Drug-induced cognitive disorders in the elderly

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PGY-2 Critical Care Pharmacy Resident

Objectives

- Explain why elderly patients are at higher risk for drug-induced cognitive disorders
- Review drug classes associated with cognitive disorders in the elderly
- Discuss common pharmacologic and non-pharmacologic approaches for treatment and/or prevention of delirium

Background

- 2010 U.S. Census Data
  - There are approximately 50 million people in the US 62 years of age and over
    - Same number that was predicted to occur in 2020
    - Increase of 21% since 2000
  - Florida has highest median ages
    - Of the top 10 cities, 2 were located in South Florida
  - 3.6 million people ≥ 65 years old have an underlying cognitive disability

- Adverse drug events have been linked to preventable problems in the elderly
  - Depression, falls, confusion
- 30% of hospital admissions are due to drug-related problems or drug toxicity in the elderly
- Delirium can increase the risk for medical complications
- In 2000, an estimated 106,000 deaths were medication related with an estimated healthcare cost of $85 billion

WHY ARE THE ELDERLY AT RISK?

- Cognitive impairment and driving
  - Estimated 33 million licensed drivers ≥65 years old
  - 69% of AAA Foundation for Traffic Safety survey participants used one or more medication that may impair driving
    - Of these, only 28% indicated they were aware of this risk
The “I’s” of geriatrics
- Immobility
- Isolation
- Incontinence
- Infection
- Inanition (malnutrition)
- Impaction
- Impaired senses

Pharmacokinetics - absorption
- Changes in gastrointestinal physiology
- Most drugs are absorbed via passive diffusion and these changes may have little influence on bioavailability
- Decreased first-pass effect and/or gut wall metabolism
- Reduced subcutaneous fat results in altered absorption of transdermal medication

Pharmacokinetics - distribution
- Dependent on blood flow, plasma protein binding, and body composition
- Age-related changes
  - ↓ Volume of distribution of water-soluble medications
  - ↑ Volume of distribution of lipophilic medications
  - Decrease in P-glycoprotein activity in the blood-brain barrier
  - Decreased albumin may lead to increased free fraction
  - Increased α1-acid glycoprotein may lead to decreased free fraction

Pharmacokinetics - metabolism
- Liver is the major organ for drug metabolism
- Decreased phase I metabolism
  - Diazepam, piroxicam, theophylline, quinidine
- Relatively unaffected phase II metabolism
- Enzyme induction or inhibition does not appear to be affected

Pharmacokinetics - elimination
- Renal excretion is the primary route of elimination
  - Age-related reduction in glomerular filtration
  - Cockcroft and Gault is a useful screening tool to assess renal function
    - Assumes stable renal function and actual body weight within 30% of ideal body weight
  - Modified Diet in Renal Disease (MDRD) equation

Altered pharmacodynamics
- 4 possible mechanisms
  - Change in receptor numbers
  - Change in receptor affinity
  - Postreceptor alterations
  - Age-related changes in homeostatic response
Beer’s criteria

- Consensus criteria for medication use in older adults
  - Literature review
  - Expert panel- experts in psychopharmacology, pharmacoeconomics, clinical geriatric pharmacology, and clinical geriatric medicine
- Adopted in 1999 by the Centers for Medicare and Medicaid Services (CMS) for nursing home regulation
  - Medications likely to cause problems in long-term care residents
  - Most commonly used medications causing cognitive impairment include analgesics, antidepressants, anticholinergics, and benzodiazepines (BZD)

Drug-induced CNS depression/sedation

- Drowsiness
- Lethargy
- Decreased respiratory rate

Medications causing CNS depression/sedation

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drugs to avoid</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiolytic</td>
<td>Meprobamate</td>
<td>Shorter acting BZDs, buspirone</td>
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<tr>
<td>Long-acting BZD</td>
<td>Clorazepate Diazepam</td>
<td>Anxiety: Shorter-acting BZD</td>
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<tr>
<td>Antihistamines</td>
<td>Chlorpheniramine</td>
<td>Cetirizine, fexofenadine, loratidine</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diphenoxylate</td>
<td>Change in diet, loperamide</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>Oxybutin</td>
<td>Behavior therapy (urge incontinence)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Indomethacin</td>
<td>Acetaminophen (APAP), ibuprofen, COX II inhibitor (short term), allopurinol (gout)</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline</td>
<td>nortriptyline, desipramine, SSRI (except fluoxetine), bupropion, mirtazapine</td>
</tr>
</tbody>
</table>

Drug-induced delirium/confusion/AMS

- Disturbance of consciousness with reduced ability to focus, sustain, or shift attention
- Change in cognition or the development of a perceptual disturbance not accounted for by dementia
- Disturbance developed over short period of time and fluctuates throughout the day
- Examination (labs, history, physical exam) finds the disturbance is caused by a medical condition, substance intoxication, or medication side effect
Risk factors for medication-induced delirium

- Polypharmacy
  - ≥9 chronic medications
  - ≥12 doses of medications per day
- ≥6 concurrent chronic diagnoses
- Creatinine clearance <50 mL/min
- Low body weight
- Age >85 years old
- Prior medication-induced delirium

Medications causing delirium/confusion/AMS

<table>
<thead>
<tr>
<th>Drug class</th>
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<th>Alternatives</th>
</tr>
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<tbody>
<tr>
<td>Antiacetylcholinesterase (anti-AChE) inhibitors</td>
<td>Rivastigmine, donepezil, memantine</td>
<td>Cholinesterase inhibitors, NMDA receptor antagonists</td>
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<tr>
<td>Antidepressants</td>
<td>Sertraline, escitalopram, paroxetine</td>
<td>Selective serotonin reuptake inhibitors, trazodone</td>
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<tr>
<td>Antipsychotics</td>
<td>Quetiapine, aripiprazole, olanzapine</td>
<td>Other antipsychotics, atypical antipsychotics</td>
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<tr>
<td>Antipsychotics</td>
<td>Haloperidol, chlorpromazine</td>
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<tr>
<td>Antipsychotics</td>
<td>Clozapine, olanzapine</td>
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<tr>
<td>Antipsychotics</td>
<td>Lithium, valproate</td>
<td>Lithium, valproate, other anticonvulsants</td>
</tr>
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<td>Antipsychotics</td>
<td>Haloperidol, clozapine</td>
<td>Benzodiazepines, atypical antipsychotics</td>
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Extrapyramidal symptoms (EPS)

- Akathisia- motor restlessness with a compelling urge to move and the inability to sit still
- Parkinsonian syndrome- mask-like faces, resting tremor, cogwheel rigidity, shuffling gait, and bradykinesia
- Dystonias- involuntary contractions of major muscle groups

Medications causing EPS

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**THE ROLE OF THE PHARMACIST**

**Optimal Pharmacotherapy**
- Effective medications to treat conditions
- Correct doses
- Correct dosage forms
- Appropriate duration
- If appropriate, dose-adjusted for age-related and/or disease-related changes in pharmacokinetics and pharmacodynamics
- If possible avoid medication that can decrease patient function

American College of Clinical Pharmacy, 2010

**Medication Appropriateness Index**
- Is there an indication for the medication?
- Is the medication effective for the condition?
- Is the dosage correct?
- Are the directions correct?
- Are the directions practical?
- Are there clinically significant drug-drug interactions?
- Are there clinically significant drug-disease interactions?
- Is there unnecessary duplication with other medication(s)?
- Is the duration of therapy acceptable?
- Is this medication the least expensive alternative compared with others of equal utility?


**Prevention- Avoiding polypharmacy**
- Common and increasing problem in the elderly
- Increased use of dietary supplements
  - Herbals
  - Vitamins
  - Minerals
- Multiple medications have a strong correlation with adverse drug reactions
- Counsel patients/caregivers regarding this risk

UpToDate, 2011. Drug prescribing in the elderly.

**Prevention- Inappropriate prescribing**
- Inappropriate prescribing
  - Medications prescribed outside of accepted medical standards
  - Prescribing of medications which should be avoided because the risk outweighs the benefit
  - 92% of patients were taking at least one medication with one or more inappropriate reasons (published 6/1/10)
- Avoid recommending medications on the Beer’s list
- After speaking with the patient/caregiver, match the medication with a diagnosis
- Question medications that may be a risk for your elderly patients and contact the physician
Prevention- Medication adherence

- Recommend cost-effective substitutions that are not at risk for causing cognitive impairment
- Counseling about most common adverse effects of medications and activities to avoid while on this medication
  - Warn patients about medications which may impair driving

Non-pharmacologic approach

- Improve balance and avoid falls
  - Tai Chi
  - Correction of vision problems
- Improve mental state
  - Reading
  - Playing games
  - Puzzles
  - Exercise
  - Sufficient sleep

Patient Case

- YC is a 70 year old woman who drives to 3 different pharmacies to pick up her medications. She is now at your pharmacy and tells you she has not been getting a sufficient amount of sleep due to her anxiety. Her elderly neighbor gave her some diphenhydramine capsules and told her “You won’t know what hit you after you take this.” She tells you it has helped her fall asleep but she doesn’t feel well rested in the morning.

Patient Case

Her current home medications include...

- Lisinopril 5 mg PO daily
- Simvastatin 20 mg PO qHS
- Fluoxetine 40 mg PO qHS
- Levothyroxine 88 mcg PO daily
- Diphenhydramine 50 mg PO qHS

What are some counseling points you can offer YC?

Patient Case

- Transfer all her prescriptions to 1 pharmacy
- Avoid diphenhydramine
  - Avoid driving when taking medications that may impair attention, focus, and coordination
- Fluoxetine should be taken in the morning or changed to a less activating SSRI

True or False?

- Risk factors for delirium include polypharmacy, creatinine clearance >50 mL/min, increased body mass index, and age >85 years old.
- The most common class of medications associated with cognitive impairment includes analgesics, benzodiazepines, anticholinergics, and antidepressants.
- Adverse outcomes associated with delirium include increased length of hospital stay and higher mortality rates.
Update on Medications Used in Autism

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Objectives
- Provide an overview on Autism Spectrum Disorders (ASD) and related conditions
- Review specific symptoms associated with ASD, and how to target medication therapy based on symptoms
- Review medications used for Autism and their side effect profiles

Symptoms of ASD

Core symptoms
- Impaired social interaction
- Impaired communication skills
- Repetitive restrictive behavior

Symptoms of ASD
- Lack of spontaneous or pretend play
- Irritability
- Aggression
- Hyperactivity
- Self-Injury
- Impaired cognitive skills and sensory perception
- Intense preoccupation with particular concepts or things

Causes of ASD
- The exact cause of ASD is unknown
- Imbalance in serotonin, dopamine, norepinephrine, glutamate/gamma-aminobutyric acid (GABA) systems, and neuropeptides have been linked to ASD

Autism Spectrum Disorders (ASD)
Disorders within the spectrum include:
- Autistic Disorder
- Asperger Syndrome
- Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS)
Current Therapy
Treatment focuses on:
- Improving deficits in social communication
- Improving challenging behaviors
- Improving difficulties associated with the disorder (anxiety, attention difficulties, sensory difficulties, agitation, hyperactivity)

Behavioral and Educational interventions seek to target the “core symptoms” of social and communicative symptoms
Medical interventions seek to target the “other symptoms” such as irritability, specific repetitive behaviors, anxiety, and other challenging behaviors

Medications Used in Autism: Antipsychotics
- Currently there are only two medications approved by the FDA for the treatment of aggression and irritability in children with ASD
- Atypical antipsychotics: Risperidone and Aripiprazole

Current Medical Therapy
- As it stands, Aripiprazole and Risperidone reduce challenging and repetitive behaviors when compared with placebo
- Insufficient evidence exists to recommend the use of other medical interventions currently used to treat ASD, although some look promising

Risperidone
- Dopamine and Serotonin Receptor Antagonist
- Multiple randomized controlled trials (RCTs) have been performed, including the federally funded Research Units for Pediatric Psychopharmacology (RUPP)
- Established evidence for its use in irritability and hyperactivity in children with autism

Risperidone RUPP (2002)
- 8-week, double-blind, placebo-controlled trial of 101 children (ages 5–17 years) to evaluate Risperidone efficacy
- Risperidone-treated group had significant statistical and clinical improvement compared with the placebo-treated group (69% vs 12%) on the primary outcome measures, the Irritability scale of the Aberrant Behavior Checklist (ABC) and Clinical Global Impressions-Improvement rating (CGI-I)
Aberrant Behavior Checklist (ABC)

This is a caregiver-rated assessment tool that has five subscales:
- Irritability
- Social Withdrawal/Lethargy
- Stereotypic Behavior
- Hyperactivity/Non-compliance
- Inappropriate Speech

ABC-Irritability (ABC-I) Subscale

- Contains 15 items that measure symptoms of irritability on a scale ranging from 0 (not at all a problem) to 3 (severe). These include:
  - Injures self
  - Aggression towards others
  - Irritable
  - Temper outbursts
  - Depressed mood
  - Mood changes
  - Yells or screams inappropriately

Aripiprazole

- Partial Agonist at Dopamine 2 and Serotonergic Receptors
- Strong evidence backed by industry-funded RCTs
- Established efficacy in reducing irritability, hyperactivity, and stereotypy in children with ASD

Aripiprazole Trials (2009)

- Two industry sponsored 8-week RCTs (flexible-dose and fixed-dose) compared a total of 213 ASD subjects receiving Aripiprazole to 103 receiving placebo
- Aripiprazole demonstrated improvement in Aberrant Behavior Checklist Irritability (ABC-I) Subscale Score as early as Week 1 or Week 2 in both studies
- Aripiprazole shown to be superior to placebo for the treatment of irritability

Secretin?

- Secretin is a gastrointestinal polypeptide used to treat peptic ulcers and in the evaluation of pancreatic function
- No studies have resulted in significantly greater improvements in measures of language, cognition, or autistic symptoms when compared with placebo

Citalopram

- Selective serotonin reuptake inhibitor (SSRI)
- Large RCT of 149 children found no significant effect on repetitive behavior (thought process being this behavior is similar to OCD)
- Insufficient evidence at this time
Guanfacine
- Selective alpha 2a agonist of central postsynaptic receptors
- One small study (7 children) showed statistically and clinically relevant impact on hyperactivity
- Requires further study

Atomoxetine
- Selective presynaptic norepinephrine transporter inhibitor
- A small RCT (16 children) showed promise in reducing symptoms of hyperactivity
- Promising, but requires further study

Methylphenidate
- Norepinephrine and Dopamine reuptake inhibitor
- A few RCTs, including the federally funded RUPP (2005), show promise in hyperactivity
- Promising, but requires further study

Methylphenidate Trial RUPP (2005)
- Double-blind, placebo-controlled, crossover trial followed by open-label continuation
- 72 drug-free children, aged 5 to 14 years, with PDD accompanied by moderate to severe hyperactivity
- Methylphenidate was superior to placebo on the primary outcome measure (ABC), with effect sizes ranging from 0.20 to 0.54 depending on dose and rater. Thirty-five (49%) of 72 enrolled subjects were classified as methylphenidate responders

Naltrexone
- Opioid antagonist
- Five RCTs, largest being a study consisting of 41 children. Some (but not all) of the studies showed significant improvement in hyperactivity
- Promising, but requires further study

Adverse Drug Effects
- Children and adolescents with autism and other developmental disabilities have very sensitive nervous systems due to their inherent neurochemical balances
- Medications need to be started at lower doses and titrated slowly in these immature immune systems
Adverse Drug Effects

- Some studies reported increased side effects in children with ASD:
  - Extrapyramidal side effects, (including pseudo-parkinsonism, akathisia)
  - Acute dystonic reactions (especially facial)
  - Neuroleptic malignant syndrome

Atypical Antipsychotics Side Effects

- Sedation
- EPS
- Tachycardia
- Fatigue
- Drowsiness
- Hyperlipidemia
- Diabetes
- Weight gain (less with Aripiprazole or Ziprasidone)

Atomoxetine Side Effects

- Dyspepsia
- Nausea vomiting
- Fatigue
- Decreased appetite
- Stomach pain
- Constipation
- Dry mouth
- Dizziness

Methylphenidate Side Effects

- Motor tics
- Social withdrawal
- Irritability
- Appetite loss

SSRIs Side Effects

- Increased suicidality
- Excitement or anxiety
- Upset stomach
- Drowsiness
- Insomnia
- Dry mouth
- Changes in appetite and weight

Summary

- Promising medications for ASD are on the rise, currently centered around atypical antipsychotics
- Further studies have yet to be done on other medications such as Methylphenidate and the SSRIs
Summary

- Although beneficial for reducing problematic behaviors, medical treatment should always be used as adjunctive treatment to behavioral and educational interventions.

Case Study

- Timmy Polk, an 8-year-old autistic child, and his father Jonathan Polk, present to the Pharmacist and Psychiatrist for help regarding Timmy's recent aggressive behavior and tantrums.
- Timmy was diagnosed with Autism at age 2 and lately has been exhibiting increasing behaviors of repetitive self-injury and irritability for the past 2 months.
- Timmy has also begun repetitively pacing around at home, sometimes for hours on end.

Case Study

- Mr. Polk is willing to try medical therapy due to Timmy's recent change in behavior. However, Mr. Polk expresses concern that obesity runs in his family, and that both he and his father had difficulty maintaining a healthy weight when they were younger. Mr. Polk and his father both also have Diabetes Mellitus Type II.
- The Psychiatrist would like to ask the Pharmacist what drug therapy is appropriate to start Timmy on.

Case Study

- Answer: Aripiprazole
- Aripiprazole is FDA indicated for Psychomotor agitation: (age 6 to 17 years) and has shown to be beneficial in controlling irritability. It is initially dosed at 2 mg ORALLY once daily, then gradually increased to 5 mg/day. If necessary it can be adjusted at 5-mg increments at a minimum of 1-week intervals to a total of 10 - 15 mg/day.
- Compared to the other FDA approved antipsychotic, Risperidone, Aripiprazole has a lesser incidence of weight gain and therefore would be appropriate in this patient. Regardless, it would be encouraged to monitor weight gain, obtain a lipid panel, and obtain fasting glucose levels at baseline and at least yearly.

True/False

1. Risperidone and Aripiprazole are the only medications approved by the United States Food and Drug Administration for the treatment of aggression and irritability in children with ASD.
   - TRUE!

2. Children with ASD are MORE sensitive to medication effects and MORE likely to have adverse effects than children without ASD. Medications should be started at LOWER doses, and doses should be increased more SLOWLY than in patients without ASD.
   - TRUE!

3. Stimulants, such as Methylphenidate and Atomoxetine, are NOT used in ASD management.
   - FALSE, they are!
References


The use of Psychotropics in Children

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Dade County Pharmacy Association

Objectives

- To understand current practice and evidence based use of psychotropics in children
- Usual recommended doses of common psychotropic medications
- Distinguish between levels of warnings associated with medication adverse effects

Major Depression

- 2% of children & 10% of teenagers
  - 35% unipolar depression
  - 48% bipolar disorder
- Luby et al., 2002
  - DSM-IV failed to accurately diagnose 76% of young children judged to be suffering with major depression
  - Recommend modified diagnostic criteria

Symptoms of Major Depression

- Depressed or irritable mood for more days than not
- Plus 4 of the following (as opposed to the 5 required for adults)
  - Anhedonia
  - Significant weight loss or gain
  - Insomnia or hypersomnia more days than not
  - Psychomotor agitation or retardation
  - Fatigue more days than not
  - Feelings of worthlessness or excessive guilt
  - Impaired concentration
  - Recurrent thoughts of death or suicide

Major Depression

- Prepubertal children
  - ~1/2 with episodes of major depression → first manifestation of bipolar disease
  - 70% initially present with depression
  - 2 to 4 depressive episodes prior to their first manic episode

Major Depression

- Tricyclic antidepressants (TCAs)
  - Response in severely depressed, hospitalized children
  - Significant side effects
  - Toxic in overdoses
  - Associated with 6 cases of sudden death in children
  - Found to be no more effective than placebos in the treatment of mild to moderate major depression


Major Depression

- Selective serotonin reuptake inhibitors (SSRIs)
  - Placebo responses in these child studies are higher than those seen in adult studies
  - Tolerated better than TCAs & are significantly more effective than either placebos or TCAs
- Fluoxetine (Prozac, Sarafem)
  - The only antidepressant approved by the FDA for the treatment of major depression in children (ages 8 and older)
- Many antidepressants are used off-label

Major Depression Treatment

- 1st wk: start with low doses
- Gradually increase while carefully watching for signs of clinical response or side effects
- Treat for a month to 6 wks and then increase the dose
- Continue treatment at same dose for a minimum of 6 months after symptomatic improvement
- Follow by gradual discontinuation

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Starting Dose (mg)</th>
<th>Daily Dose (mg)</th>
<th>Adjusted Daily Dose (mg/kg)</th>
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<tbody>
<tr>
<td>6+</td>
<td>Fluoxetine</td>
<td>Prozac, Sarafem</td>
<td>C: 5</td>
<td>5 – 40</td>
<td>0.25 – 0.75</td>
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<td>Zoloft</td>
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<td>25 – 200</td>
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<td>Paroxetine</td>
<td>Paxil</td>
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<td>10 – 30</td>
<td>0.25 – 0.75</td>
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Antidepressants & Suicidality

- Initial concern came from a study in England
  - Statistical significance of increased suicidality in young pts taking Paxil compared to placebo (3.4% & 1.2%, respectively)
  - No actual suicides
  - Suicidal "event" occurred when the children stopped taking Paxil
- Significant impact on prescribing and parental fears
- FDA Black Box warning
  - Increased risk of suicidal ideation in children or adolescence
Bipolar Disorder

- Adulthood: 1%
  - Subsyndromal symptoms: 5-6%
- Onset:
  - Prepubertal: 27%
  - Teens to 18 yo: 38%
  - Adults: 35%
- Most manic symptoms begin during mid-adolescence

Bipolar Disorder Treatment

- Aimed at the stabilization of initial presenting target symptoms, full syndrome resolution, & relapse prevention
- Mania
  - 1st line: lithium, divalproex, and atypical antipsychotics
  - Majority of children require ≥2 mood stabilizers

Bipolar Disorder Treatment

- Depression
  1) Quetiapine (Seroquel)
  2) Lamotrigine (Lamictal)
  3) Lithium
  4) Olanzapine-Fluoxetine (Symbyax)
  5) Electro-convulsive therapy (ECT)
- For very severe, psychotic, &/or treatment-resistant pts

Bipolar Disorder Treatment

- Severe agitation & sleep disturbance
  - Short-term benzodiazepines
  - Atypical antipsychotics
- Psychosis
  - Atypical antipsychotics
- Comorbid ADHD & bipolar disorder
  - Initiate treatment with mood stabilizer(s)
  - Once stability has been achieved, add stimulants gradually
- Comorbid anxiety disorders and bipolar disorder
  - SSRI

Bipolar Disorder: FDA-Approved Drugs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Age (yrs)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td></td>
<td>12+</td>
<td>manic episode or maintenance therapy</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>13 – 17</td>
<td>acute mixed or manic episodes, maintenance therapy, or agitation</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>10+</td>
<td>bipolar 1 disorder</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>10 – 17</td>
<td>manic episode, depressed phase, or maintenance therapy</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>10+</td>
<td>monotherapy for manic or mixed episodes, adjunctive therapy with lithium or valproate, or psychomotor agitation</td>
</tr>
</tbody>
</table>
### Anxiety Disorders

- **5-18% of children**
- Most common psychiatric conditions in children
- Obsessive-compulsive disorder (OCD)
  - Pharmacotherapy is the standard of treatment
  - Lifetime prevalence
    - 1% for adults
    - 2% for children & adolescents
    - 6-15 yrs old for males
    - 20-29 yrs old for females
    - Childhood onset: more common in boys (3:2)
    - Adults: 1:1

### Anxiety Disorders: OCD

- **Begin with CBT alone or CBT combined with an SSRI**
- Most children placed on SSRI monotherapy
- No adequate symptom response
  - Augment with clomipramine or atypical antipsychotic

### FDA Black Box Warnings

- **Lithium**
  - Toxicity is related to serum lithium levels & can occur at doses close to therapeutic levels
- **Divalproex**
  - Hepatotoxicity (some cases fatal) usually occurring during the first 6 months of treatment
  - Teratogenic effects
  - Life-threatening pancreatitis in children & adults
- **Carbamazepine**
  - Fatal dermatologic reactions
  - Aplastic anemia & agranulocytosis

### Anxiety Disorders: OCD

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Initial Dose</th>
<th>Daily Dose</th>
<th>Age (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonitram</td>
<td>Geleks</td>
<td>C/A: 10 mg</td>
<td>C/A: 10-60 mg</td>
<td>—</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Anafranil</td>
<td>C/A: 25 mg</td>
<td>C/A: 200 mg/day or 3 mg/kg/day, whichever is lower</td>
<td>10+ yrs</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Luxon</td>
<td>C/A: 25 mg at bedtime</td>
<td>C/A: 50-200 mg/day (higher dosages divided)</td>
<td>8-17 yrs</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>C/A: 10 mg daily</td>
<td>C/A: 10 mg daily (also higher weight children)</td>
<td>7-17 yrs</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft</td>
<td>C: 25 mg daily</td>
<td>A: 50 mg daily</td>
<td>13-17 yrs</td>
</tr>
</tbody>
</table>
Psychotic Disorders

- Schizophrenia & bipolar disorder
  - 1-2% in adolescents
- Childhood psychotic disorders
  - Schizophrenia and related disorders
    - Phases: prodromal, active, and residual
    - Types: catatonic, disorganized, paranoid, or undifferentiated
  - Psychosis related to a mood disorder
    - Depression &/or mania can present with psychotic symptoms
  - Psychosis related to a medical disorder or substance

FDA-Approved Typical Antipsychotics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Age</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
<td>6 mo – 12 yrs</td>
<td>Behavioral syndrome</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Mellaril</td>
<td>2+ yrs</td>
<td>Refractory schizophrenia</td>
</tr>
</tbody>
</table>

High Potency First Generation

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine</td>
<td>Prolixin</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>Hypersensitive behavior (short-term)</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilafon</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Navane</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine</td>
<td>Schizophrenia</td>
</tr>
</tbody>
</table>

Antipsychotic Doses

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Initial Dose (mg)</th>
<th>Daily Dose (mg)</th>
<th>Equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
<td>10</td>
<td>150 - 375</td>
<td>100</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Mellaril</td>
<td>10</td>
<td>100 - 325</td>
<td>50</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Prolixin</td>
<td>1</td>
<td>1.5 – 10</td>
<td>2</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>0.5</td>
<td>1 - 10</td>
<td>2</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Loxitane</td>
<td>5</td>
<td>50 - 100</td>
<td>10</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilafon</td>
<td>2</td>
<td>6 - 22</td>
<td>10</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Orap</td>
<td>0.25</td>
<td>1 - 5</td>
<td>1</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Navane</td>
<td>2</td>
<td>4 – 10</td>
<td>5</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine</td>
<td>1</td>
<td>2 - 15</td>
<td>5</td>
</tr>
</tbody>
</table>

FDA-approved Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Age (yrs)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>12 – 17</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>13 – 17</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>13 – 17</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>13 – 17</td>
<td>Schizophrenia</td>
</tr>
</tbody>
</table>

Antipsychotic Doses

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Initial Dose (mg)</th>
<th>Daily Dose (mg)</th>
<th>Equivalence (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>5</td>
<td>10 - 20</td>
<td>10</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>6.25</td>
<td>100 - 450</td>
<td>50</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>2</td>
<td>12 - 24</td>
<td>10</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>1.25</td>
<td>5 - 15</td>
<td>2</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
<td>5</td>
<td>40 - 140</td>
<td>10</td>
</tr>
</tbody>
</table>

Consider antipsychotic medication at the first sign of psychotic symptoms

Early intervention is important

Start with a low dose, usually given at bedtime

Gradually increase until a good response is achieved or side effects become intolerable

Continue for at least 1 yr after a psychotic episode (schizophrenia – always continue)
**Typical Antipsychotic Side Effects**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Sedation</th>
<th>Extrapyramidal</th>
<th>Anticholinergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
<td>++++</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>Seralen</td>
<td>++++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>Mellaril</td>
<td>++++</td>
<td>+</td>
<td>++++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High Potency First Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimozide</td>
</tr>
<tr>
<td>Perphenazine</td>
</tr>
<tr>
<td>Procainamide</td>
</tr>
<tr>
<td>Thiothixene</td>
</tr>
<tr>
<td>Trifluoperazine</td>
</tr>
</tbody>
</table>

