EVIDENCE-BASED SEPSIS: BEYOND THE GUIDELINES

Dawn Miller, PharmD, BCPS, BCCCP
Clinical Pharmacy Coordinator, Mount Carmel Grove City
Dawn.miller001@mchs.com

OBJECTIVES

- Identify patients with sepsis and septic shock utilizing validated assessment tools
- Design an appropriate pharmacotherapeutic and monitoring plan to treat a patient with sepsis and/or septic shock including initial fluid resuscitation, empiric broad spectrum antimicrobials, selection of vasopressors to maintain appropriate hemodynamic targets, use of inotropes, and appropriate use of corticosteroids
- Justify the therapeutic plan for the management of sepsis and septic shock with current guidelines and supporting evidence-based literature

EPIDEMIOLOGY OF SEPSIS

- Global burden of sepsis estimated at 15 – 19 million cases per year
- Sepsis accounts for 15 of every 1000 hospital admissions in the U.S.
- Mortality for septic shock remains as high as 40% despite evidence-based, guideline-driven management

Kadri SS, et al. Chest. 2017 Feb;151(2):278-285.
Marik, et al. Chest 2017; 151(6):1229-1238.

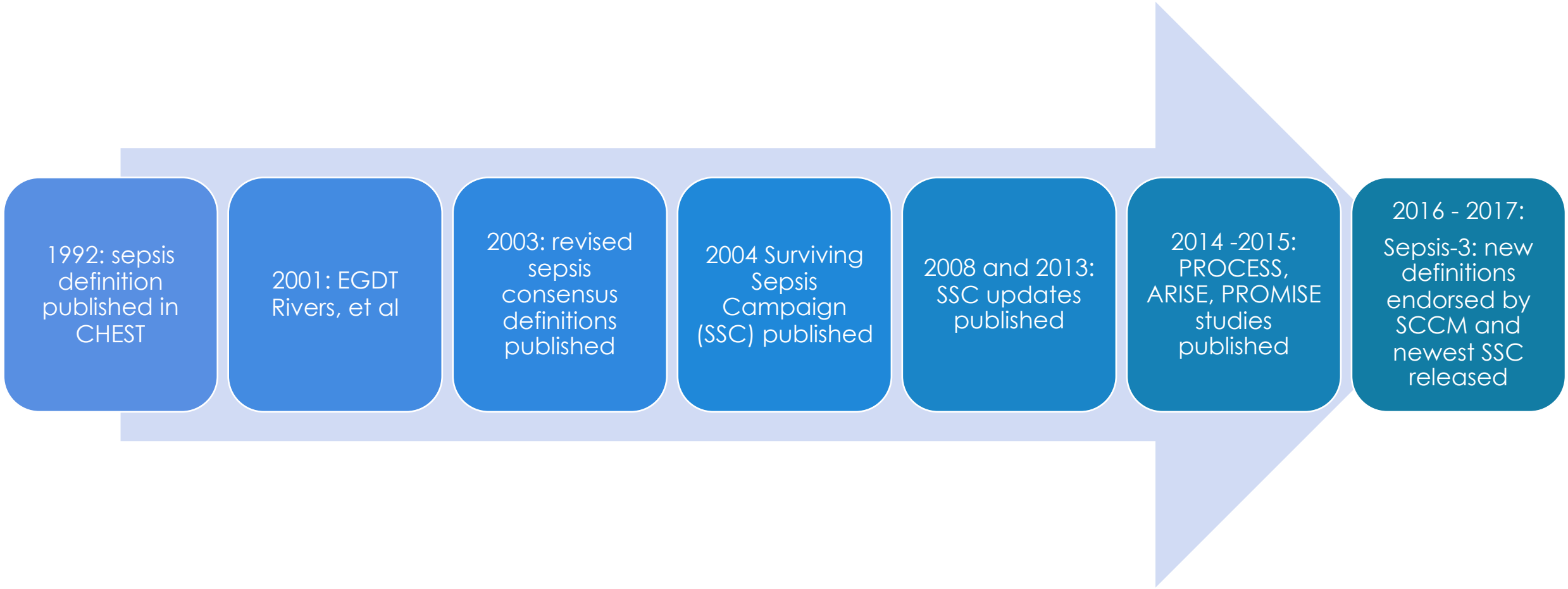
DO WE KNOW WHO WILL DEVELOP SEPSIS/SHOCK?

- Not all infections cause sepsis or progress to shock
- It is still not clear exactly why some patients can effectively fight the infection while others develop septic shock
- Focus should be on early identification of patients with sepsis that are likely to decompensate without aggressive intervention

WHY HAVE THERE BEEN SO MANY DEFINITIONS OF SEPSIS AND SHOCK?

- There is no definitive test to confirm the diagnosis of sepsis and the initial clinical presentation is often non-specific
- The definitions are difficult to validate since a sepsis diagnosis is based on "suspected infection" but in many cases the infection is never confirmed (culture negative sepsis)
- Sepsis and septic shock involve a heterogeneous population with various infectious etiologies
- Sepsis has a dynamic time course, not all clinical and laboratory manifestations may be present at a single assessment

MODERN EVOLUTION OF SEPSIS/SHOCK DEFINITION AND GUIDELINES



2021 SEPSIS GUIDELINES

Intensive Care Med (2021) 47:1181–1247
https://doi.org/10.1007/s00134-021-06506-y

GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

Laura Evans[1*], Andrew Rhodes[2], Waleed Alhazzani[3], Massimo Antonelli[4], Craig M. Coopersmith[5],

1992 ACCP/SCCM DEFINITIONS

- 1992 statement ACCP/SCCM: Systemic Inflammatory Response Syndrome (SIRS) regardless of cause is present if two or more of the following:
  - **Temperature > 38°C (100.4°F) or < 36°C (96.8°F)**
  - **Heart rate > 90 beats/min**
  - **Respiratory rate > 20 breaths/min**
  - **White blood cell count > 12 cells/µL or < 4 cells/µL**

- 1992 definitions:
  - **Sepsis** = SIRS plus infection
  - **Severe sepsis** = sepsis associated with organ dysfunction due to hypoperfusion
  - **Septic shock** = sepsis with arterial hypotension despite adequate fluid resuscitation

Bone RC, et al. Chest. 1992 Jun;101(6):1644-55.

THE NEWEST DEFINITION….

Clinical Review & Education

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

IMPORTANCE Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination.

Editorial page 757

Author Video Interview, Author Audio Interview, and JAMA Report Video at jama.com

Related articles pages 762 and

Singer, et al. JAMA. 2016 Feb 23;315(8):801-10.

DEFINITION OF SEPSIS

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

* organ dysfunction is identified as an acute change in total SOFA[a] score ≥ 2 points consequent to the infection

Septic Shock is sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg and having a serum lactate level > 2 mmol/L despite adequate volume resuscitation

[a]SOFA = sequential organ failure assessment

Singer, et al. JAMA. 2016 Feb 23;315(8):801-10.

SEPSIS DEFINITIONS: SUMMARY AND COMPARISON

	Previous Definitions	Sepsis-3 SCCM Definition 2016
SIRS	Screening tool for patients with infection to identify sepsis (≥ 2 of 4 criteria)	removed
Quick SOFA	n/a	Risk stratification tool for patients with suspected infection to predict poor outcomes (not recommended by 2021 Sepsis guidelines)
Sepsis	1992: SIRS **plus** infection	Life-threatening **organ dysfunction** caused by a **dysregulated host response** to **infection**
Severe Sepsis	Sepsis complicated by organ dysfunction	removed
Septic Shock	Sepsis with arterial hypotension despite adequate fluid resuscitation	sepsis with **persisting hypotension requiring vasopressors** to maintain MAP ≥ 65 mm Hg and having a serum **lactate level > 2 mmol/L despite adequate volume resuscitation**

Singer, et al. JAMA. 2016 Feb 23;315(8):801-10.
Levy MM, et al. Crit Care Med. 2003 Apr;31(4):1250-6.

QUICK SOFA ASSESSMENT

- Abbreviated "qSOFA" = positive if any <u>two</u> of the following:

- **Systolic Blood Pressure ≤ 100 mmHg**
- **Altered mentation (Glasgow Coma Scale < 15)**
- **Respiratory rate ≥ 22 breaths/min**

- Patients with suspected infection who are likely to have poor outcomes (prolonged ICU stay or hospital mortality) can be promptly identified at the bedside with a qSOFA

HAT = hypotension, AMS, tachypnea

Singer, et al. JAMA. 2016 Feb 23;315(8):801-10.

GLASGOW COMA SCALE

Best eye response (E)	Spontaneous--open with blinking at baseline	4
	Opens to verbal command, speech, or shout	3
	Opens to pain, not applied to face	2
	None	1
Best verbal response (V)	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate responses, words discernible	3
	Incomprehensible speech	2
	None	1
Best motor response (M)	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws from pain	4
	Abnormal (spastic) flexion, decorticate posture	3
	Extensor (rigid) response, decerebrate posture	2
	None	1

Total score ranges from 3 – 15 points

WHAT WAS WRONG WITH SIRS?

- Sepsis-3 Consensus: "The current use of 2 or more SIRS criteria to identify sepsis was unanimously considered by the task force to be unhelpful"
- SIRS (change in WBC, temperature, heart rate, and respiratory rate) reflects inflammation but this may often be an *appropriate* host response to "danger" whereas the new definitions emphasize that sepsis involves organ dysfunction, indicating a pathophysiology more complex than infection plus inflammation
- SIRS lacks specificity: many patients with positive SIRS criteria and infection do not develop hypotension or have a progressively worsening disease process
- SIRS also lacks sensitivity: 1 in 8 ICU patients with infection and organ dysfunction do not have 2 or more SIRS criteria yet may have significant hospital morbidity and mortality

Singer, et al. JAMA. 2016 Feb 23;315(8):801-10.

METHODS OF CREATING NEW CONSENSUS DEFINITIONS

- Retrospective evaluation of 148,907 patients at UPMC with suspected infection (cultures obtained and antibiotics initiated)
- Multivariable regression used to explore the performance of 21 bedside and laboratory criteria for patients both inside and outside ICU

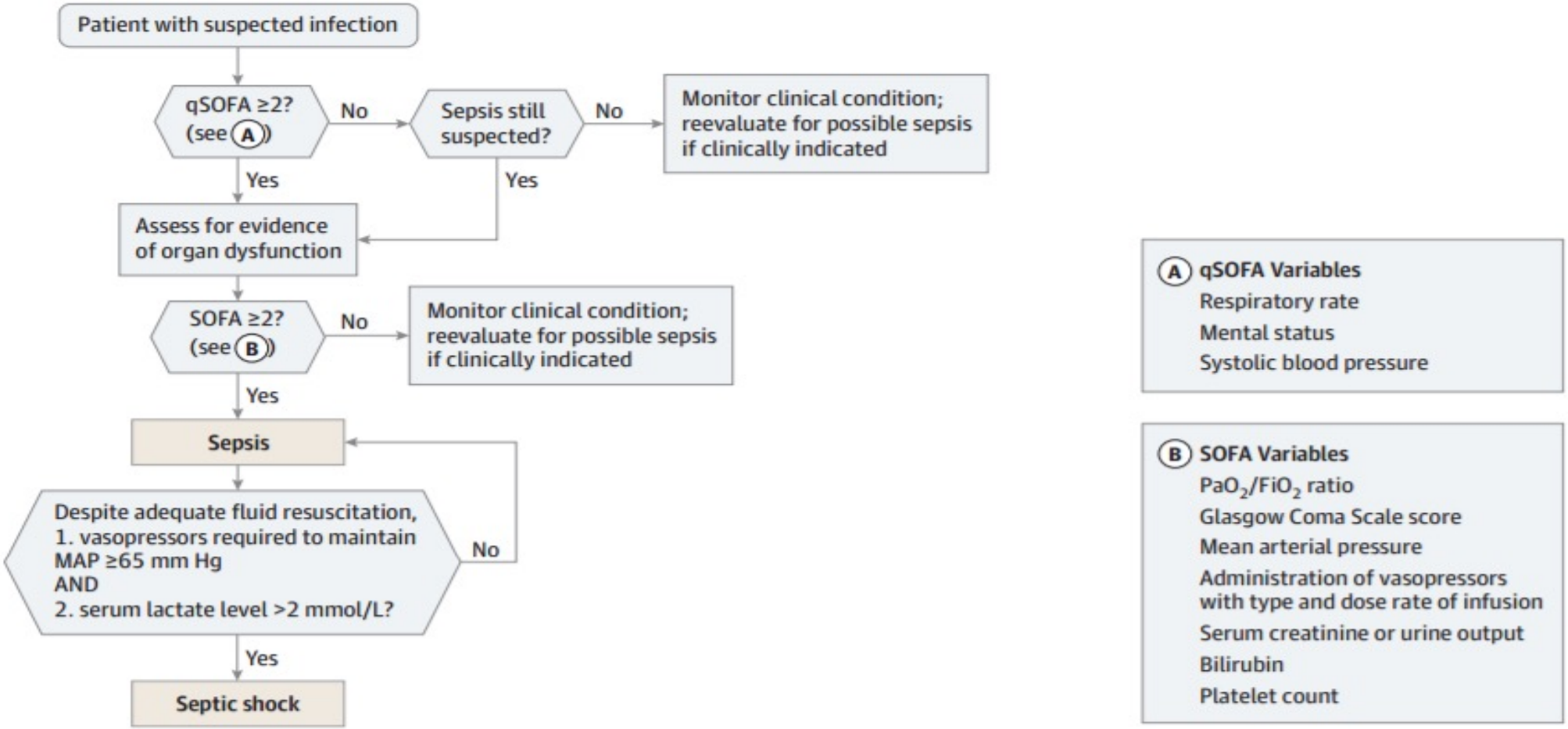
Ability to predict mortality among patients with possible infection outside the ICU

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%

Seymour CW, et al. JAMA. 2016 Feb 23;315(8):762-74.

SEPSIS-3 ALGORITHM

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

Singer, et al. JAMA. 2016 Feb 23;315(8):801-10.

SOFA ASSESSMENT

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	**0**	**1**	**2**	**3**	**4**
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Singer, et al. JAMA. 2016 Feb 23;315(8):801-10.

2021 GUIDELINES

- Now what?

Recommendation
2. We **recommend against** using qSOFA compared with SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock.
Strong recommendation, moderate-quality evidence.

  - Neither SIRS nor qSOFA are ideal screening tools for sepsis and the bedside clinician needs to understand the limitations of each.
  - Although the presence of a positive qSOFA should alert the clinician to the possibility of sepsis; given the poor sensitivity of the qSOFA, the panel issued a strong recommendation against its use as a single screening tool.

Evans L, et al. Intensive Care Medicine. 2021 Nov;47(11):1181-1247.

