

Cardiac Arrest and Shock in 2018

- Title
- Disclosures
- ▼ Objectives
 - ▼ Updates on Cardiac Arrest
 - Intra-arrest Treatments
 - Post-ROSC Treatments
 - ▼ Updates on Shock
 - How to think about lactate
 - Choosing vasopressors
 - Metabolic resuscitation
- ▼ Antiarrhythmics for Pulseless VT / VF
 - High resistance to defibrillation
 - Persists or reoccurs, correlates with worse outcomes
 - Amiodarone and lidocaine used to promote successful defib, prevent recurrences
- ▼ Amio better than lidocaine for improved ROSC success and survival to hospital admit
 - NEJM 2002;346:884
 - What about survival to hospital discharge and neurologic outcomes?
- ▼ NEJM 2016;374:1711. Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest
 - ROC-ALPS Study
 - ROC Study Group
 - RCT, Double-Blind, Placebo-controlled
 - 4653 pts
 - Excellent CPR
 - Likely definitive study
 - No significant difference in survival to hospital discharge or favorable neurologic outcome at discharge compared with placebo
- ▼ Reconfirmed usefulness in improving ROSC and hospital admission rates for both Amiodarone and Lidocaine
 - Less shocks required
- ▼ Time to treatment 19 minutes
 - Have progressed progressed to metabolic phase of OHCA
 - Cellular injury and physiologic derangements may be irreversible despite restored circulation

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- Signal that witnessed cardiac arrests did have improved outcomes with antiarrhythmic treatment
- ▼ Post-ROSC Early Head CT
 - Neurologic causes 15-20% of cardiac arrest
 - 54% of patients who survived OHCA underwent HCT in first 24H
 - ▼ 38% Acute abnormality
 - 12.2+6.1+ 7.0+6.0+3 - 34%
 - Ischemic stroke 6%
 - ▼ ICH 4+4+3+2+2+2+1+1+1 =
 - Intraparenchymal
 - Subarachnoid
 - INtraventricular
 - NO ICH survived
 - Subdural
 - ▼ Who got it
 - Previously healthy
 - Better pre-arrest functional status
 - Witnessed arrest
 - Shorter ROSC time
 - Concern for trauma or pre-arrest neurological complaints
 - Normal cardiac cath
 - ▼ 35% of abnormal scans changed management
 - NICU admission
 - Hyperosmolar therapy
 - Reversal of coagulopathy
- ▼ Survivability
 - NF = Arrest -> CPR
 - LF times = CPR -> ROSC
 - ▼ Factors affecting survivability
 - NF time
 - Initial rhythm
 - Location of cardiac arrest

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- Age
- ▼ Ann Intern Med 2016;165:770
 - ▼ Paris Sudden Death Expertise Center
 - SDEC 1-year data set
 - Validated in PRESSENCE Chort
 - ▼ Three factors with 100% PPV of non-survival to hospital discharge
 - Unwitnessed by EMS
 - Nonshockable initial rhythm
 - No ROSC before EPI x3
- ▼ Coronary Angiography
 - SCD may be the presenting manifestation of an acute coronary syndrome (ACS). Among patients with an ACS, malignant arrhythmias are significantly more common in the setting of an acute ST elevation MI (STEMI), but are also seen in approximately 2 percent of patients with a non-ST elevation MI (NSTEMI).
 - ▼ OHCA with ROSC and STE
 - Should go for coronary angiography based on standard STEMI criteria
 - ▼ OHCA with ROSC and NSTEMI
 - ▼ PROCAT (Parisian Registry Out-of-Hospital Cardiac Arrest) database
 - Culprit coronary lesion requiring PCI was found in nearly one-third of OHCA patients without STE.
 - In these patients, emergent PCI was associated with a nearly 2-fold increase in the rate of favorable outcome.
 - These findings support the use of an invasive strategy in these patients, particularly in those resuscitated from a shockable rhythm.
 - Meta-analysis of seven observational studies and one RCT, favored the use of early angiography was associated with decreased short term (OR = 0.46) and long term (OR = 0.59) mortality.
 - Despite the use of several statistical methods in an attempt to eliminate confounders, these observational studies are subject to considerable bias.
 - ARREST (A Randomised tRial of Expedited transfer to a cardiac arrest centre for non-ST elevation ventricular fibrillation out-of-hospital cardiac arrest) trial is one such study, and following a successful pilot study, recruitment to a large-scale RCT is about to start.
 - ▼ OHCA without ROSC
 - Complex but treatable CAD was prevalent in patients with refractory OH VF/VT cardiac arrest who also met criteria for continuing resuscitation in the CCL.
 - A systems approach using ECLS and reperfusion seemed to improve functionally favorable survival.
- ▼ Duration of Therapeutic Hypothermia

