

Sepsis ACP 2019

Controversial

- Are sepsis bundles good for patient care?
- Politics
 - CMS requirements
 - New York's Rory Staunton Law
- Industry involvement
- Is the science sound?
- Emergency room physician petition to retire guidelines
 - More than 5800 ER physicians signed petition

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

Critical Care Medicine 2017. 45(3):486

- Initial Resuscitation.
 - At least 30 mL/Kg of IV crystalloid fluid within first 3 hours
 - After initial resuscitation, additional fluids guided by frequent reassessment
 - MAP \geq 65 mm Hg
 - Guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.
- Appropriate routine microbiologic cultures before starting antimicrobial therapy and within one hour.
 - Empiric coverage for all likely pathogens
 - Combination therapy for initial management of septic shock
 - Procalcitonin levels to support shortening duration of therapy.

Sepsis Guidelines Continued:

- Source control intervention be implemented as soon as medically and logistically practical.
- Fluid therapy.
 - Fluid challenge technique with continued fluid administration as long as hemodynamics factors continue to improve.
- Vasopressors.
 - Norepinephrine as the first-choose vasopressor
 - Adding vasopressin 0.03 U/min or epinephrine.
- Recommend against IV hydrocortisone if adequate fluid resuscitation and vasopressor are able to restore hemodynamics stability.

Sepsis Guidelines Continued

- Transfusion only when hemoglobin concentration decreases to less than 7 g/dL
- Mechanical Ventilation using target tidal volume of 6 mL/Kg predicted body weight. Maintain plateau pressures less than 30 cm H₂O
- Glucose control. Maintain glucose \leq 180 mg/dL

The Surviving Sepsis Campaign Bundle: 2018 Update

Hour-1 Bundle

- Measure lactate level. Remeasure if initial lactate $> 2\text{mmol/L}$
- Obtain blood cultures prior to administration of antibiotics
- Administer broad-spectrum antibiotic
- Begin rapid administration of 30 ml/Kg crystalloid for hypotension or lactate $\geq 4\text{ mmol/L}$
- Apply vasopressors if patient is hypotension during or after fluid resuscitation to maintain MAP $\geq 65\text{ mm Hg}$.
 - Intensive Care Med 2018. 44:925

1 – Hour Bundle, Should it be Implemented?

- Often difficult to identify sepsis patients early; disease may be indistinguishable from many other conditions. Therefore, many patients are placed in this pathway to meet the early bundle goals who do not have sepsis
- No studies evaluating the negative implications of bundles.
- No evidence that the “bundles” work
- Mandatory fluid resuscitation may be harmful
- The science evidence is poor
- Multiple studies demonstrating hospitals with adherence to the bundles have better outcomes.

Definition and Diagnosis

Definition

- Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Suspected or Confirmed) Organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%.
- Septic shock defined as persisting hypotension requiring vasopressors to maintain MAP [mean arterial pressure] >65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

SIRS verse SOFA



• SIRS criteria

- 1. Body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
- 2. Heart rate $>90/\text{minute}$
- 3. Respiratory rate $>20/\text{minute}$ or PaCO_2 lower than 32mmHg (4.3kPa)
- 4. White blood cell count $>12000/\mu\text{L}$ ($>12 \times 10^9/\text{L}$) or $<4000/\mu\text{L}$ ($<4 \times 10^9/\text{L}$)

- When 2 or more criteria are present

SOFA Score

SOFA score	0	1	2	3	4
Respiration $\text{PaO}_2/\text{FiO}_2$ or $\text{SaO}_2/\text{FiO}_2 \text{ mmHg}$	>400	<400 221-301	<300 142-220	<200 87-141	<100 <87
Coagulation	>150	<150	<100	<50	<20
Liver Bilirubin(mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	MAP <70	Dopamine ≤ 5 or any	Dopamine >5 or norepinephrine ≤ 0.1	Dopamine >15 or norepinephrine >0.1
CNS (GCS)	15	13-14	10-12	6-9	≤ 5
Renal Creatinine (mg/dl) or urine output (ml/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <5.00	>5.0 or <200

Definition Comparison

Sepsis	Suspected Infection + SIRS	Suspected Infection plus ≥ 2 qSOFA or rise ≥ 2 SOFA
Severe Sepsis	Sepsis + organ dysfunction	Eliminated
Septic Shock	Severe Sepsis + hypotension after adequate fluid resuscitation	Sepsis + Vasopressors (after adequate resuscitation) + elevated lactate.

Inconsistent with the ICD-10-CM Official Guidelines for Coding and Reporting (OCG)

Prolactin as a Diagnostic Marker For Sepsis/Septic Shock in the Emergency Department

- Sensitivity 75% for sepsis and 66% for septic shock
- Specificity 64% for sepsis and 79% for septic shock
- qSOFA sensitivity of 17% for sepsis and 38% for septic shock.
 - Am J Emerg Med. 2019;37:272
- SIRS; need for 2 or more criteria to define severe sepsis excluded one in eight patients with infection, organ failure and substantial mortality.
 - NEJM 2015;372;17p1629

National Early Warning Score (NEWS)

National Early Warning Score (NEWS)*

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

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

- NEWS score ≥ 5 has sensitivity for sepsis of 79%
- Sensitivity of in-hospital mortality of 95%

Trouble with diagnosis

Healthcare Utilization and Infection in the Week Prior to Sepsis Hospitalization*

Vincent X. Liu, MD, MS^{1,2}; Gabriel J. Escobar, MD¹; Rakesh Chaudhary, MD²;
Hallie C. Prescott, MD, MSc^{3,4}

Objectives: To quantify healthcare utilization in the week preceding sepsis hospitalization to identify potential opportunities to improve the recognition and treatment of sepsis prior to admission.

