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Vasopressors and Inotropes (and Shock)

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Presenter Disclosures

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- This CME program and its material is peer reviewed and all the recommendations involving clinical medicine are based on evidence that is accepted within the profession; and all scientific research referred to, reported, or used in the CME/CPD activity in support or justification of patient care recommendations conforms to the generally accepted standards.

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Objectives

By the end of this presentation, the learner will:

- Better understand shock and the role of fluids.
- Learn something new about one of the 5 pressors discussed today.
- Appreciate the benefits of Norepinephrine!
- Review some of the latest in research about pressors.
- Determine an approach to shock and pressor use in the ER.

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Harold

82 year old man in the ER

- *Brought in by his son, who reports that earlier today, his father had been in his usual state of health. This evening he found his father confused, with labored breathing. On arrival, the patient has the following vital signs: temperature, 38°C; heart rate, 130 beats/min; blood pressure, 110/60 mm Hg; respiratory rate, 34 breaths/min; and oxygen saturation, 89% on room air. Weight is 88 kg. He is delirious and unable to answer questions. A focused physical examination demonstrates tachycardia without extra heart sounds or murmurs, right basilar crackles on lung auscultation, a benign abdomen, and 1+ lower extremity pitting edema. You establish intravenous access with a peripheral catheter and send basic labs. A further history obtained from the son reveals that his father has congestive heart failure with a low systolic ejection fraction, as well as a history of several prior myocardial infarctions that were treated with stent placement.*

Shock

Approach

- Shock is a condition of inadequate tissue perfusion.
- Fluids to restore perfusion?
- Tools to decide?

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Shock

- The mechanisms that can result in shock are divided into 4 categories:
  - (1) hypovolemic (vomiting, bleeding)
  - (2) distributive (leaky pipes: sepsis, neurogenic, anaphylaxis, cirrhosis)
  - (3) cardiogenic (ineffective pump)
  - (4) obstructive (circulation flow blocked: tension pneumo, tamponade, PE)

- When the production of lactate overwhelms clearance mechanisms, the serum lactate concentration will rise, making lactate a particularly useful marker in the evaluation of patients in shock.
- No Colloids

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Shock

•Emergency Medicine Practice www.ebmedicine.net • March 2014

Table 1. Categories Of Shock[2]

Category	Hemodynamics	Causes
Hypovolemic	↓ preload ↑ SVR ↓ CO	Hemorrhage, GI losses, third spacing, burns
Distributive	↓ preload ↓ SVR ↑/↓ CO	Sepsis, anaphylaxis, neurogenic shock, pancreatitis
Cardiogenic	↑ preload ↑ SVR ↓ CO	Myocardial infarction, symptomatic bradycardia, valvular disease, heart blocks, end-stage heart failure
Obstructive	↓ preload ↑ SVR ↓ CO	Pulmonary embolism, tension pneumothorax, pericardial tamponade

Abbreviations: CO, cardiac output; GI, gastrointestinal; SVR, systemic vascular resistance.

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Establishing shock

- Emerg Med Clin N Am 32 (2014) 811–822

- physical exam:
  - JVP
  - Urine output
- Filling pressure:
  - STATIC
    - 1. CVP (with catheter)
    - 2. u/s IVC right atrial pressure

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Establishing Shock

Filling Pressure

- DYNAMIC (usually intubated and ventilated for monitoring)
  - mechanical ventilation increases intrathoracic pressure and variation in preload mimics a fluid bolus.
  - PPV (pulse pressure variation) using arterial line
  - IVC distensibility index (measure IVC u/s several times with vent)
  - EEO (end expiratory occlusion test)
    - placing a 15-second expiratory hold on the ventilator (end of expiration). A prolonged state of increased preload is created by holding the positive pressure ventilation at it its lowest pressure, mimicking a fluid challenge.

Establishing Shock

Additional physical exam techniques

- Passive Leg Raise:
    - The PLR technique mobilizes pooled venous blood in the lower extremities (approximately 150–300 mL) to the central circulation as an autologous and reversible fluid bolus.
    - Extrinsic fluids are not necessary, and patients do not receive an unnecessary fluid bolus if they are not volume responsive.
    - Requires bedside echocardiography, arterial waveform analysis, and bioreactance, to determine change in cardiac output or stroke volume.