**Key:** +++: substantial side effects; ++: moderate side effects; +: mild side effects; +/0: possible side effects; 0: none

**Atypical Antipsychotic Side Effects**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Sedation</th>
<th>Extrapyramidal</th>
<th>Anticholinergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Clozaril</td>
<td>++++</td>
<td>0</td>
<td>++++</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Fanapt</td>
<td>+</td>
<td>+</td>
<td>+/0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>++</td>
<td>+/0</td>
<td>+</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega</td>
<td>+</td>
<td>+</td>
<td>+/0</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>++</td>
<td>+/0</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>+</td>
<td>+</td>
<td>+/0</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Haloperidol</td>
</tr>
<tr>
<td>Thioridazine</td>
</tr>
<tr>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Thiothixene</td>
</tr>
<tr>
<td>Pimozide</td>
</tr>
<tr>
<td>Loxapine</td>
</tr>
<tr>
<td>Lurasidone</td>
</tr>
</tbody>
</table>

**Key:** +++: substantial side effects; ++: moderate side effects; +: mild side effects; +/0: possible side effects; 0: none

---

**FDA Black Box Warnings**

- Atypical Antipsychotics (2nd Generation)
  - Elderly pts with dementia-related psychosis treated with atypical antipsychotic drugs are at increased risk of death
- Mesoridazine & Thoridazine
  - Prolongs the QT interval in a dose related manner & may cause torsade de pointes - atrial arrhythmias & sudden death
- Clozapine
  - Agranulocytosis, seizures, myocarditis, orthostatic hypotension, and/or cardiac arrest

---

**Attention-Deficit/Hyperactivity Disorder (ADHD)**

- ~5% of children
  - 13.6% have received treatment
  - 40% outgrow the disorder by early adulthood
  - 60% ongoing symptoms throughout life
- Untreated results in:
  - Accumulated disability
  - Co-occurring substance abuse, anxiety, & depression
- Treatment:
  - Contributes to more-normal brain development
  - Neuroprotective

---

**IMMEDIATE RELEASE STIMULANTS (DURATION OF EFFECT IS 3-6 HOURS)**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Age</th>
<th>Brand Name</th>
<th>Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>6+</td>
<td>Ritalin</td>
<td>10 – 60</td>
</tr>
<tr>
<td>6+</td>
<td>Metadate</td>
<td>10 – 60</td>
<td></td>
</tr>
<tr>
<td>6+</td>
<td>Methylin</td>
<td>10 – 60</td>
<td></td>
</tr>
<tr>
<td>6+</td>
<td>Concerta</td>
<td>18 – 54</td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine</td>
<td>6+</td>
<td>Focalin</td>
<td>(2.5) 5 – 20</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>3+</td>
<td>Dexedrin</td>
<td>5 – 40</td>
</tr>
<tr>
<td>Lisinoprametamine</td>
<td>6+</td>
<td>Vyanex</td>
<td>30 – 70</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>3+</td>
<td>Amphetamine mixed salts (Adderall)</td>
<td>(2.5) 5 – 20</td>
</tr>
<tr>
<td>6+</td>
<td>Methamphetamine (Desyn)</td>
<td>5 – 25</td>
<td></td>
</tr>
</tbody>
</table>

**SUSTAINED RELEASE STIMULANTS (DURATION OF EFFECT IS 6-12 HOURS)**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Age</th>
<th>Brand Name</th>
<th>Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>6+</td>
<td>Ritalin SR</td>
<td>20 – 60</td>
</tr>
<tr>
<td>6+</td>
<td>Ritalin LA</td>
<td>20 – 60</td>
<td></td>
</tr>
<tr>
<td>6+</td>
<td>Metadate ER</td>
<td>10 – 60</td>
<td></td>
</tr>
<tr>
<td>6+</td>
<td>Metadate CD</td>
<td>20 – 60</td>
<td></td>
</tr>
<tr>
<td>6+</td>
<td>Methylin ER</td>
<td>20 – 60</td>
<td></td>
</tr>
<tr>
<td>6+</td>
<td>Concerta</td>
<td>18 – 54</td>
<td></td>
</tr>
<tr>
<td>6+</td>
<td>Daytrana (patch)</td>
<td>10 – 30</td>
<td></td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>6+</td>
<td>Dexedrine spansules</td>
<td>5 – 40</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>6+</td>
<td>Adderall XR</td>
<td>5 – 40</td>
</tr>
</tbody>
</table>

**ALPHA-2 ADRENERGIC AGONISTS**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Typical Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>Catapres</td>
<td>0.15 – 0.4 mg (3-4x/day)</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Tenex</td>
<td>0.25 – 1.0 mg (2-3x/day)</td>
</tr>
</tbody>
</table>

**ANTIDEPRESSANTS**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Typical Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Wellbutrin SR/LA</td>
<td>C: 100 – 150</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Straterra</td>
<td>C/A: 1.2 – 1.8 mg/kg</td>
</tr>
</tbody>
</table>

---

**Key:** 1/7/2012
### Stimulant Side Effects

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>SOLUTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial insomnia</td>
<td>Give dose earlier, or co-administer clonidine, or trazadone given at bedtime</td>
</tr>
<tr>
<td>Reduced appetite</td>
<td>Switch to Focalin (may result in less of this effect)</td>
</tr>
<tr>
<td>Stomachache</td>
<td>Give with food</td>
</tr>
<tr>
<td>Mild dysphoria</td>
<td>Switch classes of stimulants, or add an antidepressant</td>
</tr>
<tr>
<td>Lethargy, sedation, or impair concentration</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Headache</td>
<td>Reduce dose, or change stimulants</td>
</tr>
</tbody>
</table>

### ADHD Treatment

- Begin medication on the weekend
- Start with low doses of stimulants
- Titrate dose up to adequate levels
- Initially dose 3x per day, determine optimal dose, then move to 1-2x per day dosing
- Monitor for side effects
- Provide close follow-up

### FDA Black Box Warnings

- Methylphenidate & Dextemethylphenidate
  - Give cautiously to pts with a history of drug dependence or alcoholism
- Amphetamines, Dexamphetamine, & Lisdexamphetamine
  - Have a high potential for abuse & misuse may cause sudden death & serious cardiovascular adverse events
- Bupropion & Atomoxetine
  - Increased risk of suicidal ideation in children and adolescence

### Case Study

- JB is an 8yo boy brought in for evaluation to determine if he has ADHD. He has difficulty sustaining attention in activities at school and at home. He fails to pay close attention to teachers and often makes careless mistakes in schoolwork. He gets out of his seat at inappropriate times and is constantly fidgeting in his seat. He often interrupts the teacher and classmates. His parents are very concerned that he may have to take medication at school.
  - NKDA
  - Past Med Hx: seizures

### Test Questions

1. Risperidone or aripiprazole are appropriate choices for a 15-year-old schizophrenic patient.
2. It is appropriate to prescribe Adderall® XR 30mg PO once daily for a child 5 years of age.
3. The FDA issued a black box warning describing an increased risk of suicidality (suicidal behavior and ideation) for all antidepressants used in individuals under the age of 18.
Importance of Medication Adherence in the Elderly

Waleed. Almuqbil, Pharm.D.
PGY1 Pharmacy Resident, Palmetto General Hospital

Objectives:
- Explain importance of medication adherence
- Identify factors affecting medication adherence
- Discuss helpful assessment tools for medication adherence
- Review intervention strategies to enhance medication adherence

Former Surgeon General Dr. C. Everett Koop
- Drugs don’t work in patients who don’t take them
- Prescription medications are only effective when they are taken

Terminologies
- Compliance – the degree to which a patient correctly follows medical advice
- Adherence – the extent to which a person takes medications as prescribed
- Concordance – consultative and consensual partnership between the consumer and their doctor
- Persistence – a person’s ability to continue taking medications for the intended course of therapy

Background
- Approximately 125,000 people with treatable ailments die each year in the US because they do not take their medication properly
- 14 - 20% of patients never fill their original prescriptions
- 60% of all patients cannot identify their own medications
- 30 - 50% of all patients ignore or otherwise compromise instructions concerning their medication
- 12 - 20% of patients take other people’s medicines

Non Adherence
- Failing to initially fill/refill a prescription
- Omitting doses
- Discontinuing therapy
- Taking less or more of a medication than prescribed
- Taking friend/family member’s medication
- Taking outdated medications
- Storing medications improperly
- Improperly administering medications requiring devices
Elderly Average Medication Usage

- 90% of Medicare beneficiaries report taking prescription medications
- Community dwelling elderly
  - Average 3.1-7.9 medications
- Nursing home residents
  - Average 7.2 medications

Consequences of Non-adherence

- Increased use of medical resources
- Treatment failure
- Cost > Benefit
- Tackling the adherence issue has almost no downside because every one percent improvement in adherence results in $2 billion in savings to the U.S. healthcare system

Reasons for Not Filling Prescriptions

Americans Age above 55:

- Cost of the drug 40%
- Side effect of drug 11%
- Thought drug wouldn’t help much 11%
- Didn’t think I needed it 8%
- Drug did not help 6%
- Don’t like taking prescription drugs 5%
- Condition improved 4%
- Already taking too many prescriptions 3%

Adherence Assessment Tools

- No gold standards
- Most commonly used:
  - Pill counts
  - Refill records
  - Patient self report
  - Drug therapeutic levels
- Indirect:
  - Clinical outcomes

Morisky Scale

- Validated scale that estimates the risk of medication non-adherence
- Cited in numerous articles since 1986
- Used for many different disease such as HTN, hyperlipidemia, asthma and HIV
- Simple to administer
  - Four Yes or No questions
- Scoring:
  - Yes = 0
  - No = 1

Morisky Scale

- Interpretation:
  - Score 1 point for every YES answer
  - 0 points = high adherence
  - 1-2 points = intermediate

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you ever forget to take your medicine?</td>
<td></td>
</tr>
<tr>
<td>Are you careless at times about taking your medicine?</td>
<td></td>
</tr>
<tr>
<td>When you feel better do you sometimes stop taking your medicine?</td>
<td></td>
</tr>
<tr>
<td>Sometimes if you feel worse when you take the medicine, do you complain?</td>
<td></td>
</tr>
</tbody>
</table>

Factors Affecting Medication Adherence

Social & Economic
- Lack of family or social support
- Language barriers
- Cultural beliefs
- Low health literacy
- Living conditions
- Limited access to health care
- High medical costs or co-pay

Assessment Tool Health Literacy
- **Definition:** The degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions

Assessment Tool Health Literacy
- **Rapid Estimate of Adult Literacy in Medicine, Revised (REALM-R)**
  - Brief screening instrument
  - Word recognition test (11 items)
- Fatigue
- Directed
- Colitis
- Constipation
- Osteoporosis
- Anemia

Strategies Low Health Literacy and English Proficiency
- Utilize translators
- Reinforce information with family member
- Provide information in relevant language
- Create a shame free environment
- Simplify reading level to the 5th grade
- Use teach back and show back techniques
- Limit information to two or three important points
- Use drawings, models or devices to demonstrate points
- Encourage patients to ask questions

Strategies Cost, Accessibility
- Mail order pharmacy
- Pharmacy delivery service
- Switch medications to low cost generics or lower cost alternatives
- Enroll in Medicare Part D prescription drug plan
Health Care System
- Provider-patient relationship
- Communication skills
- Disparity between health care beliefs
- Capacity for education and follow-up
- Formularies
- Lack of continuity of care
- Missed appointments
- Wait times
- Written patient care information

Strategies
Provider-Patient Relationship
- Establish trusting relationship with elderly patient
- Assess elderly understanding of disease state and treatment
- Involve elderly in setting treatment goals
- Assess elderly readiness to adhere to plan
- Tailor regimens to fit within daily routine
- Provide written instructions
- Recognize cultural beliefs
  - Nontraditional therapies

Strategies
Formularies and Continuity of Care
- Develop process for insurance formulary interactions and prevention
  - Insurance company website/link
  - Pre-defined letters
- Acquire physician information from patients

Condition-Elderly Related
- Chronic conditions
- Lack of symptoms
- Severity of symptoms
- Depression
- Psychotic disorders
- Developmental disabilities
- Cognitive impairment

Strategies
Chronic Conditions, Lack of symptoms
- Education about disease state
  - Treatment
  - Prevention
  - Consequences

Strategies
Mental Illness
- Discuss as common and treatable
- Refer to disease state as a medical condition
- Discuss chemical basis
- Discuss delayed onset of therapeutic effects
  - Minimize impact of side effects
- Discuss importance of adequate duration to prevent relapse
- Educate and involve family if appropriate (Critical)
Therapy-Related

- Complexity of medication regimen
  - Number of medications and/or daily doses
  - Administration techniques of medications
  - Duration of therapy
  - Changes in medication regimen
  - Social stigma associated with medication use
  - Side effects
  - Lifestyle or behavioral changes

Strategies

Burdensome Medication Regimen

- Identify and discontinue unnecessary medications
- Reduce dose frequency
  - Long-acting formulations
- Consider combination medications
- Identify opportunities to use one medication
- Identify medications solely being used to treat side effects of other medications
- Teach to increase mastery of administration devices
- Link medication regimen to daily activities
- Recommend compliance aids and/or reminders
- Encourage updated written medication list

Effective Patient Adherence Tools

- Medication Organizers
- Electronic Pager/Timers

Strategies

Perceived lack of benefit or side effects

- Educate about treatment plan
- Suggest ways to manage minor side effects
- Explore concerns with treatment regimen

Patient-Related

- Physical
  - Visual impairment
  - Hearing impairment
  - Cognitive impairment
  - Impaired mobility or dexterity
  - Swallowing problems

Patient-Related

- Psychological/Behavioral
  - Motivation
  - Knowledge about disease state
- Importance of medication
- Expectations toward disease state and/or medication
- Perceived benefit of treatment
- Perceived risk of adverse effects
  - Stigma of disease
  - Alcohol or substance abuse
Strategies Physical – Visual Impairment

- Communicate with elderly patient
- Tape record instructions
- Pre-measure and pre-cut
  - Check with pharmacy
- Increase font side
- Color code medication bottles

Strategies Physical – Hearing Impairment

- Use interpreter
- Use regular voice volume and lip movement
- Maintain eye contact
- Write if preferred method of communication
- Supplement with written information
- Use quiet area for counseling
- Speak to better ear
- Turn up hearing aids
- Repeat yourself when necessary

Strategies Mobility and Dexterity

- Mail order or pharmacy delivery service
- Store medications in easily accessible location
- Easy-open tops
- Pre-cut, pre-measured medications
- Dosage forms that are easy to administer

Strategies Swallowing

- Utilize alternative dosing formulations
  - Liquids, Transdermal products, ODT
- Prescribe crushable tablets or capsules that can be opened and mixed with soft foods
  - Check medication list and inquire about crushing, etc. of medications at each visit

Strategies Psychological/Behavioral

- Knowledge of disease state
  - Help break stigma
- Motivation
  - Involve elderly patient in decisions
  - "roll" with resistance
  - Provide alternatives
  - Set reasonable goals
- Alcohol and Substance Abuse
  - Ask directed question

Elderly Patient Prerequisites for Adherence

- Understand diagnosis and potential impact
- Believe the treatment will be beneficial
- Understand medication administration and duration of treatment
- Treatment favors benefit over cost
- Confidence in health care practitioners
Provider Steps to Increase Adherence

- Assess understanding of disease state and treatment plan
  - Supplement with additional education
- Link medication to daily routines
- Employ use of adherence aids
- Simplify medication regimen
- Recognize patient specific issues that may affect adherence

Questions

- High medications cost or co-pay of a prescription is an example of a medication-related factor.
  - True
  - False
- Directly observed therapy as a means of medication adherence is impractical in most clinical situations.
  - True
  - False
- Concordance is generally used as a way to define the treatment continuum from the initial prescription fill to the ongoing taking & refilling of the drug.
  - True
  - False

CASE STUDY

You have implemented an alert with the pharmacy computer system that will identify patients who have not refilled prescriptions for cholesterol lowering agents. You receive an alert that LP, a 68 year old Caucasian male who has a diagnosis of hyperlipidemia and diabetes has not filled his prescription for simvastatin. His refill records show the following:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Strength</th>
<th>Call ID</th>
<th>Date Filled</th>
<th>Days Supply</th>
<th>Days Supply</th>
<th>Days Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>40 mg</td>
<td>12/30/11</td>
<td>01</td>
<td>30</td>
<td>77</td>
<td>174</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40 mg</td>
<td>12/30/11</td>
<td>01</td>
<td>30</td>
<td>77</td>
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<td>01</td>
<td>30</td>
<td>77</td>
<td>174</td>
</tr>
</tbody>
</table>

Plot: Staff: LP

CASE STUDY

- Pharmacist: When was your last cholesterol medication refilled & your last visit to this doctor?
  - LP: I have not taken the simvastatin because his doctor said his cholesterol is perfect and his diabetes is well controlled.
- Pharmacist: Does not understand that the medication is long term.
  - LP: I do not understand simvastatin was a chronic medication.
- Pharmacist: Starting back on the simvastatin will help keep you healthy. Would it be okay if I give you a call in a few weeks to see how things are going?
  - LP: Agrees
- Pharmacist: Summarizes his intervention with LP and makes a note to contact him in 3 weeks to see how he is doing on the simvastatin

Summary

- Medication non-adherence is a significant problem
- Adherence to medications as prescribed can slow disease progression and reduce the costs of health care in the presence of multiple chronic conditions in the elderly population

References:

Peds and OTC: Little Ones, Little Doses
Amanda Brahim, Pharm.D.
PGY-1 Pharmacy Practice Resident
Cleveland Clinic Florida

Objectives
- Review available OTC products for commonly encountered pediatric disease states
- Discuss new restrictions and labeling requirements for OTC pediatric products
- Calculate correct dosages for OTC medications based on pediatric patient parameters
- Recognize contraindications and adverse effects of available pediatric OTC therapies

Peds vs. Adults:

<table>
<thead>
<tr>
<th>Absorption</th>
<th>PO: Slower gastric emptying</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Topical: Greater systemic absorption</td>
</tr>
<tr>
<td></td>
<td>Rectal: best when lipid soluble</td>
</tr>
<tr>
<td>Distribution</td>
<td>% body water decreases with age</td>
</tr>
<tr>
<td></td>
<td>% body fat increases with age</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Low glucuronidation</td>
</tr>
<tr>
<td></td>
<td>Low alcohol dehydrogenase</td>
</tr>
<tr>
<td>Elimination</td>
<td>Lower compared to adults</td>
</tr>
</tbody>
</table>

Common Sources of Medication Errors in Pediatrics
- Dosage Errors
  - Calculation Errors
    - Incorrect weight (lbs vs. kg)
    - Mg/kg/day vs. mg/kg/dose
- Transcription Errors
- Formulation Errors

Dosing Directions

2009 FDA guidelines in response to unintentional overdoses
- All OTC liquid drug products should include a measuring device
- Device and directions should use same abbreviations and units of measurement
- Devices should bear only necessary markings
- Devices should not hold significantly more than largest dose
- Abbreviations should conform to standards
- Decimals and fractions should be used with care
- Studies should be done to confirm accurate use

2010 study to determine prevalence of inconsistent dosing directions
- Design: top 200 pediatric oral liquid OTC medications
- Outcome measures:
  - Inclusion of measuring device
  - Inconsistency between directions and measuring device
  - Use of nonstandard units and abbreviations
  - Presence of abbreviation definitions
### Results

- Measuring devices included with 74% of products
- Inconsistencies found in 98.6% of products:
  - Missing markings (24.3%)
  - Superfluous markings (81.1%)
- Nonstandard abbreviations used by 97 products
- No definition of abbreviations in 163 products

### Dosing Device Inconsistencies

![Image of a dosing device with inconsistencies](image)

### Fever: When to Refer to Physician

- > 6 mo old with rectal temp $\geq 104^\circ F$ (40°C)
- < 6 mo old with rectal temp $\geq 101^\circ F$ (38°C)
- History of seizures/febrile seizures
- Fever persists $\geq 3$ days with/without treatment
- Development of spots/rash
- Refusing to drink or cannot hold down fluids
- Very sleepy, irritable or hard to wake up

![Image of fever symptoms](image)

### Fever/Pain Treatment Options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Acetaminophen | > 2 years old  
10-15 mg/kg            |
| Ibuprofen  | > 2 years old  
7.5 mg/kg  
Max 1200 mg/day             |
| Naproxen   | > 12 years old  
220-440mg, then 220mg Q8-12h  
Max 660 mg/day             |

### Acetaminophen Concentration

- Now single concentration of 160mg/5ml for all OTC APAP products
- Both infants’ and children’s product same concentration
- Dosing recommendations have NOT changed

![Image of acetaminophen concentration](image)

### APAP Enhanced Dosing Directions

- FDA Advisory Panel recommends enhanced dosing directions
- Single-ingredient pediatric APAP
- Will include dosing directions for children 6-23 months old
- Weight-based and age-related dosing
- For now, still need PCP instructions

![Image of APAP enhanced dosing directions](image)
Cough, Cold, Allergies

Cough/Cold

- More than 60% of OTC recommendations involved cough and cold products
- Common cold is leading cause of missed school days
- From 1969 to 2006, more than 120 pediatric deaths related to cough and cold products


Cough/Cold: When to Refer to Physician

- Fever > 101.5°F (38.6°C)
- Infants < 9 mo of age
- Worsening of symptoms during self treatment
- Cough with thick yellow sputum or green phlegm
- Drenching nighttime sweats

Cough/Cold: Treatment Options

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Usual Dosage</th>
<th>Max Dosage</th>
<th>ADRs related to excessive doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brompheniramine (Dimetapp®)</td>
<td>2-6y: 1mg Q4-6 6-12y: 2mg Q4-6</td>
<td>2-6y: 5mg/24h 6-12y: 12mg/24h</td>
<td>Palpitations, paradoxical excitability</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>2-6y: 5mg 6-12y: 10mg</td>
<td>2-6y: 5mg/24h 6-12y: 10mg/24h</td>
<td>Hypertension, tachycardia, chest pain</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>2-6y: 5mg 6-12y: 10mg</td>
<td>2-6y: 5mg/24h 6-12y: 10mg/24h</td>
<td>Hypertension, angina, nervous system damage, peripheral vasoconstriction</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>2-6y: 5mg 6-12y: 10mg</td>
<td>2-6y: 5mg/24h 6-12y: 10mg/24h</td>
<td>Convulsions, dysarthria, dizziness, ataxia, coma, seizures</td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>2-6y: 5mg 6-12y: 10mg</td>
<td>2-6y: 5mg/24h 6-12y: 10mg/24h</td>
<td>Nausea, vomiting, diarrhea, respiratory depression</td>
</tr>
</tbody>
</table>


Cough/Cold: FDA Recommendations

- 2008 Public Advisory: OTC cold medications should not be given to children < 2yo because of lack of efficacy and high risk for adverse events and death
**Allergic Rhinitis**

- A systemic disease with prominent nasal symptoms
- An estimated 40% of children in the US have this disease
- Treatment steps:
  - Allergen avoidance
  - Pharmacotherapy
  - Immunotherapy

**Allergy: When to Refer to Physician**

- Children <12yo
  - Unless already diagnosed by PCP and approved for OTC treatment
- Symptoms of otitis media, sinusitis, bronchitis, or other infection
- Symptoms of undiagnosed asthma
- Symptoms unresponsive to treatment

**Allergy: Treatment Options**

- Loratadine (Claritin®)
- Cetirizine (Zyrtec®)
- Fexofenadine (Allegra®)
- Intranasal Cromolyn (NasalCrom®)
  - More effective if started before symptoms begin
- Diphenhydramine (Benadryl®)
  - Should be avoided due to paradoxical excitation

**GI Diseases**

**Nausea/Vomiting**

- Commonly caused by viral gastroenteritis
  - Rotavirus and norovirus
- May lead to dehydration
- Treatment is directed at preventing and correcting dehydration and electrolyte disturbances

**Nausea/Vomiting: When to Refer to Physician**

- S/S of severe dehydration
- Stiff neck
- <6 mo or <8 kg, vomited clear fluids 3 times
- Refusal to drink
- Lack of urination in past 8-12 hrs
- Vomiting with each feeding
- Vomitus contains red, black, green fluid
### Nausea/Vomiting: Treatment Options

<table>
<thead>
<tr>
<th>Dosage (Max Daily Dose)</th>
<th>Agent</th>
<th>Children 2 to &lt;6 Years</th>
<th>Children 6 to &lt;12 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimenhydrinate (Dramamine®)</td>
<td>12.5-25 mg Q 6-8 hrs (75 mg)</td>
<td>25-50 mg Q 6-8 hrs (150 mg)</td>
<td></td>
</tr>
<tr>
<td>Calcium Carbonate (Children’s Pepto®)</td>
<td>1 tablet (161 mg), may repeat (3 tablets)</td>
<td>2 tablets (322 mg), may repeat (6 tablets)</td>
<td></td>
</tr>
<tr>
<td>Phosphorated carbohydrate solution (Emetrol®)</td>
<td>5 to 10 ml Q 15 min (1hr, 5 doses)</td>
<td>5 to 10 ml Q 15 min (1hr, 5 doses)</td>
<td></td>
</tr>
</tbody>
</table>

### Diarrhea

- Each year, acute gastroenteritis associated with diarrhea accounts for:
  - 1.5 million outpatient visits
  - 200,000 hospitalizations
  - ~300 deaths

### Diarrhea: When to Refer to Physician

- <6 mo of age
- Severe dehydration
- >6 months with persistent high fever
- Blood, mucus or pus in the stool
- Protracted vomiting
- Severe abdominal pain/distress
- Inability of caregiver to administer ORT

### Diarrhea: Treatment Options

<table>
<thead>
<tr>
<th>Agent</th>
<th>Children 6-8 years (48-59 lbs)</th>
<th>Children 9-11 years (60-95 lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide (Imodium®)</td>
<td>2 mg initially, then 1 mg after each loose stool. Max 4 mg/24 hrs</td>
<td>2 mg initially, then 1 mg after each loose stool. Max 6 mg/24 hrs</td>
</tr>
</tbody>
</table>

### Dehydration

- Dry mouth and tongue
- Sunken and/or dry eyes
- Sunken fontanel
- Decreased urine output
- Dark urine
- Fast heartbeat
- Thirst
- Absence of tears when crying
- Decreased skin turgor
- Unusual listlessness/sleepiness
- Weight loss

### Dehydration: Treatment Options

- Oral rehydration solution (ORS) is preferred treatment
- Give 1-2 tsp every 1-2 min if needed
- Premixed solutions are preferred
- 50-100 ml/kg over 3-4 hours
- 10 ml/kg for each loose stool
- Continue 4-6 hrs
- Resume feeding
Constipation

- May be described as:
  - Straining to have a stool
  - Passage of hard, dry stool
  - Passage of small stools
  - Feelings of incomplete bowel evacuation
  - Bloating or decreased stool frequency

Constipation: When to Refer to Physician

- Significant distention or cramping
- Fever
- Daily laxative use
- Blood in stool, or dark/tarry stool
- Change in character of stool
  - (i.e., becomes pencil thin)
- Bowel symptoms persist > 2 weeks

Constipation: Treatment Options

- Glycerin suppositories
  - Onset within 15-60 minutes
- Barley malt extract
  - Safe for infants younger than 2 months
- Avoid:
  - Mineral oil (aspiration risk)
  - Stimulant laxatives (dehydration risk)

Teething

- Mild pain, irritation, reddening, excessive drooling
- Eruption cysts: bluish, soft, round
- Goals:
  - Relieve gum pain and irritation
  - Reducing child’s irritability
  - Reducing sleep disturbances

Teething: Treatment Options

- Benzocaine 5-10% (Baby Orajel®)
  - Benzocaine 20% too potent for infants
  - Beware of hypersensitivity
  - Gels are best choice
  - No more than 4 times a day
- Phenol 0.5% (Anbesol®)
  - Not currently marketed for teething pain

Diaper Dermatitis

- Commonly known as diaper rash
- Most common dermatologic disorder of infancy
- Caused by a combination of factors
- Goals:
  - Relief of symptoms
  - Prevent recurrences
  - Prevent secondary infection
Diaper Dermatitis: When to Refer to Physician

- Lesions present > 7 days
- Secondary infection
- Dermatitis outside of diaper region
- Broken skin due to disease progression
- Oozing, blood vesicles, or pus
- Constitutional symptoms
  - Fever, diarrhea, vomiting, swollen lymph nodes

Diaper Dermatitis: Treatment Options

- Zinc Oxide
- Calamine
  - Mixture of zinc and ferrous oxides
- Petrolatum
- Dimethicone
  - Repels water, soothes and counteracts inflammation
- Lanolin
  - Bacteriostatic, hypoallergenic
- Topical cornstarch
  - Warning against inhalation of powder

Review Questions

- True or False:
  - Acetaminophen will no longer be produced in concentrated infant drops. Liquid acetaminophen products for children under 12 will be sold as a 160 mg/5ml concentration.
  - The drug of choice for an 8 year old child presenting with a fever is a baby aspirin
  - When used for teething pain, topical benzocaine (10%) may be used up to 4 times daily

Patient Case:

“We really need your advice!”
Concerned parents state that their 3 year old daughter has felt warm and is not eating well.

