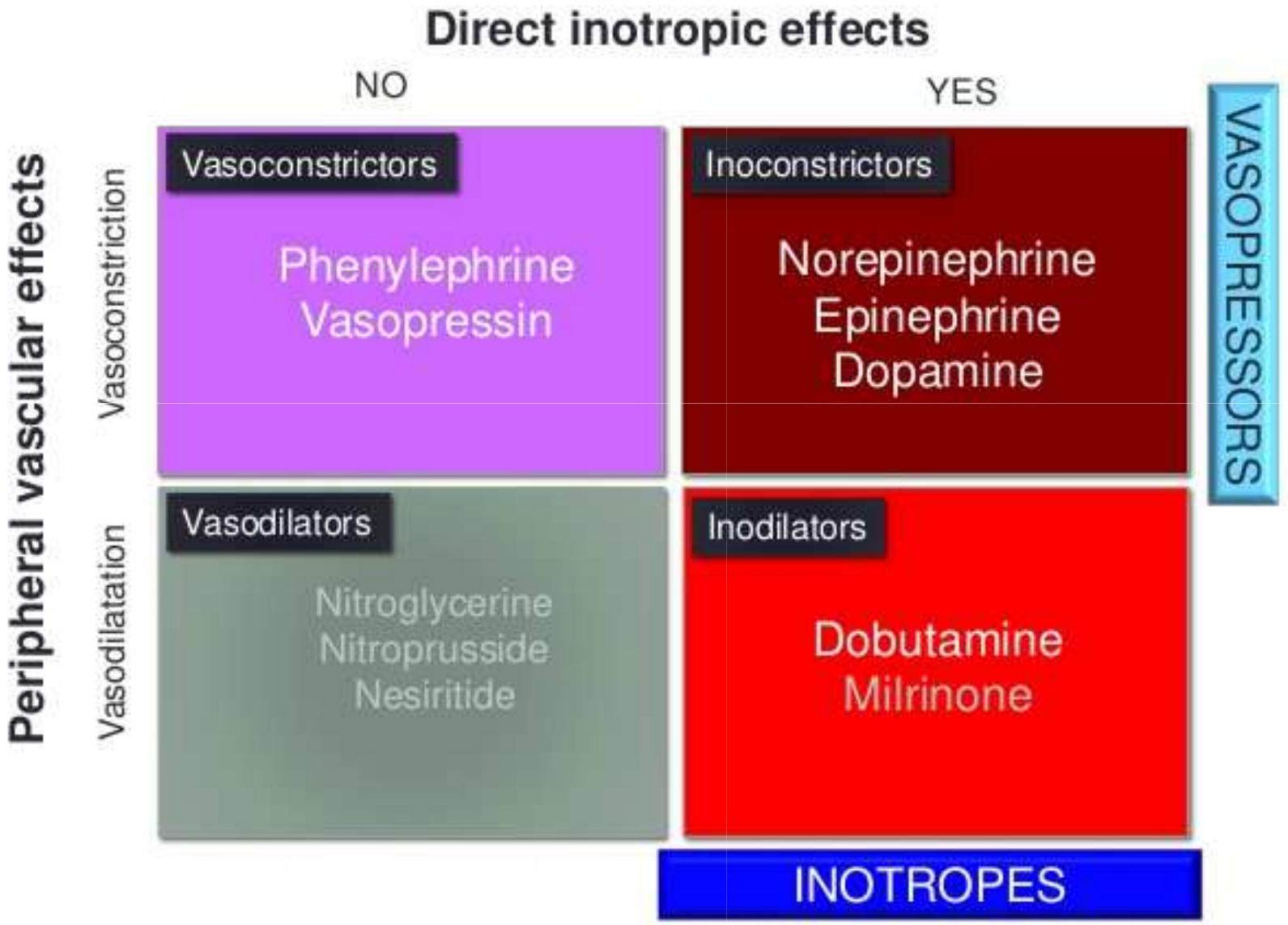
Vasopressor Use for Adult Septic Shock (with guidance for steroid administration)

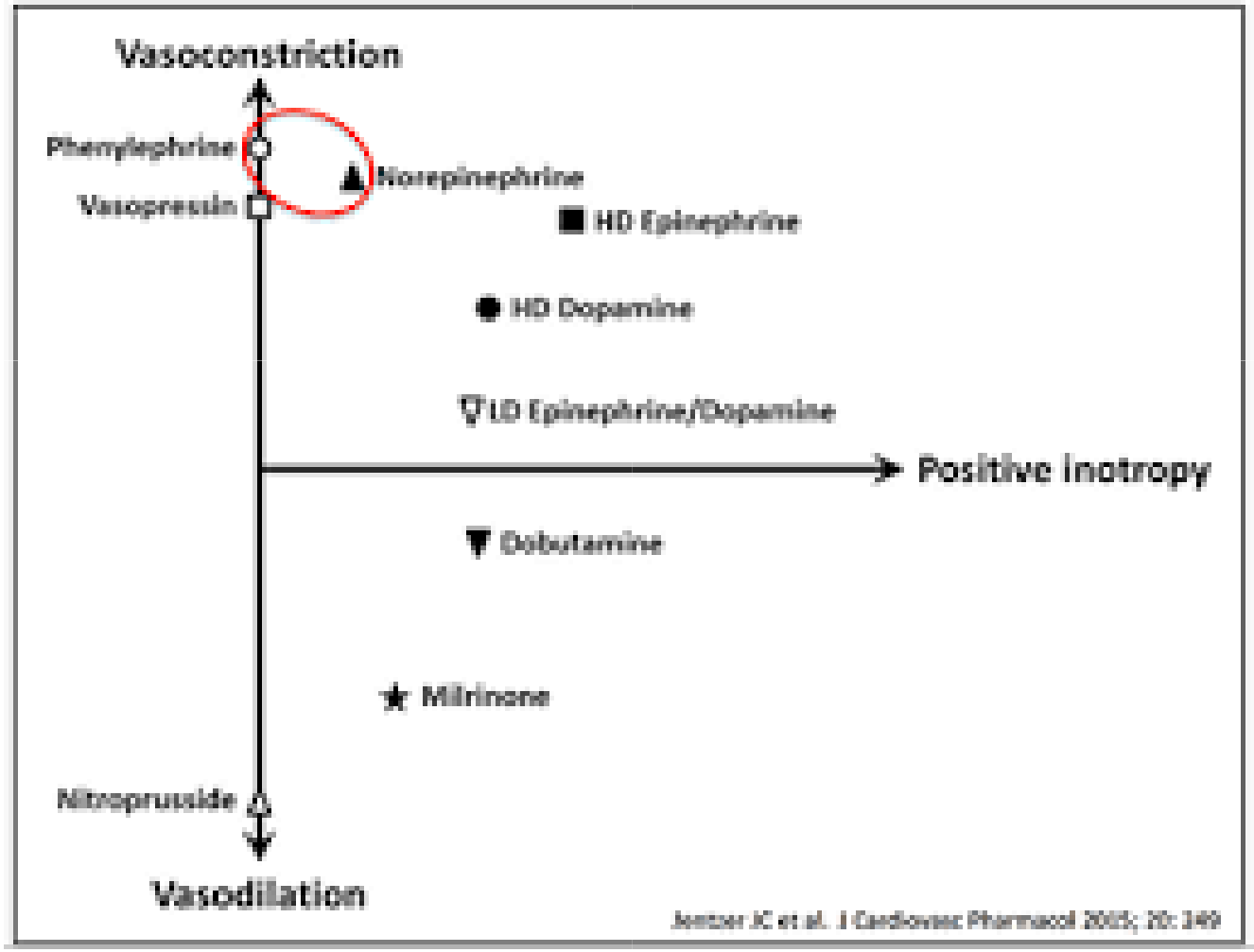


* Consider IV steroid administration
** Administer IV steroids
*** SSC guidelines are silent on phenylephrine

Notes:

- Consider dopamine as niche vasopressor in the presence of sinus bradycardia.
- Consider phenylephrine when serious tachyarrhythmias occur with norepinephrine or epinephrine.
- Evidence based medicine does not allow the firm establishment of upper dose ranges of norepinephrine, epinephrine and phenylephrine and the dose ranges expressed in this figure are based on the authors interpretation of the literature that does exist and personal preference/experience. Maximum doses in any individual patient should be considered based on physiologic response and side effects.


