

Update in Sepsis

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2021

Conflict of Interest

- Advisory Board for Merck
- Consultant for Genentech

Online: October 4, 2021

ONLINE SPECIAL ARTICLE

**Surviving Sepsis Campaign: International
Guidelines for Management of Sepsis and
Septic Shock 2021**

Critical Care Medicine, November 2021

Case

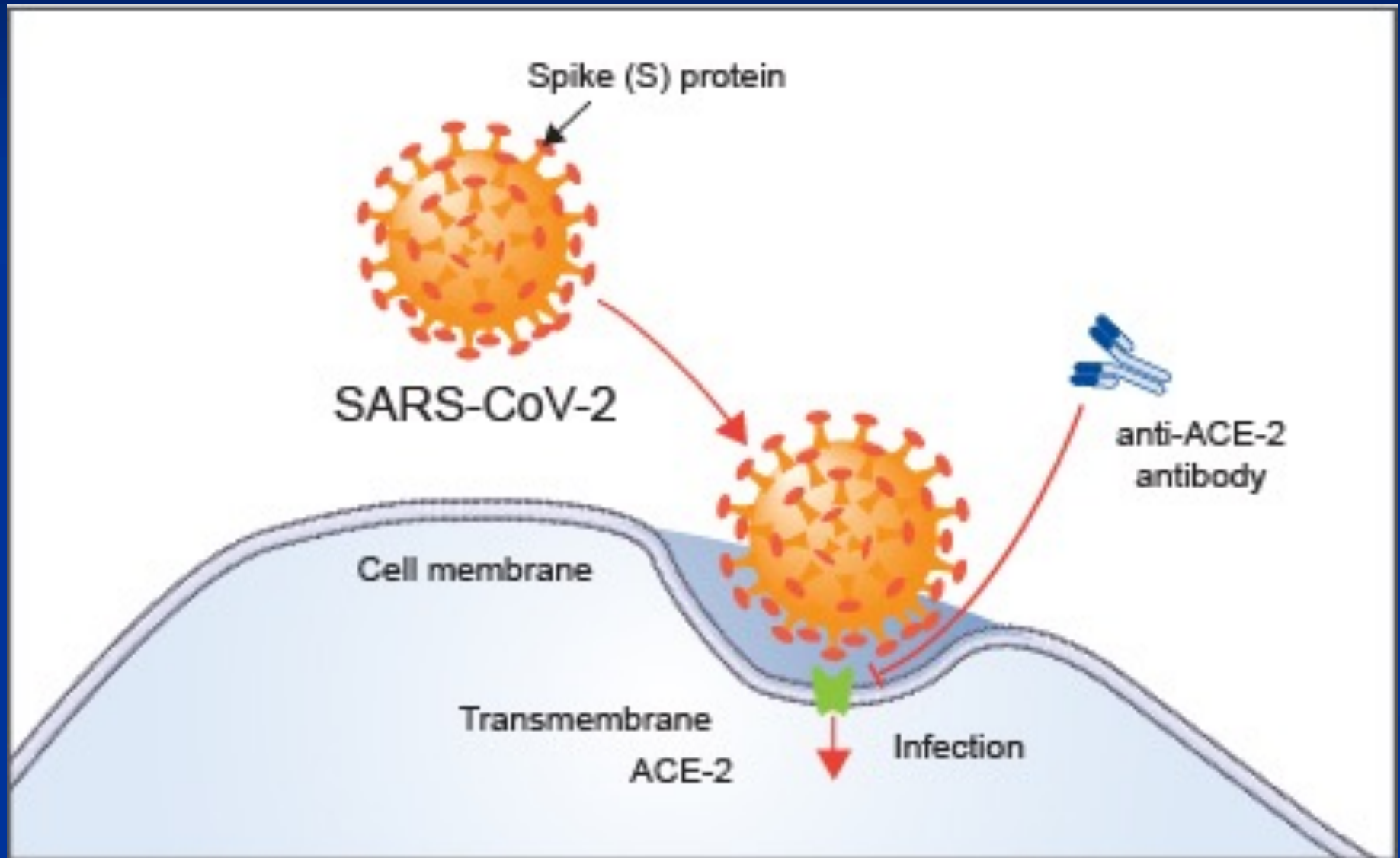
A 47 yo woman with alcoholic cirrhosis is brought to your ER with fevers, confusion, shortness of breath, and worsening ascites. Temp is 37°C, SBP is 50 mmHg, HR 150 bpm, RR 40/min, CVP 4 mm Hg, and O₂ sat 90% (RA). CXR shows diffuse infiltrates, and peritoneal fluid returns with a leukocyte count of 1000/ μ L (95% polys).

Question #1:

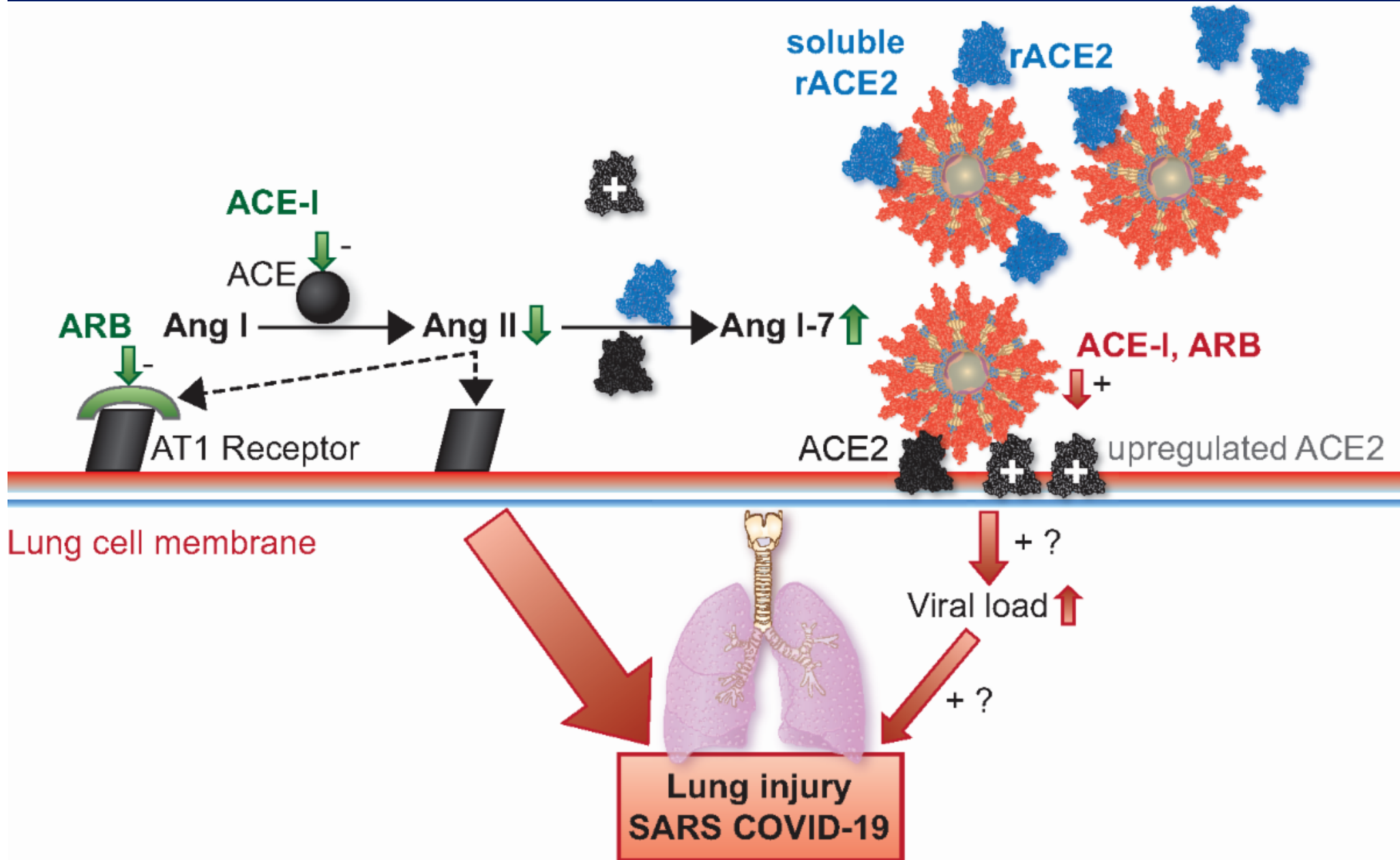
Does this patient have sepsis?