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- TH at 33°C – treatment for 24 hours versus 48 hours following resuscitation from cardiac arrest.
- Randomized 355 eligible survivors
- ▼ No difference.
 - Confidence intervals, however, were quite wide – for example, the relative risk for CPC 1 or 2 was 1.08 with 95% CI of 0.93 to 1.25, the top end of which represents a fairly meaningful difference.
 - One clear loser: ICU length-of-stay, and by association, healthcare costs, which will obviously favor the group with a shorter period of TTM.
- ▼ Lastly, it is reasonable to note one of the elements of causality generally entails a dose-response relationship, in which the magnitude of exposure to a beneficial therapy relates in some fashion a continuum of outcomes.
 - Lacking such an apparent relationship, as in this trial, does not refute an association between TTM/ TH and improved outcomes, but certainly continues to raise points regarding the precise elements of post-arrest care resulting in improved outcomes.
 - Cooling to 33°C does not appear to confer an advantage to 36°C, nor does an extended exposure to the treatment.
 - What is it really, then, that helps achieve the greater proportion of CPC 1 and 2 survivors?
- ▼ Therapeutic Hypothermia for In-Hospital Cardiac Arrest
 - ▼ JAMA 2016;316:1375
 - AHA Getting with Guidelines Cohort
 - Retrospective
 - 26183 pos with IHCA
 - 1568 treated with therapeutic hypothermia
 - ▼ Survival
 - 27.4% TH
 - 29.2% None
 - ▼ Favorable Neurologic Outcome
 - 17% TH
 - 20.5% None
 - ▼ TH has been shown to have worse outcomes for
 - TBI
 - Bacterial meningitis
 - ▼ Explanation
 - ▼ Faster response time in hospital
 - <1 min to chest compressions

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- 3 min to first EPI
- 80% of IHCA have non-shockable initial rhythm

▼ Shock

- Inadequate tissue perfusion to meet metabolic needs of tissues

▼ Lactate

- It is an important energy shuttle
- Not a “waste product” of anaerobic metabolism
- Glycolysis metabolizes glucose to pyruvate
- Lactate production arises mainly from skeletal muscle (25%), skin (25%), brain (20%), intestine (10%), and erythrocytes (20%).

▼ Pyruvate is also in equilibrium with lactate in the cytosol

- Bidirectionally catalyzed by LDH
- Under AEROBIC conditions, pyruvate enters the mitochondria to produce ATP

▼ If pyruvate is prevented from entering Krebs cycle, it is shunted to lactate and an abnormal lactate/pyruvate ratio develops

▼ This occurs when:

- Hypoxia
- Exceeds capability of mitochondria
- Mitochondrial dysfunction (sepsis induced cytokines)
- Thiamine deficiency

▼ Increased glycolytic flux

- Severe exercise
- High work of breathing
- Catecholamine administration
- Sepsis

▼ Lactic in septic shock

▼ Tissue Hypoxia Myth

- Not produced by anaerobic metabolism
- Septic patients have hyperdynamic circulation
- Oxygen delivery to tissues is adequate

▼ Produced by beta-2 adrenergic stimulation

- Endogenous catecholamines stimulate beta-2 receptors

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- This upregulates glycolysis, generating pyruvate
- Pyruvate is generated in excess of mitochondrial capability to use in the TCA cycle
- Excess pyruvate is converted into lactate
- This is entirely AEROBIC
- ▼ Lactate is ultimately a marker of catecholamine release
 - This makes it useful for detection of occult shock
- ▼ Usefulness of lactate
 - Correlated with increased mortality regardless of etiology
 - Lactate Clearance as marker of adequate resuscitation
 - Lactate clearance has repeatedly been shown to independently predict survival from sepsis
- ▼ Fluid Resuscitation
 - “When you have an hemodynamically unstable patient, give all the fluid they need but not one drop more”
 - Ensure adequate preload to maximize cardiac output
 - Diminishing-Accelerating Effects
- ▼ Static Measures
 - Exam (mucus membranes, capillary refill, pulses, JVD, mottling)
 - Laboratory studies (BUN/Cre, lactate, UOP, central venous saturation)
 - Invasive (PAC, CVP)
 - US (IVC)
 - Noninvasive (pulse contour, bioimpedance)
- ▼ Dynamic Measures
 - Very accurate
 - Rely on interaction of respiratory cycle and cardiac preload
 - Requires mechanical ventilation
 - Pulse Pressure Variation, Cardiac Output on Echo, Passive Leg Raise
- ▼ Vasopressors
 - Vasopressors and inotropes demonstrate rather predictable receptor activity
- ▼ Patient response may vary considerably
 - Based on endogenous sympathetic response
 - Variable end-organ sensitivity
 - Individual physiology (preload/afterload and right/left ventricular systolic function)

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- Hemodynamic targets need to be individualized

▼ Cardiogenic Shock

- Defined as ineffective cardiac output caused by a primary cardiac disorder results in both clinical and biochemical manifestations of inadequate tissue perfusion.

