ACLS Pharmacology/Algorithms

Kristin Engebretsen, PharmD, CSPI
Clinical Toxicologist
Emergency Department
Regions Hospital, St. Paul, MN

DRUGS: Describe indications, contraindications, Dosages for:
- Epinephrine
- Vasopressin
- Amiodarone
- Lidocaine
- Magnesium sulfate
- Sotolol/Ibutilide
- Procainamide
- Sodium bicarbonate
- Diltiazem/Verapamil
- Atenolol/Metoprolol
- Atropine
- Adenosine

MEMORIZATION!!!!
- Cookbook Science
- Memorize algorithms

Pharmacological Categories
- Antiarrhythmics in ACLS
- Vasopressors
- Antiplatelet Drugs
- Reperfusion
- Algorithms

Classes of Recommendations
- Class I:
  - Definitely recommended
  - Supported by excellent evidence
  - Proven efficacy and effectiveness
- Class IIa:
  - Acceptable and useful
  - Good /very good evidence provides support
  - Intervention of choice
- Class IIb:
  - Acceptable and useful
  - Considered within the standard of care
  - Optional alternative
- Indeterminate
  - Preliminary research stage
  - Available evidence insufficient to support a decision
- Class III:
  - Unacceptable, not useful, may be harmful
### TracheAL Drug Administration
- Epinephrine
- Atropine
- Lidocaine
- Give 2-2.5x the recommended IV dose,
- Dilute in 10ml of NS or distilled water
- NAVEL: Narcan, Atropine, Vasopressin, Versed, Epi, Lidocaine

### Agents for Dysrrhythmias
- Adenosine
- Atropine
- Class IA Antiarrhythmics: Procainamide/Disopyramide
- Amiodarone
- Magnesium
- Lidocaine
- Ibutilide
- Sotolol/BB blockers
- CCB: Verapamil/Diltiazem
- Class IC: Propafenone, Flecainide, Ecaainide

### Antiarrhythmics

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug(s)</th>
<th>Conduction Velocity</th>
<th>Refractory Period</th>
<th>Automaticity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Moricizine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>1a</td>
<td>Procainamide, Disopyramide Quinidine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Ib</td>
<td>Mexiletine, Lidocaine, Flecainide, Ecaainide, Phenytoin</td>
<td>✓/✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Ic</td>
<td>Flecainide, Ecaainide, Endocaine, Propafenone</td>
<td>✓/✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>II</td>
<td>Beta Blockers</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>III</td>
<td>Amiodarone, Bretyllium, Sotalol, Ibutilide, Dofetilide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>IV</td>
<td>CCB Diltiazem, Verapamil</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</table>

### Vaughan Williams Classification

### Adenosine
- Narrow complex tachycardias
- Narrow supraventricular tachycardia
- Wide complex tachycardias confirmed as supraventricular in origin
- **WARNINGS:**
  - Vasodilatory effects (hypotension). TI/2 of 5 seconds
  - Angina, vasospasm, proarrhythmia, and acceleration of accessory pathway conduction.
  - Not good for atrial fibr, flutter, vtach.

### Adenosine
- Dose 6mg rapid IV bolus. Follow with flush
- If no response in 1-2 minutes: give 12mg rapid IV bolus
- **Drug Interactions:**
  - Theophylline, caffeine, theobromine- block receptor for adenosines effects
  - Dipyridamole-blocks adenosine uptake – potentiates its effects
  - Carbamazepine-prolongs its effects
Atropine

- Reverses cholinergic mediated decreases in SVR, HR and BP
- Uses:
  - Treat Sinus Bradycardia (Class I)
  - AV block at the nodal level (Class IIa)
  - Ventricular asystole

**WARNINGS:**
- Use with caution in AMI—may worsen ischemia
- Not indicated in bradycardia from type II AV block and 3rd degree block with new wide-QRS complexes.
- Asystole and slow pulse electrical activity
  - 1.0mg IV
  - May repeat in 3-5min if asystole persists
- Bradycardia
  - 0.5mg-1mg IV q 3-5min for a total dose of 0.4mg/kg (3mg)

**Warmings:**
- Only give maximum dose in asystolic arrest. (Atropine increases myocardial demand and can initiate tachyarrhythmias)
- Doses <0.5mg may be parasympathetic and further slow the cardiac rate.

