Learning Objectives

- Select and monitor for acute & preventative treatment for adult patients with asthma, COPD & conditions requiring anticoagulation.
- Classify a patient according to asthma severity class, and assess his/her control, according to NHLBI guidelines.
- Discuss indications for warfarin, goal INR and duration of therapy for specific patients, and adjust therapy according to INR, other clinical findings and/or patient factors.
- Design a treatment plan for a patient receiving warfarin who needs to undergo an invasive procedure.
- Determine appropriate immunizations for an adult.

Ambulatory Topics Covered

- Asthma
- COPD
- Anticoagulation
- Adult Immunizations

Patient Case 1

BW is a 20-year-old woman who started attending aerobics class twice weekly. She is coughing and having trouble breathing during each class but it does not limit her activity.

What asthma severity class is BW in?

A. Intermittent
B. Mild persistent
C. Moderate persistent
D. Severe persistent

Conflict of Interest Disclosures

Ila M. Harris, Pharm.D.:
I have no conflicts of interest to disclose
Classifying Asthma Severity ≥ age 12

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Intermittent</th>
<th>Mild Persistent</th>
<th>Moderate Persistent</th>
<th>Severe Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Night awakenings</td>
<td>≤2 x/month</td>
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<td>&gt;once/week but not nightly</td>
<td>Often 7 x/week</td>
</tr>
<tr>
<td>B-agonist use for symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
<td>Several times per day</td>
</tr>
<tr>
<td>Interference with activity</td>
<td>None</td>
<td>Minor</td>
<td>Some</td>
<td>Extreme</td>
</tr>
<tr>
<td>Lung Function</td>
<td>Normal</td>
<td>Normal</td>
<td>FEV1, 60-80%</td>
<td>FEV1, &lt;60%</td>
</tr>
<tr>
<td>Risk</td>
<td>&lt;2 x/yr</td>
<td>≥2 x/yr</td>
<td>≥2 x/yr</td>
<td>≥2 x/yr</td>
</tr>
<tr>
<td>Treatment Step to Initiate</td>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 3</td>
<td>Step 4 or 5</td>
</tr>
</tbody>
</table>

Patient Case 2

- Which of the following medications is best to recommend for B.W. (intermittent asthma), in addition to albuterol MDI 1 or 2 puffs prior to exercise?
  - A. Albuterol MDI 1-2 puffs QID PRN
  - B. Montelukast 10 mg daily
  - C. Omalizumab 150 mg SC Q4 weeks
  - D. Mometasone MDI 220 mcg 1 puff daily

Classifying Asthma Severity ≥ age 12

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<td>Step 3</td>
<td>Step 4 or 5</td>
</tr>
</tbody>
</table>

Patient Case 3

- Your recommendation has slightly improved B.W.’s symptoms. However, now she started coughing at night about once weekly. What is the preferred medication to add?
  - A. Budesonide-formoterol MDI 80/4.5 2 puffs BID
  - B. Montelukast 10 mg daily
  - C. Salmeterol MDI 2 puffs BID
  - D. Fluticasone 110 mcg/puff 1 puff BID

Stepwise Therapy for Asthma for > 12 years of age

Assessing Control in Adults
Stepwise Therapy for Asthma for ≥ 12 years of age

Patient Case 4

BW returns one month later. No longer awakening at night. Uses albuterol MDI 2 puffs once per week to treat symptoms. She also uses albuterol MDI 2 puffs 5 days per week prior to working out at the gym; she does not have symptoms while working out. Which of the following is correct?

A. No medication change needed
B. Increase fluticasone to 110 mcg 2 puffs BID
C. Add formoterol inhalation BID
D. Add montelukast 10 mg/d

Patient Case 5

D.B. is a 9 year old boy with asthma symptoms 1-2 x/week. He is awakened twice weekly at night with coughing and trouble breathing. What is his asthma severity classification?

A. Intermittent
B. Mild persistent
C. Moderate persistent
D. Severe persistent

ICS Comparative Daily Doses ≥12 y/o

Classifying Asthma Severity: Age 5-11
**Patient Case 6**

- In addition to albuterol MDI 1-2 puffs every 4-6 hours as needed, which is best for D.B’s initial therapy?
  