Direct inotropic effects
NO
YES
Peripheral vascular effects
Vasoconstriction
Vasodilatation
Vasoconstrictors
Phenylephrine
Vasopressin
Inoconstrictors
Norepinephrine
Epinephrine
Dopamine
Vasodilators
Nitroglycerine
Nitroprusside
Nesiritide
Inodilators
Dobutamine
Milrinone
VASOPRESSORS
INOTROPES


Vasoconstriction
Phenylephrine
Norepinephrine
Vasopressin
HD Epinephrine
HD Dopamine
LD Epinephrine/Dopamine
Positive Inotropy
Dobutamine
Milrinone
Nitroprusside
Vasodilation
Jentzer JC et al. J Cardiovasc Pharmacol 2015; 20: 349

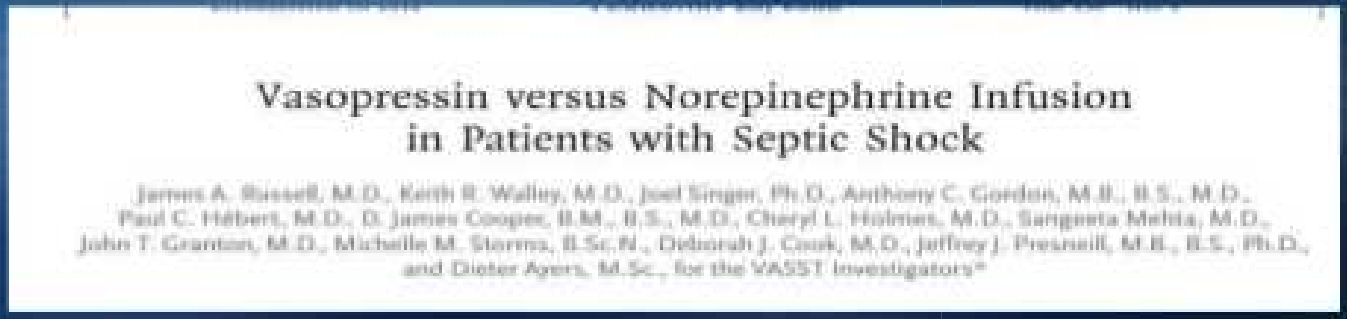
Should we tailor vasopressors to the patient's physiology?

Sympathetic Activation

Inadequate sympathetic drive	Most septic patients	Excessive sympathetic drive
- Low heart rate - Heart hypokinetic - Low lactate*		- Very tachycardic - Heart excessively hyperkinetic
Epinephrine	**Norepinephrine**	**Vasopressin**

Choice of Vasopressors

- VAAST trial in 2008 looked at 779 patients over 28 days and divided groups into Norepinephrine vs. Vasopressin
- Hypothesized that low-dose vasopressin as compared with norepinephrine would decrease mortality among patients with septic shock who were being treated with conventional (catecholamine) vasopressors.
- No mortality reduction – adjunctive therapy



Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D., Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D., John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D., and Dieter Ayers, M.Sc., for the VASST Investigators*

able 2: Comparison of antihypotensive drugs and their effects

		Physiologic effect				Patient presentation effect		
Drug	Usual Dose	Vd.	Vc.	In.	Chr.	HR	MAP	CO
lorepinephrine	5–30 mcg/min	Ø	♥♥♥♥	♥	♥♥	♥/Ø	♥♥♥	Ú
Dobutamine	2–10 mcg/kg/min	♥	♥	♥♥♥	♥	♥	♥	♥
	> 10–20 mcg/kg/min	♥♥	♥	♥♥♥♥	♥♥	♥♥	Ú	♥
Dopamine	1–3 mcg/kg/min	♥	Ø	♥♥	♥	Ø	Ø	Ø
	3–10 mcg/kg/min	♥	Ø	♥♥♥♥	♥♥	♥	♥	♥
	> 10–20 mcg/kg/min	Ø	♥♥♥	♥♥♥	♥♥♥	♥♥	♥	♥
pinephrine	1–5 mcg/min	♥	♥	♥♥♥♥	♥♥	♥	♥	♥♥
	> 5 mcg/min	Ø	♥♥♥	♥♥♥	♥♥♥	♥♥	♥♥	♥♥
henylephrine	20–200 mcg/min	Ø	♥♥♥♥	Ø	Ø	Ø/–♥	♥	Ú
Milrinone	0.375–0.75 mcg/kg/min	♥♥	Ø	♥♥♥	♥♥♥	♥♥	Ú	♥
asopressin	0.01–0.04 units/min	Ø	♥♥♥♥	Ø	Ø	Ø	♥♥♥	Ø/–♥

his table schematically shows the effects of each medication using the following key: Vd.-vasodilation, Vc.-vasoconstriction, In.-inotropy, Chr.-chronotropy; HR: heart rate, MAP: mean arterial ressure, CO: cardiac output; Ø-No or insignificant change, ♥-slight, ♥♥-mild, ♥♥♥-moderate, ♥♥♥♥-maximum, –♥-slight decrease, Ú or / -variable effect depending on clinical ondition and/or individual patient response.

Vasopressor Choice in Sepsis

Norepinephrine

1st LINE

Sepsis guidelines recommend norepinephrine as the first-choice vasopressor

+/-

Vasopressin

Vasopressin 0.03 units/min can be added to further raise MAP or decrease the dose of norepinephrine

Epinephrine

2nd LINE

Add epinephrine when an additional agent is needed to maintain adequate MAP

Dopamine

3rd LINE

Almost never used in septic shock, unless the patient has bradycardia and low risk of tachyarrhythmia

Phenylephrine

4th LINE

Not for use in sepsis except as salvage therapy when other vasopressors have failed