Patient Case

- What questions would you ask?
- What would you recommend?
  1. Refer for medical attention
  2. Monitor symptoms and fever and recommend nondrug measures only
  3. Recommend a medication alone or combined with nondrug measures
  4. Make no recommendations
- Any additional patient education?

Conclusion

- Always take a complete history when advising on pediatric OTC medications
- Stay informed about new products and dosage recommendations
- Know when to say NO!
A Review of the Pediatric Immunization Schedule

Michaela Christian
PGY-1 Pharmacy Practice Resident
Mercy Hospital,
A Campus of Plantation General Hospital
Michaela.Christian@Hcahealthcare.com

Objectives

- Identify age-appropriate vaccinations for pediatric patients ages 0-18
- Determine vaccinations which should be administered to patients who fall behind the recommended immunization schedule
- Recognize precautions and contraindications associated with certain vaccines within the schedule guidelines

The Importance of Vaccinations

- Prevent disease and protects the public
- Responsible for infectious control of once common childhood illnesses in US
  - e.g. Polio, measles (German measles), diphtheria, pertussis (Whooping cough), rubella, mumps, tetanus, and H.Influenza
- Passive immunity only lasts for up to 1 year
- Vaccine-preventable illness reduce overall healthcare expenditures
**Contraindications and Precautions (All vaccines)**

- **Contraindications**
  - Anaphylaxis to a previous vaccine dose or to a vaccine component

- **Precautions**
  - Moderate or severe acute illness with or without fever

**Live Vaccines**

- Influenza
  - FluMist®
  - Varicella
  - Measles, Mumps, and Rubella (MMR)
  - Rotavirus

**Influenza Vaccine**

- Primary Series: 2 doses
  - Ages 6 months – 8 years
  - Separate doses by 1 month

- After completion of primary series:
  - 1 dose annually

**FluMist® Contraindications:**

- Anaphylaxis to egg byproducts
- Patients < 2 years of age
- Children/adolescents receiving long-term aspirin therapy

**Precautions (FluMist® and TIV):**

- Guillain-Barre syndrome ≤ 6 weeks following previous dose of influenza vaccine

**Varicella Vaccine**

- Herpes virus that causes:
  - Primary infection: Chickenpox
  - Secondary infection: Herpes Zoster, Shingles

- **Live** attenuated virus:
  - May cause a varicella-like rash after vaccination
  - Virus transmission has been reported
  - Can result in a lower incidence of Herpes Zoster

**Influenza Vaccine**

- Vaccines contain three antigenic components:
  - Type A/H1N1
  - Type A/H3N2
  - Type B Antigens

- Available in U.S.
  - **Live** attenuated influenza vaccine
  - FluMist®
  - Trivalent inactivated influenza vaccine (TIV)

- FluMist®
  - Contains all three influenza viruses
  - Replicates in nasopharynx
  - For < 2 years of age

- TIV
  - Contains same viruses as FluMist®
  - Cannot cause influenza
  - For 2 years and older

- The following does not need vaccination:
  - Proven documentation or evidence of a previous illness or vaccination
  - Birth in the U.S. before 1980
**Varicella Vaccine**
- Primary series: 2 doses
  - First dose: Age 1 year old
  - Second dose: Age 4 years old
- Ages 7-18 years without evidence of immunity:
  - Give 2 doses if not previously vaccinated or if schedule is incomplete
    - Interval between doses: 3 months
  - If 13 years or older
    - Interval between doses: 1 month

**Measles, Mumps, Rubella (MMR) Vaccine**
- Do not give before 1st birthday!
- First dose: 1 year old
- Second dose: 4 years old
- Contraindications:
  - Severe anaphylaxis to Neomycin and Gelatin byproducts
- Precautions:
  - Administration of an antibody-containing blood product (within the last 11 months)
    - e.g. Immune globulin, Whole blood, or Packed red blood cells
  - History of thrombocytopenia or thrombocytopenic purpura

**Varicella Vaccine**
- Contraindications
  - Severe anaphylaxis to Neomycin and Gelatin byproducts
- Precautions
  - Administration of an antibody-containing blood product (within the last 11 months)
    - e.g. Immune globulin, Whole blood, or Packed red blood cells
  - History of thrombocytopenia or thrombocytopenic purpura

**Measles, Mumps, Rubella (MMR) Vaccine**
- Measles/Mumps
  - Caused by paramyxovirus
  - Spread by respiratory transmission
  - Measles
    - Characterized by rash
  - Mumps
    - Characterized by painful swelling of salivary glands
- Rubella
  - Caused by togavirus family
  - Spread by respiratory transmission
  - Can cause Congenital rubella syndrome

**Rotavirus Vaccine**
- Double-stranded RNA virus
- Transmitted by fecal-oral route through person-to-person or fomite contact
- Two Live vaccines:
  - RotaTeq® and Rotarix®
  - Both oral vaccines

**Rotavirus Vaccine**
- Ages 0-6 years:
  - May give to infants born before 37 weeks if they are:
    - At least 6 weeks old
    - Are being discharged from the hospital
    - Clinically stable
  - Rotarix®: Give 2 doses at 2 and 4 months
  - RotaTeq®: Give 3 doses at 2, 4 and 6 months
Rotavirus Vaccine

- **Contraindications:**
  - For Rotarix® only:
    - Severe anaphylaxis to latex

- **Precautions:**
  - Pre-existing gastrointestinal disease
  - Previous history of intussusceptions
  - Spina bifida or bladder extrophy

Pneumococcal Vaccine

- **All patients 2 years and older:**
  - 1 dose of PPSV-23, 5 years after PCV-13

- **Special Populations:** 2 years and older
  - Sickle cell disease
  - Damaged spleen or asplenia
  - Cochlear implants
  - Cerebrospinal fluid leaks
  - HIV infection/AIDS
  - Immunosuppression
  - Chronic heart or lung disease*
    - Unnecessary for ages 6-18

Conjugated Vaccines

- **Indicated for children < 2 years of age**
  - Cannot conjugate encapsulated polysaccharides
  - Pneumococcal and Meningococcal vaccines
    - Conjugated to Diptheria proteins
  - Haemophilus Influenzae Type B vaccine
    - Conjugated to either Tetanus toxoid or Meningococcal group B protein

Meningococcal Vaccine

- **Caused by Neisseria Meningitidis**
- **Transmitted by respiratory route and causes meningitis**
- **MCV4**
  - Menactra® and Menveo®
- **Who should be vaccinated?**
  - Unvaccinated adolescents ages 11-18
  - College freshmen living in dormitories
  - Patients with anatomic or functional asplenia
  - Patients with immunodeficiencies (e.g., complement component deficiencies)
  - People who travel to countries where N. meningitidis is endemic or required

Pneumococcal Vaccine

- **Conjugated Vaccines**
  - PCV-7
  - PCV-13
- **Pure Polysaccharide vaccine:**
  - PPSV-23
  - For all patients > 2 years of age
  - Give 5 years after the first dose of PCV-13

- **Primary Series:**
  - 4 doses at age ≥ 2 months
  - 1 dose
    - 2, 4, 6, and 12 months

- **Catch-Up:**
  - Primary series: 3 doses
    - At ages 7-11 months
    - 2 doses with the 3rd dose at 1 year
  - Separate by 3 months
  - Primary series: 1 dose
    - 1 year and older

Meningococcal Vaccine

- **Ages 11 and older:**
  - Give 1 dose of MCV with a booster at age 16
  - If first dose given between ages 13-15, give booster dose at ages 16-18
Meningococcal Vaccine

- High risk patients 2 years and older:
  - Give 2 doses and 1 additional dose every 5 years after the first dose
  - Separate by 2 months

  High risk patients:
  - Persistent complement component deficiency
  - Anatomical or functional asplenia
  - Sickle Cell disease
  - HIV infection/AIDS

Inactivated Vaccines

- Killed organisms which helps the body develop an immune response
- Cannot cause the particular disease

Available:
  - Tetanus, Diptheria, and Pertussis
  - Human Papillomavirus
  - Hepatitis A
  - Hepatitis B
  - Poliomyelitis (Polio)

Haemophilus Influenzae Type B (H-flu) Vaccine

- Caused by coccobacillus species
- Spread by respiratory transmission
- Three vaccines available for patients 2 months – 5 years of age:
  - Pedvax HIB®:
    - 1 dose at 2 and 4 months
  - ActHIB®:
    - 1 dose at 2, 4, and 6 months
  - Hiberix®:
    - 1 dose at 1 year and older

Tetanus, Diphtheria, and Pertussis Vaccines

- Pertinent Vaccines:
  - DTaP: Diphtheria and tetanus toxoids and acellular pertussis
  - Tdap: Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis
  - Td (Adult): Tetanus and diphtheria toxoids

Haemophilus Influenzae Type B (H-flu) Vaccine

- Catch-up:
  - If first dose given between 1-2 years of age:
    - Booster dose 2 months later
  - If first dose given between 2-5 years old:
    - 1 dose of H-flu only
  - First dose > 5 years of age:
    - Not recommended unless immunocompromised

Tetanus, Diphtheria, and Pertussis Vaccines

- Children aged 2 months – 4 years:
  - Give DTaP at 2, 4, 6, 15 months, and 4 years of age
- Ages 7 and older:
  - Give 1 single dose of Tdap
  - Followed by 1 booster dose of Td every 10 years

- Contraindications:
  - Anaphylaxis to formaldehyde
  - Encephalopathy within 7 days following administration of a pertussis containing vaccine
Tetanus, Diphtheria, and Pertussis Vaccines

- Additional precautions following a previous dose:
  - Progressive or unstable neurological disorder; seizure
  - Temperature ≥105°F
  - Collapse or shock-like state
  - Persistent, inconsolable crying lasting hours
  - History of Arthus-type hypersensitivity reactions
  - Guillain-Barré syndrome ≤ 6 weeks

Hepatitis A/Hepatitis B Vaccines

- Hepatitis A
  - Caused by a picornavirus
  - Spread by fecal-oral route
  - Leads to liver failure
  - Vaccines available:
    - Havrix® and Vaqta®
    - Ages 1 year and older:
      - Give 3 doses, separated by 6 months

- Hepatitis B
  - Blood borne pathogen
  - Transmitted by exposure to infected blood or body fluids
  - Vaccines available:
    - Engerix-B®
    - Recombivax HB®
    - Adults and pediatric patients 11-15 years of age

Human Papillomavirus Vaccine (HPV)

- Leading cause of genital warts and cervical, anal, and penile cancers
- Two types of vaccines:
  - HPV4 (Gardasil®)
    - Contains 4 serotypes
    - Licensed for use in females ages 9-26
  - HPV2 (Ceravix®)
    - Contains 2 serotypes
    - Licensed for use in males and females ages 9-26

Hepatitis B Vaccine

- Primary series: 3 doses
  - At birth, 2, and 6 months of age
- Mother HBsAg positive?
  - Give 1 dose and hepatitis B immune globulin (HBIG) within 12 hours of birth
- Catch-up:
  - Ages 7 and older:
    - Administer the 3 dose series to those not previously vaccinated
    - Separate doses by 4 months
  - Ages 11-15 years:
    - May give a 2 dose series of adult formulation Recombivax HB®
    - Separate doses by 4 months

Human Papillomavirus Vaccine (HPV)

- Males and females 9 years and older:
  - Primary series: 3 doses
    - Separate by 0, 2, and 6 months per dose
- Additional precautions
  - Pregnancy

Polio Vaccine (IPV)

- Caused by enterovirus
- Enters the bloodstream and attacks the nervous system
  - Leads to paralysis of the muscles
Polio Vaccine (IPV)

- Primary series: 4 doses
  - At ages 2, 4, 6 months, and 4 years:
- Catch-Up:
  - For females of child-bearing age: Pregnancy

Vaccines:

- Live vaccines:
  - Influenza
  - FluMist® Only
  - Varicella
  - MMR
  - Rotavirus
- Inactivated vaccines:
  - Tetanus, Diphtheria, and Pertussis
  - HPV
  - Hepatitis A
  - Hepatitis B
  - Polio
- Conjugated vaccines:
  - Pneumococcal
  - Meningococcal
  - H. Influenzae Type B

Seizure Risk?
- Commonly linked to MMR vaccines
- Risk?
  - 1 febrile seizure out of every 3-4,000 children vaccinated with MMR vaccine compared with unvaccinated children

Autism Risk?
- Thimerosal containing vaccines
- Risk?
  - Institute of Medicine (IOM) concluded that "the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism"
  - CDC supports the IOM conclusion

Catch-Up:
- Rotavirus
- MMR
- Influenza

Case Study

Lucy is 16 years old and has been diagnosed with sickle cell disease within the last month. As her pharmacist, you notice that she has:
- Completed her primary series of Tetanus, Diphtheria, and Pertussis using DTaP
- Had her first dose of MCV at age 14
- Completed Pneumococcal primary series with PCV-13 at age 5
- Since she is up-to-date on all other vaccines, what additional vaccinations would you recommend for Lucy according to her age and disease state?
  - A. Influenza, 1 dose of TD, 1 dose of MCV, 1 dose of PPSV-23, HPV
  - B. Influenza, 1 dose of DTaP, 1 dose of MCV, 1 dose of PCV-13, HPV
  - C. Influenza, 1 dose of Tdap, 1 dose of MCV, 1 dose of PPSV-23, HPV
  - D. Influenza, 1 dose of TT, 1 dose of MCV, 1 dose of PCV-13, HPV

Parental Concerns

- Seizure Risk?
  - Commonly linked to MMR vaccines
  - Risk?
    - 1 febrile seizure out of every 3-4,000 children vaccinated with MMR vaccine compared with unvaccinated children
- Autism Risk?
  - Thimerosal containing vaccines
  - Risk?
    - Institute of Medicine (IOM) concluded that "the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism"
    - CDC supports the IOM conclusion

Testing your knowledge

Dr. Mitchell was reviewing 6 year old Marjorie’s immunization records prior to her cochlear implant fitting and saw that she received the primary series of the pneumococcal vaccine (PCV-13) by age 1.

True or False: Dr. Mitchell should recommend that Marjorie receive an additional pneumococcal vaccination (PPSV-23) prior to receiving her cochlear implant.

True

Max, age 12, never received any portion of the Hepatitis B series vaccine from birth and is about to start public school. He is afraid of needles and wishes he didn’t have to get so many shots.

True or False: Max’s age qualifies him for two doses of the adult vaccination schedule.

False

Jamie, 7, has an outbreak of Chickenpox in her elementary school. Her mother goes to her neighborhood pharmacist and asks about precautions with the varicella vaccine since Jamie had an anaphylactic reaction to Gentamicin when she was younger.

True or False: The pharmacist should recommend the varicella vaccine from birth and is about to start public school. He is afraid of needles and wishes he didn’t have to get so many shots.

False

Summary

Vaccines:
- Prevent disease and protect the public
- Reduce overall healthcare expenditures
- Live vaccines:
  - Influenza
  - FluMist® Only
  - Varicella
  - MMR
  - Rotavirus
- Inactivated vaccines:
  - Tetanus, Diphtheria, and Pertussis
  - HPV
  - Hepatitis A
  - Hepatitis B
  - Polio
- Conjugated vaccines:
  - Pneumococcal
  - Meningococcal
  - H. Influenzae Type B

References

Adult Immunization Schedule Review
With a Focus on Flu Vaccine

Jordan Walter
PGY-1 Pharmacy Resident
Baptist Hospital Miami

Goals and Objectives
- Provide brief overview of common adult vaccines
- Review significant revisions in the 2011 adult vaccine schedule
- Compare and contrast the various influenza vaccine products available and their effectiveness in specific patients
- Review the CDC guidelines for influenza vaccination in all age groups

Introduction
- The pharmacist’s unique role
  - Most trusted and available healthcare professional
  - Vital role as advocates
- “Prevent all the disease you can... then treat the rest.”
  - John D. Grabenstein, RPh, PhD, FAPhA

Where We Stand

<table>
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<th>Disease</th>
<th>Baseline 30th Century Pre-Vaccine Annual Cases</th>
<th>2005 Cases</th>
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<tr>
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<tr>
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<td>Haemophilus influenzae meningitis</td>
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<tr>
<td>Polio</td>
<td>18,376</td>
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<tr>
<td>Tetanus</td>
<td>11,316</td>
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</tr>
</tbody>
</table>

Where We Stand (continued)

- National Institute of Allergy and Infectious Diseases; www.niaid.nih.gov/topics/vaccines/understanding/Pages/vaccineBenefits.aspx

Outline
- Tetanus, Diphtheria, Pertussis
- Pneumococcal
- Meningococcal
- Human Papillomavirus
- Varicella
- Herpes Zoster
- Measles, Mumps, and Rubella
- Hepatitis A and B
- Influenza

Recommended Adult Immunization Schedule

- CDC Website: www.cdc.gov/vaccines/schedules/html/adult.html - Updated December 2011
Tetanus, Diphtheria, Pertussis

- Tetanus
  - Caused by *Clostridium tetani*
  - Infects through wounds
  - Toxin released affects CNS
  - Lock jaw, neck stiffening, muscle rigidity then spasms

- Diphtheria
  - Caused by *Corynebacterium diphtheriae*
  - Infects through respiratory tract

- Pertussis - “Whooping Cough”
  - Caused by *Bordetella pertussis*
  - Spread by respiratory droplets
  - Trend of increased rates from 1995-2005

Tetanus, Diphtheria, and acellular Pertussis Vaccines

- TT - Tetanus Toxoid (adsorbed)
- Td - Tetanus and diphtheria toxoids adsorbed (Decavac®)
- Tdap (Adacel®, Boostrix®) - Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis adsorbed
- All inactivated vaccines
  - Intramuscular (IM) injection
  - Booster needed every 10 years
  - Substitute a one time Tdap for Td (19 - 65 years old)
  - As soon as possible for pregnant women (2nd/3rd trimester)
  - Close contacts of infants <12 months old
  - Healthcare personnel with direct patient contact
  - Precaution- history of Guillain-Barré syndrome
  - Community Pharmacist’s role

Tetanus, Diphtheria, and acellular Pertussis Vaccines

- Td/Tdap Vaccine Target groups
  - All patients > 65 may get Tdap vaccine
  - Patients > 65 years old and in contact with infants <12 months old should get a Tdap vaccination
  - No longer a required time frame between doses of Td containing vaccines and Tdap

Pneumococcal Disease

- *Streptococcus pneumoniae*
  - Transmission - Airborne or direct contact
  - Responsible for up to 1/3 of community pneumonia
  - Up to 1/2 of all hospital acquired
  - Primary infection or complication of disease
  - Can progress to bacteremia and meningitis
  - Up to 50% mortality in the elderly
  - High drug resistance
  - Pneumovax® 23 - 23 Valent Pneumococcal Polysaccharide Vaccine
    - IM or subcutaneous (SubQ) injection
    - Efficacy diminishes with age
  - Keep an eye out for Prevnar 13™-13- valent conjugate vaccine recently approved for use in adults >50

Pneumococcal Vaccination Clarification

- 1 time revaccination with pneumococcal polysaccharide vaccine (PPSV) for patients aged 19-64 years old only applies to patients who have chronic conditions
  - Chronic renal failure or nephrotic syndrome
  - Functional or anatomic asplenia
  - Immunocompromised
- For persons aged 65 years and older (same recommendation)
  - A one-time revaccination is still recommended if
    - Vaccinated 5 or more years ago AND
    - Were aged less than 65 years at the time of primary vaccination

Meningococcal Disease

- Caused by *Neisseria meningitidis*
  - 5 serogroups specified to cause major disease
  - Respiratory transmission
  - Prevalence
    - 1.2 million cases worldwide annually
    - Top 10 most common infectious causes of death
  - Disease presentation
    - Meningitis – headache, myalgia, fever, stiff neck
    - Sepsis, pneumonia, otitis media, epiglottitis
Meningococcal Vaccination

- Clarification of 2-dose series meningococcal conjugate vaccine recommended for
  - Adults with anatomic or functional asplenia, or
  - Persistent complement component deficiencies, or
  - Human immunodeficiency (HIV) virus infection

- Single dose of meningococcal vaccine is still recommended for those with other indications
  - College freshman (dormitories) and military recruits
  - Certain microbiologists
  - Travel to meningitis prevalent regions

Significant Revisions 2011

Meningococcal Vaccine

- 2 Vaccines available
  - Menactra (MCV4)® - quadrivalent polysaccharide conjugated to diphtheria toxoid protein
    - Preferred in patients ≤55 years old
    - IM injection
  - Menomune(MPSV)® - quadrivalent polysaccharide
    - Preferred in patients >55 years old
    - Not recommended for children <2 years old
    - SubQ injection

- Precaution - Association with Guillain-Barré
  - FDA and CDC issued advisory
  - Benefits still outweigh the possible risk

Human Papillomavirus

- Most prevalent sexually transmitted infection in the U.S.
  - Causing cervical cancer and genital warts
    - HPV types 16 & 18 cause about 70% of cervical cancers
  - Highest incidence in women aged 20–24
  - Initially asymptomatic presentation
    - Progression to cervical dysplasia and cancer
  - Vaccine Indication
    - 3 dose series for girls aged 11-26
    - 0, 2, 6 month schedule
    - Quadrivalent vaccine (Gardasil®) may be administered to males aged 22-26
    - Reduces likelihood of genital warts and transmission

Significant Revisions 2011

Varicella (Chickenpox)

- Varicella zoster virus
  - Transmission through respiratory droplets or direct contact with lesions

- Vaccine indication
  - All adults who have no evidence of immunity
    - Administer a 2 dose vaccine series - 4 week interval
  - Not for pregnant women (live attenuated vaccine)

- Varicella vaccine - SubQ injection
  - Highly temperature regulated
    - Reconstitute with provided diluent
    - Must administer within 30 minutes of reconstitution

Varicella Vaccine

- Contraindications
  - Anaphylactic allergy to neomycin and gelatin
  - Immunosuppression
  - Pregnancy

- Precautions:
  - Recent blood product administration (within 11 months)
    - Moderate or severe acute illness

- Potential side effects
  - Rash
    - Possible transmission of virus
      - More common if rash develops
    - Potential for herpes zoster infection
Herpes Zoster (Shingles)
- Reactivation of varicella virus
  - 1 in 3 people experience shingles in adulthood
  - Can progress to postherpetic neuralgia
- Vaccine indication
  - Patients >60 years old
- Zoster Vaccine – SubQ dose x 1
  - Live attenuated vaccine
    - Similar precautions as varicella vaccine
    - Contraindications: untreated active tuberculosis, severe neomycin and gelatin allergy, pregnancy

Zoster Vaccination
- New FDA approval!
  - Keep an eye out for 2012 immunization schedule
- New approval for 50 years of age and older
  - Previously indicated for patients 60 years of age or older
  - Changes should be seen in the 2012 update

Measles, Mumps, and Rubella (MMR)
- Measles – paramyxovirus
  - Respiratory transmission, extremely contagious
  - Presentation: fever, runny nose, cough, conjunctivitis, maculopapular rash, Koplik spots
- Mumps – paramyxovirus
  - Respiratory transmission
  - Presentation: some asymptomatic
    - Fever, headache, malaise, myalgia
    - Parotitis
- Rubella – togavirus
  - Respiratory transmission
  - Presentation: maculopapular rash
  - Concern for congenital rubella syndrome

MMR vaccine
- Vaccination target groups
  - All adults lacking vaccination born after 1957
  - Patients at high risk for disease
    - Exposure to an outbreak setting
    - College students
    - International travelers
    - Healthcare workers
- Vaccine Schedule
  - 1 or 2 dose series, SubQ injection
  - Give booster at 4 week interval if necessary
- M-M-R II® trivalent vaccine – live attenuated virus
  - Preferred over single-antigen vaccines
  - Contraindications-neomycin & gelatin allergy, pregnancy, and immunodeficiency
  - Precaution – blood product exposure (within 11 months), or severely ill

Hepatitis A
- Fecal-oral transmission
- Viral replication in liver
- Prevalence
  - 20,000-30,000 U.S. cases annually prior to vaccine
  - Decreased to 2,708 cases in 2007
- Presentation
  - Abdominal pain, loss of appetite, jaundice, fever, dark urine
  - Complications – liver failure, death
- Vaccination target groups
  - Behavioral- certain sexual behavior, drug abuse, travelers
  - Occupational- research lab work
  - Medical- chronic liver disease, recipients of clotting factor concentrates

Hepatitis B
- DNA virus, bloodborne pathogen
- Prevalence
  - Affects >150 million people worldwide
  - 1.25 million infected in the U.S.
- Presentation – similar to Hepatitis A
  - Complications – acute and chronic hepatitis, cirrhosis, hepatic cancer, and death
- Vaccination target groups
  - Behavioral- sexual, certain travelers, illicit drug use
  - Medical - chronic liver and renal disease, and HIV
  - NEW - recommended for all unvaccinated adults with type 1 and type 2 diabetes aged 19 to 59
Adult Hepatitis A & B Vaccines
- Hep A vaccines: Havrix® and Vaqta®
  - Inactivated vaccine
  - 2 dose series (booster dose 6-18 months later)
  - 1mL IM injection (deltoid)
- Hep B vaccines: Recombivax® & Energix-B®
  - Inactivated vaccine
  - 3 dose series (0, 1, 6 months)
  - 1mL IM injection (deltoid)
  - Use caution switching between brands
  - Varying mcg content and volume per dose
  - Titer recommendations
- Combination Vaccine: Twinrix®
  - Also a 3 dose series (0, 1, 6 months)

Special Populations
- Pregnancy
- Immunocompromising conditions
- HIV infection
- Diabetes, heart disease, chronic lung disease, chronic alcoholism
- Asplenia
- Chronic liver disease
- Kidney failure, end-stage renal disease, hemodialysis
- Healthcare personnel

Refer to the CDC website


Vaccine Pearls

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<th>Route</th>
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*Live vs. inactivated vaccine considerations

Influenza

- Epidemiology
  - >200,000 hospitalizations annually
  - 63% of hospitalizations in patients >65
  - Attributed to >36,000 deaths annually
- Complications of disease
  - Pneumonia, bronchitis, sinus infection, Reye syndrome (children), myocarditis
  - Disease exacerbations – heart failure or asthma
  - Hospitalization
- Symptoms
  - Fever, nonproductive cough, sore throat, muscle aches

Influenza Vaccine Guidelines

- Recommended for all persons 6 months of age and older
  - Children in their first year of vaccination require 2 doses
    - Given at 4 week interval
- Who should not receive vaccine
  - Patients less than 6 months of age
  - Severe allergic reaction to previous flu vaccine
  - Severe egg allergy – must consult with physician
- Precaution
  - History of Guillain-Barré within 6 weeks of prior flu vaccination

Significant Revisions 2011

- Indications simplified and expanded
  - Updated to include ALL patients aged 6 months and older
  - Shown to be safe and effective in this population
- Fluzone® High-Dose inactivated influenza vaccine
  - Optional for patients greater than 65 years old
- CDC and the Advisory Committee on Immunization Practices (ACIP) still show no preference
Influenza Vaccine

- Those at highest risk for complications
  - Pregnant women
  - Children <5 (especially < 2 years old)
  - People > 50 years of age
  - People with chronic medical conditions
  - People who live in nursing homes and other long-term care facilities
  - People who live with or care for those at high risk for complications from flu, including:
    - Health care workers
    - Household contacts of persons at high risk for complications from the flu
    - Household contacts and caregivers of children <6 months of age

- Changes as necessary every season
  - Vaccine usually released in August
  - Administer as soon as available through March
  - 2011-2012 vaccine is the same as last season
  - Protection against 3 viruses
  - Influenza A, Influenza B, and 2009 H1N1 virus

- Traditional influenza vaccines
  - Trivalent influenza vaccine (TIV)- killed virus
    - Afluria®, Fluarix®, FluLaval®, Fluvirin®, Fluzone®, Fluzone® High-Dose, Fluzone® Intradermal
  - Live attenuated influenza vaccine (LAIV)- FluMist®

- Influenza Vaccines
  - Traditional flu shot
    - All people >6 months old
  - Intradermal flu shot
    - Patients 18-64 years old
  - High-dose flu shot
    - Patients 65 and older
  - FluMist® Nasal-Spray
    - Patients 2-49 years old

- Fluzone® Intradermal
  - New this season
    - FDA approved as of May 2011
  - Indicated for ages 18-64
  - Proven “non-inferior” effectiveness to IM
    - Remember CDC shows no preference
  - Formulation
    - Inactivated trivalent vaccine
    - Pre-filled syringes
    - Contains 9mcg of hemagglutinin of each virus strain
  - Administration
    - Single, 1 time IM injection in the deltoid muscle

- Fluzone High-Dose
  - Inactivated influenza virus
  - Indicated for patients 65 and older
    - High risk for complications
    - Better immune response compared to Fluzone®
  - Formulation
    - 4 times the traditional amount of antigen
      - Each dose contains 180mcg of virus hemagglutinin (60mcg of each influenza virus strain)
      - Traditional contains 15mcg of each virus strain
    - Supplied in pre-filled syringes, preservative free
  - Administration
    - Single, 1 time IM injection in the deltoid muscle

- Flumist® Nasal-Spray
  - Live Attenuated Influenza Vaccine (LAIV)
  - Approved for healthy, non-pregnant patients age 2-49 years of age
    - Do not administer if nasal congestion present
    - Risk of virus transmission rare
    - Not recommended if in contact with severely immunocompromised patients
  - Contraindication
    - Children <17 receiving aspirin
  - Precautions
    - Recent antiviral use, moderate to severe acute illness, and asthma/wheezing in children <5
Influenza Vaccine Concerns

- Will I get the flu?
  - Most common side effects
    - Runny nose or congestion, headache, sore throat, cough
    - Soreness at injection site, low grade fever, aches

- Egg allergy controversy

- Safety in pregnancy (category C)
  - TIV: recommended by CDC in all trimesters
  - LAIV: NOT recommended

Important Websites

- CDC Website
  - www.cdc.gov

- Vaccine Information Statements
  - http://www.immunize.org/vis/vis_ppsv.asp

- VAERS- Vaccine Adverse Event Reporting System
  - CDC and FDA monitoring
  - Healthcare providers encouraged to report
    - http://vaers.hhs.gov/index

Patient Case Review

- SC is a 68 yo female who presents to the pharmacy with her 2 yo grandson to pick up her heart failure medications and insulin refill. She inquires about getting the flu shot but hates needles and would rather get the nasal spray vaccine.
  - When questioned, her immunization history shows...
    - Annual influenza vaccine: inconsistent
    - Pneumococcal vaccine: 7 years ago
    - Tetanus-diphtheria: 15 years ago
    - Hepatitis A series: 6 years ago

- What influenza vaccine is best for SC?
- What other vaccines should be recommended?

