

Session Title: Resuscitation Pharmacotherapy and the Role of the ED Pharmacist

Session overview

This talk is focused on medication updates in resuscitation. Topics covered include ventricular tachycardia/ventricular fibrillation, hypoglycemia during hyperkalemia treatment, naloxone dosing, alteplase dosing in cardiac arrest, and tranexamic acid in various bleeding scenarios. We will also highlight scenarios in which ED pharmacists improve care.

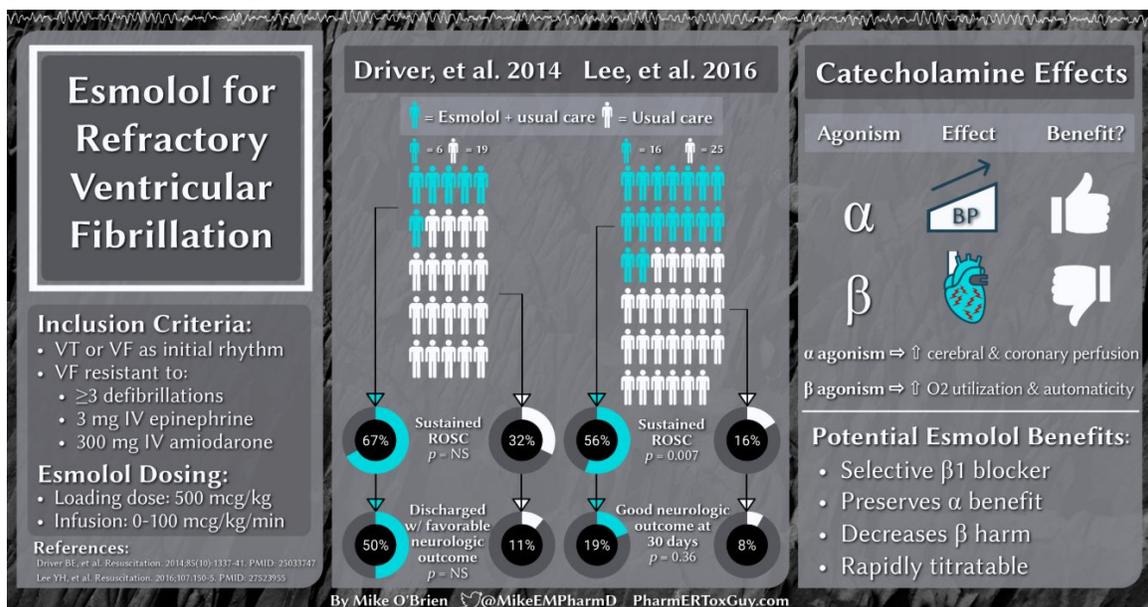
Objectives

- Discuss the role of lidocaine and esmolol in ventricular tachycardia/ventricular fibrillation
- Utilize a low-dose naloxone dosing scheme for opioid overdoses
- State the cardiac arrest dosing of thrombolytics
- Determine the indications for using tranexamic acid in critical bleeding patients

Lidocaine is Back for Ventricular Fibrillation and Pulseless Ventricular Tachycardia!

With the recent 2018 AHA Focused Update, lidocaine is back in the Adult Cardiac Arrest Algorithm with an equally weak recommendation as amiodarone (Class IIb; Level of Evidence B-R). ([Panchal 2018](#)) The AHA continues to acknowledge that an antidysrhythmic medication is unlikely to cardiovert VF or pVT into normal sinus rhythm. Read more about the lidocaine and other medication-related updates in the focused guideline update. ([PharmERToxGuy blog 2019](#))

Esmolol is an additional option to consider for refractory VF ([PharmERToxGuy blog 2016](#)). Here is an [infographic](#) from the blog.