Procainamide

- Classification: 1A (VW)
  - Slows conduction velocity and prolongs the refractory period
- Recommendation: Class IIa and IIb
- Uses: SVT, atrial fibr and atrial flutter, ventricular arrhythmias and wide complex arrhythmias which you cannot discern to be either atrial or ventricular in origin

**WARNINGS:**
- Vasodilatory Effects
- Negative inotropic Effects
- Adverse effects related to dose and rate given
- Most cases, amiodarone is used first over Procainamide

- Dose:
  - Infusion of 20mg/min until Arrhythmia is suppressed
  - Hypotension ensues
  - The QRS complex is prolonged 50% from original duration or
  - A total of 17mg/kg of drug has been given

- Avoid Procainamide if:
  - Pre-existing QT prolongation
  - Torsades de Pointes
  - Avoid injecting too fast, may cause hypotension

Disopyramide

- Class IA antiarrhythmic
- Slows conduction velocity and prolongs the refractory period.

**WARNINGS:**
- Anticholinergic effects
- Negative inotropic effects
- Hypotension
- Needs to be infused over 10 minutes
- Overall, not used much

Amiodarone

**ARREST Trial (Amiodarone in out-of Hospital Resuscitation of Refractory Sustained Ventricular Tachyarrythmias)**
- Higher rate of survival to hospital admission when given amiodarone vs placebo
  - 27% more patients overall survived to hospital admission
  - 26% more successful resuscitations in VF subset
  - 56% more successful resuscitations in pts treated with IV amiodarone when electrical defibrillation produced a transient return of circulation
  - 1/10 patients benefited
- Did not show any difference in survival to discharge from the hospital
Amiodarone

- **Class III (VW) antiarrhythmic agent:**
  - K channel blocker, Na channel blocker, Adrenergic blockade, CCB class IV negative inotropic effects
  - Class IIa if LV function is normal or Class IIb if ventricular function is impaired
  - Use: SVT (2nd choice after Adenosine if CHF, or EF < 40%)
  - Use: Hemodynamically unstable VT and VF
  - Use: Hemodynamically stable VT.

- **WARNINGS:**
  - Vasodilatory effects
  - Proarrhythmic effects
  - Negative inotropic effects
  - May decrease CO
  - May decrease SVR/MAP
  - Increases QT interval

- **Loading bolus dose for cardiac arrest:**
  - Supplement bolus dose for cardiac arrest:
  - Loading infusion after return of spontaneous circulation:
  - Maintenance infusion:

- **Amiodarone**
  - Amiodarone 300mg IV push –flush with 10ml D5W or NS
  - Amiodarone 150mg IV push–flush with 10ml D5W or NS
  - Amiodarone 360mg over 6 hours (1mg/min). Admix 18ml of Amiodarone IV (900mg) in 500ml D5W or NS (1.8mg/ml)
  - Amiodarone 540mg over 18 hours. Administer by reducing the aforementioned rate to 0.5mg/min

- **Amiodarone 300mg (6cc) IV push –flush with 10ml D5W or NS**
- **Amiodarone 150mg (3cc) IV push- flush with 10ml D5W or NS**
- Amiodarone 540mg over 18 hours. Administer 18ml of Amiodarone IV (900mg) in 500ml D5W or NS (1.8mg/ml) *0.28ml/min

- **Lidocaine**
  - **Mechanism of action:**
    - Class Ib antiarrhythmic – blocks sodium and potassium channels
    - Decreases excitability of cells
    - **Indications include**
      - VF/pulseless VT that persists after defibrillation and epinephrine (and amiodarone)
      - Hemodynamically stable VT (ACLS class IIb)

- **Dose:**
  - 1-1.5mg/kg IV
  - Additional bolus 0.5-0.75mg/kg given over 3-5min.
  - Total dose should not exceed 3mg/kg
  - Continuous infusion of 1-4mg/min (controversial) Class indeterminate

- **WARNINGS:**
  - Half life increases after 24-48 hours
  - Decrease dose after 24 hours.
  - Decrease dose in AMI with hypotension or shock
  - CHF
  - Patients >70yo
  - Hepatic dysfunction.
Magnesium
- Magnesium Deficiency
- Torsades de Pointes
- No longer used routinely in AMI or cardiac arrest
- Dose:
  - 1-2 grams diluted in 100ml D5W and administered over 5-60 min (emergent situations can give it over 1-2min)
  - Followed by an infusion of 0.5-1 gram per hour.
  - If administered too fast, hypotension or asystole may occur

Ibutilide
- Dose:
- For adults >60kg, administer 1mg (10ml) over 10min (diluted or undiluted)
  - 2nd dose of 1mg may be given 10mg after the first dose.
  - If patient weighs <60kg, dose as 0.01mg/kg
- Continuous Monitoring for 4-6 hours after administration for arrhythmias
- Avoid giving other class III agents (amiodarone, sotatol, PDQ)
- K, Mg should be corrected prior to start of infusion
- Pacer pads, IV magnesium, defibrillator pads should be available