By what criteria?

Question #1 revised: Does this patient have COVID?



COVID Treatment thoughts: Targeting the virus and/or specific pathways?



What is Sepsis (2001-15)?

- Systemic Inflammatory Response Syndrome (SIRS):
 - Temp $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
 - Heart Rate > 90 bpm
 - Resp Rate $> 20/\text{min}$
 - WBC >10000 , <4000 , or Bandemia $>10\%$
- Sepsis: SIRS + Infection
- Severe Sepsis: Sepsis+ Organ Dysfunction
- Septic Shock: Sepsis+Refractory Hypotension

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

- SEPSIS: (>10% mortality)
 - Life-threatening organ dysfunction
 - Caused by *dysregulated response* to infection
 - Increase SOFA score of ≥ 2
- SHOCK: (>40% mortality)
 - Vasopressors for MAP ≥ 65 mmg Hg
 - Lactate > 2 mmol/L
 - In absence of hypovolemia

SOFA Score: 6 Organ Systems, 0-4 Points

<i>Points</i>	0	1	2	3	4
PaO₂/FiO₂	≥400	<400	<300	<200 + mechanical ventilation	<100 + mechanical ventilation
Platelets	≥150	<150	<100	<50	<20
Bilirubin	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Blood Pressure	MAP ≥70	MAP <70	Dopamine <5 or Dobutamine	Dopamine 5.1-15 or Epinephrine <0.1 or Norepinephrine <0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Creatinine	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500cc urine/d	>5.0 or <200cc urine/d

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qSOFA

- Out of hospital, ED, Ward settings
- *Worse outcomes* predicted from sepsis with 2 of:
 - Respiratory Rate $\geq 22/\text{min}$
 - Altered mental status (GCS ≤ 13)
 - SBP ≤ 100 mmHg
- Ongoing inquiry as to its validation
- *LESS SENSITIVE* but *MORE SPECIFIC* than SIRS
for sepsis screening.

Limitations

- Lab testing required (lactate, SOFA) not feasible in low-resource settings
- Prospective validation underway for qSOFA score vs. other metrics
- No use of biologic markers of sepsis to help define subgroups or predictors
- Practicality of definition for screening patients vs. billing vs. epidemiologic vs. research tools, etc.

In the future: Machine Learning/Artificial Intelligence?

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS; Scott Berry, PhD; Gilles Clermont, MD, MSc; Gregory Cooper, MD, PhD; Hernando Gomez, MD, MPH; David T. Huang, MD, MPH; John A. Kellum, MD, FACP, MCCM; Qi Mi, PhD; Steven M. Opal, MD; Victor Talisa, MS; Tom van der Poll, MD, PhD; Shyam Visweswaran, MD, PhD; Yoram Vodovotz, PhD; Jeremy C. Weiss, MD, PhD; Donald M. Yealy, MD, FACEP; Sachin Yende, MD, MS; Derek C. Angus, MD, MPH

Used 'big data' machine learning approaches to derive 4 sepsis subphenotypes not otherwise predicted from conventional severity indices. **Big data playing a big role in COVID epi studies and growing role in sepsis.

JAMA. 2019;321(20):2003-2017. doi:10.1001/jama.2019.5791
Published online May 19, 2019.

Surviving Sepsis Campaign

Surviving Sepsis Campaign Responds to Sepsis-3

March 1, 2016

SSC's approach: essentially no different than before!

- Step 1: Screen for Infection

- *SIRS may be a sign of infection – 2021: recommend against qSOFA as a single screening tool*

- Step 2: Screen for Organ Dysfunction

- Use organ dysfunction to target initial treatment and qSOFA to target closer monitoring for deterioration from sepsis

- Step 3: If hypotensive or lactate $\geq 2.0 \rightarrow 30$ ml/kg crystalloid, with reassessment of volume responsiveness or tissue perfusion

My bottom line: DON'T MISS SEPSIS. SCREEN with SIRS, PROGNOSTICATE with qSOFA, Dx SEPSIS w SOFA

Case, Question #2

A 47 yo woman with alcoholic cirrhosis is brought to your ER with fevers, confusion, shortness of breath, and worsening ascites. Temp is 37°C, SBP is 50 mmHg, HR 150 bpm, RR 40/min, CVP 4 mm Hg, and O₂ sat 90% (RA). CXR shows diffuse infiltrates, and peritoneal fluid returns with a leukocyte count of 1000/ μ L (95% polys). You initiate your sepsis bundle. Initial management of hemodynamics should entail use of:

- a. Vasopressin
- b. Norepinephrine
- c. Norepinephrine + Furosemide
- d. Intravenous fluids
- e. Dobutamine

Question #2:

What are we supposed to be doing with fluids in sepsis?

