Basic Pharmacology of EMS Drugs

Christina Candeloro, PharmD, BCPS
Clinical Pharmacy Specialist, Emergency Medicine, VCUHS
Assistant Clinical Professor, VCU School of Pharmacy
Richmond, VA
Objectives

- Explain the pharmacology and pharmacokinetics of the drugs you use often and infrequently
- Review from head to toe how to appropriately treat common chief complaints
- Discuss drug administration issues that impact your practice
What is pharmacology?

“Study of substances that alter living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes.”

What are PK/PD?

- **Pharmacodynamics**

  *The actions of the drug on the body*
  - Receptor binding – agonist/antagonist
  - Mechanisms of action

- **Pharmacokinetics**

  *The actions of the body on the drug*
  - ADME
  - Of great practical importance in the choice of a particular drug for a particular patient, ie. renal impairment

And most importantly…pharmacotherapy!

“The treatment of disease through the administration of drugs.”

Pharmacology 101

- **Agonist**
  - A chemical substance that upon binding to a specific receptor, activates it and produces a response

- **Antagonist**
  - A chemical substance that upon binding to a specific receptor, blocks the binding of agonists and opposes response on that receptor

http://www.uic.edu/classes/bios/bios100/f05pm/art_agonist.gif
Status epilepticus:

- 5 minutes or more of
  - continuous clinical and/or electrographic seizure activity, OR
  - recurrent seizure activity without recovery (returning to baseline) between seizures

Neurocrit Care 2012;17:3-23.
Neuro – Seizures: Pathophysiology

Pathologic Mechanism

Inhibition Failure
GABA-Responsive

Excess Excitation
GABA-Unresponsive

Pathophysiology

Receptor Trafficking:
↓GABA (endocytosis)
↑NMDA upregulation
Rapid Synaptic Plasticity:
GABA Receptor composition changes

Altered Gene Expression:
Multi-Drug Efflux Transporters (i.e. P-Glycoprotein)
Drug Resistance Proteins
Drug Target Alterations

Systemic Pathology

Sympathetic Overdrive

Clinical Stages

Acute Sz  Early or Impending Status  Established SE  Refractory SE  Malignant SE

Mortality

< 2 min  10 min  30 min
< 1%  < 5%  < 20%
60%  30%  40%
60%

1 hr  6 hr  10 hr  Days

Neurol Clin 30 (2012) 11-41
Neuro – Seizures: Treatment

Benzodiazepines

- Mechanism of action \(\rightarrow\) binds to benzodiazepine receptors at the GABA neuron in the central nervous system
- Lorazepam
- Diazepam
- Midazolam
- Other uses: Acute agitation/anxiety; pre-med prior to cardioversion

Neurocrit Care 2012;17:3-23.
Neuro – Seizures: Treatment

Which agent should I use?

- All acutely stop seizures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Dose</th>
<th>Administration</th>
<th>Onset</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>0.15 mg/kg IV (max 10 mg); repeat in 5 min</td>
<td>Up to 5 mg/min (IVP)</td>
<td>IV: Immediate</td>
<td>20-50 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CNS: 20-30 mins</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg IV up to 4 mg (2mg) per dose; repeat in 5–10 min</td>
<td>Up to 2 mg/min (IVP)</td>
<td>IV: up to 5 mins</td>
<td>6-8h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CNS: up to 24h</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg IM (max 10 mg)</td>
<td>Max 5 mL IM per injection (1 mg/ml)</td>
<td>IV: 1-5 mins</td>
<td>IV: ~30 mins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IM: &gt; 3 mins</td>
<td>IM: 2-6 hours</td>
</tr>
</tbody>
</table>

Neurocrit Care 2012;17:3-23.
# Neuro – Seizures: Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lorazepam (n=66)</th>
<th>Diazepam (n=68)</th>
<th>Placebo (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status epilepticus terminated, n (%)</td>
<td>39 (59.1)</td>
<td>29 (42.6)</td>
<td>15 (21.1)</td>
</tr>
</tbody>
</table>

p=0.001

![Graph showing the proportion of patients in status epilepticus over time for Lorazepam, Diazepam, and Placebo. The graph indicates a significant difference between Lorazepam and Placebo with a p-value of 0.001.](image_url)

Neuro – Seizures: Treatment

Practical Issues with Lorazepam

- Establishing intravenous (IV) access
  - Convulsing patients
  - Pediatric population
  - Requires healthcare providers skilled with obtaining IV access
  - Risk of needle sticks to healthcare providers

- Poorly absorbed when given intramuscularly (IM) or across mucus membranes

- Short stability when stored in non-refrigerated conditions

What about midazolam? After IM admin:

Neuro – Seizures: Treatment

What about midazolam?

- Randomized, double-blind, phase 3, noninferiority trial
  - 4314 paramedics, 33 EMS agencies, and 79 receiving hospitals

Subjects >40 kg:
- 10 mg IM midazolam
  OR
- 4 mg IV lorazepam

Subjects 13 - 40 kg:
- 5 mg IM midazolam
  OR
- 2 mg IV lorazepam

Neuro – Seizures: Treatment

What about midazolam?