Beta Blockers
- Recommended for all pts with ACS, non-Q wave MI, and unstable angina
- BB -shown to reduce the incidence of VF in the reperfusion era.
- With fibrinolytic therapy, BB may reduce the rate of nonfatal reinfarction and recurrent ischemia.
- BB reduce mortality if administered early to pts ineligible for fibrinolytic therapy
  - Atenolol, Metoprolol, Propranolol-shown to reduce incidence of VF significantly in post-MI pts who did not receive fibrinolytic therapy

Beta Blockers
- MOA
  - Prevent infarction by decreasing oxygen consumption and demand
  - Decrease dysrrhythmias by decreasing catecholamine levels
  - Lower BP
  - Reduce myocardial contractility
  - Block catecholamine stimulation

Beta Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>Atenolol</td>
<td>5mg slow IV (over 5min), wait 10min, if tolerated give 5mg more. Oral regimen 50mg q 12 hours</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>5mg slow IV push every 15min up to a total dose of 15mg. Give oral dose 15min after last IV dose (50mg qd, increase to 100mg bid as tolerated)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0.1mg/kg slow IV push Divided into 3 equal doses given at 2-3min intervals</td>
</tr>
<tr>
<td>Esmolol- B1 selective BB-SVT’s, Torsades,</td>
<td>5.0mg/kg over 1min, maintenance infusion of 50ug/kg/min for 4-min. If response is inadequate give a second bolus 0.5mg/kg and titration of the dose (addition of 50ug/kg/min) can be repeated every 4min up to a maximum of 300ug/kg/min</td>
</tr>
</tbody>
</table>

Beta Blockers
- Adverse Effects
  - Bradycardias
  - AV conduction delays
  - Hypotension

  - Avoid in
    - severe CHF, monitor in mild and moderate CHF
    - 2nd and 3rd degree heart block
    - Hypotension
    - Lung disease associated with bronchospasm
Calcium Channel Blockers
- Diltiazem/Verapamil
- Slow conduction and increase refractoriness in the AV node.
- AF, Aflutter.
- Use Verapamil ONLY in pts with narrow complex PSVT or arrhythmias of supraventricular origin.
- Avoid verapamil in pts with impaired ventricular rate or heart failure.

Calcium Channel Blockers
- Diltiazem
  - 0.25mg/kg followed by a second dose of 0.35mg/kg.
  - Maintenance infusion: 5-15mg/hr.
- Verapamil
  - 2.5-5mg IV over 2min. Repeated doses of 5-10mg may be given q 15-30min to a max of 20mg.

Statistics & Background
- Survival rates: for pts undergoing CPR=5-15%.
- Changes in use of epinephrine vs. vasopressin.

Blood pressure and CO Regulators
- Epinephrine
- Vasopressin
- Norepinephrine
- Dopamine
- Dobutamine
- Amrinone/milrinone
- Sodium Bicarbonate
- Sodium Nitroprusside
- Calcium
- Digitalis

Epinephrine
- Works by α receptor stimulation.
- Increases myocardial and cerebral blood flow during CPR.
- Enhances internal carotid and coronary perfusion.
- Questionable value/safety of Epi's B-adrenergic effects.
- Increases oxygen consumption demands.
- Dose not based on weight, assumed 1mg of intracardiac Epi is the same as 1mg IV.
- No longer use high dose epinephrine.
Epinephrine
- Results from 4 clinical trials compared high-dose epi with standard dose.
- Overall rate of return of spontaneous circulation was increased with higher doses of epi (0.07-0.2mg/kg).
- However, no statistically significant improvement in the rate of survival to hospital discharge occurred.
- Initial or escalating high-dose epi has occasionally improved initial ROSC and early survival.
- No significant harm from administration of high dose epi was found.
- Initial or escalating high-dose epi has occasionally improved initial ROSC and early survival.
- No evidence of worse outcome.
- Retrospective studies have suggested that high dose cumulative epi is associated with worse hemodynamic and neurological outcome, but they do not show causality.

Epinephrine Summary
- Initial high IV dose epi in cardiac arrest may increase coronary perfusion pressure and increase ROSC, but it may exacerbate postresuscitation myocardial dysfunction.
- Higher doses have not improved long-term survival or neurological outcome (when used as initial therapy).
- Therefore, high dose epi is not recommended for routine use, but may be used if 1mg dose fails. (class indeterminate)
- Dose 1mg q 3-5min. Followed by a 20ml flush.