SIRS Criteria:
- Temperature > 38°C (100.4°F) or < 36°C (96.8°F
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min
- White blood cell count > 12 cells/µL or < 4 cells/µL

qSOFA criteria:
- Systolic Blood Pressure ≤ 100 mmHg
- Altered mentation (Glasgow Coma Scale < 15)
- Respiratory rate ≥ 22 breaths/min

CASE #1

- 55/F who brought to ED by her husband with lethargy (GCS 13) and flank pain. Her husband states that she had been complaining of increased frequency, pain and burning with urination.
- Vital signs: HR 110 beats/min Tmax: 100.1° F WBC: 11 RR: 19 breaths/min
  Blood pressure: 75/45 mmHg (MAP = 55)
- Labs: Na: 135 Cl: 100 K: 5.8 BUN: 40 SCr: 2 (baseline 0.9) HCO3: 14 Lactate: 7

- SIRS *negative* (only 1 point): Temperature 100.1° F is < 38° C (100.4° F), **HR 110 bpm is > 90** beats/min; RR 10 breaths/min is < 20 breaths/min; WBC 11 is < 12 cells/µL
- qSOFA *negatvie* (2 points): Alert and oriented (GCS 15), RR 19 breaths/min < 22, **SBP 75 mmHg is < 100 mmHg**
- New onset organ failure (AKI), lactatemia, profound hypotension →organ dysfunction due to a dysregulated host response to infection = sepsis

MINI CASE #2

SIRS Criteria:
- Temperature > 38°C (100.4°F) or < 36°C (96.8°F
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min
- White blood cell count > 12 cells/μL or < 4 cells/μL

qSOFA criteria:
- Systolic Blood Pressure ≤ 100 mmHg
- Altered mentation (Glasgow Coma Scale < 15)
- Respiratory rate ≥ 22 breaths/min

- 58/M patient with PMH of HTN and HLD, presents to ED complaining of productive cough x 3 days along with fever and chills. CXR reveals diffuse bilateral infiltrates. He is alert and oriented during physical exam (GCS = 15)

- HR: 130 beats/min RR: 35 breaths/min BP: 101/50 (MAP 67) O2sat: 85% of 6L NC
- WBC: 25 cells/μL 10% bands Tmax 102°C
- SCr: 1.6 mg/dL (baseline 0.8 mg/dL)

- qSOFA *negative*: only 1 point for **tachypnea (RR ≥ 22)**
- All 4 SIRS criteria *positive*: **Temperature > 38° C (100.4° F), HR > 90 beats/min; RR > 20 breaths/min; WBC > 12 cells/μL**
- This patient should still be treated as sepsis since he has organ dysfunction (AKI) likely due to a dysregulated host response to infection. He is clinically hypotensive despite not meeting the qSOFA cutoff. He has a history of hypertension, which makes a BP of 101/50 more concerning.

MINI CASE #3

SIRS Criteria:
- Temperature > 38°C (100.4°F) or < 36°C (96.8°F
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min
- White blood cell count > 12 cells/μL or < 4 cells/μL

qSOFA criteria:
- Systolic Blood Pressure ≤ 100 mmHg
- Altered mentation (Glasgow Coma Scale < 15)
- Respiratory rate ≥ 22 breaths/min

- 35/M patient presents to the ED with altered mental status, acute agitation and tachycardia
- HR: 130 beats/min RR: 23 breaths/min BP: 180/100 O2 sat: 100% on RA
- Tmax 100.9°F GCS: 13 BMP: within normal limits WBC: 9 cells/μL

- Toxicology screen is positive for cocaine
- If no suspected source of infection and no obvious organ dysfunction; no need to review qSOFA or SIRS since these screening tools would be positive but this patient has another reason for abnormal vital signs and altered metation (cocaine ingestion)
  - qSOFA positive (1 point GCS < 15, 1 point for RR ≥ 22)
  - SIRS positive (HR > 90, Tmax > 100.4 F) but not relevant since no suspected infection

PATHOPHYSIOLOGY OF SEPSIS

- Sepsis and septic shock result when an infectious microorganism triggers a SYSTEMIC host inflammatory, immune and coagulation response
- *Excessive* inflammatory mediators (TNF-α, IL-1, IL-6) activate neutrophils and endothelial cells leading to an inappropriate circulatory vasodilatation and failure of vasoconstrictive pathways
- Vascular endothelial cell injury leads to loss of tight junctions resulting in capillary leak and decreased preload
- Sepsis activates coagulation cascade and suppression of anticoagulant pathways leading to microvascular thrombosis which further impairs tissue perfusion
- As septic shock progresses patients experience profound metabolic acidosis which further impairs vasopressor responsiveness and cardiac output

Toxic stimulus
(infection/endotoxin)

*Amplified **proinflammatory response**: cytokines, TNFα, IL-1, IL-6 and production of **reactive oxygen species** (free radicals: superoxide, hydrogen peroxide, peroxynitrite)*

*Damaged glycocalyx, decreased tight junctions, capillary leak → **relative hypovolemia***

***Mitochondrial dysfunction** induced by free radical oxidation of enzymes*

***Relative adrenal insufficiency** due to oxidation of glucocorticoid receptor*

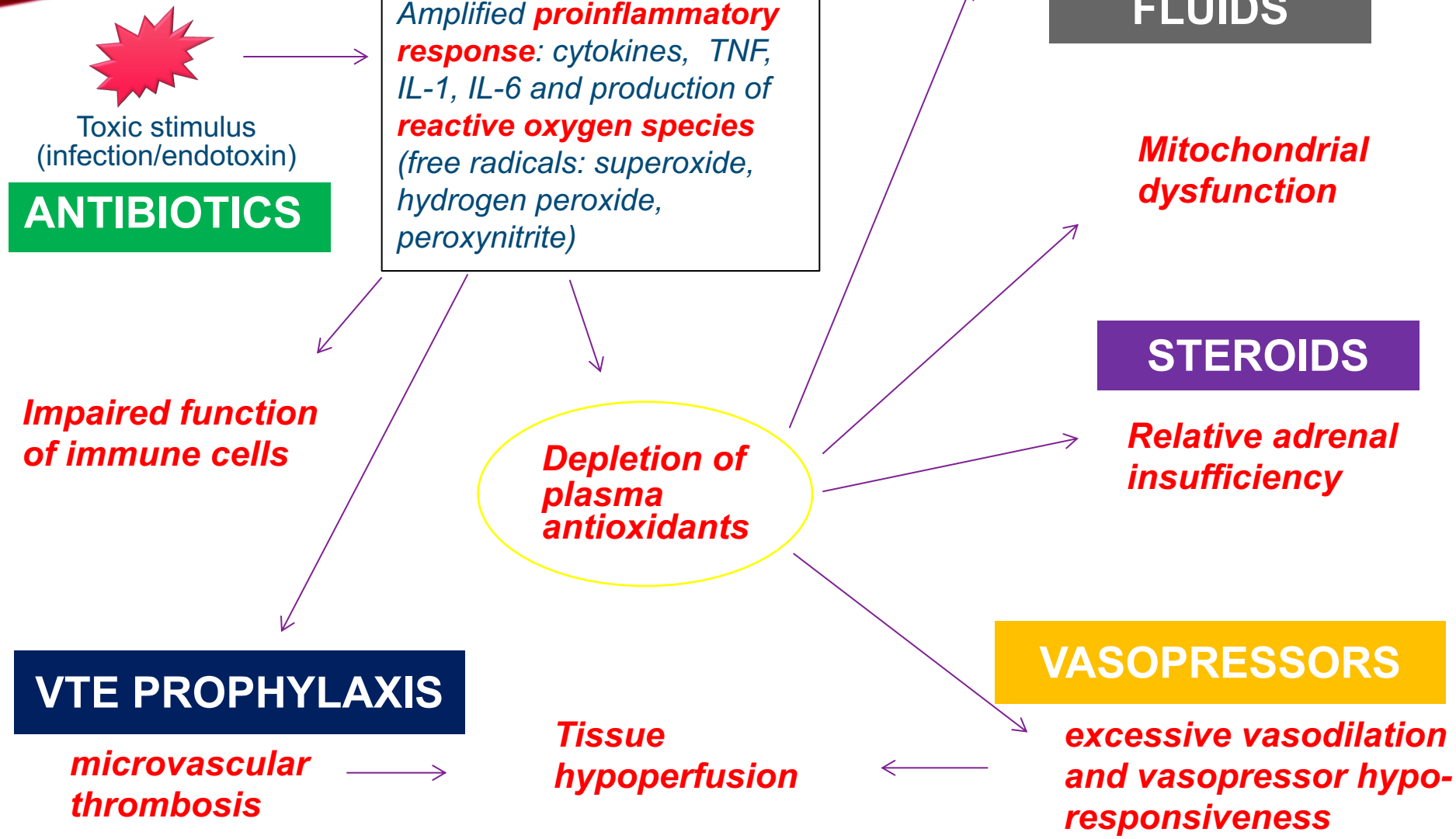
***Impaired function of immune cells** (apoptosis of T and B cells, impaired phagocytosis)*

Depletion of plasma antioxidants

*Activated coagulation cascade, capillary obstruction by platelet clotting, leading to **microvascular thrombosis***

***Tissue hypoperfusion**, lactic acidosis, cardiovascular instability*

*Damage to vascular endothelial cells, release of nitric oxide leading to **excessive vasodilation and vasopressor hypo-responsiveness***


Toxic stimulus
(infection/endotoxin)
ANTIBIOTICS
Amplified proinflammatory response: cytokines, TNF, IL-1, IL-6 and production of reactive oxygen species (free radicals: superoxide, hydrogen peroxide, peroxynitrite)
relative hypovolemia
FLUIDS
Mitochondrial dysfunction
STEROIDS
Relative adrenal insufficiency
Impaired function of immune cells
Depletion of plasma antioxidants
VTE PROPHYLAXIS
microvascular thrombosis
Tissue hypoperfusion
VASOPRESSORS
excessive vasodilation and vasopressor hypo-responsiveness

EARLY GOAL-DIRECTED THERAPY (EGDT)

Emanuel Rivers, MD and colleagues, 2001: published in the New England Journal of Medicine

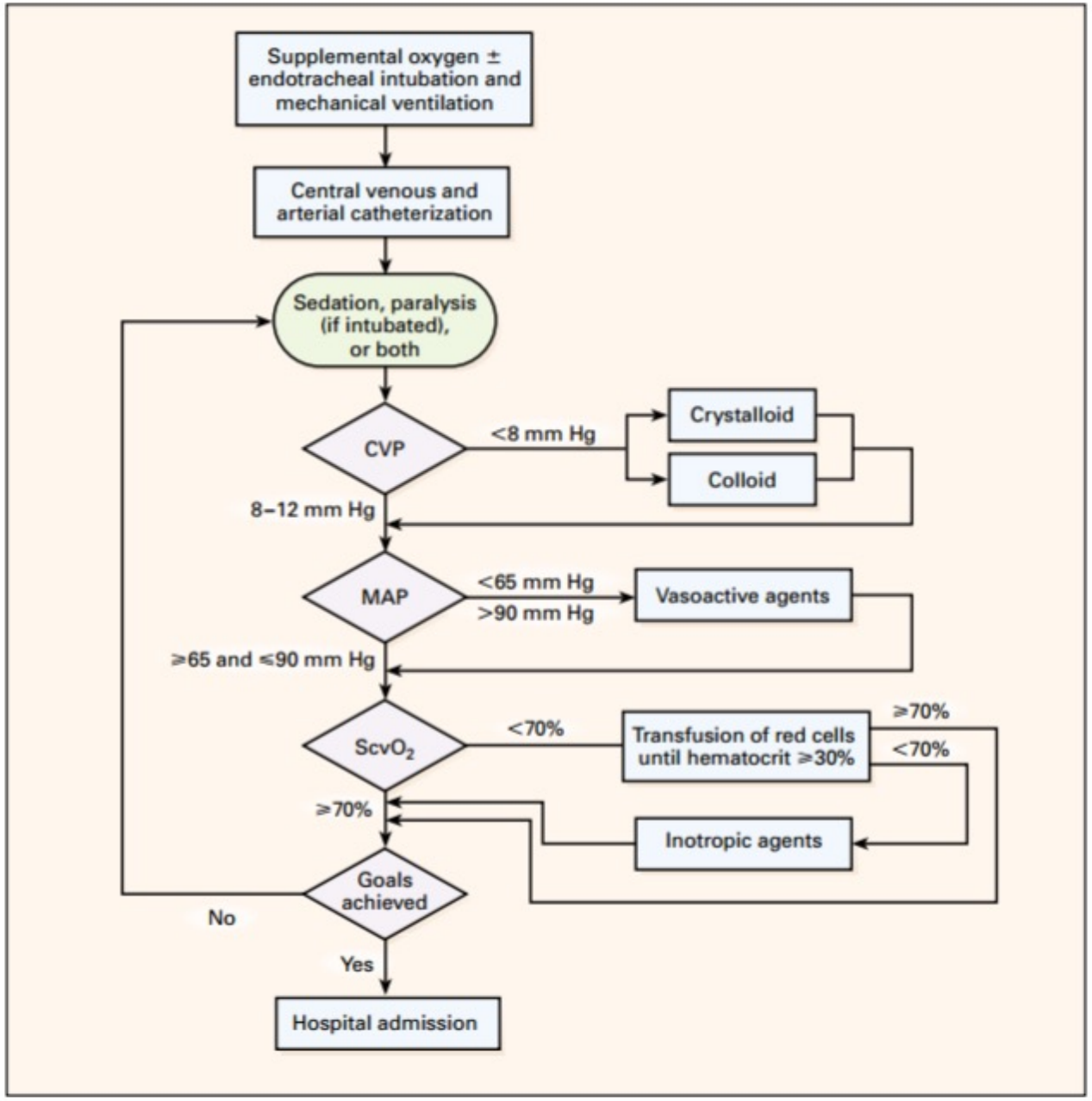


Figure 2. Protocol for Early Goal-Directed Therapy.
CVP denotes central venous pressure, MAP mean arterial pressure, and $ScvO_2$ central venous oxygen saturation.

Rivers E, et al. N Engl J Med. 2001 Nov 8;345(19):1368-77.