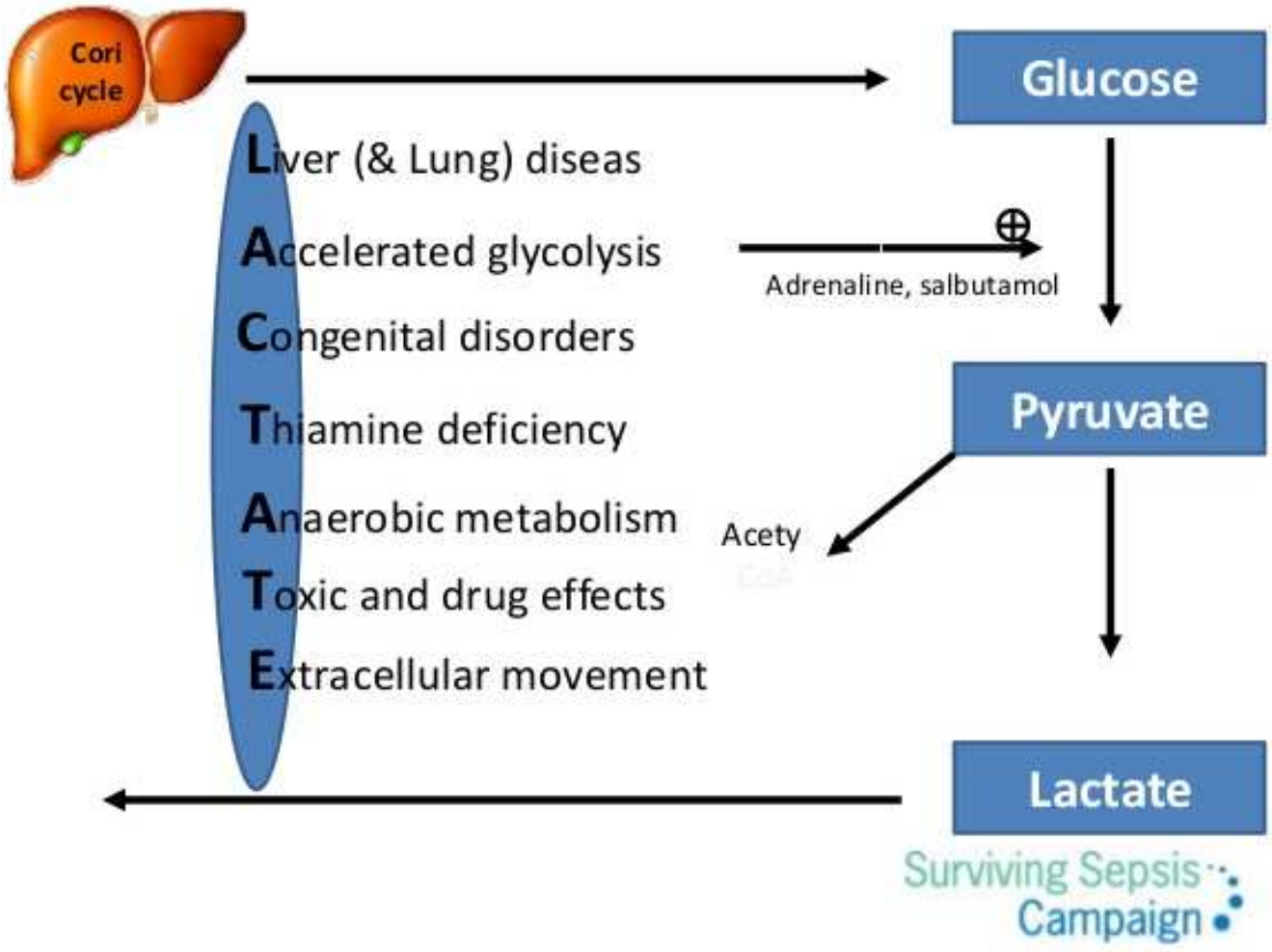
Recommendations from: www.survivingsepsis.org/guidelines

- 1 prospective RCT and a subsequent meta-analysis show equivalent outcomes comparing epinephrine vs. norepinephrine (Myburgh 2008, Avni 2015).

- VANISH and VANCS trials support the use of vasopressin as a front-line vasopressor in patients with sepsis.

- Overall, norepinephrine, epinephrine, and vasopressin are *all* supported by evidence as potential first-line vasopressors.

Lactate

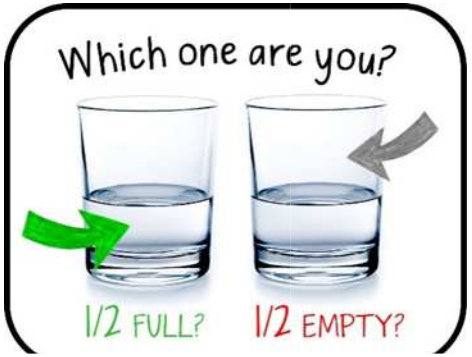

Cori cycle
Glucose
Liver (& Lung) diseas
Accelerated glycolysis
Adrenaline, salbutamol
Congenital disorders
Pyruvate
Thiamine deficiency
Anaerobic metabolism
Acety
Toxic and drug effects
Extracellular movement
Lactate
Surviving Sepsis Campaign


CLEARANCE
LACTATE
10% OFF


ELEVATED LACTATE
CAUSES
sepsis
shock states
cardiac arrest
liver disease
seizures
asthma
ischemic tissue
trauma
bowel dysfunction
medications
alcoholism
straightanursingstudent.com

Table 4. Characteristics of Serum Lactate Level Cutoff Values for Complete Case Analysis and Imputation Analysis Using Surviving Sepsis Campaign Database

	Serum Lactate Level, mmol/L					
	>2		>3		>4	
Characteristic	Died/Total	% (95% CI)	Died/Total	% (95% CI)	Died/Total	% (95% CI)
Complete Case Analysis (n = 18 795)						
Hospital mortality, %	5757/18 795	30.6 (29.9-31.4)	6101/18 795	32.5 (31.8-33.2)	6456/18 975	34.3 (33.7-35.0)
Sensitivity, %	5372/6509	82.5 (81.6-83.4)	3779/6509	58.1 (56.8-59.3)	2811/6509	43.2 (42.0-44.4)
Specificity, %	2748/12 286	22.4 (21.6-23.1)	6418/12 286	52.2 (51.4-53.1)	8564/12 286	69.7 (68.9-70.5)
PPV, %	5372/14 910	36.0 (35.3-36.8)	3779/9647	39.2 (38.2-40.2)	2811/6533	43.0 (41.8-44.2)
NPV, %	2748/3885	70.7 (69.3-72.2)	6418/9148	70.1 (69.2-71.1)	8564/12 286	69.8 (69.0-70.7)



Lactate can help guide resuscitation

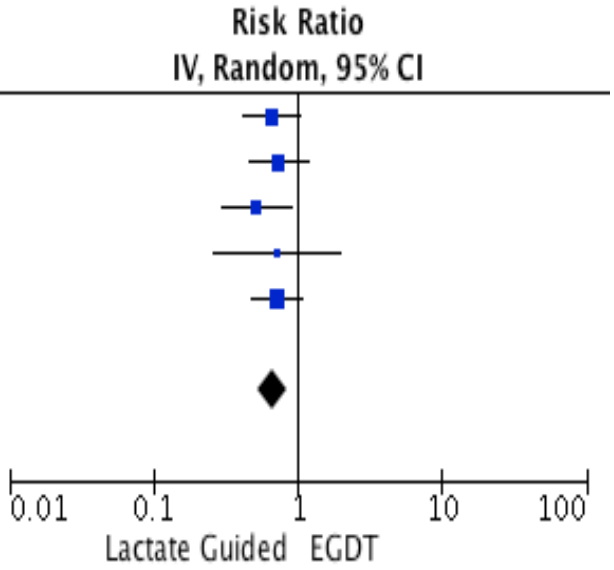
- Guiding resuscitation to **normalize lactate** in patients with elevated lactate levels as a marker of tissue hypoperfusion.