▼ Treatments

- Adequate volume resuscitation
- Mechanical ventilation

▼ Inotropes / Vasopressors

- DOP vs NE
- Vasopressor and inotrope selection for cardiogenic shock follows similar physiologic principles as septic shock. There is not a single preferred vasoactive therapy, with the strategy dependent upon the etiology (left heart failure, right heart failure, outflow obstruction, aortic stenosis/regurgitation, or mitral stenosis/regurgitation) and clinical presentation. Fluid and vasoactive strategies are often guided by dynamic bedside exam and invasive monitoring devices to enable optimization of preload, afterload, pulmonary vascular resistance, atrioventricular synchrony, and contractility. It is generally recommend to utilize low doses (and often combination vasoactive therapies) to minimize demands on myocardial oxygen consumption, especially in cases of acute ischemia.¹² Listed below are considerations for various presentations or conditions:

▼ Reperfusion

- Thrombolytics or PCI

▼ SHOCK Trial

- The first major breakthrough in CS treatment was achieved by the randomized SHOCK trial.
- Although an early invasive strategy coupled with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) did not reduce 30-day mortality (the primary outcome of the trial), a significant mortality reduction emerged at 6 and 12 months that persisted at longer-term follow-up.
- Subsequent registries confirmed the survival advantage of early revascularization.

- Mechanical Circulatory Support

▼ Specific Conditions

▼ Right Ventricular Failure

- Ideally, maintain preload, reduce right ventricular afterload, and prevent bradycardia.
- Vasopressin increases preload without increasing pulmonary vascular resistance (and RV afterload), unlike norepinephrine.
- Dopamine is preferred in the presence of bradycardia.
- Pulmonary vasodilators can be utilized to reduce right ventricular afterload.
- It is important to ensure that vasopressor selection maintains atrioventricular synchrony.

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▼ Aortic Stenosis

- Cardiogenic shock secondary to aortic stenosis is afterload-dependent.
- Accordingly, phenylephrine or vasopressin are commonly utilized to optimize afterload.
- If left ventricular dysfunction is present, addition of an inotrope following hemodynamic stabilization may be beneficial.

▼ Aortic Regurgitation

- Dopamine may be preferred to maintain relative tachycardia, a shortened diastolic filling time, and a reduced preload.

▼ Mitral Stenosis

- Contrary to aortic stenosis, cardiogenic shock secondary to mitral stenosis is pre-load dependent.
- Phenylephrine or vasopressin may be utilized in this setting to enhance preload.
- Positive chronotropes should be avoided, as they shorten diastolic filling time, thereby reducing preload.

▼ Mitral Regurgitation

- Norepinephrine or dopamine are preferred for initial hemodynamic stabilization.
- If left ventricular dysfunction is present, addition of an inotrope following hemodynamic stabilization may be beneficial.

▼ Bradycardia

- Positive chronotropes (isoproterenol, dopamine, dobutamine or epinephrine) should be utilized to optimize heart rate.

▼ Milrinone

- May have a larger inotropic role in subsets of cardiogenic shock, especially in patients on aggressive beta-blockade prior to presentation (and not responsive to dobutamine) or those cases benefiting from a reduction in pulmonary vascular resistance.

▼ Septic Shock

- Physicians can consider the Surviving Sepsis Guideline expert recommendations during initial therapy selection; however, therapy should be individualized for each patient based on observed response and supporting bedside dynamic monitoring.

▼ Vasodilatory shock

- Catecholamines elevated and RAAS activate
- Response failure of vascular smooth muscle

▼ Causes

- Activation of AT-Sensitive Potassium Channels
- Increased synthesis of Nitric oxide

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- Deficiency of vasopressin

▼ Norepinephrine

- First line vasopressor per Surviving Sepsis Guideline (strong, moderate quality).
- It increases vascular resistance (α_1) with variable, but often minimal responses on heart rate and cardiac contractility (β_1), particularly at doses < 0.2 mcg/kg/min. Tachycardia may manifest as the dose escalates with a variable impact on cardiac contractility, which is largely dependent upon preload and resultant afterload.
- SOAP II study compared norepinephrine and dopamine in shock. The norepinephrine arm had less incidence of arrhythmias and was associated with lower mortality in the cardiogenic shock subset.
- A meta-analysis found that norepinephrine displayed decreased mortality and was less arrhythmogenic than dopamine.