PROCESS, ARISE AND PROMISE CLINICAL TRIALS

Reference	# of Patients	Intervention	Primary outcome	Results
EGDT[1] (Rivers, et al 2001 NEJM)	263	Single center (Henry Ford Hospital): EGDT vs. standard care	In-hospital mortality Secondary endpoint: 60-day mortality	30.5% vs. 46.5% (p = 0.009) 44.3% vs. 56.9% (p = 0.03)

Reference	# of Patients	Intervention	Primary outcome	Results
PROCESS[2] (2014 NEJM)	1,341	31 EDs in the US: protocolized EGDT vs. protocol-based standard vs. usual care	60-day mortality	21% (EGDT), 18.2% (standard), 18.9% (usual) (p = 0.83)
ARISE[3] (2014 NEJM)	1,600	51 centers in Australia or New Zealand: EGDT vs. usual care	90-day mortality	18.6% vs. 18.8% (p = 0.9)
PROMISE[4] (2015 NEJM)	1,260	56 hospitals in England: EGDT vs. usual care	90-day mortality	29.5% vs. 29.2% (p = 0.9)

1. Rivers E, et al. N Engl J Med. 2001 Nov 8;345(19):1368-77.
2. Process Investigators, et al. N Engl J Med. 2014 May 1;370(18):1683-93.
3. ARISE Investigators, et al. N Engl J Med. 2014 Oct 16;371(16):1496-506.
4. Mouncey PR, et al. N Engl J Med. 2015 Apr 2;372(14):1301-11.

WHY DID THESE NEWER EGDT TRIALS FIND NO DIFFERENCE COMPARED TO USUAL CARE?

- Prior to 2001 there was no recognized standard for **early** management of sepsis starting in the emergency room when the patient first presents to the hospital
- Mortality was high for patients presenting with "severe sepsis and septic shock" as seen in the Rivers, et al 2001 publication where 60-day mortality was 56.9% in the "standard care" treatment arm
- "Usual care" may contain elements of EGDT since the Surviving Sepsis Campaign was first published in 2004 and recent studies were conducted in an era where protocolized sepsis management is considered the standard of care

WHAT WAS "USUAL CARE" IN 2014

- Example from the ARISE study: no difference in fluid resuscitation, early antibiotics but more central lines, vasopressors, inotropes and blood transfusions

Intervention	Protocol-based EGDT	Protocol-based standard therapy	Usual Care	P-value
Pre-intervention				
Fluids	2,254 mL ± 1,472 mL	2,226 mL ± 1,363 mL	2,083 mL ± 1,405 mL	0.15
Antibiotics	75.6%	76.9%	76.1%	0.91
Randomization to hour 6				
Central venous catheter	93.6%	56.5%	57.9%	< 0.0001
Central venous oximeter	93.2%	4%	3.5%	< 0.0001
Antibiotics	97.5%	97.1%	96.9%	0.9
Vasopressor use	54.9%	52.2%	44.1%	0.003
Dobutamine use	8%	1.1%	0.9%	< 0.001
Blood transfusions	14.4%	8.3%	7.5%	0.001

ARISE Investigators, et al. N Engl J Med. 2014 Oct 16;371(16):1496-506.

When do you call a Sepsis Alert?
2 SIRS Criteria + Infection or Suspected Infection+ New Organ Dysfunction= SEPSIS ALERT

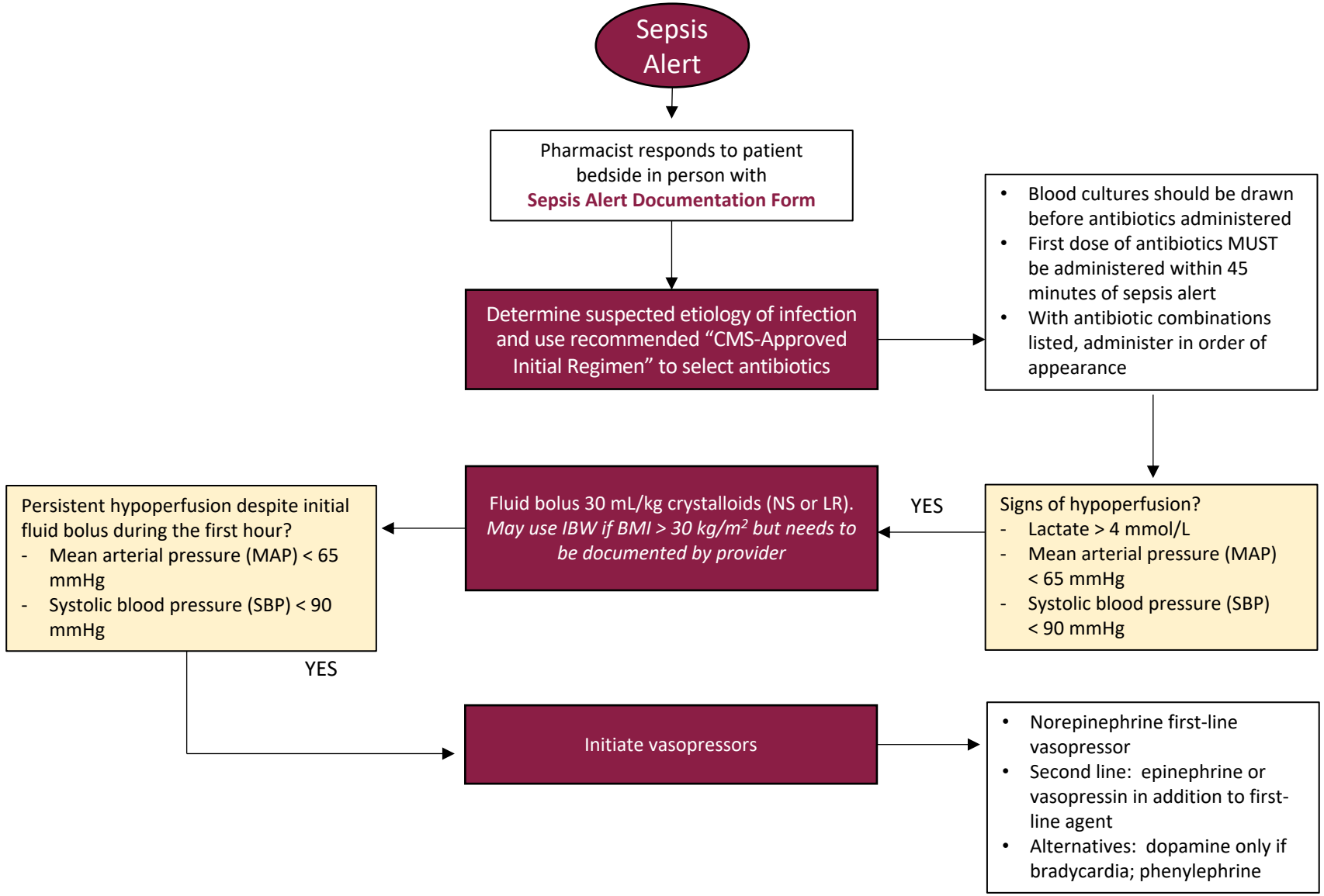
2 SIRS Criteria

- Temperature >38 C or < 36 C (>100.4 F - < 98.6 F)
- Heart rate > 90 BPM
- Respiratory Rate > 20 breaths/min
- White blood cells > 12,000/mm or <4,000/mm or Bands >10%

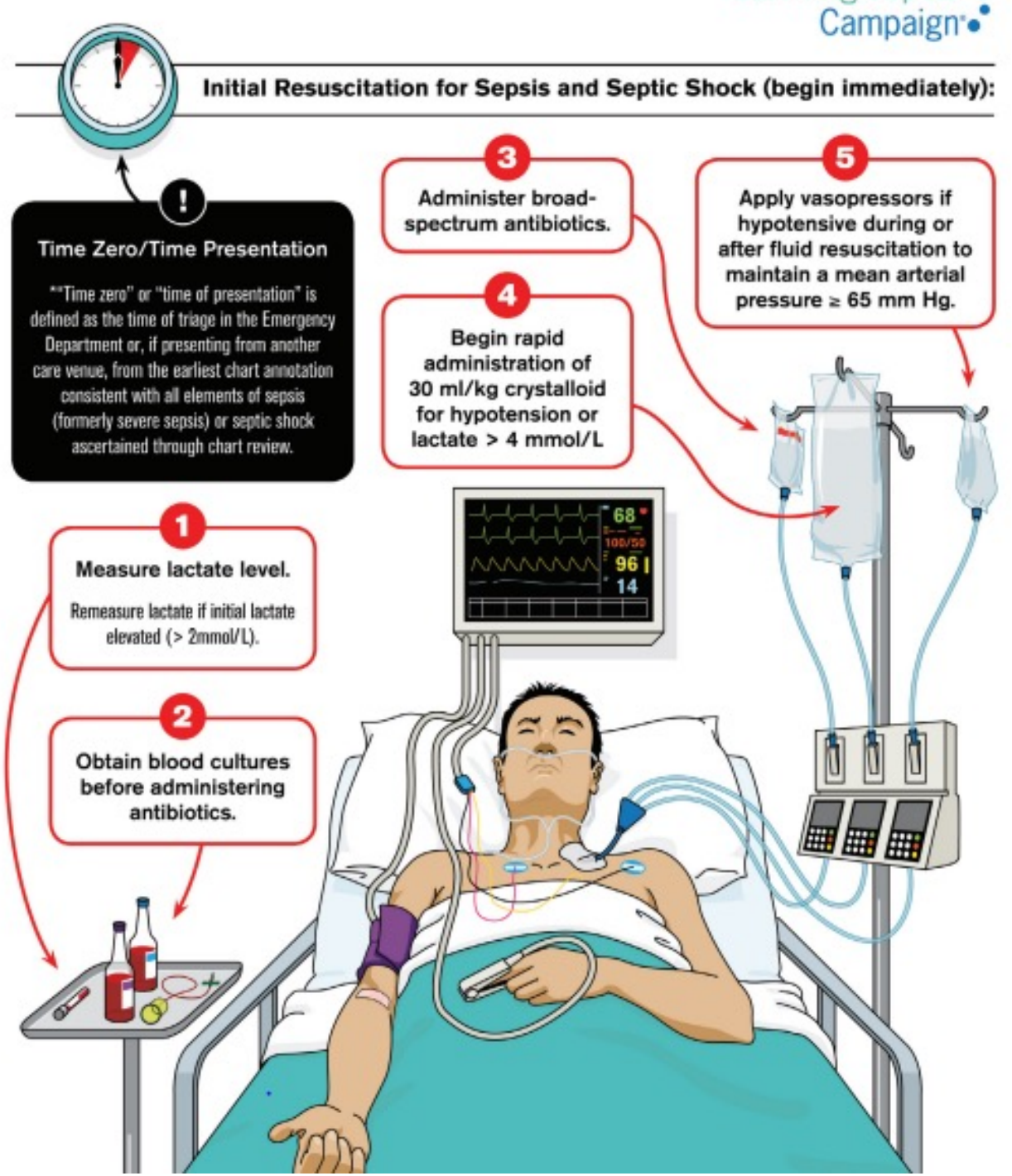
Known or Suspected Infection

1 or new organ Dysfunction

- Change in mental status (new)
- Decrease in urine output (0.5 ml/kg/hrX24 hrs)
- Creatinine > 2 or 0.5 mg dl from baseline
- Change in mental status
- Lactate > 2 mmol/L
- Hypotension SBP <90
- Hypoperfusion MAP < 65
- Platelets < 100,000
- Total Bili > 2
- INR > 1.5 (unrelated to anticoagulation therapy)


Sepsis Alert
Pharmacist responds to patient bedside in person with Sepsis Alert Documentation Form
Determine suspected etiology of infection and use recommended "CMS-Approved Initial Regimen" to select antibiotics
• Blood cultures should be drawn before antibiotics administered
• First dose of antibiotics MUST be administered within 45 minutes of sepsis alert
• With antibiotic combinations listed, administer in order of appearance
Signs of hypoperfusion?
- Lactate > 4 mmol/L
- Mean arterial pressure (MAP) < 65 mmHg
- Systolic blood pressure (SBP) < 90 mmHg
YES
Fluid bolus 30 mL/kg crystalloids (NS or LR).
May use IBW if BMI > 30 kg/m2 but needs to be documented by provider
Persistent hypoperfusion despite initial fluid bolus during the first hour?
- Mean arterial pressure (MAP) < 65 mmHg
- Systolic blood pressure (SBP) < 90 mmHg
YES
Initiate vasopressors
• Norepinephrine first-line vasopressor
• Second line: epinephrine or vasopressin in addition to first-line agent
• Alternatives: dopamine only if bradycardia; phenylephrine

SEPSIS 1-HOUR BUNDLE



Note: in the newest sepsis guidelines, fluid bolus is within 3 hours (instead of within 1 hour), but initial blood culture, early antibiotics, and assessment of lactate still need to be within 1 hour

COMPONENTS OF EARLY GOAL-DIRECTED THERAPY

1. Broad-spectrum antibiotics
2. Fluid resuscitation
3. Vasopressors/ Inotropes
4. Corticosteroids

RATIONALE FOR EARLY ANTIBIOTICS IN SEPSIS

- In sepsis and septic shock the organ dysfunction and mortality is not necessarily caused by the infection itself, rather by the systemic physiologic inflammatory response to the infection

- Early antibiotics may prevent injury caused by microbial activity and/or toxin production by killing the causative microorganism → dampen the excessive inflammatory response

EARLY ANTIBIOTICS: THE EVIDENCE

- **Kumar, et al study 2006**; Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock
- Retrospective cohort of 2,731 septic shock patients from the US and Canada from 1989 to 2004 studied from the onset of hypotension to the first appropriate antibiotic (median 6 hours, mean 13.5 hours)

- Overall mortality was 56.2%; **every hour of delay in initiation of appropriate antimicrobial agent resulted in mean 7.6% increase in mortality**

Kumar A, Roberts D, Wood KE, et al. Crit Care Med. 2006 Jun;34(6);1589-96.