Sepsis: Source Control

- EARLY, BROAD, EMPIRIC antibiotic therapy
 - Not the time to be elegant!; Appropriate dosing*
- Think of sources needing SURGICAL INTERVENTION
 - Catheter / device → Remove it
 - Soft tissue abscess → Drain it
 - Empyema → Chest tube
 - Cholangitis → ERCP
 - Endocarditis → Abx/Valve replacement
 - Septic arthritis → Joint debridement
- Narrow therapy after 48 – 72H of cultures

****COVID: Remdesivir shortened time to recovery in less sick patients, perhaps; *2021 guidelines emphasize appropriate abx dosing** 17

Septic Shock: *EARLY* Goal-Directed Therapy 2001- 2014

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*

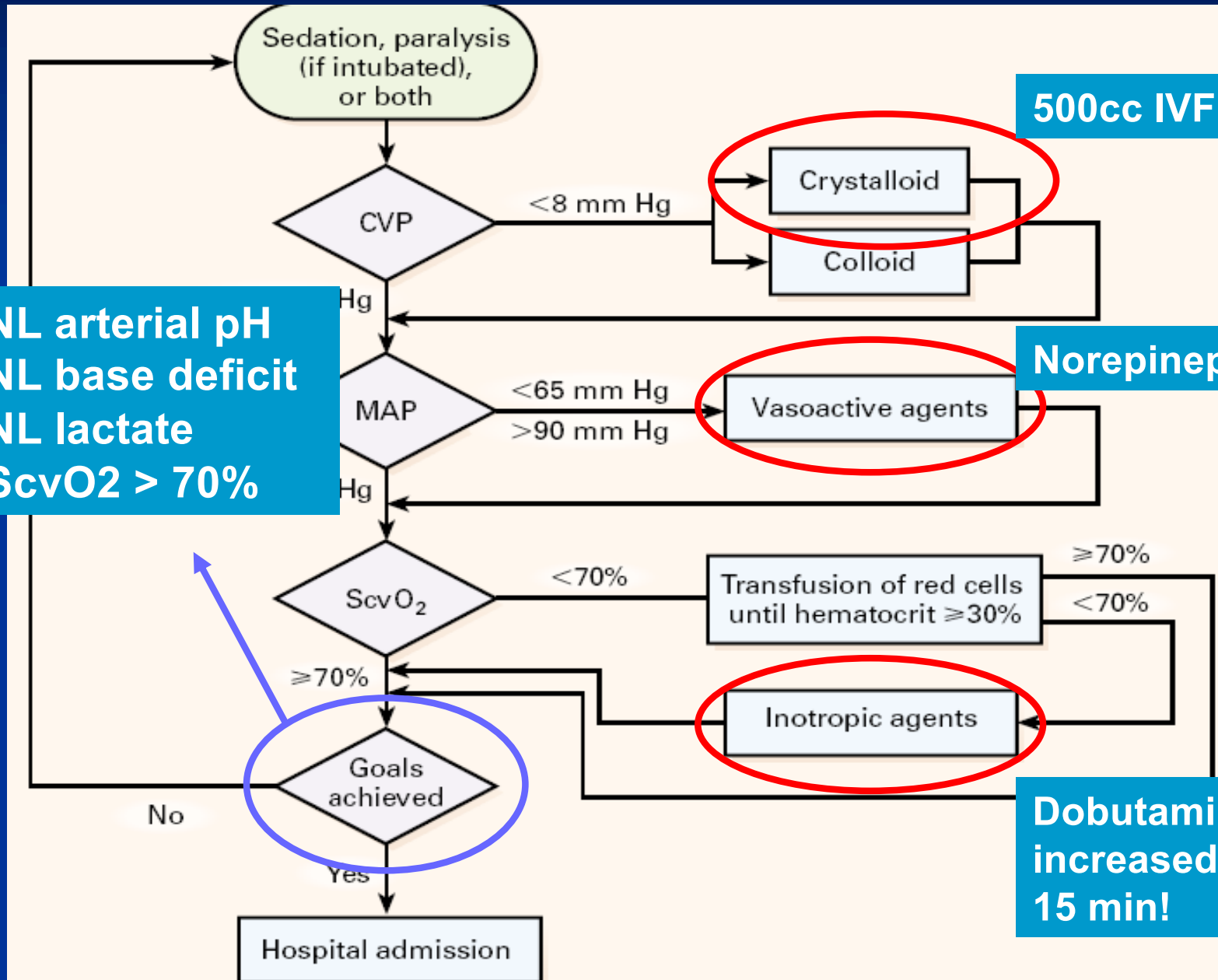
*Treatment began in E.D.: 6-hours

*A-line, Central line insertion

*Monitored: Mean arterial BP (MAP)
Central venous pressure (CVP)
Central venous O₂ sat (S_{CV}O₂)
Hematocrit

EARLY Goal-Directed Therapy

INTERVENTION



500cc IVF Q 30 min!

Norepinephrine

Dobutamine: dose increased 2.5 mcg Q 15 min!

EARLY Goal-Directed Therapy

HOW'D THEY DO THAT??

TREATMENT	HOURS AFTER THE START OF THERAPY		
	0-6	7-72	0-72
Total fluids (ml)			
Standard therapy	3499 ± 2438	10,602 ± 6,216	13,358 ± 7,729
EGDT	4981 ± 2984	8,625 ± 5,162	13,443 ± 6,390
P value	<0.001	0.01	0.73
Red-cell transfusion (%)			
Standard therapy	18.5	32.8	44.5
EGDT	64.1	11.1	68.4
P value	<0.001	<0.001	<0.001
Any vasopressor (%)†			
Standard therapy	30.3	42.9	51.3
EGDT	27.4	29.1	36.8
P value	0.62	0.03	0.02
Inotropic agent (dobutamine) (%)			
Standard therapy	0.8	8.4	9.2
EGDT	13.7	14.5	15.4
P value	<0.001	0.14	0.15

EARLY Goal-Directed Therapy

IT WORKED!!

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

However, what are the key components and broader applicability of EGDT?