Neuro – Seizures: Treatment

Benzodiazepines, other considerations:

- Precautions/warnings/adverse reactions
  - Depending on drug/route used, can be short acting, seizure may recur
  - Respiratory depression (especially in combination with opioids)
  - ↓ blood pressure
  - CNS depression (especially in combination with opioids/antipsychotics)
  - Transient amnesia
Psych – Acute Agitation

- **Causes**
  - Psychiatric illness – mostly schizophrenia, manic phase of bipolar
  - Medical (thyroid disorders, infections)
  - Substance induced
  - Medications (anticholinergics, steroids)

- **Goals of treatment**
  - Protect and calm patients without side effects
  - Protect self
  - Make patient more available for treatment

Drugs 2005; 65: 1207-1222.
### Psych – Acute Agitation: Treatment

- **Benzodiazepines**
  - Primarily lorazepam (Ativan); midazolam

- **Antipsychotics**
  - Ziprasidone (Geodon)

<table>
<thead>
<tr>
<th>Pharmacologic Class</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>• Use when etiology is unknown (ie. w/d suspected) \    • Less adverse events</td>
<td>• Do not address underlying disorder \  • Excessive/short-term sedation</td>
</tr>
<tr>
<td><strong>Second-generation Antipsychotics</strong></td>
<td>• Reduced propensity to cause EPS \  • Improve underlying psychosis</td>
<td>• Longer term sedation \  • Requires reconstitution \  • Cost</td>
</tr>
</tbody>
</table>

Psych – Acute Agitation: Treatment

Benzodiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>2 mg IM/IV</td>
<td>20-30 mins</td>
<td>8-10 hours</td>
<td>2 mg/ml</td>
</tr>
<tr>
<td>Midazolam</td>
<td>2-5 mg IM/IV</td>
<td>&lt;15 mins</td>
<td>2-6 hours</td>
<td>5 mg/5 ml</td>
</tr>
</tbody>
</table>

Second-generation Antipsychotic

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td>10-20 mg IM (max 40 mg)</td>
<td>30 mins</td>
<td>2-5 hours</td>
<td>20 mg powder Dilute with 1.2 ml SWFI</td>
</tr>
</tbody>
</table>

Psych – Acute Agitation: Treatment

- **Ziprasidone (Geodon)**
  - **MOA:** dopamine & 5-HT$_{2A}$ receptor blockade
  - **AE:** somnolence (clinical advantage, ↑ when combined with benzodiazepines), QT prolongation, EPS
  - **Precautions:** congenital long QT syndrome; history or cardiac arrhythmias
  - **Drug-drug Interactions:** amiodarone, dofetilide, sotalol, tacrolimus, elderly patients with dementia-related psychosis
  - **Co-administration in a patient already compliant with po ziprasidone not recommended**
  - **Administration only for IM use (NOT IV)**
Psych – Acute Agitation: Treatment

- Ziprasidone (Geodon) & Reconstitution

**WHY THIS?**

**INSTEAD OF THIS?**
Psych – Acute Agitation: Treatment

- Ziprasidone (Geodon) & Reconstitution

As of February 9, 2012, a search of the published medical literature has failed to identify any data regarding the use of normal saline for reconstituting ziprasidone IM. Pfizer has not conducted any studies evaluating the use of normal saline as reconstituting agent for ziprasidone IM. Pfizer does recommend or suggest the use of ziprasidone outside of the storage, handling and/or compatibility information noted in the approved product labeling. Pfizer cannot guarantee the stability, efficacy or safety of the product when used outside of these recommendations.

Letter from Shulman E, PharmD. Pfizer Medical Information. 10/2012
Airway Definitions

- **Rapid Sequence Intubation (RSI)**
  - Simultaneous administration of a sedative and a neuromuscular blocker to facilitate the process of endotracheal intubation

- **Induction**
  - Rapidly producing unconsciousness
Rapid Sequence Intubation

Timeline of Rapid Sequence Intubation

Step 1: Preparation
Assemble all necessary equipment and drugs

Step 2: Preoxygenation
Replace the nitrogen in the patient’s functional reserve with oxygen (“nitrogen wash out–oxygen wash in”)

Step 3: Pretreatment
Administer ancillary medications to mitigate adverse physiological consequences of intubation

Step 4: Paralysis with induction
Administer sedative induction agent via i.v. push, followed immediately by administration of paralytic via i.v. push

Step 5: Protection and positioning
Position patient for optimal laryngoscopy; Sellick’s maneuver, if desired, is applied now

Step 6: Placement with proof
Assess mandible for flaccidity; perform intubation, confirm placement

Step 7: Postintubation management
Long-term sedation, analgesia, or paralysis as indicated

Am J Health-Syst Pharm 2011; 68: 1320-30
RSI - Pretreatment

Why pretreat?