Harold

- You rapidly determined that the patient was in shock.
- Although his blood pressure was within acceptable limits, he had clear clinical evidence of impaired end-organ perfusion as evidenced by altered mental status (impaired cerebral perfusion) and respiratory insufficiency. While you recognized the possibility of a cardiogenic process contributing to his presentation, the majority of the clinical data supported an infectious process (specifically, a right lower lobe pneumonia) resulting in a systemic inflammatory response and distributive pathophysiology due to septic shock. You administered a bolus of 30 mL/kg of NS. You requested a comprehensive laboratory panel be sent, including CBC, chem 7, venous blood gas, serum lactate concentration, and blood cultures. You ordered a chest x-ray to better characterize his presumptive pneumonia.

Harold

- You ordered empiric broad-spectrum antibiotics based on your hospital's antibiogram – in this case you elected to administer cefTRIAXone 2 g IV q24h (based on weight over 80 kg) AND Azithromycin 500 mg IV q24h. Despite these interventions, his blood pressure progressively decreased in the setting of an increasing temperature and worsening oxygenation. Given his clinical deterioration, you made the decision to intubate him and initiate mechanical ventilation with low-tidal-volume ventilation. Then, you called the ICU and initiated a continuous infusion of norepinephrine, titrated for a MAP goal of > 65 mm Hg.
- His laboratory studies demonstrated WBC 27, platelets 90, creatinine 310, and lactate 7.2, bicarb 16 mmol/L, and base excess of -10 mEq/L. After receiving high-quality, evidence-based care in the ED, he was admitted to the ICU in critical condition, but ultimately made a full and uneventful recovery.

Shock

Bottom line

- The goal during resuscitation is to administer intravenous fluids to optimally fill the left ventricle, which will increase the stroke volume, but not overfill it.
- All of these assessments discussed recently in the literature are going to take too long for a decision about fluids or not. (Including starting central lines and CVP catheters.)
- If no cardiogenic shock or fluid overload evident on quick physical exam, give 1-2 L NS. If ineffective, then initiate pressors. Don’t delay.
- BP is not the goal…perfusion of tissue is the goal.

Shock Therapy

No survival benefit with early goal-directed therapy for septic shock

- **Bottom line:**
- As compared with usual resuscitation care, early goal-directed therapy (EGDT) using central venous monitoring does not improve mortality in patients presenting to the emergency department with septic shock.

- **Reference:**
- ARISE Investigators; ANZICS Clinical Trials Group, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371(16):1496-1506.

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Pressors?

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Pressors

To adequately perfuse tissues

- 1. Critical perfusion pressures
  - to the brain: MAP 50?
  - coronary perfusion pressure: MAP 65
  - renal perfusion pressure: MAP 65
- 2. Aim to increase venous return
  - NE is balanced arterial and venous pressor
  - venous stores are unstressed and get converted to stressed volume by pressors to increase venous return
- 3. Avoid gut ischemia (which leads to translocation of bacteria and further sepsis)

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Pressors

Beyond volume replacement

- Once a patient is determined to be euvolemic, but there is still ineffective oxygen delivery, vasoactive medications are likely required. Various pressor medications may be used to support the mean arterial pressure by increasing systemic vascular resistance and/or cardiac output.
- pure vasopressor (vasoconstriction): vasopressin and phenylephrine, high dose dopamine
- inopressor (CO and HR, increase cardiac contractility): norepinephrine, epinephrine, low dose dopamine
- inodilator: dobutamine

Norepinephrine

•Scott Weingart Emcrit podcast138

- Norepinephrine is a strong alpha agonist with some beta-1 activity, and it is a recommended initial choice for most categories of shock, particularly when the etiology of shock is unknown.

- first choice except anaphylaxis, accomplishes all 3 goals, best evidence
- alpha 1 and alpha 2 vasoconstriction, slight beta 1 (inotropy, chronotropy but not vasodilation of beta 2)
- ok peripherally then go central
- Can do weight-based dosing or The usual dose is 2-15 mcg/min
- does not cause bradycardia
- increases afterload
- Start low and let the nurse titrate to MAP of 65