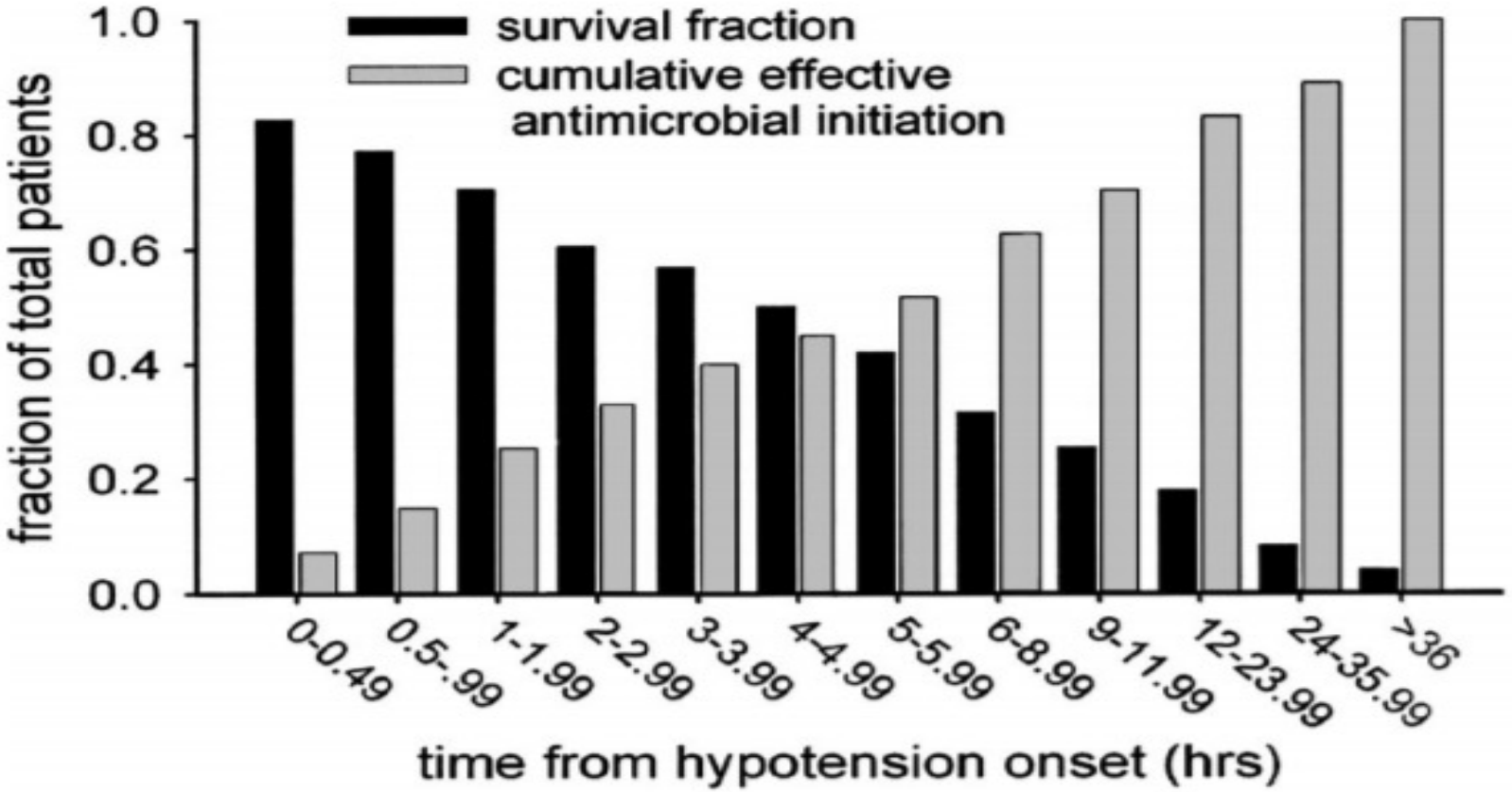


Figure 1. Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hrs) following first documentation of septic shock-associated hypotension. *Black bars* represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The *gray bars* represent the cumulative fraction of patients having received effective antimicrobials at any given time point.

Kumar A, Roberts D, Wood KE, et al. Crit Care Med. 2006 Jun;34(6):1589-96.

ANTI-PSEUDOMONAL BETA-LACTAM COMPARISON

	Piperacillin-tazobactam (Zosyn)	Cefepime
Anaerobic coverage	Yes	No
Severe PCN allergy?	Avoid with severe PCN allergy, may cross-react	Cefepime has distinct side chain; unlikely cross-reactivity
Empiric enterococcus coverage	Yes (including VRE)	No, intrinsic resistance
CNS penetration	Poor CNS penetration	Penetrates CNS
Renal dose adjustment	Yes	Yes

DOES EVERY SEPTIC PATIENT NEED MRSA COVERAGE?

- Empiric MRSA coverage is important in patients with sepsis secondary to soft tissue infections (especially if purulent), line infections, endocarditis, pneumonia

- MRSA coverage not necessary for sepsis secondary to urinary source or community acquired intraabdominal infections

Source	CMS-Approved Initial Regimen	Alternatives for severe cephalosporin allergy
CAP	Ceftriaxone + Azithromycin	
	MRSA w/in 1 yr, cavitation or necrosis, HD, IVDA, prior influenza: Add Vancomycin	Levofloxacin
	Pseudomonas w/in 1 yr, recently hospitalized AND rec'd IV ATB w/in 90d, structural lung dz, severe COPD and frequent steroid +/- ATB: Substitute ceftriaxone to Cefepime OR Piperacillin/Tazobactam	
HAP or VAP	[Cefepime OR Piperacillin/Tazobactam] + Vancomycin	Levofloxacin + Aztreonam + Vancomycin
	Prior IV ATB w/in 90days, High risk for mortality, Structural lung dz: Add Aminoglycoside OR Ciprofloxacin	
Intra-Abdominal Community Acquired	Mild/Moderate: Ceftriaxone + Metronidazole	Levofloxacin + Metronidazole
	Severe (>24h delay in initial intervention, advanced age, immunocompromised): Piperacillin/Tazobactam OR Cefepime + Metronidazole	Levofloxacin + Metronidazole OR Aztreonam + Metronidazole + Vancomycin
Intra-Abdominal Healthcare Associated	Piperacillin/Tazobactam + Vancomycin OR Cefepime + Metronidazole + Vancomycin	Levofloxacin + Metronidazole OR Aztreonam + Metronidazole + Vancomycin
Bacterial Meningitis (>50years old)	Dexamethasone 0.15mg/kg (max 10mg) + Ceftriaxone + Ampicillin + Vancomycin **Give dexamethasone prior to antibiotics**	Meropenem + Vancomycin
Bacterial Meningitis ≤50yrs old)	Dexamethasone 0.15mg/kg (max 10mg) + Ceftriaxone + Vancomycin **Give dexamethasone prior to antibiotics**	Meropenem + Vancomycin

UTI	Ceftriaxone	Levofloxacin
SSTI Non-purulent	Ampicillin/Sulbactam OR Ceftriaxone	Aztreonam + Vancomycin
SSTI Purulent	Ampicillin/Sulbactam + Vancomycin OR Ceftriaxone + Vancomycin	Aztreonam + Vancomycin
SSTI Necrotizing	Piperacillin/Tazobactam + Vancomycin + clindamycin for toxin suppression	Levofloxacin + Vancomycin + Clindamycin
Diabetic Foot Infection	Ceftriaxone + Vancomycin + Metronidazole OR Piperacillin/Tazobactam + Vancomycin	Aztreonam + Vancomycin + Metronidazole
Joint Infection Community Acquired	Ceftriaxone + Vancomycin	Ciprofloxacin + Vancomycin
Joint Infection Healthcare Associated	Cefepime + Vancomycin OR Ceftriaxone + Vancomycin	Ciprofloxacin + Vancomycin
Unknown Source	Piperacillin/Tazobactam + Vancomycin OR Cefepime + Metronidazole + Vancomycin	Aztreonam + Vancomycin + Metronidazole

Reference Doses (All routes are IV); with combinations listed, administer in order of appearance:

- Ampicillin 2g
- Ampicillin/Sulbactam 3g
- Azithromycin 500mg
- Aztreonam 2g
- Cefepime 2g
- Ceftriaxone 2g
- Ciprofloxacin 400mg
- Levofloxacin 750mg
- Meropenem 2g
- Metronidazole 500mg
- Piperacillin/Tazobactam 4.5g over 30 min
- Vancomycin/Aminoglycoside – Rx to Dose

2021 SEPSIS GUIDELINES: ABX

illness is demonstrated or strongly suspected.

12. For adults with possible septic shock or a high likelihood for sepsis, we recommend administering antimicrobials immediately, ideally within 1 hr of recognition.

als, as compared to clinical evaluation alone.

17. For adults with sepsis or septic shock at high risk of MRSA, we recommend using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage.

to 16% in North America) and by patient related characteristics (133, 136, 137). Patient-related risk factors for MRSA include prior history of MRSA infection or colonization, recent IV antibiotics, history of recurrent skin infections or chronic wounds, presence of invasive devices, hemodialysis, recent hospital admissions and severity of illness (136, 138–142).

19. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we suggest using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent.

20. For adults with sepsis or septic shock and low risk for multidrug resistant (MDR) organisms, we suggest against using two gram-negative agents for empiric treatment, as compared to one gram-negative agent.

21. For adults with sepsis or septic shock, we suggest against using double gram-negative coverage once the causative pathogen and the susceptibilities are known.

COMPONENTS OF EARLY GOAL-DIRECTED THERAPY

1. Broad-spectrum antibiotics
2. Fluid resuscitation
3. Vasopressors/ Inotropes
4. Corticosteroids

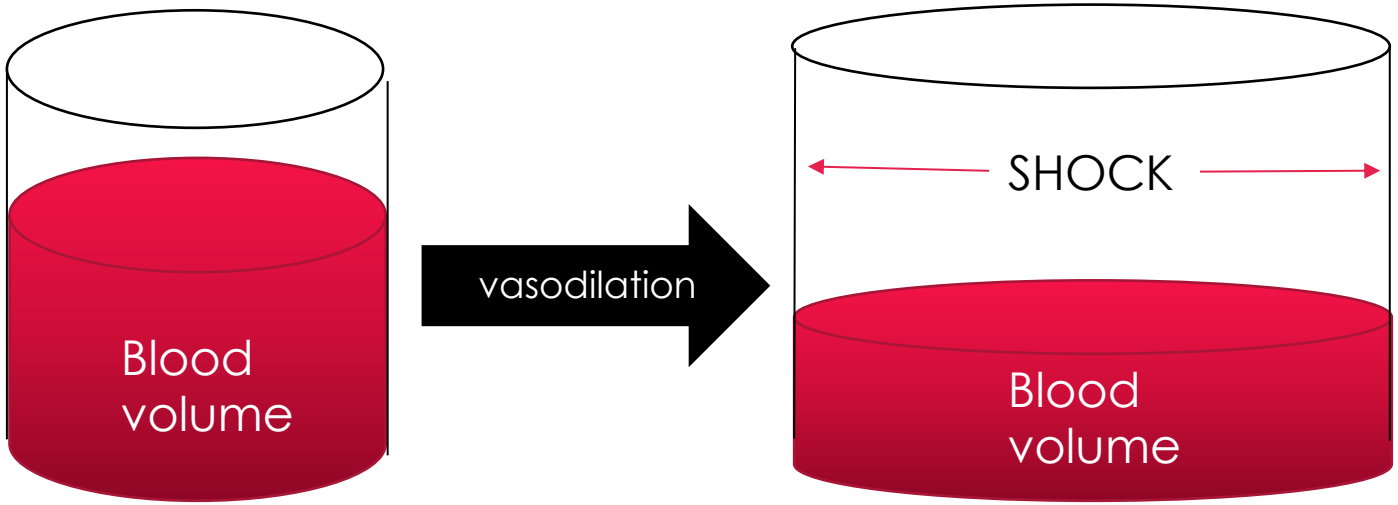
IS IT THE PUMP OR THE PIPES??

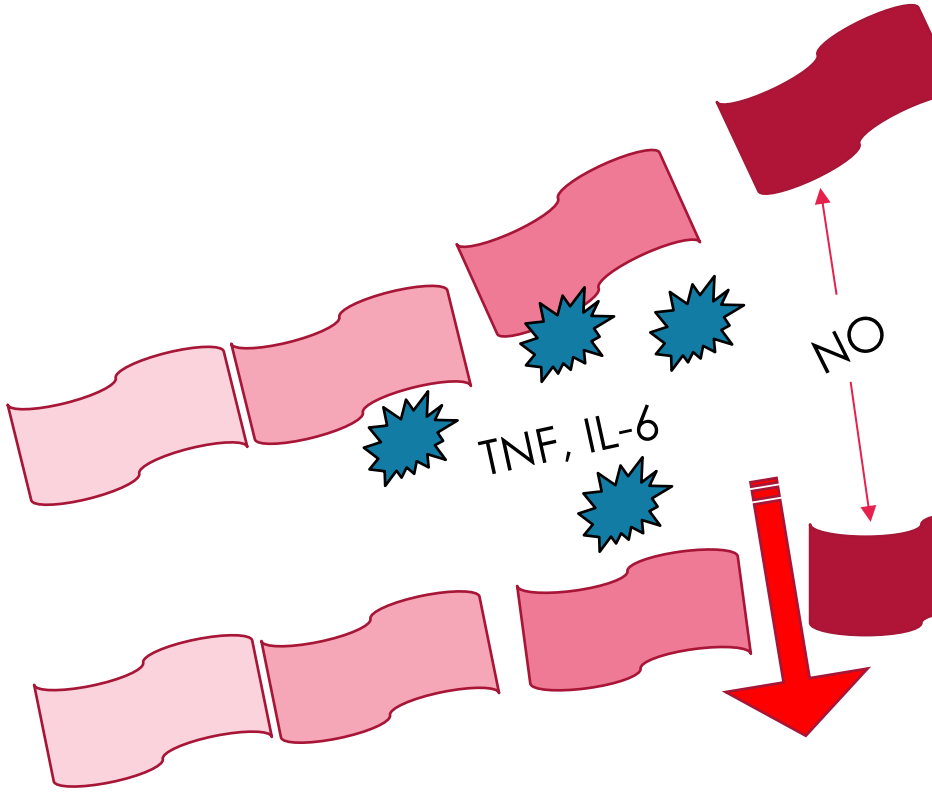
BASIC PRINCIPLES: TYPES OF SHOCK

Shock Type	Preload	Stroke Volume	Heart Rate	Cardiac Output	Systemic Vascular Resistance
Hypovolemic [Hemorrhage, Burn, Pancreatitis]	↓	↓	↑	↓/↔	↑
Cardiogenic [Post MI, HF]	↑	↓	↑	↓	↑
Distributive [Septic Shock, Anaphylaxis, Toxic Shock Syndrome, Adrenal Crisis, Neurogenic]	↓	↑/↔	↑	↑	↓