  A. Beclomethasone 80 mcg/puff 1 puff BID  
  B. Montelukast 10 mg daily  
  C. Fluticasone-salmeterol 100/50mcg 1 puff BID  
  D. Fluticasone 110 mcg/puff 1 puff BID

**Classifying Asthma Severity: Age 5-11**

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Intermittent</th>
<th>Mild Persistent</th>
<th>Moderate Persistent</th>
<th>Severe Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>≤2 days / week</td>
<td>&gt;2 days / week but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Night Awakenings</td>
<td>≤2 x / month</td>
<td>&gt;3 x / month</td>
<td>&gt;once / week but not nightly</td>
<td>Often 7 x / week</td>
</tr>
<tr>
<td>B-agonist Use</td>
<td>≤2 days / week</td>
<td>&gt;2 days / week</td>
<td>Daily</td>
<td>Several times per day</td>
</tr>
<tr>
<td>Interference with activity</td>
<td>None</td>
<td>Minor</td>
<td>Some</td>
<td>Extreme</td>
</tr>
<tr>
<td>Lung Function</td>
<td>Normal</td>
<td>Normal</td>
<td>FEV1 60-80%</td>
<td>FEV1/FVC 75-80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FEV1 &lt;60%</td>
<td>FEV1/FVC&lt; 75%</td>
</tr>
<tr>
<td>Risk</td>
<td>Systemic Steroids</td>
<td>&lt;2 x / yr</td>
<td>≥2 / yr</td>
<td>≥2 / yr</td>
</tr>
</tbody>
</table>

**Stepwise Therapy for Asthma**

for 5-11 years of age

**ICS Comparative Daily Doses: Age 5-11**

*Recently approved for use < age 12; doses from package insert*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Dose Step 2 – 3</th>
<th>Medium Dose Step 3 – 4</th>
<th>High Dose Step 5 – 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide DPI (Pulmicort 90, 180)</td>
<td>180 – 400 mcg</td>
<td>&gt;400 – 800 mcg</td>
<td>&gt; 800 mcg</td>
</tr>
<tr>
<td>Fluticasone MDI (Flovent 44, 110, 220)</td>
<td>88 – 176 mcg</td>
<td>&gt;176 – 352 mcg</td>
<td>&gt; 352 mcg</td>
</tr>
<tr>
<td>Beclomethasone MDI (QVAR 40, 80)</td>
<td>80 – 160 mcg</td>
<td>&gt;160 – 320 mcg</td>
<td>&gt; 320 mcg</td>
</tr>
<tr>
<td>Mometasone DPI (Asmanex 110, 220)</td>
<td>110 mcg (QD)</td>
<td>110 mcg (QD)</td>
<td>110 mcg (QD)</td>
</tr>
<tr>
<td>Ciclesonide MDI (Alvesco 80, 160)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Budesonide for nebulizer use</td>
<td>0.5 mg</td>
<td>1 mg</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

**Patient Case 7**

- JH is a 25 year old woman is using Advair® (fluticasone/salmeterol) 250/50 1 puff BID and albuterol HFA 1-2 puffs q 4-6 hr PRN. You are developing an asthma action plan for her. What are her green zone instructions?
  
  A. Discontinue fluticasone/salmeterol  
  B. Use fluticasone/salmeterol regularly; may use albuterol HFA 1-2 puffs q 4-6 hr PRN  
  C. Use albuterol HFA 2 puffs; repeat in 20 minutes if needed, then reassess.  
  D. Use albuterol HFA 6 puffs; repeat in 20 minutes; start prednisone 50mg QD x 5 days

**Asthma Action Plan (Adults): Green Zone**

- Doing well, no symptoms  
- Take controller drug only  
- Use 2 puffs of SABA 5-15 min before exercise if exercise-induced asthma  
- May use SABA as needed for periodic mild symptoms
Patient Case 8

What are J.H.’s yellow zone instructions?

A. Albuterol HFA 1-2 puffs every 4-6 hr if needed
B. Albuterol HFA 2 puffs; repeat in 20 min, if needed, then reassess
C. Albuterol HFA 6 puffs; repeat in 20 min; start prednisone 50mg QD x 5 days, then reassess
D. Albuterol HFA 10 puffs; repeat every 20 min x 4 hours; start prednisone 50mg QD x 5 days, then reassess

Asthma Action Plan (Adults):
Yellow Zone

- Getting worse; some symptoms of wheezing and dyspnea
- Use SABA 2-6 puffs by MDI or 1 neb treatment; may repeat in 20 minutes if needed
  - Lower dose of 2-4 puffs SABA MDI usually recommended
- Reassess 1 hour after initial treatment

AAP: Yellow Zone
1 hour after initial treatment

Complete Response
- Consider OCS burst
- Contact clinician for f/u

Incomplete Response
- Repeat SABA; add OCS burst
- Contact clinician that day

Poor Response
- Repeat SABA; add OCS burst
- Contact clinician immediately; go to ER/call 911 if severe distress

Patient Case 9

What are J.H.’s red zone instructions?