Design: Retrospective study.

Setting: Two large integrated healthcare delivery systems in the United States.

Participants: Hospitalized sepsis patients.

Interventions: None.

Measurements and Main Results: We quantified clinician-based encounters in each of the 7 days preceding sepsis admission, as well as on the day of admission, and categorized them as: hospitalization, subacute nursing facility, emergency department, urgent care, primary care, and specialty care. We identified the proportion of encounters with diagnoses for acute infection based on 28 single-level Clinical Classification Software categories. We also quantified the use of antibiotics over the same interval and used linear regression to evaluate time trends. We included a total of 14,658 Kaiser Permanente Northern California sepsis hospitalizations and 31,369 Veterans Health Administration sepsis hospitalizations. Over 40% of patients in both cohorts required intensive care.

A total of 7,747 Kaiser Permanente Northern California patients (52.9%) and 14,280 Veterans Health Administration patients (45.5%) were seen by a clinician in the week before sepsis. Prior to sepsis, utilization of subacute nursing facilities remained steady, whereas hospital utilization declined. Primary care, specialty care, and emergency department visits increased, particularly at admission day. Among those with a presepsis encounter, 2,648 Kaiser Permanente Northern California patients (34.2%) and 3,858 Veterans Health Administration patients (27.0%) had at least one acute infection diagnosis. An increasing percentage of outpatient encounters also had infectious diagnoses (3.3%/d; 95% CI, 1.5%–5.1%; $p < 0.01$), particularly in primary and specialty care settings. Prior to sepsis hospitalization, the use of antibiotics also increased steadily (2.1%/d; 95% CI, 1.1%–3.1%; $p < 0.01$).

Conclusions: Over 45% of sepsis patients had clinician-based encounters in the week prior to hospitalization with an increasing frequency of diagnoses for acute infection and antibiotic use in the outpatient setting. These presepsis encounters offer several potential opportunities to improve the recognition, risk stratification, and treatment prior to sepsis hospitalization. (*Crit Care Med* 2018; 46:513–516)

Key Words: critical care outcomes; patient readmission; sepsis; subacute care; utilization

*See also p. 644.

Do Bundles Work?

- PROMISE. Hemodynamics management according to strict EGDT protocol did not lead to an improvement in outcome.
 - ARISE. EGDT did not reduce all-cause mortality at 90 days.
 - ProCESS. Protocol based resuscitation of patients did not improve outcomes.
-
- NEJM 2015. 372 (14): 1301
 - NEJM 2014. 371(16): 1496
 - NEJM 2014. 370 (18): 1683

The Evidence is Poor.

- Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg.

**“Time zero” or “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 sepsis (formerly severe sepsis) or septic shock ascertained through chart review.*

Fig. 1 Hour-1 Surviving Sepsis Campaign Bundle of Care

Table 1 Bundle elements with strength of recommendations and under-pinning quality of evidence [12, 13]

Bundle element	Grade of recommendation and level of evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg	Strong recommendation, moderate quality of evidence

Antibiotic- and Fluid-Focused Bundles Potentially Improve Sepsis Management, but High-Quality Evidence is Lacking for the Specificity Required by the Centers for Medicare and Medicare Service's Sepsis Bundle (SEP-1)

- 16 studies found improved survival with serial lactate measurements, a 30 mL/Kg fluid infusion or both. None met criteria for high or moderate high level evidence
- Fluid responsiveness testing evaluated in 3 randomized trials that demonstrated no benefit in survival.
- Single retrospective trial of entire SEP-1 bundle found borderline survival benefit – low evidence

- Crit Care Med: July 31, 2019. Volume Online First

Antibiotics

- Each additional hour from ED arrival to antibiotic initiation was associated with a 10% increased odds of 1 year mortality. CHEST 2019 155 (5):938
- Every hour of delay to antibiotic treatment increased the risk of hospital mortality, especially those with septic shock. AJRCCM 2017 196(7):856
- Rapid administration of antibiotic associated with lower in-hospital mortality. NEJM 2017 376 (23):2235
- Statistically significant increase risk of death after delays greater than 125 minutes. CCM 2018; 46:500
- Delay in antibiotic administration associated with increased hospital mortality. CCM 2017; 45:759
- Prehospital antibiotics per EMS with no effect on mortality. Lancet Respir Med 2018: 6(1):40