FLUIDS: PHYSIOLOGIC RATIONALE

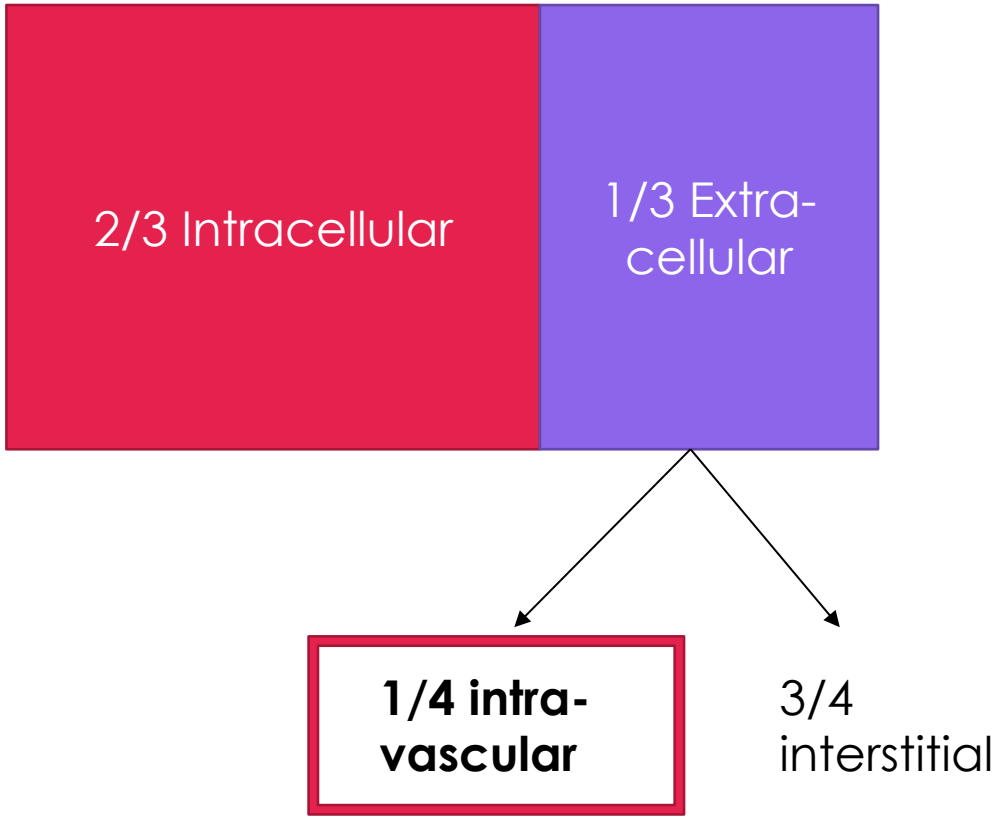
Increased proinflammatory cytokines increase release of nitric oxide, decreases vascular tone → reduced systemic vascular resistance





Vascular endothelial cell injury → shedding endothelial glycocalyx and loss of tight junctions resulting in capillary leak

FLUID COMPARTMENTS



Fluid	Volume Given	Resuscitation Volume
Dextrose 5%	1000 mL	100 mL
0.9% sodium chloride	1000 mL	250 mL
Lactated Ringers	1000 mL	250 mL
Albumin 5%	500 mL	500 mL
Albumin 25%	100 mL	500 mL
Hetastarch 6%	500 mL	500 mL

Crystalloids

Colloids

CRYSTALLOIDS VS. COLLOIDS

- **SAFE study**, NEJM 2004: A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit
  - 6,997 ICU patients requiring fluid administration to increase intravascular volume (17% trauma, 18% severe sepsis)
  - Primary outcome: no difference in 28-day mortality between albumin and saline (20.9% vs. 21.1%, p = 0.87)
  - No difference in duration of mechanical ventilation, length of ICU stay
  - Conclusion: For ICU patients requiring fluid resuscitation, there is no difference in the studied outcomes comparing albumin to normal saline

Finfer S, Bellomo R, Boyce N, et al. N Engl J Med. 2004 May 227; 350(22):2247-56.

CRYSTALLOIDS VS. COLLOIDS

- **CRISTAL study**, JAMA 2013: Effects of Fluid Resuscitation with Colloids vs. Crystalloids on Mortality in Critically Ill Patients Presenting with Hypovolemic Shock
  - 2,857 patients requiring fluid resuscitation for hypovolemia (hypotension with signs of hypoxia/hypoperfusion)
  - Methods: non-blinded crystalloid (85% received normal saline, 18% lactated ringers) administration or colloid (69% hydroxyethyl starch, 35% gelatins, 6% albumin); dose of fluid at discretion of investigator
  - Primary outcome: no difference in 28-day mortality (27% vs 25.4%, = 0.26)
  - Conclusion: In hypovolemic ICU patients requiring fluid resuscitation, there was no difference in the primary outcome comparing crystalloid administration to colloid administration

Annane D, Siami S, Jaber S, et al. JAMA 2013 Nov 6;310(17):1809-17.

WHAT IS MEANT BY "BALANCED CRYSTALLOIDS"?

- Crystalloids with relatively low chloride content
- "Chloride-poor" or "balanced salt" solutions) = lactated ringers or Plasmalyte-A
  - 0.9% normal saline = 154 mEq/L of sodium chloride
  - Lactated ringers = 130 mEq/L of sodium chloride and 109 mEq/L chloride
    - Lactated ringers better approximates the electrolyte composition of plasma
- Hypothesis that administration of chloride-rich fluids may cause a metabolic acidosis (hyperchloremic) and lead to afferent renal arteriole vasoconstriction (causing a decrease in renal perfusion and kidney injury)

Rhodes A, Evans LE, Alhazzani W, et al. Crit Care Med. 2017 Jan 17. [Epub ahead of print]

LACTATED RINGERS VS "NORMAL" SALINE

	Osmolarity (Osm/L)	Na (mEq/L)	Cl (mEq/L)	K (mEq/L)	Lactate (converts to HCO_3)	Ca
0.9% Sodium Chloride	308	154	154	0	0	0
Lactated Ringer's Solution	273	130	109	4	28	3

- Normal serum sodium: 135 – 145 mEq/L
- Normal serum chloride: 97 – 107 mEq/L

BALANCED CRYSTALLOIDS

- **SMART study** (Isotonic Solutions and Major Adverse Renal Events Trial); NEJM 2018: Balanced Crystalloids vs Saline in Critically Ill Adults
  - 15,802 patients admitted to 5 ICUs within Vanderbilt Medical Center randomized to receive either balanced crystalloid (lactated ringer's or plasmalyte-A) or 0.9% sodium chloride during hospitalization
  - Primary outcome = MAKE (Major Adverse Kidney Event at 30 days: mortality, receipt of renal replacement therapy, or persistent renal dysfunction (final inpatient SCr > 200% baseline): balanced crystalloid 14.3% vs Saline 15.4% (p = 0.04; OR 0.91, CI 0.84 – 0.99), NNT = 94
  - Secondary outcome: no difference in 30-day mortality: 10.3% vs 11.1%, p = 0.06
  - Subgroup of sepsis: statistically significant difference in-patient mortality: 25.2% vs. 29.4%, p = 0.02

Semler MW, et al. NEJM. 2018: 378:829-839

BaSICS (2021) (Balanced Solution versus Saline in Intensive Care Study) Randomized Clinical Trial

- 75 ICUs, 11,052 patients, double-blind, randomized trial in Brazil, to receive balanced solution (Plasma-Lyte) vs 0.9% sodium chloride
- Only 6% of patients had hypotension and/or vasopressor use
- Median fluid bolus volume only 1.5 L during the first day
- 90-day mortality not statistically significantly different (26.4% vs 27.2%, p = 0.47)
- Author's conclusion: Among critically ill patients requiring fluid challenges, use of a balanced solution compared with saline did not significantly reduce 90-day mortality"
- Take-home consideration: the choice of crystalloid (either balanced or saline) may not be clinically significant unless larger volumes are given (> 2 – 3L), so for patients in septic shock requiring 30 mL/kg IV fluid bolus, still consider using lactated ringers

Zamperi FG, et al. JAMA 2021;326(9):818-829.

2021 GUIDELINES: FLUIDS

- Within 3 hours for sepsis: administer at least 30 mL/kg IV crystalloids (balanced crystalloid preferred over saline)
- Any further fluid resuscitation should be guided by re-assessment of dynamic patient-specific variables

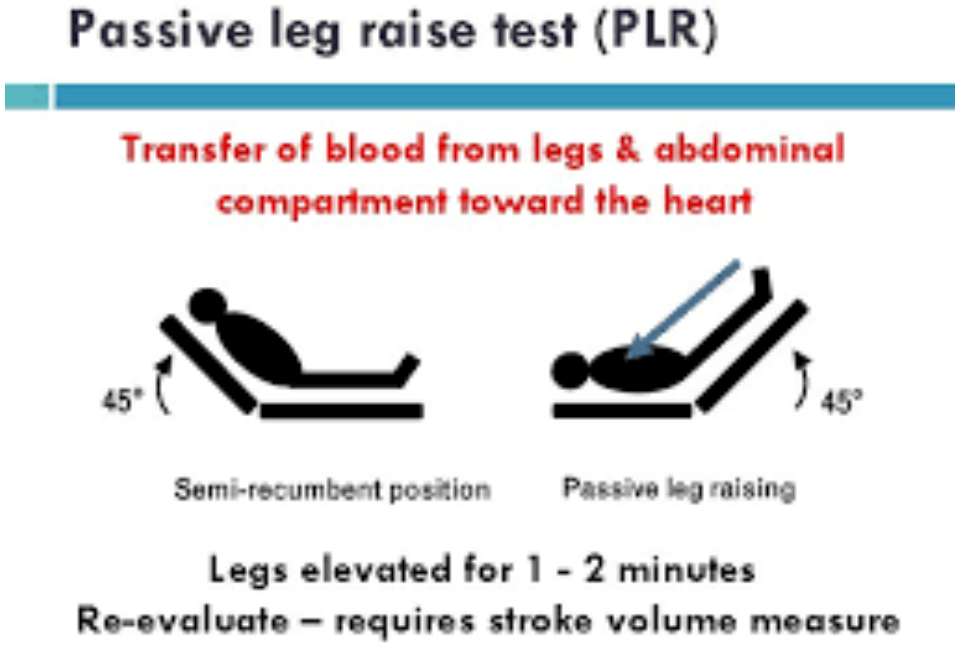
Initial Resuscitation

Recommendations
4. Sepsis and septic shock are medical emergencies, and we **recommend** that treatment and resuscitation begin immediately. *Best practice statement.*
5. For patients with sepsis induced hypoperfusion or septic shock we **suggest** that at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 hours of resuscitation. *Weak recommendation, low-quality evidence.*
6. For adults with sepsis or septic shock, we **suggest** using dynamic measures to guide fluid resuscitation over physical examination or static parameters alone. *Weak recommendation, very low-quality evidence.* **Remarks:** Dynamic parameters include response to a passive leg raise or a fluid bolus, using stroke volume (SV), stroke volume variation (SVV), pulse pressure variation (PPV), or echocardiography, where available.

HEMODYNAMIC MANAGEMENT		
32. For adults with sepsis or septic shock, we recommend using crystalloids as first-line fluid for resuscitation	***Strong,*** *moderate-quality evidence*	
33. For adults with sepsis or septic shock, we suggest using balanced crystalloids instead of normal saline for resuscitation.	***Weak,*** *low quality of evidence*	**CHANGED from *weak recommendation*,** *low quality of evidence.* "We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock"
34. For adults with sepsis or septic shock, we suggest using albumin in patients who received large volumes of crystalloids.	***Weak,*** *moderate-quality evidence*	
35. For adults with sepsis or septic shock, we recommend against using starches for resuscitation.	***Strong,*** *high-quality evidence*	

2021 SEPSIS GUIDELINES

- Heart rate, central venous pressure (CVP), and systolic blood pressure alone are poor indicators of fluid status
- Dynamic measures have demonstrated better diagnostic accuracy at predicting fluid responsiveness compared with static techniques
- Dynamic measures include:
  - Passive leg raise combined with cardiac output(CO) measurement
  - Fluid challenges against stroke volume (SV) or pulse pressure
- If fluid therapy is required beyond the initial 30 mL/kg administration – clinicians should use small repeated boluses guided by objective measures of SV and/or CO



LACTATE CLEARANCE

- Serum lactate is not a *direct* measure of tissue perfusion; elevated levels may be due to hypoxia, accelerated aerobic glycolysis driven by excess beta-adrenergic stimulation, or failure of hepatic clearance

- **Jones 2010 study** : Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial
  - 300 patients presenting to ED with sepsis or shock randomized to either ScvO2 > 70% or lactate clearance > 10% (after achieving CVP > 8 mmHg and MAP > 65 mm Hg); dobutamine or pRBCs were given to achieve goals
  - Primary outcome: hospital mortality was non-inferior between ScvO2 and lactate clearance (23% vs 75%; 95% CI -3 to 15%)
  - Conclusion: lactate clearance may be used as an alternative to ScvO2 monitoring and does not require invasive monitoring

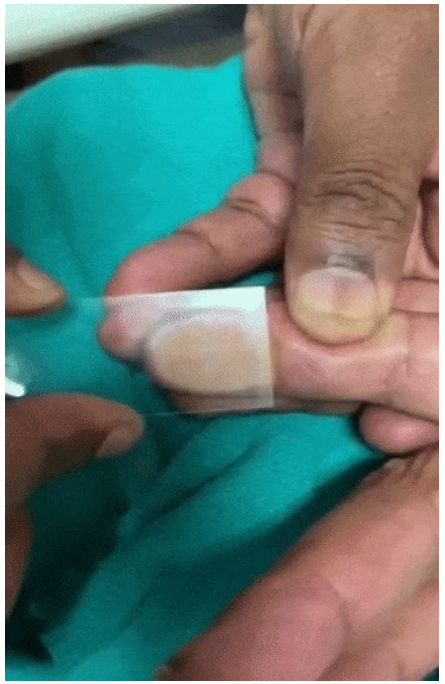
Jones AE, Shapiro NI, Trzeciak S, et al. JAM 2010 Feb 24;303(8):739-46.

LACTATE CLEARANCE

- **ANDROMEDA SHOCK** (Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients with Septic Shock), JAMA 2019
- 424 patients with septic shock randomized to capillary refill time measurements every 30 min until normalization then every 8 hours vs. lactate measurements every 2 hours until normalization then every 8 hours
- Primary outcome: no difference in 28-day mortality (34.9% capillary refill vs. 43.4% lactate clearance; p = 0.06; HR 0.75, CI 0.55-1.02)
  - More resuscitation fluids in the lactate clearance group
- Conclusion: capillary refill may be considered as an alternative to lactate clearance as a resuscitation target in sepsis

Study Interventions

The intervention period was 8 hours. Before starting the study, all centers were trained to assess capillary refill time with a standardized technique.[15] Briefly, CRT was measured by applying firm pressure to the ventral surface of the right index finger distal phalanx with a glass microscope slide. The pressure was increased until the skin was blank and then maintained for 10 seconds. The time for return of the normal skin color was registered with a chronometer, and a refill time greater than 3 seconds was defined as abnormal.



Hernandez G, et al. JAMA 2019;32(7):654-664.

2021 SEPSIS GUIDELINES

- Assess patient responsiveness to resuscitation and vasopressors using dynamic measures, lactate clearance, and capillary refill time

6. For adults with sepsis or septic shock, we suggest using dynamic measures to guide fluid resuscitation, over physical examination, or static parameters alone.	I
7. For adults with sepsis or septic shock, we suggest guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate.	I
8. For adults with septic shock, we suggest using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion.	I

HEMODYNAMIC CONSEQUENCES OF SEVERE METABOLIC ACIDOSIS IN SHOCK

- Severe lactic acidosis with pH ≤ 7.15 is detrimental to organ function
- In cardiac cells, intracellular drop in pH has considerable impact on the amplitude of the systolic calcium transient and subsequent excitation-contraction coupling pathway (desensitization of the ryanodine receptor and decreased calcium release by the sarcoplasmic reticulum, inhibition of the sarcoplasmic reticulum Ca^{2}+-ATPase)
- Drop in extracellular pH reduces the number of beta adrenergic receptors on myocardial cell surfaces (adrenoreceptor internalization)
- Lactic acidosis induces vascular smooth muscle relaxation via the opening of ATP-sensitive potassium channels and leads to the expression of inducible nitric oxide synthase

Kimmoun A, et al. Crit Care. 2015 Apr 9;19:175.

