DEBUGGING SEPSIS

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DISCLOSURES

1. I have no relevant financial or commercial interests.
2. Off label use of products denoted by †
3. Our understanding of sepsis and its best treatment is continuing to change rapidly.

OBJECTIVES

Describe the pathophysiology of sepsis

Recognize sepsis early and initiate appropriate therapy quickly

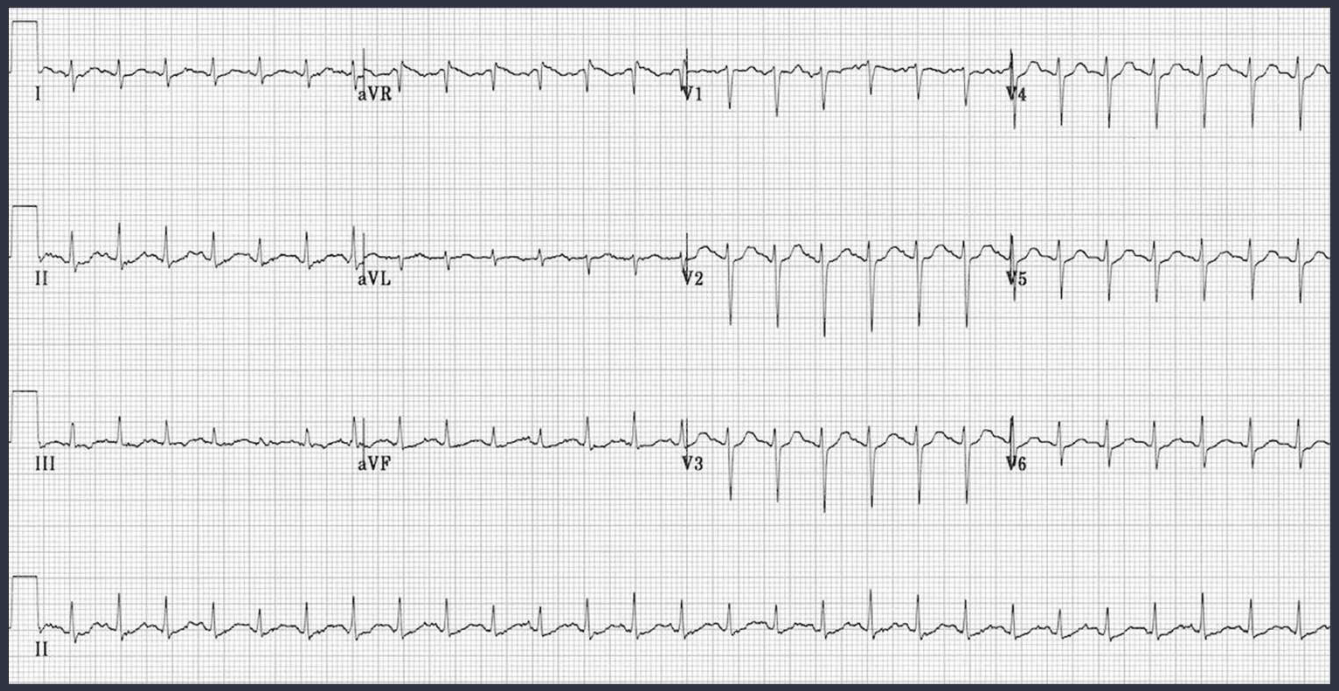
Discuss novel approaches to sepsis treatment

CASE PRESENTATION

- A 68yo M with a hx of HTN, HLD, and alcohol abuse presented to the ED via EMS with abdominal pain.
- He was drowsy, confused, peripherally cold, and cyanotic. His BP was 75/50 with a HR of 125 BPM.
- What next?

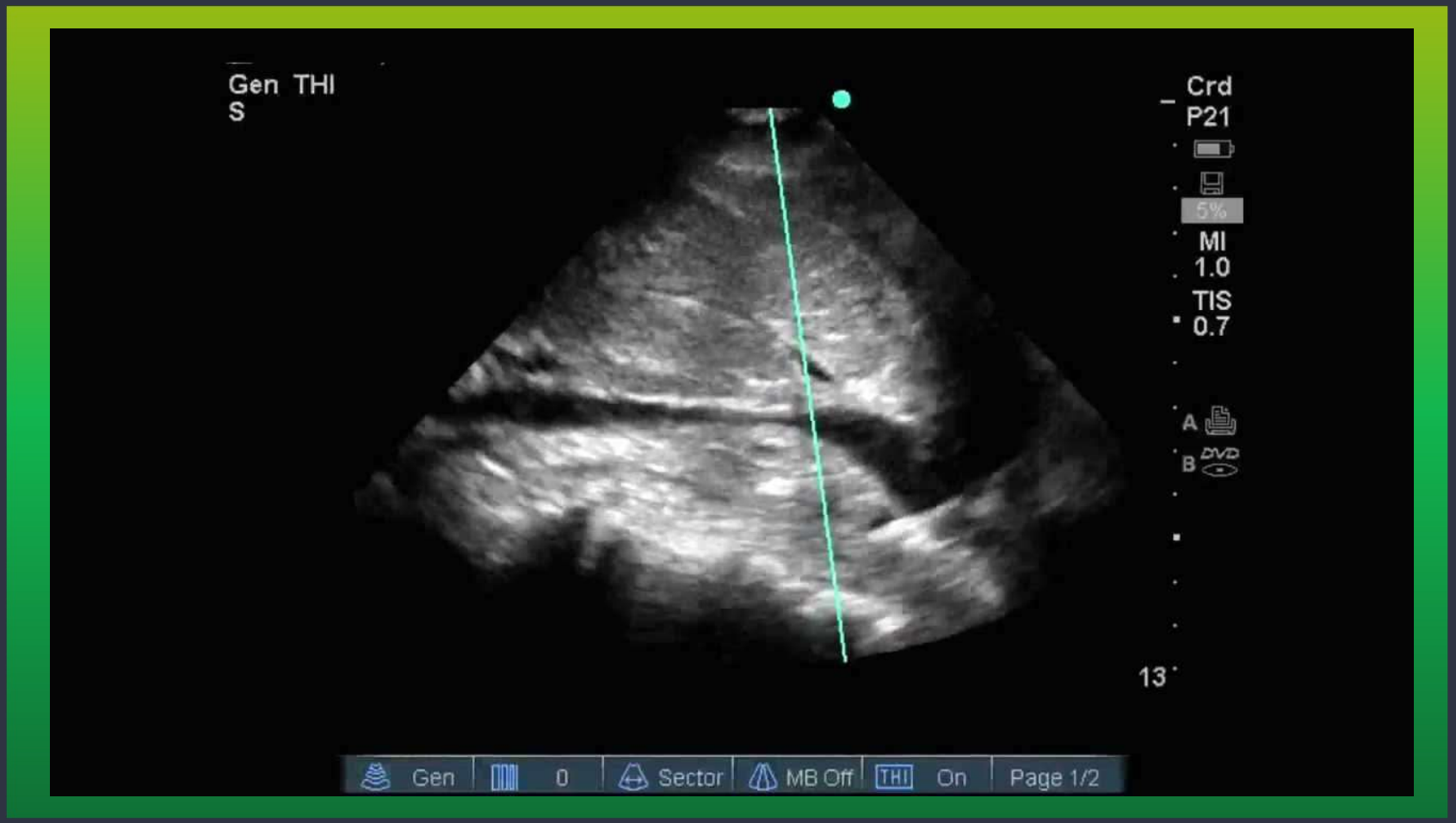
E.D. COURSE

- His abdomen was tight and distended and an EKG showed:

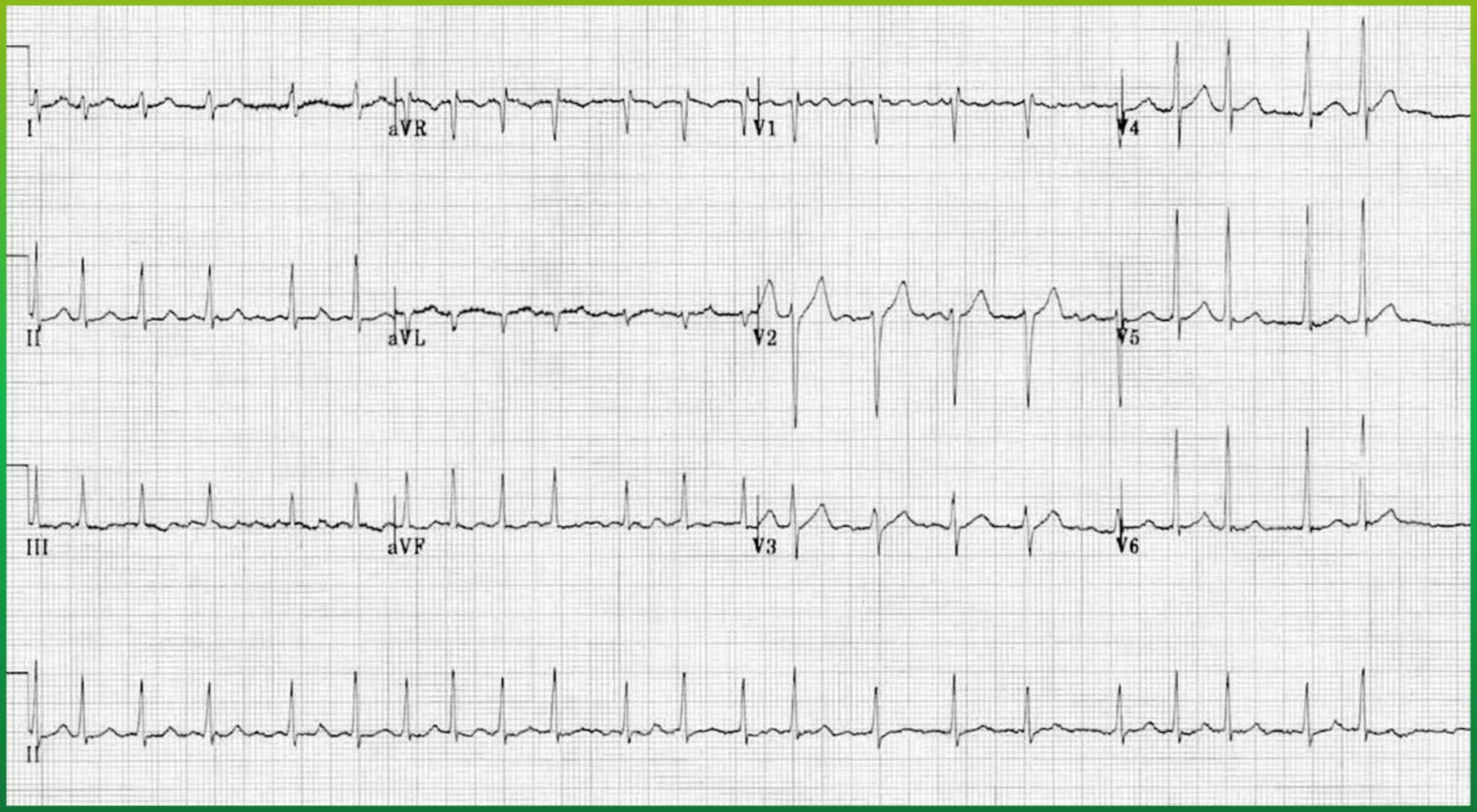


- He received 1L of NS and a CT of the abdomen showed extraluminal gas & free fluid consistent with a perforated sigmoid colon.

BEDSIDE ULTRASOUND



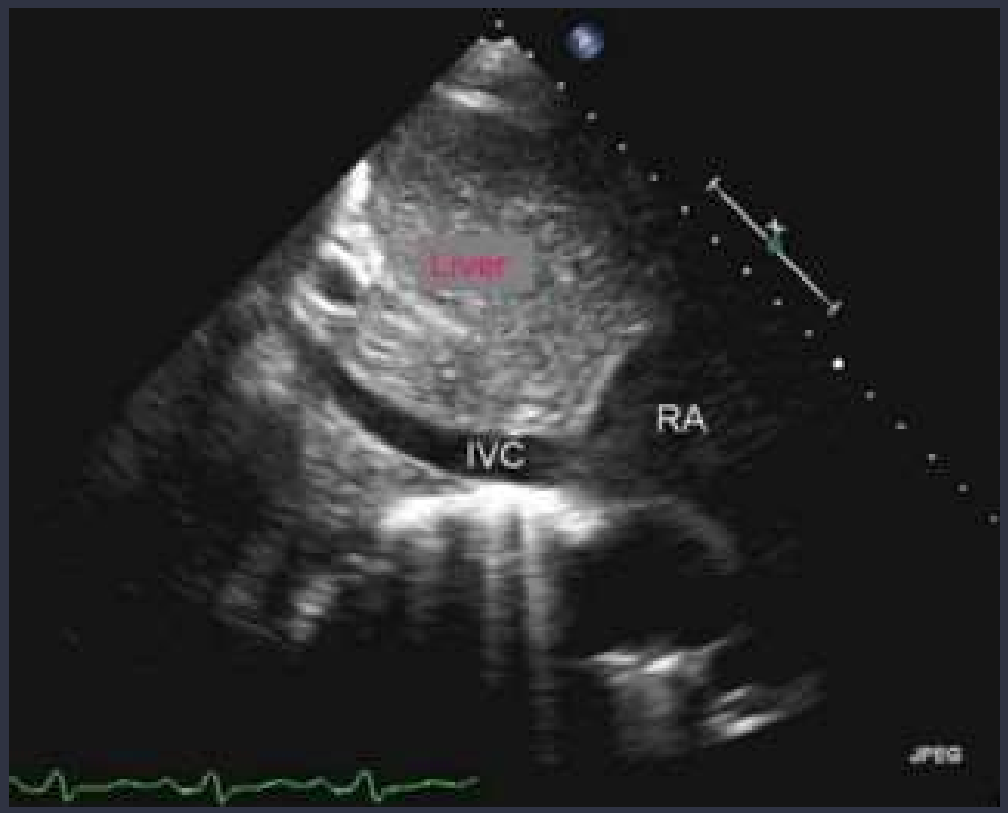
During laparotomy, gross fecal peritonitis from a perforated sigmoid colon was confirmed. Resection of the sigmoid colon with closure of the rectal stump and creation of an end colostomy was performed with extensive peritoneal washout. He was transferred to the ICU intubated and still under anesthesia with FiO_2 of 0.4.


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

- Blood pressure 88/52 mmHg
- CVP 7 mmHg
- Temperature 35.6˚
- ABG pH 7.22 with pCO_2 25
- WBC 15k
- Lactate 3.0 mmol/L

- Diagnosis?

BEDSIDE ULTRASOUND



TREATMENT

Fluids?	Antibiotics?	Sodium bicarbonate?	Beta-blocker?
Calcium channel blocker?	Mechanical device?	Steroids?	Vitamin C?
Thiamine?	Statin?	Vasopressors?	Inotropes?

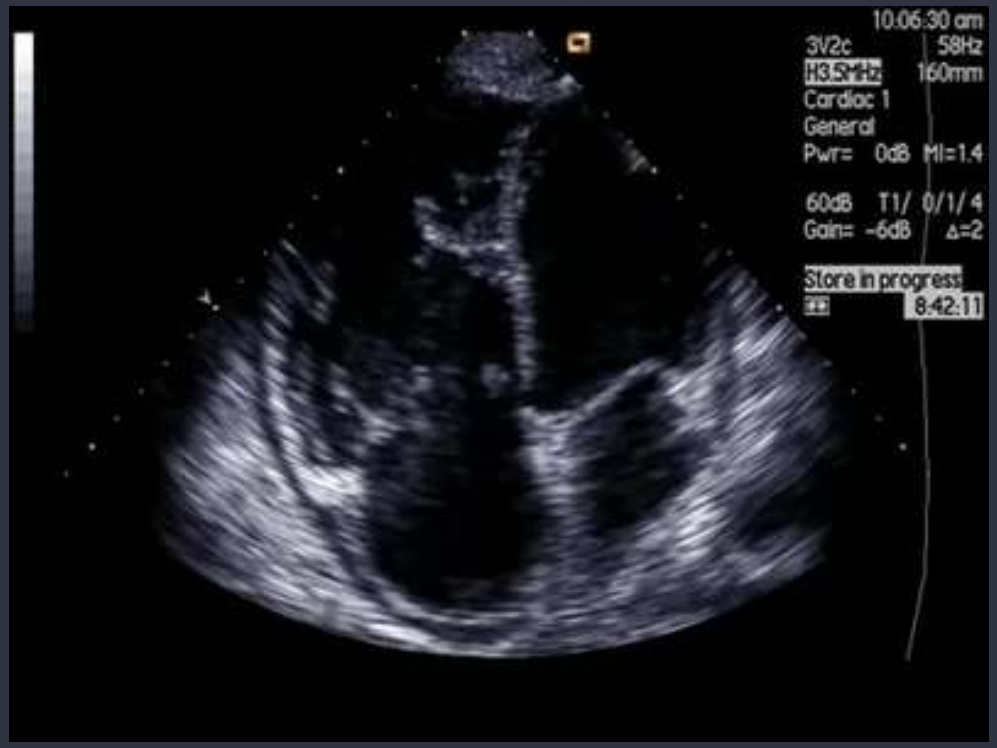
NOW WHAT?