▼ Vasopressin

- The Surviving Sepsis Guideline recommends adding low dose vasopressin (0.03 units/min) as a norepinephrine sparing measure (weak, low quality).
- At low doses (< 0.04 units/min), it moderately increases vascular resistance (V1) without substantial effects on heart rate and cardiac contractility. It will demonstrate mild fluid retention (V2), but with little expected clinical relevance.
- It may serve to restore catecholamine receptor responsiveness, particularly in cases of severe metabolic acidosis.
- The VASST study compared norepinephrine vs norepinephrine + vasopressin in septic shock. The addition of low dose vasopressin to norepinephrine did not result in lower mortality.
- The VANISH study compared norepinephrine vs early vasopressin and the impact on kidney failure in septic shock. The vasopressin arm utilized less renal replacement therapy, but did not reduce the incidence of kidney failure.

▼ Epinephrine

- The Surviving Sepsis Guideline recommends the addition of epinephrine to norepinephrine to achieve targeted MAP (weak, low quality).
- At low doses (< 0.05 mcg/kg/min), it increases heart rate and cardiac contractility (β_1) with minimal effect on vascular resistance (α_1). As the dose escalates, an increase in vascular resistance is expected with a variable response on cardiac contractility, largely dependent upon preload and resultant afterload.
- It may stimulate glycolysis (2), thus increasing serum glucose and lactate production, which may limit the utility in monitoring lactate clearance.
- In a prospective, randomized trial, both epinephrine and norepinephrine displayed similar times to achieve perfusion target; however, the epinephrine arm had more metabolic effects.

▼ Dopamine

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- The Surviving Sepsis Guideline recommends dopamine as an alternative to norepinephrine if absolute or relative bradycardia (weak, low quality). It is not recommended to use low dose dopamine for renal protection (strong, high quality).
- At low doses (< 5 mcg/kg/min), it is expected to have minimal effect on restoring hemodynamics as affinity for dopamine (DA) receptors predominate. As the dose escalates, an increase in heart rate and cardiac contractility (β_1) is expected, with an increased vascular resistance (α_1) occurring at the higher end of the dose range.

▼ Phenylephrine

- The Surviving Sepsis Guideline does not make rated recommendations on its use given limited clinical trial data.
- It increases vascular resistance (α_1) with variable, but often an observed decrease in heart rate mediated by the carotid baroreceptor reflex. The cardiac output may vary, largely dependent upon preload and resultant afterload.
- It may be a reasonable strategy in patients whom are particularly susceptible to beta-adrenergic generated arrhythmia.

▼ Dobutamine

- Per the Surviving Sepsis Guideline, it should be considered if there is persistent hypoperfusion despite adequate volume status and vasopressor augmentation (weak, low quality).
- It increases heart rate and cardiac contractility (β_1), with a variable response on mean arterial pressure, depending upon the degree of concomitant systemic vasodilation (β_2).
- It may be a reasonable adjunctive agent to norepinephrine in patients with a component of low output heart failure.

▼ Milrinone

- The use of milrinone is unrated in the Surviving Sepsis Guideline given lack of supporting clinical trial data.
- It increases heart rate and cardiac contractility (cAMP), with a decrease in both systemic and pulmonary vascular resistance (cAMP).
- An initial bolus is generally not recommended in any patient population. It is excreted via the kidney (83% unchanged), thus caution must be taken if used in patients with renal impairment to avoid adverse hypotensive effects.

▼ Angiotensin II

▼ Search for holy grail of vasopressors

- Should be potent
- Non-adrenergic mechanism of action to contribute to the de-catecholamination of intensive care therapy.
- Norepinephrine 0.2 $\mu\text{g}/\text{kg}/\text{min}$ nor equivalent have a mortality risk of >50%.