BICARBONATE USE FOR SEPSIS

- **BICAR- ICU** (Sodium bicarbonate therapy for patients with severe metabolic acidemia in the intensive care unit); Lancet 2018
- 389 patients in 26 French ICUs, included with metabolic acidosis (pH ≤ 7.20 and PaCO2 ≤ 45 and serum HCO3 ≤ 20) AND SOFA score ≥ 4 or lactate ≥ 2 randomized to receive 4.2% sodium bicarbonate (125 – 250 mL over 30 min per infusion; maximum 1000 mL within 24 hr) to target pH ≥ 7.3 vs. placebo
- Primary outcome: no statistically significant difference in composite of 28-day mortality or presence of at least one organ failure at 7 days (71% bicarbonate vs. 66% placebo, p = 0.24)
  - 28-day mortality: 45% bicarbonate vs 54% placebo, p = 0.07
  - Secondary outcome: reduction in RRT: 35% vs. 52%; p = 0.0009
  - Subgroup: patients with acute kidney injury: statistically significant difference in composite outcome: 70% vs 82%, p = 0.0462
    - Difference in 28-day mortality: 46% vs. 63%, p = 0.0166
- Conclusion: although bicarbonate therapy did not reduce mortality in this study, it did reduce the need for dialysis. Bicarbonate therapy did reduce mortality in the subgroup of patients with acute kidney injury.

Jaber S, et al. Lancet. 2018(392):10141:31-40.

2021 SEPSIS GUIDELINES

- Overall, the quality of the evidence is low and the new guidance is essentially unchanged from the 2016 recommendation
- When considering the subset of patients with septic shock, severe metabolic acidosis, and AKI, the balance of effects favors IV bicarbonate

Bicarbonate Therapy

Recommendations
71. For adults with septic shock and hypoperfusion-induced lactic acidemia, we **suggest against** using sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements. *Weak recommendation, low quality of evidence.*
72. For adults with septic shock, severe metabolic acidemia (pH ≤ 7.2) and AKI (AKIN score 2 or 3), we **suggest** using sodium bicarbonate therapy. *Weak recommendation, low quality of evidence.*

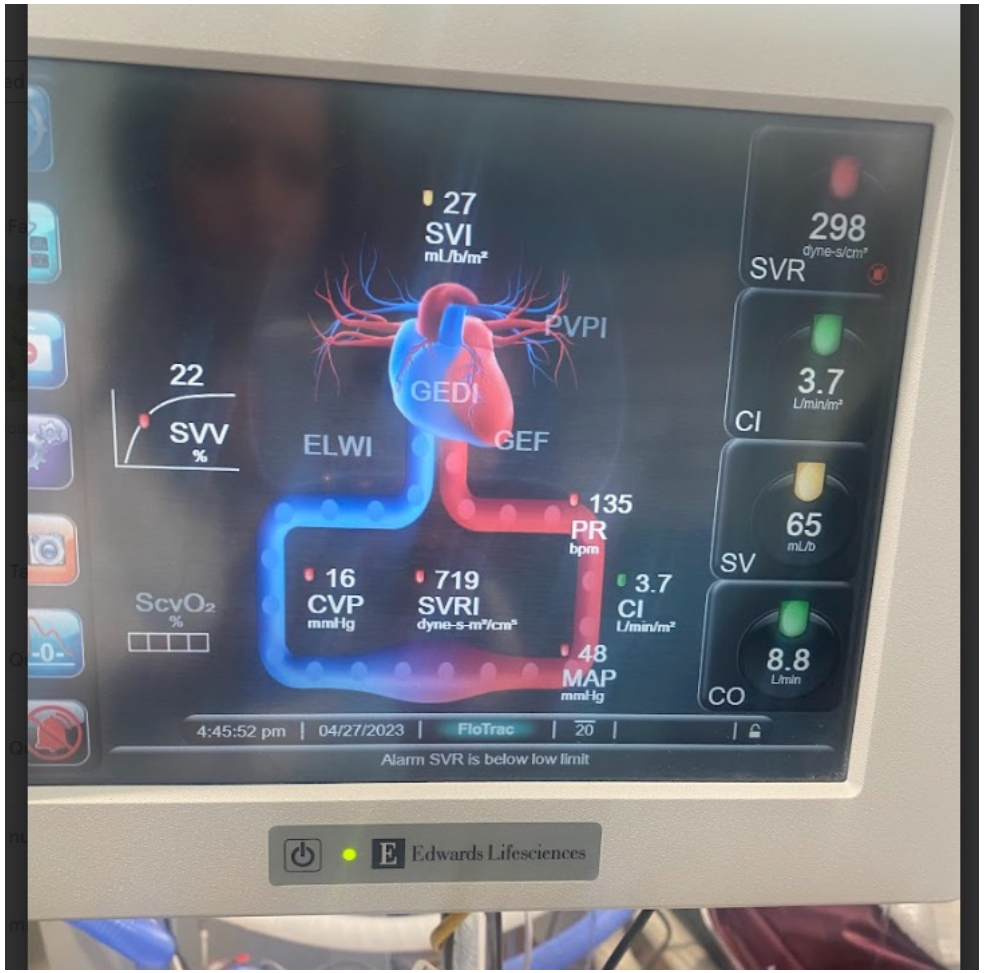
COMPONENTS OF EARLY GOAL-DIRECTED THERAPY

1. Broad-spectrum antibiotics
2. Fluid resuscitation
3. Vasopressors/ Inotropes
4. Corticosteroids

BASIC PRINCIPLES: TYPES OF SHOCK

Shock Type	Preload	Stroke Volume	Heart Rate	Cardiac Output	Systemic Vascular Resistance
Hypovolemic [Hemorrhage, Burn, Pancreatitis]	↓	↓	↑	↓/↔	↑
Cardiogenic [Post MI, HF]	↑	↓	↑	↓	↑
Distributive [Septic Shock, Anaphylaxis, Toxic Shock Syndrome, Adrenal Crisis, Neurogenic]	↓	↑/↔	↑	↑	↓

VIGILEO MONITOR EXAMPLE



Vigileo Monitor measures continuous cardiac output with used with the FloTrac Sensor. It can also measure stroke volume and stroke volume variation. Vigileo calculates the Systemic Vascular Resistance (SVR)

Hemodynamic Variable	Equation	Normal Value
Mean arterial Pressure (MAP)	1/3 SBP + 2/3 DBP	70 – 105 mmHg (goal in sepsis management > 65 mmHg)
Cardiac output (CO)	HR x SV/1000	4 – 8 L/min
Cardiac index (CI)	CO/BSA	2.5 – 4 L/min/m^2
Stroke volume (SV)	CO/HR x 1000	60 – 100 mL/beat
Stroke volume index (SVI)	CI/HR x 1000	33 – 47 mL/m2/beat
Stroke volume variation	100x(Svmax-Svmin)/meanSV	< 10 – 15%
Systemic vascular resistance (SVR)	MAP-RApx80/CO	800 – 1200 dynes/sec/cm-5
Systemic vascular resistance index	MAP-RAPx80/CI	1970-2390 dynes/sec/cm-5/m2

BASIC PRINCIPLES: DETERMINANTS OF BLOOD PRESSURE

MAP = CO x SVR

CO = HR x SV

- Preload
- Contractility
- Afterload

MAP = mean arterial pressure [MAP = 1/3 * SBP + 2/3 * DBP]
CO = cardiac output
SVR = systemic vascular resistance
HR = heart rate
SV = stroke volume

- Beta receptor:
  - β1: located mainly at the heart and kidneys → increase inotropy (force), chronotropy (heart rate), dromotropy (AV nodal conduction velocity), increase renin release from the kidney (activating renin-angiotensin system)
  - β2: located mainly in respiratory system and smooth muscle → vascular smooth muscle relaxation (vasodilation), bronchodilator activity

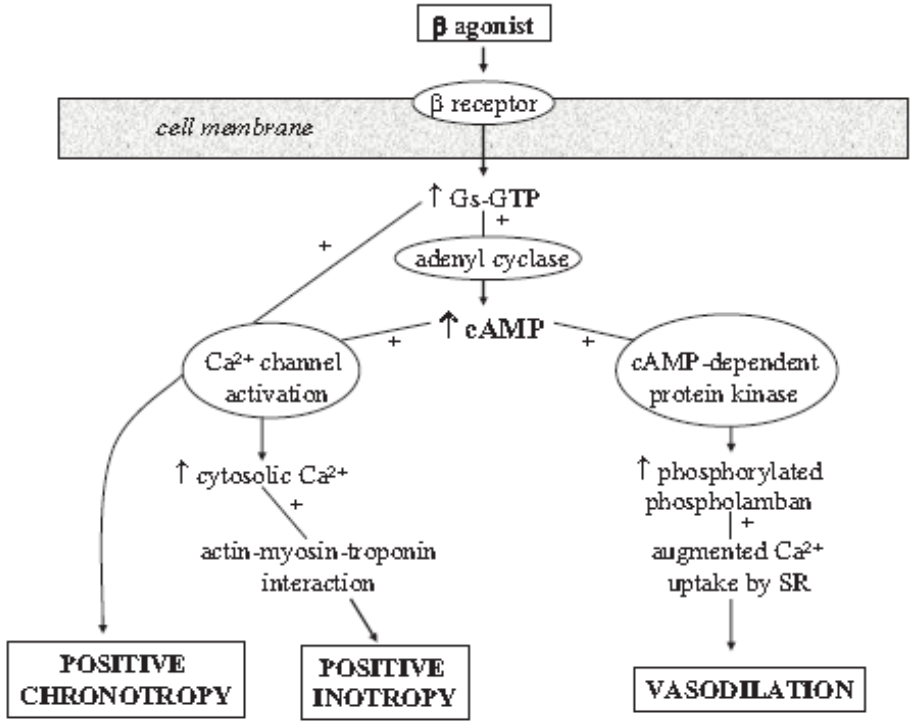


Figure 1. Simplified schematic of postulated intracellular actions of β-adrenergic agonists. β-Receptor stimulation, through a stimulatory Gs-GTP unit, activates the adenyl cyclase system, which results in increased concentrations of cAMP. In cardiac myocytes, β_1-receptor activation through increased cAMP concentration activates Ca^{2+} channels, which leads to Ca^{2+}-mediated enhanced chronotropic responses and positive inotropy by increasing the contractility of the actin-myosin-troponin system. In vascular smooth muscle, β_2-stimulation and increased cAMP results in stimulation of a cAMP-dependent protein kinase, phosphorylation of phospholamban, and augmented Ca^{2+} uptake by the sarcoplasmic reticulum (SR), which leads to vasodilation. Adapted from Gillies et al[3] with permission of the publisher.

Overgaard CB, et al. Circulation. 2008 Sep 2;118(10):1047-56.

- Alpha Receptor:

- Alpha-adrenergic agonists (a-agonists) bind to a-receptors on vascular smooth muscle and *induce smooth contraction* and *vasoconstriction*
- Primary effects:
  - Vascular = vasoconstriction
  - Cardiac = reflex bradycardia

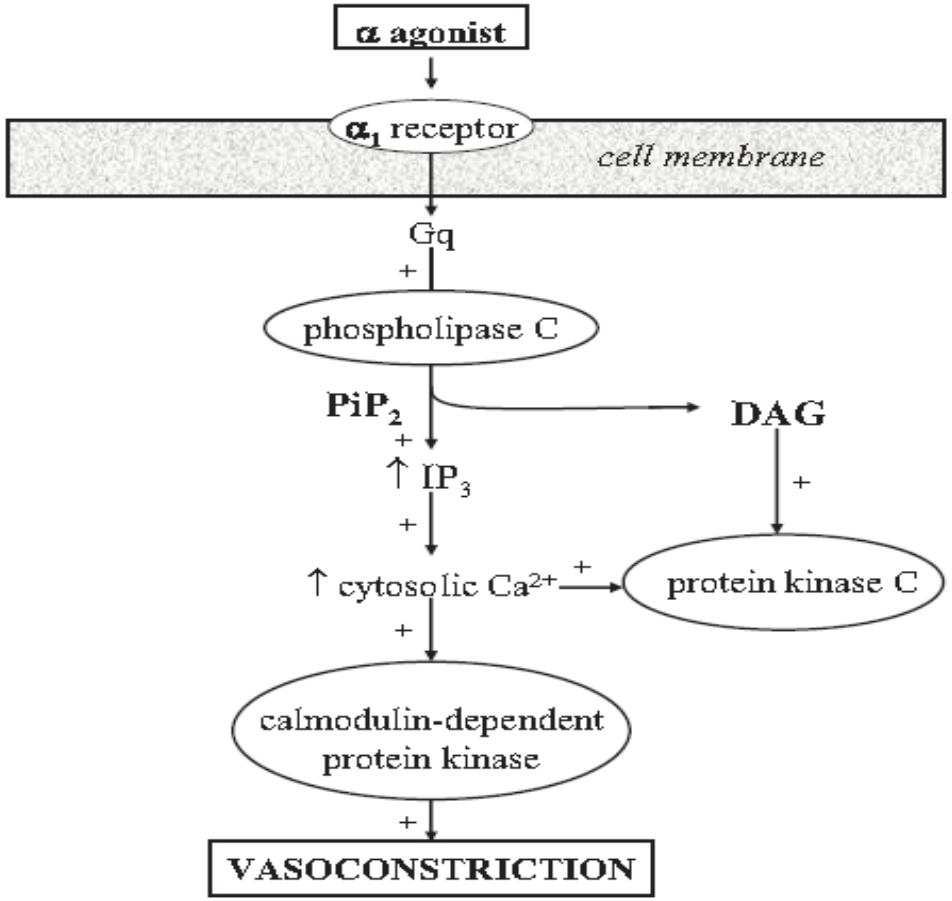
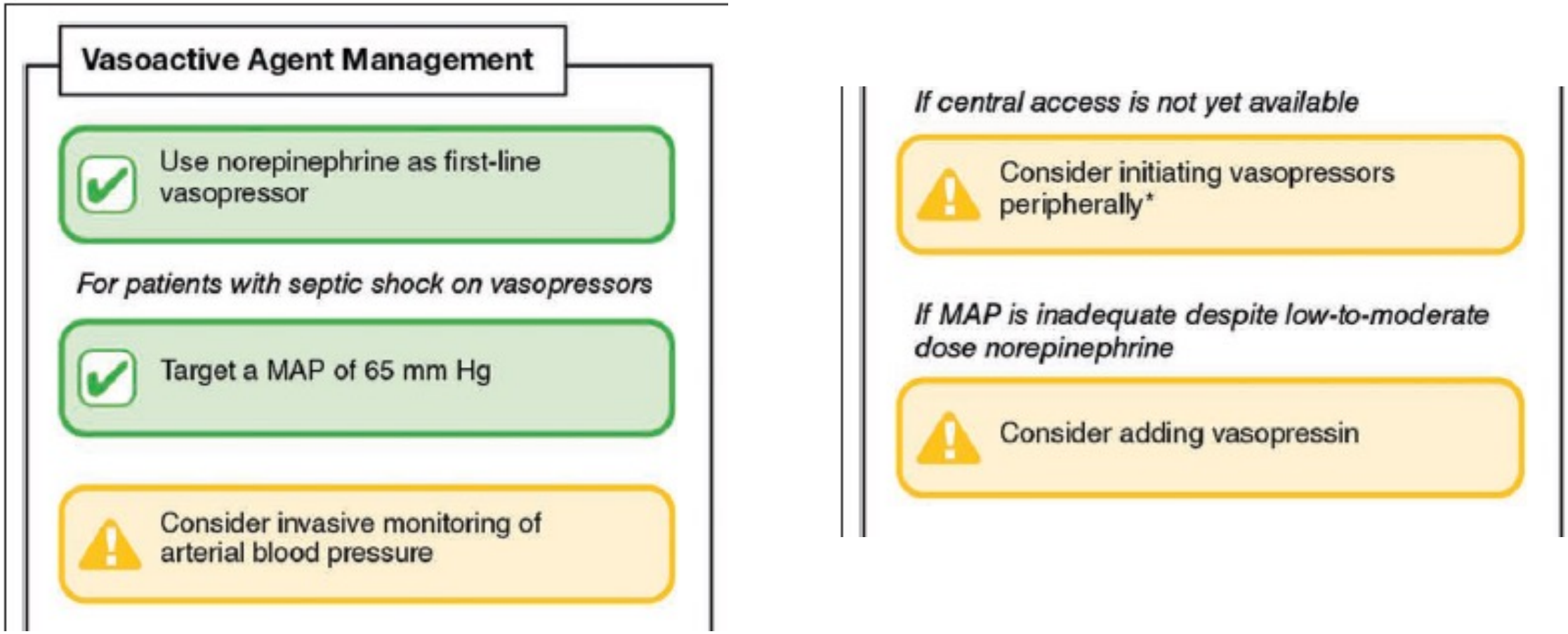