Mandatory Fluid Resuscitation

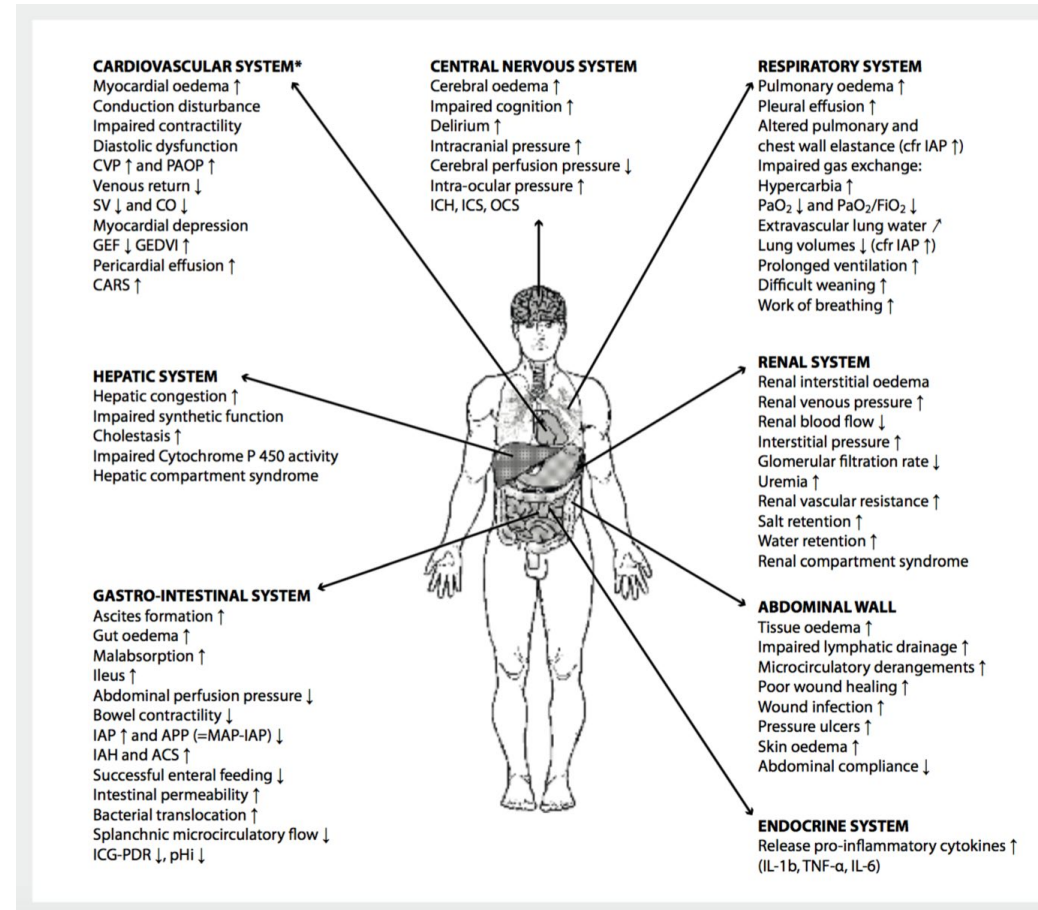
4 Phases of Septic Shock

- Rescue
 - Recommended goal of 30 mL/Kg of IV crystalloid
- Optimization phase
 - Ischemia and reperfusion phase
 - Repeated assessments of intravascular fluid status and determination for further fluid administration
- Stabilization
 - Maintain intravascular volume, replace ongoing fluid losses, support organs dysfunction, avoid iatrogenic harm with unnecessary fluid administration
- De-escalation

Fluid Responsiveness.

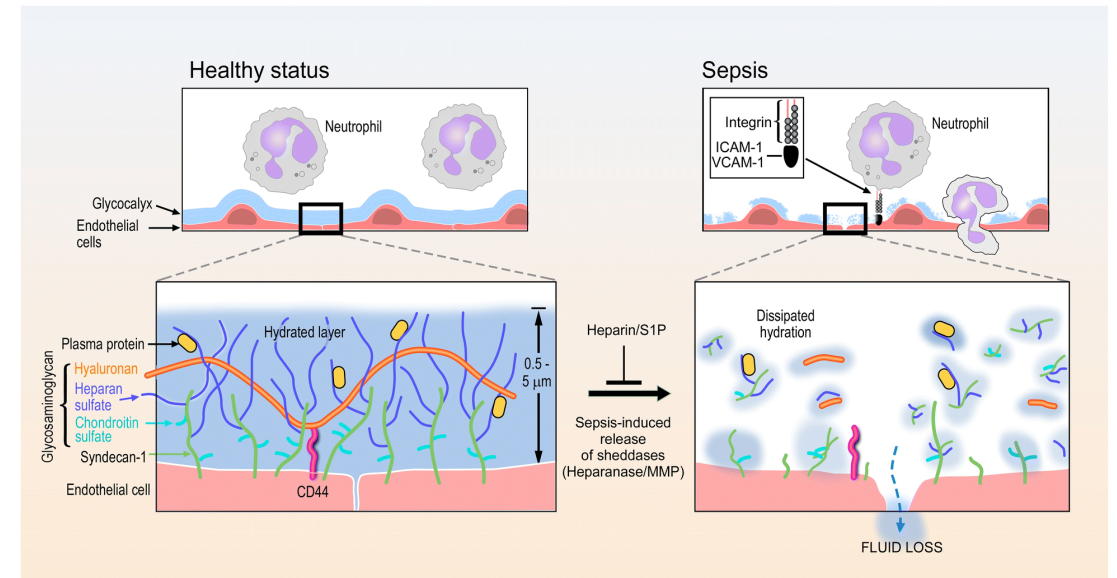
- Retrospective trial of 3686 patients.
- Fluid responsiveness defined as a static measurement of sustained reversal of hypotension with resultant systolic blood pressure >90 mmHg or MAP > 65 mmHg after initial fluid resuscitation without the use of vasopressors for 24 hours
- 36.2% refractory to fluid bolus.
- Fluid refractory patients had higher in-hospital mortality, mechanical ventilation, longer ICU stays, longer hospital length of stay.
- Predictors of being fluid refractory: delayed fluid resuscitation with time to fluid > 120 minutes*, CHF, hypothermia, lactate > 4, coagulopathy, immunocompromised.
 - CCM 2018;46:189