- Intubation introduces noxious stimulus into the trachea
  - Sympathetic/parasympathetic nerves in airway are stimulated
    - Release catecholamines
      - ↑ HR ~30 bpm; ↑ MAP ~20-25 mmHg
  - Activates cough reflex
    - ↑ ICP
    - ↑ risk of hemorrhagic stroke/herniation

Chest 2005; 127:1397-1412
Anesth Analg 2010; 110:1318-25
Am J Health-Syst Pharm 2011; 68: 1320-30
## Rapid Sequence Intubation

### Pre-treatment

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
| L | Lidocaine | Used to mitigate bronchospasm in patients with reactive airway disease  
Attenuate ICP response to laryngoscopy & intubation in patients with elevated ICP |
| O | Opioid | Attenuate sympathetic response to laryngoscopy & intubation |
| A | Atropine | Prevent bradycardia in children ≤10 yo or those receiving succinylcholine |
| D | Defasciculation | Attenuate ICP response to those receiving succinylcholine for RSI (1/10 paralyzing dose of competitive NMB) |

*Chest* 2005; 127:1397-1412
RSI – Pretreatment (L)

- Lidocaine
  - Class 1B antiarrhythmic/amide anesthetic
  - Blocks sodium channels in neurons
  - Onset 45-90 secs; duration 10-20 mins
  - Proposed benefits
    - Cough suppression
    - Attenuation of cardiovascular response to intubation
    - Attenuate ↑ ICP during RSI
  - Opposing evidence and opinions

---

Chest 2005; 127:1397-1412
Anesth Analg 2010; 110:1318-25
Am J Health-Syst Pharm 2011; 68: 1320-30
RSI – Pretreatment (L)

- **Lidocaine & ICP**
  - Cough suppression
  - No studies in emergency RSI evaluating ICP as a primary end point
  - Many questions still exist
  - If time, would consider until further data released

- **To be effective**: administer THREE minutes prior to intubation at a dose of 1.5mg/kg

_Chest_ 2005; 127:1397-1412
_Anesth Analg_ 2010; 110:1318-25
_Am J Health-Syst Pharm_ 2011; 68: 1320-30
RSI – Pretreatment (L)

- Lidocaine – the bad
  - Half-life may double in patients with hepatic impairment
  - Contraindications: severe bradycardia, heart block
  - Major D-DI: dofetilide; amiodarone; MAOIs
  - May cause hypotension

Chest 2005; 127:1397-1412
Anesth Analg 2010; 110:1318-25
Am J Health-Syst Pharm 2011; 68: 1320-30
RSI – Pretreatment (O)

- Opioids – fentanyl
  - Opioid receptor agonist
  - Onset immediate; duration ~1hr
  - Proposed benefit
    - Attenuate catecholamine response to intubation
  - Concerns: apnea; ↓ BP; chest wall rigidity
  - Data not robust
  - Typical dose 1-3 mcg/kg pre induction

Chest 2005; 127:1397-1412
Anesth Analg 2010; 110:1318-25
Am J Health-Syst Pharm 2011; 68: 1320-30
RSI – Pretreatment (A)

- Atropine
  - Blocks action of acetylcholine at parasympathetic sites
  - Onset immediate
  - Proposed benefit
    - Attenuate bradycardic response of succinylcholine in pediatric patients
  - No compelling data support use of atropine as pretreatment; not recommended for routine use
  - Kept on hand during intubation…
  - Remember: 0.5 mg

---

Chest 2005; 127:1397-1412
Anesth Analg 2010; 110:1318-25
Am J Health-Syst Pharm 2011; 68: 1320-30
Defasciculating dose

- Giving 1/10th paralyzing dose of non-depolarizing NMBA
- Proposed benefit
  - Mitigate succinylcholine induced fasciculations that may promote transient ↑ ICP in those at risk
- No evidence that this practice is beneficial in acute brain injury
- Not recommended

References:
- Chest 2005; 127:1397-1412
- Anesth Analg 2010; 110:1318-25
Rapid Sequence Intubation

Timeline of Rapid Sequence Intubation

Step 1: Preparation
Assemble all necessary equipment and drugs

Step 2: Preoxygenation
Replace the nitrogen in the patient’s functional reserve with oxygen (“nitrogen wash out–oxygen wash in”)

Step 3: Pretreatment
Administer ancillary medications to mitigate adverse physiological consequences of intubation

Step 4: Paralysis with induction
Administer sedative induction agent via i.v. push, followed immediately by administration of paralytic via i.v. push

Step 5: Protection and positioning
Position patient for optimal laryngoscopy; Sellick’s maneuver, if desired, is applied now

Step 6: Placement with proof
Assess mandible for flaccidity; perform intubation, confirm placement

Step 7: Postintubation management
Long-term sedation, analgesia, or paralysis as indicated

Am J Health-Syst Pharm 2011; 68: 1320-30
RSI - Induction

What Are My Options?
# RSI – Induction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Advantages/Indications</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td>0.3 mg/kg IVP</td>
<td>30-60 secs</td>
<td>3-5 mins</td>
<td>PK/PD Multitrauma CV neutral lots of data</td>
<td>Inhibits cortisol synthesis ↓ seizure threshold</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.1-0.2 mg/kg IV</td>
<td>1-5 mins</td>
<td>15 mins - 1 h</td>
<td>Seizures</td>
<td>PK/PD Dosing Hypotension Controlled substance Sub therapeutic dosing Pt awareness</td>
</tr>
</tbody>
</table>

---

*Chest 2005; 127:1397-1412
Anesth Analg 2010; 110:1318-25
Am J Health-Syst Pharm 2011; 68: 1320-30
What’s Wrong With Etomidate?