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MAY 1, 2014

VOL. 370 NO. 18

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

The ProCESS Investigators*

1341 Patients, Compared:

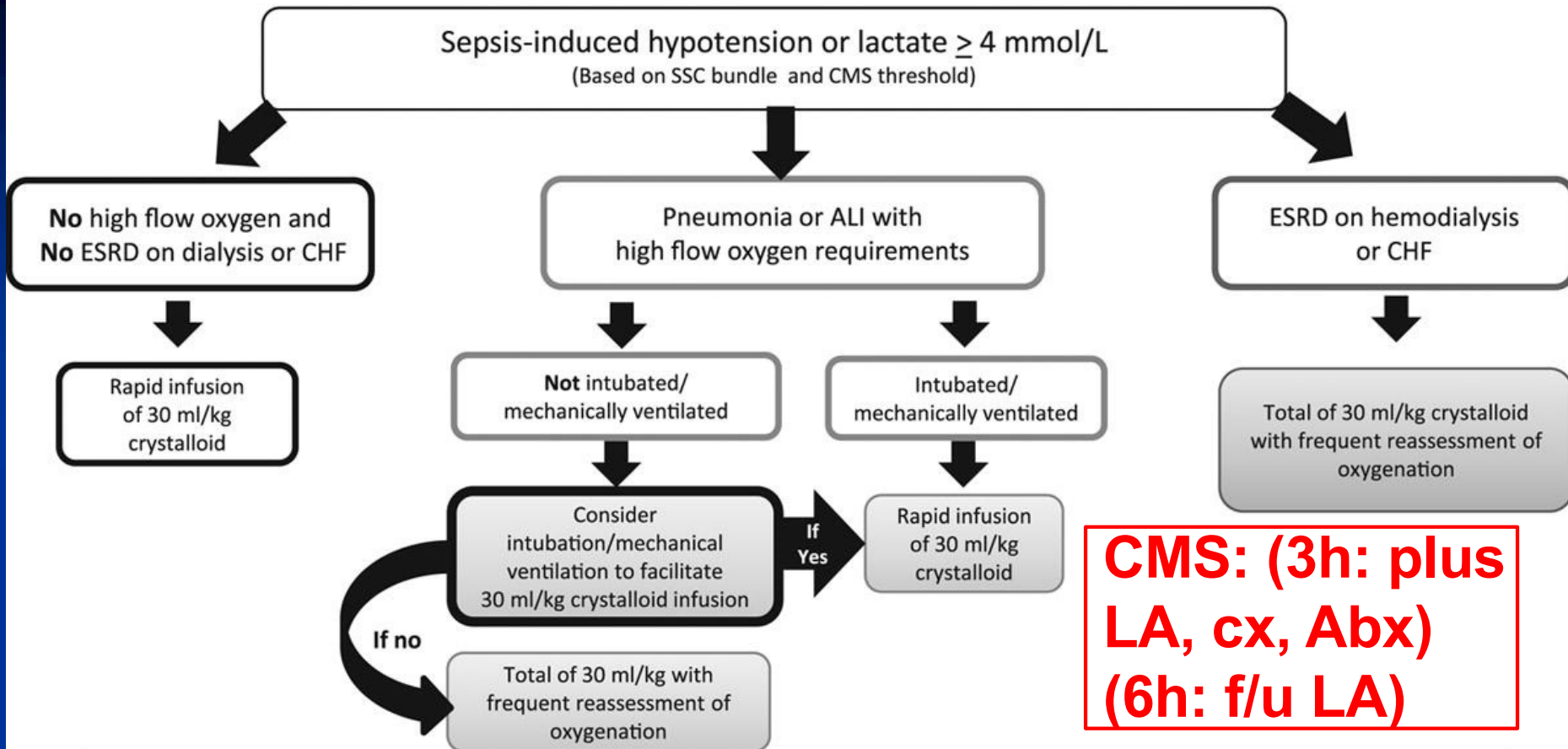
1. EGDT, vs.
2. Protocolized care *without* CVC, inotropes, blood, vs.
3. Usual care

NO DIFFERENCE in Primary outcome of 60d in-hospital mortality or other outcomes

ProCESS*: What does it mean?

- Mortality in usual care group substantially lower than in EGDT in first trial (18% vs. 46%), thus “usual care” has evolved.
- Severe sepsis without septic shock wasn't studied in ProCESS.
- This trial and general practice supports *early* antibiotics and fluids and uncertain re: CVC for everyone, PRBCs**, dobutamine.
- Targeted fluid resuscitation now the goal.

Application of Fluid Resuscitation in Adult Septic Shock



**CMS: (3h: plus LA, cx, Abx)
(6h: f/u LA)**

- Considerations post 30ml/kg crystalloid infusion**
- Continue to balance fluid resuscitation and vasopressor dose with attention to maintain tissue perfusion and minimize interstitial edema
 - Implement some combination of the list below to aid in further resuscitation choices that may include additional fluid or inotrope therapy
 - blood pressure/heart rate response
 - urine output
 - cardiothoracic ultrasound ***capillary refill time added, 2021 guidelines**
 - CVP, ScvO₂
 - pulse pressure variation
 - lactate clearance/normalization ***lactate recommended in 2021 guidelines**
 - dynamic measurement such as response of flow to fluid bolus or passive leg raising
 - Consider albumin fluid resuscitation, when large volumes of crystalloid are required to maintain intravascular volume.

ALI=acute lung injury; CHF=congestive heart failure; CMS= US Centers for Medicare and Medicaid Services; CVP=central venous pressure; ESRD=end stage renal disease; kg=kilograms; ml=milliliters; oxyhgb=oxyhemoglobin; ScvO₂=superior vena cava oxygen saturation

From: Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids?

JAMA. 2016;316(12):1298-1309. doi:10.1001/jama.2016.12310

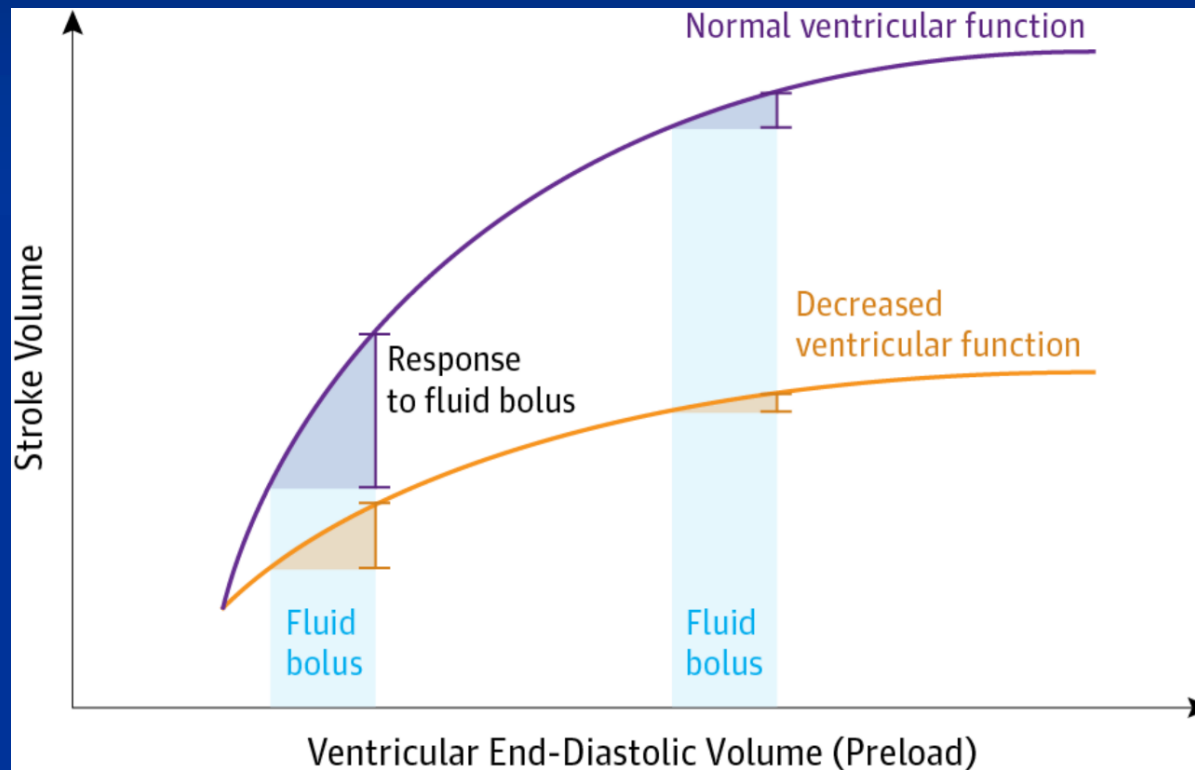


Figure Legend:

Effect of Increase in Preload on Stroke Volume of Ventricles With Normal and Decreased Contractility. Frank-Starling curves illustrate that the effect of a given increase in preload on stroke volume is dependent both on ventricular contractility and on baseline preload.