True or False Quiz

- Ten year Td boosters should be substituted with a 1-time dose of Tdap in adults who have not received one previously or if vaccine status is unknown.
  - True

- Annual influenza vaccination is recommended for all persons six months of age and older, without contraindications.
  - True

- Pregnant women should not receive the nasal-spray flu vaccine, since it is a live attenuated virus.
  - True

- Fluzone High-Dose results into stronger immune response and greater protection against influenza disease after vaccination.
  - False
Community-Acquired Pneumonia in infants and children

Review of Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America - 2011

Sabah Charania, B.S., Pharm.D.
PGY-1 Pharmacy Resident
Baptist Hospital of Miami

Objectives
- Define pneumonia
- Define criteria for community acquired pneumonia (CAP) severity of illness
- Review guidelines for management of infants and children with CAP
- Explain treatment modalities for children with failure to initial antibiotic therapy
- Discuss strategies to prevent CAP in infants and children

Pneumonia
A lower respiratory tract infection with mild to severe signs and symptoms

Image: http://www.thequietworld.com/healthyworld/images/pneumoniacause.jpg

Epidemiology
- ~ 155 million cases of pneumonia occur in children annually worldwide
  - Over 2 million children die annually from pneumonia worldwide
- Annual incidence of pneumonia in US is ~ 3-4 cases per 100 children < 5 years old
  - CDC estimates that pneumonia kills a child every 20 seconds
- Pneumonia represents approximately 20% of all deaths in children < 5 years of age


Prevalence

Risk Factors

- Young age
- Pre-existing lung or other serious disease (asthma, diabetes)
- Weakened or suppressed immune system
- Malnourished
- Difficulty in coughing or swallowing

Etiology

- Most common bacterial pathogens:
  - *Streptococcus pneumoniae* (*S. pneumoniae*)
  - *Haemophilus influenzae* (type b) (*H. influenzae*)
  - Atypical bacteria
- Most common viral pathogens:
  - Influenza
  - Parainfluenza
  - Respiratory syncytial viruses (RSV)

Age-Specific Etiology

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Most Common Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>All age groups</td>
<td>Typical bacteria</td>
</tr>
<tr>
<td>Children &lt; 2 years</td>
<td>Viral</td>
</tr>
<tr>
<td>Children 2 - 5 yrs</td>
<td>Viral</td>
</tr>
<tr>
<td>Children ≥ 5 yrs</td>
<td>Atypical bacteria</td>
</tr>
</tbody>
</table>

Clinical Presentation

- Simple
  - Mild to severe illness
  - Coughing
  - Fever
  - Fatigue
  - Nausea
  - Vomiting
- Complicated
  - Rapid breathing or shortness of breath
  - Chills
  - Chest pain
  - Abdominal Pain

Severity of Illness

**Major Criteria**

- Invasive mechanical ventilation
- Fluid refractory shock
- Acute need for noninvasive positive pressure ventilation (NIPPV)
- Hypoxemia requiring fraction of inspired oxygen (FiO2) greater than inspired concentration or flow feasible in general care area
- Respiratory rate higher than WHO classification for age
- Alarms
- Increased work of breathing
- Arterial oxygen pressure (PaO2)/FiO2 ratio < 250
- Multi-lobar infiltrates

**Minor Criteria**

- Pediatric early warning score (PEWS) > 6
- Altered mental status
- Hypotension
- Presence of effusion
- Comorbid conditions
- Unexplained metabolic acidosis
**Pediatric Early Warning Score (PEWS)**

<table>
<thead>
<tr>
<th>Behavior</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior</td>
<td>Playing/</td>
<td>Appropriate</td>
<td>Sleeping</td>
<td>Intubated</td>
<td>Lethargic/confused OR Reduced response to pain</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Pink OR capillary refill 1-2 seconds</td>
<td>Grey or cyanotic OR Capillary refill 4 seconds OR Taquenyesia of 20 above normal rate</td>
<td>Grey or cyanotic AND notched OR Capillary refill 5 seconds or above OR Toxichydria of 30 above normal rate OR Bradycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Within normal parameters, no retractions</td>
<td>≥ 10 above normal parameters OR using accessory muscles OR 30/15/12 or 34 respirations</td>
<td>≥ 20 above normal parameters OR Retractions OR 12/10/8 or 4 respirations</td>
<td>≤ 10 below normal parameters with retractions/ear grunting OR ≥ 50/30/20 or ≥ 6 respirations</td>
<td></td>
</tr>
</tbody>
</table>

*Score 1 by adding the most severe parameter first. *Score 2 extra for every 5 (continuous rubs) or persistent postural vomiting. *Use “Test/retest” to score high flow nasal cannula.

---

**Care Setting**

**Hospitalization**
- Moderate to severe CAP (SH)
- Suspected pathogen with increased virulence [e.g., Community-acquired Methicillin Resistant Staphylococcus aureus (CA-MRSA)] (SL)
- Infants < 3-6 months with suspected bacterial CAP (SL)
- Patients with issues towards careful observation at home or compliance (SL)

**Intensive Care**
- Children requiring invasive ventilation (SH)
- Acute need for noninvasive positive pressure ventilation (SVL)
- Impending respiratory failure (SM)
- Pulse oximetry measurement <92% on inspired oxygen of ≥ 0.5 (SL)
- Sustained tachycardia or in need of pharmacologic blood pressure (BP) or perfusion support (SH)
- Children with pneumonia-related altered mental status (SL)

---

**Diagnostic Testing**

**Pulse oximetry (SM)**

**Blood cultures**
- Outpatient: Only in children with worsening CAP symptoms after initiation of antibiotic therapy (SM)
- Inpatient: In children with presumed bacterial moderate-to-severe CAP (SL)
- Repeated blood cultures
  - Should be performed for bacteremia caused by Staphylococcus aureus regardless of clinical status (SL)
  - Not necessary for pneumococcal bacteremia with clinical improvement (WL)

**Diagnostic Testing**

- Specific diagnostic testing is recommended for influenza and other respiratory viruses (SH)
  - Antibacterial therapy is unnecessary in patients with positive influenza test with lack of signs indicative of bacterial co-infection (SH)
- Atypical bacteria
  - Testing for Mycoplasma pneumoniae should be performed in children with clinical signs and symptoms suggestive of this pathogen (WM)
  - Chlamydia pneumoniae testing is not recommended (SH)

---

**Chest Radiology**

- Outpatient
  - Unnecessary for confirmation of CAP in well enough patients (SH)
  - Recommended for patients with hypoxemia or significant respiratory distress or inadequate response to initial therapy (SM)
- Inpatient
  - Should be obtained for all hospitalized patients (SM)
Outpatient Management

- **Outpatient**
  - **Age**
    - **Children < 5 years**
    - **Children > 5 years**
  - **Etiology**
    - **Bacterial**
    - **Viral**
    - **Typical**
    - **Atypical**

**Treatment: Children < 5 years**

- Preschool-aged children do not routinely require antimicrobial therapy (SH)

<table>
<thead>
<tr>
<th>Typical Pneumonia</th>
<th>Atypical Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin 90 mg/kg/day PO in 2 divided doses (max: 4 g/day) (SM)</td>
<td>Azithromycin 10 mg/kg PO on day 1, then 5 mg/kg/day PO day 2-5</td>
</tr>
<tr>
<td>Alternatives: Clarithromycin 15 mg/kg/day PO in 2 divided doses for 7-14 days</td>
<td>Alternatives: Erythromycin 40 mg/kg/day PO in 4 divided doses</td>
</tr>
<tr>
<td>Alternatives:</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment: Children ≥ 5 years**

- Typical Pneumonia
  - Amoxicillin 90 mg/kg/day PO in 2 divided doses (max: 4 g/day) (SM) ± macrolide if atypical pneumonia is suspected (IM)
  - Alternative: Amoxicillin/clavulanate

- Atypical Pneumonia
  - Azithromycin 10 mg/kg PO on day 1, then 5 mg/kg/day PO day 2-5
  - Alternatives:
    - Clarithromycin 15 mg/kg/day PO in 2 divided doses for 7-14 days
    - Erythromycin 40 mg/kg/day PO in 4 divided doses

**Prophylaxis: Influenza Pneumonia**

- **Oseltamivir**
  - Age-based dosing
    - < 3 months: not recommended - limited data
    - 3-23 months: 3.5 mg/kg once daily
    - 23-40 kg: 500 mg on day 1 and 250 mg on days 2-5
  - Weight-based dosing
    - ≤ 15 kg: 30 mg/day
    - >15 – 23 kg: 45 mg/day
    - > 23 – 40 kg: 60 mg/day
    - > 40 kg: 75 mg/day

- Alternative: Zanamivir (children ≥ 7 years old) 2 inhalations (10 mg / dose) once daily for 10 days

**Prophylaxis: RSV**

- Immune prophylaxis with RSV – specific monoclonal antibody is recommended for high-risk infants:
  - Infants and children < 24 months with bronchopulmonary dysplasia
  - Preterm birth (<35 weeks)
  - Hemodynamically significant congenital heart disease

- Palivizumab (Synagis®) 15 mg/kg IM monthly during the RSV season (November – April)
Inpatient Management

- **Immunization status**
  - Fully immunized: vaccinated against S. pneumoniae and H. influenzae
  - Minimal resistance: minimum inhibitory concentrations (MICs) for penicillin ≤ 2.0 µg/mL
  - Resistant: MICs for penicillin ≥ 4.0 µg/mL

- **Etiology**
  - Typical bacteria
  - Atypical bacteria

- **PCN resistance**
  - PCN susceptible
  - PCN resistant

Empiric Regimen: Typical Pneumonia

<table>
<thead>
<tr>
<th>Status</th>
<th>Fully Immunized</th>
<th>Not Fully Immunized or Suspected PCN Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ampicillin or penicillin G (SM)</td>
<td>Ceftriaxone or cefotaxime (WM)</td>
</tr>
<tr>
<td></td>
<td>Alternative:</td>
<td>Alternative:</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone or cefotaxime</td>
<td>Vancomycin or clindamycin (if CA-MRSA is suspected) (SL)</td>
</tr>
<tr>
<td></td>
<td>Vancomycin or clindamycin (if CA-MRSA is suspected)</td>
<td>Levofloxacin</td>
</tr>
<tr>
<td></td>
<td>(if CA-MRSA is suspected)</td>
<td>Vancomycin or clindamycin (if CA-MRSA is suspected)</td>
</tr>
</tbody>
</table>

Treatment: Typical Pneumonia

- **Fully immunized**
  - PCN Sensitive
    - Ampicillin 150-200 mg/kg/day IV q6h OR
    - Penicillin G 200,000-250,000 units/kg/day IV q4-6h (SM)
  - Alternatives:
    - Ceftriaxone 50-100 mg/kg/day IV q12-24h
    - Cefotaxime 150 mg/kg/day IV q8h
    - Vancomycin 40-60 mg/kg/day IV q6-8h OR
    - Clindamycin 40 mg/kg/day IV q6-8h (SL)

- PCN Resistant
  - Ceftriaxone 100 mg/kg/day IV q12-24h (WM)
  - Alternatives:
    - Ampicillin 300-400 mg/kg/day q6h OR
    - Levofloxacin (6 months - 5 years old): 16-20 mg/kg/day q12h; (5 - 16 years old): 8-10 mg/kg/day; max. 750 mg/day
    - Vancomycin OR
    - Clindamycin (SL)

- **Not fully immunized**

Empiric Regimen: Atypical Pneumonia

- Azithromycin (WM) ±
- β-lactam (if etiology is doubtful)

- Alternatives:
  - Clarithromycin
  - Erythromycin
  - Doxycycline (children > 7 years old)
  - Levofloxacin (children who have reached growth maturity or are macrolide-intolerant)

Treatment: Atypical Pneumonia

- **Preferred**
  - Azithromycin 10 mg/kg IV (max 500 mg) on days 1 and 2 of therapy and transition to oral therapy (WM)
  - β-lactam (if etiology is doubtful)

- **Alternative**
  - Clarithromycin 15 mg/kg/day in 2 doses
  - Doxycycline (children > 7 years old): 2-4 mg/kg/day in 2 doses

Severe disease
- Erythromycin 20 mg/kg/day IV q6h
- Levofloxacin 16-20 mg/kg/day IV q12h; max. 750 mg/day
**Penicillin Allergy**

**Treatment is not well-defined**
- Non-serious allergic reaction:
  - Trial of amoxicillin under supervision
  - Oral cephalosporin (e.g. cefuroxime)
- Serious allergy:
  - Respiratory fluoroquinolone
  - Clindamycin (if susceptible)
  - Macrolide (higher resistant rates)
  - Linezolid

**Duration of Therapy**
- Shortest effective duration is recommended (SM)
- Most commonly, duration of 10 days has been studied
- Varies based on severity of illness and pathogen involved
  - CA-MRSA may require longer treatment (SM)

**Treatment Failure**
- Clinical improvement should be seen with 48-72 hours of adequate anti-infective therapy (SM)
- If inadequate response:
  - Assess current severity of illness (SL)
  - Imaging evaluation (WL)
  - Scrutinize to identify resistance versus presence of another pathogen (WL)

**Complicated Pneumonia**
- Additional Considerations:
  - Size of the effusion (SM)
  - Extent of respiratory compromise (SM)
- Recommendations:
  - Small effusions can usually be managed with antibiotic therapy (SM)
  - Drainage for moderate, complicated effusions with anti-infective therapy (SM)

**Discharge Eligibility**
- Clinical improvement for at least 12-24 hrs (SVL)
- Consistent pulse oximetry measurements >90% in room air (SM)
- Stable and/or baseline mental status (SVL)
- Documentation demonstrating tolerance to home anti-infective and oxygen therapy (SL)
- Assessment of barriers to adequate care post-discharge (WVL)
- Chest tube removed for at least 12-24 hrs (SVL)
- Ineligible if increased work for breathing or sustained tachypnea or tachycardia (SH)

**Prevention Strategies**
- Children should be immunized for S. pneumoniae, H. influenzae, and pertussis (SH)
- Immunizations for bacterial pathogens:
  - *S. pneumoniae*
    - 13-valent pneumococcal vaccine
  - *H. influenzae*
    - PRP-OMP
    - PRP-T (ActHIB & Hiberix)
  - Pertussis
    - DTap
Prevention Strategies

- Annual influenza vaccine is strongly recommended for all:
  - Infants ≥ 6 months of age (SH)
  - Children (SH)
  - Adolescents (SH)

- Influenza and pertussis vaccines are strongly recommended for:
  - Parents and caretakers of infants < 6 months of age (SW)
  - Pregnant adolescents (SW)

Patient Case

- A mother walks into a pediatrician’s office with her 6 year-old boy, JW. JW has been experiencing cough, fever, and sore throat for the past couple of days and is not responding to his mom’s home remedies.
  - Weight: 22 kg
  - Height: 3’4”
  - SpO2: 94%

- Relevant immunization history: Influenza vaccine
- Based on physical examination, the physician diagnosed JW with CAP.
- JW’s anti-infective therapy should cover for?
- How would you treat?

Is it true...

- Parents and caretakers of infants < 6 months of age, including pregnant adolescents, should be immunized with influenza and pertussis vaccines to protect infants from exposure. True
- Antimicrobial therapy is routinely required for preschool-aged children with CAP. False
- Children on adequate therapy should demonstrate clinical and laboratory signs of improvement with 24-48 hours. False

Additional References

- Centers for Disease Control and Prevention. QuickStats: Percentage Distribution of Hospitalizations for Types of Respiratory Diseases Among Children Aged <15 Years --- National Hospital Discharge Survey, United States, 2005. MMWR 2007;56(19);713.

Community-Acquired Pneumonia in infants and children

Review of Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America - 2011

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New Treatment Guidelines for Methicillin-Resistant Staphylococcus Aureus (MRSA)

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Post Graduate Year One (PGY-1)
Pharmacy Resident
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JacquelineRu@baptisthealth.net

Objectives

- Review the management of clinical syndromes associated with MRSA disease, including skin and soft tissue infections, pneumonia, bacteremia, endocarditis, bone and joint infections, and central nervous system infections in adults and children
- Evaluate guideline recommendations regarding vancomycin dosing and monitoring
- Describe the role of adjunctive therapies for the treatment of MRSA infections
- Identify core and supplemental MRSA prevention strategies

Definition

- Methicillin-resistant staphylococcus aureus (MRSA)
  - Gram-positive staphylococcus bacteria resistant to beta-lactam antibiotics
  - Occurs when an isolate carries an altered penicillin-binding protein (PBP2a)
- The Clinical and Laboratory Standards Institute (CLSI) breakpoint criteria
  - Oxacillin MIC* ≥ 4 mcg/ml
  - Oxacillin disk diffusion ≤ 10 mm
  - Cefoxitin disk diffusion ≤ 21 mm
*MIC = minimum inhibitory concentration

Classification

- Healthcare-associated MRSA (HA-MRSA)
  - Occurs > 48 hours following hospitalization
  - Occurs outside of the hospital within 12 months of exposure to healthcare
    - Surgery, hospitalization, dialysis, residence in long-term care facility
    - Leading cause of surgical site infection in both tertiary and community hospitals
    - Bacterial strains tend to carry multi-drug resistance
- Community-associated MRSA (CA-MRSA)
  - Occurs < 48 hours following hospitalization
  - Absence of healthcare exposure
    - Skin and soft tissue infections
    - Leading cause of skin and soft tissue infections in the young, otherwise healthy individual

Modeled Incidence and Percent Change for All Invasive Hospital-Onset and Healthcare-Associated, Community-Onset MRSA infections, 2005-2007

<table>
<thead>
<tr>
<th>Year</th>
<th>Hospital-onset incidence per 100,000 population</th>
<th>Modeled percent change from previous year</th>
<th>Total modeled percent change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>9.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>8.96</td>
<td>-9.97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>8.24</td>
<td>-8.08%</td>
<td>(17.2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Healthcare-associated, Community-onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>22.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>21.11</td>
<td>-4.59%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>19.70</td>
<td>-6.71%</td>
<td>(21.0%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Infectious Diseases Society of America-US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for or against use</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for or against use</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from ≥ 1 properly randomized, controlled trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from ≥ 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities; based on clinical experience, descriptive studies, or reports of expert committees</td>
</tr>
</tbody>
</table>
Skin and Soft Tissue Infections (SSTI)

- Abscesses
  - Primary treatment: Incision and drainage for simple abscesses or boils (AII)

- Antibiotic benefit (AII)
  - Severe, extensive disease, rapidly progressive with associated cellulitis or septic phlebitis
  - Signs and symptoms of systemic illness
  - Associated comorbidities or immunosuppression
  - Extremes of age
  - Difficult to drain areas
  - Face, hands, genitalia
  - Failure of prior incision and drainage

Additional Antimicrobial Benefit?

- Multiple observational studies:
  - High cure rates without antibiotic

- Three randomized controlled (RCT) trials of uncomplicated skin abscesses with a primary outcome of clinical cure of MRSA infection

- Rajendran: cephalexin vs. placebo

- Duong and Schmitz: TMP-SMX vs. placebo

Microbiology of Skin and Soft Tissue Infections

- Cellulitis
  - Non-purulent drainage/exudate without drainable abscess
  - β-hemolytic streptococcus identified in 73% of infections
  - Empiric antimicrobial for β-hemolytic streptococcus (AII)
  - Empiric antimicrobial for CA-MRSA recommended for patients who do not respond to therapy and/or systemic toxicity (AII)

- Duration of therapy: 5 – 10 days

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin (Keflex™)</td>
<td>500 mg PO QID</td>
<td>25 – 50 mg/kg PO divided TID – QID</td>
<td>AII</td>
</tr>
<tr>
<td>Clindamycin (Cleocin®)</td>
<td>600 mg PO BID</td>
<td>10 mg/kg/dose PO Q 8 – 12 H</td>
<td>AII</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg PO BID</td>
<td>4 mg/kg PO Q 12 H</td>
<td>AII</td>
</tr>
<tr>
<td>Minocycline</td>
<td>100 mg PO BID</td>
<td>4 mg/kg PO Q 12 H</td>
<td>AII</td>
</tr>
<tr>
<td>Linezolid (Zyvox®)</td>
<td>600 mg PO BID</td>
<td>10 mg/kg/dose PO Q 12 H</td>
<td>AII</td>
</tr>
</tbody>
</table>

NTE= not to exceed; TMP-SMX= trimethoprim / sulfamethoxazole * provide coverage for both β-hemolytic strep and CA-MRSA

Skin and Soft Tissue Infections

- Cellulitis
  - Purulent drainage/exudate without drainable abscess
  - MRSA accounts for nearly 60% of cases followed by MSSA
  - Empiric antimicrobial for CA-MRSA recommended (AII)
  - Empiric antimicrobial for β-hemolytic streptococcus not required (AII)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP-SMX (Bactrim™)</td>
<td>10 – 20 mg/kg PO</td>
<td>≤ 45 kg: 2 mg/kg/dose PO Q 12 H</td>
<td>AII</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg PO BID</td>
<td>4 mg/kg PO Q 12 H</td>
<td>AII</td>
</tr>
<tr>
<td>Minocycline</td>
<td>100 mg PO BID</td>
<td>4 mg/kg PO Q 12 H</td>
<td>AII</td>
</tr>
<tr>
<td>Linezolid (Zyvox®)</td>
<td>600 mg PO BID</td>
<td>10 mg/kg/dose PO Q 12 H</td>
<td>AII</td>
</tr>
</tbody>
</table>
Skin and Soft Tissue Infections

- Complicated SSTI (cSSTI)
  - cSSTI – deep soft-tissue infections, surgical/traumatic wound infection, major abscesses, cellulitis-infected ulcers/burns
  - Surgical debridement, broad-spectrum antibiotic therapy, and empiric coverage for MRSA pending cultures

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin (Vancocin®)</td>
<td>15 – 20 mg/kg/dose IV Q 8 – 12 H</td>
<td>15 mg/kg/dose IV Q 8 – 12 H</td>
<td>AII</td>
</tr>
<tr>
<td>Linezolid (Zyvox®)</td>
<td>600 mg PO/IV BID</td>
<td>&lt; 12 years: 10 mg/kg/dose PO/IV Q 8 H (NTE 500 mg/dose)</td>
<td>AII</td>
</tr>
<tr>
<td>Daptomycin (Cubcin®)</td>
<td>4 mg/kg/dose IV daily</td>
<td>Ongoing study 10 mg/kg (max 120 mg) Q 8 H</td>
<td>ND</td>
</tr>
<tr>
<td>Telavancin (Vibativ™)</td>
<td>10 mg/kg/dose IV daily</td>
<td>40 mg/kg (max 600 mg)</td>
<td>ND</td>
</tr>
<tr>
<td>Clindamycin (Cleocin®)</td>
<td>600 mg PO/IV TID</td>
<td>10 – 13 mg/kg/dose PO/IV Q 6 – 8 H (NTE 40 mg/kg/day)</td>
<td>BII/AII</td>
</tr>
</tbody>
</table>

NTE = not to exceed; ND = no data available

MRSA Pneumonia

- Severe, community-acquired pneumonia
  - ICU admission, necrotizing or cavitary infiltrates, or empyema
  - Empirical therapy for MRSA is recommended pending sputum and/or blood cultures (AIII)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin (Vancocin®)</td>
<td>15 – 20 mg/kg/IV Q 8 – 12 H</td>
<td>15 mg/kg/dose IV Q 8 – 12 H</td>
<td>AII</td>
</tr>
<tr>
<td>Linezolid (Zyvox®)</td>
<td>600 mg PO/IV BID</td>
<td>&lt; 12 years: 10 mg/kg/dose PO/IV Q 8 H (NTE 500 mg/dose)</td>
<td>AII</td>
</tr>
<tr>
<td>Clindamycin (Cleocin®)</td>
<td>600 mg PO/IV TID</td>
<td>10 – 13 mg/kg/dose PO/IV Q 6 – 8 H (NTE 40 mg/kg/day)</td>
<td>BII/AII</td>
</tr>
</tbody>
</table>

MRSA Bacteremia and Endocarditis

- Uncomplicated bacteremia
  - Positive blood cultures PLUS
    - Exclusion of endocarditis, no implanted prosthesis, no recent antibiotic therapy
    - Normal C&G cultures
  - Duration of therapy: at least 2 weeks

- Complicated bacteremia
  - Positive blood cultures not meeting above criteria
  - Duration of therapy: at least 4 – 6 weeks

Infected endocarditis, native valve
  - Duration of therapy: at least 6 weeks
MRSA Bacteremia and Endocarditis

- Bacteremia and native valve infection
  - Therapy
    | Antibiotic      | Adult Dose     | Pediatric Dose | Class |
    |-----------------|----------------|----------------|-------|
    | Vancomycin      | 15 – 20 mg/kg IV Q 8 – 12 H | 15 mg/kg/dose IV Q 6 H | AII |
    | Daptomycin      | 6 mg/kg/dose IV daily | 6 – 10 mg/kg/dose IV daily | BII |
    | Linezolid       | 600 mg PO/V 8 H | 10 mg/kg/dose PO/V 8 H | BII |
    | Clindamycin     | 600 mg PO/TID | 10 – 12 mg/kg/dose PO/V Q 6 – 8 H | BII |
    | TMP-SMX (Bactrim®) + Rifampin | 3.5 – 4 mg/kg/dose PO/Q 8 – 12 H | 600 mg PO daily | BII |

- Addition of gentamicin (AII) or rifampin (AI) to vancomycin is not recommended
  - ↑ risk of nephrotoxicity
  - ↑ risk of elevated transaminases (≥ 5x baseline), drug interactions with rifampin, resistance concerns

- Infective endocarditis, prosthetic valve (BII)
  - IV vancomycin + rifampin 300 mg PO/IV Q 8 H
    - Duration of therapy: at least 6 weeks
  - Gentamicin 1 mg/kg/dose IV Q 8 H
    - Duration of therapy: 2 weeks
    - Early evaluation for valve replacement surgery is recommended (AII)