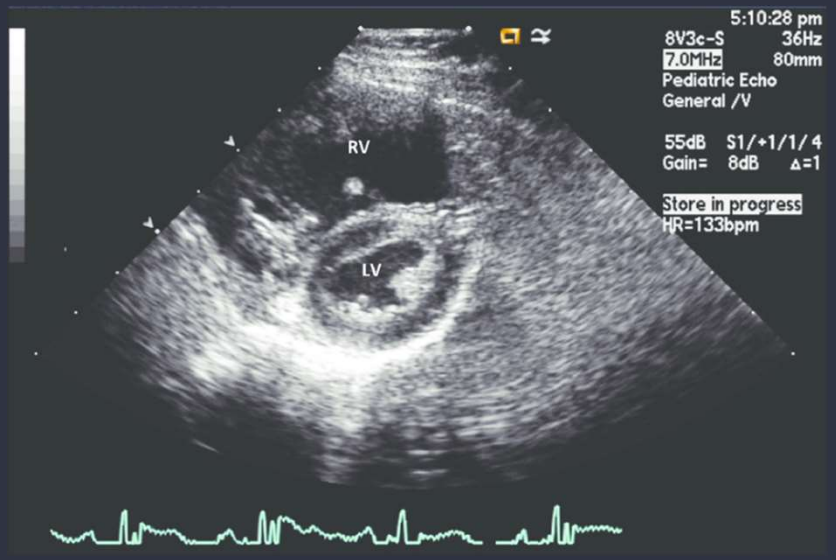
He’s treated with broad spectrum antibiotics, vasopressors, and is successfully weaned off mechanical ventilation over the course of three days. He’s transferred to the floor and suddenly develops shortness of breath.

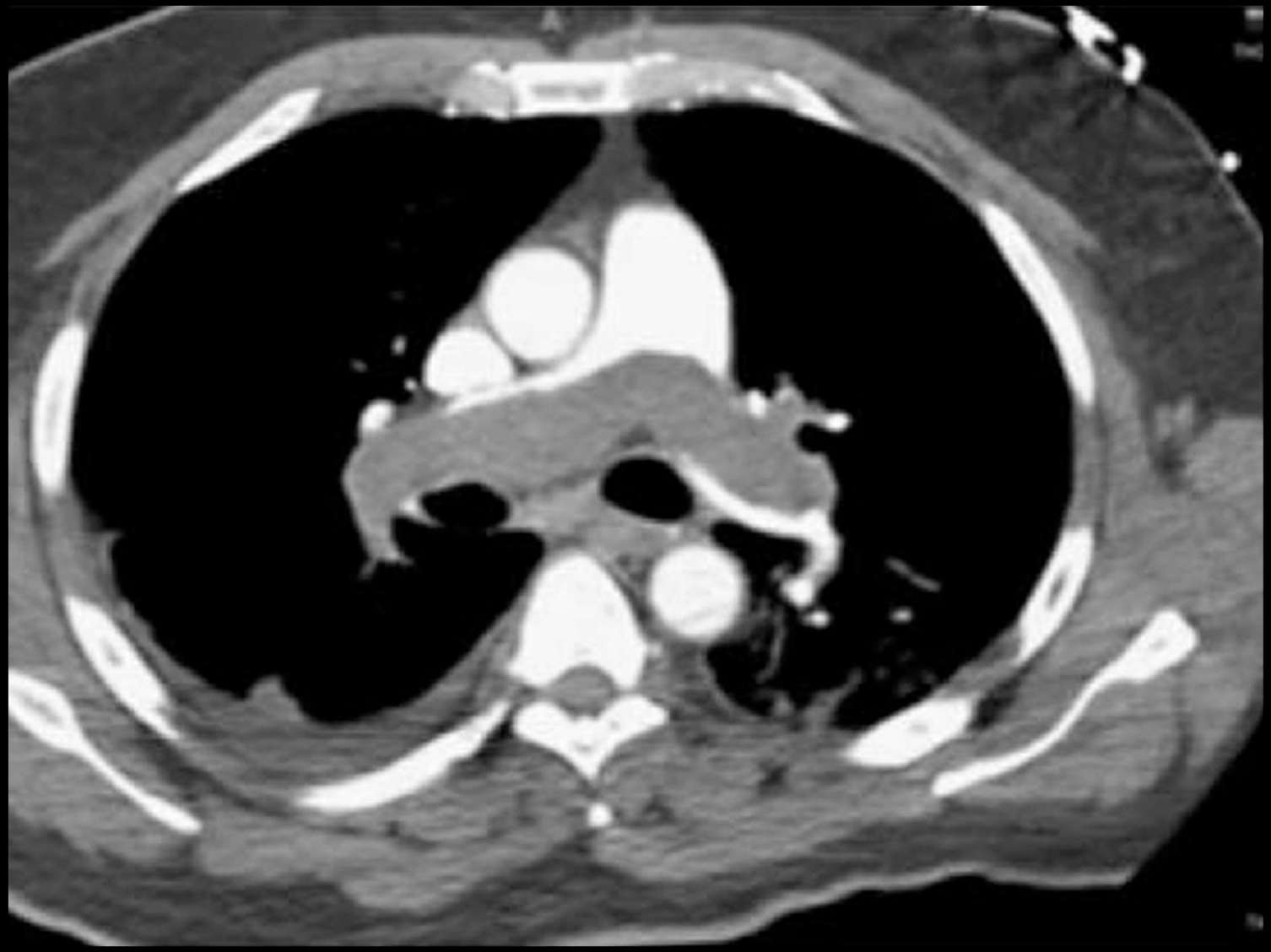
SaO_2 82% on pulse oximetry. He’s tachycardic and tachypneic. SBP 84/35.

BESIDE ULTRASOUND

- Diagnosis?







EPIDEMIOLOGY

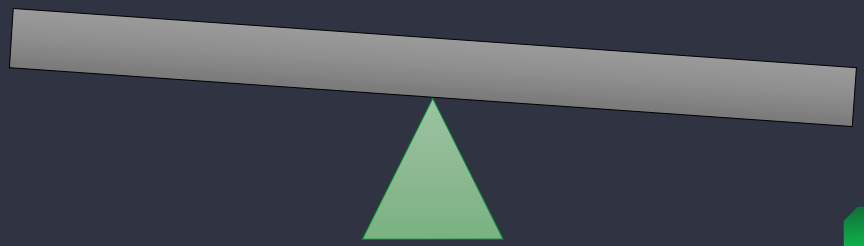
Scope of the burden

- Approximately 31 million people develop sepsis each year globally.
- 6 million deaths/year.
- Increased incidence due to increased chemotherapy, immunosuppression, transplantation, chronic health conditions, and coding.