Fluid Response Evaluation in Sepsis Hypotension and Shock

A Randomized Clinical Trial



*Ivor S. Douglas, MD; Philip M. Alapat, MD; Keith A. Corl, MD; Matthew C. Exline, MD, MPH;
Lui G. Forni, PhD; Andre L. Holder, MD; David A. Kaufman, MD; Akram Khan, MD; Mitchell M. Levy, MD;
Gregory S. Martin, MD; Jennifer A. Sahatjian, PsyD; Eric Seeley, MD; Wesley H. Self, MD;
Jeremy A. Weingarten, MD; Mark Williams, MD; and Douglas M. Hansell, MD*



Fluid responsiveness assessed by Passive Leg Raise to guide fluid resuscitation (n=83) vs. Usual Care (n=41). With intervention:

- Lower net positive fluid balance
- Lower risk of renal replacement and mechanical ventilation

Enrolling now at an ICU near you: CLOVER trial design (PETAL Network)

GROUP ASSIGNMENT

You will receive either a **medicine to raise blood pressure** and then fluids (if needed) OR a **larger amount of fluids** first and then medicine to raise blood pressure (if needed).

This is assigned by chance (like a coin flip).



Medicine to Raise Blood Pressure First

One group will get **medicine to raise blood pressure** **pressure** FIRST and then fluids (if needed).
Both are given through a tube in the vein (IV).



Fluids First

One group will get a **larger amount of fluids** FIRST and then medicine to raise blood pressure (if needed).
Both are given through a tube in the vein (IV).

Small studies recently examining earlier pressors initiation and suggest volume overload not beneficial.

What 'flavor' of fluid should we be using in sepsis?

NO: Hetastarch

Mostly NO: Albumin

Yes: Crystalloid... *Balanced crystalloids favored over saline in 2021 guidelines

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H., Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D., Avinash B. Kumar, M.D., Christopher G. Hughes, M.D., Antonio Hernandez, M.D., Oscar D. Guillaumondegui, M.D., M.P.H., Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SMART Investigators and the Pragmatic Critical Care Research Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

Wesley H. Self, M.D., M.P.H., Matthew W. Semler, M.D., Jonathan P. Wanderer, M.D., Li Wang, M.S., Daniel W. Byrne, M.S., Sean P. Collins, M.D., Corey M. Slovis, M.D., Christopher J. Lindsell, Ph.D., Jesse M. Ehrenfeld, M.D., M.P.H., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SALT-ED Investigators*

NEJM March 1, 2018

FLUIDS in SEPSIS BOTTOM LINE:

Bolus crystalloid, but don't overdo it.

Find your favorite way(s) to target resuscitation.

Case, Question #3

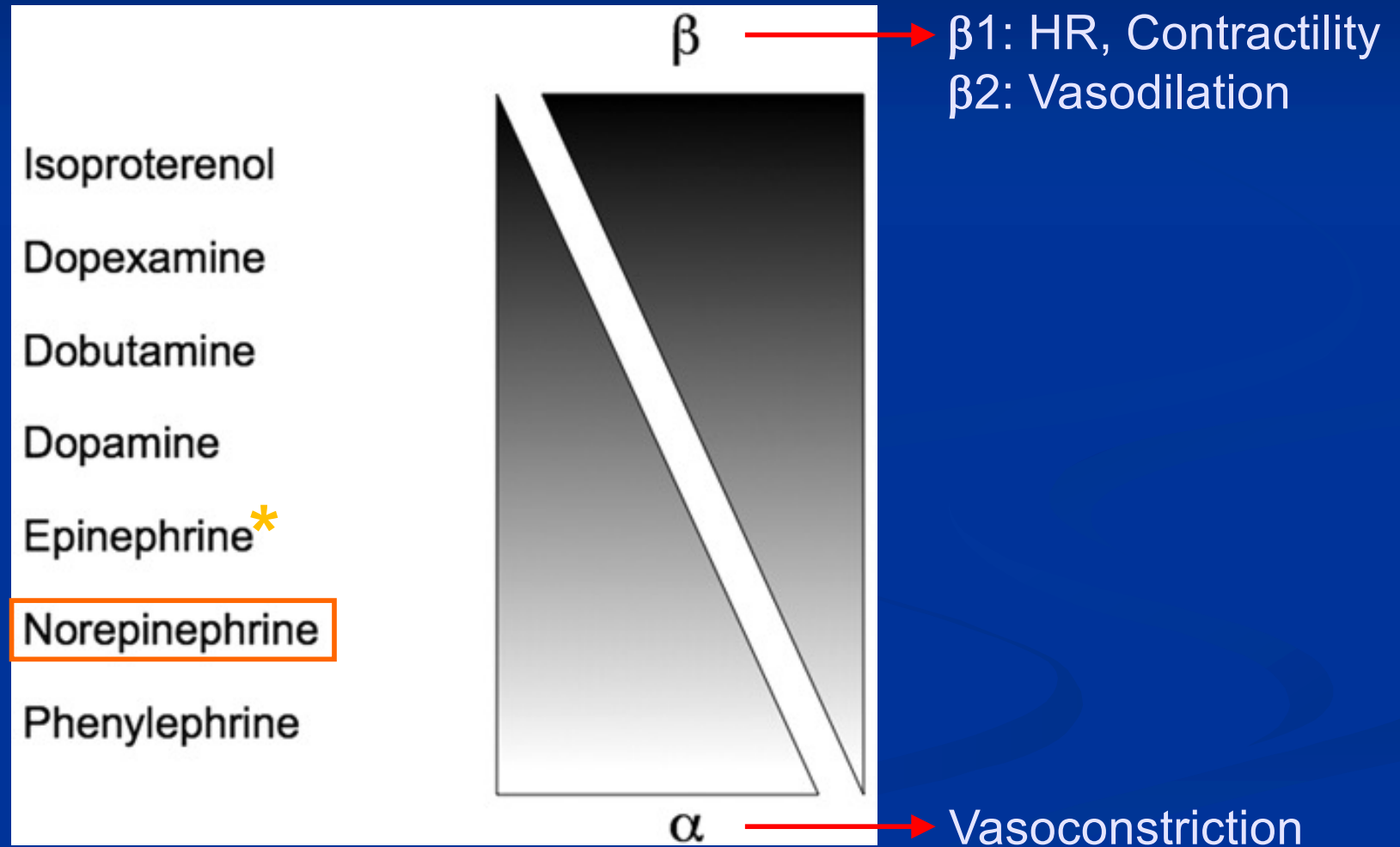
You have administered broad-spectrum antibiotics to treat presumed spontaneous bacterial peritonitis, give her supplemental O₂ (now saturating 90% on 100% FM), and after fluid resuscitation with 3L of crystalloid, her HR comes down to 100 bpm, her SBP has risen to 65 mm Hg with a mean arterial pressure (MAP) of 50 mm Hg, and the CVP is 13 mm Hg. You next order:

- a. Vasopressin
- b. Norepinephrine
- c. Norepinephrine + Furosemide
- d. 1 Unit of PRBCs
- e. Dobutamine

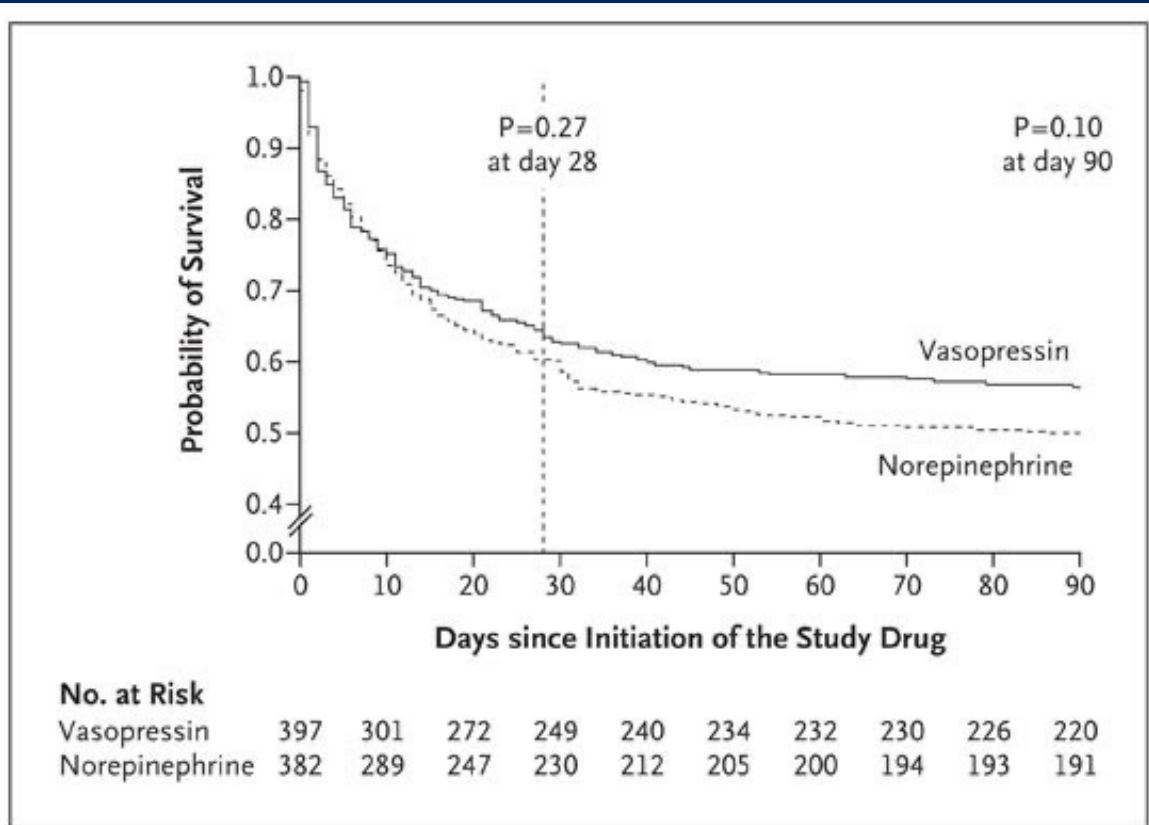
Question #3:

What about Vapressors?

Action of Vasoactive Catecholamines 2001- 2008



Vasopressin as a 'Pressor'



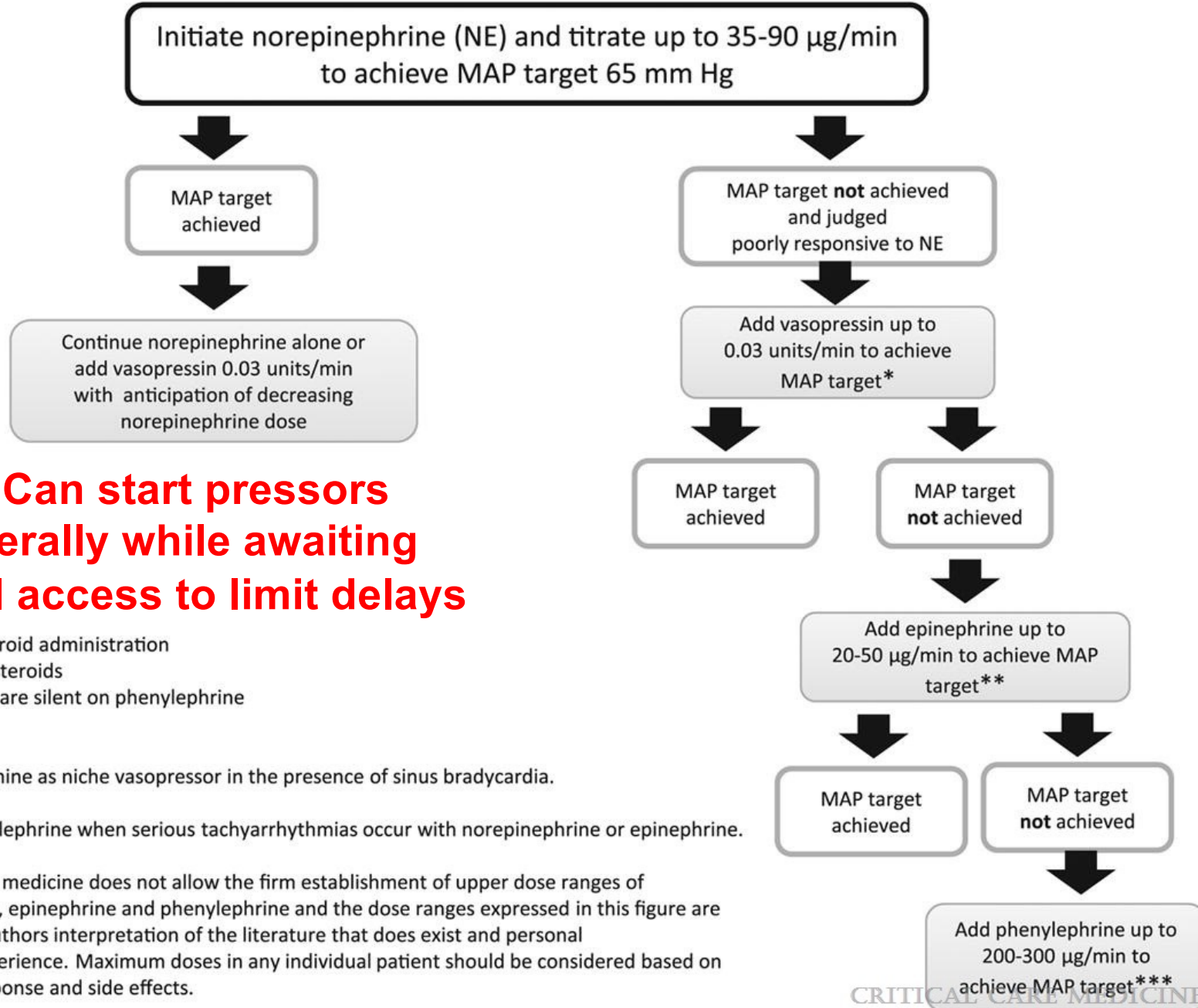
- Multi-center RCT with ~800 patients
- No significant mortality benefit in adding vasopressin to norepinephrine
- Less sick people did better with addition of vasopressin
- Widespread use as an adjunctive support with norepinephrine

VASST Trial

Russell et al. NEJM 2008; 358:877-887, Feb 28, 2008.