Excessive Resuscitation



Glycocalyx

- Matrix lining endothelial cells serving as a barrier opposing vascular permeability and limits transvascular movement of fluid.
- Degradation in sepsis
 - Inflammatory cytokines
 - Hypervolemia
- Critical care (2019) 23:16



Liberal Fluid Administration associated with poor outcomes

- Boyd. CCM 2011. Patients with lower quartiles of fluid balance had lower risk of mortality
- Micek. CCM 2013. Positive fluid balance at 24 hours had increased hospital mortality compared to those with lowest fluid
- Sedaka. J Int Care Med 2014. Patients with > 6 liters of fluid had higher mortality compared to those with < 6 liters of fluid
- Acheampong. CCM 2015. More positive fluid balance associated with higher mortality
- De Oliverira . J Crit Care 2015. Net fluid balance > 3 liters associated with increased hospital mortality
- Kelm. Shock 2017. Higher fluid balance at 72 hours but not 24 hours associated with increased mortality
- FEAST Trial. NEJM 2011. Higher mortality in with liberal fluids.

Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER)

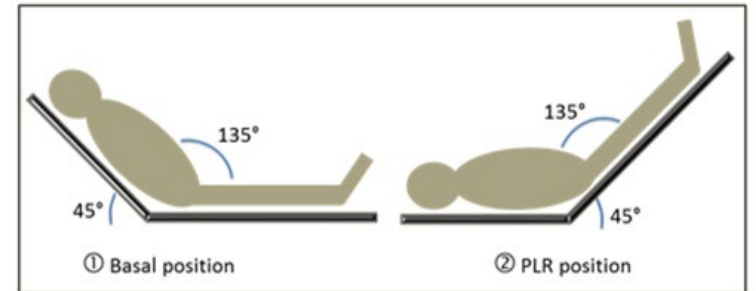
- Early Norepinephrine verse standard care
- Early Norepinephrine group
 - Improved shock control by 6 hours. 76.1% verse 48.4%
 - Lower incidences of cardiogenic edema. 14.4% verse 27.7%
 - Lower incidences of new-onset arrhythmias. 11% verse 20%
 - No difference 28 day mortality. 15.5% verse 21.9% (standard therapy)

Restrictive IVF Therapy in Sepsis

- Early use of vasopressors
- Smaller volumes if IV fluid bolus often ≤ 30 mL/Kg
- Judicious fluid administration only when proven fluid responsive.
- CLOVERS Trial. Multicenter unblinded clinical trial comparing liberal and restrictive fluid resuscitation strategies. 40 enrolling centers.

