Sepsis in the Hospital

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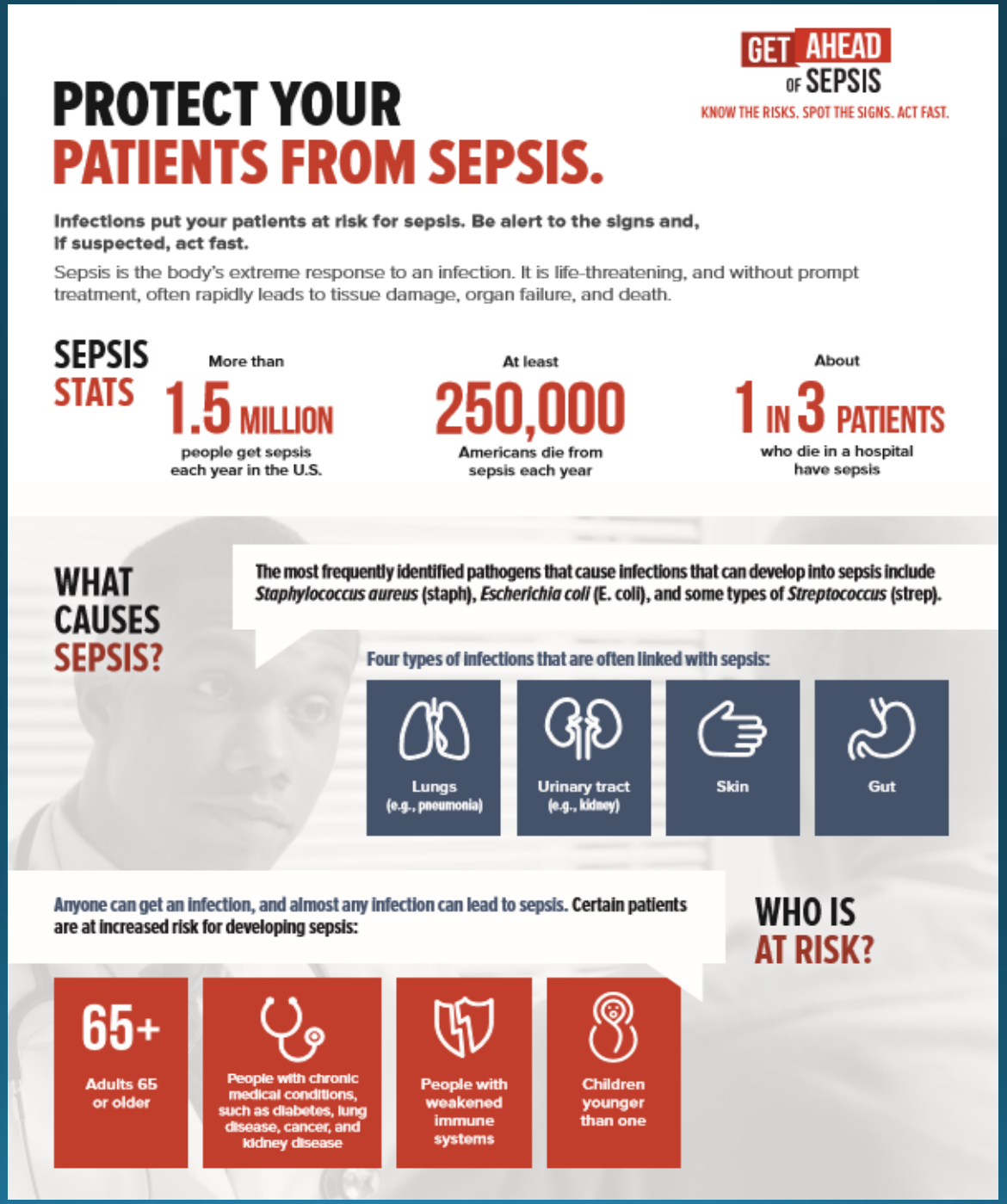
Objectives

- Review the new definitions of SIRS, sepsis, and septic shock and SOFA/qSOFA scoring
- Review updates from Sepsis-3 as well as updates on the Surviving Sepsis campaign with comparison to "old" guidelines
- Discuss use of lactic acid and procalcitonin levels in the management of septic patients
- What's next?
- Take home points