Gaeiski et al Crit Care Med 2013
Martin et al NEJM 2003

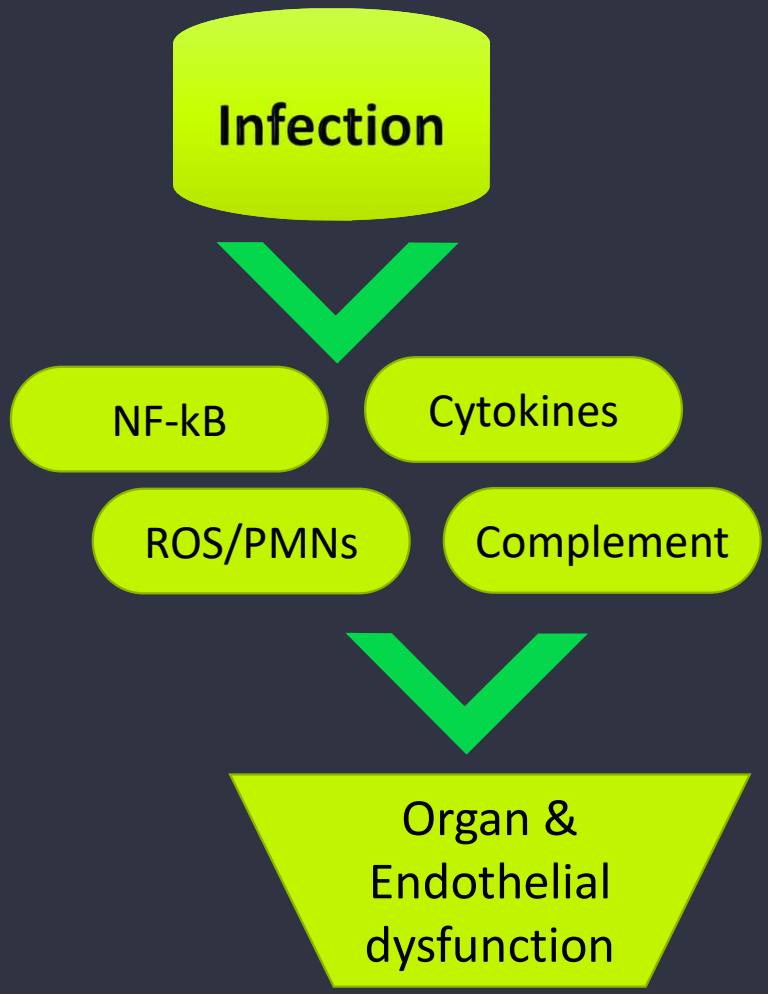
SEPSIS INCIDENCE

- Today >1.7 million people/yr in the U.S. acquire sepsis and >270,000 will die.
- Claims-based vs EHR-based data
  - Which would you suspect is greater?
  - What are the trends in death?
- Mortality appears to be improving but data are conflicting.



Trzeciak, Stephen et. al. Septic Shock. Chapter 23. July 03, 215.
JAMA. 2017 Oct 3;318(13):1241-1249. doi: 10.1001/jama.2017.13836.

PATHO-PHYSIOLOGY



- Pro-inflammatory activation
- Mitochondrial, endothelial, and coagulation dysfunction
- Immunosuppression, oxidative stress, and cellular necrosis leads to MODS and death

HISTORY

How did we get here?

BACKGROUND

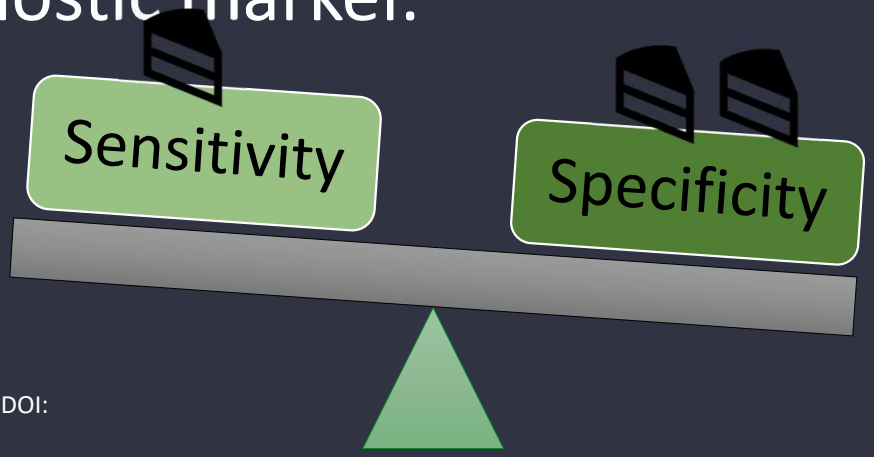
- “Hectic fever, at its inception, is difficult to recognize but easy to treat; left unattended it becomes easy to recognize and difficult to treat.”

  - Niccolò Machiavelli

- Dr. Rivers pioneering work in 2001 EGDT showed a 16% absolute reduction in hospital mortality.
- Aftermath

BACKGROUND CONT.

- Previously Sepsis = Infection + 2 or more SIRS criteria
  - HR>90, Temp >38.3, RR>20, WBC >12k
- One in eight patients with severe sepsis will be missed using SIRS criteria
- Ideally, we could develop an early detection method and a definitive diagnostic marker.



Kaukonen, Kirsi-Maija et. al. NEJM 2015;372:1629-38. DOI: 10.1056/NEJMoa1415236

DEFINITIONS AND GUIDELINES

- Definitions and guidelines continue to evolve (Sepsis-1 in 1991, Sepsis-2 in 2001, and Sepsis-3 in 2016)
  - Currently CMS (and ICD-10) differ from Surviving Sepsis Campaign.
  - There is no gold standard "sepsis test" – *it is a syndrome.*
  - Sepsis is "life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the SOFA score of 2 points or more, which is associated with an in-hospital mortality >10%."

Singer, et. Al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis -3). JAMA 2016 February 23; 315(8): 801–810. doi:10.1001/jama.2016.0287.

DEFINITIONS AND GUIDELINES CONT.

- Definitions and guidelines continue to evolve (Sepsis-1 in 1991, Sepsis-2 in 2001, and Sepsis-3 in 2016)
  - Septic shock is "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%."
- Decoupled sepsis from uncomplicated infections meeting SIRS criteria.
- In April 2018, the SSC provided a 1-hour bundle for treatment when diagnosed.

Singer, et. Al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis -3). JAMA 2016 February 23; 315(8): 801–810. doi:10.1001/jama.2016.0287.


qSOFA SCORE
Q
SBP < 100
RR > 22
GCS < 15

QUICK SOFA (qSOFA)

- SOFA score is an illness-severity score used to predict mortality of critically ill patients.
- Patients with suspected sepsis can be rapidly identified if they meet *at least 2 of three criteria* of the score.
- Lactate is superior to qSOFA for sepsis prognostication.
- Take home:
  - SIRS may over AND under diagnose but still has a role to play
  - SOFA is cumbersome in the ED but great for ICU patients
  - qSOFA is a screening tool NOT a diagnostic tool

Liu et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine (2019) 27:51 https://doi.org/10.1186/s13049-019-0609-3
Zhigiang, Liu et. Al. Prognostic accuracy of the serum lactate level, the SOFA score and the qSOFA score for mortality among adults with Sepsis JO - Scandinavian Journal of Trauma, Resuscitation and Emergency Medicinevolume 27, Article number: 51 (2019)

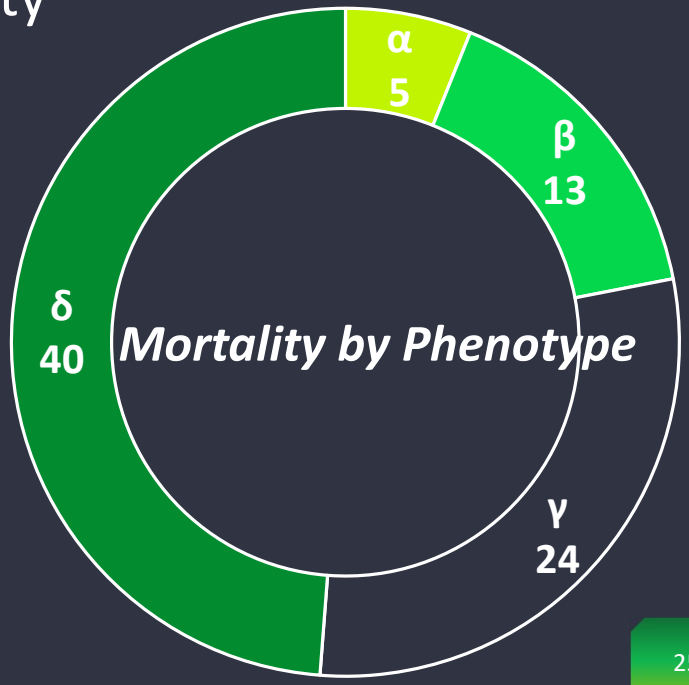
DEFINITIONS CONT.