- Pediatric considerations:
  - Insufficient data to support routine use of combination therapy with rifampin or gentamicin in bacteremia or infective endocarditis (CII)
  - Echocardiogram evaluation (AIII)
    - Congenital heart disease, bacteremia > 2 – 3 days in duration, or other clinical findings suggestive of endocarditis

- Early evaluation for valve replacement surgery is recommended (AII)

- Clinical assessment to identify source and extent of infection (AII)
  - Identify, eliminate, and debride other sites of infection
  - Repeat blood cultures 2 – 4 days after initial positive cultures; document clearance of bacteremia
  - Echocardiography recommended for all patients with bacteremia (TEE > TTE)*
  - Evaluate for valve replacement surgery:
    - Vegetation > 10 mm, ≥ 1 embolic event, severe valvular insufficiency, valvular perforation, decompensated heart failure, perivalvular/myocardial abscess

- Osteomyelitis/septic arthritis therapy options
  - Optimal route of administration not established (AII)

- Optimal duration is unknown; at least 8 weeks (AII)
- Hematogenous MSSA vertebral osteomyelitis: 8 weeks vs. < 8 weeks associated with improved outcomes2,3

MRSA Bone and Joint Infections

- Bone and joint infections arise from the following:
  - Hematogenous seeding
  - Adjacent focus of infection
  - Direct inoculation (i.e. trauma, medical procedure)

- Surgical debridement is mainstay of therapy along with antimicrobial therapy (AII)
  - Debridement of necrotic bone or joint space
  - Osteomyelitis
  - Drainage of adjacent abscesses
  - Septic arthritis

- Duration of therapy
  - Optimal duration is unknown; at least 8 weeks (AII)
  - Hematogenous MSSA vertebral osteomyelitis: 8 weeks vs. < 8 weeks associated with improved outcomes2,3
MRSA Central Nervous System (CNS) Infections

- CNS infections occur as a complication of the following:
  - Neurosurgical procedure
  - Associated with adjacent focus of infection
  - Secondary to bacteremia or infective endocarditis

- Manifestations of CNS infection include:
  - Meningitis
  - Brain abscesses
  - Subdural empyema, spinal epidural abscess
  - Septic thrombosis
  - Cavernous or dural venous sinus

Guideline Recommendations Vancomycin

- Recommendations based on a consensus statement
  - American Society of Health-System Pharmacists, Infectious Disease Society of America, Society of Infectious Diseases Pharmacists

  - IV vancomycin 15 – 20 mg/kg (actual body weight) Q 8 – 12 H, not to exceed 2 g/dose (BIII)
  - Seriously ill patients with suspected MRSA infection, loading dose of 25 – 30 mg/kg may be considered (CIII)
    - Consider prolonged infusion (2 hours) and pre-medication with antihistamine, given risk of red man syndrome and possible anaphylaxis

  - Continuous infusion vancomycin is unlikely to substantially improve patient outcome, compared with intermittent dosing (AII)

Vancomycin Therapeutic Monitoring

- Obtain serum troughs at steady state (before 4th or 5th dose) (BII)
- Monitoring of peak vancomycin concentrations is not recommended (BII)
- Target trough concentrations:
  - 15 – 20 mcg/mL (BII)
  - Serious infections (i.e., severe SSTI, pneumonia, bacteremia, endocarditis, osteomyelitis)
- For most patients with SSTI, normal renal function, not obese, traditional doses of 1 gram IV Q 12 H is adequate
  - Trough monitoring is not required (BII)
- Efficacy and safety of targeting trough concentrations of 15 – 20 mcg/mL in pediatrics requires additional study
  - Consider in serious infections

Pharmacotherapy of Vancomycin

- Evidence for higher target trough concentrations
  - Probability of achieving target area under the curve (AUC)/minimum inhibitory concentration (MIC) ratio
    - AUC/MIC ≥ 400 vs. < 400 associated with improved clinical and microbiologic response

- Mean Trough Mean AUC
  - 9.4 mcg/mL 318 +/- 111 mcg/h/mL
  - 20.4 mcg/mL 418 +/- 152 mcg/h/mL

- Lower troughs may select for resistance subpopulations (i.e., vancomycin-heteroresistant S. aureus (VWISA))
- Clinical outcomes are unclear
  - Few clinical studies
  - Potential for increased nephrotoxicity

MRSA-CNS Infections

- Treatment is poor due to the blood brain barrier

- Therapy
  - Adult Dose
  - Pediatric Dose
  - CSF Penetration
  - CSF Concentration

- IV vancomycin (Vancocin®)
  - 15 – 20 mg/kg/dose IV Q 8 – 12 H
  - 15 mg/kg/dose IV Q 6 H
  - 1 – 5 % 2 – 6 mcg/mL BII

- Linezolid (Zyvox®)
  - 600 mg PO/IV BID
  - 10 mg/kg/dose PO/IV Q 8 H
  - 66% Peak 7 – 10 mcg/mL
    - Trough 2.5 – 6 mcg/mL

- TMP-SMX (Bactrim™)
  - 5 mg/kg/dose PO/IV Q 8 – 12 H
  - ND
  - TMP 11 – 10 mcg/mL
    - SMX 17 – 65 mcg/mL
    - ND 0.5 – 1.24 mcg/mL BIII
Vancomycin Susceptibility Testing

- There is a considerable variability in MIC results depending on the method used
- Acceptable variability for MIC methods is +/- one doubling dilution
- For isolates with a vancomycin MIC ≤ 2 mcg/mL, the clinical response should determine the continued use of vancomycin, independent of MIC (AIII)
- For isolates with a vancomycin MIC > 2 mcg/mL, alternative therapy should be used (AIII)

CLSI Zone | MIC Breakpoints
----------|------------------
Susceptible | ≤ 2 mcg/mL
Intermediate | 4 – 8 mcg/mL
Resistant | ≥ 16 mcg/mL

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Vancomycin Treatment Failure – Persistent MRSA Bacteremia

- Consideration factors when contemplating change in therapy (AIII)
  - Overall clinical response, vancomycin trough concentrations, results of susceptibility testing (i.e., MIC), presence of and ability to remove other foci of infection

<table>
<thead>
<tr>
<th>Antibiotic Considerations</th>
<th>Adult Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daptomycin (Cubicin®)</td>
<td>10 mg/kg IV daily PLUS</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1 mg/kg IV Q 8 H</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg PO/IV daily or 300 – 450 mg PO/IV BID</td>
</tr>
<tr>
<td>Linezolid (Zyvox®)</td>
<td>600 mg PO/IV BID</td>
</tr>
<tr>
<td>TMP-SMX (Bactrim®)</td>
<td>5 mg/kg (TMP) IV BID</td>
</tr>
</tbody>
</table>

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Reduced Susceptibility to Vancomycin and Daptomycin?

- Quinupristin-dalfopristin 7.5 mg/kg/dose IV Q 8 H (CIII)
  - Low response rates for endocarditis and bacteremia of unknown source
- TMP-SMX 5 mg/kg/dose (TMP component) IV BID (CIII)
- Linezolid 600 mg PO/IV BID (CIII)
  - Poor outcomes for left-sided endocarditis
- Telavancin 10 mg/kg/dose IV daily (CIII)
  - A case report of persistent MRSA bacteremia successfully treated

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Role of Adjunctive Therapy – Treatment of MRSA

- Protein synthesis inhibitors (i.e., clindamycin, linezolid) and intravenous immunoglobulin (IVIG) are not routinely recommended as adjunctive therapy (AIII)
  - Limited and conflicting in vitro and animal model data
  - Some experts may consider these agents in selected scenarios (CIII)
    - Toxic shock syndrome
    - Necrotizing/cavitary pneumonia
    - Severe sepsis

Center for Disease Control – MRSA Prevention Strategies

- MRSA interventions primarily target two broad areas
  - Preventing transmission from colonized to uncolonized persons
  - Preventing infection in colonized individuals
- Core Strategies
  - High levels of scientific evidence supporting use
  - Demonstrate high levels of feasibility
- Supplemental Strategies
  - Variable scientific evidence supporting use
  - Demonstrate variable levels of feasibility

Prevention Strategies

Core Strategies
- Assessing hand hygiene practices
- Implementing contact precautions
- Recognizing previously colonized patients
- Rapidly reporting MRSA lab results
- Providing MRSA education for healthcare providers and family members

Supplemental Strategies
- Active surveillance testing
- Decolonization
- Chlorhexidine bathing in high-risk patient population

http://www.cdc.gov/mrsa/

Liu C CID 2011
For methicillin-susceptible S. aureus infections, in vitro susceptibility to an alternative to vancomycin is advisable. Vancomycin should be dosed according to actual body weight, 15–20 mg/kg/dose IV Q 8–12 H, to not exceed 2 g/dose and target trough 15–20 mcg/ml in patients with serious infections. Document in vitro susceptibility when an alternative to vancomycin is being considered.

For methicillin-susceptible S. aureus infections, a β-lactam antibiotic is the drug of choice.

For methicillin-resistant S. aureus (MRSA) infections, the management of all MRSA infections should include:

- Identification, elimination, and/or debridement of the primary source of infection and other sites of infection when possible.
- In patients with MRSA bacteremia, document clearance of bacteremia (follow-up blood cultures 2–4 days after initial positive cultures and as needed thereafter).
- Vancomycin should be dosed according to actual body weight, 15–20 mg/kg/dose IV Q 8–12 H, to not exceed 2 g/dose and target trough 15–20 mcg/ml in patients with serious infections.
- Document in vitro susceptibility when an alternative to vancomycin is being considered.
- For methicillin-susceptible S. aureus infections, a β-lactam antibiotic is the drug of choice.

**True or False Questions**

- The management of all MRSA infections should include identification, elimination and/or debridement of the primary source and other sites of infection when possible?
  - True
  - False

- Bactericidal agents should not be used in children less than 8 years of age?
  - True
  - False

- To optimize serum trough concentrations in adult patients, vancomycin should be dosed according to ideal body weight (15–20 mg/kg/dose)?
  - True
  - False

**References**

Goals and Objectives

- Review new medications recently approved by the FDA
- Describe their clinical indications, dosages, and adverse effects
- Discuss safety and monitoring information

**Acute Coronary Syndrome (ACS)**

**Class/Indication**
- Antiplatelet
- Prevention of cardiovascular events for patients with ACS (combined with aspirin)

**Brilinta® (ticagrelor)**

**Dosage**
- Loading dose of 180 mg with maintenance dose of 90 mg twice daily
- Aspirin loading dose (usually 325 mg) with maintenance aspirin dose of 75-100 mg daily (maximum)

**MOA**
- Reversibly binds to adenosine diphosphate receptors

**Special Considerations**
- PLATO study: for every 1000 patients treated for up to one year, it prevents 11 more CV deaths, 11 more heart attacks, and at least six more stent thromboses compared to Plavix
- Faster onset but short duration of action
- Discontinue 5 days before surgery

**AEs**
- Bleeding (4.5-8.7%), dyspnea (13.8%), headache (6.5%), cough (4.9%), dizziness (4.5%), nausea (6.3%), non-cardiac chest pain (3.7%), and diarrhea (3.7%)

**Anticoagulation**

**Class/Indication**
- Anticoagulant
- Prevention of DVT and PE following hip or knee replacement surgery; reduce risk of stroke/systemic embolism in nonvalvular atrial fibrillation
**Xarelto® (rivaroxaban)**

**Dosage and Dose Adjustments**
- 10 mg, 15 mg, 20 mg tablets
- DVT prophylaxis:
  - 10 mg daily starting six to ten hours post-op; continued for 12 days for knee replacement
  - 10 mg daily starting six to ten hours post-op; continued for 35 days for hip replacement
- Caution advised in CrCl 30-50 mL/min
- CrCl < 30 mL/min: avoid use
- Stroke/thromboembolism prophylaxis:
  - 20 mg daily with evening meal
  - CrCl 15-50 mL/min: 15 mg daily with evening meal
  - CrCl < 15 mL/min: avoid use

**MOA**
- Factor Xa inhibitor

**AEs**
- Bleeding (5.6%), epidural/spinal hematoma, thrombocytopenia, hypersensitivity reaction

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**Chronic Obstructive Pulmonary Disease (COPD)**

**Class/Indication**
- Beta-2 adrenergic agonist
- Maintenance treatment of airflow obstruction in patients with COPD to include chronic bronchitis and/or emphysema

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**Arcapta Neohaler® (indacaterol)**

**Dosage**
- 75 mcg inhalation capsule
- Once daily oral inhalation of the contents of one capsule

**MOA**
- Actively in the lungs as a bronchodilator
- Stimulates intracellular adenyl cyclase converting ATP to cAMP
- Increased cAMP levels causes relaxation of bronchial smooth muscles

**AEs**
- Cough (6.5% - 24%), nasopharyngitis (5.3%), headache (5.1%), paradoxical bronchospams

**Dis**
- Exercise extreme caution when used with drugs that cause QT prolongation, e.g., tricyclic antidepressants
- Exercise extreme caution when used with MAOIs which may result in increased risk of tachycardia, agitation, or hypomania
- Concurrent use with beta-blocker(s) may interfere with the efficacy of either agent

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**Daliresp® (roflumilast)**

**Class/Indication**
- Phosphodiesterase inhibitor
- Reduce risk of COPD exacerbations in severe COPD associated with chronic bronchitis

**Dosage**
- 500 mcg once daily

**MOA**
- Exact mechanism unknown, selectively inhibits PDE4 leading to increased intracellular cAMP in lung cells

**AEs**
- Diarrhea (9.5%), weight decrease (7.5%), nausea (4.7%), headache (4.4%), back pain (3.2%), influenza (2.8%), insomnia (2.4%), dizziness (2.1%), decreased appetite (2.1%), abdominal pain (1%-2%), and suicidal thoughts
**Daliresp® (roflumilast)**

- Concomitant use with strong CYP450 inducers is not recommended (e.g. rifampin, phenobarbital, carbamazepine, phenytoin).
- Metabolized by CYP3A4 and 1A2; use caution with these enzyme inhibitors.

- **DIs**
  - Moderate to severe hepatic impairment (Child-Pugh Class B or C).

- **Monitor**
  - Weight, new or worsening depressive symptoms.

- **Cost**
  - $200 per month.

- **Special Considerations**
  - Should not be used to treat acute bronchospams.
  - Maximize bronchodilators before trying roflumilast.

**Viibryd® (vilazodone)**

- **Formulation Dosage**
  - 10 mg, 20 mg, 40 mg tablets
  - 10 mg daily X 7 days, then 20 mg daily X 7 days, then 40 mg once daily when used with strong CYP3A4 inhibitors (e.g. clarithromycin, ritonavir).

- **MOA**
  - Selectively inhibits serotonin 5-HT1A receptors.

- **AEs**
  - Diarrhea (28%), nausea (23%), dizziness (9%), dry mouth (8%), insomnia (6%), vomiting (5%), and decreased libido (male 5%, female 3%).

- **DIs**
  - Avoid use with warfarin, NSAIDs, and aspirin.
  - Avoid use with other serotonergic drugs (e.g. triptans, buspirone, tramadol, SSRIs).

- **BBW**
  - Increases suicidality risk in children, adolescents, and young adults with major depressive or psychiatric disorders.

- **CIs**
  - Do not use with or within 14 days of MAOIs.

- **Monitor**
  - Worsening of depression or unusual behavior changes.

- **Cost**
  - $150 for a 30-day supply.

- **Special Considerations**
  - Not found to be more effective for depression than fluoxetine or citalopram and causes more GI side effects.
  - Continue to recommend SNRI/SSRIs first.

**Tradjenta® (linagliptin)**

- **Class/Indication**
  - Dipeptidyl peptidase-4 (DPP-4) inhibitor
  - Type 2 diabetes mellitus in adults as an adjunct to diet and exercise.

- **Dosage**
  - 5 mg once daily.

- **MOA**
  - Inhibits DPP-4, resulting in increased active levels of incretin hormones, increasing insulin synthesis/release, and decreasing glucagon levels.

- **AEs**
  - Hypoglycemia (monotherapy 7.6%, combination therapy 22.9%), nasopharyngitis (4.3%-5.8%), pancreatitis, hypersensitivity reaction.

- **DIs**
  - Avoid use with rifampin or other drugs that induce P-glycoprotein or CYP3A4.
**Tradjenta® (linagliptin)**

<table>
<thead>
<tr>
<th>CI(s)</th>
<th>Hypersensitivity to linagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor</td>
<td>Blood glucose levels and HbA1c periodically</td>
</tr>
<tr>
<td>Cost</td>
<td>$8 per tablet</td>
</tr>
<tr>
<td>Special Considerations</td>
<td>- Not to be used as initial choice as monotherapy, only lowers A1C by about 0.7%</td>
</tr>
<tr>
<td></td>
<td>- No dosage adjustment required in renally impaired patients</td>
</tr>
</tbody>
</table>

**Head Lice**

**Class/Indication**
- Pediculicide
- Treatment of head lice (pediculosis capitis) infestation in patients > 4 years

**Natroba® (spinosad)**

**Formulation**
- 0.9% topical suspension

**Dosage**
- Apply sufficient amount (max of 120 mL); may repeat application in seven days if live lice are present

**MOA**
Derived from the fermentation of a bacteria found in soil, *Saccharopolyspora spinosa*; causes neuronal excitation, leading to lice paralysis and death

**AEs**
Application site erythema (3%), ocular erythema (2%), irritation (1%)

**DIs**
Studies were not performed

**Natroba® (spinosad)**

<table>
<thead>
<tr>
<th>CI(s)</th>
<th>None identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>$220 per bottle (120 mL) compared to $10-$20 for Nix</td>
</tr>
<tr>
<td>Special Considerations</td>
<td>- Continue to recommend over the counter products of permethrin or pyrethrins as first-line agents; they are typically effective and inexpensive</td>
</tr>
<tr>
<td></td>
<td>- Ovicidal activity, allows for single application in most cases</td>
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<tr>
<td></td>
<td>- Recommend spinosad in areas where resistance is problematic</td>
</tr>
<tr>
<td></td>
<td>- Disadvantages: requires prescription, no generic formulation, only approved for children four years and older</td>
</tr>
</tbody>
</table>

**Hepatitis C**

**Class/Indication**
- Protease inhibitor
- Chronic hepatitis C, genotype 1 and compensated liver disease in combination with peginterferon-alfa and ribavirin

**Incivek® (telaprevir)**

**Formulation**
- 375 mg tablets
- 750 mg three times daily (every 7-9 hours)

**Dosage**
- with food for 12 weeks
- plus peginterferon-alfa and ribavirin
- Discontinue if HCV RNA levels > 1000 units/mL at week 4 or 12
- Avoid use in Child Pugh B or C hepatic impairment

**MOA**
Inhibits replication of HCV in host cells by binding to active site of HCV protease

**AEs**
Increased uric acid levels (73%), rash (36%), fatigue (52%), pruritus (47%), nausea (39%), anemia (36%)
Incivek® (telaprevir)\textsuperscript{5,13,14}

**Dis**
- CYP3A substrate and strong inhibitor, p-glycoprotein substrate and inhibitor
- Contraindicated: alfuzosin, atorvastatin, simvastatin, cisapride, ergots, lovastatin, oral midazolam, pimozide, rifampin, sildenafil (Revatio), St. John's wort, tadalafil (Adcirca), triazolam

**Cls**
- Pregnant women and men whose female partners are pregnant
- Co-administration with drugs discussed in drug interactions section

**Monitor**
Hgb at baseline; CBC w/ diff, Cr, LFT, TSH, electrolytes, and uric acid at weeks 2, 4, 8, and 12

**Cost**
$26,500 - $45,000 for a course of treatment

**Special Considerations**
Recommended by AASLD (combined w/ peginterferon alfa and ribavirin) as optimal therapy for HCV infection genotype 1

AASLD: American Association for the Study of Liver Diseases

Victrelis® (boceprevir)\textsuperscript{5,15}

**Formulation**
- 200 mg capsules

**Dosage**
- 800 mg three times daily (every 7-9 hours) with food starting on week five of peginterferon plus ribavirin
  - Cirrhotic patients: treatment is continued for 44 more weeks (48 weeks total treatment duration)
  - Non-cirrhotic patients: total treatment duration is 28 - 48 weeks, depending on viral response and response history

**AEs**
- Fatigue (51%-58%), anemia (45%-50%), nausea (43%-46%), diarrhea (35%-44%)

**Dis**
- CYP3A substrate and strong inhibitor; p-gp substrate/inhibitor
- Contraindicated: alfuzosin, atorvastatin, cisapride, drospirenone, ergots, lovastatin, oral midazolam, pimozide, phenobarbital, phenytoin, rifampin, sildenafil (Revatio), simvastatin, St. John's wort, tadalafil (Adcirca), triazolam

Some Cl, monitoring, and cost data as incivek

Human Immunodeficiency Virus (HIV)

**Class/Indication**
- Antiviral agent
- HIV (treatment naive patients)

Edurant® (rilpivirine)\textsuperscript{5,19}

**Dosage**
- 25 mg once daily with a meal

**MOA**
A non-nucleoside reverse transcriptase inhibitor (NNRTI) and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase

**Moderate Intensity (≥ grade 2) AEs**
- Nausea, abdominal pain, vomiting, fatigue, headache, dizziness, depressive disorders, insomnia, abnormal dreams, rash, increased LFTs, increased LDL and serum cholesterol levels

**Dis**
Numerous; metabolized mainly by CYP3A

Edurant® (rilpivirine)\textsuperscript{5,19}

**Cls**
Concomitant administration with anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin; antimycobacterials rifabutin, rifampin, rifapentine; proton pump inhibitors; more than a single dose of systemic dexamethasone; and St. John's wort

**Monitor**
↑ in CD4+ cell count and ↓ in HIV-1 RNA copies; ↑ adverse effects in patients with severe renal impairment or ESRD

**Cost**
$324 per tablet

**Special Considerations**
Recommended as an alternative NNRTI when used as part of Dual ART in treatment naive, non-pregnant adult with HIV

Hypertension

**Class/Indication**
- Angiotensin Receptor Blocker (ARB)
- HTN
Edarbi® (azilsartan)\(^5,16\)

- **Formulation:** 40 mg, 80 mg tablets
- **Dosage:**
  - 80 mg once daily
- **Dose adjustment:** 40 mg once daily if on high dose diuretics
- **AEs:** Diarrhea, renal failure
- **Dis:** NSAIDs
- **BBW:** Discontinue as soon as possible once pregnancy is detected; fetal/neonatal morbidity and mortality may occur
- **Monitor:** BUN/Cr at baseline, then periodically; blood pressure
- **Cost:** $90 per month
- **Special Considerations:** Only approved for HTN, no evidence of improved cardiovascular outcomes compared to other ARBs

Horizant® (gabapentin enacarbil)\(^5,17\)

- **Indication:** Treatment of moderate to severe restless leg syndrome (RLS)
- **Dosage:**
  - 600 mg extended release tablet once daily with food at 5 pm
  - CrCl 30-59 mL/min: 600 mg x1 on day 1 and 3, then 600 mg daily
  - CrCl <30 mL/min: do not administer
- **MOA:** Prodrug of gabapentin; exact mechanism of action in RLS is unknown
- **AEs:** Somnolence (20%-27%), dizziness (13%-22%), headache (12%-15%), suicidal thoughts
- **Dis:** None identified
- **CI:** Hypersensitivity to drug
- **Monitor:** CR at baseline; signs/symptoms of depression, unusual behavior or mood changes, suicidality
- **Cost:** $120 per month
- **Special Considerations:** Not interchangeable with plain gabapentin
- Doses >600 mg/day:
  - Recommend taking half the dose in the late afternoon and the remainder up to 2 hours before bedtime
  - Discontinuation:
    - Patients receiving dose of 600 mg once daily can be discontinued without tapering
    - Patients receiving doses >600 mg daily:
      - Reduce dose to 600 mg once daily for 1 week prior to discontinuation to minimize the potential of withdrawal seizures
- Geriatric patients:
  - Known CYP2C19 poor metabolizers
  - Mild or moderate hepatic impairment
- **MOA:** Not fully understood, may bind to GABA\(_\text{A}\) receptor and potentiate neurotransmission

Horizant® (gabapentin enacarbil)\(^5,17\)

- **Class/Indication:** Benzodiazepine/adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older
- **Formulation:** 5 mg, 10 mg, 20 mg tablets
- **Dosage:**
  - Patients ≤30 kg body weight: start at 5 mg daily and titrate as tolerated up to 20 mg daily
  - Patients >30 kg body weight: start at 10 mg daily and titrate as tolerated up to 40 mg daily
- **Dose adjustment:** Geriatric patients:
  - Known CYP2C19 poor metabolizers
- **MOA:** Not fully understood, may bind to GABA\(_\text{A}\) receptor and potentiate neurotransmission
Onfi® (clobazam) 5,20

**AEs**
- Somnolence (16%-25%), fever (10%-17%) drooling (up to 14%), constipation (2%-10%), sedation (2%-9%), cough (2%-7%), urinary tract infection (2%-9%), aggression (1%-14%), insomnia (2%-1%), dysarthria (2%-5%), irritation of skin or mucous membranes (1%-2%)

**DXs**
- Alcohol increases the blood levels of clobazam by about 50%
- Dosage adjustment may be necessary when given with strong or moderate CYP2C9 inhibitors (e.g., fluconazole, omeprazole)
- Lower doses of some drugs metabolized by CYP2D6 may be required when used concomitantly with clobazam (e.g., tramadol)

**Monitor**
- CNS depression, unusual mood or behavior changes, suicidality

**Cost**
- $15 per tablet

**Special Considerations**
- Doses > 5 mg/day should be administered in two divided doses
- Safe and effective in reducing frequency of weekly drop seizures

Potiga® (ezogabine) 5,21

**Dis**
- Concurrent use of phenytoin or carbamazepine with ezogabine plasma levels may result in decreased ezogabine plasma levels
- Concurrent use of lamotrigine and ezogabine may result in increased lamotrigine plasma concentrations
- Concurrent use of digoxin and ezogabine may result in increased digoxin concentrations

**Clis**
- None identified

**Monitor**
- Seizure control, QIT interval, urologic symptoms, suicidality

**Special Considerations**
- Reduce the dosage gradually over a period of at least 3 weeks when discontinuing drug
- Perform comprehensive evaluation of urologic symptoms prior to and during therapy

**Class/Indication**
- Anticonvulsant/adjunctive treatment of partial-onset seizures in patients aged 18 years and older

**Formulation**
- 50 mg, 200 mg, 300 mg, and 400 mg tablets
- Administer in three divided doses daily

**Dosage**
- Start at 100 mg TID for 1 week. ↓ dose by no more than 150 mg/day at 1 week intervals
- Maintenance dose of 200 to 400 mg TID

**Special Considerations**
- Dosing adjustments are required for geriatric patients and patients with moderate to severe renal or hepatic impairment

**MOA**
- Potassium channel opener, stabilizes the resting membrane potential and reduce brain excitability

**AEs**
- Dizziness (15%-32%), somnolence (13%-27%), fatigue (13%-16%), confusion (4%-16%), tremor (3%-12%), incoordination (1%-14%), vertigo (6%), blurred vision (2%-10%), memory impairment (3%-9%), diplopia (6%-8%), urinary retention, prolonged QT interval

Case Studies

**Case 1:** 75 yo female describes to the pharmacist her home medications for reconciliation. She describes that she takes a 15 mg pill with her evening meals for “heart problems." She has a calculated CrCl of 40 ml/min

**Case 2:** A doctor might write for this drug in a 65 yo male patient in addition to Lamictal 250 mg bid, unless the patient has BP...