Disclosures

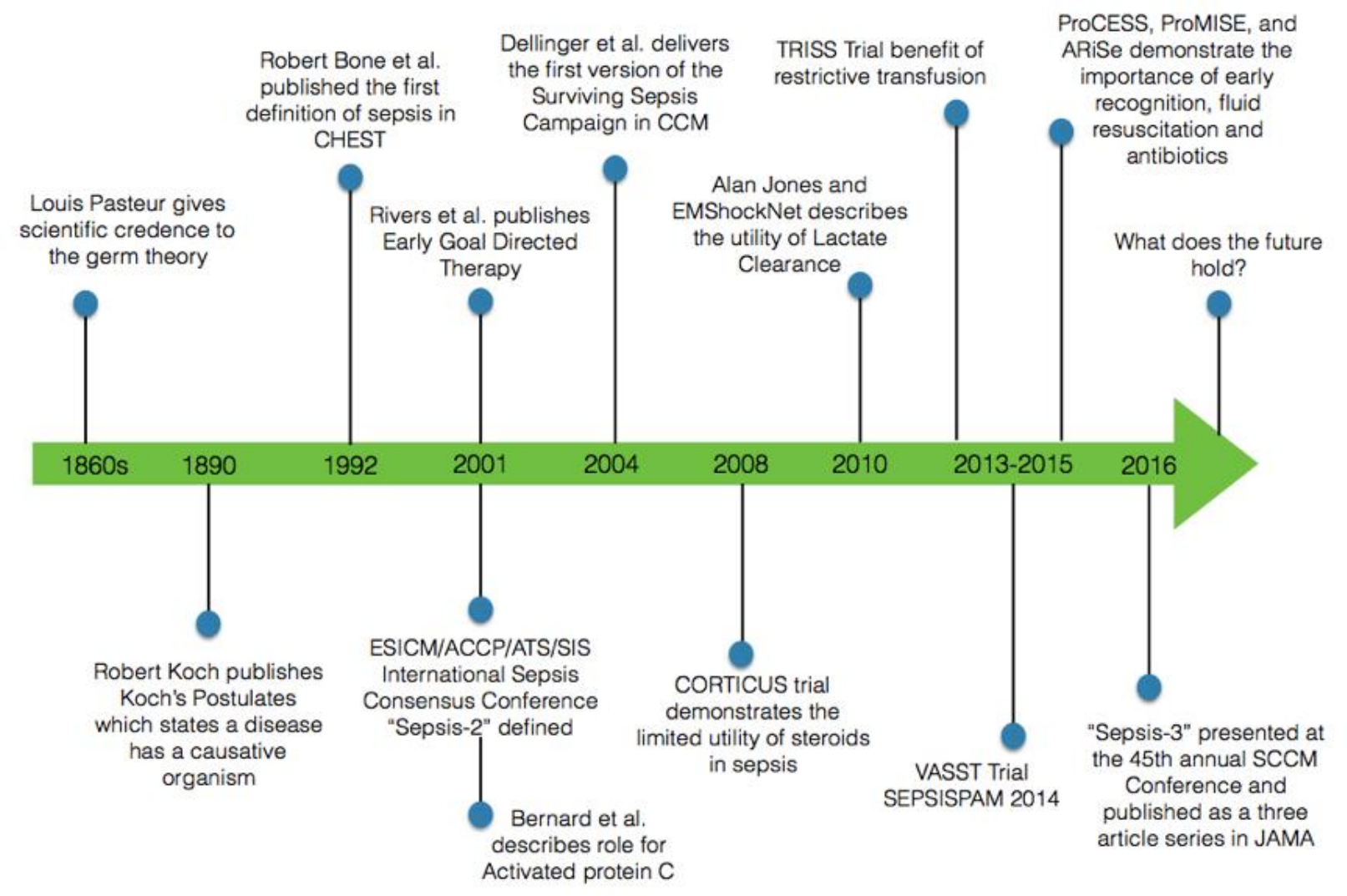
- None

Why Sepsis?



www.cdc.gov/sepsis

Timeline Review…



"Early Goal Directed Therapy"

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ORIGINAL ARTICLE

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*

N Engl J Med 2001; 345:1368-1377 | November 8, 2001 | DOI: 10.1056/NEJMoa010307

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Abstract | Article | References | Citing Articles (4570)

BACKGROUND

Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

Full Text of Background ...

METHODS

We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who

MEDIA IN THIS ARTICLE

FIGURE 2

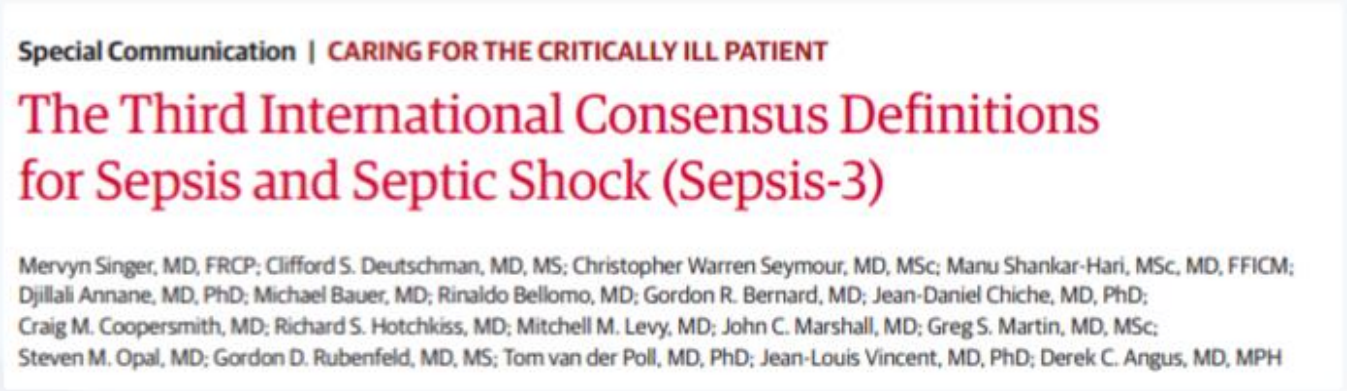
Protocol for Early Goal-Directed Therapy.