DRUG RATIONS IN AMERICA
What’s Wrong With Etomidate?

http://etomidat.de/_images/fig_3_adrenocortical_effects.jpg
What’s Wrong With Etomidate?

Figure 2. Percent normal cosyntropin stimulation test. Midaz = midazolam; Etom = etomidate.
What’s Wrong With Etomidate?

Advantages and Disadvantages of Etomidate Use for Intubation of Patients with Sepsis

Antoine J. Cherfan, Pharm.D., FCCP, Talat A. Arab, M.D., FCCP, FCCM, Hasan M. Al-Dorzi, M.D., MSc, and Lisa P. Kenny, M.D., FRCPc

Etomidate is a potent imidazole hypnotic used widely in single doses in the rapid sequence intubation of critically ill patients with sepsis due to its presumed hemodynamic safety, fast onset, and short duration of action. However, the literature is conflicting regarding the hemodynamic advantages of etomidate over other induction agents, and its safety in this population is a matter of strong debate in the critical care community. The drug is associated with suppression of adrenal steroidsogenesis, which can last up to 72 hours after a single dose, primarily through potent inhibition of the 11β-hydroxylase enzyme. However, the clinical impact of this adrenal suppressive effect is not certain. The use of continuous-infusion etomidate in critically ill patients was abandoned more than 20 years ago due to reports of increased mortality. Nevertheless, mortality data of single-dose etomidate are still controversial, with no strong evidence of benefit over other agents and a tendency toward harm (keeping in mind the limitations of the available literature). Proponents of single-dose etomidate use in patients with sepsis suggest that the increased mortality associated with etomidate is merely a reflection of the patients’ severity of illness and not related to the drug itself, whereas others believe that the drug causes true harm and increases mortality in this population. In view of the lack of a clear clinical advantage of etomidate over other agents used in rapid sequence intubation, it would be prudent to favor other agents until further conclusive evidence of etomidate safety is available in critically ill patients with sepsis.

Key Words: sepsis, etomidate, mortality, relative adrenal insufficiency, hydrocortisone, intubation.

(Pharmacotherapy 2012;32(8):1144-50)
RSI – Paralysis

What Are My Options?

[Images of medical vials and containers]
## RSI – Paralysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Succinylcholine</th>
<th>Vecuronium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Depolarizing NMBA. Binds to the Ach receptor</td>
<td>Non-depolarizing NMBA. Blocks Ach from binding</td>
</tr>
<tr>
<td>Dosage</td>
<td>1-1.5 mg/kg IVP</td>
<td>0.08-0.15 mg/kg IVP</td>
</tr>
<tr>
<td>Onset</td>
<td>30-60 sec</td>
<td>60-120 sec</td>
</tr>
<tr>
<td>Duration</td>
<td>5 – 15 min</td>
<td>25-65 min</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Plasma pseudocholinesterases</td>
<td>Has active metabolite (1/2 the activity of parent)</td>
</tr>
<tr>
<td>Elimination</td>
<td>Urine</td>
<td>Urine (30%); Feces (70%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>Faster onset; shorter duration</td>
<td>Few side effects</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Contraindications; ↑ K Bradycardia; Fasciculations</td>
<td>Onset/duration Reconstituted</td>
</tr>
</tbody>
</table>

*References:*
- Chest 2005; 127:1397-1412
RSI – Paralysis

Succinylcholine – the bad

- Contraindications
  - Personal or family history of malignant hyperthermia
  - Increased risk of hyperkalemia
    - Burn over 72 hours old
    - Crush injuries over 72 hours old
    - Denervating diseases
    - Rhabdomyolysis

Chest 2005; 127:1397-1412
Anesth Analg 2010; 110:1318-25
Am J Health-Syst Pharm 2011; 68: 1320-30
RSI – Paralysis

Anesthesiology 2006;104:158-69
RSI – Paralysis

Succinylcholine – hyperkalemia

- Most deaths due to hyperkalemia involve children with undiagnosed myopathies who underwent surgery
- Deaths are rare
- Changes in potassium range from 0.04-0.6 mmol/L
- Disease states that potentiate ↑K:
  - Myopathies; strokes; critical illness polyneuropathy; corticosteroid myopathies; burns; intraabdominal infections; sepsis; crush injuries

Chest 2005; 127:1397-1412
Anesth Analg 2010; 110:1318-25
Am J Health-Syst Pharm 2011; 68: 1320-30
RSI – Paralysis

Succinylcholine – the bad

- Other adverse drug events
  - Defasciculations
  - Bradycardia
    - Stimulation of muscarinic receptors
    - Most common in pediatrics
    - DO NOT repeat dose
  - Increased ICP
    - defasciculations
  - Increased intraocular pressure

Chest 2005; 127:1397-1412
Anesth Analg 2010; 110:1318-25
Am J Health-Syst Pharm 2011; 68: 1320-30
### RSI - Compatibility Info