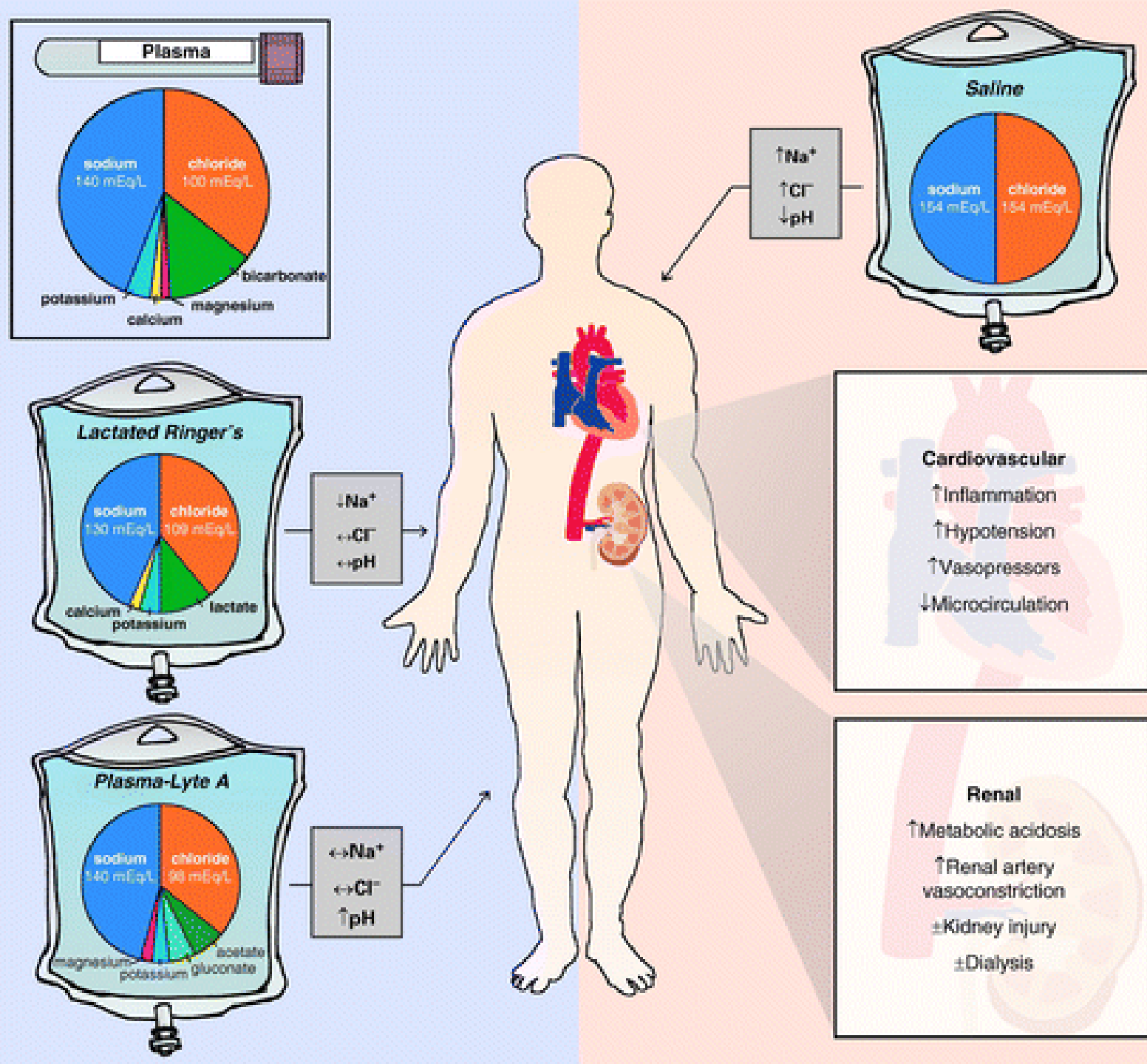
Fluid Responsiveness

- Determined by a change in the stroke volume or cardiac output of approximately 12-15% after a bolus dose of fluid.
- CVP, PAOP: poor sensitivity and specificity.
- The caval index = $\text{IVC max (expiration)} - \text{IVC min (inspiration)} / \text{IVC Max}$
- Stroke Volume Variation or Pulse Pressure Variation
- Velocity Time Index (VTI). A 12.5% change in the VTI had a sensitivity of 77% and specificity of 100%
- Passive leg raise equivalent to 500cc fluid bolus.
- Expiratory occlusion test.



Balanced Crystalloid Solutions

- AJRCMM 2019. Vol 199;952



Balance Crystalloid Solutions

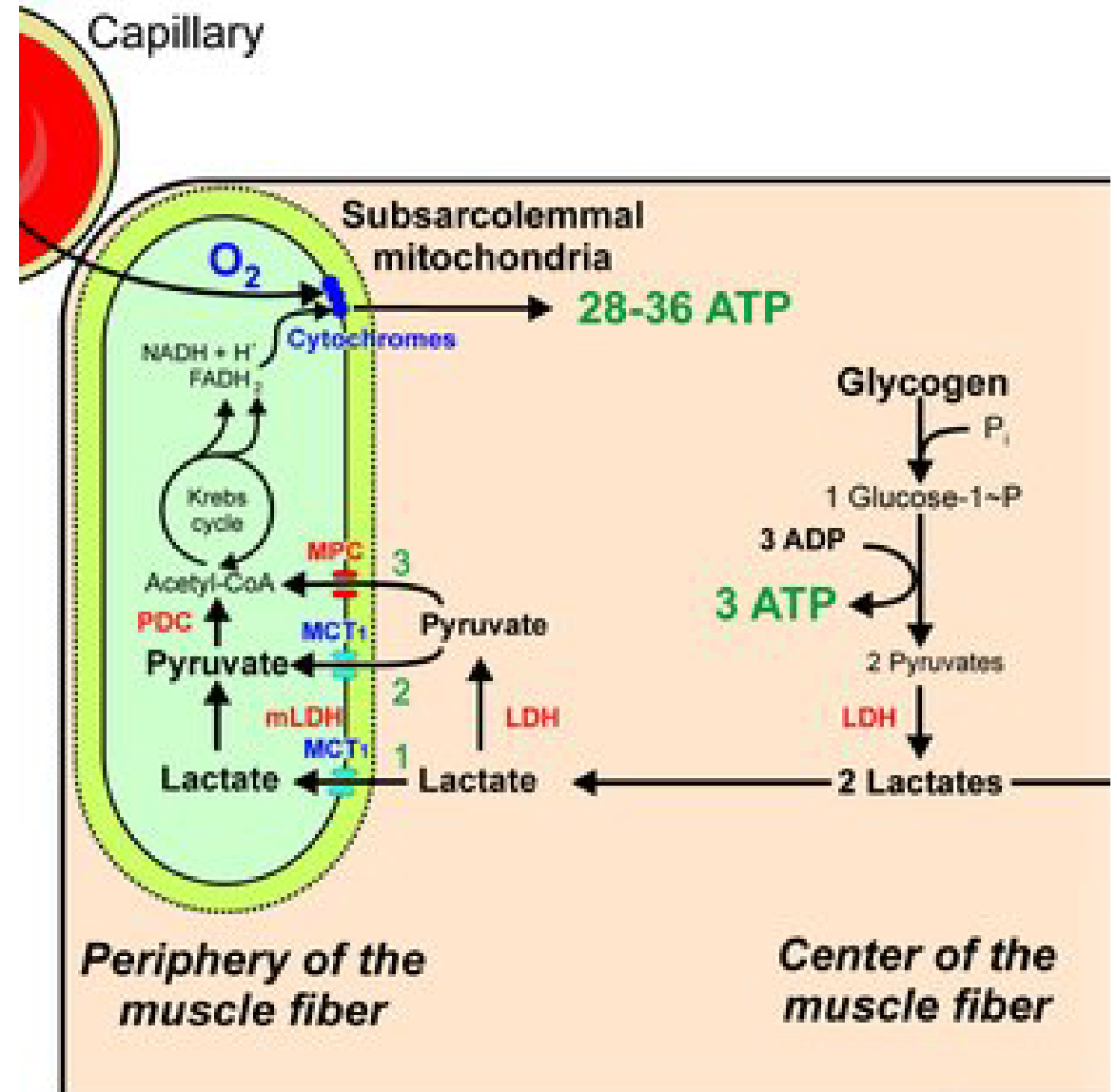
- SMART trial. NEJM. 378;829
 - Composite decrease death, doubling of creatinine, initiation renal replacement therapy from 15.4% in NS group to 14.3% in Balanced group
- SALT-ED. NEJM 378; 819
 - No difference in hospital free days
 - Decrease Major Adverse Kidney Events within 30 days. NNT 111
- Secondary Analysis SMART trial – publication pending AJRCCM
 - 1641 patient with sepsis. 30 Day mortality 26.3% balanced group verse 31.2% in the NS group. $P=0.01$
- Two large ongoing multicenter trials: PLUS and BaSICS