(**Weak** recommendation; low quality of evidence)

Study or Subgroup	Lactate Guided Events	Total	Standard Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Jansen, 2010	20	68	30	67	24.9%	0.66 [0.42, 1.03]	2010
Jones, 2010	25	150	34	150	23.8%	0.74 [0.46, 1.17]	2010
Tian, 2012	14	43	12	19	16.9%	0.52 [0.30, 0.89]	2012
Yu, 2013	5	25	7	25	5.1%	0.71 [0.26, 1.95]	2013
Lyu 2015	20	50	28	50	29.2%	0.71 [0.47, 1.09]	2015
Total (95% CI)		**336**		**311**	**100.0%**	**0.67 [0.53, 0.84]**	
Total events	84		111				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.14$, $df = 4$ ($P = 0.89$); $I^2 = 0\%$

Test for overall effect: $Z = 3.51$ ($P = 0.0004$)

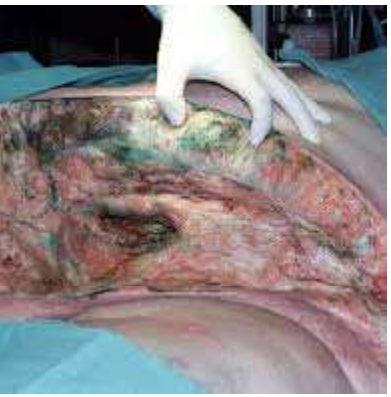


Resuscitative goals used in five trials

	Lactate Clearance Group	Control Group
Jones 2010	CVP > 8 mm MAP > 65mm Lactate clearance >10%	CVP > 8 mm MAP > 65mm svcO2 >70%
Jansen 2010	MAP > 60 mm HR < 100/min CVP 8-12 mm UOP > 0.5 cc/kg HgB > 7 mg/dL svcO2 monitoring allowed Lactate clearance >20%	MAP > 60 mm HR < 100/min CVP 8-12 mm UOP > 0.5 cc/kg HgB > 7 mg/dL svcO2 monitoring allowed
Lyu 2015	CVP > 8 mm MAP > 65 UOP > 0.5 ml/kg/hr svcO2 > 70% Lactate clearance > 10% (or <2 mM)	CVP > 8 mm MAP > 65 UOP > 0.5 ml/kg/hr svcO2 > 70%
Tian 2012	Lactate clearance >30% Other targets not specified*	Lactate clearance >10% Other targets not specified*
Yu 2013	CVP > 8 mm MAP > 65mm Lactate clearance >10%	CVP > 8 mm MAP > 65 svcO2 > 70%

*The full manuscript is in Chinese. This table is based on the abstracts published in English.

Source Control



ANAGEMENT OF SEPSIS
SOURCE CONTROL

eradicate the source of the infection are
l component of therapy This may

rainage
ent of devitalized infected tissue
of infected prosthesis.

- **We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made.**

Best Practice Statement).

Timing of Antibiotics

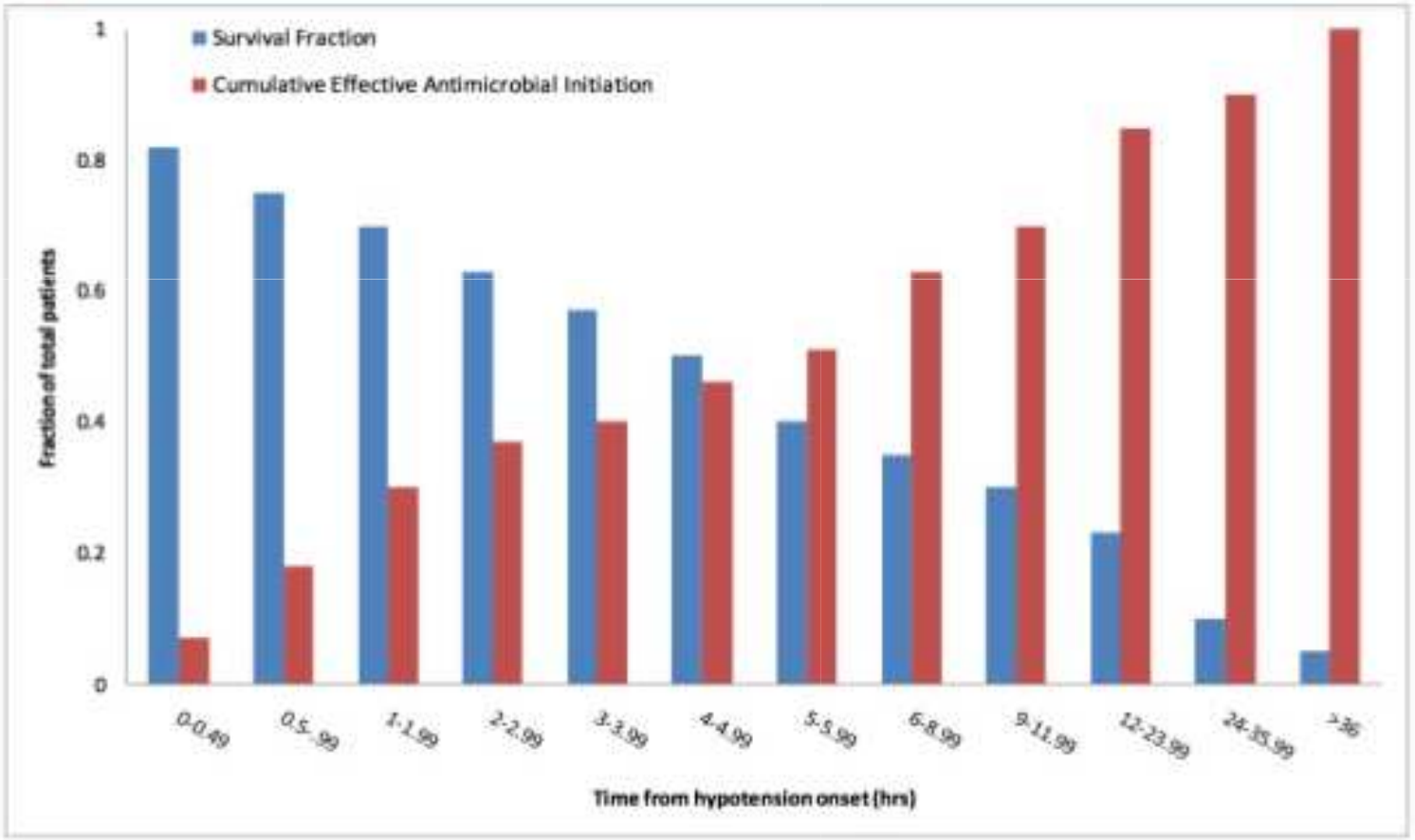
Antibiotics

IV antimicrobials be initiated ASAP after recognition and within **1 h** for both sepsis and septic shock.

(**Strong** recommendation, moderate quality of evidence)

Start antibiotics within 1 hour

Each hour of **DELAY** initial effective antibiotics increased mortality of **7.6%**.



Kumar A. et al., Crit Care Med 2006, 34:1286

Early antibiotics are good !