	CMS	SEP-3
Sepsis	Infection + >= 2 SIRS criteria	>= 2 qSOFA including hypotension
Severe Sepsis	Sepsis + organ dysfunction*	N/A
Septic Shock	Sepsis + refractory hypotension +/- lactate >=4	Vasopressors and lactate >2 mmol/L

SEPSIS PHENOTYPES

Pheno-type	Characteristics
alpha	Least vasopressors
Beta	Older, more chronic illness and renal dysfunction
Gamma	More inflammation and pulmonary dysfunction
Delta	More cardiovascular and liver dysfunction. Increased septic shock

- Heterogenous syndrome with an overly broad definition
- Different biomarker elevation and mortality
- Directed treatment may improve mortality



Seymour, Christopher et. Al. JAMA. Doi:10.1001/jama.2019.5791

PROBLEMS WITH RECENT GUIDELINES

- Several financial conflicts of interest exist, and several strong recommendations are based on weak evidence (e.g lactate, 1hr).
- Various medical societies were not consulted and have refused to endorse them.
- Disregard clinician judgement with fixed time frames and fluid volumes.
- qSOFA is specific but not sensitive for organ dysfunction (96.1 % vs 29.7) and early risk assessment.
- However, checklists and reminders can be beneficial. Hospitals with higher compliance rates have lower mortality.
- Other risk-stratification scores are available (e.g. MEWS and NEWS) to recognize *critical illness.*

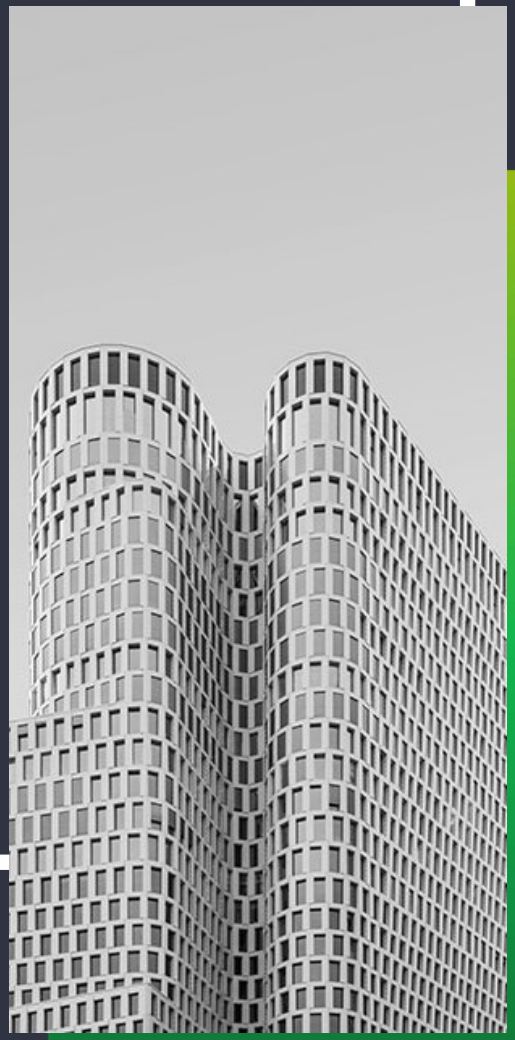
Williams JM, Greenslade JH, McKenzie JV, et al. SIRS, qSOFA and organ dysfunction: insights from a prospective database of emergency department patients with infection. Chest 2017;151:586-596.
Giamarellos-Bourboulis EJ, Tsaganos T, Tsangaris I, et al. Validation of the new Sepsis-3 definitions: proposal for improvement in early risk identification. Clin Microbiol Infect 2017;23:104-9.

RISK FACTORS FOR SEPSIS

1. Advanced age
2. Immunosuppression/steroid use/malnutrition
3. DM/CA/HIV/liver disease
4. Recent abx/drug-resistance
5. Recent procedures or travel
6. Alcohol/drug use

Initial Signs and Symptoms

- Temp >38.3 or <36˚C
- HR >90 BPM
- RR>20/min

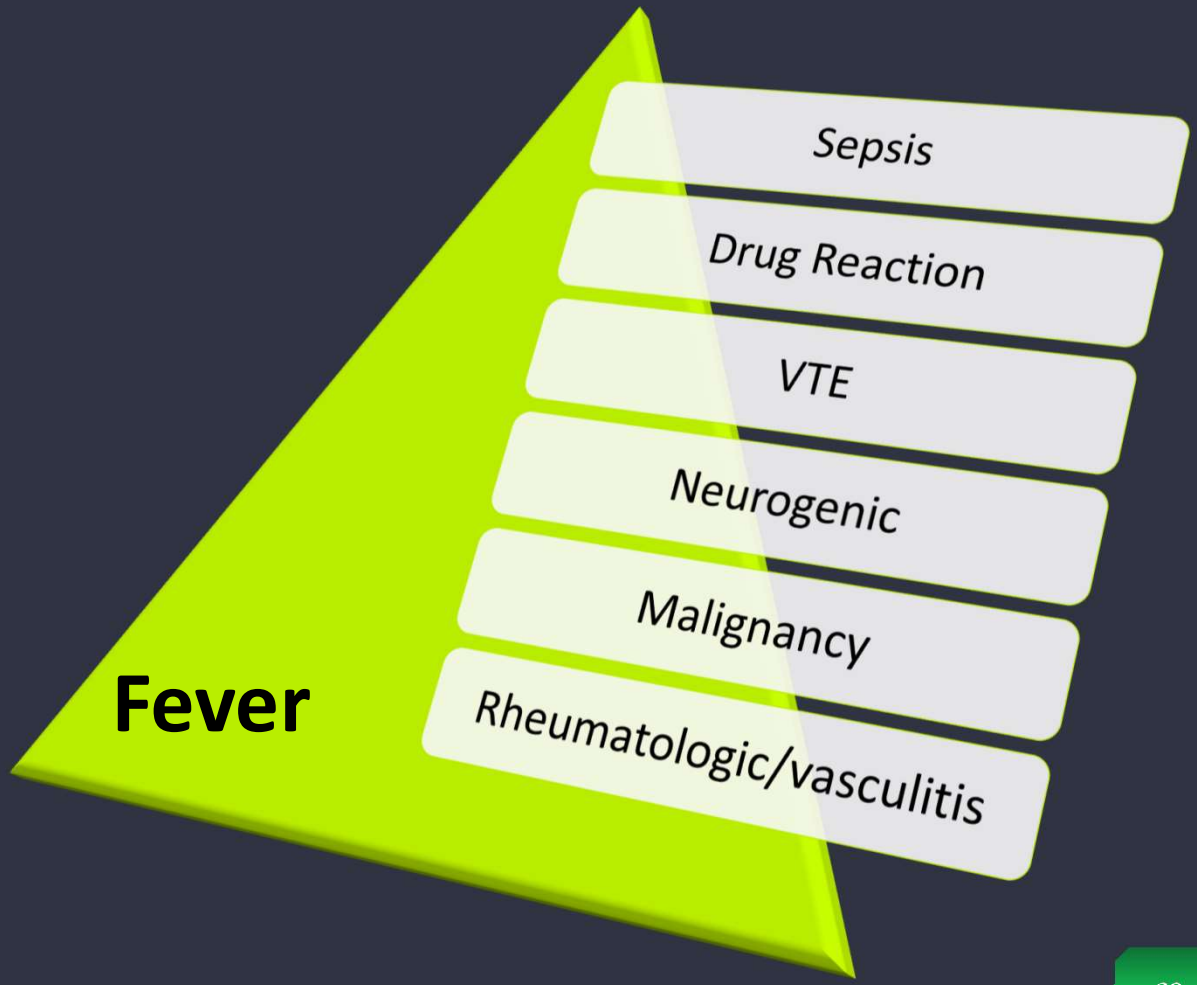


Signs of end organ hypoperfusion

- Warm diaphoretic skin -> cool, cyanotic, mottled, and delayed capillary refill in shock
- AMS, restlessness, agitation, or obtundation
- Oliguria or anuria
- Ileus or absent bowel sounds