Vasopressin
- Naturally occurring antidiuretic hormone.
- High doses it acts as non-adrenergic peripheral vasoconstrictor.
- Direct stimulation of smooth muscle V1 receptors.
- Adverse Effects:
  - Smooth muscle constriction also causes:
    - Pallor, nausea, intestinal cramping, defecation, bronchial constriction, and uterine contractions.

Vasopressin
- Endogenous levels of Vasopressin are higher in cardiac patients who survive.
- Increase coronary perfusion pressure, vital organ flow, cerebral oxygen delivery (VF and prolonged cardiac arrest and PEA).
- Repeated doses of Vasopressin were more effective than epi in maintaining coronary perfusion pressure above the critical threshold associated with ROSC.
- Produces no increased myocardial oxygen demand.
- Combo of Epi and Vasopressin vs. vasopressin alone resulted in only comparable left ventricular myocardial blood flow but significantly decreased cerebral perfusion.
- Decreases splanchic blood flow but infusion of low dose dopamine after CPR can return blood flow to baseline within 60min.

Pre-Hospital Use of Vasopressin
- Clinical evaluation after approximately 40min of unsuccessful ACLS: 4 of 10 patients responded to vasopressin and had a mean increase in coronary perfusion pressure of 28mmHg.
- Another study found larger proportion of patients initially treated with vasopressin were successfully resuscitated and survived 24 hours compared to with Epi (1mg).
- No difference in survival to hospital discharge:
  - A second study by Ian Stiell reviewed, again no difference in survival at 1 hour or discharge for either pharmacological tx.
  - Response times were similar/short.
  - Animal studies suggest that vasopressin may be especially beneficial in prolonged cardiac arrest.
  - Vasopressin’s response in severe acidosis remains intact where adrenergic response (epi) in severe acidosis is blunted.

Vasopressin for Asystole
- NEJM-January 8th, 2004
- Comparison of Vasopressin and Epinephrine for Out of Hospital Cardiopulmonary Resuscitation
  - 2 Injections of of either 40 units vasopressin or 1mg epinephrine-followed by additional doses of epinephrine if needed.
- The primary endpoint was survival to hospital admission and the secondary endpoint was survival to hospital discharge.
Vasopressin for Asystole

- 1219 patients randomized
- No significant differences in the rates of hospital admission between the vasopressin group and the Epi group in patients with VFib or PEA.
- However, among patients with asystole, vasopressin was associated with significantly higher rates of admission (29% vs 20.3%) and hospital discharge (4.7% vs 1.5%)
- Also found that in patients in whom spontaneous circulation was not restored, additional doses of epinephrine resulted in significant improvement in the rates of survival to hospital admission and discharge in the vasopressin group, but not in the epinephrine group (25.7% vs. 16.4%-small numbers –3 fold increase to hospital discharge as compared to epi)

What does this mean?

- There are 1000 sudden deaths in the U.S. each day – and it is estimated that 20-40% of these are the result of asystole
- Asystole has been the most refractory rhythm to resuscitation attempts.
- Acidosis and progressive ischemia are always present in asystole- and Epi is known to lose much of its effectiveness as a vasopressor in hypoxic, acidic environments-vasopressin does not.
- Epi consumes oxygen whereas vasopressin, increases coronary blood flow and the availability of oxygen to the myocardium
- Catecholamines may actually exacerbate hypoxemia and advance acidosis – and be detrimental in asystole.

Hurray for Vasopressin!!!

- NEJM recommending it as the New Standard of Care!

Hey What’s Your Problem?

- Other therapies (bicarb, atropine, lidocaine, amiodarone, and fibrinolysis) were also used at the discretion of treating physicians.
  - Of course out-of-hospital fibrinolysis in cardiac arrest is not being used in the U.S. –
  - Nor are physicians typically present during the pre-hospital phase of care, as they were in this study.
- The finding of a difference in response for patients in asystole is the result of a post-hoc subgroup analysis. As we all know, the findings of a post-hoc subgroup analysis cannot be used to draw a conclusion - only to generate a hypothesis for further study in a trial in which that hypothesis is tested as a primary endpoint.

Lets Break it Down.

- The number of patients in asystole was 528 (44.5% of the total), so this subset contains a relatively small number of patients from which to attempt to derive a meaningful result. (It is actually a sizable number as resuscitation studies go, but still small.)
- The absolute number of patients in asystole who survived to hospital discharge was 12 in the vasopressin group versus 4 in the epinephrine group.
- Many of us believe that the only outcome that matters is neurologically intact survival to hospital discharge. So the question, then, is how many of those twelve patients were neurologically intact? The answer is not in the paper, for reasons that are unclear. The authors use terms to describe neurologic outcome that are not defined in the paper ("good cerebral performance," "moderate cerebral disability," "severe cerebral disability," and "coma or vegetative state").