Treating Hyperkalemia with Insulin

- How insulin works

- Temporarily shifts potassium intracellularly through a complex process of activating Na⁺-K⁺ ATPase and by recruitment of intracellular pump components into the plasma membrane. Insulin binding to specific membrane receptors results in extrusion of Na⁺ and cellular uptake of K⁺. ([Hundal 1992](#))
- The right insulin dose
 - 5 unit boluses up to 20 unit/hr infusions have been used ([Blumberg 1988](#)). Most common dose is 10 units IV regular insulin bolus (lowers K⁺ ~ 0.5-1 mEq/L).
- Preventing hypoglycemia
 - Incidence of hypoglycemia
 - A 10 unit dose of IV regular insulin has an onset of action ~5-10 minutes, peaks at 25-30 minutes, and lasts 2-3 hours. IV dextrose lasts < 1 hour.
 - Overall incidence of hypoglycemia appears to be ~10%, but could be higher ([Allon 1990](#); [Schafers 2012](#); [Apel 2014](#), [Scott 2019](#))
 - Risk factors for developing hypoglycemia ([Apel 2014](#))
 - No prior diagnosis of diabetes; no use of diabetes medication prior to admission; lower pretreatment glucose (104 mg/dL vs 162 mg/dL, P = 0.04); renal dysfunction (insulin may be partially renally metabolized) ([Dickerson 2011](#)); higher insulin dose ([LaRue 2017](#))
 - Strategies for avoiding hypoglycemia
 - Here is a [suggested strategy](#) for administering enough dextrose to counter the initial insulin bolus of 10 or 20 units. It is loosely based on the Rush University protocol. ([Apel 2014](#))
 - ISMP highlighted this issue in a [February 2018 Safety Alert](#)

Naloxone

- Patients typically receive 2 mg in the prehospital setting, a dose much too high for patients chronically taking opioids that can precipitate withdrawal. [Important caveat is that with fentanyl (and fentanyl derivatives) mixed with heroin, high-dose naloxone (up to 10 mg) may be needed]
- A more conservative strategy is to start with 0.04 mg and administer 0.04-0.08 mg increments to achieve desired respiratory rate ([Kim 2016](#), [Wong 2019](#))
- Here is a great [trick-of-the-trade](#) for preparing the naloxone to give these smaller doses

Cardiac Arrest Dosing of tPA

This is a tough question in the middle of a critical resuscitation. A full summary of the data is available on [Academic Life in EM blog 2013](#).

- The dose of tPA in cardiac arrest is somewhere between 50-100 mg given as a bolus +/- infusion.
 - We generally give 50 mg as an IV push and often repeat with the other 50 mg in 10-15 minutes, if indicated.
- According to the AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, "Ongoing CPR is not an absolute contraindication for fibrinolysis."

- Some studies suggest allowing 15 minutes of CPR for drug to work, though the 2019 ESC Guidelines for the Diagnosis and Management of Acute PE recommend up to 90 minutes ([Konstantinides 2019](#))
- Evidence is 'best' for PE; data does NOT support for undifferentiated cardiac arrest.
- Anticoagulants, such as heparin, were used in most studies along with the fibrinolytic.