SIRS AND FEVER DIFFERENTIAL

- SIRS
  - Sepsis
  - Trauma/Burns/Surgery
  - Pancreatitis
  - Chemical pneumonitis
  - Anaphylaxis
  - Post operative
  - Pulmonary emboli

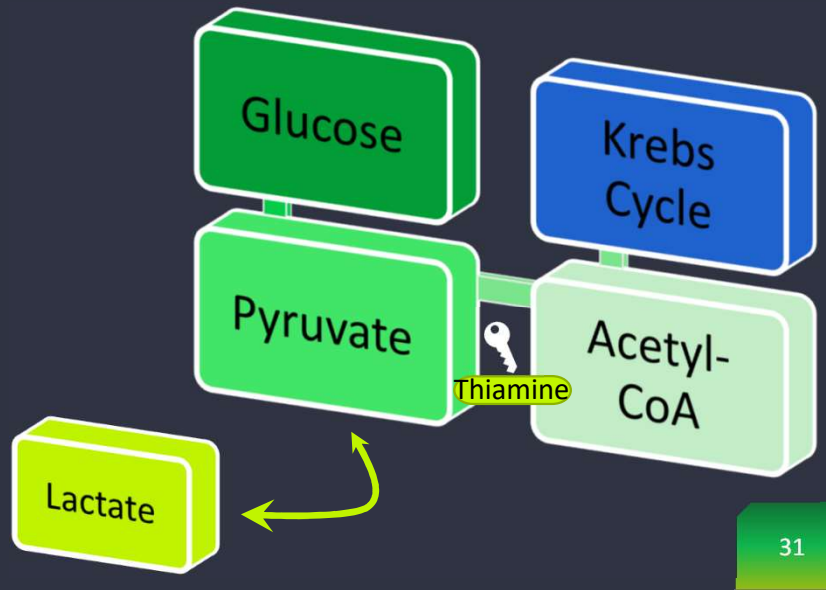


LABORATORY FINDINGS

- WBC >12,000 or <4,000
- Glucose >140 mg/dL in the absence of diabetes.
- CRP > 2 S.D. above normal
- Arterial hypoxemia
  - (p/f <300)
- Cr increase > 0.5 mg/dL
- INR >1.5 or aPTT >60s
- Platelet count <100,000
- Total bilirubin >4 mg/dL
- Lactate >2 mmol/L
- Procalcitonin >2 S.D. above normal
- Adrenal insufficiency or euthyroid sick syndrome

LACTATE

- Produced daily by many organs under normal conditions but ↑ during inadequate O_2 delivery resulting in tissue hypoxia and anaerobic metabolism.
- Elevated in ~⅔ of pts with severe sepsis or septic shock & ∝ ↑ mortality rate.
- However, sepsis results in an *impaired ability* of the tissues to extract O_2 and ↑ delivery does not entirely reverse lactate formation.
- Using cap refill may be just as good (if not better) to guide resuscitation.
- Other causes of hyperlactatemia:
  - Hepatic dysfunction / ↓ clearance
  - Cancer
  - Hyperadrenergia
  - Thiamine deficiency
  - Toxins/drugs/ethanol
  - Ketoacidosis
  - Inborn errors of metabolism



1. Bandarn Suetrong, MD; and Keith R. Walley, MD. Lactic Acidosis in Sepsis: It's Not All Anaerobic: Implications for Diagnosis and Management. CHEST 2016; 149(1):252-261
2. Casserly B, Phillips GS, Schorr C, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign Database. Crit Care Med. 2015;43(3):567-573.
3. Hernandez G et. al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA. 2019 Feb 19;321(7):654-664. doi: 10.1001/jama.2019.0071.

TREATMENT

GOALS

1. Stabilize hemodynamically
2. Obtain source control
3. Manage host complications

THE SURVIVING SEPSIS CAMPAIGN BUNDLE: 2018 UPDATE

1. Measure lactate (recheck if >2mmol/L)
2. Obtain blood cultures prior to administering antibiotics
3. Administer broad-spectrum antibiotics
4. Rapidly administer 30mL/kg crystalloid for hypotension or lactate ≥4
5. Apply vasopressors if hypotensive during or after fluid resuscitation to maintain MAP ≥ 65

ANTIBIOTICS

IV administration **ASAP after recognition and within one hour** for sepsis and septic shock (strong recommendation, moderate quality of evidence).

Recommendation based upon data demonstrating ↑ mortality for every hour of delay in antibiotic administration for infected pts with organ dysfunction and/or shock. *However, some meta-analyses report no benefit of rapid antibiotic administration.*

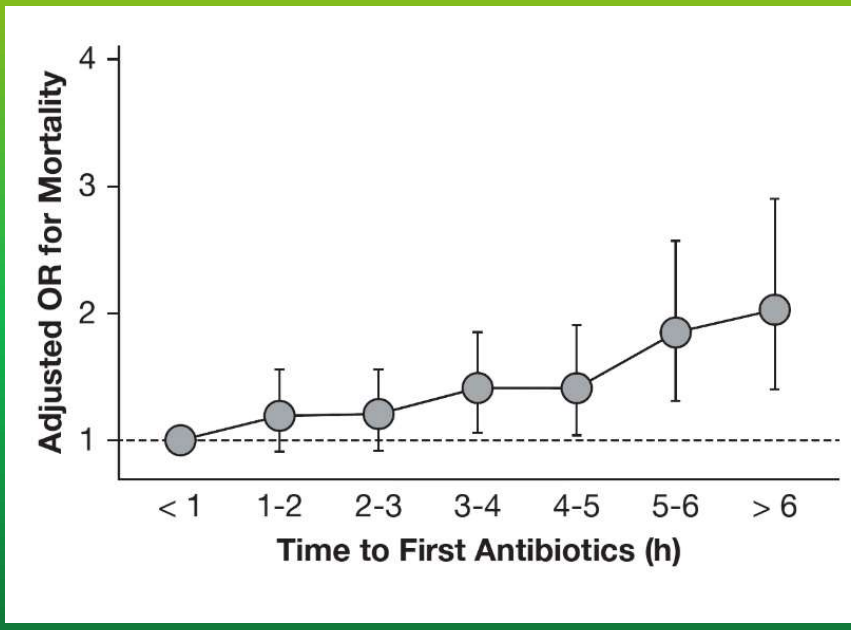
It is currently unclear if antibiotic administration within one hour is better than within three in sepsis compared to septic shock.

Current CMS guidance is to administer antibiotics ASAP and within 3 hours of sepsis or septic shock diagnosis.

https://www.acepnow.com/article/acep-endorses-latest-surviving-sepsis-campaign-recommendations/?singlepage=1

ANTIBIOTICS

- Start early
  - Each hour delayed ↑ 1-year mortality by 10%
- Start broad for likely source and base on any prior susceptibility data
- Utilize pharmacists to ensure appropriate dosing
- Practice good stewardship
- Deescalate ASAP



Peltan, Ithan et. al. CHEST 2019; 155(5):938-946

OBTAIN SOURCE CONTROL

CNS

HEART

PULM

GI

GU

SKIN

BONE

INTRAVENOUS FLUID

- Volume
  - Guidelines suggest 30 mL/kg
  - Document reasons for deviation
  - How do we measure response?
  - A positive daily fluid balance is strongly associated with increased mortality
  - CLOVERS trial underway (restricted vs liberal fluids)

Acheampong and Vincent Critical Care (2015) 19:251 DOI 10.1186/s13054-015-0970-1

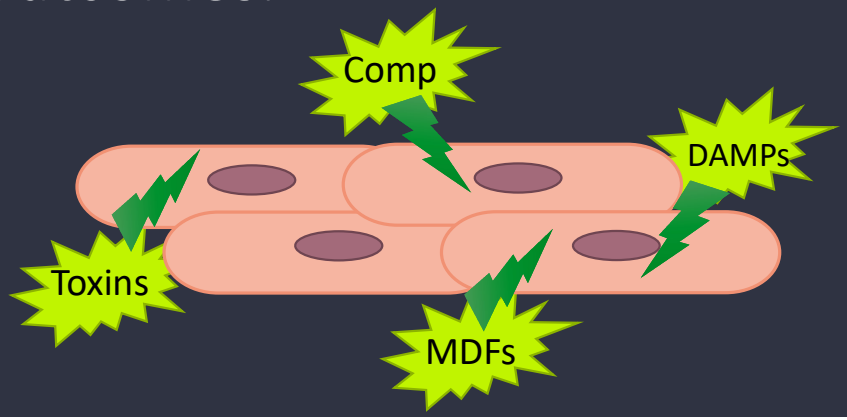
INTRAVENOUS FLUID CONT.