Author	N	Setting	Median time (mins)	Odds ratio for death
Gaieski CCM 2010; 38;1045-53	261	ED, USA (shock)	119	0.30 (1st hour vs all times)
Daniels Emerg Med J 2010; doi:10.1136	567	Whole hospital, UK	121	0.62 (1st hour vs all times)
Kumar CCM 2006; 34(6): 1589-1596	2154	ED, Canada (shock)	360	0.59 (1st 3 hours vs delayed)
Appelboam CCM 2010; 14(Suppl 1):50	375	Whole hospital, UK	240	0.74 (1st 3 hours vs delayed)
Levy CCM 2010; 38(2): 1-8	15022	Multi-centre		0.86 (1st 3 hours vs delayed)

- **Increased mortality associated with delays in antibiotic administration either from shock recognition or time from ED triage.**

Puskarich MA et al. One year mortality of patients treated with an emergency department based early goal directed therapy protocol for severe sepsis and septic shock: a before and after study. Crit Care. 2009; 13(5):R167.

Ferrer R et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med. 2014 Aug; 42(8):1749–55.

Gaieski DF et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med. 2010 Apr; 38(4):1045–53

Kumar A et al.Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun; 34(6):1589–96.

eptic shock patients suffer most from delayed antibiotics !

(Am J Respir Crit Care Med. 2017 March 27.
Vincent X Liu, , Oakland, California

To quantify the impact of antibiotic timing on mortality rates in different types of sepsis

35,000 adults treated for sepsis at 21 ED in northern California 2010 and 2013.

The median time to the first antibiotics was **2.1 hours**

Hospital mortality for sepsis =9% > likely with each hour of delayed antibiotics

Absolute mortality after 1 hour's delay in antibiotics

3% for sepsis

8% for septic shock patients

Broad Spectrum Antibiotics

- **Empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.**

(**Strong** recommendation, moderate quality of evidence).

Failure to initiate appropriate empiric therapy in sepsis and septic shock is associated with > in morbidity and mortality

Barie PS etal.(2005) Influence of antibiotic therapy on mortality of critical surgical illness caused or complicated by infection. Surg Infect. 6(1):41–54

Ibrahim EH etal. (2000) The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 118(1):146–155

Survival < X5 for septic shock treated with an empiric regiment that fails to cover the offending pathogen

Kumar A, et al (2009) Initiation of inappropriate antimicrobial therapy results in a five-fold reduction of survival in human septicshock. Chest 136(5):1237–1248

Empiric Combination

- **Empiric combination therapy** (using at least two antibiotics of different antimicrobial classes) aimed at th most likely bacterial pathogen(s) for the **initial** management of septic shock.

(**Weak** recommendation; low quality of evidence)

Routine Combination therapy ?

- Combination therapy **not be routinely used** for on-going treatment of most other serious infections, including **bacteremia and sepsis without shock.**

  (Weak recommendation; low quality of evidence).

- **Against combination therapy** for the routine treatment of **neutropenic sepsis/bacteremia.**

  (Strong recommendation; moderate quality of evidence).

Met analytic Studies of Combination therapy

Produces higher survival in **septic shock**

Benefit in **mortality risk > 25%.**

- Mortality risk **in low-risk (<15% mortality risk) with- out septic shock**

Kumar A et al. (2010) A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. Crit Care Med 38(8):1651–1665

Kumar A et al. (2010) Early combination antibiotic therapy yields improved survival compared with mono-therapy in septic shock: a propensity-matchedanalysis. Crit Care Med 38(9):1773–1785

- Direct evidence from adequately powered RCTs of Combination therapy

Not available !

- Clinical outcome in bacteremia and sepsis without shock for Combination therapy

Evidence =**No !**

Safdar N, (2004) Does combination antimicro-bial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis. 4(8):519–527

Paul M, (2006) Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database Syst Rev 1:CD003344

Antibiotic Stewardship

- Empiric antimicrobial therapy be **narrowed** once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.
  - **(BPS)**

- Antimicrobial treatment **duration of 7-10 days** is adequate for most serious infections associated with sepsis and septic shock.
  - **(**Weak recommendation; low quality of evidence)

- **Procalcitonin** levels can be used to support **shortening the duration** of antimicrobial therapy in sepsis patients.
  - **(**Weak recommendation; low quality of evidence)

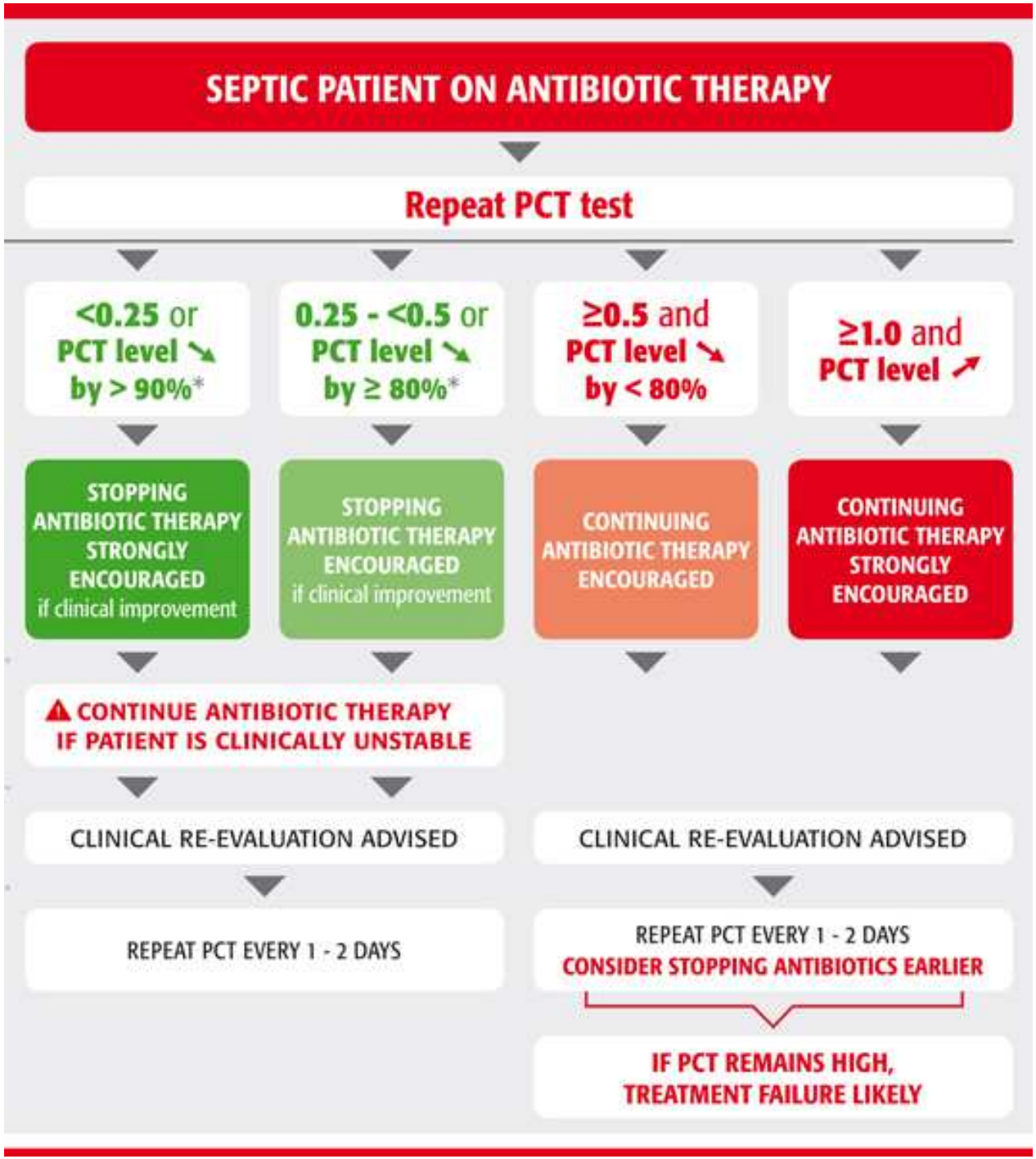
De-escalation

Observational studies

Early de-escalation of multidrug therapy is associated **with equivalent or superior clinical outcomes in sepsis and septic shock**