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

Lactate Shuttle Theory.

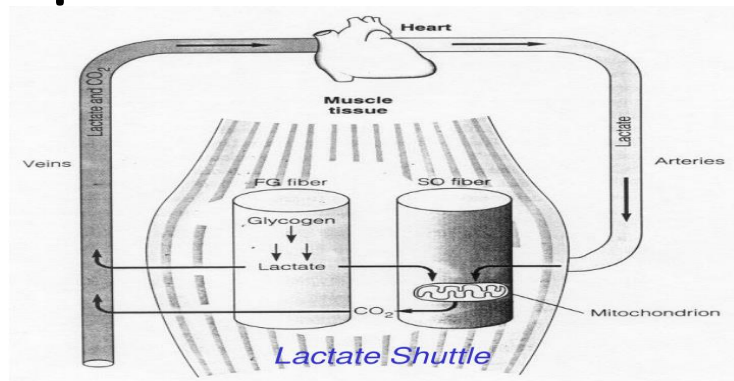
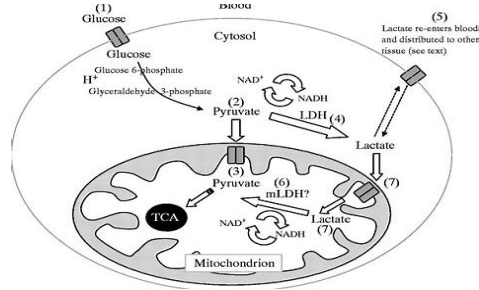
Dr. George Brooks

- Lactate is the terminal step of glycolysis not pyruvate
- Lactate is a major energy source
- Lactate is the major gluconeogenic precursor
- Signaling molecule with autocrine, paracrine, and endocrine effects



Lactate Shuttle

- Intracellular lactate shuttle
- Direct cell to cell transfer within a tissue bed



Lactate Shuttle in Sepsis.

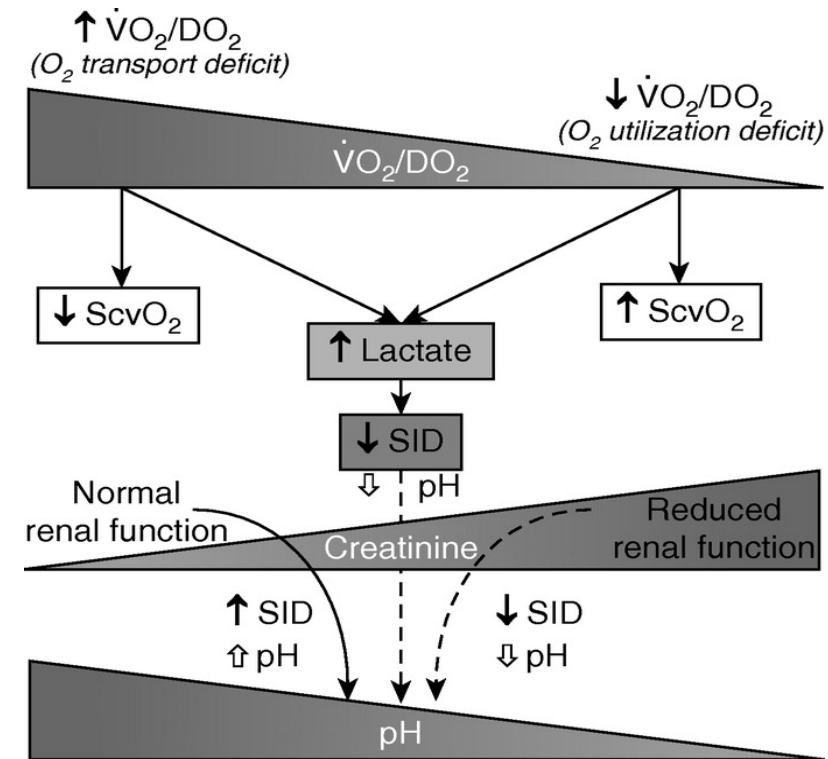
- Huge lactate clearance capacity in healthy individual
- Lactate key part of glucose metabolism, not anaerobiosis
- Elevated lactate when production exceeds oxidative metabolism
 - Overwhelm the endogenous pathway for lactate clearance
 - Excessive *B*-adrenergic stimulation
 - Exercise
 - Limit the endogenous capacity for lactate clearance
 - Respiratory chain impairment
 - Hypoxia
 - Thiamine deficiency
 - Liver failure