#### Compatibility Chart

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Etomidate</th>
<th>Midazolam hydrochloride</th>
<th>Succinylcholine chloride</th>
<th>Vecuronium bromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam hydrochloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinylcholine chloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vecuronium bromide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **C**: Indicates compatibility for this method.
- **U**: Uncertain or variable for this method.
- **I**: Indicates incompatibility for this method.
- **X**: No data for any method.
Rapid Sequence Intubation

Timeline of Rapid Sequence Intubation

Step 1: Preparation
Assemble all necessary equipment and drugs

Step 2: Preoxygenation
Replace the nitrogen in the patient's functional reserve with oxygen ("nitrogen wash out–oxygen wash in")

Step 3: Pretreatment
Administer ancillary medications to mitigate adverse physiological consequences of intubation

Step 4: Paralysis with induction
Administer sedative induction agent via i.v. push, followed immediately by administration of paralytic via i.v. push

Step 5: Protection and positioning
Position patient for optimal laryngoscopy; Sellick's maneuver, if desired, is applied now

Step 6: Placement with proof
Assess mandible for flaccidity; perform intubation, confirm placement

Step 7: Postintubation management
Long-term sedation, analgesia, or paralysis as indicated

Am J Health-Syst Pharm 2011; 68: 1320-30
RSI – Post-intubation sedation

- Paralytics DO NOT have analgesic, amnestic, or sedative properties; patients are fully aware of surroundings and can sense pain.

In most adult patients:
50-100 mcg fentanyl IV +
2-4 mg midazolam IV

Will provide ~ 15 to 30 mins sedation

Am J Health-Syst Pharm 2011; 68: 1320-30
RSI: What if I Don’t Have an IV?

Succinylcholine

- **Onset**
  - IM → 2-6 minutes (max 150 mg)

- **Duration**
  - IM → 10-30 minutes

- **Dosing (RSI)**
  - IM → 3-4 mg/kg

Midazolam

*Ann Emerg Med 2011;57:449-461*
Asthma

- Asthma Exacerbation
  - Progressive increases in SOB, cough, wheezing, chest tightness, ↓ expiratory airflow
  - Morbidity/mortality most frequently associated with failure to recognize severity → inadequate tx/referral

- Goals of therapy
  - Maintenance of adequate arterial oxygen saturation
  - Relieve airflow obstruction
  - Reduce airway inflammation

*Chest 2004;125:1081-1102*
Pulmonary – Asthma Exacerbations

Treatment

- Oxygen
- Ventilation if necessary
- Bronchodilators
  - Albuterol
  - Ipratropium
- Corticosteroids
- Magnesium
- SQ Epinephrine
Pulmonary – Asthma Exacerbations

Treatment

- Albuterol
  - Short-acting beta-2 agonist – relax airway smooth muscles; provides 4x > bronchodilation than ipratropium
  - Mast cell stabilization; inhibition of release of inflammatory mediators
  - Onset 5 mins; Duration 3-6 hours
  - Comes in 2.5 mg/3ml neb (0.83 mg/ml) ready to go
  - Dose: 2.5-5 mg q20mins x 3 doses
  - Precautions: tachyarrythmias; history of CAD
  - AEs: sinus tachycardia, tremor, hypokalemia, anxiety, nausea, hyperglycemia
  - D-DI: MAOIs, TCAs, atomoxetine, marijuana (can ↑ albuterol levels); beta-blockers

GOLD guidelines 2011
Chest 2004;125:1081-1102
Pulmonary – Asthma Exacerbations

Treatment

- Ipratropium
  - Short-acting anticholinergic- bronchodilator
  - Should be given with beta-agonist; Overall: provide additional benefit to those treated with albuterol, with minimal side effects
  - Comes in 0.5 mg/2.5 ml neb (Can mix with 2 pre-filled albuterol)
  - Duration 2-5 hours
  - Dose: 0.5 mg (1 neb) q20mins x 3 doses
  - Precautions: myasthenia gravis, narrow-angle glaucoma; BPH
  - AEs: dry mouth, headache, nausea

*Chest* 2004;125:1081-1102
GOLD guidelines 2011
Treatment

**Ipratropium and peanut allergy**

- Severe, life-threatening anaphylactic reactions have been reported in peanut-allergic patients who have used ipratropium (Atrovent) or ipratropium/albuterol (Combivent) metered-dose inhalers (MDIs).
- Both products utilize a suspension agent, soy lecithin, which contains trace amounts of soy protein.
- While the MDIs should be avoided, patients may safely be prescribed ipratropium nebulizer solutions, as these formulations do not contain soy lecithin.
Pulmonary – Asthma Exacerbations

Treatment

- Prednisone
  - Corticosteroid
  - Dose: 60 mg orally (3x 20 mg tabs)
  - Benefits may not be seen for 6-12 hours
  - Why do we give steroids?
    - ↓ inflammation associated with asthma exacerbation
    - Moderate – severe exacerbation
  - Why not just give IV? Doesn’t oral take too long?
    - PK/PD – complete bioavailability; peak levels at 1h
      - IV reserved for impending/resp arrest; NPO
    - Cost
Pulmonary – Asthma Exacerbations