▼ Angiotensin II

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- Angiotensin II targets the renin-angiotensin-aldosterone system (RAAS), a powerful mediator of arterial blood pressure.
- Octapeptide hormone
- Cleaved from angiotensinogen by actions of renin and ACE
- Circulating half-life of approximately 30 seconds, and in the tissues it can last as long as 15 to 30 minutes.
- Affects a totally separate vasopressor pathway and is therefore synergistic with noradrenaline and vasopressin
- Has no inotropic or chronotropic properties, which makes it a perfect agent for preserving a nice long diastolic filling time.
- ▼ Synthetic human angiotensin II
 - Giapreza
 - Manufactured by La Jolla pharmaceuticals
 - Approved by the FDA Dec 21, 2017 for use in patients with distributive, predominantly septic shock
- ▼ ATHOS-3
 - Shock despite receiving more than 0.2 µg/kg/min of norepinephrine or another vasopressor in a similar dose.
 - Randomized 321 patients with vasodilatory shock (80% in septic shock) to receive either angiotensin II or placebo.
 - About 70% of patients receiving angiotensin II for three hours achieved a mean arterial pressure of 75 mm Hg, or an increase of at least 10 mm Hg, without an increase in their other vasopressors.
 - ▼ Primary endpoint was achieved in 69.9% of patients receiving angiotensin II infusion as compared to 23.4% of those receiving placebo (OR 7.95; CI [95%] 4.76 – 13.3; P<0.001).
 - Only 23% of patients receiving placebo (and their other vasopressors) achieved this primary endpoint.
 - After 28 days, mortality was 46% in the angiotensin II group and 54% in the placebo group (hazard ratio 0.78 with a confidence interval just barely crossing 1).
- ▼ DVT Complications
 - Incidence of arterial and venous thrombotic and thromboembolic events was 13%, compared with 5% in the placebo group, largely driven by deep vein thrombosis.
 - Endogenous angiotensin-II is implicated as a factor in microvascular thrombosis associated with hypertension
- ▼ Indications
 - ▼ Severe ARDS (where ACE levels are low because of pulmonary parenchymal destruction)

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- There is not enough lung to convert angiotensin-I to angiotensin-II
- Counteract premonitory ACE-inhibitor treatment.
- Counteract the sepsis-associated downregulation of the angiotensin-II receptor.
- These are straightforward: angiotensin is genuinely absent in the first case, and its receptors are disabled in the second, and missing in the third
- ▼ Use
 - At present, place in therapy is likely as a third line pressor.
 - General strategy is to wean off vasopressin first, then catecholamines, while titrating up angiotensin-II.
- ▼ Steroids
 - ▼ Annane Trial
 - 2002
 - 299 patients
 - Short-term mortality benefit with IV hydrocortisone and fludrocortisone among patients with evidence of adrenal insufficiency on ACTH stimulation testing
 - ▼ CORTICUS Trial
 - 2008
 - 499 patients
 - Hydrocortisone in patients with and without adrenal insufficiency
 - Faster reversal of shock but no mortality benefit in either subgroup
 - Suggestion of increased infection rates in patients receiving hydrocortisone.
 - ▼ HYPRESS
 - 2016
 - 380 patients showed no difference in mortality
 - Showed decrease time to reversal of shock.
 - Two new articles published this year in same edition of NEJM
 - ▼ ADRENAL Trial
 - Randomized 3,800 patients with septic shock requiring mechanical ventilation in 69 medical-surgical ICUs (2/3 medical, 1/3 surgical) around the developed world
 - Hydrocortisone (200 mg/day) or placebo for 7 days for as long as they were in the ICU
 - ▼ Results
 - ▼ No difference in 90-day mortality (the primary outcome)
 - Negative trial

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- However, patients receiving steroids had resolution of shock 1 day sooner overall (median 3 vs. 4 days).
- They also were liberated from the ventilator faster (6 vs. 7 days)
- Median of two fewer ICU days during their hospitalizations.
- Came at an expected cost of more hyperglycemia, which was virtually always manageable.

▼ Summary

- Stress-dose corticosteroids appear safe and generally beneficial in patients with septic shock undergoing mechanical ventilation, without improving survival.
- No increased rate of infections observed in the steroid group.
- Shift clinical practice away from a general reluctance to give steroids (reserving them only for patients with septic shock refractory to vasopressors) to a more liberal approach.
- Encouraged by the risk/benefit balance in ADRENAL, many intensivists will likely provide stress-dose IV hydrocortisone (which equates to a mere 50 mg/day of prednisone) to patients with septic shock on any dose of vasopressor, earlier in their clinical course, in the hopes of resolving shock and respiratory failure faster. Some may choose to add a dose of 50 µg fludrocortisone, for good measure.

▼ APROCCHSS Trial

▼ Details

- 2008-2015
- 1241 patients in France
- Septic shock for less than 24 hours
- Enrollment criteria selected for patients with more-severe septic shock: SOFA scores of 3 or 4 for at least two organs for at least 6 hours, and receipt of vasopressors for at least 6 hours.
- Received either hydrocortisone 50 mg IV every 6 hours along with a daily dose of fludrocortisone 50 µg through a nasogastric tube, or placebo, for 7 days.