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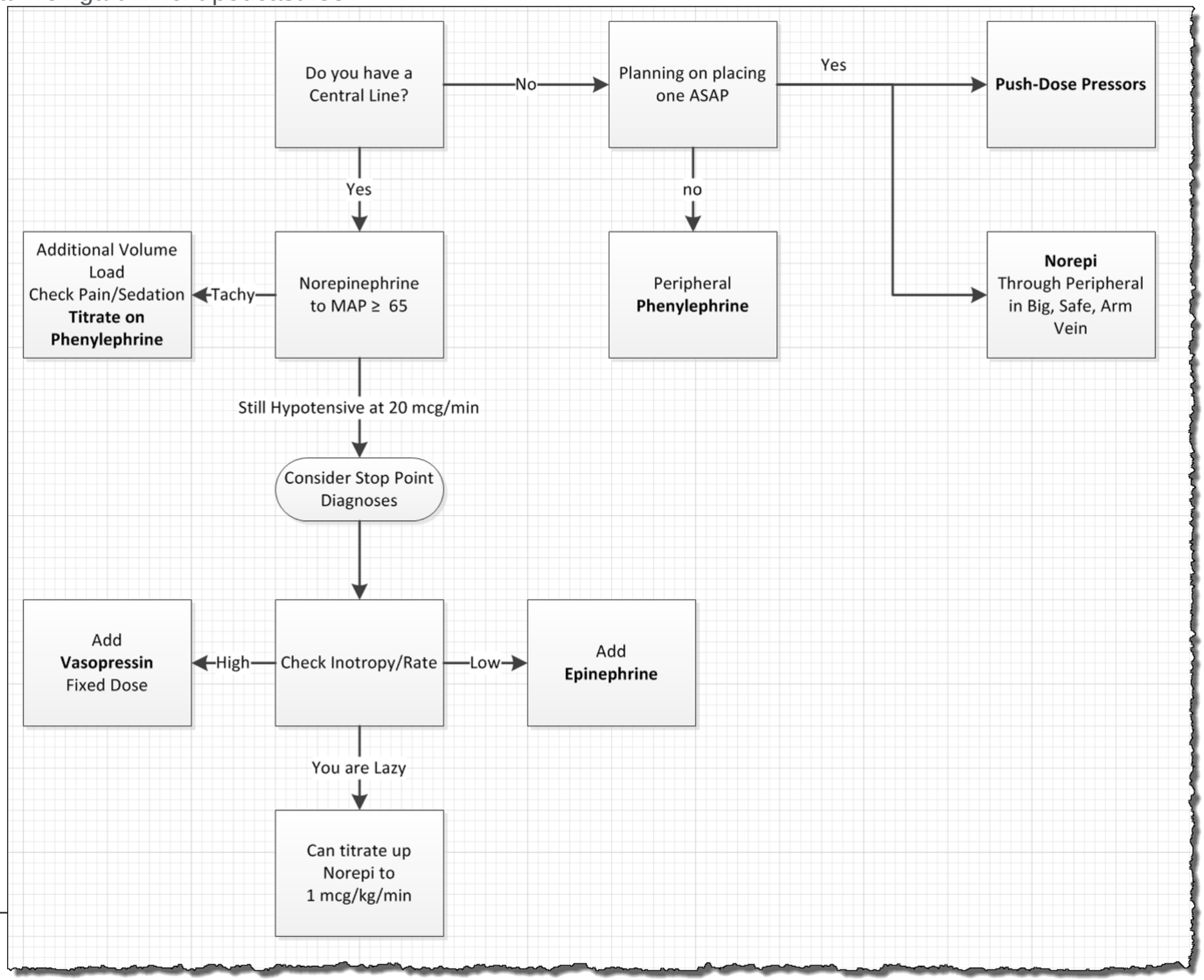
Pressor flow chart

- Scott Weingart Emcrit podcast138



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Summary of Pressors

•Nightmares 2014 Fil Gilic

Name	SVR	HR	Contractility	Types of shock	Dose
Dopamine	Low dose: + High Dose: ++	++ +++	+++ +++	Any	2-10 mcg/kg/min 10-20 mcg/kg/min
Norepi	+++	0	+	Any	2-15 mcg/min
Phenylephrine	++++	0/-	0	Distributive Hypovolemic	50-300 mcg/min
DoBUTamine	--	+++	+++	Cardiogenic Obstructive	2-20 mcg/kg/min

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Dopamine

Emerg Med Clin N Am 32 (2014) 811–822

- Emerging data indicate that dopamine is associated with increased morbidity and potential mortality as compared to other first-line pressors. Specifically, a multicenter prospective trial of 1679 patients presenting with shock randomized patients to receive either dopamine or norepinephrine as the initial vasopressor.
- There was no difference in mortality between patients receiving dopamine or norepinephrine, but patients receiving dopamine had a statistically significant higher incidence of arrhythmias.
- Furthermore, a meta-analysis of 11 trials demonstrated a statistically significant increased risk of death associated with dopamine.
- These results indicate that dopamine should not be used as a first-line pressor for patients in shock, including patients presenting with cardiogenic shock.