Tranexamic Acid (TXA) in Trauma

1. MOA: TXA inhibits fibrinolysis by forming a reversible complex that displaces plasminogen from fibrin. It also inhibits the proteolytic activity of plasmin. [Lexicomp 2018]
 - a. Theory: Blood clots in trauma patients and up to 60% of trauma patients may have massive underlying lysis
 - b. There are over 70 RCTs evaluating TXA for non-traumatic bleeding (overall benefit)
2. Landmark trials
 - a. CRASH-2 ([Lancet 2010](#))
 - i. Design
 1. Multi-center RCT in 274 hospitals (40 countries)
 2. Over 20,000 pts randomized to receive TXA or placebo
 - ii. Results
 1. All-cause mortality: TXA (1463 [14.5%]) vs. placebo (1613 [16.0%]); relative risk 0.91, 95% CI 0.85–0.97; p=0.0035). **ARR 1.5% = NNT 67**
 2. Risk of death due to bleeding was significantly reduced (4.9% vs 5.7%; relative risk 0.85, 95% CI 0.76–0.96; p=0.0077). **ARR 0.8% = NNT 125**
 - b. Subanalysis of CRASH-2 trial focused on time to TXA administration ([Lancet 2011](#))
 - i. Early treatment (≤ 1 h from injury) significantly reduced the risk of death due to bleeding (198/3747 [5.3%] events in TXA group vs 286/3704 [7.7%] in placebo group; relative risk [RR] 0.68, 95% CI 0.57–0.82; p<0.0001). **ARR 2.4% = NNT 42**
 - ii. Treatment between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4.8%] vs 184/2996 [6.1%]; RR 0.79, 0.64–0.97; p=0.03)
 - c. MATTERS ([Morrison 2012](#))
 - i. Design - Retrospective observational study comparing TXA with no TXA in military combat patients (Afghanistan) receiving ≥ 1 unit of PRBCs
 - ii. Results - The TXA group had lower unadjusted mortality than the no-TXA group (17.4% vs 23.9%, respectively; $P = .03$) **despite being more severely injured** (mean ISS, 25.2 vs. 22.5, respectively; $P < .001$). Benefit greatest in group who received massive transfusion (14.4% vs 28.1%, $p = .004$), where TXA was also independently associated with survival (odds ratio = 7.228; 95% CI, 3.016-17.322) and less coagulopathy ($P = .003$).
 - d. MATTERS II ([Morrison 2013](#))
 - i. Expanded sample size of MATTERS I study to 1,332 patients (identified from prospectively collected UK/US trauma registries) who required ≥ 1 RBC units.
 - ii. Despite greater ISSs and RBC transfusion requirements, mortality was lowest in patients who received TXA (18.2%) or TXA/CRYO (11.6%) compared with CRYO alone (21.4%) or no-TXA/CRYO (23.6%).

- e. Prehospital administration ([El-Menyar 2018](#))
 - i. Effect of TXA on 24-hour mortality had a pooled odds ratio (OR) of 0.49 (95% CI 0.28-0.85), 30-day mortality OR of 0.86 (95% CI, 0.56-1.32), and thromboembolic events OR of 0.74 (95% CI, 0.27-2.07).
 - f. [PATCH trial](#) underway in Australia - aims to determine the effects of early administration of tranexamic acid on survival and recovery of severely injured patients treated within advanced trauma systems
3. When to consider using TXA in trauma ([Napolitano 2013](#); [Ker 2015](#), [REBEL EM blog](#))
- a. Adult trauma patients with severe hemorrhagic shock (SBP < 90 mm Hg) who are at risk for bleeding (ie, cross-matched or receiving blood)
 - b. Only administer TXA if less than 3 hours from time of injury
 - c. TXA administration: 1 g IV over 10 minutes, then 1 g IV over 8 hours

Inhaled TXA in Hemoptysis

Consider inhaled/nebulized TXA for patients with stable, non-massive hemoptysis ([Wand 2018](#)). A great summary of the Wand trial on [REBEL EM blog](#) and an infographic summary of the case reports is available on the [PharmERToxGuy blog](#).

Nebulized Tranexamic Acid

For acute treatment of stable hemoptysis

The diagram illustrates the fibrinolytic pathway. Plasminogen is converted to Plasmin by t-Pa. Plasmin then converts Fibrinogen to Fibrin. Fibrin is further broken down into Fibrin degradation products. Tranexamic acid is shown with red 'X' marks indicating inhibition at two points: the conversion of Plasminogen to Plasmin and the conversion of Fibrin to Fibrin degradation products.

Product Characteristics

- IV solution pH 6.5-8.0 (nearly physiologic)
- Low risk for bronchospasm based on formulation
- Only contains tranexamic acid and sterile water
- Increased local concentrations & decreased systemic exposure
- Theoretically, decreased major adverse effects

Clinical Application

- Successful in 12 case reports
- One patient had bronchospasm which resolved with bronchodilator
- No additional adverse effects
- Dosing: 250-500 mg every 6-8 hours or 1000mg once
- Straight drug or diluted with NS
- May be used as a temporizing measure or continued palliatively
- No need to reverse anticoagulation
- Avoids intubation and advanced therapies