Treatment

- **Magnesium**
  - Inhibits smooth muscle cell Ca channels = relaxes bronchioles
  - Dose: 1-2 g IV over 20 mins
  - Comes in: 1gm/2ml vial → needs to be reconstituted
    - Hypotension/asystole can occur with rapid admin
  - Why do we give magnesium?
    - Improves lung function and only when given as an adjunct to standard therapy in a very select group of patients

*All Asthma Proc* 2004;25:S31-33
*Chest* 2004;125:1081-1102
Pulmonary – Asthma Exacerbations

Treatment

- Epinephrine
  - α1, β1, β2 agonist = relaxation of smooth muscle in bronchial tree; at lower doses β effects predominate
  - Dose: 0.3 mg SQ (IM preferred in anaphylaxis) x1 dose (USE 1:1000)
  - Onset ~5-10 mins
  - When do we give epinephrine?
    - Part of a generalized anaphylaxis
    - Aerosolized albuterol is ineffective or not possible

- MAJOR DRUG ERRORS HAVE OCCURRED

- Precautions: cardiac history, age >50
Chronic Obstructive Pulmonary Disease

- Acute Exacerbation of COPD
  - Acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations

- Goals of therapy
  - Minimize impact of current exacerbation
  - Prevent development of subsequent exacerbations

GOLD guidelines 2011
Pulmonary - COPD

Treatment

- Oxygen
- Ventilation if necessary
- Bronchodilators
  - Albuterol
  - Ipratropium
- Corticosteroids

GOLD guidelines 2011
Pulmonary - COPD

Treatment

- Prednisone
  - Corticosteroid
  - Dose: 60 mg orally (3x 20 mg tabs)
  - Why do we give steroids?
    - Shorten recovery time
    - Improve lung function (FEV$_1$) and hypoxemia (PaO$_2$)
    - ↓ risk of early relapse, treatment failure, hospital LOS
  - Why not just give IV? Doesn’t oral take too long?
    - PK/PD – complete bioavailability; peak levels at 1h
      - IV = PO in clinical trials
      - IV reserved for impending/resp arrest; NPO
- Cost

GOLD guidelines 2011
Allergic Reactions/Anaphylaxis

- Anaphylaxis
  - Severe, multisystem allergic reaction that occurs suddenly after contact with an allergen
  - Classic presentation: urticaria, angioedema, hypotension, bronchospasm
  - Pathophys: IgE mediated mast cell degranulation; inflammatory mediators released
    - ↑ vascular permeability
    - Peripheral vasodilation
    - ↑ mucous production
    - Bronchial smooth muscle contraction

*Can Fam Phys 2010;56:1009-1011*
Allergic Reactions/Anaphylaxis

Treatment

- Epinephrine – for anaphylaxis with airway compromise
  - $\alpha_1, \beta_1, \beta_2$ agonist = relaxation of smooth muscle in bronchial tree; vasoconstriction
  - Dose: **0.3mg** IM x1 dose (USE 1:1000)
    - Anterolateral thigh preferred → faster/↑ concentrations; avoid buttocks
  - Onset ~5-10 mins

- MAJOR DRUG ERRORS HAVE OCCURRED
  - Inadvertent overdose can cause coronary artery dissection, AMI, cardiomyopathy, arrhythmias, death

- In severe anaphylaxis, no absolute contraindications
Pulmonary – Anaphylaxis/Asthma

Treatment

- Epinephrine – the math

\[
1:1000 = 1g/1000mL
\]

\[
1g/1000mL = 1000mg/1000mL
\]

\[
1000mg/1000mL = 1 mg/1mL
\]

\[
1 mg/1mL = 0.3 mg/0.3 mL
\]

\[
1:10,000 = 1g/10,000mL
\]

\[
1g/10,000mL = 1000mg/10,000mL
\]

\[
1000mg/10,000mL = 0.1 mg/mL
\]

\[
0.1 mg/mL = 0.3 mg/3 mL
\]
Acute Decompensated Heart Failure

- ADHF
  - Failure of circulation to provide for the needs of the body

- Goals of early therapy
  - Prevent progression to respiratory or cardiac arrest

Pulmonary edema leading to hypoxemia
Treatment required

*Curr Opin Crit Care* 2012; 18: 301-307
CV - ADHF

Treatment – wet and warm

- Airway
- Relief of pulmonary congestion
  - Diuresis
  - Vasodilation

*Can J Cardiol* 2008;24:9B-14B
*Curr Opin Crit Care* 2012; 18: 301-307
CV – ADHF Treatment

Diuresis – furosemide

- MOA: inhibits Na/Cl reabsorption in loop of Henle, ↑ excretion of H₂O, Na, Cl, Mg, Ca
- What does it do?
  - Removes fluid, relieves symptoms
- Dosing is more of an art than a science: 20-100mg IV
  - Twice the home oral dose - data doesn’t support
  - 40 mg for every SCr 1.5
  - PO:IV furosemide is 2:1
- Administration: 40 mg undiluted over 1-2 mins
- Precautions: hypotension, pregnancy, sulfa allergy
- AEs: ototoxicity, N/V, ↓electrolytes