**Case 3:** 55 yo male w/ a PMH of CAD, Hyperlipidemia and HTN who smokes 3ppd had a poorly written order for 900mg po bid and Aspirin 81mg po daily

**Answer Choices:**
- a. Onfi (clobazam)
- b. Xarelto (rivaroxaban)
- c. Potiga (ezogabine)
- d. Brilinta (ticagrelor)

True/False Test Questions

1. Horizant (gabapentin enacarbil) is an immediate release form of gabapentin
   - Answer: False, Horizant is an extended release form of gabapentin

2. Tradjenta (linagliptin) does not require renal dose adjustment
   - Answer: True

3. Onfi (clobazam) is an oral benzodiazepine use to treat patients with Lennox-Gastaut syndrome
   - Answer: True

References

**Clostridium difficile Infection: A Review of Pharmacologic and Non-Pharmacologic Treatment Options**

Yesenia Camero, Pharm.D.
PGY-1 Pharmacy Practice Resident
Baptist Hospital of Miami

**Objectives**

- Compare and contrast available pharmacotherapeutic options for *Clostridium difficile* infection (CDI)
- Discuss the role of fidaxomicin in the treatment of CDI
- Formulate the most suitable treatment regimen based on patient specific parameters
- Describe various infection control strategies to prevent CDI

**Outline**

- Definition
- Epidemiology
- Etiology
- Risk Factors
- Pathophysiology
- Clinical Presentation
- Diagnosis
- Treatment
- Prevention
- Role of the Pharmacist

**Definition**

Presence of diarrhea (3 or more unformed stools in ≤ 24 hours) and
Positive stool test result for *C. difficile* toxins or
Evidence of pseudomembranous colitis

**Epidemiology**

- Twenty to 30% of antibiotic-associated diarrhea
- Leading cause of infectious diarrhea in healthcare settings
- Recurrent CDI in ~20% of patients
- Increased incidence and virulence since 2001
  - Hypervirulent NAP1/BI/027 epidemic strain associated with increased fluoroquinolone use

**Etiology**

- *Clostridium difficile*
  - Anaerobic gram-positive rod
  - Spore-forming
    - Vegetative vs spore
  - Toxin-producing
    - Toxin A
    - Toxin B
    - Binary toxin?
Risk Factors
- Advanced age
- Exposure to antimicrobials
- Length of hospitalization
- Severe or multiple underlying diseases
- Cancer chemotherapy
- Gastrointestinal manipulation
- Acid-suppressing agents
- Low serum IgG anti-toxin A concentrations

Rates of CDI Among Hospitalized Patients > 65 years

Pathophysiology
- Disruption of normal bacterial flora of colon
- C. difficile exposure and colonization
- Release of toxins
- Mucosal damage and inflammation
- Diarrhea

Clinical Presentation
- Asymptomatic
- Mild to moderate diarrhea
- Fever, cramping, abdominal discomfort
- Leukocytosis and occult colonic bleeding
- Pseudomembranous colitis
- Fulminant colitis
- Toxic megacolon
- Hypotension, sepsis, death

Classification of CDI

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Supportive data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to Moderate</td>
<td>WBC &lt; 15,000 cells/mL, SCr &lt; 1.5x baseline level</td>
</tr>
<tr>
<td>Severe</td>
<td>WBC &gt; 15,000 cells/mL, SCr &gt; 1.5x baseline level</td>
</tr>
<tr>
<td>Severe Complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
</tr>
</tbody>
</table>

Risk Factors
- Low serum antibody response to Toxin A
- Severe underlying disease

Protective Factors
- High serum antibody response to Toxin A
- Mild underlying disease

Low Risk Medium Risk High Risk
- Aminoglycosides
- Aminopenicillins
- Clindamycin
- Vancomycin
- Macrolides
- Cephalosporins
- Metronidazole
- Tetracyclines
- Rifampin
- Fluoroquinolones*
- Antipseudomonal penicillins
- Trimethoprim/sulfamethoxazole

*Now may be high risk due to resistance of NAP1/B1 strain
Diagnosis
- Toxin testing
  - Cell cytotoxin assay
  - Enzyme immunoassay (EIA)
- Organism identification
  - Stool culture
  - EIA for detection of glutamate dehydrogenase
- Visualization of colon
  - Sigmoidoscopy
  - Colonoscopy


Treatment
General Principles
- Discontinue inciting antibiotic when possible
- Implement infection control strategies
- Avoid antimotility agents
- Initiate supportive care
- Consider surgical intervention in severe cases
- Administer antibiotics for 10 – 14 days


Guideline Recommendations

<table>
<thead>
<tr>
<th>Episode</th>
<th>Severity</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Episode</td>
<td>Mild to Moderate</td>
<td>Metronidazole 500 mg PO q8h</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Vancomycin 125 mg PO q6h</td>
</tr>
<tr>
<td></td>
<td>Severe Complicated</td>
<td>Vancomycin 500 mg PO/NG q6h + Metronidazole 500 mg IV q8h + Vancomycin rectal instillation</td>
</tr>
<tr>
<td>Second Episode (1st recurrence)</td>
<td></td>
<td>Same as for initial episode</td>
</tr>
<tr>
<td>Third Episode (2nd recurrence)</td>
<td></td>
<td>Vancomycin tapered/pulsed regimen 125 mg PO q6h for 10 – 14 days 125 mg PO q12h for 7 days 125 mg PO daily for 7 days 125 mg PO every 3 days for 2 – 8 weeks</td>
</tr>
</tbody>
</table>


Standard Treatment Comparison

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin</th>
<th>Metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>PO</td>
<td>PO and IV</td>
</tr>
<tr>
<td>Cost</td>
<td>$$$</td>
<td>$</td>
</tr>
<tr>
<td>Fecal concentration</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nausea/vomiting Bitter taste Fever, chills</td>
<td>Nausea Metallic taste Disulfiram reaction w/ alcohol Discoloration of urine Neurotoxicity (long-term use)</td>
</tr>
</tbody>
</table>


Alternative Therapies
- Antimicrobials
  - Fidaxomicin (Dificid®)
  - Rifamixin (Xifaxan®)
  - Nitazoxanide (Alinia®)
  - Tigecycline (Tygacil®)
- Probiotics
- Anion-binding resins
- Cholestryramine
- Colestipol
- Intravenous immunoglobulin

Fidaxomicin (Dificid®)
- Classification
  - Narrow spectrum macrolide
- FDA approved indication
  - Treatment of CDI in patients ≥ 18 years old
  - Dose: 200 mg PO BID for 10 days
- Mechanism of action
  - Inhibits RNA polymerase resulting in inhibition of protein synthesis and cell death
  - Bactericidal against C. difficile
- Pharmacokinetics
  - Minimal systemic absorption
  - Intestinal hydrolysis to active metabolite OP-111B

Fidaxomicin (Dificid®)

- Drug interactions
  - P-glycoprotein inhibitors may increase fidaxomicin serum concentrations → no dosage adjustment required
- Adverse effects
  - Nausea (11%)
  - Vomiting (7%)
  - Abdominal pain (6%)
  - Gastrointestinal hemorrhage (4%)
  - Anemia (2%)
  - Neutropenia (2%)

Clinical Trial Background

<table>
<thead>
<tr>
<th>Objective</th>
<th>To compare the efficacy and safety of fidaxomicin with vancomycin in the treatment of CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective, multicenter, randomized, double-blind, non-inferiority, phase 3 trials</td>
</tr>
<tr>
<td>Intervention</td>
<td>Fidaxomicin 200 mg PO twice daily for 10 days versus Vancomycin 125 mg PO four times daily for 10 days</td>
</tr>
<tr>
<td>Participants</td>
<td>Adults ≥ 16 yo, 37% with severe CDI, 84% with first episode</td>
</tr>
</tbody>
</table>

Intervention

- Primary
- Secondary
- Recurrence of infection
- Global cure
- Safety

Outcomes

Safety

- Physical exam, laboratory data, adverse events

Economic Considerations

- Cost of therapy
  - Fidaxomicin (10-day course): $2800
  - Vancomycin (10-day course): ~ $1300
  - Reconstituted injectable solution: < $60

- Healthcare costs associated with CDI
  - Primary episode: $2,871 - $4,846
  - Recurrent episode: $13,655 - $18,067

Place in therapy

- Potential cases for use
  - High-risk patients
  - Patients with recurrent episodes

Fidaxomicin vs Vancomycin

Study conclusions

- Similar efficacy in clinical cure
- Lower recurrence rate
- Higher global cure rate
- Similar safety profile

Key points

- Majority of patients had mild-to-moderate CDI
- No comparison with metronidazole
- Recurrence rate was a secondary endpoint → unable to draw definite conclusions

Does the high cost of recurrent CDI justify the use of fidaxomicin?
**Rifaximin (Xifaxan®)**
- Analog of rifampin with minimal systemic absorption
- Off-label for CDI
- May be effective as a “chaser” following treatment with vancomycin for recurrent infection
- Concerns for resistance
- Dose: 400 – 800 mg/day
- Cost of therapy: ~$250 - $300

**Nitazoxanide (Alinia®)**
- Thiazole compound with antibacterial, antiviral and antiparasitic activity
- Off-label for CDI
- Similar clinical efficacy compared to metronidazole and vancomycin
- Potential role as salvage therapy for refractory or recurrent CDI
- Dose: 500 mg PO BID x 10 days
- Cost of therapy: ~$450

**Tigecycline (Tygacil®)**
- Glycyclcline antibiotic
- Off-label for CDI
- Effective for severe, refractory CDI in a small case series of four patients with complicated infection
- Dose: 100 mg IV x 1, then 50 mg IV q12h
- Cost of therapy: ~$1500

**Probiotics**
- Live, non-pathogenic bacteria
- Therapeutic mechanisms
  - Alteration of intestinal flora
  - Intestinal barrier protection
  - Immunomodulation
- Inconsistent evidence for efficacy in CDI
- **Saccharomyces boulardii**: effective for recurrent CDI
- Safety concerns
  - Bacteremia: *Lactobacillus rhamnosus*
  - Fungemia: *Saccharomyces boulardii*

**Probiotic Product Regimen Notes**
- **Saccharomyces boulardii**: Florastor® 500 mg BID x 28 days
- With vancomycin 500 mg PO QID x 10 days
- **Lactobacillus rhamnosus**: Culturelle® 1-2 caps daily x 7-10 days

**Probiotic**
- **Treatment of Recurrent CDI**

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Product</th>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Saccharomyces boulardii</em></td>
<td>Florastor®</td>
<td>500 mg bid x 28 days</td>
<td>With vancomycin 500 mg PO QID x 10 days</td>
</tr>
<tr>
<td><em>Lactobacillus rhamnosus</em></td>
<td>Culturelle®</td>
<td>1-2 caps daily</td>
<td>x 7-10 days</td>
</tr>
</tbody>
</table>

**Prevention of CDI**

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Product</th>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lactobacillus acidophilus</em></td>
<td>Caps (from UK)</td>
<td>1 cap daily x 20 days</td>
<td>Initiate within 36h of antibiotic</td>
</tr>
<tr>
<td><em>Bifidobacterium bifidum</em></td>
<td></td>
<td>100g bid 30 min before meals or 1-2h after meals</td>
<td>Initiate within 48h of antibiotic, continue for 1 wk after completion</td>
</tr>
<tr>
<td><em>Lactobacillus casei</em></td>
<td>Actimel® yogurt</td>
<td>drink</td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus bulgaris</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus thermophilus</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Emerging Therapies**
- Tolevamer
- Ramoplanin
- Fecal Bacteriotherapy
- Monoclonal antibodies
- *C. difficile* vaccine
**Prevention**

- Hand Hygiene
- Contact precautions
- Isolation of infected patients
- Environmental cleaning and disinfection
- Antimicrobial stewardship

**Role of the Pharmacist**

- Educate patients and healthcare workers
- Recommend appropriate antibiotic treatment regimens for CDI
- Counsel patients about drug therapy
- Streamline antimicrobial therapy through antimicrobial stewardship programs

**Frequently Asked Questions**

- When to seek medical attention?
  - Recent antimicrobial use accompanied by severe abdominal pain, multiple episodes of watery diarrhea per day, blood or pus in stool, signs of dehydration
- How can I prevent spreading C. difficile to family or household members?
  - Wash hands with soap and water after using the bathroom and before eating
  - Dry hands with paper towels instead of cloth towels
  - Disinfect bathroom surfaces using bleach (1:10 dilution)
  - Use detergent and bleach to wash clothes
- What else can I do to help my symptoms?
  - Drink lots of fluids
  - Eat starchy foods as tolerated
  - Avoid lactose-containing products

**Patient Case**

- MD is a 52 yo female who was receiving levofloxacin for treatment of an intra-abdominal infection. Following completion of therapy she began to complain of abdominal pain and diarrhea. Her home medications include lisinopril 10 mg PO daily, omeprazole 20 mg PO daily, and simvastatin 20 mg PO HS. Her current vitals and lab values are: T: 101°F, BP: 110/72 mmHg, WBC: 11,500 cells/mm³, Scr: 0.9 mg/dL, C. diff toxin +

- What risk factors does MD have for CDI?
  - Omeprazole use, recent antibiotic use
- What treatment would you recommend for MD?
  - Metronidazole 500 mg PO q8hrs
- How long would you treat MD?
  - 10 – 14 days

**True or False?**

- Using soap and water has proven to be more effective than alcohol-based hand rubs in reducing the risk of transmitting C. difficile infection. True
- The clinical trials for fidaxomicin showed superiority for fidaxomicin when compared to vancomycin for the primary endpoint of clinical cure rate. False
- The efficacy of probiotics has been proven in controlled clinical trials. False
Atrial Fibrillation and Prevention of Thrombotic Complications: Therapeutic Update

Andrea C. Flores Pharm.D
Pharmacy Resident at the Miami VA Healthcare System

Objectives
- Review the epidemiology, pathophysiology and complications of Atrial Fibrillation (AF)
- Identify anticoagulation therapy in AF
- Explain new anticoagulant agents
  - Outline current literature supporting the role of new anticoagulant agents in the prevention and treatment of thromboembolic disorders
  - Differentiate new anticoagulant agents with respect to their pharmacokinetics, pharmacodynamics, and recommended dosing strategies

Epidemiology of Atrial Fibrillation (AF)
- Most common arrhythmia in the U.S.
- Affects men more than women
- Incidence and prevalence increase with age
- Lifetime risk of AF in patients >40 yr ~25%

Stroke in AF
- Stroke is the most common and devastating complication of AF
- Incidence of all-cause stroke in patients with AF is 5%
- AF is an independent risk factor for stroke
- Approximately 15% of all strokes in the U.S. are caused by AF
- Stroke risk persists even in asymptomatic AF

Pathophysiology of Stroke in AF: Role of Virchow’s Triad

- Abnormal blood stasis
  - Blood pools in the left atria
  - Due to loss of organized atrial contraction and atrial dilation

- Hypercoagulable state
  - Increase concentration of prothrombotic factors

- Endothelial/Endocardial injury
  - Structural changes occur in the atria

Stroke Risk Stratification in AF

CHADS2 score
- Congestive heart failure = 1 point
- Hypertension = 1 point
- Age ≥75 years = 1 point
- Diabetes = 1 point
- Stroke/TIA = 2 points
CHADS2 Score and Risk

Adjusted Stroke Rate per 100 patient years

<table>
<thead>
<tr>
<th>Score</th>
<th>Number of patients</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>1.9(1.2 – 3)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>2.8(2 – 3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>3.0(3.1 – 5.1)</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>5.9(4.6 – 7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>8.5(6.3 – 11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>12.5(8.2 – 17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>18.2(10.5 – 27.4)</td>
</tr>
</tbody>
</table>

Oral Anticoagulation

Warfarin

- Main agent for prevention and treatment of thromboembolic disease > 50 years
- Challenges still exist in determining optimal and safest dose
- Associated with adverse events
- Bleeding

Ideal Anticoagulant

- Fast onset of action, allows post-procedure use
- Fast resolution of actions, allows pre-procedure use
- No routine blood monitoring
- No drug interactions
- No interactions with diet
- Fixed doses
- Predictable dose response
- Safe in pregnancy
- Immediate reversibility

New and Emergent Oral Anticoagulants

<table>
<thead>
<tr>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand Name</td>
<td>Pradax®</td>
<td>Xarelto®</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Direct IIa inhibitor</td>
<td>Direct Xa inhibitor</td>
</tr>
<tr>
<td>Approval Status</td>
<td>• 2008: approved in Eur/Can for VTE px in ortho surgery</td>
<td>• 2008: approved in Eur/Can for VTE px in ortho surgery</td>
</tr>
<tr>
<td>Approval Status</td>
<td>• 10/2010: approved by FDA for stroke prevention in AF</td>
<td>• 7/2011: approved by FDA for VTE px in ortho surgery</td>
</tr>
</tbody>
</table>

RE-LY Trial

- Dabigatran Etexilate vs. Warfarin (INR 2-3) in AF
- Randomized open label
  - N = 18,113 patients (mean CHADS: 2.1)
  - Non-inferiority design
  - 64% time in range to warfarin
- Drug and dose: Dabigatran 150mg and 110 mg BID
### RE-LY Trial

- Primary Outcome: Stroke or systemic embolism
  - Warfarin vs. Dabigatran 150mg
    - 1.69 vs. 1.11, p < 0.001
  - Warfarin vs. Dabigatran 110mg
    - 1.69 vs. 1.53, p < 0.001
- Dabigatran 150 mg is NON-INFERIOR and possibly SUPERIOR to warfarin
- Dabigatran 110 mg is NON-INFERIOR to warfarin

### RE-LY Trial

- Major bleeding (%/year):
  - Warfarin vs. Dabigatran 150mg
    - 3.36 vs. 3.11, p = 0.31
- Intracranial bleeding (%/year)
  - Warfarin vs. Dabigatran 150mg
    - 0.74 vs. 0.30, p < 0.001

### ROCKET- AF Trial

- Rivaroxaban vs. Warfarin (INR 2-3) in AF
- Randomized double blind
  - N = 14,171 patients (mean CHADS: 3.5)
  - Non-inferiority design
  - 58% time in range for warfarin
- Drug and dose: Rivaroxaban 20 mg daily
  - If CrCl 30-49 ml/min: 15mg daily

### ROCKET- AF Trial

- Primary endpoint: Stroke of systemic embolism
  - Warfarin vs. rivaroxaban:
    - 2.42 vs. 2.12, p = 0.12
- Major bleeding:
  - Warfarin vs. rivaroxaban:
    - 3.45 vs. 3.6, p = 0.58
- Rivaroxaban is non-inferior to warfarin

### ARISTOTLE Trial

- Apixaban vs. warfarin (INR 2-3)
- Randomized double blind, placebo controlled
  - N = 18,201 (mean CHADS: 2.1)
  - Non-inferiority design
  - 66% time in range to warfarin
- Drug and dose: Apixaban 5 mg BID
  - If 2 of: age >80, wt <60 kg or SrCr>1.5: 2.5 mg BID

### ARISTOTLE Trial

- Primary efficacy endpoint: Stroke or systemic embolism
  - Warfarin vs. apixaban
    - 1.60 vs. 1.27, p < 0.001 for noninferiority and P = 0.01 for superiority
- Major bleeding:
  - Warfarin vs. Apixaban
    - 3.09 vs. 2.13, p < 0.001
- Apixaban was possibly superior to warfarin in preventing stroke or systemic embolism
AVERROES Trial

- Apixaban vs. aspirin (81-324 mg)
- Randomized, double blind, placebo controlled
  - N = 5,599 (CHADS ≥1)
  - Failed or unsuitable for warfarin therapy
- Superiority design
- Drug and dose: Apixaban 5 mg BID
  - If 2 of: age >80, wt <60 kg or SrCr>1.5: 2.5 mg BID

Warfarin Comparison Trials in AF

<table>
<thead>
<tr>
<th>Trial</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dabigatran 150 mg BID</td>
<td>Rivaroxaban 20 mg daily</td>
<td>Apixaban 5 mg BID</td>
</tr>
<tr>
<td>Efficacy vs. Warfarin</td>
<td>1.69 vs. 1.11 p &lt; 0.001</td>
<td>2.42 vs. 2.12 p = 0.12</td>
<td>1.60 vs. 1.27 p &lt; 0.001</td>
</tr>
<tr>
<td>Major Bleeding %</td>
<td>3.36 vs. 3.11 p = 0.31</td>
<td>3.45 vs. 3.6 p = 0.58</td>
<td>3.09 vs. 2.13 p &lt; 0.001</td>
</tr>
<tr>
<td>ICH %</td>
<td>0.74 vs. 0.30 p &lt; 0.001</td>
<td>0.74 vs. 0.49 p = 0.619</td>
<td>0.47 vs. 0.24 p &lt; 0.001</td>
</tr>
<tr>
<td>Summary</td>
<td>Possibly superior efficacy</td>
<td>Non-inferior on efficacy and safety measures</td>
<td>Possibly superior efficacy</td>
</tr>
<tr>
<td></td>
<td>Similar bleeding</td>
<td>Less ICH</td>
<td>Less major and ICH</td>
</tr>
<tr>
<td></td>
<td>Less ICH</td>
<td>Lower mortality</td>
<td></td>
</tr>
</tbody>
</table>

2011 ACCF/AHA/HRS Guidelines

Dabigatran given a Class I (LOE B) recommendation

- Dabigatran is useful as an alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have the following:
  - Prosthetic heart valve or hemodynamically significant valve disease
  - CrCl <15 mL/min
  - Advanced liver disease

2011 ACCF/AHA/HRS Guidelines

Patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran because of dabigatran’s:
- Twice-daily dosing
- Greater risk of nonhemorrhagic side effects

2011 ACCF/AHA/HRS Guidelines

Selection of patients with AF and ≥1 additional risk factor for stroke who could benefit from treatment with dabigatran as opposed to warfarin should consider individual factors, including:
- Ability to comply with twice-daily dosing
- Availability of an anticoagulation management program to sustain routine monitoring of INR
- Patient preferences
- Cost
- Other factors
Pharmacology of Novel Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor IIa (reversibly binds to site)</td>
<td>Factor Xa (reversibly binds to site)</td>
<td>Factor Xa (reversibly binds to site)</td>
</tr>
<tr>
<td><strong>Dosage Form (mg)</strong></td>
<td>Capsule (75, 150)</td>
<td>Tablet (10, 15, 20)</td>
<td>Tablet</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6%</td>
<td>60-80%</td>
<td>50-85%</td>
</tr>
<tr>
<td><strong>Time to peak</strong></td>
<td>1-2 hours</td>
<td>2-4 hours</td>
<td>1-3 hours</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Conjugation; NO CYP involvement</td>
<td>Oxidation (via CYP3A4 &amp; CYP2J2) + hydrolysis</td>
<td>Oxidation (via CYP3A4) + conjugation</td>
</tr>
<tr>
<td><strong>Renal Excretion</strong></td>
<td>80%</td>
<td>66%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Half-Life</strong></td>
<td>14-17 hours</td>
<td>9-13 hours</td>
<td>9-14 hours</td>
</tr>
<tr>
<td><strong>Dosing frequency, major Trials</strong></td>
<td>BID</td>
<td>Daily</td>
<td>BID</td>
</tr>
</tbody>
</table>

New Anticoagulants Renal Dosing

- **Dabigatran**
  - CrCl > 30 ml/min: 150 mg po BID
  - CrCl 15-29 ml/min: 75mg po BID
  - CrCl < 15 ml/min: not recommended

- **Rivaroxaban**
  - CrCl ≥ 30 ml/min: 20 mg po daily
  - CrCl 30-49 ml/min: 15 mg po daily
  - CrCl < 30 ml/min: Excluded from ROCKET AF

- **Apixaban**
  - 5 mg po BID
  - 2.5 mg po BID for patients: ≥ 80 years old, wt ≤ 60kg or SrCr ≥ 1.5 mg/dl in ARISTOTLE (CrCl <25 ml/min: excluded)

Potential Drug Interactions New Anticoagulants

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant and antiplatelet agents</td>
<td>Increased bleeding</td>
<td>Increased bleeding</td>
<td>Increased bleeding</td>
</tr>
<tr>
<td>H2 antagonist and PPIs</td>
<td>Minimal interaction</td>
<td>No interaction</td>
<td>Likely no interaction</td>
</tr>
<tr>
<td>CYP 450 enzyme metabolism</td>
<td>No</td>
<td>Yes (3A4)</td>
<td>Yes (3A4)</td>
</tr>
<tr>
<td>P-Glycoprotein substrate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Potential Advantages of New Oral Anticoagulants

- Oral administration
- Rapid onset of action
- Predictable effect with fixed or weight-based dosing
- Less food/drug interactions
- Short half-life
- More cost effective
- Possibly superior efficacy
- Possibly superior safety

Potential Disadvantages of New Oral Anticoagulants

- Renal dose adjustment
- P-glycoprotein drug interactions
- Lack of reversibility
- Less provider face to face encounters
- Twice daily dosing vs. daily dosing with warfarin therapy

CYP 3A4 Drug Interactions

- Inducers: Carbamazepine, phenytoin, rifampin, St John's Wort
- Inhibitors: Itraconazole, ketoconazole, ritonavir

P-glycoprotein Drug Interactions:

- Inducers: St John's Wort, phenytoin, rifampin
- Inhibitors: Itraconazole, ketoconazole, dronedarone
Other factor Xa Inhibitors in Clinical Trials

- Betrixaban
  - Oral, once daily dosing
- Edoxaban
  - Oral, once daily dosing
- Idraparinux
  - Subcutaneous injection, weekly
- Darexaban
  - Oral, once or twice daily

Questions (True/False)

AF is an independent risk factor for stroke

Questions (True/False)

Dabigatran FDA – labeled indication includes postoperative deep vein thrombosis prophylaxis

Patient Case

AC is a 66 yo WM with AF and a CHADS score of 3. His baseline SrCr is 1.3, CrCl 54 ml/min. The patient has been on warfarin therapy with a history of subtherapeutic INR despite compliance to medication therapy (patient can not stop eating greens). AC is interested in starting the new medication for his heart condition that does not require monitoring.

What parameters do you need to keep in mind when recommending dabigatran to a patient?

A) Ability to comply with twice daily dosing
B) Patient preferences
C) Renal Function
D) Cost
E) All of the above

Patient Case

What parameters do you need to keep in mind when recommending dabigatran to a patient?

Conclusions

Dabigatran is a currently available alternative to warfarin for stroke prevention in AF and has been shown to be cost effective for the highest risk stroke patients (CHADS ≥3) unless there is excellent INR control
Conclusions

Rivaroxaban has been shown to be non-Inferior to warfarin for stroke prevention in AF with comparable rates of major bleeding (recently approved by FDA)

Conclusions

Apixaban has shown superiority to aspirin and warfarin for preventing stroke in AF, with a lower rate of bleeding and reduction in mortality compared to warfarin

References

- Wann LS et al. Heart Rhythm. 2011; 8:e1-e8
- Gage BF et al. JAMA. 2001;285:2864-70
Effect of β-Blockers in Treatment of Chronic Obstructive Pulmonary Disease

Wei Li Pharm.D.
PGY-1 Pharmacy Resident
Palmetto General Hospital
January 2012

Objectives

- Review β-adrenergic blockers
- Discuss the risks and benefits of β-blocker usage in COPD patients
- Discuss new studies that suggest addition of β-blockers can be beneficial in patients with COPD
- Discuss pharmacist’s role

Conundrum

Should patients with a diagnosis of chronic obstructive pulmonary disease (COPD), which is a relative contraindication to β-blocker therapy, receive a β-blocker when a strong indication exists?