References:
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 Segrelles-calvo G, et al. Chest. 2016;149(2):504, PMID: 26867844
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	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Age (years)	43	49	52	59	46	82	58	84	71	75	79	69
Primary diagnosis	Metastatic disease in lung	ITP s/p BMT for AML	Lung cancer	None	Sinus and thyroid cancer	Lung cancer	Lung cancer	Bronchiectasis	Lung cancer	Bronchiectasis	ITP and COPD	Lung cancer and PE
Dosing regimen	250-500 mg 2-3 times daily	500 mg 4 times daily	500 mg 4 times daily	500 mg 4 times daily	1000 mg once	250 mg 3 times daily	500 mg 3 times daily	500 mg 3 times daily	250 mg 2 times daily	500 mg 3 times daily	500 mg 3 times daily	1000 mg once
Time to resolution of hemoptysis	15-20 minutes	2-3 hours	Rapid	Almost instantly	15 minutes	48 hours	24 hours	12 hours	6 hours	Resolved in < 48 hours	Dramatically improved in < 12 hours	< 10 minutes
Duration of therapy	3 months	1 week	3 days	2 days	Once	N/A	N/A	N/A	N/A	> 48 hours	> 48 hours	Once

TXA in Postpartum Hemorrhage

TXA may have a small survival benefit in postpartum hemorrhage patients with no increased risk of clotting ([WOMAN trial 2017](#)). The REBEL EM blog provides a [great summary with additional resources](#).

Tricyclic Antidepressant Poisoning (during a sodium bicarbonate shortage)

- ASHP has a great resource center for [drug shortages](#)
- If sodium bicarbonate is not available, it may actually be the sodium that is the most important factor in reversing ECG findings from TCA poisoning, as opposed to pH manipulation. Consider administering hypertonic saline ([McKinney 2003](#); [McCabe 1998](#))
- One amp/syringe (50 mL) of 8.4% sodium bicarbonate contains the same amount of sodium as 97 mL of 3% sodium chloride or 38 mL of 7.5% sodium chloride.
- A central line is recommended if giving > 3% hypertonic saline.

ED Pharmacists

1. Background
 - a. At the 2014 American College of Emergency Physicians Scientific Assembly, ACEP passed [Resolution 44](#) on Clinical Pharmacy Services in the ED
 - b. In 2017, The American College of Medical Toxicology published a position statement on [The Role of Clinical Pharmacists in the ED](#)
2. [The training of EM pharmacists](#)
3. Optimizing Patient Care
 - a. Improved patient oriented outcomes [[ASHP 2008](#), [Cohen 2009](#)] such as reduced time to thrombolytic therapy for acute ischemic stroke, reduced door-to-balloon time for acute myocardial infarction, reduced time to antibiotics for sepsis, and reduced time to first analgesic in trauma patients [[Acquisto 2012](#), [Lada 2007](#), [Flynn 2014](#), [Montgomery 2015](#)].
 - b. Expedite medication administration for emergent intubations, optimize post-intubation sedation and analgesia [[Johnson 2015](#), [Amini 2013](#)], improve safety in cardiac resuscitations [[Groth 2016](#), [Bond 2007](#), [Porter 2014](#), [Ernst 2012](#)], and optimize antimicrobial therapy in sepsis [[Weant 2012](#), [Flynn 2014](#), [Morganti 2013](#)].
 - c. Recommend interventions that improve quality of medication use/adherence to evidence-based medicine and national quality standards [[Abu-Ramaileh 2011](#)].
 - d. Improve transitions of care for ED patients by improving medication reconciliation [[Okere 2015](#), [Becerra-Camargo 2013](#), [Ajdukovic 2007](#)], reducing errors and outpatient antibiotic treatment failures [[Cesarz 2013](#), [Randolph 2011](#)].
 - e. Reduce medication errors in the ED through providing real-time consultation and order verification [[Sin 2015](#)], intercepting order entry (prescribing) errors before patient harm occurs [[Stasiak 2014](#), [Brown 2008](#), [Rothschild 2010](#), [Patanwala 2012](#)], and increase error reporting to allow for identification of trends and improve safety systems [[Weant 2010](#)].
 - f. Pharmacists improve ED cost savings through interventions mentioned above [[Lada 2007](#), [Hamblin 2012](#)].

- g. ED pharmacist review of post-discharge cultures improves regimen modifications while also decreasing return visits and subsequent admissions [[Baker 2012](#), [Miller 2014](#), [Randolph 2011](#), [Dumkow 2014](#), [Van Devender 2014](#)].