FIGURE 1

- EGDT was devised by Emanuel Rivers, et. al. in 2001 with the goal of intensive monitoring and aggressive management of hemodynamics in a septic patient with a high risk of morbidity and mortality
  - For a time, this formed the basis of the initial "Surviving Sepsis" campaign
- Subsequent to this – several studies have been published reporting that the concepts of EGDT should be abandoned
  - ProCESS, ARISE, ProMISE trials – large, multicenter studies demonstrated no benefit of expensive, invasive management in sepsis patients

What's New?

- JAMA, Feb. 23, 2016: Sepsis-3, New criteria for defining sepsis



Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

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

Sepsis-3

- Biggest change – no longer a "severe sepsis" definition
  - Redundant, as sepsis has a ~10% mortality rate and is already severe
- Potential for organ dysfunction is assessed via the Quick Sequential Organ Failure Assessment score (qSOFA)
  - Altered mental status (GCS <15)
  - Systolic BP <100mmHg
  - Respiration rate >22 breaths/min
  - If 2 of 3 met, patient at substantially greater risk for >3 night ICU stay, death
  - Poorly sensitive

Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-810.

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

System	0	1	2	3	4
Respiration PaO2/FiO2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, $x10^3$/uL	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (umol/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 ≥70mmHg	MAP <70mmHg	Dopamine <5 or Dobutamine (any dose)	Dopamine 5.1 - 15 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
CNS GCS Score	15	13 - 14	10 -12	6 - 9	<6
Renal Creatinine, mg/dL (umol/L) Urine Output, mL/d	<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
*Catecholamine Doses = ug/kg/min for at least 1hr					

Revised Definitions

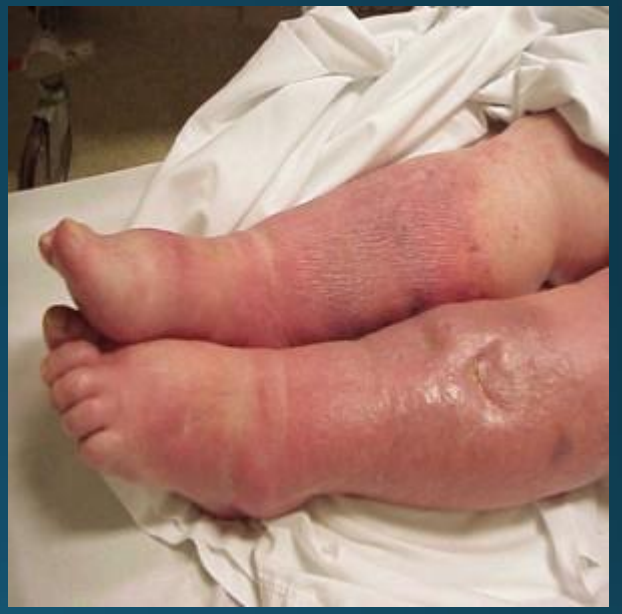
- Systemic Inflammatory Response Syndrome (SIRS)
  - A systemic response to a nonspecific infectious or noninfectious insult with the presence of two or more of the following clinical criteria
    - Body temperature higher than 38C (100.4F) or lower than 36C (96.8F)
    - Hear rate >90 beats per minute
    - Respiratory rate >20 breaths per minute or hyperventilation with $PaCO_2$ <32mmHg
    - Abnormal WBC count >12K or <4K or >10% bands
- Sepsis (formerly severe sepsis)
  - Life-threatening organ dysfunction due to a dysregulated host response to infection
- Septic Shock
  - A subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality
    - Vasopressors required to achieve MAP >65
    - Persisting blood lactate >2.0 mmol/L in spite of adequate fluids

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Patient with Suspected Sepsis

- Best Practice Statement – Updated Surviving Sepsis Campaign:

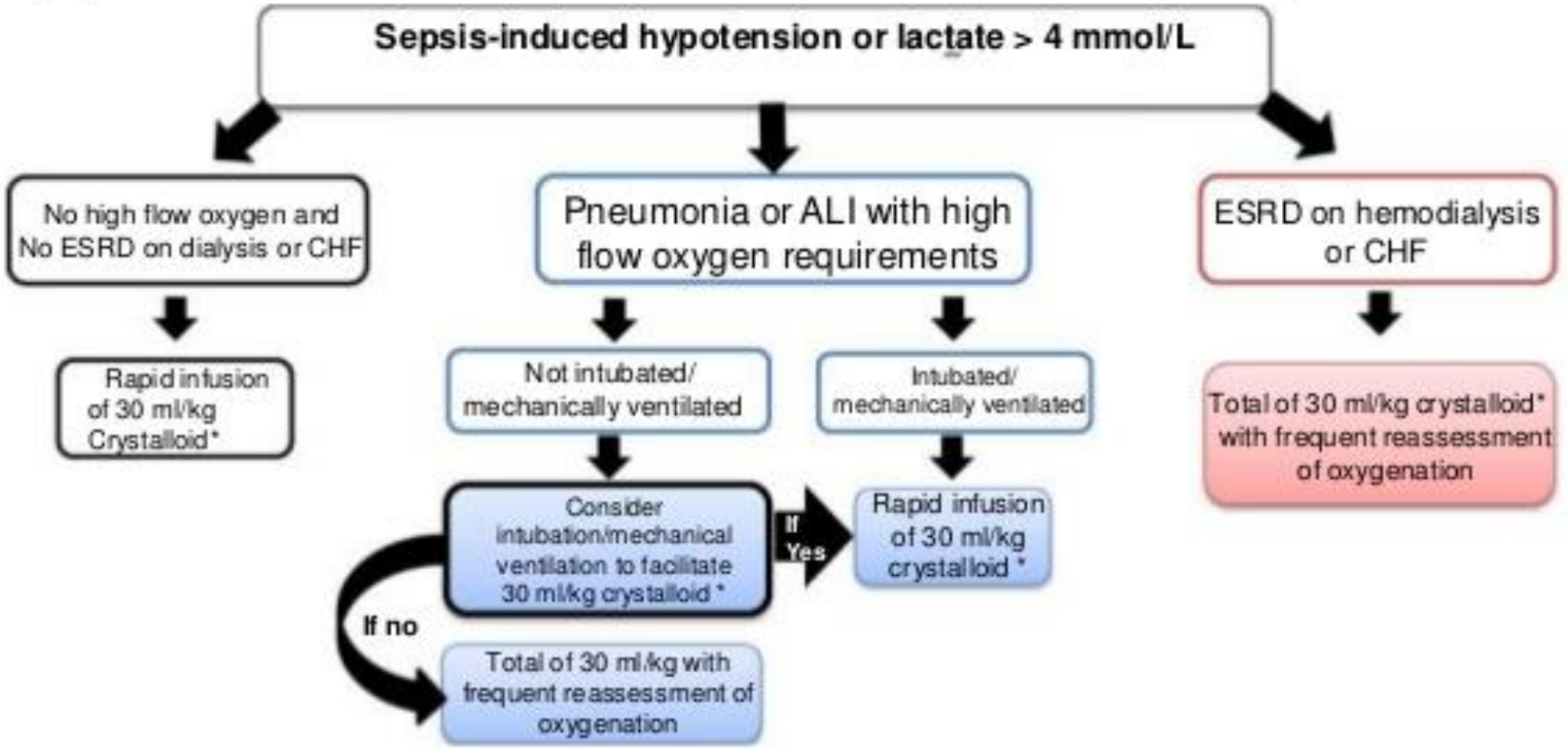
- *"We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical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



Patient with Suspected Sepsis

- Recommendations of Surviving Sepsis Campaign:
  - ***"We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock."***
    - **Appropriate cultures (including 2 sets of blood cultures) should be obtained prior to first dose if no substantial delay in therapy**
  - ***"We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens."***
  - ***"We recommend that in the resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours."***
    - **Avoid starch containing solutions**