Morel J, et al (2010) De-escalation as part of a global strategy of empiric antibiotherapy management. A retrospective study in a medico-surgical intensiv care unit. Crit Care 14(6):R225

Joung MK, et al (2011) Impact of de-escalation therapy on clinical outcomes for intensive care unit-acquired pneumonia. Crit Care 15(2):R79


SEPTIC PATIENT ON ANTIBIOTIC THERAPY
Repeat PCT test
<0.25 or PCT level ↘ by > 90%*
0.25 - <0.5 or PCT level ↘ by ≥ 80%*
≥0.5 and PCT level ↘ by < 80%
≥1.0 and PCT level ↗
STOPPING ANTIBIOTIC THERAPY STRONGLY ENCOURAGED if clinical improvement
STOPPING ANTIBIOTIC THERAPY ENCOURAGED if clinical improvement
CONTINUING ANTIBIOTIC THERAPY ENCOURAGED
CONTINUING ANTIBIOTIC THERAPY STRONGLY ENCOURAGED
CONTINUE ANTIBIOTIC THERAPY IF PATIENT IS CLINICALLY UNSTABLE
CLINICAL RE-EVALUATION ADVISED
CLINICAL RE-EVALUATION ADVISED
REPEAT PCT EVERY 1 - 2 DAYS
REPEAT PCT EVERY 1 - 2 DAYS
CONSIDER STOPPING ANTIBIOTICS EARLIER
IF PCT REMAINS HIGH, TREATMENT FAILURE LIKELY

irect de-escalation of antimicrobial therapy in severe infections nd sepsis

Matthaiou DK, (2012) An ESICM **systematic review and meta-analysis** of **procalcitonin-guided antibiotic therapy** algorithms in adult critically ill patients. Intensive Care Med 38(6):940–949

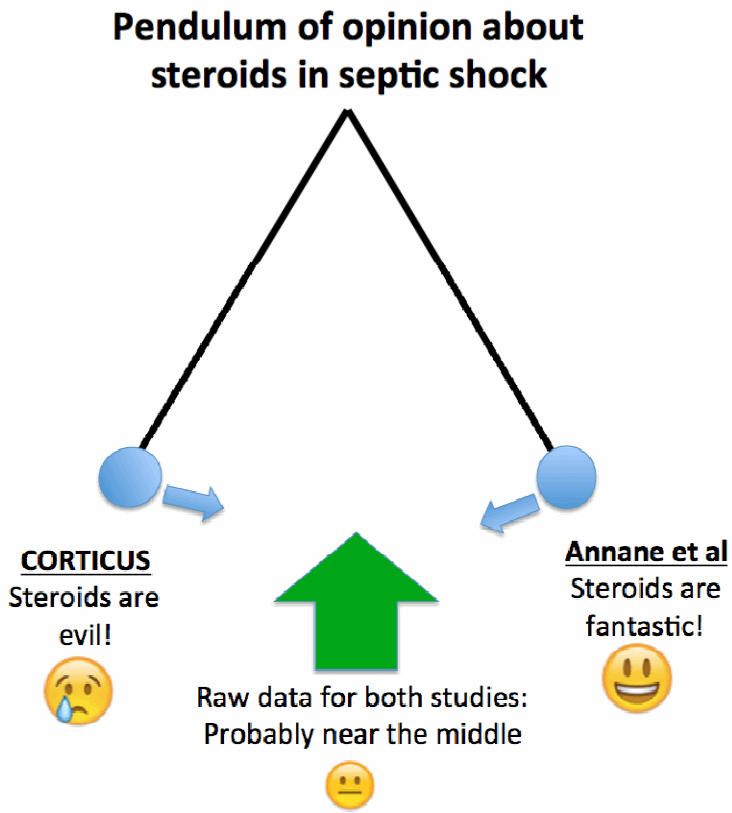
Prkno A, (2013) **Procalcitonin guided therapy** in intensive care unit patients with severe sepsis and septic shock—a **systematic review and meta-analysis**. Crit Care 17(6):R291

Westwood M, et al (2015) **Procalcitonin testing to guide antibiotic therapy** for the treatment of sepsis n intensive care settings and for suspected bacterial infection in emergency department settings: a **systematic review** and cost-effectiveness analysis.Health Technol Assess 19(96):v–xxv, 1–236

Soni NJ, et al (2013) **Procalcitonin-guided antibiotic therapy**: a **systematic review and meta-analysis**. J Hosp Med. 8(9):530–540

De Jong E, et al (2016) Efficacy and safety of **procalcitonin guidance in reducing the duration of antibiotic treatment** in critically ill patients: a **randomised,** controlled, open-label trial. Lancet Infect Dis. 16(7):819–827

Steroids


Pendulum of opinion about steroids in septic shock
CORTICUS
Steroids are evil!
Annane et al
Steroids are fantastic!
Raw data for both studies:
Probably near the middle


NO STEROIDS FOR ME
IF I GET SEVERE SEPS

CORTICOSTEROIDS

Against using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability.

If this is not achievable, we suggest intravenous hydrocortisone at a dose of 200 mg per day.

(Weak recommendation; low quality of evidence)

Why was this recommended?

COCHRANE review: 2004

Annane, Bellisant, Bollaert, Briegel, Keh and Kupfer : Names recognizable from previously mentioned studies

Corticosteroids for treating severe sepsis and septic shock

15 trials identified (N = 2023)

- **Corticosteroids did not improve 28 day mortality from all causes**
- **Corticosteroids DID improve ICU mortality**
- **Corticosteroids DID increase the proportion of shock reversal by day 7**
- **Low dose steroids over > 5 days DID reduce 28 day mortality**

2008

- **CORTICUS study: Corticosteroid Therapy of Septic Shock**
- multicenter, randomized, double-blind, placebo-controlled trial
- Close to 500 pts
- Major outcome measure: death at 28 days
- CONCLUSION:
  - **No survival benefit**
  - Hydrocortisone reverses shock faster, but increases the rate of secondary infections
  - Shock is reversed faster IN THOSE IN WHO SHOCK WAS REVERSED
  - i.e. if you were going to get better... You would get better faster with steroids

Sprung et al, **Hydrocortisone therapy for patients with septic shock.** N Engl J Med. 2008 Jan 10;358(2):111-24.

Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults

N = 2138

Analysis of the since-1998 subgroup: consisently good quality, 12 trials with only low-dose long-course steroids (200-300mg daily), only in vasopressor-dependent adults

Uniformly, short courses of high dose steroids are **not supported.**

Annane et al, **Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults A Systematic Review** *JAMA.* 2009;301(22):2362-2375.

Póvoa *et al. Critical Care* (2015) 19:193
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CRITICAL CARE

RESEARCH Open Access

Clinical impact of stress dose steroids in patients with septic shock: insights from the PROWESS-Shock trial

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Abstract

Introduction: The aim of our study was to evaluate the clinical impact of the administration of intravenous steroids, alone or in conjunction with drotrecogin-alfa (activated) (DrotAA), on the outcomes in septic shock patients.