- dopamine may give kidney malperfusion (urine output even when kidneys poor), may cause atrial fibrillation or tachycardia-->”could do without” (Scott Weingart)

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Dopamine & Dobutamine in Sepsis Order Sets at LH

- DOPAMINE-what do we like about it?
- It is a VASOPRESSOR
- stimulates the alpha receptors
- increases SVR, HR=leading to an increase in cardiac output and MAP
- has the flexibility of using one drug to create various outcomes according to dose
- Readily available in a pre-mixed formulation
- Cost effective
- Familiar to health care providers

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Dopamine & Epi: ACLS 2010

- 2010 ALS guidelines indicate a role for Dopamine infusion for symptomatic Bradycardia associated with hypotension when Atropine fails
- Dose 2-10 mcg/kg/hr-to increase heart rate however may cause some vasodilation and hypotension when given in low doses- for this reason –assess for an adequate fluid status

Dopamine & Epi in ACLS

- Epinephrine infusion of 2-10 mcg/min can be started for symptomatic bradycardia that is unresponsive to Atropine and Dopamine
- Titrated based on HR, BP and systemic perfusion
- Not an LH Medical Directive

Lakeridge Health Medical Directives and Order sets

- LH Medical Directive reflects these ACLS guidelines
- Administered by RNs and RTs in pts with Symptomatic bradycardia
- Dopamine is also part II of LH Early Goal Directed Sepsis Treatment for pts with septic shock and low risk of arrhythmias (despite fluid resuscitation)
- requires a physician order
- Starting dose – 5 mcg/kg/min IV or IO with goal directed titration for MAP greater then 65

Dopamine

- What do we hate about Dopamine?
- Although useful in patients with systolic dysfunction, is associated with more tachycardia and dysrrhythmias
- There has long-been controversy about the possible superiority of norepinephrine compared to dopamine in the treatment of shock..

Why Dr. Kassirer is changing his mind about Dopamine

- Crit Care Medicine (2012) Mar 725-30

- **2010 meta analysis of Dopamine verses Norepinephrine in the treatment of shock-** The objective was to evaluate the effects of norepinephrine and dopamine on outcome and adverse events in patients with septic shock

- **METHODS AND MAIN RESULTS:**
- Five observational (1,360 patients) and six randomized (1,408 patients) trials, totaling 2,768 patients
- In observational studies there was no difference in blood pressure however, Dopamine was associated with an increased risk of death.
- In randomized trials Dopamine was associated with an increased risk of death -two trials that reported arrhythmias, these were more frequent with Dopamine than with Norepinephrine.

DOBUTAMINE (Dobutrex)- what do we like about it?

- NOT A VASOPRESSOR, B1 effects
- + INOTROPE
- +SQUEEZE
- + CARDIAC OUTPUT
- B1 receptors are located in the heart “FIGHT OR FLIGHT”
- Increases Heart rate and Cardiac output
- Other advantages-
- Less tachycardic effect then Dopamine at similar doses
- B1 agonist with some B2 effects- no a2 effect
- Increases cardiac and renal output – although not as much as Dopamine- however no good evidence to support renal protection

Dobutamine

- Although the recommended drug for cardiogenic shock we dislike it as a first line for some of the same reasons as Dopamine- arrhythmias and tachycardia in the absence of adequate fluids
- Hypotension frequently occurs
- Beta 1 stimulates potassium migration- therefore may see hypokalemia

Norepi not working??

.Pharmacotherapy Jul (2010) 702

So you've tried the preferred Norepinephrine and its not working…now what?

Some notable mentions:

Methylene Blue

- Methylene blue given IV is thought to decrease vasodilation while increasing the responsiveness to vasopressors
- Observational studies with methylene blue have demonstrated beneficial effects on hemodynamic parameters and oxygen delivery, but use of methylene blue may be limited by adverse pulmonary effects
- Methylene blue administration is associated with increases in mean arterial pressure while reducing catecholamine requirements in patients experiencing septic shock; its effects on morbidity and mortality remain unknown.
- SO……Your numbers will look better but not for long

VASOPRESSIN

Intensive Care Medicine (2012) 38:9.