Card in Rev 2011;19:122-129
Can J Cardiol 2008;24:9B-14B
Curr Opin Crit Care 2012; 18: 301-307
CV – ADHF Treatment

Vasodilators – nitroglycerin

- **MOA:** mimics nitric oxide in vascular endothelium; preferential venous vasodilator
- **What does it do?**
  - Off-load the heart
  - Vasodilate the renal vasculature/facilitate diuresis
  - ↑ venous capacitance/ ↓ fluid burden returning to heart
- **Dosing:** 0.4 mg SL q5mins x3 doses (quicker than paste)
- **Half-life:** 1-4 minutes
- **Precautions:** hypotension hold if SBP <90; erectile dysfxn meds, ie. Viagra, Cialis
- **AEs:** reflex tachycardia, headache

*Can J Cardiol 2008;24:9B-14B  
Curr Opin Crit Care 2012; 18: 301-307*
**SIRS Criteria**

**Systemic**

**Inflammatory**

**Response**

**Syndrome**

- Heart rate > 90 bpm
- Respiratory rate > 20
- Temperature > 38°C or < 36°C
- WBC > 12,000 or < 4,000 cells/mm³ or bands >10%

*Chest* 1992; 101:1644-55
Sepsis definitions

**Sepsis**

= Infection + ≥ 2 SIRS criteria

**Severe Sepsis**

= Sepsis + organ dysfunction, hypoperfusion or hypotension

**Septic Shock**

= Severe Sepsis + hypotension despite adequate fluid resuscitation

Type of distributive shock

*Chest* 1992; 101:1644-55
Sepsis Interventions – First 6h

- **Surviving Sepsis 2008**
  - Begin resuscitation immediately in patients with hypotension or lactate >4 (1C)
  - Resuscitation goals (1C)
    - MAP ≥ 65 mmHg
    - UOP ≥ 0.5 mL/kg/hr; lactate clearance; ScVO₂ ≥ 70%; CVP 8-12 mmHg

- **2012 summary of changes:**
  - Big concentration on resuscitation bundle & performance improvement; Rapid lactate clearance (2C)
  - Minimum of 30 mL/kg fluids in first 4-6h

- What does this mean? FLUIDS, FLUIDS, FLUIDS!!!
Nausea/Vomiting

- Really just have one option
  - Ondansetron (Zofran)
    - Selective 5-HT₃ receptor antagonist

http://www.pedsoncologyeducation.com/img/clip_image002_006.gif
Nausea/Vomiting

- Ondansetron (Zofran)
  - MOA
    - Blocking 5-HT$_3$ receptors peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone
  - Dosing:
    - Adults: 4 mg IV
    - Pediatrics: 0.1 mg/kg IV; >40kg: 4 mg IV
  - Administration: undiluted over 2-5 mins; can be given IM
  - ADEs: headache, constipation, malaise/fatigue, ↑ QTc
  - Onset ~30 mins
  - Should only need one dose except chemo patients

MICROMEDEX 2012
Hypoglycemia

- One of the easiest problems to fix!
- With an IV: dextrose
- No IV: IM glucagon
Hypoglycemia

Dextrose

- D50W = 50% = 25g/50ml = 0.5g/ml = used for those >8yo
  - Remember: has half amount of drug as name, ie. whatever your volume you have 50% of that drug
- D25W = 25% = 25g/10ml = 0.25g/ml = used 30d – 8yo
- D10W = 10% = 0.1g/ml = used for those <30d
  - Not available in boxes - have to mix
    - Take 10 mL (5g) D50W & mix with 40 ml normal saline (50mL total)
    - Take 2 ml (1g) D50W & mix with 8 ml normal saline (10ml total)
- ADEs: tissue necrosis $\rightarrow$ flush or mix in sodium chloride

% = x grams / 100 ml

Micromedex 2012
Osmolarity

- Measure of solute concentration
- In general,
  - To give a medication peripherally: < 900 mOsm/liter
  - If > 900 mOsm/liter, should be given centrally
- D50W = 2526 mOSm/liter
- D50W in 100ml D5W = 1010 mOsm/liter
- D50W in 50ml NS = 1417 mOsm/liter
Hypoglycemia

Glucagon

- MOA: promotes hepatic glycogenolysis and gluconeogenesis
- What does it do? ↑ glucose
- Dosing: 1 mg IM (must be diluted only with SWFI)
  - Administer with dextrose, may precipitate with NS
- Onset 30 mins (IM) Duration 60-90 mins
- Give IV dextrose or food asap
- Precautions: insulinoma; pheochromocytoma
- ADEs: N/V (seen with high doses given IV)
Pain/Analgesia

- **Pain**
  - Most common complaint of patients presenting to an ED
  - Optimal management a challenge
  - Opioids are high risk meds and med errors can have serious consequences, especially when given IV

- **Opioids**
  - Bind to opiate receptors in CNS
    - Inhibition of ascending pain pathways
    - Alters perception and response to pain
  - Morphine and fentanyl