Methods: We performed a sub-study of the PROWESS-Shock trial (septic shock patients who received fluids and vasopressors above a predefined threshold for at least 4 hours were randomized to receive either DrotAA or placebo for 96 hours). A propensity score for the administration of intravenous steroids for septic shock at baseline was constructed using multivariable logistic regression. Cox proportional hazards model using inverse probability of treatment weighting of the propensity score was used to estimate the effect of intravenous steroids, alone or in conjunction with DrotAA, on 28-day and 90-day all-cause mortality.

Results: A total of 1695 patients were enrolled of which 49.5% received intravenous steroids for treatment of septic shock at baseline (DrotAA + steroids N = 436; DrotAA + no steroids N = 414; placebo + steroids N = 403; placebo + no steroids N = 442). The propensity weighted risk of 28-day as well as 90-day mortality in those treated vs. those not treated with steroids did not differ among those randomized to DrotAA vs. placebo (interaction p-value = 0.38 and p = 0.27, respectively) nor was a difference detected within each randomized treatment. Similarly, the course of vasopressor use and cardiovascular SOFA did not appear to be influenced by steroid therapy. In patients with lung infection (N = 744), abdominal infection (N = 510), Gram-positive sepsis (N = 420) and Gram-negative sepsis (N = 461), the propensity weighted risk of 28-day as well as 90-day mortality in those treated vs. those not treated with steroids did not differ among those randomized to DrotAA vs. placebo nor was a difference detected within each randomized treatment.

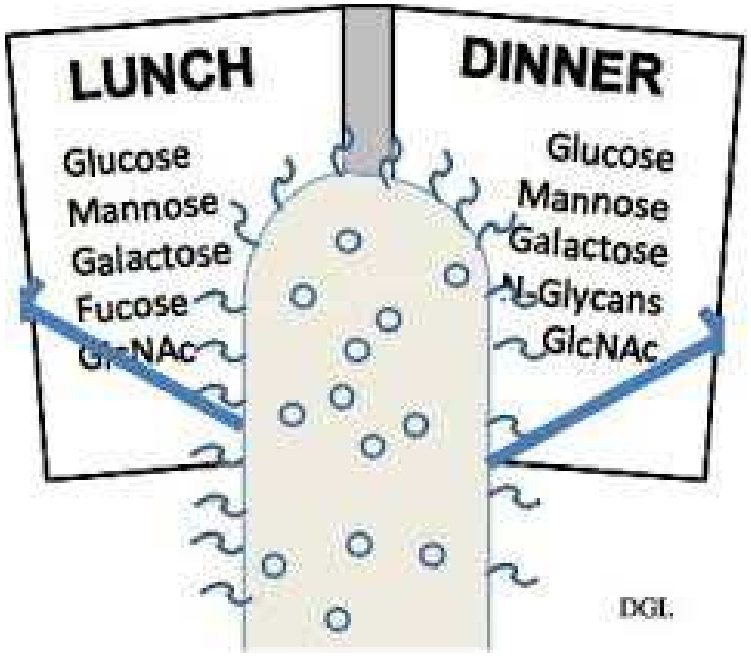
Conclusions: In the present study of septic shock patients, after adjustment for treatment selection bias, we were unable to find noticeable positive impact from intravenous steroids for treatment of septic shock at baseline either in patients randomized for DrotAA or placebo.

The ADRENAL study: ADjunctive corticosteroid tREatment iN criticAlly IlL patients with septic shock

Comparative timelines

- Annane trial 3.5 years, n=299, 19 sites
- CORTICUS 3.5 years, n=499, 52 sites
- VASST 5 years, n=778, 27 sites
- ADRENAL 3 years, n=2700, 70 sites

Glucose Control



Causes of Hyperglycemia in Critically Ill Patients

- Increased catecholamines (endogenous or exogenous)
- Increased glucocorticoids (endogenous or exogenous)
- Insulin resistance
- TPN
- Dextrose infusion
- Surgery
- Anesthesia
- Inflammatory mediators

GLUCOSE CONTROL

Commencing insulin dosing when -**2 consecutive blood glucose levels are >10 mmol/L.**

Target an upper blood glucose level **≤10 mmol/L** rather than an upper target blood glucose ≤6.1 mmol/L.

(Strong recommendation**; high** quality of evidence)

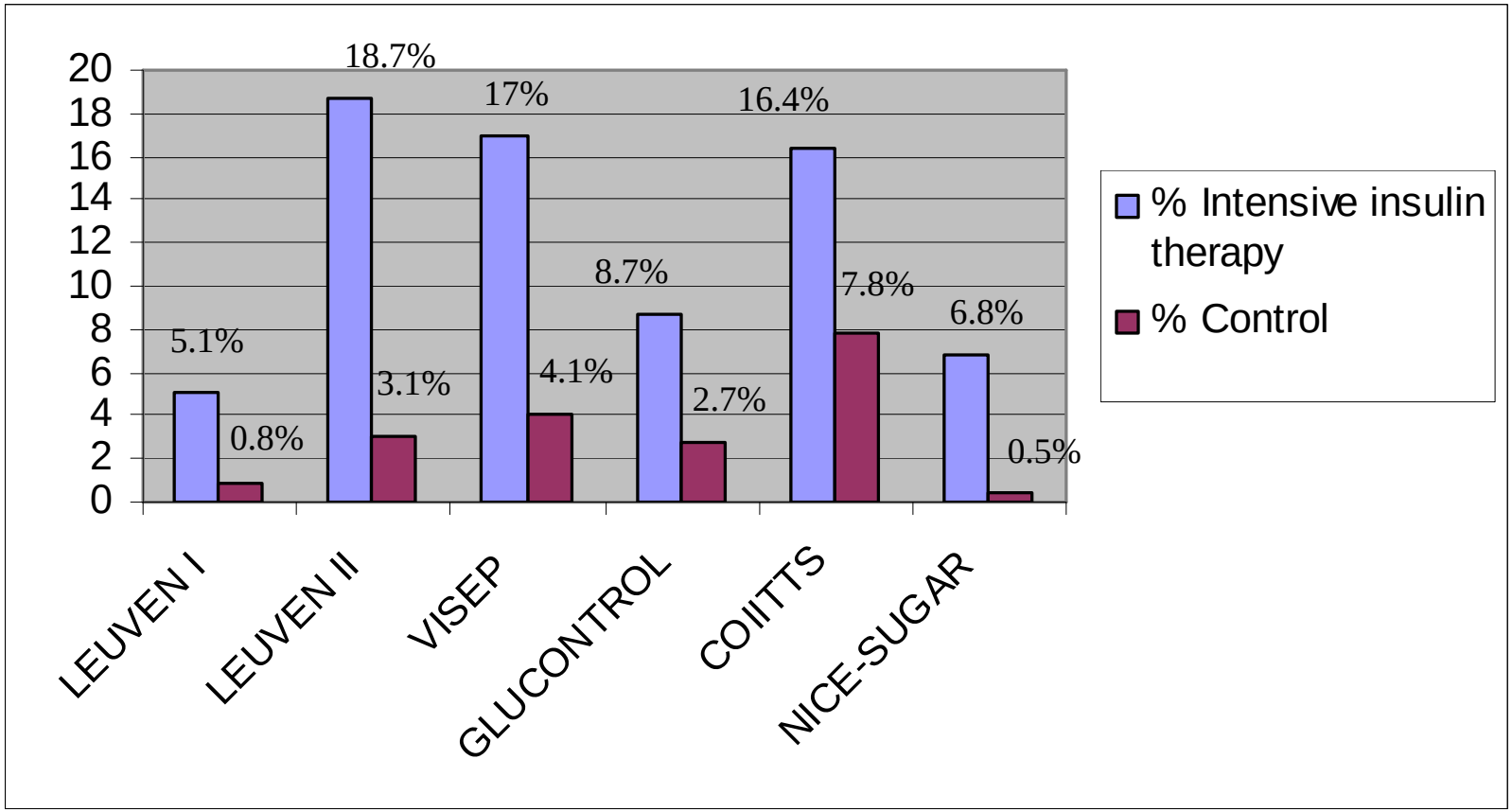
Glucose Control

No evidence that targets between **7.8 and 10** mmol/L are different from targets of **6.1 to 7.8** mmol/L

Treatment should avoid hyperglycemia (>10 mmol/L), hypoglycemia, and wide swings in glucose levels.