- Risks vs. Benefits
- Review literature available

COPD

- Fourth leading cause of death worldwide
- Characterized by airflow limitation that is not fully reversible and usually progressive
- Diagnosis: Post-bronchodilator FEV1/FVC < 0.70 confirms the presence of airflow limitation in:
  - Dyspnea
  - Chronic cough
  - Chronic sputum production
  - History of exposure to risk factors

β-blockers

- Block the action of endogenous catecholamines on:
  - β1-adrenergic receptors: Heart and in the kidneys.
  - β2-adrenergic receptors: Mainly in the lungs, gastrointestinal tract liver, uterus, vascular smooth muscle, and skeletal muscle.
  - β3-adrenergic receptors: are located in fat cells
- Cardiac Effects
  - Decrease contractility = (negative inotropy)
  - Decrease relaxation rate = (negative lusitropy)
  - Decrease heart rate = (negative chronotropy)
  - Decrease conduction velocity = (negative dromotropy)

Management of COPD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I: Mild</td>
<td>FEV1 ≥ 80% predicted</td>
<td>Regimen A: Reduction of risk factor(s); influenza vaccination + SABA as needed</td>
</tr>
<tr>
<td>Stage II: Moderate</td>
<td>50% ≤ FEV1 &lt; 80% predicted</td>
<td>Regimen B = Regimen A + Regular treatment with one or more long-acting bronchodilators</td>
</tr>
<tr>
<td>Stage III: Severe</td>
<td>30% ≤ FEV1 &lt; 50% predicted</td>
<td>Regimen C = Regimen B + ICS if repeated exacerbations and rehabilitation</td>
</tr>
<tr>
<td>Stage IV: Very severe</td>
<td>FEV1 ≤ 30% predicted</td>
<td>Regimen D = Regimen C + Long-term oxygen therapy and consider surgical procedures</td>
</tr>
</tbody>
</table>
**β-blockers**

- **Vascular Effects**
  - Smooth muscle contraction = (mild vasoconstriction)
- **Kidneys**
  - Inhibit renin by the kidneys
  - Tone down the Renin Angiotensin Aldosterone System (RAAS)
- **Nervous system**
  - Blockade of adrenaline and noradrenaline
  - Decrease anxiety, tremor and migraines

- **Therapeutic use of β-blockers**
  - Hypertension
  - Angina
  - Myocardial infarction
  - Heart failure
  - Significantly reduces mortality and hospitalizations in
  - Post MI
  - HF with LVEF dysfunction

**Types of β-blockers**

- **Non-Cardioselective**
  - propranolol
  - nadolol
  - timolol
  - pindolol
- **Mixed beta and alpha-1 activity**
  - carvedilol
  - labetalol
- **Cardioselective**
  - acebutolol
  - atenolol
  - bisoprolol
  - esmolol
  - metoprolol
  - nebivolol

**Risks of β-blockers in COPD**

- Historically β-blockers have been avoided in asthma and COPD
- β blockers → potential bronchoconstriction
  - Reduction in forced expiratory volume in one second (FEV)
  - Increased airway hyperresponsiveness
  - Inhibition of bronchodilator response to β agonists
  - Exacerbation of COPD and complications

**GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD)**

Q “Cardiovascular disease (including ischemic heart disease, heart failure, atrial fibrillation, and hypertension) is a major comorbidity in COPD and probably both the most frequent and most important disease coexisting with COPD”

Q “Cardioselective β-blockers are NOT contraindicated in COPD”

**What does ACC/AHA say?**

- 2009 ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction Suggest that β-blocker therapy after acute MI IS APPROPRIATE for many patients with COPD or other relative contraindications
- 2009 ACC/AHA Focused Update Guidelines for the Diagnosis and Management of Heart Failure in Adults
  - “MOST patients with chronic obstructive pulmonary disease do not have a bronchospastic component to their illness and remain REASONABLE candidates for β-blockade”

**Package Inserts**

**Warnings and Precautions**

- Chronic obstructive pulmonary disease ...
  - "metoprolol should be used with caution, in ...COPD with a bronchospastic component."
  - "Use only if the potential benefit outweighs the potential risk"

**Study Design**

- **Objective**: To examine the effect of β blockers in all-cause death and COPD exacerbation associated with the use of β blockers in COPD patients
- **Design**: Retrospective cohort study using Cox proportional (CP) hazards regression analyses
- **Setting**: 23 general practices in Netherlands
- **Population**:
  - Total 2230 patients, β-blocker use N = 665, non-β-blocker use N = 1565
  - Subjects > 45 yr with an incident or prevalent diagnosis of COPD between 1996 – 2006
  - Study length: ~7.2y

**Results**

- All cause mortality adjusted HR in patients on β-blocker was 0.68 (95% CI, 0.56-0.83)
- Adjusted HR for COPD exacerbation in patients on β-blocker was 0.68 (95% CI, 0.46-1.02)

**Critique**

- Retrospective and observational study
- Misclassification and misdiagnosis of patients
- Cannot completely correct for cofounders
  - Severity of COPD illness
  - Benefits of concomitant drug use (ACE –I, ARB’s and statins)
Study Design

- **Objective**: To examine the effect of β blockers in the management of COPD assessing effect on mortality, hospital admissions, and exacerbations of COPD
- **Design**: Retrospective cohort study
- **Setting**: Tayside, Scotland (2001–2010)
- **Population**: 5977 patients aged >50 years with a diagnosis of COPD

Results

- B-blocker use was associated with an overall 22% reduction in mortality HR = 0.78 (95% CI of 0.67 to 0.92)
- 2005 patients died equating to an annual mortality of 34%

Critique

- Author’s conclusions: β blockers may reduce mortality and COPD exacerbations when added to established inhaled stepwise therapy for COPD
- However, it’s retrospective study. Results should be interpreted cautiously
- Many confounding variables (severity of CV disease COPD among groups)
- Prospective randomized double blinded controlled trial needed to confirm these findings

Role of Pharmacist

- It is necessary:
  - To properly understand management of COPD
  - Evaluate literature in this controversial topic
  - No definite clinical trial exists to safely recommend β-blockers for all COPD patients.
  - Monitor initiation and up-titration of dose of β-blockers closely
  - Reduce dose/hold β-blocker if bronchospam or complication occurs

Keep in Mind

- Smoking cessation
- Influenza vaccine annually
- Pneumococcal vaccine
- Not recommended
  - Antibiotics, other than for treating infectious exacerbations of COPD
  - Mucolytic agents
  - Antioxidant agents such as N-acetylcysteine
  - Regular use of antitussives
**Patient Case**

- B.P. is a 55 yo male who comes to the ER with CC of SOB due to COPD exacerbation and constant productive cough. This is the 3rd time in this year B.P. is admitted to the hospital due to SOB.

- PMH: CAD with a MI 8 years ago with stent X 1, HTN, COPD (1 pack of cigarettes X 50 years), CHF.

- Vitals: BP 145/85, HR: 88 bpm, RR: 24, Temp: 98.4F

- Allergic to PCN

- Home Rx: crestor 20mg daily, lisinopril 40mg daily, pravix 75 daily, aspirin 325 mg, carousal 6.25 mg q12h, advair diskus 250/50 mg 1 puff BID, isotropium 1 puff daily and albuterol MDI q6hs PRN for SOB.

- Last spirometry test shows FEV 1 = 45% and FEV1/FVC = 55%. In the hospital he was started on oxygen therapy, prednisolone 40mg IV q8h, furosemide 20mg IV q12h, Duranb qhs ATC as well as continuing his home medications in the hospital.

- CXR rules out pneumonia, Echocardiogram shows mild mitral regurgitation with LVEF of ~50%.

**True or False Questions**

- β-blockers are indeed contraindicated in asthmatic and COPD patients.

- β-blockers may actually be beneficial for those with mild and moderate COPD and CV disease.

- β blockers (predominantly cardioselective) reduced mortality and COPD exacerbations when added to stepwise inhaled therapy for COPD in one of the studies.

**Summary**

- β-Blocker therapy for cardiovascular indications is underutilized in patients with COPD.

- Mortality benefits are seen in patients with mild to moderate COPD who receive cardioselective β-blockers.

- In conclusion patients with MILD TO MODERATE COPD should receive cardioselective β-blocker therapy when a strong indication exists.

- A reliable prospective randomized controlled trial needed to answer this conundrum.

**References**


**Thank You**

Questions?
Overview of Enteral & Parenteral Nutrition

Diana Carolina Andrade, Pharm.D.
Pharmacy Practice Residency
Cleveland Clinic Florida

Objectives

- Discuss nutrition screening and assessment
- Examine the gastrointestinal anatomy and its role in nutrition
- Review the ASPEN guidelines as it pertains to the adult critically ill patients
- Discuss nutrition requirements in special populations
- Review short and long term complications of nutrition support

Importance of Nutritional Screening

- Malnutrition
  - 10-40% hospitalized patients
  - 1 in 7 patients over 65 yo
  - ↑ LOS
  - ↑ hospital costs

- Obesity
  - Class I, II, III
  - 1 in 5 adults
  - ↑ health problems

Nutritional Screening

- Nutritional screening is the 1st step
  - Weight & height status, weight Δ, food intake, disease severity
- Nutritionally-at-Risk:
  - Involuntary weight loss/gain of > 10% of UBW within 6 months or:
    - ≥ 5% in 1 month
    - ≥ 20% over or under IBW
  - Presence of chronic disease
  - Inadequate nutrition intake

Nutrition Assessment

- Medical & nutrition history
- Physical examination
- Anthropometric parameters
- Nitrogen balance
  - Starvation, catabolism, PEM

Assessment for Protein-Calorie Malnutrition

- Hormonal and cell-mediated response to stress
  - Acute illness or trauma causes inflammatory stress
  - Cytokines re-orient hepatic synthesis of plasma proteins
  - Interpretation could be problematic
- Respondents
  - Negative acute-phase
  - Positive acute-phase
**Laboratory Testing**

- Hepatic transport proteins
  - Valuable tool in non-ICU setting
  - Negative acute phase proteins: albumin, transferrin, pre-albumin
  - Positive acute phase proteins: Complement system, coagulation & fibrinolytic system, transport proteins, CRP
- Vitamins and minerals
  - B12, folate, vitamin D & K, calcium, magnesium
- Lipids
- CMP

---

**Conditions Affecting Nutrition**

- Gastro-paresis
- GI bleeding
- Malignancy
- Gastric Outlet Obstruction (GOO)
- Malabsorption
  - Multiple surgeries
  - Medication
- Endocrine disorders
- End organ disease
- GI disorders
  - Ulcerative colitis
  - Crohn’s Disease
  - Fistulas
- Depression & dysphoria

---

**Overview of Upper GI Tract**

- **Stomach**
  - Volume: 45mL-4 L
  - Converts food boluses to chyme
  - 40min~2 hours by peristaltic contractions
  - Passes food through pyloric sphincter to duodenum
- **Liver & gallbladder**
  - Bile
- **Pancreas**
  - Bicarbonate, trypsin, lipase, amylase

---

**Overview Small & Large Intestine**

- **Duodenum**
  - Nutrient extraction & chemical digestion begins
  - 10-12" long
- **Jejunum**
  - 8ft in length
  - Majority of nutrients absorbed
- **Ileum**
  - 7.5ft in length
  - Vitamin B12 & bile salts absorbed
- **Colon**
  - 5 ft length: ascending, transverse, descending, sigmoid
  - Water balance, vitamin absorption

---

**Small Bowel Obstruction (SBO)**

- **Definition**
  - Partial or complete, simple or strangulated obstruction
  - Obstruction → dilation → necrosis + strangulation → perforation + sepsis
- **S&S**
  - Dehydration, N/V, abdominal pain, constipation
- **Treatment**
  - IVF, NG tube, surgery
  - Early post-op obstruction: Bowel rest, hydration, parenteral nutrition (PN)
**Crohn’s Disease**

- **Definition:**
  - Inflammatory bowel disease leading to ulcerations and nutrient deficiency (65-75%)
  - PO intake, malabsorption, malnutrition, drug-nutrient interaction, nutrient deficiency
- **S&S:**
  - Abdominal pain, diarrhea, weight loss
- **Treatment:**
  - Induce & maintain remission
  - Corticosteroid therapy, immunomodulatory agents, biologic therapy, 5-ASA products, antibiotic therapy
  - Surgery requiring peri-operative PN
  - Restricted to 1) seriously malnourished 2) non-responding to pharmacological therapy

---

**Fistula**

- **Definition:**
  - An abnormal communication between 2 epithelialized surfaces
  - Rectovaginal, anovaginal, uro-genital tract, anal-rectal, pancreatic fistula
  - Enterocutaneous fistula
    - Low output fistula drains less than 200 mL/day
    - Moderate output fistula drains between 200 and 500 mL/day
    - High output fistula drains more than 500 mL/day
- **S&S:**
  - Fever, leukocytosis, abdominal tenderness, wound infection, anorexia, failure to recover, malnutrition

---

**Post Operative Ileus**

- **Definition:**
  - Inflammatory process inhibits smooth-muscle contraction and decreases the normal propulsive activity
  - + time for hospital D/C, $750 million - $1 billion/year
- **S&S:**
  - N/V, abdominal distention, inability to tolerate liquids/solids
  - Gradual resolution (small intestine (24hrs) > stomach (48 hrs) > colon (3-5 days))
- **Treatment:**
  - Prevention is the key
  - Early feedings to mucosal immunity, mucosal atrophy

---

**Enterocutaneous Fistula**

- **Definition:**
  - Intestinal or stomach contents can leak through this connection

- **Treatment:**
  1. Fluid & electrolyte replacement
  2. Abscess drainage
  3. Infection treatment
  4. Nutrition
     - CHO & lipid: 30 kcal/kg/day
     - Protein: 1.5-2.5 g/kg/day
  5. Surgery

---

**Short Bowel Syndrome (SBS)**

- **Definition:**
  - < 200 cm residual small bowel without a colon
  - Significant energy and fluid loss requiring PN
- **S&S:**
  - Diarrhea, weight loss, malabsorption
- **Important factors:**
  - Intact colon
  - Presence of ileocecal valve
  - Condition of remaining bowel (micronutrient supplements)
  - Segment of bowel removed (dietary management)
- **Treatment:**
  - TPN (intestinal adaptation with time)
  - Diet: high carbohydrate-low fat (HCLF) if colon is present
  - Vitamin B12, folic acid, iron supplements
**Ulcerative Colitis**

- **Definition:**
  - Continuous inflammation of colon (50% left colon)
  - Malnutrition (18-62%), anemia (80%), electrolyte depletion
- **S&S:**
  - Bloody diarrhea, distension, incontinence
- **Treatment:**
  - Pharmacological (corticosteroids, 5-ASA products)
  - PN & EN have no therapeutic role in uncomplicated UC
    - 0.4 mg-1 mg/d folate
    - Omega-3 fatty acids

**Diverticular Disease**

- **Definition:**
  - Chronic contraction resulting in muscular hypertrophy and presence of diverticula
  - Diverticulosis (diverticula) vs. diverticulitis (diverticula perforation + inflammation)
- **S&S:**
  - Diverticulitis (90% colon), diverticular bleeding → macro-perforation → peritonitis, abscess, fistula, strictures
- **Treatment:**
  - Dietary restrictions (avoid pieces of fiber)
  - Antibiotic therapy (GNB rods, anaerobes) 7-14 days
  - Surgery (complicated cases)

**A.S.P.E.N: Nutrition Assessment**

- **Functional GI Tract**
  - Yes
  - Enteral Nutrition
  - GI Function
  - Normal
  - Standard Nutrients
  - Adequate: PO feedings
  - Tolerance
  - Inadequate: PN

- **No**
  - Parenteral Nutrition
  - Short-term
  - Long-term or fluid restriction
  - PPN
  - Central PN

**Selection of Enteral Feeding Route**

- **Time**
  - Short-term (<3 weeks)
  - Long-term (>4-8 weeks)
- **Access requirement**
  - Prior or post pyloric
    - Severe reflux, delayed gastric emptying, tube feeding related-aspiration (TFRA)
- **Personnel & resources available**
- **Complications**
  - Clogging, esophageal perforation, pulmonary intubation, nasal mucosal ulceration, wound infection, dislodgment

**If the guts works use it!**

**If you don't use it you lose it!**

Adapted from: [Website](http://www.serovera.com/images/colorectal-cancer-sm.jpg)

Adapted from: [Website](http://media.tumblr.com/tumblr_lh9vmwSvqm1qe7aj0.jpg)

Adapted from: [Website](http://www.webmm.ahrq.gov/media/cases/images/case184_fig01.jpg)
**Enteral Nutrition Access**

- **Short-Term non-surgical pre-pyloric tube**
  - Nasogastric (NGT) or orogastric
  - Nasoenteric or oroenteric
- **Short-Term surgical Pre and Post pyloric tube**
  - Gastrostomy (PEG)
  - Jejunostomy
- **Long-Term pre-pyloric tube**
  - Gastrostomy (PEG)
- **Long-Term post-pyloric tube**
  - Jejunostomy (PEJ or JET-PEG)

**Appropriate Indications for EN**

- Malnourished, expected unable to eat >5-7 days
- Nourished, expected unable to eat >7-9 days
- Adaptive phase of SBS
- NPO but functional bowel
- Surgery

**Contraindications**

- Malnourished, expect to eat within 5-7 days
- Severe acute pancreatitis
- High output proximal fistula
- Inability to gain access
- Intractable vomiting, diarrhea
- Nourished, expect to eat within 7-9 days

**Choosing Appropriate Formulas**

- **Carbohydrate**
  - 40-90% of total caloric content
- **Fiber**
  - Soluble (trophic effect, ↓ diarrhea) vs. insoluble (↑ stool consistency)
  - Requirement 20-35 g/d
- **Lipid**
  - Corn and soybean oil (<10% to >50% Ω-6 fatty acids)
  - MCT do not stimulate pancreatic lipase secretion
- **Protein**
  - Whole vs. hydrolyzed vs. free amino acid
  - Arginine, glutamine, BCAA

**Common Enteral Feeding Formulas**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jevity® 1.2</td>
<td>Standard</td>
<td>High protein w/ fiber</td>
</tr>
<tr>
<td>Glucerna® 1.2</td>
<td>Glycemic control</td>
<td>Contains chromium, Ω-3 fatty acids</td>
</tr>
<tr>
<td>Nepro®</td>
<td>Hemodialysis</td>
<td>Low in Na, K, Phosphate</td>
</tr>
<tr>
<td>Multiple formulations</td>
<td>Immune-enhancing</td>
<td>Arginine, glutamine, Ω-3 fatty acids, nucleotides</td>
</tr>
<tr>
<td>Perative®</td>
<td>Metabolic stress, wound healing</td>
<td>Contains added Arginine &amp; hydrolyzed peptide-based protein</td>
</tr>
</tbody>
</table>

**Common Enteral Feeding Formulas**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCT-oil</td>
<td>Fat supplement</td>
<td>EFA deficiency</td>
</tr>
<tr>
<td>Vital AF 1.2</td>
<td>Malabsorption</td>
<td>Contains antioxidants, EPA &amp; DHA</td>
</tr>
<tr>
<td>NutriHep®</td>
<td>Hepatic encephalopathy</td>
<td>High in BCAA &amp; MCT</td>
</tr>
<tr>
<td>Oexpa®</td>
<td>ARDS, ALI, SIRS</td>
<td>High in antioxidants</td>
</tr>
<tr>
<td>Juven® packet</td>
<td>Wound healing</td>
<td>HMB, Arginine, Glutamine</td>
</tr>
<tr>
<td>ProPass® packet</td>
<td>Protein supplement</td>
<td>May be added to TF</td>
</tr>
</tbody>
</table>

**Monitoring Enteral Feedings**

- **GI:**
  - Pain, abdominal distension, diarrhea, N/V
- **Mechanical:**
  - Tube placement, feeding tube, clogging, aspiration
  - Gastric residual volume
    - Holding < 500 mL w/o symptoms not recommended
    - 200 mL may be reasonable to hold, recheck in 2 hrs
- **Metabolic:**
  - CMP, glucose, calcium, magnesium
  - Fluid and electrolytes imbalances

**Labs + clinical judgment**
### Appropriate Indications for PN

- Post-op ileus
- Failed tube feeding
- High-output fistula
- Prolonged NPO
  - Malnourished
  - Greater than 5-7 days

### Parental Nutrition Access

#### Central Venous Access (CVC)
- Long term: non-tunneled (weeks), PICC (months), tunneled or port (month-yrs)
- Complications: pneumothorax, pericardial tamponade

#### Peripheral Access
- Short term: 10-14 days
- Formulation osmolarity <600-900 mOsm/L
- Complication: peripheral vein thrombophlebitis

### Adult Energy Requirement *

- **Maintenance (Mild stress)**: 25-30 kcal/kg/day
- **Moderate Stress**: 30-35 kcal/kg/day
- **Severe Stress**: 35-40 kcal/kg/day

(*) Based on Actual BW in non-obese patients

### Adult Protein Requirements *

- **Maintenance**: >0.8 – 1 g/kg/day
- **Mild stress**: >1 – 1.2 g/kg/day
- **Moderate Stress**: >1.2 – 1.5 g/kg/day
- **Severe Stress**: >1.5 – 2 g/kg/day

(*) Based on Actual BW in non-obese patients

### Adult Electrolyte Requirements *

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>70-100 mEq/day</td>
</tr>
<tr>
<td>Potassium</td>
<td>40-100 mEq/day</td>
</tr>
<tr>
<td>Calcium</td>
<td>10-15 mEq/day</td>
</tr>
<tr>
<td>Chloride</td>
<td>As needed for acid/base</td>
</tr>
<tr>
<td>Magnesium</td>
<td>8-20 mEq/day</td>
</tr>
<tr>
<td>Phosphate</td>
<td>20-40 mmol/day</td>
</tr>
<tr>
<td>Acetate</td>
<td>As needed for acid/base</td>
</tr>
</tbody>
</table>

(*Assuming normal age-related organ function

### Importance of Electrolyte Repletion

- **Sodium (Na⁺):**
  - Hyponatremia (<135 mmol/L), hypernatremia (>145 mmol/L)
  - Osmolality, volume of body fluids, neuromuscular activity
- **Potassium (K⁺):**
  - Hypokalemia (< 3.5 mEq/L), hyperkalemia (> 5 mEq/L)
  - Membrane potential activity, neuromuscular function
- **Calcium (Ca²⁺):**
  - Hypocalcemia (< 9.2 mg/dL), hypercalcemia (> 11 mg/dL)
  - Cofactor (i.e. clotting cascade), muscle contraction
- **Magnesium (Mag²⁺):**
  - Hypomagnesemia (< 1.6 mEq/L), hypermagnesemia (>2.4 mEq/L)
- **Phosphorus (P):**
  - Hypophosphatemia, hyperphosphatemia (>4.7 mg/dL)
  - Metabolic reactions, electrolyte homeostasis
- **Acetate:**
  - Structural support, synthesis of RBCs, tissue oxygenation
Obesity

- **Protein requirements**
  - BMI 30-40: ≥2g/kg IBW/day
  - BMI >40: 2.5g/kg IBW/day

- **Kcal requirements**
  - 15-20kcal/kg Actual BW/day (non-ICU)

Renal Disease

- **Protein requirements**
  - ARF: No adjustment
  - Stage III/IV CKD: 0.6-1.2g/kg/day
  - Maintenance HD: 1.2g/kg/day
  - CRRT: 1.8-2.5g/kg/day
    - Removes 20 g protein/day

Short-term Metabolic Complications

- **Electrolyte and fluid abnormalities**
- **Macronutrient related complications**
  - Hyperglycemia or hypoglycemia
  - Azotemia, ↑ BUN, hyperammonemia
  - Essential Fatty Acid Deficiency (EFAD) or hyperlipidemia
- **Re-feeding syndrome**
  - CHO metabolism → ↑ insulin secretion → ↑ cellular uptake of anabolic electrolytes
  - Potassium and magnesium
  - Start slow go slow + replenish electrolytes

Conclusion

- Nutritional screening is an important part of patient assessment
- Enteral route is preferred for functional GI tract
- Continuous reassessment of patient and adjusting nutritional plan is the key

Review Questions (T or F)

- Gastroparesis, gastro-intestinal bleeding and malignancies are conditions that can affect absorption of nutrient
- Parenteral nutrition should not be terminated until >90% of target requirements are being delivered by enteral nutrition
- Re-feeding syndrome occurs usually within 24 hours of PN initiation
Medications to Avoid After Bariatric Surgery

Jayme L. Dinsmore, Pharm.D.,
PGY-1 Pharmacy Practice Resident
Miami VA Medical Center

Goals

- Goal 1: To provide an introduction of the physical changes that occur to the gastrointestinal tract after bariatric surgery.
- Goal 2: To describe the ways drug absorption is affected after bariatric surgery
- Goal 3: To provide recommendations for medication management based on theoretical and evidence-based medicine in patients after bariatric surgery

Introduction

- Bariatric surgery has become the preferred therapy for severely obese patients who are refractory to traditional medical therapy.
- Traditional medical therapy is largely behavioral modification therapy +/- medications.
- Almost all weight loss medications reaching the market have been withdrawn due to increased cardiovascular risks

Obesity is epidemic

- Obesity affects over 300 million individuals worldwide.
- Over the past 20 years, the subgroup of obese considered ‘severe’ has nearly quadrupled throughout Northern America and Europe.
- In 2008, medical costs associated with obesity were estimated at $147 billion; the medical costs paid by third-party payors for people who are obese were $1,429 higher than those of normal weight.

Obesity Trends

Consequences of Obesity

Obesity is associated with extensive morbidity and premature mortality.

- Type 2 Diabetes
- Dyslipidemia
- Hypertension
- Obstructive sleep apnea
- Heart Disease
- Stroke
- Asthma
- Weight-bearing degenerative problems
- Depression
- Cancer


Obesity Trends: Among U.S. Adults

http://creamtablates.com/2008/07/
Relative Risk of Morbidities from Obesity

<table>
<thead>
<tr>
<th>Greatly increased (relative risk &gt;&gt;3)</th>
<th>Moderately increased (relative risk 2-3)</th>
<th>Slightly increased (relative risk 1-2)</th>
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<tbody>
<tr>
<td>Diabetes</td>
<td>Coronary heart disease</td>
<td>Cancer polycystic kidney disease</td>
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<tr>
<td>Gall bladder disease</td>
<td>Osteoarthritis (knees)</td>
<td>Endometrial cancer, colon cancer</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hyperuricemia and gout</td>
<td>Reproductive hormone abnormalities</td>
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<tr>
<td>Dyslipidemia</td>
<td></td>
<td>Polycystic ovary syndrome</td>
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<tr>
<td>Insulin resistance</td>
<td></td>
<td>Impaired fertility</td>
</tr>
<tr>
<td>Breathlessness</td>
<td></td>
<td>Low back pain</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td></td>
<td>Increased anesthetic risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fetal defects arising from maternal obesity</td>
</tr>
</tbody>
</table>

Bariatric Surgery

National Institute of Health recommendations for patients over age of 18:

- **Body Mass Index (BMI) greater than 40**
- **Body Mass Index (BMI) greater than 35 + significant comorbidities**

Types of Bariatric Surgery

- **Purely Restrictive**
  - Vertical-banded gastroplasty
  - Adjustable gastric banding
- **Restrictive > Malabsorptive**
  - Roux-en-Y gastric bypass (RYGB)
- **Malabsorptive > Restrictive**
  - Biliopancreatic diversion
- **Purely Malabsorptive**
  - Jejunoejejunostomy bypass
  - Jejunocolonic bypass

Demand

- In 2008, over 350,000 procedures performed globally
- Most popular worldwide
  1. Adjustable gastric banding (AGB; 42%)
  2. Roux-en-Y gastric bypass (RYGB; 39%)
  3. Sleeve gastrectomy (SG; 5%) (14).
- Most popular in United States: Roux-en-Y

Adjustable Gastric Banding

[Diagram of Adjustable Gastric Banding]

Vertical Banded Gastroplasty

[Diagram of Vertical Banded Gastroplasty]
Sleeve Gastrectomy

Restrictive & Malabsorptive

Roux-en-Y Gastric Bypass

Restrictive

Malabsorptive

Efficacy for Weight Loss

Mean percentage excess weight loss:
- 61.2% - All Patients
- 47.5% - Gastric Banding
- 61.6% - Gastric Bypass
- 68.2% - Gastroplasty


Oral drug absorption is a prerequisite for pharmacological effects.


Drug Absorption

1. Disintegration
2. Dissolution
3. Gastric emptying
4. Intestinal transit time
5. Blood flow to gastrointestinal tract
6. Metabolism of drug within gastrointestinal tract


Disintegration & Dissolution

Stomach
- Main role is to mix, reduce, & dissolve ingested food/drugs for delivery to the small intestine
- Not a major site of drug absorption except weak acidic drugs (aspirin)
Post-Bariatric Surgery

Stomach
- Surface area reduced
  - Impaired drug disintegration/dissolution
- Loss of gastric acid production
  - Increased pH of stomach
Medications dependent on acidic pH for bioavailability:
1. Itraconazole
2. Ketoconazole
3. Atorvastatin

Small Intestine
- Most important site of drug absorption in the body
- Villi & micro-villi (caves) = Huge surface area
- Presence of numerous drug influx and efflux pumps along lining of the small intestine
- Most recognizable, P-glycoprotein

Drug Transporters

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<th>Drug substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>PepT1</td>
<td>Beta lactam antibiotics, ACE inhibitors, antivirals</td>
</tr>
<tr>
<td>OATP2B1</td>
<td>DHEA, salicylate, valproate, pravastatin, atorvastatin, fexofenadine</td>
</tr>
<tr>
<td>PCFT</td>
<td>Folate, methotrexate, pemetrexed,</td>
</tr>
</tbody>
</table>

Pharmacokinetics/Dynamics

- Paucity of clinical studies comparing the pharmacokinetics/dynamics of medications pre- and post-bariatric surgery.
- Most clinical data was obtained from outdated bypass procedures.
- Reduction of small intestine length and/or stomach size not consistently reported.
- Lack of comparators in trials & case reports makes data interpretation difficult.
Evidence-Based Medicine

Trial Design
- Comparison of acetaminophen pharmacokinetics/dynamics in subjects before, at 3 months, and 1 year after surgery
- Oral, liquid acetaminophen
- Post-surgery
  - \( C_{\text{pmax}} \) Goubled \((p<0.01)\)
  - \( T_{\text{max}} \) 10 minutes vs. 45 minutes
- Results consistent with a previous, analogous trial

Clinical Translation
- Nutrient deficiencies
  - Most studied
  - Endocrine Society published guidelines in 2010 on the Nutritional Management of the Post-Bariatric Surgery Patient
- Medication pharmacokinetic data
  - Case studies
  - In vitro testing
  - Theoretical

Vitamin Supplementation
- Daily multivitamin and calcium supplementation with added vitamin D for all weight-loss surgery patients.
- Calcium citrate preferred
  - Salt is better absorbed in the absence of gastric acid production.