Ann Pharmacother 2010; 44: 1800-9
Pain/Analgesia

- Morphine
  - Prototypical opiate
  - Onset 5-15 mins; peak 20 mins (hydrophilic)
    - Potential for dose stacking
  - Duration 3-4 hours
  - Has active metabolite that is renally cleared
  - Has potential for histamine release
  - Will screen positive on drug screens
  - ADEs: CNS depression; respiratory depression; hypotension; bradycardia; N/V

*Ann Pharmacother 2010; 44: 1800-9*
Pain/Analgesia

- **Fentanyl**
  - Synthetic opioid receptor agonist
  - 100x more potent than morphine
  - Will not screen on most drug screens
  - Onset immediate
  - Duration 30-60 mins (need for more repeat doses)
  - Less pro-emetic than morphine
  - Clinically significant histamine release rarely happens
  - ADEs: chest wall rigidity

*Ann Pharmacother 2010; 44: 1800-9*
### Pain/Analgesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protocol type</th>
<th>IV Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Weight-based</td>
<td>0.1 mg/kg</td>
<td>10-15 min</td>
</tr>
<tr>
<td></td>
<td>Fixed dose</td>
<td>5-10 mg</td>
<td>10-15 min</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Weight-based</td>
<td>1 mcg/kg</td>
<td>5 min</td>
</tr>
<tr>
<td></td>
<td>Fixed dose</td>
<td>50-100 mcg</td>
<td>5 min</td>
</tr>
</tbody>
</table>

- Patient weight has not been shown to be predictive of analgesic response; max dose limits for obese patients
- Lower doses may be considered in patients at high-risk for sedation and respiratory depression

*Ann Pharmacother 2010; 44: 1800-9*
Pain/Analgesia

Dartmouth-Hitchcock Medical Center Trauma Analgesia Protocol

**GROUP A: Unstable Physiology:**
Patient has one or more of the following findings:
- Glasgow Coma Scale (GCS) 8 or less (indication for intubation)
- Heart Rate (HR) < 60 or >120 without a chronic explanation
- Systolic Blood Pressure (SBP) < 90 mm/Hg without a chronic explanation
- Acute Mental Status (MS) changes, including psychosis, intoxication, head injury or metabolic changes which complicate trauma assessment

**Intervention:**
Analgesics are not recommended.
Re-evaluation every 15 minutes.

**GROUP B: Stable Physiology:**
Patient does not have Group A criteria and has:
- GCS 9-12 and
- HR 60 – 120 beats/min with
- SBP 90-120 mmHg
- No MS changes complicating surgical/trauma assessment

**Intervention:**
Analgesics should be administered in individual doses with continuous assessment of physiological status.
For weight >40kg: Fentanyl 25-50 mcg IV q 15 minutes prn pain
(For weight <40kg: Fentanyl 10-25 mcg IV q 15 minutes prn pain)

**GROUP C: Normal Physiology:**
Patient does not meet criteria of Groups A or B, and has all of:
- GCS >13
- HR 60-120 beats/min
- SBP > 120 mmHg or (<120 if documented normal for patient)
- Injury mechanism which would require narcotic analgesia

**Intervention:**
Analgesics should be administered in individual doses with continuous assessment of physiologic status.
For weight >40kg: Fentanyl 25-50 mcg IV q 5 minutes prn pain
(For weight <40kg: Fentanyl 10-25 mcg IV q 5 minutes prn pain)

_J Trauma 2007; 63: 819-826_
Pain/Analgesia

Special populations

- Opioid allergy
- Renal Failure
- Opioid Tolerance
  - Initial dose 5% of the patient’s total daily dose but not <0.1 mg/kg IV morphine
- High-risk groups
  - Elderly (>65yo)
  - Obstructive sleep apnea
  - Pulmonary disease
  - Obesity

Ann Pharmacother 2010; 44: 1800-9
Opioid OD – reversal

Naloxone
- Most commonly used antidote in the ED
- Competitive antagonist at all opioid receptors
- Efficacy and safety are dose-dependent
  - Starting dose can range from 0.4-2 mg IV, can be titrated
  - Will depend on patient specific factors
    - Airway status
    - Opioid withdrawal – vomiting/aspiration/ALI
    - Chronic opioid users (ie. cancer pts)
    - Buprenorphine 2-4 mg IV
- Onset 2 mins (IV) 2-5 mins (IM/SQ); ETT 2-2.5x the dose
- Duration 30-90 mins, longer if given IM/SQ
- Can also be considered for: diphenoxylate; dextromethorphan; clonidine

Am J Health-Syst Pharm 2012; 69: 199-212
Non-drug stuff
Non-drug stuff
Summary

- When giving any medication
  - Handling
  - Indication
  - Contraindication
  - Safety
  - Appropriate Dose
  - Response
Basic Pharmacology of EMS Drugs

Christina Candeloro, PharmD, BCPS
Clinical Pharmacy Specialist, Emergency Medicine, VCUHS
Assistant Clinical Professor, VCU School of Pharmacy
Richmond, VA