▼ Results

- 43% mortality at 90 days (the primary outcome), compared to 49% for the placebo group.
- NNT of about six patients to help one survive to 90 days.
- Mortality was improved at other time points, as well.
- Those receiving steroids also had two fewer days of vasopressor use or organ failure, and had one fewer day (non-significant) receiving mechanical ventilation.
- Hyperglycemia occurred significantly more often in patients receiving steroids, but there were no increased infection rates or other adverse events noted in the steroid-treated group.

▼ Problems with study

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- The trial initially had two other arms testing activated protein C alone or with the steroid cocktail; the trial continued with the steroid vs placebo arms after aPC was withdrawn from the market for lack of efficacy.
- The long timeframe of the APROCCHSS trial (spanning the publication of the Process, Arise, and Promise trials showing no benefit of protocolized goal-directed therapy for sepsis)
- High mortality rate relative to recent sepsis trials (at least partly due to its selection for more-severe septic shock)
- Single-nation design invite caution rather than immediate global application of its conclusions to all patients in septic shock.
- Has a Fragility Index of 3 (if 3 more people in hydrocortisone group died, it would have been non-significant result).

▼ Overall

- Results from CORTICUS, ADRENAL, and APROCCHSS point in the same general direction: stress-dose corticosteroids and mineralocorticoids appear safe and generally beneficial for patients with septic shock.
- Hyperglycemia should be expected and managed to avoid its adverse effects.
- Lot of academic argument
- Seems to be no where near as good as proponents want to think nor as bad as detractors think.

▼ Vitamin C

- Metabolic Resuscitation

▼ Vitamin C becomes depleted in sepsis

- Cofactor required for the production of catecholamines and cortisol
- Helps maintain the integrity of the endothelium (i.e. glycocalyx)

▼ Administration of high-dose Vitamin C helpful?

- Ascorbic acid IV 25 mg/kg or 1.5 g every 6 hours\

▼ Generally safe at high doses

- Can rarely cause acute renal failure through oxalate crystal deposition.

▼ Studies

- In Tanka 2000, among 37 patients with major burns, those randomized to receive infusion of vitamin C at high doses (e.g., 4-5 grams an hour) for 24 hours on admission required less fluid resuscitation and had fewer ventilator days than those who got usual care.
- Fowler 2014 found less organ dysfunction among the 24 patients with severe sepsis randomized to vitamin C infusion vs placebo, with a significant dose-response (up to a maximum dose of ~3-5 grams IV every 6 hours). No safety issues in this Phase I trial.

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- Zabet 2016 randomized 24 post-surgical patients with septic shock to vitamin C infusion (~1.5-2.5 grams IV every 6 hours) or placebo; the vitamin-C treated patients had significantly lower mortality and need for vasopressors.
- ▼ Marik 2017 enrolled 47 septic patients with a cocktail of 1.5 g vitamin C IV every 6 hours, hydrocortisone 50 mg IV every 6 hours, and thiamine 200 mg IV every 12 hours (thiamine inhibits oxalate production and has potential benefits in septic shock. Controls were 47 patients matched in baseline characteristics).
 - Hospital mortality was 4 of 47 (8.5%) in those treated with the cocktail, compared to 19 of 47 (40%) in those not.
 - Vasopressors were weaned off all cocktail-treated patients, usually in <24 hours (vs. 4 days for the controls).
 - Renal function reportedly improved in all patients with acute kidney injury.
- ▼ So why don't we already rush to replace this vital nutrient in septic patients?
 - Lots of endogenous substances are depleted in sepsis, but as most are markers of illness rather than contributors
 - ▼ Normalization Fallacy
 - Replacing them may be useless or harmful
 - Skeptics will demand additional efficacy and safety data before changing practice.
- ▼ Refractory Shock
 - ▼ Patient example
 - Antibiotics given
 - Lungs are so full that you won't consider another fluid bolus
 - Norepinephrine at double strength
 - Vasopressin is at 2.4 units per hour.
 - Corticosteroids have been thrown in
 - But the mean arterial pressure just won't stay up. Lactate remains high, extremities remain mottled, urine output has dwindled to zero.
 - Mortality rate of over 50%
 - Prepare for a difficult discussion with the family.
 - Is there anything left?
 - ▼ More norepinephrine
 - NE dose in excess of 0.5 $\mu\text{g}/\text{kg}/\text{min}$ is generally held to be "high dose".
 - ▼ Kind of arbitrary cutoff, but does predict mortality
 - At 0.5 $\mu\text{g}/\text{kg}/\text{min}$, the AUROC was 0.85 and the sensitivity and specificity for the likelihood of mortality was 96% and 76%, respectively.