- Type
  - **Physiologically balanced solutions** make physiologic sense but have failed to demonstrate a definitive decrease in mortality
    - SALT-ED trial did not show a ↓ in hospital LOS but ↓ major adverse kidney events within 30 days compared to NS
    - SMART trial showed balanced crystalloids ↓ death and renal dysfunction compared to NS. Non-blinded, single-center study of critically ill. and SALT-ED
  - When choosing colloid, **choose albumin** particularly if 3rd spacing is present
  - Cost vs benefit
  - More trials pending

Semler, M et. al.March 1, 2018 N Engl J Med 2018; 378:829-839 DOI: 10.1056/NEJMoa1711584
Self, W et. al. March 1, 2018 N Engl J Med 2018; 378:819-828 DOI: 10.1056/NEJMoa1711586

INOTROPES

- Patients with septic shock may develop impaired myocardial function.
- The pathophysiology of this “septic cardiomyopathy” is not fully established.
- Patients may benefit from inotropic support (e.g. dobutamine) but targeting a specific SvO_2 within a specific timeframe does not improve outcomes.



STEROIDS

- Indicated only for patients with septic shock refractory to fluids and vasopressors
- Stress dosing according to studies is 50mg hydrocortisone q6 hrs or the equivalent
- No need to perform an ACTH
- Tapering not necessary if used for short duration.
  - Consider tapering when vasopressors are no longer needed.

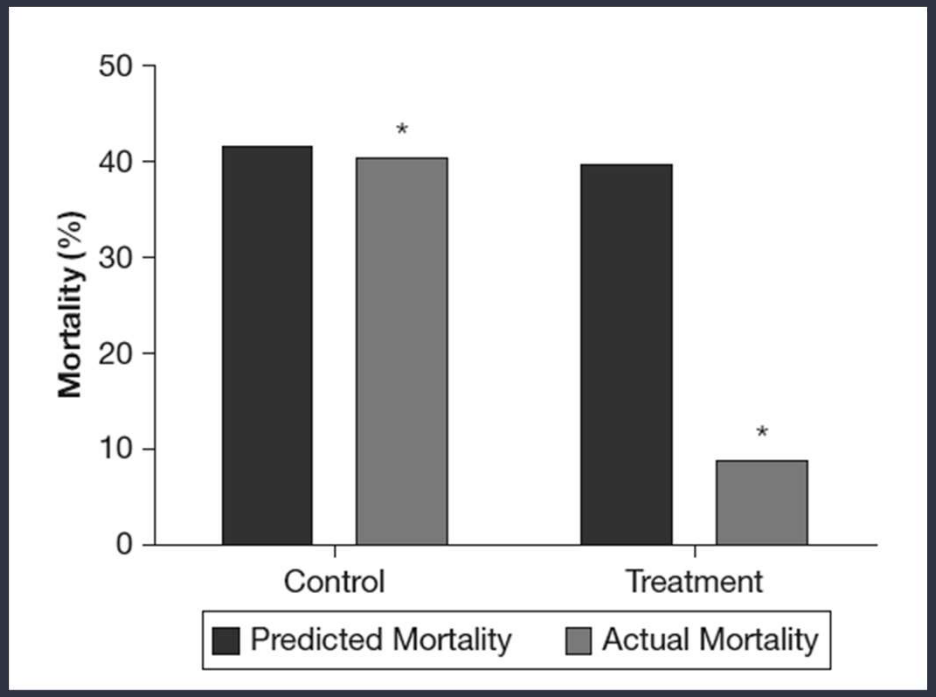
VITAMIN C†

- Rooted in biologic rationale.
  - Key cofactor in endothelial function and catecholamine synthesis
- Headlines vs data
  - 2016 retrospective before-after study of 94 patients (half received placebo) in a single ICU in Virginia.
  - **HAT** = **h**ydrocortisone, **a**scorbic acid (1.5g IV q6h), and **t**hiamine.
  - Retrospective before-after study comparing mortality over 7 months with those treated showed a decrease from 40.4% to 8.5%!
  - Not controlled, lots of exciting results but follow up research has shown no benefit or even harm *(e.g. J. Clin. Med. 2019, 8(4), 478; or Crit Care Med. 2019 Jun;47(6):774-783, Crit Care Med. 2020 July, 48(7) p e620-e628, and JAMA. 2021;325(8):742-750 VICTAS RCT)*

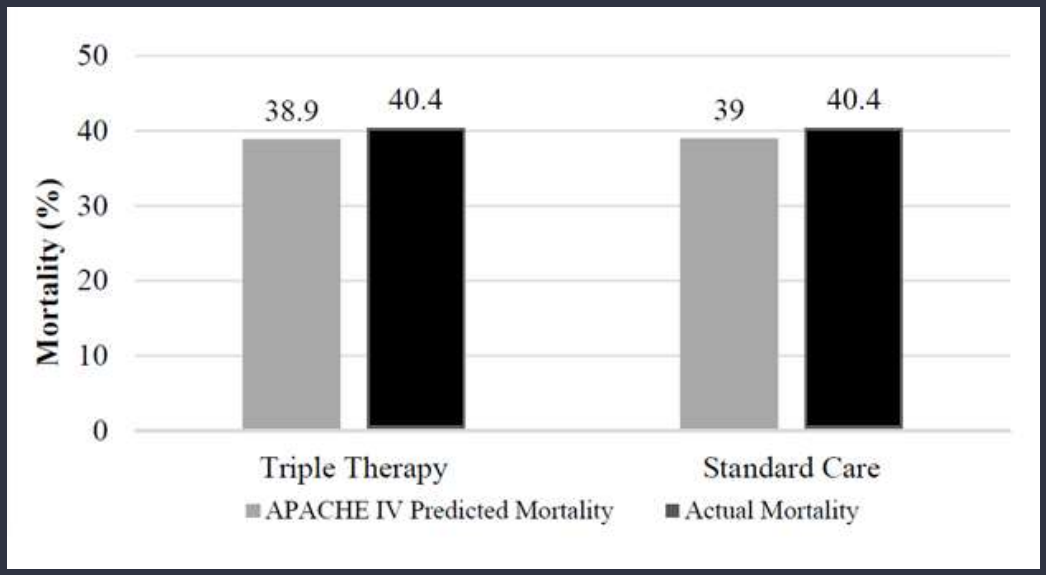
Marik Paul et al. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock. CHEST, Volume 151, Issue 6, 1229 - 1238

DIFFERING RESULTS

Marik



Litwak

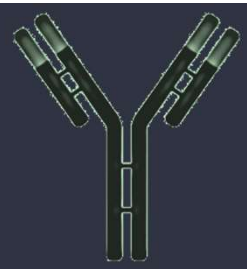


FECAL MICROBIOTA TRANSPLANT†

- Gut microbiota serves as a physical barrier and immune modulator with disruption leading to extraintestinal disease.
- FMT may be used to reestablish the normal microbial system if dysbiosis and reduced bacterial variability occur due to steroids, sepsis, and/or antibiotics.
- Currently success demonstrated in limited small case studies but there is strong prior evidence for FMT in recurrent C.diff colitis.
- Utilize *caution* when introducing a high antigenic load in the setting of increased membrane permeability.
- FDA released a warning June 13, 2019 about the risk of MDR organisms being transplanted.