Application of Fluid Resuscitation in Adult Septic Shock



Considerations post 30ml/kg crystalloid infusion

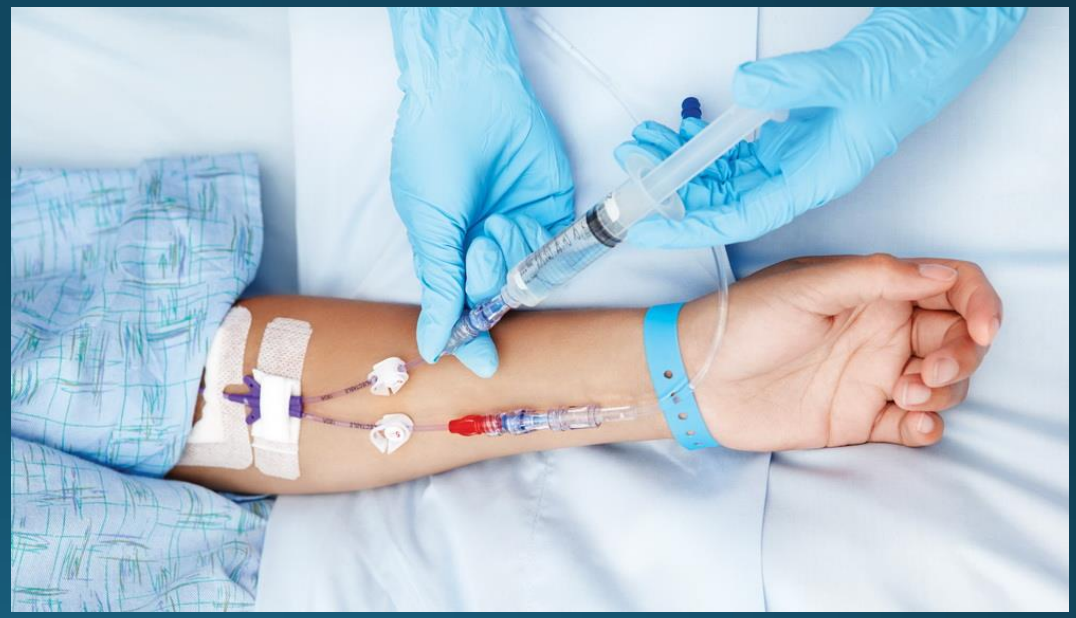
1. Continue to balance fluid resuscitation and vasopressor dose with attention to maintain tissue perfusion and minimize interstitial edema
2. Implement some combination of the list below to aid in further resuscitation choices that may include additional fluid or inotrope therapy
   - blood pressure/heart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

Empiric Antibiotic Selection

- Empiric antibiotic therapies should be initiated with combination therapy aimed at the most likely bacterial pathogens for the initial management of septic shock
  - Vancomycin + piperacillin-tazobactam
- Combination therapy should NOT be used for ongoing treatment of most other serious infections – including bacteremia and sepsis without septic shock
  - No more "double coverage" for pseudomonas/neutropenia
- Procalcitonin can be used for de-escalation of therapy

Antimicrobial Stewardship

- Antibiotics should be narrowed once pathogen is identified and sensitivities are established and/or patient has shown response to therapy
  - Daily consideration for de-escalation of therapies
- Duration of therapy for most serious cases of sepsis is 7-10 days



When Shock Does Not Improve

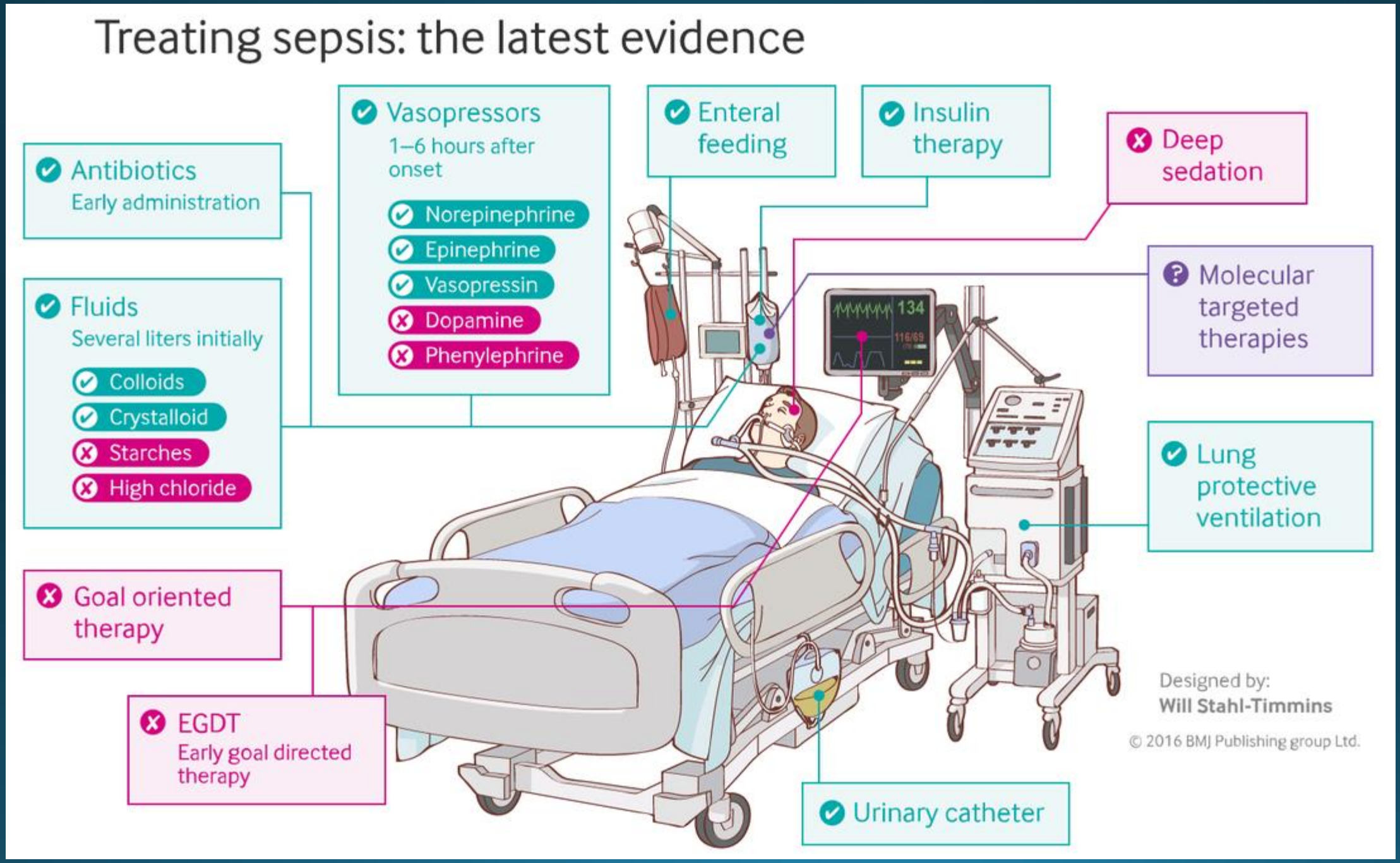
- Strong evidence to support norepinephrine as the first choice vasopressor
- Vasopressin or epinephrine can be added with a goal of achieving a MAP >65 or vasopressin can be used to decrease the norepinephrine dosage
- Consideration for initiation of high dose corticosteroids
- Assessment for other possible sources of shock (neuro, cardiac, etc.)