Dellinger P. *Crit Care Med.* 2013;41:580–637
Dellinger P. *Intensive Care Med.* 2013;39:165-228

Severe Hypoglycemia ≤40mg/dL (2.2 mmol/L)



Treatment vs control *P*<0.001

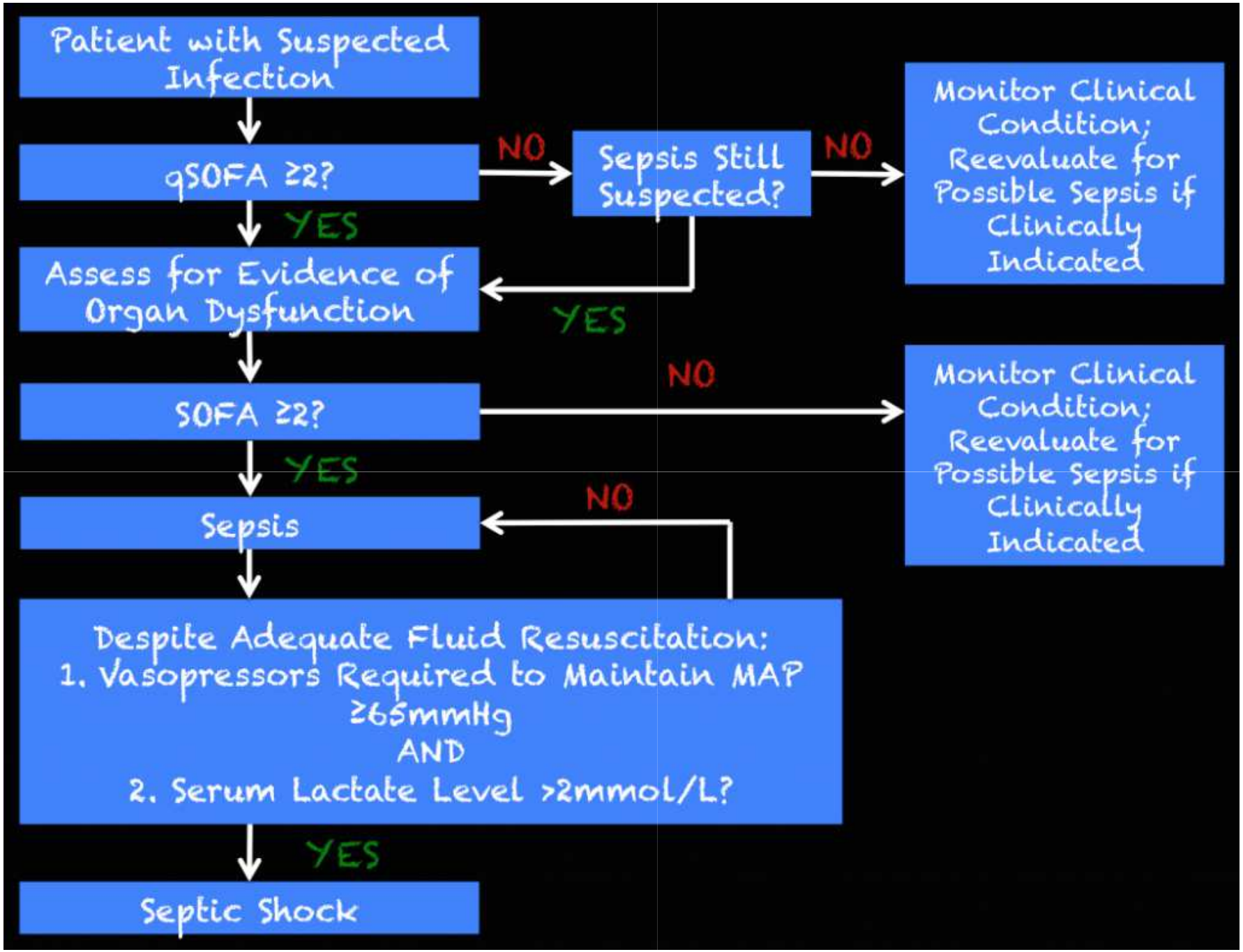
Take Home Points:

- **Sepsis** = life-threatening organ dysfunction caused by a dysregulated host response to infection

- **Septic Shock** = Need for Vasopressors AND Lactate >2 mmol/L

- **Severe Sepsis** is OUT

- **SIRS** is **OUT** and **qSOFA/SOFA** are **IN**


Patient with Suspected Infection
qSOFA ≥2?
NO
Sepsis Still Suspected?
NO
Monitor Clinical Condition; Reevaluate for Possible Sepsis if Clinically Indicated
YES
Assess for Evidence of Organ Dysfunction
YES
NO
SOFA ≥2?
Monitor Clinical Condition; Reevaluate for Possible Sepsis if Clinically Indicated
YES
NO
Sepsis
Despite Adequate Fluid Resuscitation:
1. Vasopressors Required to Maintain MAP ≥65mmHg
AND
2. Serum Lactate Level >2mmol/L?
YES
Septic Shock

SURVIVING SEPSIS CAMPAIGN RECOMMENDATION HIGHLIGHTS

	2012	2016
S DEFINITION	Systemic manifestation of infection + suspected infection Severe sepsis: sepsis + organ dysfunction	Life threatening organ dysfunction caused by dysregulated response to infection No severe sepsis category
NITIAL USCITATION	at least 30 cc/kg in first 3 hours Crystalloid fluid (no recommendations on 0.9% NaCl vs balanced solution) Albumin if patients require "substantial" fluids (weak)	
	Protocolized care including CVP ScVO2 Normalize lactate	Use dynamic resuscitation markers (passive leg raise) Target MAP of 65mmHg Reassess hemodynamic status to guide resuscitation Normalize lactate
PRESSORS	target MAP of 65 mmHg 1. Norepinephrine 2. Epinephrine if not at target MAP OR vasopressin to reduce norepinephrine requirement 3. Avoid dopamine in most patinets	
TEROIDS	Only indicated for patients with septic shock refractory to adequate fluids and vasopressors	
TIBIOTICS	One or more antibiotics active against presumed pathogen Combination therapy (double coverage) for neutropenic patients and pseudomonas	Initial broad spectrum antibiotics (ex: vancomycin + piperacillin-tazobactam) Against combined therapy (i.e. do not double cover pseudomonas) May use procalcitonin to guide de-escalation
CE CONTROL	Achieve within 12 hours, if feasible	Achieve as soon as medically and logically feasible

Please No More Recommendations ! Please !

Than
you !