Wurm P, Spindelböck W, Krause R, et al. Antibiotic-associated apoptotic enterocolitis 1 in the absence of a defined 2 pathogen: The role of intestinal microbiota depletion. Crit Care Med. 2017 Jun; 45(6): e600–e606.
Wei et al. Critical Care Successful treatment with fecal microbiota transplantation in patients with multiple organ dysfunction syndrome and diarrhea following severe sepsis (2016) 20:332 DOI 10.1186/s13054-016-1491-2
Kassam Z, et al. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol. 2013; 108(4):500.

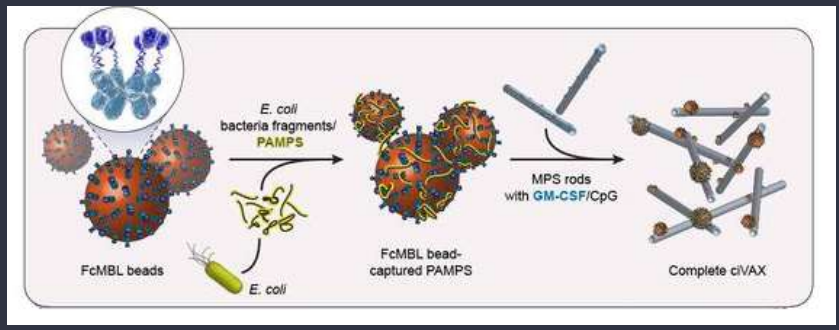
OTHERS†

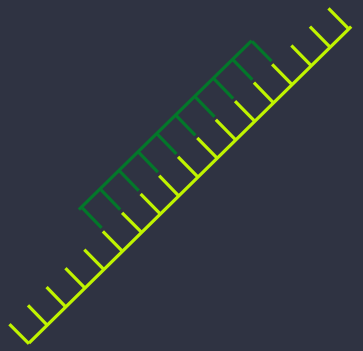


- Antibodies
  - anti-endotoxin, anti-enterobacteriaceae, anti-TNF, adrecizumab
- Antagonists
  - IL1, TLR-4, TNF receptor, bradykinin
- Anti-inflammatories/antioxidants
  - N-acetylcysteine, NO inhibitors, ibuprofen, selenium, HAT
- Others
  - G-CSF, antithrombin, tifacogin, GH, calcitriol, levosimendan, hypothermia, hyperoxia, HTS, angiotensin II, alkaline phosphatase, recombinant human soluble thrombomodulin, adrenomedullin, angiotensin II, InnovoSep (cilengitide), immune checkpoint inhibitors (e.g. BMS-936559), etc.

NOVEL/EUA APPROACHES†

- Vaccines
  - ciVAX is injected or implanted under the skin. It combines immunogenic antigens from multiple pathogens and immune cell-recruiting biomaterial scaffolds.
- Blood purification
  - Cytokine removal with CytoSorb®
- miRNA as a rapid diagnostic biomarker and prognostication
  - miR-486-5p increased in patients with sepsis and associated with severity.





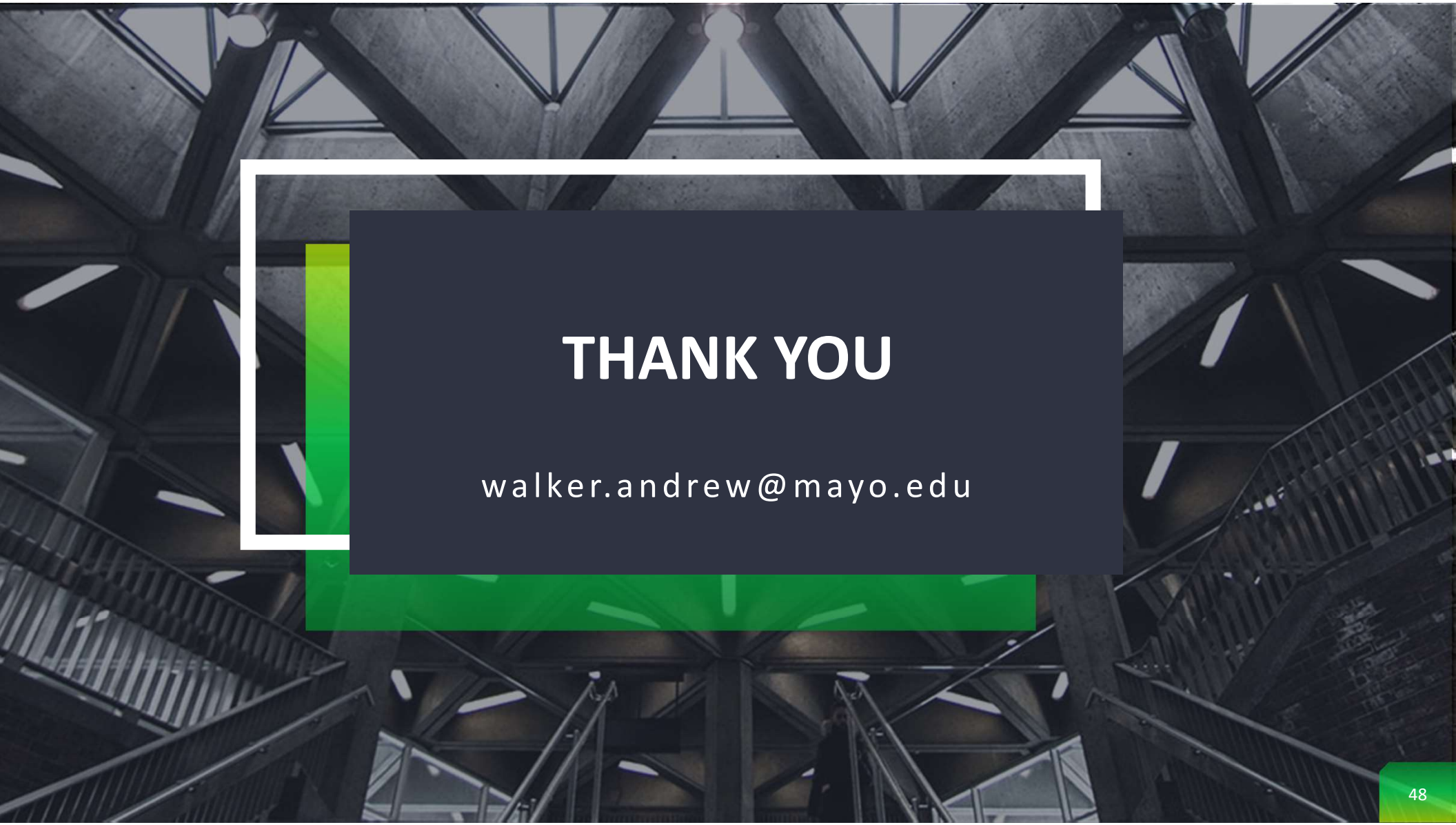
https://www.seas.harvard.edu/news/2021/07/biomaterial-vaccines-ward-broad-range-bacterial-infections-and-septic-shock
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7805252/
https://www.dovepress.com/mir-486-5p-serves-as-a-diagnostic-biomarker-for-sepsis-and-its-predict-peer-reviewed-fulltext-article-JIR

TX SUMMARY

Therapy	Specifics	Pearls
Initial resuscitation	30cc/kg in first hour?	Consider LR/albumin
	MAP >= 65 mmHg	PLR, cap. refill, lactate
Antibiotics	Initiate broad spectrum	E.g. vanc/pip-tazo Consider procalcitonin
	Obtain source control	
Steroids	Only if septic shock refractory to fluids/vasopressors	
Vasopressors	1. NE 2. VP or Epi	Avoid dopamine for most

TAKE HOME POINTS

1. Sepsis is a life-threatening response to an infection that must be diagnosed early.
2. Sepsis should be treated quickly based on protocols with IV fluids and broad-spectrum antibiotics while incorporating clinical expertise for personalized care.
3. Source control must be obtained.
4. Novel diagnostic markers and therapeutics are needed to improve patient outcomes.


THANK YOU
walker.andrew@mayo.edu