Lactate Shuttle

- Traumatic brain injury
 - >50% of brain fuel from lactate
 - L-lactate treatment is anti-inflammatory
 - L-Lactate enantiomer binds to putative lactate receptor GPR81 and inhibits activation of inflammatory pathways
- Heart Failure
 - Preferred fuel of exercising hearts over glucose and free fatty acids
- BAD – Cancer
 - Carcinogenesis, angiogenesis, tumor microenvironmental, cell migration

Understanding Lactatemia in Human Sepsis. Potential Impact for Early Management. AJRCCM 2019. 200(5): 582

- Lactate is powerful marker of illness severity
- Hyperlactatemia more frequently caused by impaired tissue oxygen use rather than by impaired oxygen delivery.
- Acidemia only observed in the presence of renal dysfunction.
- Clinical significance – patients with impaired oxygen delivery benefit from goal directed therapy. However, the majority of patients with good O₂ delivery but impaired cellular O₂ use may have worse outcome after aggressive fluid replacement.



ADROMEDA-SHOCK

- Target goal Lactate level decrease by 20% every 2 hours verse normalization of capillary refill time
- All patients had initial resuscitation and norepinephrine to maintain a MAP 65mmHg or higher.
 - Step 1. Fluid responsiveness. Fluid challenges with 500mL of crystalloids every 30 minutes in fluid responders until the goal was achieved.
 - Step 2. If not meeting goal, patients with chronic hypertension transiently increased norepinephrine to reach MAP 80-85mmHg. If goals met, then the higher MAP was maintained.
 - Step 3. Inodilator test; milrinone or dobutamine.
- Mortality decreased from 43.4% in peripheral percussion group to 34.9% in the lactate group, not statistically significant.
 - JAMA 2019. 321(7): 654

Steroids

- Decrease the duration of shock
- Unclear survival benefit
- Annane et al. 2002.
 - Hydrocortisone + fludrocortisone. Improved mortality
- CORTICUS TRIAL
 - Hydrocortisone. No mortality improvement
- ADRENAL trail. 2018. No change mortality.
 - Hydrocortisone + Fludrocortisone. Improved mortality
- APROCCHSS. 2018
 - Hydrocortisone. No mortality improvement

Transcriptomic Signatures in Sepsis and a Differential Response to Steroids

From the Vanish Randomized Trial

- Endotypes were determined: SRS1 and SRS 2
- Transcriptomic profile at onset of septic shock was associated with response to corticosteroids
- Both SRS1 and SRS2 had decreased time to shock resolution
- SRS1; higher vasopressor use. Higher SOFA scores. More severe disease.
- SRS2; significantly higher mortality when administered corticosteroids. (Odds ratio 7.9%, CI = 1.6-39.9)
 - Am J Respir Crit Care Med Vol 199, pp 980-986. April 2019.
 - VANISH. JAMA 2016; 316:509

Mitochondrial DNA Haplogroups and Delirium During Sepsis. CCM 2019;47:1065

- Retrospective cohort study of 810 patients.
- Variations in mitochondrial DNA are associated with development of delirium and protection from delirium during Sepsis.

Vasogenic Shock Physiology

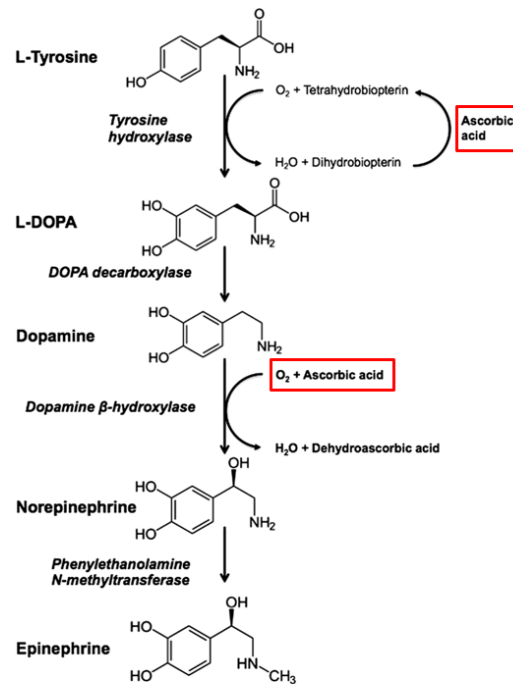
- Inducible Nitric Oxide
 - Increased expression with inflammation
 - Overproduction in Sepsis and myocardial depression
 - Nitric oxide maintains microcirculatory patency and function. Overproduction in unevenly distributed causing shunting.
- ATP – sensitive channels.
 - Inactive with normal levels of ATP. ATP deficiency (decreased O₂), NO overproduction, vasoactive hormones open the channels causing vasorelaxation
 - Steroids improved vascular tone probably due to inhibition of ATP channels
- Vasopressin - produced by hypothalamus and mediates vasoconstriction
 - Sepsis, Late-phase hemorrhagic shock/cardiogenic shock, vasoplegia of CABG