Figure 2. Schematic representation of postulated mechanisms of intracellular action of α_1-adrenergic agonists. α_1-Receptor stimulation activates a different regulatory G protein (Gq), which acts through the phospholipase C system and the production of 1,2-diacylglycerol (DAG) and, via phosphatidyl-inositol-4,5-biphosphate (PiP_2), of inositol 1,4,5-triphosphate (IP_3). IP_3 activates the release of Ca^{2+} from the sarcoplasmic reticulum (SR), which by itself and through Ca^{2+}-calmodulin–dependent protein kinases influences cellular processes, leading in vascular smooth muscle to vasoconstriction. Adapted from Gillies et al[3] with permission of the publisher.

Overgaard CB, et al. Circulation. 2008 Sep 2;118(10):1047-56.

2021


Vasoactive Agent Management
Use norepinephrine as first-line vasopressor
For patients with septic shock on vasopressors
Target a MAP of 65 mm Hg
Consider invasive monitoring of arterial blood pressure
If central access is not yet available
Consider initiating vasopressors peripherally*
If MAP is inadequate despite low-to-moderate dose norepinephrine
Consider adding vasopressin

Norepinephrine: MCHS standard concentration = 8 mg in 250 mL NS

NOREPINEPHRINE (LEVOPHED®)

- Mechanism of action:
  - Catecholamine which is a potent vasoconstrictor and also increases heart rate and contractility
  - Acts primarily as alpha-1 agonist but also stimulates beta receptors
  - Clinically, alpha effects much greater than beta effects
- Clinical use: first-line for septic shock
  - Usual dose: 1 – 50 mcg/min (0.01 – 1 mcg/kg/min)
- Major side effects: Tachyarrhythmias, peripheral ischemia, tissue necrosis with extravasation

NOREPINEPHRINE EPIC ORDER

norepinephrine (LEVOPHED) infusion 8 mg/250 mL (premix)

0.01-0.99 mcg/kg/min × 82.5 kg (1.5469-153.1406 mL/hr, rounded to 1.55-153.14 mL/hr), intravenous, Continuous, Starting today at 1800

GOAL EFFECT: SBP GREATER than 90 mmHg or MAP GREATER than 65 mmHg

INITIAL RATE: 0.01 mcg/kg/min

USUAL DOSE RANGE: 0.01 - 0.99 mcg/kg/minute

TITRATION DOSE: 0.02 mcg/kg/minute

TITRATION FREQUENCY: 5 min

CONTACT PRESCRIBER:

- -HR LESS than 60 BPM
- -HR GREATER than 120 BPM
- -SBP LESS than 80 mmHg
- -SBP GREATER than 140 mmHg

Individual cases may require deviation from parameters (with prescriber approval)

premix bag

EPINEPHRINE

Epinephrine: MCHS standard concentration = 5 mg in NS 250 mL

- Mechanism of action:
  - Potent beta and alpha adrenergic agonist
- Clinical uses: Septic shock, cardiogenic shock, cardiac arrest, bronchospasm, anaphylaxis, heart block unresponsive to atropine
  - Usual dose: 1 – 10 mcg/min (0.01 – 0.5 mcg/kg/min)
- Major side effects: Ventricular arrhythmias, cardiac ischemia, sudden cardiac death, tissue necrosis with extravasation
- Note: produces hyperlactatemia (increases aerobic lactate production via stimulation of skeletal muscle beta-2 adrenergic receptors)

EPINEPHRINE IN EPIC

EPINEPHrine (ADRENALIN) 5 mg in sodium chloride 0.9 % 250 mL infusion

0.01-0.5 mcg/kg/min × 82.5 kg (2.475-123.75 mL/hr, rounded to 2.48-123.75 mL/hr), intravenous, Continuous, Starting today at 1800

GOAL EFFECT: SBP GREATER than 90 mmHg or MAP GREATER than 65 mmHg

INITIAL RATE: 0.01 mcg/kg/min

USUAL DOSE RANGE: 0.01 - 0.5 mcg/kg/min

TITRATION DOSE: 0.01 mcg/kg/min

TITRATION FREQUENCY: 5 min

CONTACT PRESCRIBER:

- -HR LESS than 60 BPM
- -HR GREATER than 120 BPM
- -SBP LESS than 80 mmHg
- -SBP GREATER than 140 mmHg

Individual cases may require deviation from parameters (with prescriber approval)

DOPAMINE

- Mechanism of action = Dose-dependent effects:
  - 1 - 3 mcg/kg/min: dopaminergic
  - 3 -10 mcg/kg/min: Beta-1 and dopaminergic
  - > 10 mcg/kg/min: Alpha-1/beta
- Clinical uses: alternative therapy for septic shock, only in highly selected patients (i.e. patients with low risk of tachyarrhythmias and absolute or relative bradycardia)
- Major side effects: Atrial and ventricular arrhythmias, tissue ischemia/gangrene (at high doses or due to extravasation), cardiac ischemia

Pre-mixed bag: Dopamine 400 mg in D5W 250 [final concentration = 1600 mcg/mL]

PHENYLEPHRINE

- Mechanism of action: pure alpha-1 agonist (vasoconstriction)
- Clinical uses: Hypotension (vagally mediated, medication-induced), salvage therapy in septic shock
  - Usual dose: 10 – 200 mcg/min
- Major side effects: Peripheral and visceral vasoconstriction, tissue necrosis with extravasation

phenylephrine (NEO-SYNEPHRINE) infusion

phenylephrine (NEO-SYNEPHRINE) 20 mg in sodium chloride 0.9 % 250 mL infusion

0.4-5 mcg/kg/min × 82.5 kg (24.75-309.375 mL/hr, rounded to 24.8-309.4 mL/hr), intravenous, Continuous, Starting today at 1800
GOAL EFFECT: SBP GREATER than 90 mmHg or MAP GREATER than 65 mmHg
INITIAL RATE: 0.4 mcg/kg/min
USUAL DOSE RANGE: 0.4-5 mcg/kg/min
TITRATION DOSE: 0.1 mcg/kg/min
TITRATION FREQUENCY: 5 min
CONTACT PRESCRIBER:
-HR LESS than 60 BPM
-HR GREATER than 120 BPM
-SBP LESS than 80 mmHg
-SBP GREATER than 140 mmHg

Individual cases may require deviation from parameters (with prescriber approval)

Vasopressin: MCHS standard concentration: 20 units in NS 50 mL

VASOPRESSIN

- Mechanism of action: Antidiuretic hormone analog with direct vasoconstriction without inotropic or chronotropic effects
- Clinical use: only FDA labeled indication is central diabetes insipidus but is used off label for other indications including <u>septic shock</u>
  - When utilized for septic shock, vasopressin is used in combination with another vasopressor never as monotherapy
  - <u>Usual dose</u>: 0.03 units/minute
- Major side effects: Severe peripheral vasoconstriction at high doses, mesenteric ischemia, splanchnic vasoconstriction, arrhythmia (asystole > 0.04 units/min), decreased cardiac output, vesicant (extravasation may cause localized tissue necrosis)

VASOPRESSIN IN EPIC

Vasopressors

vasopressin (VASOSTRICT) 20 Units in sodium chloride 0.9 % 50 mL (0.4 Units/mL) infusion

0.03 Units/min (4.5 mL/hr), intravenous, Continuous, Starting today at 1815

DO NOT TITRATE

VASOPRESSOR COMPARISON

Drug	Clinical Indication	Dose Range		α1	β1	β2	DA	HR	MAP	CI	SVR	Major Side Effects
Vasopressors												
Norepinephrine (Levophed®) 16 mg/250 mL α1/β1 agonist	Septic shock First line sepsis	Usual dose range: 1 – 50 mcg/min		++++	+++	0	NA	↑	↑↑	↔	↑↑	Tachyarrhythmias, peripheral (digital) ischemia, tissue necrosis with extravasation
Phenylephrine (NeoSynephrine®) 50 mg/250 mL α1 agonist	Hypotension (vagally mediated, medication-induced), salvage therapy septic shock Not first line for sepsis unless patient too tachycardic to tolerate NE/Epinephrine	Usual dose range: 10 - 200 mcg/min **Maximum rate:** 200 mcg/min		++++	0	0	NA	↔	↑	↔	↑	Peripheral and visceral vasoconstriction, tissue necrosis with extravasation
Epinephrine 5 mg/250 mL α1/ β1/ β2 agonist	Septic shock, cardiogenic shock, cardiac arrest, bronchospasm, anaphylaxis, heart block unresponsive to atropine Second line sepsis; add on to norepinephrine	Usual dose range: 1 – 10 mcg/min **Maximum rate:** 30 mcg/min		+++	++++	+++	NA	↑↑	↑↑	↑↑	↑	Ventricular arrhythmias, cardiac ischemia, sudden cardiac death, tissue necrosis with extravasation, hyperlactatemia
Dopamine premix DA/ β1 agonist	2nd line septic shock, symptomatic bradycardia unresponsive to atropine Not first choice for sepsis unless patient is bradycardic	Usual dose range: 2.5 – 10 mcg/kg/min **Maximum rate:** 40 mcg/kg/min	1 – 3 mcg/kg/min: dopaminergic	0	+	0	++++	↔	↔	↔	↔	Atrial and ventricular arrhythmias, tissue ischemia/gangrene (at high doses due to extravasation), cardiac ischemia
			3 – 10 mcg/kg/min: β1 and dopaminergic	0/+	+++	++	++++	↑	↑	↑	↔	
			> 10 mcg/kg/min: α1/beta	+++	++++	+	0	↑↑	↑	↑	↑	
Vasopressin (Pitressin®) 20 units/100 mL V1 agonist	Septic shock: adjunctive therapy only; never monotherapy	Usual dose 0.03 units/min **Maximum rate:** 0.03 units/min		Vasopressin-1 peripheral receptors (Note: effective even in acidodic environment when catecholamines may be less effective)				↔	↑	↔	↑	Severe peripheral vasoconstriction at high doses, splanchnic vasoconstriction, arrhythmia (asystole > 0.04 units/min), decreased cardiac output, vesicant (extravasation may cause localized tissue necrosis)
Inotropes												
Dobutamine (Dobutrex®) premix β agonist	Low cardiac output states (decompensated HF, cardiogenic shock, sepsis-induced myocardial dysfunction), symptomatic bradycardia unresponsive to atropine	Usual dose range: 2 – 20 mcg/kg/min Higher risk of toxicity with rates > 20 mcg/kg/min **Maximum rate:** 40 mcg/kg/min		+	++++	+++	NA	↑↑	↔ ↑ ↓	↑	↓	Ventricular arrhythmias, cardiac ischemia, hypotension (due to beta 2 agonist activity on vasculature)
Milrinone (Primacor®)	Low cardiac output (decompensated HF)	Usual dose range: 0.125 – 0.75 mcg/kg/min **Maximum rate:** 0.75 mcg/kg/min		Phosphodiesterase inhibitor				↑↑	↔ ↑ ↓	↑	↓↓	Hypotension (especially with bolus doses), ventricular arrhythmias, cardiac ischemia

2021 SEPSIS GUIDELINES

37. For adults with septic shock, we recommend using norepinephrine as the first-line agent over other vasopressors.

38. For adults with septic shock on norepinephrine with inadequate mean arterial pressure levels, we suggest adding vasopressin instead of escalating the dose of norepinephrine.

39. For adults with septic shock and inadequate mean arterial pressure levels despite norepinephrine and vasopressin, we suggest adding epinephrine.

44. For adults with septic shock, we suggest starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured.

WHY IS NOREPINEPHRINE FIRST LINE?

- **SOAP II study**: Comparison of dopamine and norepinephrine in the treatment of shock, NEJM 2010
  - 1,689 patients requiring vasopressor support for shock despite fluid challenge (60% septic, 20% cardiogenic, 15% hypovolemic) randomized to receive dopamine or norepinephrine
  - Primary outcome: 28-day mortality was not different between the two groups (52.5% vs 48.5%, p = 0.1); no difference in secondary outcomes: ICU or hospital length of stay, 6 and 12-month mortality
  - Dopamine group had more arrhythmias, mostly atrial fibrillation, compared to norepinephrine (24.1% vs. 12.4%, p< 0.001)
  - Pre-specified subgroup of cardiogenic shock showed higher 28-day mortality with dopamine (p = 0.03)

De Backer D, Biston P, Devriendt J, et al. N Engl J Med 2010 Mar 4;362(9):779-89.