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- At 90 days, people receiving 1.0 $\mu\text{cg/kg/min}$ (or around 35ml/hr of "double strength" noradrenaline) had a mortality of 83%
- Many of us will become somewhat anxious when the nurses ask whether they can load up four times the usual dose of norepinephrine into the infusion bags so that they don't have to keep hanging them up every hour.
- Much of the literature on alternative vasopressors discusses things in terms of their "noradrenaline-sparing" effect.
- Is there an irrational fear of high dose noradrenaline among intensive care professionals?
- ▼ Katsaragakis 2006
 - Retrospectively reviewed data from 1999 - 2002 to determine whether high dose norepinephrine was really as bad as it is made out to be.
 - Patients included in this review were receiving over 4 $\mu\text{cg/kg/min}$ of noradrenaline
 - 12 pts with survival rate was 33%.
 - Lost digits and limbs?
 - Maybe we are being pansies
- ▼ Sodium Bicarbonate
 - ▼ In metabolic acidosis, alpha-1 receptor responses are blunted.
 - The correction of acidosis by bicarbonate should therefore improve the catecholamine receptor sensitivity, and in turn improve the vasoplegia.
 - ▼ Acidosis is probably not the main player in septic hemodynamics.
 - Consider: ketoacidosis patients frequently turn up with a pH of 6.8, but they never have such severe hemodynamic instability as the septic public.
 - Sodium bicarbonate should also have a series of other positive effects, such as volume resuscitation (it is hyperosmolar and it has plenty of sodium in it).
 - ▼ Bicarbonate certainly has not had much haemodynamic effect in clinical studies.
 - ▼ Cooper 1990.
 - Gave bicarbonate to patients in whom the pH was as low as 6.9, and did not find any hemodynamic improvement.
 - These authors did not correct ionised calcium, allowing it to drift dangerously low (0.87 mmol/L) which might explain some of the effect failure.
 - ▼ Consider buffer therapy if the patient has a pH under 7.15
 - Thought to be the threshold below which catecholamine receptors are particularly insensitive
 - When myocardial depression by metabolic acidosis begins to play a role
 - While acidosis might play a minor role, correcting severe acidosis is worth a shot if nothing else is working.

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▼ Calcium

- Ionised hypocalcemia is a well-acknowledged cause of hypotension in critically ill patients
- ▼ Hypocalcemic patients respond well to calcium administration
 - Blood pressure and cardiac output improve
 - Correction of hypocalcemia leads to significant improvement of hemodynamics only if the ionized calcium level was severely decreased (i.e. down by one third, to about 0.9-0.8 mmol/L).
- ▼ Contemporary studies did not show any benefit in terms of survival
 - Some animal evidence of increased mortality
 - Apparently, the increased serum calcium sends a really powerful pro-apoptotic signal to near-death injured tissues
 - In short, correction of hypocalcemia is at least transiently helpful, but induction of hypercalcemia is probably completely pointless.

▼ Esmolol

- Diastolic dysfunction and tachycardia have both been associated with increased mortality in sepsis.
- Improved diastolic filling with heart rate reduction
- Idea of slowing down the heart rate and increasing diastolic filling time to improve stroke volume has come up several times in the history of critical care literature.
- Retrospective audits and case series also exist which have related the chronic use of β -blockers with an improved mortality in sepsis (Christensen 2011)

▼ Morelli 2013

- Randomized 77 patients to receive esmolol (aiming for a heart rate between 80 and 94) and another 77 to remain tachycardic.
- Esmolol group had massively improved mortality (49.4% in the esmolol group vs 80.5% in the control group)
- Decreased fluid requirements
- This rings alarm bells, because no sepsis control group should ever have 80% mortality
- Results were probably affected by the fact that 49.4% of the esmolol group and 40.3% of control patients received levosimendan.

▼ Methylene blue

- Methylene blue is a dirty drug with numerous effects
- Among which is the inhibition of inducible nitric oxide synthase and guanylate cyclase.
- ▼ Nitric oxide synthase inhibition has a long rich history in the sepsis literature, and most of it is bad news.
 - For example, a 2004 trial of stupidly named "Agent 546C88" (Lopez) was terminated prematurely because of increased mortality in the treatment group.