JAMA. 2016;316(5):509-518. doi:10.1001/jama.2016.10485

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



***2021: Can start pressors peripherally while awaiting central access to limit delays**

* 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.

CRITICAL CARE MEDICINE

Question #4:

What are we supposed to be doing with steroids in sepsis?

RELATIVE Adrenal Insufficiency

Basic Background

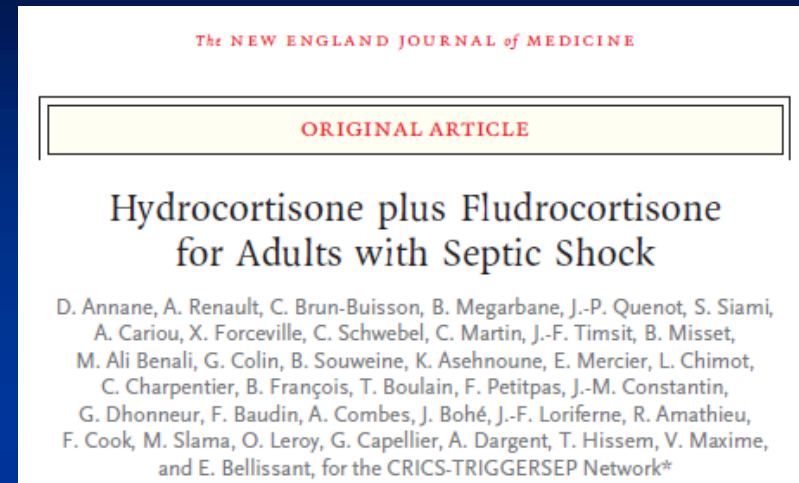
- “High-dose” corticosteroids DO NOT improve sepsis outcomes¹
- Absolute adrenal insufficiency in sepsis is RARE
- What about RELATIVE adrenal insufficiency?
 - 2002-2008: Cort-stim to select ‘nonresponders’ based upon a subgroup analysis
 - 2008: low dose steroids hastened shock reversal in those in whom shock was reversed

¹NEJM 1984 311: 1137; Crit Care Med 1995 23: 1430; JAMA 2002; NEJM⁶2008

Low-Dose Steroids in Sepsis, 2018:



- 3800 patients, RCT
- Less sick patients
- HC continuous infusion
- No fludrocortisone
- No mortality benefit 90d
- Faster resolution of shock
- Fewer blood transfusions with steroids (unclear why)



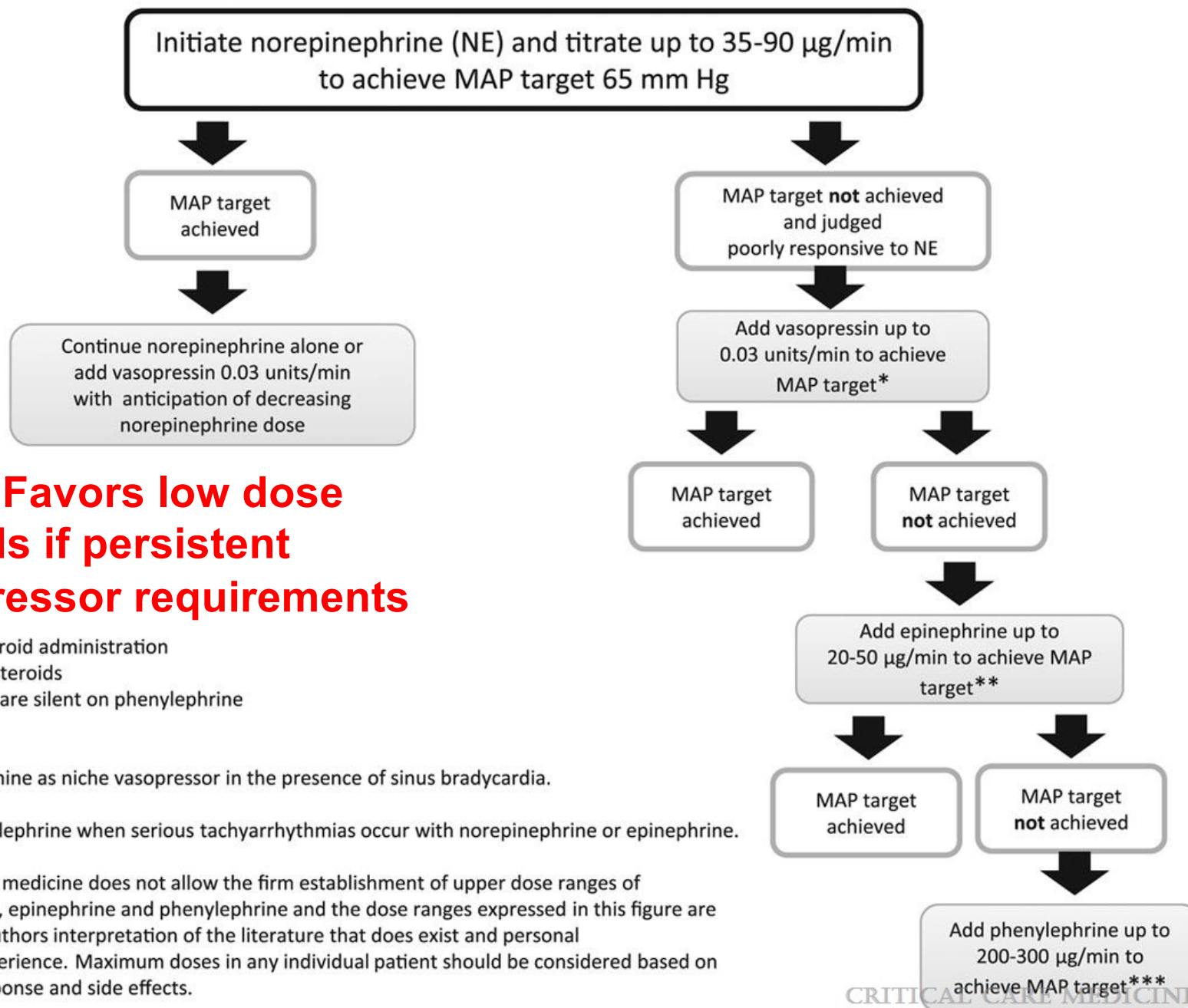
- 1241 patients, RCT
- Activated Protein C removed
- Sicker patients
- Included fludrocortisone
- 90d mortality benefit
- Similar infections though more viral with HC/FC
- More hyperglycemia with HC

Steroids in Sepsis Bottom Line?