Paul E. Marik's Cocktail for Sepsis

- Hydrocortisone 50mg IV q 6 hours x 7 days
- Vitamin C 1.5 grams IV 6 hours x 4 days
- Thiamine 200 mg IV q 12 hour x 4 days

Vitamin C

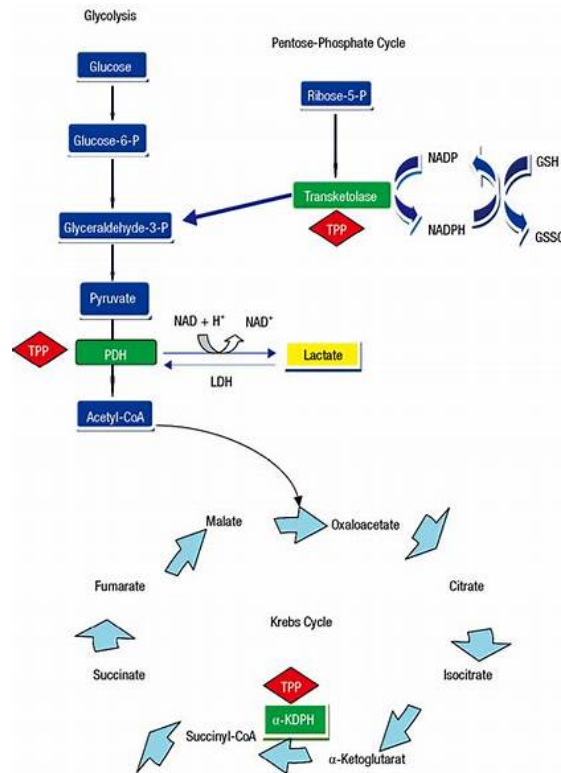
Vitamin C is required to synthesize catecholamines



Zipursky JS et al. *BMJ Case Rep* 2014; PMID 24859547

- Cofactors for synthesis of norepinephrine, dopamine, vasopressin, cortisol
- May increase vasomotor responsiveness
- Preserves endothelial barrier and microcirculation
- Increases host defenses by improving macrophage and T-cell function

Thiamine



- Cofactor for metabolism of branch chained amino acids
- Mitochondrial synthesis of ATP
- Glucose metabolism to pyruvate
 - J Thoracic Disease 2016. 8(6):2062
- Coenzyme that promotes oxidation of glyoxylate to carbon dioxide – prevents oxalate crystallization from Vitamin C metabolism

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of severe Sepsis and Septic Shock.

Chest 2017. 151(6):1229

- Retrospective before-after study.
- Mortality; 8.5% treatment group verse 40.4% control
- SOFA score; no patients in treatment group developed progressive organ failure.
- Decreased duration of vasopressor use. 18.3 ± 9.8 hours in treatment group verse 54.9 ± 28.4 hours
- Treatment with combination decreases mortality and organ dysfunction.

Readmission

- Very common: approximately 1/5
- High cost: 3.5 billion dollars (2013-2014)
- Decreased mortality has increased sepsis survivors at risk for readmission and “treat and release” from ER.
- Readmission for recurrent sepsis within 90 days discharge
 - 68.6% Infection at same site
 - 19% Same organism. (53% same site and organism)
 - CCM 2017; 45.1702
- Sepsis survivors discharge to nursing home have very poor prognosis

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 - Intensive Care Med 2018. 44:925

Summary

- Sepsis is a medical emergency warranting immediate and aggressive treatment.
- Heterogeneous syndrome
 - Organism, associated virulence factors, and site of infection
 - Patient genetics
 - Patients comorbidity
- Judicious (restricted) fluid strategy
 - Early vasopressors
 - Assess fluid responsiveness
- Physiologic based resuscitation
- Frequent reassessment of interventions and treatment

Selected Readings

- Management of Refractory Vasodilatory Shock
 - Chest 2018; 154 (2): 416-426
- Septic shock in the ER: diagnostic and management challenges
 - Open Access Emergency Medicine 2019: 11; 77-86
- Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial
 - Ann Emerg Med. 2018: 72(4); 457-466.
- The Science and Translation of the Lactate Shuttle Theory
 - Cell Metabolism 2018: 27; 757-785

Alactic Base Excess.

AJRCCM 2019. 200(5): 582

- Standard BE = $[\text{HCO}_3(\text{mmol/L}) - 24.8 \text{ mmol/L} + 16.2 \text{ mmol/L} \times (\text{pH} - 7.4)]$
- Alactic BE = standard base excess (mmol/L) + lactate mmol/L
- Alactic BE < 0; concentration of fixed acids other than lactate increased in plasma.
- Alactic BE = 0; suggests acidemia fully explained by lactate
- Alactic BE > 0; additional metabolic alkalosis.
- 1. Estimate of renal capability of handling acid-base equilibrium
- 2. Direct correlation to fluid balance.

Angiotensin II

- Naturally occurring peptide hormone of the renin-angiotensin-aldosterone system that causes vasoconstriction and increases aldosterone release, which raises blood pressure.
- Indication for vasodilatory shock not responsive to high doses of conventional vasopressors.
- Effectively increases blood pressure in refractory vasodilatory shock
- No change in mortality
- Very expensive \$1800 per 2.5 mL vial (NE \$2-6 per 1 mg/mL vial)
 - NEJM 2017; 377(5):419