Vasopressin

- Its precise role in shock remains undefined
- Primarily used as a second line agent in refractory vasodilatory shock particularly in sepsis that is unresponsive to Epi
- Also used occasionally to reduce the dose of the first line agent
- In a systematic review of 10 RCTs, Vasopressin was evaluated and showed no significant improvement in mortality; however, did show that pts required less Norepinephrine
- Vasopressin may be dose dependent
- higher doses were more effective at increasing blood pressure without an increase in adverse effects, however, doses above 0.03 u/min have been associated with gut ischemia and skin necrosis
- Rebound hypotension is also common following withdrawal of Vasopressin

What about some calcium?

- The addition of Calcium with a pressor can assist to increase blood pressure by improving contractility and vascular tone resulting in cardiac and smooth muscle contraction
- While increasing the muscle contraction it has no effect on heart rate
- It is readily available on all crash carts and can be administered IV in doses of 10-20 kcg/kg for Calcium Gluconate and 20-30 mcg/kg for Calcium Chloride
- The effects may be transient but given IV the dose will last up to 15 minutes
- And of course fluids….fluids….fluids

So far…

- Sepsis, fluids and beyond.
- Pressors:
  - Norepi
  - Epi
  - Dopamine
  - Dobutamine
  - Vasopressin
- Additions:
  - Calcium
  - Methylene Blue
- Next?

Jordan

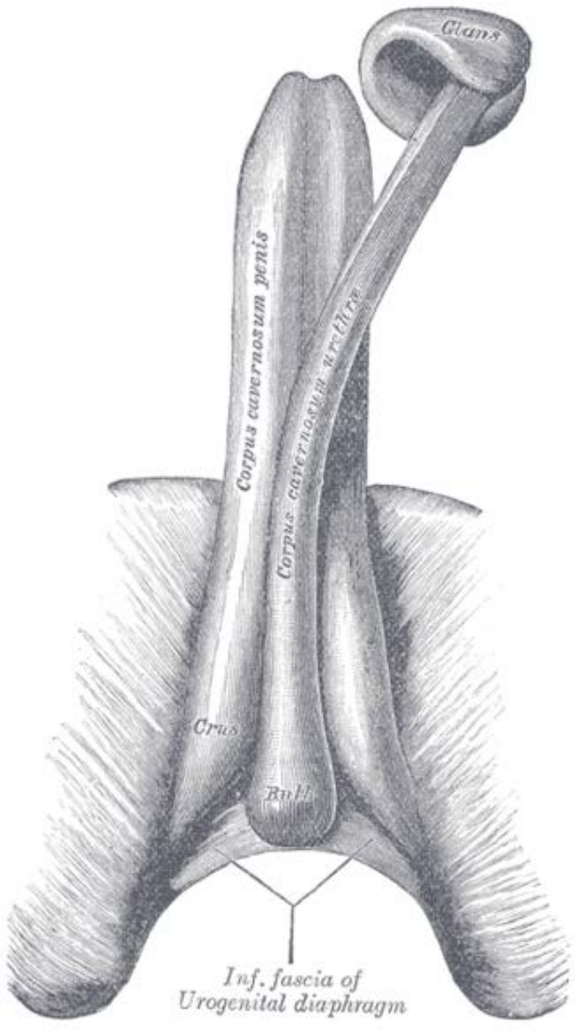
Priapism and Pressors

- 27 year old male presents to ER with 6 hour erection!
- Admits to cocaine use
- Adamant cocaine is not the cause of his problem, as he has used cocaine many times before
- He was advised to stop using cocaine
- Presents to ER at least 2 more times over the next few weeks with the same problem, each time after use of cocaine
- Did he stop?
- What is the treatment?

Case 2

Priapism and Inotropes

- 27 year old male presents to ER with 6 hour erection!



Drain 5 cc blood from corpus cavernosum (either side) using butterfly 21 ga

Add phenyephrine 100 mcg/mL 1-5 mL q3-5 minutes until effective

Reassess after 1 hr if effective and call urology if not

up to date 2013 mar

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Shock and Pressors

The End

- An initial approach to undifferentiated shock includes establishing vascular access, empiric volume resuscitation, find the cause and treat it in order to improve mortality outcomes.
- 1-2 L of NS is usually useful.
- For specific situations, phenylephrine or others can be most effective.
- Teamwork in the ER to stabilize the patient!
- Recent research suggests norepinephrine is a best first choice of pressor.
- Stabilize in the ER and further therapies in the ICU.

Questions?

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