SURVIVING SEPSIS CAMPAIGN RECOMMENDATION HIGHLIGHTS

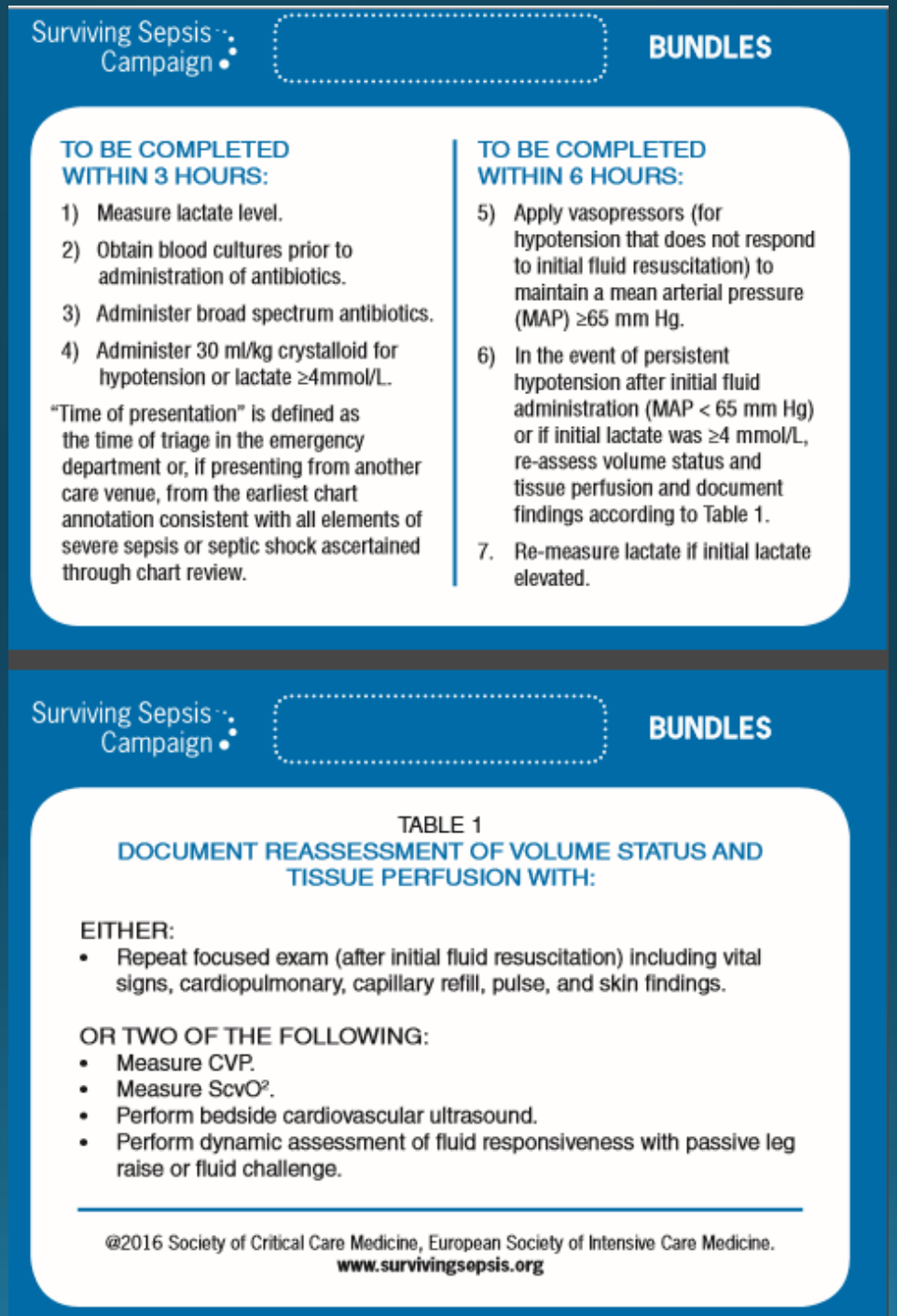
	2012	2016
SEPSIS DEFINITION	Systemic manifestation of infection + suspected infection Severe sepsis: sepsis + organ dysfunction	Life threatening organ dysfunction caused by dysregulated response to infection No severe sepsis category
INITIAL RESUSCITATION	at least 30 cc/kg in first 3 hours Crystalloid 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
VASOPRESSORS	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	
STEROIDS	Only indicated for patients with septic shock refractory to adequate fluids and vasopressors	
ANTIBIOTICS	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
SOURCE CONTROL	Achieve within 12 hours, if feasible	Achieve as soon as medically and logically feasible
VENTILATOR	6 cc/kg tidal volume prone patients with severe ARDS (P/F <150 in 2017 guideliens)	
	no recommendation	Against high frequency oscillatory ventilation (HFOV)
	weak recommendation for noninvasive ventilation in select patients with sepsis induced ARDS	Unable to make recommendation on noninvasive ventilation

Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med [Internet] 2017;1.

Treating sepsis: the latest evidence



Code Sepsis



Surviving Sepsis Campaign

BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level.
2) Obtain blood cultures prior to administration of antibiotics.
3) Administer broad spectrum antibiotics.
4) Administer 30 ml/kg crystalloid for hypotension or lactate ≥4mmol/L.

"Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg.
6) In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.

Surviving Sepsis Campaign

BUNDLES

TABLE 1

DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

EITHER:

- Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

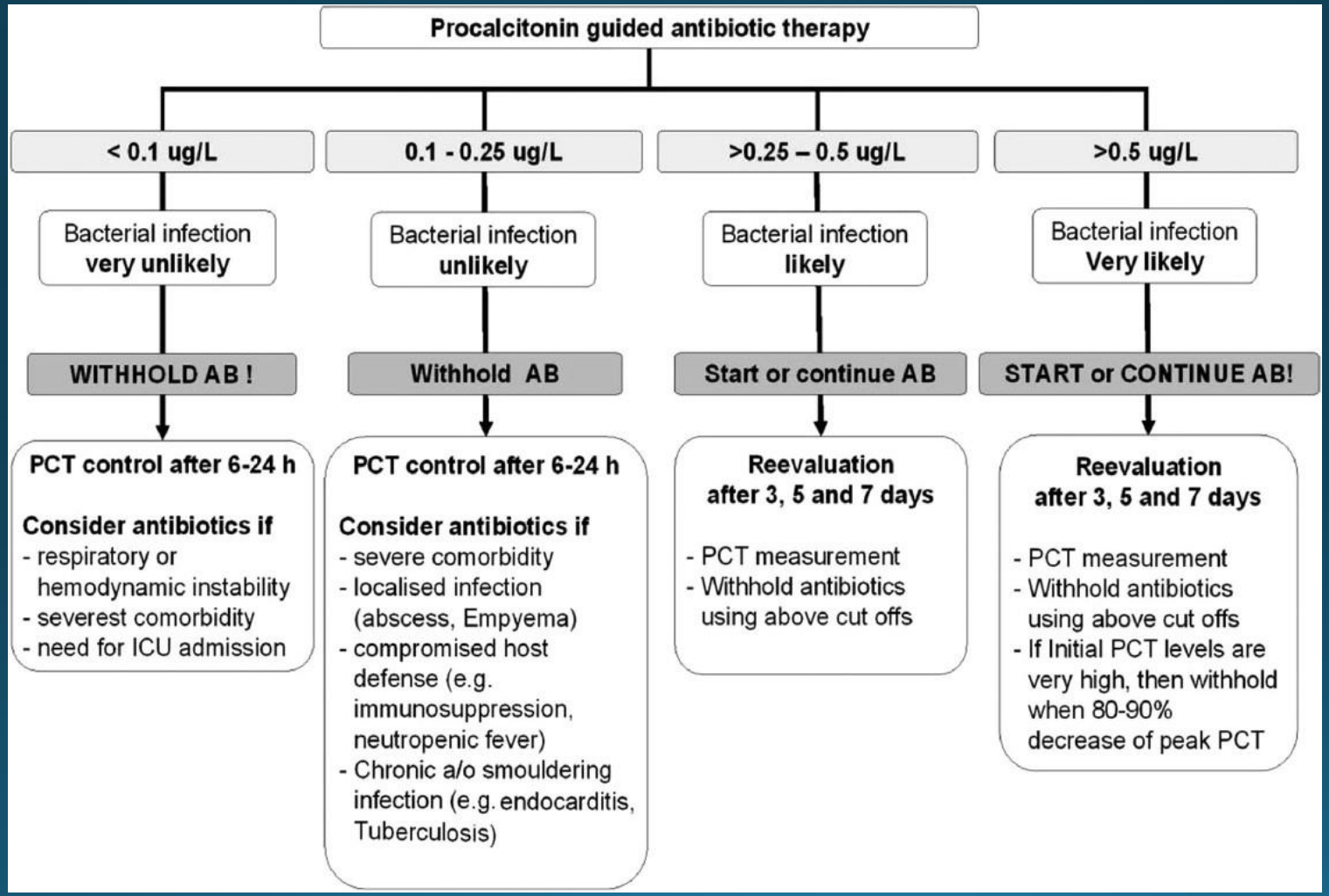
OR TWO OF THE FOLLOWING:

- Measure CVP.
- Measure $ScvO^2$.
- Perform bedside cardiovascular ultrasound.
- Perform dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.

Lactic Acid, Procalcitonin

- When sepsis is suspected, lactic acid/serum lactate levels and procalcitonin levels can be drawn
  - Initial lactic acid levels should be trended until resuscitation has normalized lactate in patients with elevated levels as a marker of tissue hypoperfusion
- Procalcitonin is a peptide precursor of calcitonin and is usually below the level of detection in healthy persons
  - Procalcitonin rises in response to an inflammatory stimulus, especially of bacterial origin
  - 85% sensitive and 91% specific for differentiating patients between SIRS and sepsis
  - Low levels can be used to support de-escalation or shortening antibiotic duration in patients without obvious bacterial source of sepsis

Procalcitonin Algorithm



Kaur K, Mahajan R, Tanwar A. A novel marker procalcitonin may help stem the antibiotic overuse in emergency setting. Int J App Basic Med Res 2013;3:77-83

The "Marik Protocol"

- Standard ICU treatment PLUS:

- Intravenous vitamin C 1.5g q6hr x4d or until ICU discharge
- Hydrocortisone 50mg q6hr x7d or until ICU discharge followed by a taper over 3d
- Intravenous thiamine 200mg q12hr x4 or until ICU discharge

Marik, PE et.al. Chest 2016

Vitamin C?

Vitamin C: The next step in sepsis management?

Teng J[1], Pourmand A[2], Mazer-Amirshahi M[3].

Author information

Abstract

Sepsis is a life-threatening medical condition, affecting approximately 26 million people worldwide every year. The disease is a continuum, marked by dysregulated inflammation and hemodynamic instability leading to shock, multi-system organ dysfunction, and death. Over the past decades, there has been a focus on the early identification and treatment of sepsis primarily with bundled and goal directed therapy. Despite these advances, morbidity and mortality has remained high, prompting investigation into novel therapies. Vitamin C is a water-soluble vitamin that plays a role in mediating inflammation through antioxidant activities and is also important in the synthesis of cortisol, catecholamines, and vasopressin, which are key mediators in the disease process. Emerging evidence provides cursory data in support of the administration of vitamin C in addition to standard therapy to ameliorate the effects of inflammation and improve hemodynamic stability in patients with sepsis and septic shock; however, further evidence is needed to support this practice. This review discusses the physiologic role of vitamin C as well as the recent literature and evidence for the use of vitamin C in patients presenting with sepsis.

- Vitamin C has a role in mediating inflammation as an antioxidant
  - Also helps synthesize cortisol, catecholamines and vasopressin
- Some evidence to suggest using Vitamin C in addition to standard treatment to negate the effects of inflammation and improve hemodynamic stability in septic patients

J Crit Care. 2017 Sep 18;43:230-234. doi: 10.1016/j.jcrc.2017.09.031

Some discussion…

- Small number of patients in the study (94)
  - NONE of the treatment patients died of sepsis, mortality was due to underlying disease
- Apparently inexpensive/safe protocol
- Concept of a synergistic effect of these 3 medications on many pathways in the management of sepsis
- Vitamin C dosing remains vague – risk of oxalate formation/renal deposition at high dose
- External validation required before any implementation

Take Home Points

- 3 Diagnostic categories – SIRS, sepsis, septic shock
- Antibiotics should be administered within 60min for all patients with suspected sepsis/septic shock
- Lactic acid trends can be monitored as a part of documenting response to treatment/therapies
- Procalcitonin levels can help foreshorten antibiotic courses when presentation of sepsis is unclear
- Protocols containing less expensive/relatively safe components ie Vitamin C/thiamine/steroids may be the all the rage moving forward

Questions?

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