What’s Your Problem?

- While the reader may not know exactly what these terms mean, we may surmise that the latter two groups did not have the outcome we look for in a resuscitation study, and it is entirely uncertain how many in the first two groups returned to neurological intact life. In any case, the paper offers overall numbers of survivors falling into these four categories, but no such numbers are provided for survivors of asystole.
- If one looks at the statistical calculations for these numbers (12/257 survivors to hospital discharge in the vasopressin-treated asystole patients versus 4/262 in the epinephrine group), the P value is 0.04 and the odds ratio is 0.3. But the 95% confidence interval for the odds ratio is 0.1-1.0. As we know, when the 95% confidence interval touches 1.0, that includes the possibility that there is NO statistically significant difference between the two groups.
**Awe Man!**

**Vasopressin Summary**
- Alternative to Epi in adult shock-refractory VF
- Possibly more effective than Epi in asystole but not in Vfib or or PEA.
- Some individuals believe that Epi and Vasopressin may actually need to be used together- data pending
- Need more data
- Cardiac response unresponsive to Epi (class indeterminate)
- Hemodynamic support in vasodilatory shock when standard therapy is inadequate.

**Take Home Messages**
- A single dose of vasopressin is considered to be an alternative to agent to Epinephrine for ventricular fibrillation and pulseless v-tach.
- Vasopressin may be more effective than epi in asystole but not for PEA or Vfib.
- Although vasopressin has been shown to improve the ROSC and possibly increase rate of survival to discharge for asystole, neither epinephrine nor vasopressin has been shown to improve survival to hospital discharge for vfib, or PEA.
- No vasopressor has been shown to increase survival to hospital discharge with good neurological outcome.
- No antiarrhythmic agent has been found to improve survival to hospital discharge. Amiodarone, Lidocaine and procainamide are all options for v-fib/pulseless v-tach.
- Antiarrhythmics are just as likely to induce arrhythmias in acutely damaged or impaired hearts as they are to exert antiarrhythmic effects
- The best treatment for v-fib/pulseless v-tach is early defibrillation.

**So Now What?**
- Back to the Blackboard: However – most will use vasopressin instead of epi- for asystole as it is not any worse than epi and the possibility of benefit is there.

**Dopamine**
- Hypotension: especially shock
- Precursor of NE
- Both $\alpha$ & $\beta$ receptor stimulation
- DA1, DA2 receptors
- Stimulates the heart through $\alpha$ & $\beta$ receptors
- Peripherally-DA releases NE from stores in the nerve endings
  - NE-vasoconstriction
  - DA-counters NE with vasodilation
- Do not mix with Sodium Bicarb
- Dose:
  - Dopaminergic Doses: 1-4ug/kg/min
  - Beta doses: 5-10ug/kg/min
  - Alpha doses: >10-20ug/kg/min
Dobutamine

- B1 selective inotrope-
  - Increases cardiac contractility
  - Decrease in left ventricular filling pressure
  - Increase in stroke volume, reflex peripheral vasodilation
- Decreased sympathetic tone while augmenting cardiac output-heart failure
- Dose: 5-20ug/kg/min
- Elderly have decreased response to dobutamine

Norepinephrine

- Naturally occurring catecholamine
- Potent vasoconstrictor and inotropic agent.
- Systolic BP<70
- Contraindicated in patients with hypovolemia
- Ischemic necrosis and sloughing of superficial tissues may result from extravasation of NE.
- Dose: Initial dose is 0.5-1ug/min
- Do not administer w/ alkaline solutions

Amrinone/milrinone

- Phosphodieserase III inhibitors
- Inotropic and vasodilatory properties
- Amrinone has > effect on preload and hemodynamic effects are similar to dobutamine.
- Indication: Heart failure or cardiogenic shock not adequately controlled by standard therapy.
  - Patients unresponsive to catecholamine therapy
  - Tachyarrythmias
  - May exacerbate myocardial ischemia or worsen ventricular ectopy.
- Dose:
  - Amrinone: 0.75mg/kg given initially over 2-3 min.
  - Follow with an infusion of 15ug/kg/min
  - Milrinone: Slow IV loading dose 50ug/kg over 10 min, followed by an IV infusion at a rate of 375-750 ng/kg/min for 2-3 days. (adjust dose in renal failure)