“It is unlikely that in the near future sufficiently powered trials will provide us with better data. Thus, clinicians will have to use these data and subsequent meta-analyses to decide how best to treat patients with septic shock. Estimating 90-day mortality at the bedside is not practical. It is likely that some practitioners caring for a patient with a deteriorating condition who is receiving escalating doses of vasopressors, in whom other core interventions have been instituted (i.e., appropriate antibiotics and adequate volume resuscitation and source control), will consider that the short-term benefits of low-dose hydrocortisone may exceed any risks (e.g., antiinflammatory effects) as an added therapy in selected patients.”

Vasopressor Use for Adult Septic Shock

→ (with guidance for steroid administration)



***2021: Favors low dose steroids if persistent vasopressor requirements**

* 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.
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CRITICAL CARE MEDICINE

Preliminary Communication

Caring for the Critically Ill Patient

October 1, 2019

Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure

The CITRIS-ALI Randomized Clinical Trial

Preliminary Communication

Caring for the Critically Ill Patient

January 17, 2020

Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock The VITAMINS Randomized Clinical Trial

**At least 5 trials negative for primary endpoint.
2021 guidelines recommend against Vitamin C.**

JAMA

Adjunctive Sepsis Care

- Tight Glucose Control²
 - Target glucose ≤ 180 mg/dl rather than tighter control.
- Low Tidal Volume Ventilation in ARDS³
- Judicious Fluid Management in Acute Lung Injury⁴
- Protocolized Central Line Insertion and Care and attention to ICU 'bundles' and prophylactic care^{5,6,7}

¹NEJM 2008;358:111; ²NEJM 2009;360:1283; ³NEJM 2000;342:1301;

⁴NEJM 2006;354:2564; ⁵NEJM 2006;355:2725; ⁶JAMA 2009;301:1231; ⁷CCM 2016 41

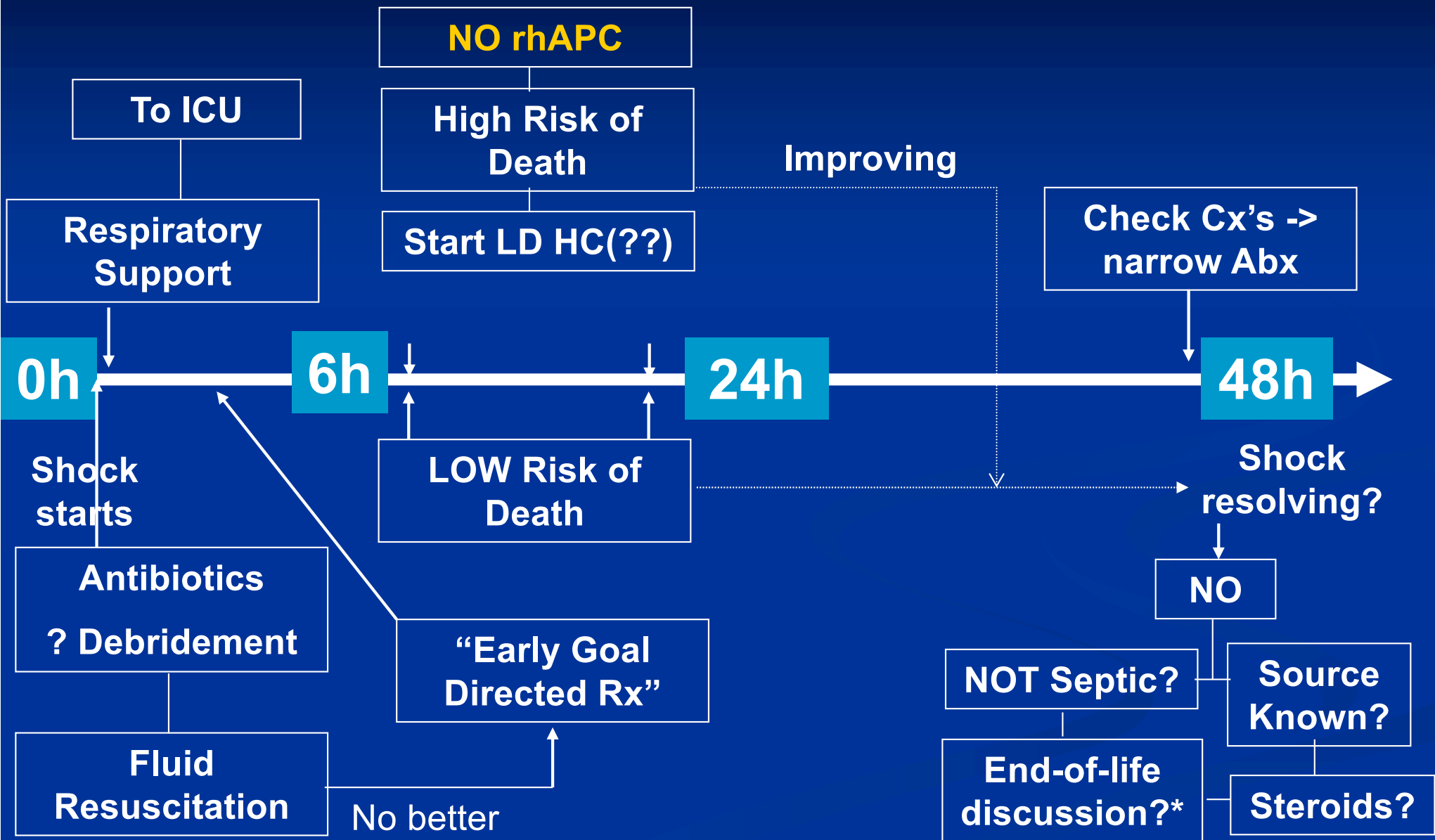
Take-Home Points

- Early Identification of Patients with Sepsis*
- Source Control and Early Broad-Spectrum Antibiotics
- Early fluid resuscitation, primarily with crystalloid (“Early Goal Directed Therapy” targeted fluids)
- Norepinephrine as First Pressor of Choice
- Addition of Vasopressin to Norepinephrine to limit higher NE doses
- Epinephrine as 2nd-line Agent for Refractory Hypotension to Norepinephrine
- Limited role for Dopamine and Neosynephrine as initial agents of choice.

Take-Home Points, Cont'd

- Activated Protein C is no longer available.
- Consider low-dose hydrocortisone for patients with sepsis-induced refractory hypotension despite fluids and pressors (without use of ACTH stim test to guide decision-making) – perhaps in the sicker patients.
- Uncertain goal of glucose control, but target ≤ 180 mg/dL (instead of tighter control) suggested until more data available. Hourly monitoring of glucose levels while on an insulin drip is critical, and avoid hypoglycemia.
- Attention to standard ICU care (e.g., ventilator bundle, DVT and GI prophylaxis, central line care, etc).

Sepsis: Summary



*2021 guidelines address referral for post-ICU/recovery care/support

Selected Key References

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- Fowler AA, et al. Effect of Vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure. The CITRIS-ALI randomized clinical trial. JAMA 2019; 322(13): 1261-1270.