Osteoporosis
- Well documented, especially in women
- Several studies have documented the high incidence of secondary hypoparathyroidism (30-60%) at one year
- Medications contributing to hypocalcemia:
  1. Loop diuretics
  2. Carbamazepine
  3. Oxcarbazepine

Bisphosphonates
- Increased risk of esophagitis with adjustable gastric band
- Potentiates risk of developing malabsorptive hypocalcemia
- However, extensive weight loss leads to bone demineralization
- Risk vs. benefit
- Recommend once yearly IV zoledronic acid to minimize risk of esophagitis

NSAIDs
- Chronic use of NSAIDs increases risk of gastric ulcers
- 11-fold increased risk of ulcers with chronic NSAID use after bariatric surgery
- Recommendation: avoid use
  - topical alternatives (diclofenac gel, capsaicin, menthol, camphor)
  - Switch to another class of medications (tramadol)
Gout

- Both surgery and weight loss after bariatric surgery increase risk of acute gout attacks
- Prophylactic gout therapies should be initiated prior to surgery to minimize risk
- Avoid medications known to precipitate gout
- Consider use of colchicine over NSAIDs for acute gout attacks


Warfarin

- Very close INR monitoring suggested in patients after bariatric surgery
- Unknown if warfarin bioavailability affected
- Vitamin K intake unpredictable
  - Diet restrictions post-operatively
  - Unstable diet
  - Change in eating habits
- Consider low-molecular weight heparins, which have established safety and efficacy in this population

Case

- A 50-year-old, 250 lb woman suffered idiopathic proximal right popliteal and calf deep vein thrombosis (DVT) 3 years previously. Her warfarin has been managed successfully by a centralized pharmacist-run anticoagulation service, and she has easily achieved and maintained her target international normalized ratio range between 2.0 and 3.0. She has had no bleeding or thrombotic complications. The surgeon calls to notify you the patient will undergo RYGB surgery in two weeks. As a pharmacist, what will you recommend?


Tamoxifen

- Three case reports documenting subtherapeutic tamoxifen levels in patients after RYGB.
- Therapeutic range 95-520 ng/ml
- Recommend steady-state tamoxifen levels or use of intravenous chemotherapy agents, when appropriate


Contraception

- Women of child-bearing age are advised to avoid pregnancy for up to 2 years post-surgery
- Evidence limited
- Efficacy of contraception medication has not been established
- Recommendation: IV, transdermal, intrauterine, or barrier contraceptive methods that do not rely on gut absorption

Summary

In lack of evidence-based medicine to support safety & efficacy of a given medication, the pharmacist should:

1. Suggest an alternative dosage form that does not depend on gut absorption
2. Recommend liquid dosage forms whenever possible to avoid problems associated with drug disintegration and dissolution
3. Remember pharmacokinetics/dynamics of drug absorption
4. Use therapeutic drug monitoring to evaluate efficacy

5. Use medications that do not depend on food for bioavailability
6. Ask physician and/or patient for surgical details in order to make educated conclusions as to the degree of restriction and/or malabsorption
7. Remember that older studies are mostly based on outdated surgical procedures causing extensive malabsorption and should be interpreted with caution

True or False?

- True/False. A patient who has received a Roux-en-Y bypass procedure will have decreased surface area of the small intestine?
  - Answer: True

- True/False. Calcium carbonate is the best choice for calcium supplementation in a patient after bariatric surgery.
  - Answer: False, calcium citrate

- True or False. Ketoconazole is a medication that relies on an acidic medium for absorption and so will have increased drug absorption necessitating dose reduction following bariatric surgery.
  - Answer: False, decreased drug absorption possibly necessitating dose increase
Strategies in Pain Management: Scheduled, Breakthrough, and Dose Adjustments

Tamara M. Green, Pharm.D
PGY-1 Resident
Florida A & M University

Objectives
- Classify and distinguish between different types of pain
- Discuss processes of risk-stratification
- Identify indications required for use of opioid therapy
- Organize an opioid treatment plan
- Determine when and how to initiate scheduled and breakthrough pain management
- Identify indications for dose adjustments
- Evaluate the need for discontinuation of pain management
- Discuss current therapies in pain management

Pain
- In 2001, JCAHO endorsed pain as a 5th vital sign
- Chronic pain is defined as pain that persists beyond normal tissue healing time, which is assumed to be three months
- Pain is subjective
- Neuropathic pain is defined as pain that results from damage to or pathology within the nervous system.
  - I.e. diabetes mellitus and stroke
- Nociceptive pain is defined as pain that is caused by stimuli that threatens or provokes actual tissue damage.
  - I.e. inflammation and musculoskeletal conditions

Controversy
- Chronic opioid use has been acceptable in cancer patients
- Controversy exist in regards to chronic use in non-cancer patients due to:
  - Diversion
  - Tolerance
  - Abuse
  - Physical and Psychological Dependence
  - Lack of evidence of efficacy

Risk Stratification
- All clinicians prescribing opioids should be knowledgeable about risk factors for opioid abuse and methods for assessing risk
- Documentation of benefit-harm evaluation
  - All patients should complete a thorough history and physical examination
    - Medical, family, psychosocial, drug/alcohol abuse, suicidal risk
  - When assessing a patient, it is important to determine if the patient should be treated non-opioid vs. opioid
    - Diagnostic tests and assessments
    - Attempt to determine a specific diagnosis
      - Nociceptive vs. Neuropathic
Stratify Low vs. High risk patients

- Factors that have been associated with opioid misuse, abuse, and diversion:
  - Personal or family history of alcohol/drug abuse
  - Young age w/ psychiatric condition

**Factors that have been associated with opioid misuse, abuse, and diversion:**
- Personal or family history of alcohol/drug abuse
- Young age with psychiatric condition

**Indications for Chronic Opioid Therapy (COT)**

- May be initiated in patients in which the benefits of the use of COT outweigh the risk AND there is no alternative therapy that will be of benefit to the patient
- Patients that are risk stratified and are carefully selected for COT
- Patients that will be closely monitored
- Patients that have failed to respond to non-opioid treatments

**Opioid Management Plan**

- Discuss goals of therapy
- Describe how opioids will be prescribed and should be taken
- Explain expectations for clinic follow-up and monitoring
- Explain expectations in the total management of COT
- Discuss potential indications for tapering or discontinuing COT
- Discuss possible adverse effects
- Determine and discuss consequences of aberrant drug-related behaviors

**Non-Opioid Management of Pain**

**Acetaminophen (Tylenol, Ofirmev)**
- MOA: unknown; but may inhibit central prostaglandin synthesis and ↑ pain threshold
- Analgesic and Antipyretic properties
- Max dose: 3000 mg daily
- 325 mg per dosage unit limit
- Does not cover OTC products
- Caution: Renal Impairment
- BBW: Potential for severe liver injury
NSAIDS

- **MOA:** Reversibly binds to COX 1 & 2 enzymes which inhibits prostaglandin synthesis
- Analgesic, Antipyretic, and Anti-inflammatory
- **BBW:**
  - May ↑ risk of serious cardiovascular events
  - May ↑ risk of serious GI bleeding/perforation
- Adverse Effects: Dyspepsia, ↑ BP, GI irritation, Dizziness, Confusion, and Fatigue
- Pregnancy: C/C/D

Gamma Aminobutyric Acids

- **MOA:** Binds to the voltage-gated calcium channels at the alpha 2-delta subunit and inhibit neurotransmitter release.
- **Gabapentin (Neurontin)**
  - Max 3600 mg divided in 3 doses
  - Side Effects: Peripheral edema, dizziness, somnolence
- **Pregabalin (Lyrica)**
  - 50-450 mg daily
  - Side Effects: Peripheral edema, angioedema, and renal dysfunction

Tricyclic Antidepressants

- **Amitriptyline:**
  - 5-100 mg at bedtime
- **Nortriptyline:**
  - 25 mg TID/QID Max: 150 mg/day
- Side Effects: Dry mouth, sweating, orthostatic hypotension, dizziness, and constipation
- **CI:** Cardiac conduction disturbances

SNRI

- **Duloxetine (Cymbalta)**
  - 30-60 mg daily
- **Venlafaxine (Effexor)**
  - 37.5 – 300 mg daily
- Side Effects: BP, sexual dysfunction, sweating

Initiating COT

- Initiation of COT is referred to as a short term, therapeutic trial
  - Used to determine whether COT will be appropriate
  - Duration: weeks to months
- Opioid selection, initial dosing, and titration should be individualized according to:
  - Health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms
"Start low and go slow"

There is insufficient evidence to recommend specific optimal starting doses and methods of dose titration.

There is insufficient evidence to recommend short acting versus long-acting opioids, or as-needed versus around-the-clock dosing of opioids.

For continuous, persistent daily pain

- **Option One:** Initiate a short acting opioid
  - **Advantages:** Shorter half-life
  - **Disadvantages:** Rapid rise and fall in serum level

- **Option Two:** Initiate a long acting opioid
  - **Advantages:** Gradual increase to therapeutic level, half-life, more-consistent control, may ↑ adherence, and lower risk of abuse
  - **Disadvantages:** Exaggerated side effects

For episodic pain

- **Option Three:** Initiate a short acting opioid as needed

### Titrating Doses

- Always evaluate a need for dose titration
- Careful titration is warranted in COT to:
  - Allow time to build tolerance to side effects
  - Reduce risk of toxicity
  - Attain optimal dose to reduce pain symptoms
- Daily dose can be ↑ by 25-100% at a given time
- Do not dose more than every five half lives
- If patient is on more than one opioid, titrate one medication at a time
- Titrate up to a 200 mg/day morphine equivalent.
  - May be increased further until side effects limit dosing

### Changing to another oral opioid

**Question:**
A patient is taking sustained-release oxycodone, 100 mg every 12 hours, but has developed intolerable side effects. Would you like to try an immediate-release opioid agent, hydrocodone? What is the equivalent dose of hydrocodone?

**Answer:**
The "Dosing and Conversion Chart for Opioids Analgesics" will help you calculate the equivalent dose of the new opioid, but you must allow for the incomplete or delayed onset of side effects.

After patients take the same opioid dose for a week or two, they become tolerant of the opioid's side effects and may require higher doses to maintain their pain relief.

Opioids with a longer half-life, such as oxycodone, have a longer duration of action. This means that patients may need less of the new opioid to achieve the same effect. However, it's important to adjust the dose to the patient's individual needs and tolerance.

### Opioid conversion tips

1. **Calculate the total daily dose of the opioid to be converted:**
   - Use this formula:
     \[ \text{Total Daily Dose (mg day)} = \text{mg dose x 24 hours} \]

2. **Choose an appropriate opioid:**
   - Consider the patient's response to the current opioid.
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3. **Titrate the new opioid:**
   - Start with a lower dose and gradually increase as needed.
   - Monitor for side effects and adjust the dose accordingly.

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<thead>
<tr>
<th>Opioid</th>
<th>Acute Equivalent Dose (mg)</th>
</tr>
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<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
</tr>
<tr>
<td>Codeine</td>
<td>130</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>50</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>75</td>
</tr>
<tr>
<td>Levoorphine</td>
<td>6.3</td>
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<tr>
<td>Oxydextro</td>
<td>50</td>
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After patients take the same opioid dose for a week or two, they become tolerant of the opioid's side effects and may require higher doses to maintain their pain relief.

Opioids with a longer half-life, such as oxycodone, have a longer duration of action. This means that patients may need less of the new opioid to achieve the same effect. However, it's important to adjust the dose to the patient's individual needs and tolerance.

**Opioid conversion tips**

1. **Calculate the total daily dose of the opioid to be converted:**
   - Use this formula:
     \[ \text{Total Daily Dose (mg day)} = \text{mg dose x 24 hours} \]

2. **Choose an appropriate opioid:**
   - Consider the patient's response to the current opioid.
   - The "Dosing and Conversion Chart for Opioid Analgesics" can help determine the appropriate opioid.

3. **Titrate the new opioid:**
   - Start with a lower dose and gradually increase as needed.
   - Monitor for side effects and adjust the dose accordingly.

**Dose Chart**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Acute Equivalent Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
</tr>
<tr>
<td>Codeine</td>
<td>130</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>50</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>75</td>
</tr>
<tr>
<td>Levoorphine</td>
<td>6.3</td>
</tr>
<tr>
<td>Oxydextro</td>
<td>50</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
</tr>
</tbody>
</table>

**Reference:**
Opioid Rotation

- Studies have shown that patients with non-cancer pain may switch opioids approximately 3-4 times before achieving optimal analgesia.
- Shown effective in noncancer pain.
- Manages adverse effects and inadequate analgesia in patients on long-term COT.
- May improve efficacy.
- Patients may respond differently to different types of opioids.


Adequate Pain Relief but Adverse Effects
- Starting dose of new drug should be ↓ by 50-75% equianalgesic dose of old drug.

Poor Pain Control and Adverse Effects
- Starting dose of new drug should be ↑ by 75-100% equianalgesic dose of old drug.

Multimodal Analgesia

- The administration of two or more analgesics acting by different mechanisms with the goal of providing analgesic efficacy superior to a single analgesic.
- Targets different pain pathways.


Opioids

- MOA: Work by binding to mu, kappa, and delta opioid receptors to decrease pain perception and reaction to pain.
- Adverse Effects are dose dependent:
  - Constipation
  - Nausea/Vomiting
  - Sedation
  - Pruritus
  - Rare: CV effects, hyperalgesia, respiratory depression

Clinical Pearls

- Fentanyl
  - Δ Patch q 72 hrs
  - Should not be used PRN or as INITIAL therapy
  - Use caution with heat
  - Do not use more than 1 patch at a time
- Hydromorphone
  - CI in opioid naïve patients
  - 2 week washout with Exalgo and MAOIs
- Meperidine
  - Seizures: Normeperidine (active metabolite)
- Methadone
  - T ½: 15-55 h
  - Arrhythmias: QT prolongation

### Opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
</table>
| Morphine (MS Contin, Avinza, Kadian, Oramorph SR, Roxanol, Embeda) | IR: 10-30 mg q 4 h  
ER: 15-30-60-100-200 mg q 8-12 h |
| Fentanyl (Duragesic) | Patch: 12,35,50,75, 100 mcg/h |
| Hydromorphone (Olahudid) | 2,4,8 mg |
| Oxycodone (Oxycetin, Endocet, Percocet, Revsicet) | IR: 5,10,15,20,30 mg  
CR: 10, 15, 20, 30, 60, 80, 160 mg |
| Oxymorphone | Opana ER: 5-30 mg BID  
Opana IR: 5-10 mg PRN |
| Methadone (Dolophine, Methadose) | 2.5 – 10 mg q 8-12 h |
| Nalbuphine (Nemotar) | 50-150 mg q 2-4 h |
| Hydrocodone + APAP (Lorcet, Lortab, Vicodin, Norco) | 2.5, 7.5, 10 mg hydrocodone w/ 500, 650, 660, 750 APAP |
| Codeine + APAP (Tylenol #2,3,4) | 15-120 mg q 4-6 h PRN |
| Tramadol (Ultram, Ultram ER, Ryzolt-ER) | 50 mg: 37.5 mg with 325 mg APAP  
1-2 tabs q 4 h PRN |
| Tapentadol (Nucynta) | 50-100 mg q 4-6 h PRN |
Oxymorphone
- Take on an empty stomach
- Do not consume alcohol
- CI in moderate to severe liver impairment
Oxycodone
- BBW: Providers must report abuse/diversion
Tramadol
- ↓ Seizure threshold
Tapentadol
- ↓ Seizure threshold, renal/hepatic impairment
- Do not crush, chew, or break extended release
- CI within 2 weeks of MAOIs

Follow-up Visits
- Every week to 6 months
- Evaluate progress towards therapeutic goals
  - Physical and psychosocial assessment
  - Evaluate pain severity
  - Determine patients functional ability
  - Evaluate actual or potential adverse effects
- Drug screenings
  - Re-emphasizes expectations regarding appropriate and safe use of opioids
- Restructure opioid treatment plan as needed

Discontinuing COT
- Discontinue in pts who:
  - Continue aberrant drug-related behaviors
  - Lack progress toward therapeutic goals
  - Experience intolerable adverse effects
  - Slow Taper
    - ↓ dose by 10% weekly
  - Rapid Taper
    - ↓ dose by 25-50% every few days

True OR False?
- Total pain relief with chronic opioid therapy is common.
  - False
- Opioids do not have a ceiling effect.
  - True
- Patients become tolerant to constipation with continuous exposure to opioids.
  - False

A.K is a 57 year old male who presents to the pain clinic today with a chief complaint of chronic, dull, lower back pain. A.K describes the pain as a 6/10, however during work his pain may escalate to 8/10. A.K has been a truck driver for a local soda company for the past 20 years. He states that lately it is very difficult to bend and lift crates, and is very concerned about the pain and its interference with his performance at work.
- A.K has a past medical history of hypertension, diabetes, and hyperlipidemia. His labs are within normal limits.
- His current medications include Amlodipine 10 mg daily, Crestor 20 mg at bedtime, Actos 30 mg daily, Metformin 1000 mg twice daily, and Diovan-HCTZ 160 mg/25 mg.

References
Florida’s Claim to Fame: Pain Clinics and Narcotic Fraud
Dr. Cheryl A. Lindo, PharmD
Miami VA Medical Center
Miami, FL
January 20, 2012

Objectives
- Highlight Florida’s pharmaceutical trends
- Review diversion methods
- Discuss HB 7095 and E-FORCSE
- Review concerns about the Pill Mill Laws
- Discuss effects of Florida’s new laws

Where We Live
- South Florida’s Metropolitan Statistical Area includes Miami-Dade, Broward, and Palm Beach Counties
- International transportation hub and gateway to commerce and trade between the Americas
  - Port of entry for illicit drugs
- Lacked prescription monitoring system in Florida
- South Florida, specifically Broward County leading the nation in “Pill Mill” clinics

Florida Trends 2010
- 5,647 deaths with at least one prescription medication
- 7.4 deaths each day
- Broward County greatest number of deaths
- Miami-Dade County lowest per capita rates of prescription drug abuse
- Palm Beach County reported decline in mortalities

Graph: Pharmaceutical-Related Deaths in Florida, 2006-2010

Exhibit 1: Numbers of Substances Identified among Decedents in Florida: 2010

Source: Florida Department of Law Enforcement; Florida Medical Examiners Commission Report 2010


Florida Trends 2010

- Oxycodone
  - Nonmedical use in Florida
  - Higher ED reports than national rate
  - 93% deaths in combination with other drugs
- Oxymorphone
  - Fastest rising among opioid deaths
- Methadone
  - Most lethal prescription opioid


Florida Trends 2010

- Leading benzodiazepine occurrences
  - Alprazolam
  - Diazepam
- Greatest increase in total drug-related death occurrences
  - Nordiazepam (Nordaz®)
  - Oxazepam (Serax®)
  - Temazepam (Restoril®)


Drug Overdose Deaths

- Study in Palm Beach County
  - White male, late 30’s, high school diploma or GED
  - Death at home while asleep
  - One-third with substance abuse history and drug-related arrests
  - Most had prior non-fatal drug overdose
  - Most death were preventable with early intervention and public education


Oxycodone Sources 2009

- Dispensed by Practitioner, 83,000,000
- Dispensed by Pharmacist or Hospital, 446,000,000

Dispensing in Florida

- Average dose unit of oxycodone: 18mg compared to 13mg nationally
- 16.9% of the total grams of oxycodone distributed in the US
- Ranked #1 in total grams of oxycodone distributed nationally


Pain Clinics

- "Pill mills" - nickname for walk-in rogue pain-management clinics
- Source of prescription painkillers
- Florida’s reputation as “Oxy Express”
- Broward County
  - ~130 pain clinics operating
  - >1 million oxycodone tablets prescribed every month

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Pain Clinic Doctors

- Complicit doctors agreed to prescribe oxycodone and other controlled substances without regard to medical necessity
- Only cursory physical examination
- Prescribed “cocktail” of controlled substances
- No individualized treatment plans or showing medical need
- Physicians paid on per capita basis depending on number of patients examined each day

Diversion Methods

- Pain Management Clinics and inappropriate prescribing
- Doctor shopping
- Prescription fraud (forged, stolen, altered prescriptions)
- Pharmacy thefts; employee thefts
- Internet websites


Pain Clinics

- Knowingly prescribe large quantities of pain medications and other lucrative drugs
- No legitimate medical purpose
- Not within the usual course of professional medical practice
- Inferior, over-aggressive interpretations of radiological exams to justify prescriptions
- Drug tests falsified for a fee
- Required immediate cash payments or "visit fee"

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Doctor Shopping

- Individual visits several different doctors to obtain prescriptions for the same medication
- Prescriptions filled at different pharmacies
- Allows individual to obtain more of a prescribed substance than any one physician or pharmacist would allow
- Primary means for addicts to obtain prescription medication for illicit use
- Felony, punishable by up to 5 years in prison

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Prescription Fraud

- Prescriptions issued by physicians
  - Not for legitimate medical purpose
  - Not usual course of professional practice
- Use of blank prescription forms by unauthorized persons
  - Filled in the controlled substance, dosage to be prescribed, or DEA number of a physician without his or her knowledge or participation
  - Forged signature of physician

Prescription Fraud

- Providing false documentation in patient files to support issuance of fraudulent prescriptions for controlled substances
- Allowing the dispensing of controlled substances at the pharmacy
  - by persons not authorized to fill prescriptions
  - without the presence of supervision by a pharmacist
- Unlawful distribution of controlled substances without any prescription

Trafficking & Health Care Fraud

- Facilitators recruited beneficiaries of Medicare
- Provided transportation to pain clinics and pharmacies prior to taking and distributing drugs
- Beneficiaries brought prescriptions to complicit pharmacies that billed Medicare, knowing drugs medically unnecessary and are being re-sold
- Proceeds from drug trafficking $40,000,000

Pharmacy Theft

- Pharmacy employees
  - Manipulate computer inventory systems
  - Drug addiction
  - Trafficking
- Drug addicts and dealers
  - Robbing stores
  - Posing as repairman
  - Activate “false” alarm
  - Hide in stores until closed

Internet Websites

- Delivery to front door
- Offer to sell narcotics without a prescription
- “Membership fee” for no prior-prescription access
- Cursory written or oral “exam” with a physician
- Websites selling access to other sites that directly sells drugs without face-to-face physician consultation
- May sell real, similar, or counterfeit drugs

Consequence to Florida

- Prescription drug abuse fastest growing drug problem
- Pill mills facilitating the growth of this epidemic
- Increased numbers in
  - Drug addiction
  - Overdose
  - Pain and suffering
  - Death
- Rogue doctors running facilities and violating professional oath
House Bill 7095

- New Pill Mill Law, July 1, 2011
- Provides $3 million to support law enforcement and state prosecutors
- Requires doctors to report to Health Department within 10 days when starting or stopping work at a pain clinic.
- Levies fines of $10,000 and 6-month suspensions, on physicians who "over-prescribe" painkillers

Florida’s New Pill Mill Law

- Prescriptions and pain treatment plans technically more difficult for average doctor to write
- Requiring of electronic or counterfeit-proof prescription pads purchased from Health Department-approved vendors
- Pharmaceutical wholesaler/suppliers required to report all sales of controlled substances to the state
- Eliminates requirement for search warrant by law enforcement officers to view and copy a pain clinic’s records

HB 7095 Impacts Pharmacy

- Additional licensure requirements intended to prevent ownership and operation of pharmacies by felons and “other nefarious persons”
- Pharmacies required to develop policies and procedures to minimize dispensing based on fraudulent representations or invalid practitioner-patient relationships
- Annual criminal background screening required for principals associated with a pharmacy

Counterfeit-Proof Prescription Blanks/Pads

- Resist erasures and reproductions
- Blue or green background ink that resists reproduction
- “VOID” or “ILLEGAL” when copied
- Preprinted name, address, & category of professional licensure of prescribing practitioner and space for DEA number
- List of security features and description
- Unique tracking identification number
- No advertisement on blank
**Florida’s New Database**
- Creation of prescription drug monitoring database program
- Live November 1, 2011
- E-FORCSE
  - Electronic-Florida Online Reporting of Controlled Substances Evaluation
- To discourage doctor shopping and overprescribing
- Reduction of timeframe for dispensers to report from 15 days to 7 days

**Reporting Requirements**
- Doctor’s name and DEA number
- Date prescription filled
- Method of payment
- Full name, address, and DOB of person obtaining the prescription
- Name, quantity, and dosage of controlled substance
- Name & address of pharmacy or office dispensing medication
- Number of refills authorized and whether first-time request from medical practitioner

**Who Can Access Information**
- Health care practitioners (pharmacists and physicians) registered with the DOH
- Requests to database’s program manager (PM) by
  - Appropriate medical regulatory board
  - Attorney General’s Medicaid Fraud Unit
  - Law enforcement
  - Patients
  - Department of Health
  - Implementation & Oversight Task Force

**Benefits of E-FORCSE**
- Physicians or pharmacist can access database for patients
  - To avoid drug interactions
  - To determine if doctor shopping
- Identification of potential illegal diversion pattern for drugs
  - Patient Activity Report (PAR) disseminated
- Allows law enforcement, medical regulatory board/Medicaid fraud unit to request information for an active investigation

**Opposition to HB 7095**
- Restricts small, independently owned retail pharmacies from filling narcotic prescriptions
- The cost of record keeping will drive local community pharmacists out of business
- Loss of quality of standard of care provided by independent pharmacies
- Inconvenience to patients in need of chronic pain management therapy

**Patient Concerns**
- Requirement of using state Health Department-approved prescription pads
- Approximately 50,000 licensed physicians prescribing controlled substances in Florida
- Fear of inability to obtain legitimate prescriptions
- Requirement suspended until August 29 by State Surgeon General Frank Farmer
Drug Treatment Center Concerns
- Centers prepare for influx of new patients seeking help to overcome addiction
- State treatment facilities already at capacity prior to bill’s passing
- Funding by Florida Department of Children and Families (DCF) of locally-based drug programs ~$215 million possibly no longer enough
- Assistance with drug addiction issues can call the South Florida hotline 211 (Ft. Lauderdale) or 305-358-HELP (Miami)

Internet Concerns
- Online drugstores remain for drug seekers
- “Foreign” drugstores having ties to the U.S.
- Social internet medias, web browsers used
- Rising purchases in the last year
- 1,000+ Rogue internet pharmacies vanish and reappear
- Many pill mills have Internet businesses established

Other Concerns
- Addicts turning to other drugs
- Increase in heroin use
  - Increase prescription drug prices -$15 from $8 per pill
  - Increase difficulty of obtaining prescription medications
- Increase crime rate
- Lag time of reporting to database
- Not required to check database before writing prescription or dispensing drug
- Smaller pharmacies difficulty reporting

Florida War on Pill Mills
- Organized Crime Drug Enforcement Task Force (OCDETF)
- Crackdown on Pill Mills
  - Operation Oxy Alley
  - Operation Pill Nation
  - Operation Snake Oil
  - Operation Juice Doctor 2
- DEA Pill Mill Tip Line

Case Presentation
- A patient comes into the pharmacy and presents a prescription for oxycodone. What should you do?
  - Check E-FORSCE
  - Evaluate prescription for fraud
  - Enter prescription into E-FORSCE
  - Bonus question: It is discovered that the prescription is fraudulent. What does the new law require a pharmacist to do?
  - Report to the sheriff within 24 hours after learning of fraud or attempt at fraud

True of False?
- The length of time pharmacies are given to report prescription information into the state drug database is 15 days
  - False, it was shortened from 15 days to 7 days.
- People who are looking for assistance with drug addiction issues can call the South Florida 211 hotline
  - True, 211 (Ft. Lauderdale) or 305-358-HELP (Miami)
- The name of the new Florida drug database is called The Electronic Florida Online Reporting of Controlled Substances Evaluation
  - True, also known as E-FORSCE