Cardiac Arrest and Shock in 2018

- However, methylene blue does not seem to have the same negative stigma.
- ▼ One of the major concerns with this class of drugs is the potential for pulmonary vasoconstriction.
 - Kirov (2001) did not find this to be a problem in their small open-label trial.
- ▼ The drug was given as a loading bolus (1.0mg/kg) followed by an infusion of 0.5 mg/kg/hr for 4 hours.
 - A total dose of about 7mg/kg is thought to be the daily maximum (adverse effects such as methemoglobinemia tend to develop beyond that dose range).
 - Everybody seems to give a short course as described above; nobody has ever studied infusions going for 24 hours or longer.
- El Adawy (2016) found that hemodynamic goals were achieved faster with methylene blue as compared to vasopressin.
- Good quality trial evidence for the use of methylene blue is hard to find, likely at least in part because of the fact that it is a relatively old cheap drug and nobody is going to make money from an increase in its use (in fact, its cheaper than noradrenaline).
- Most of the observational studies throw methylene blue at the patient in the desperate hours prior to death, which completely obliterates any chances of a positive effect being observed.
- In spite of this, a clear signal from the literature is that it increases systemic vascular resistance and acts to decrease the requirements of other vasopressors.
- ▼ High dose insulin in septic shock
 - The use of glucose insulin and potassium (GIK) as an infusion has been extrapolated from the experience of toxicologists in treating β -blocker overdose.
 - Theoretically, the use of insulin to "force" more glucose into the myocardium should somehow enhance its contractility, and the activation of c-AMP second messenger system should bypass the catecholamine receptors which have been disabled by severe acidosis.
 - Like methylene blue, this strategy has seen more use in the setting of post-bypass vasoplegia.
 - In 2006, Hamdulay published a report of two cases where septic shock with myocardial depression was treated with glucose insulin and potassium. The dose rate was 1.5 units/kg/hour, similar to the β -blocker overdose protocol (the patient ends up getting about 100 units per hour).
 - Apart from the cardiotoxic effects, insulin has a variety of immunomodulatory effects, including decrease in the circulating levels of IL-6 and TNF- α .
 - One can conceive of a situation where all possible inotropes have been employed, with persisting severe global systolic dysfunction.
- ▼ Mechanical Circulatory Support
 - VA ECMO
 - The ultimate response to a failing circulatory system is to replace the failing motor with a reliable external alternative
- ▼ Brechot 2013

Cardiac Arrest and Shock in 2018

- Reported retrospectively on the experiences of their single centre from 2008-2011.
- During that time, 14 patients underwent VA ECMO for septic shock (all had severe cardiac dysfunction as the main problem, rather than vasoplegia).
- All appeared doomed (mean SOFA scores were 18).
- There was a surprising 71% survival to discharge, which suggests that this strategy is not without merit.
- That is probably the only large series of such aggressive therapy for sepsis. Indications for VA ECMO (apart from an LVEF < 25%) were sustained hypotension in the face of high dose vasopressors and inotropes (dobutamine > 20 µg/kg/min and noradrenaline > 1.0 µg/kg/min).
- Patients were excluded if their cardiac index was preserved.

▼ PIV Infusions

▼ Central Venous Catheters

- Decreased usage for CVP, ScvO₂
- Focus on infection and complications
- There's only one sure way to prevent complications from a central line: don't place one.
- Two recent studies suggest that risk is likely lower than was thought, and vasopressors might be safely administered through peripheral IVs in the large majority of patients— at least temporarily

▼ Study

- 730 patients with vasopressors through peripheral IVs

▼ More than 2/3 were given norepinephrine

- Considered to be a relatively dangerous vasoconstrictor in peripheral tissues
- At up to 0.70 mcg/kg/min

▼ Rates of extravasation

▼ Norepinephrine 3.2%

▼ Norepinephrine may have a greater risk of extravasation and tissue injury

- Given its degree of vasoconstrictive (α₁) potency
- Lack of concomitant dermal vasodilation (β₂) activity
- Level of acidity (pH 3 – 4.5).

- Dopamine 2.9%

- Phenylephrine 0%

- No cases of tissue ischemia.

▼ Strict line-management Protocol

- Veins had to be measured by ultrasound and confirmed > 4 mm diameter

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- 18-20 gauge IVs had to be placed in the opposite arm from the blood pressure cuff
- Not in the hand, wrist, or antecubital fossa
- IV sites were maintained less than 72 hours
- ▼ Checked every 2 hours for signs of extravasation or absent blood return
 - These checks necessitated frequent brief interruptions in vasopressor infusions
- ▼ Management of extravasation
 - Stop the vasoactive peripheral infusion, aspirate residual medication, and remove the catheter.
 - Elevate the extravasation site and apply warm compresses proximally.
 - Demarcate the extravasation margins
 - Phentolamine 5 mg/5 mL normal saline, 0.5 – 1 mL local aliquot injections around leading edge of extravasation margins.
 - Nitroglycerin paste (2.5 cm) applied to extravasation area.