NOREPINEPHRINE VS DOPAMINE IN SEPTIC SHOCK

- Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis: meta-analysis of 11 randomized trials (n=1,710) comparing norepinephrine to dopamine for treatment of septic shock

- Results: Norepinephrine use resulted in lower mortality (RR 0.89, 95% CI 0.81-0.98) and lower risk of arrhythmia (RR 0.48; 95% CI 0.4 – 0.58)

- Conclusion: norepinephrine is preferred for first-line treatment in septic shock over dopamine because it may be associated with reduced mortality (it is a more potent vasopressor and less arrhythmogenic)

Avni T, et al. PLoS One 2015;10:e129305.

VASOPRESSIN IN SEVERE SEPSIS

- Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state (*relative physiologic deficiency*)
- Physiologic vasopressin replacement (low dose continuous infusion) may be effective in raising blood pressure in patients refractory to other vasopressors
- Vasopressin may be useful for:
  - Patients requiring high dose norepinephrine > 10 - 15 mcg/min (> 0.2 mcg/kg/min)
  - Patients who develop tachyarrhythmias on norepinephrine (may be norepinephrine sparing)
  - Extremely acidotic patients (vasopressin activity not inactivated by low pH)

Rhodes A, Evans LE, Alhazzani W, et al. Crit Care Med. 2017 Jan 17. [Epub ahead of print]

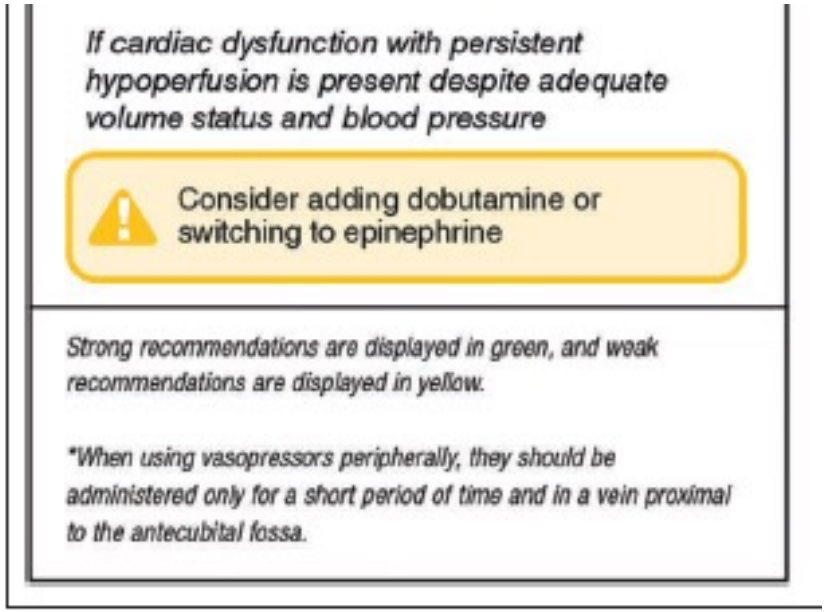
VASOPRESSIN IS NOREPINEPHRINE SPARING

- **VASST study** (Vasopressin vs additional norepinephrine for septic shock), NEJM 2008
- 778 patients with septic shock requiring at least 5 mcg/min norepinephrine or equivalent randomized to additional norepinephrine or vasopressin 0.01 – 0.03 units/min
- Results: no difference in primary outcome 28-day mortality: 35.4% NE vs. 39.3% vasopressin, p = 0.26)
- Subgroup: lower severity (baseline NE 5 – 14 mcg/min) had trend towards lower 28-day mortality (NE 35.7% vs 26.5%, p = 0.05)
- Conclusion: this study demonstrated that although the addition of vasopressin did not improve mortality compared to increasing norepinephrine, it proved to be a catecholamine-sparing option

Russel JA, et al. NEJM. 2008: 358(9):877-887.

2021

- Sepsis-induced myocardial dysfunction may be a major contributor to the hemodynamic instability in some patients
- Myocardial dysfunction consequent to infection occurs in a subset of patients with septic shock, but cardiac output is usually preserved by ventricular dilation, tachycardia, and reduced vascular resistance
- Some portion of these patients may have diminished cardiac reserve and may not be able to achieve a cardiac output adequate to support oxygen delivery
- Inotropic therapy can be used in patients with persistent hypoperfusion after adequate resuscitation who demonstrate myocardial dysfunction based on suspected or measured low CO and elevated cardiac filling pressures



Recommendations

41. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we **suggest** either adding dobutamine to norepinephrine or using epinephrine alone.

Weak recommendation, low quality of evidence.

DOBUTAMINE

- Mechanism: dobutamine is works as an inotrope → non-selective beta agonist resulting in increased contractility and heart rate (some alpha 1 stimulation but overcome by beta-2 activation by offsetting effects)
- Adverse effects: ventricular arrhythmias, cardiac ischemia, hypotension
  - Hypotension may occur due to beta-2 agonism which results in vasodilatation which may be desired in cardiogenic shock when cardiac index is low and systemic vascular resistance is high → so inotrope with ability to reduce afterload is desired. However, in septic shock (distributive) decision to use dobutamine may be detrimental when attempt to increase MAP is not considering the underlying cause (i.e. if SVR is too low and cardiac output is not the problem, in which case patient may experience tachycardia and worsening hypotension if dobutamine is added)

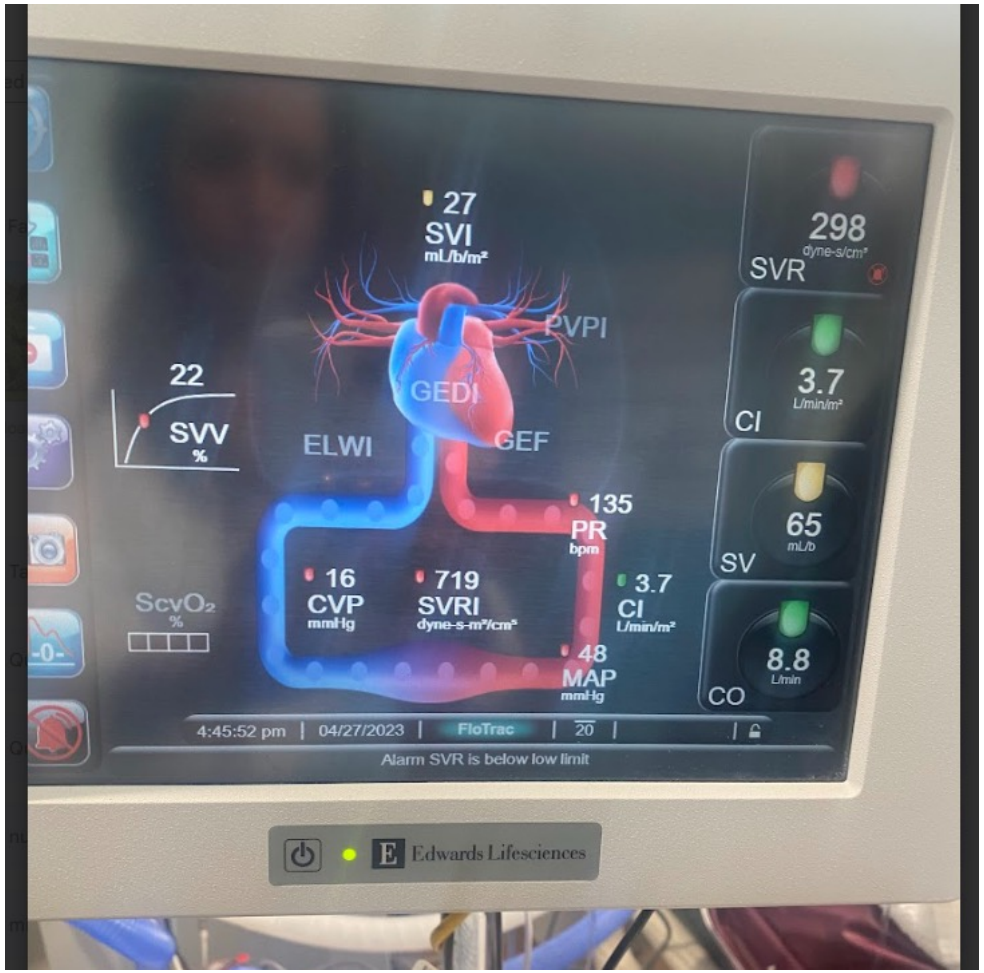
DOBUTAMINE

New Orders

Inotropes

DOBUTamine (DOBUTREX) 500 mg in dextrose 5% 250 mL (2 mg/mL) infusion (premix)
2-10 mcg/kg/min × 63.2 kg (3.792-18.96 mL/hr, rounded to 3.79-18.96 mL/hr), intravenous, Continuous, Starting today at 1145
GOAL EFFECT FOR SEPSIS: Hemodynamic goal (per prescriber) ***
INITIAL RATE: 2 mcg/kg/min
DOSE RANGE: 2-10 mcg/kg/min
TITRATION DOSE: 2 mcg/kg/min
TITRATION FREQUENCY: 5 minutes
CONTACT PRESCRIBER: HR less than 60 or greater than 120 BPM; SBP less than 80 or greater than 180 mmHg. Individual cases may require deviation from parameters

VIGILEO MONITOR EXAMPLE



Vigileo Monitor measures continuous cardiac output with used with the FloTrac Sensor. It can also measure stroke volume and stroke volume variation. Vigileo calculates the Systemic Vascular Resistance (SVR)

Hemodynamic Variable	Equation	Normal Value
Mean arterial Pressure (MAP)	1/3 SBP + 2/3 DBP	70 – 105 mmHg (goal in sepsis management ≥ 65 mmHg)
Cardiac output (CO)	HR x SV/1000	4 – 8 L/min
Cardiac index (CI)	CO/BSA	2.5 – 4 L/min/m^2
Stroke volume (SV)	CO/HR x 1000	60 – 100 mL/beat
Stroke volume index (SVI)	CI/HR x 1000	33 – 47 mL/m2/beat
Stroke volume variation	100x(Svmax-Svmin)/meanSV	< 10 – 15%
Systemic vascular resistance (SVR)	MAP-RApx80/CO	800 – 1200 dynes/sec/cm-5
Systemic vascular resistance index	MAP-RAPx80/CI	1970-2390 dynes/sec/cm-5/m2

COMPONENTS OF EARLY GOAL-DIRECTED THERAPY

1. Broad-spectrum antibiotics
2. Fluid resuscitation
3. Vasopressors/ Inotropes
4. Corticosteroids

STEROID COMPARISON

Steroid	Equivalent Dose	Glucocorticoid	Mineralocorticoid	Biologic half-life
Methylprednisolone	4 mg	4	0.5	18 – 36 hr
Prednisone	5 mg	4	0.8	18 – 36 hr
Hydrocortisone	20 mg	1	1	8 - 12 hr
Dexamethasone	0.75 mg	25	0	36 - 54 hr
Fludrocortisone	(0.05 mg)	Not used as anti-inflammatory (10)	125	18 – 36 hr

STEROIDS IN SEPTIC SHOCK

2002

Annane: (99 pts) **improvement in 28-day mortality in septic shock** ACTH non-responders (53% HC vs 63% placebo, p = 0.04). Faster resolution of shock.

Dose: HC 50 mg IV q6 hr plus FC 50 mcg PO daily x 7 days

2008

CORTICUS (499 pts): no difference in 28-day mortality in septic shock ACTH non-responders; but **overall faster resolution of shock in regardless of ACTH response** 3.3 vs 5.8 days (p < 0.001)

Dose: HC 50 mg IV q6 hr x 5 days then taper, 50 mg IV q12 hr x 3 days, then 50 mg IV q24 hr x 3 days

2016

HYPRESS: (353 pts) HC does not prevent the development of shock within 14 days in patients with sepsis.

Dose: HC 50 mg IV bolus, followed by 200 mg/day continuous infusion x 5 days then taper

2018

ADRENAL: (3,658 pts) no difference in 90-day mortality **but faster resolution of shock** (3 days vs 4 days (p < 0.01)

Dose: HC 200 mg/day continuous infusion x 7 days

APROCCHSS: (1,241 pts) **improvement in 90-day mortality** (43% vs 49.1%, p = 0.03; NNT = 17) and vasopressor free days

Dose: HC 50 mg IV q6hr plus FC 50 mcg PO daily x 7 days

SUMMARY OF TRIALS: STEROIDS IN SEPSIS

Trial	Hydrocortisone Dose	Taper	Fludrocortisone Use	Mortality Benefit
Annane, et al (French study)	**Bolus**	**No**	**Yes**	**Yes**
CORTICUS	Bolus	Yes	No	No
HYPRESS	Continuous Infusion	Yes	No	N/A
ADRENAL 2018	Continuous Infusion	No	No	No
APROCCHSS 2018	**Bolus**	**No**	**Yes**	**Yes**

STEROIDS YES OR NO?

- A patient diagnosed with urosepsis, who has been volume resuscitated and initially started on norepinephrine and now weaning off; current rate 2 mcg/min → NO
- A patient diagnosed with urosepsis who despite volume resuscitation and vasopressor initiation is requiring dose escalation and is having evidence of end-organ dysfunction → YES
- A patient diagnosed with pneumonia with history of COPD on home prednisone 20 mg daily for months; given fluid bolus and is requiring low dose norepinephrine 4 mcg/min → YES

2021 SEPSIS GUIDELINES

ADDITIONAL THERAPIES

Corticosteroids

Recommendation
58. For adults with septic shock and an ongoing requirement for vasopressor therapy we **suggest** using IV corticosteroids.
Weak recommendation; moderate quality of evidence.
Remarks:
The typical corticosteroid used in adults with septic shock is IV hydrocortisone at a dose of 200 mg/d given as 50 mg intravenously every 6 hours or as a continuous infusion. It is suggested that this is commenced at a dose of norepinephrine or epinephrine ≥ 0.25 mcg/kg/min at least 4 hours after initiation.

BOTTOM LINE

- Heterogeneity in sepsis and septic shock make it complicated to apply RCT data directly to individual patients
- Patients with suspected infection should be screened using clinical judgment and multiple tools such as SIRS or qSOFA score instead of any single tool and assessed for organ dysfunction
- Early empiric broad spectrum antibiotics within 1 hour (find the source)
- Initial fluid resuscitation with balanced crystalloids
- Start norepinephrine if MAP still ≤ 65 mmHg → add vasopressin if levophed dose escalating
- Septic shock patients should receive stress dose steroids (hydrocortisone 50 mg IV q6hr) (refractory to fluids and pressors)

QUESTIONS