A. Albuterol HFA 1-2 puffs every 4-6 hr if needed
B. Albuterol HFA 2 puffs; repeat in 20 min, if needed, then reassess
C. Albuterol HFA 6 puffs; repeat in 20 min; start prednisone 50mg QD x 5 days, then reassess
D. Albuterol HFA 10 puffs; repeat every 20 min x 4 hours; start prednisone 50mg QD x 5 days, then reassess

Asthma Action Plan (Adults):
Red Zone

- Medical alert; marked wheezing and dyspnea, inability to speak more than short phrases, use of accessory muscles, drowsiness
- Use SABA: 2-6 puffs by MDI or 1 neb tx; repeat in 20 minutes; if incomplete or poor response, repeat SABA again in 20 minutes
  - Higher dose of 4-6 puffs SABA MDI usually recommended
- Add OCS burst (prednisone 40-60mg/d x 5-10 d)

Asthma Action Plan (Adults):
Red Zone

- Proceed to ED or call 911 if distress is severe and unresponsive to treatment
- Call 911 or go to ED immediately if lips or fingertips are blue or gray, or if trouble walking or talking due to SOB
- Contact clinician immediately
- Continue SABA every 3-4 hr regularly for 1-2 days
**Patient Case 10**

- R.D. is a 25 y/o male presenting to the ED with SOB at rest. He is having trouble with conversation. He used 4 puffs of his albuterol MDI at home but it didn’t seem to help completely. FEV₁ is checked and it is 38% predicted. What is his severity of asthma exacerbation?
  - A. Mild
  - B. Moderate
  - C. Severe
  - D. Life-threatening

**Classifying Asthma Exacerbations in Urgent or ED Setting**

<table>
<thead>
<tr>
<th></th>
<th>Symptoms/Signs</th>
<th>Initial FEV₁/PEF (% predicted or personal best)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Dyspnea only with activity</td>
<td>≥ 70%</td>
</tr>
<tr>
<td>Moderate</td>
<td>Dyspnea limits or interferes with usual activity</td>
<td>40-69%</td>
</tr>
<tr>
<td>Severe</td>
<td>Dyspnea at rest; interferes with conversation</td>
<td>&lt; 40%</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>Too dyspneic to speak; perspiring</td>
<td>&lt; 40%</td>
</tr>
</tbody>
</table>

**Patient Case 11**

What is the best initial therapy for R.D. in the ED, in addition to oxygen?

- A. Oxygen alone is sufficient
- B. Inhaled albuterol MDI 8 puffs every 20 minutes for 1 hour
- C. Inhaled albuterol plus ipratropium via nebulizer every 20 minutes for 1 hour plus IV corticosteroids
- D. Inhaled albuterol plus ipratropium via nebulizer every 20 minutes for 1 hour plus OCS

**Initial Management of Exacerbation: ED or Hospital**

<table>
<thead>
<tr>
<th>Severity of Exacerbation</th>
<th>Initial Management</th>
</tr>
</thead>
</table>
| Mild-moderate (FEV₁ > 40%) | - Oxygen to achieve SaO₂ ≥ 90%  
- Inhaled SABA (MDI/spacer or neb) up to 3 doses in 1st hour  
- OCS if no response to initial therapy or if patient recently took OCS |
| Severe (FEV₁ < 40%)        | - Oxygen to achieve SaO₂ ≥ 90%  
- High-dose inhaled SABA plus ipratropium (MDI/spacer or neb) q 20 min or continuously for 1 hour  
- OCS  
- Consider adjunctive therapies (IV magnesium or heliox) if still not responsive |
| Life-threatening/Impending respiratory arrest | - Intubation and mechanical ventilation with oxygen ≥ 100%  
- Nebulized SABA plus ipratropium  
- Intravenous corticosteroids  
- Consider adjunctive therapies (IV magnesium or heliox) if still not responsive  
- Admit to intensive care |

**Diagnosis**

- **GOLD guidelines:**
- Consider COPD and perform spirometry if > 40 years old with any of the following:
  - Dyspnea
  - Chronic cough
  - Chronic sputum production
  - History of exposure to risk factors
  - Most common: tobacco smoke
## Diagnosis

- Criteria for diagnosis of COPD:
  - Symptoms and risk factors plus
  - FEV$_1$/FVC < 70%

## Validated Symptom Scales

- **Modified British Medical Research Council breathlessness scale (mMRC)**
  - Only measures severity of breathlessness
  - Score of 0-1: less symptoms
  - Score of ≥ 2: more symptoms
- **COPD Assessment Test (CAT)**
  - Measures health status impairment in COPD
  - [www.catestonline.org](http://www.catestonline.org)
  - Score of < 10: less symptoms
  - Score of ≥ 10: more symptoms

## Patient Case 12

S.H. is a 50 year old male smoker with COPD.
- Spirometry showed: FEV$_1$/FVC: 60%; Pre-bronchodilator FEV$_1$: 70% predicted; Post-bronchodilator FEV$_1$: 72% predicted
- Symptoms very bothersome; mMRC grade 2
- 1 exacerbation in past year

Which is most appropriate GOLD patient group?
- A. Patient Group A
- B. Patient Group B
- C. Patient Group C
- D. Patient Group D

## Patient Case 13

Which of the following is the most appropriate for S.H. to be started on, in addition to albuterol MDI 2 puffs q 4-6 hr PRN?
- A. Albuterol PRN alone is sufficient
- B. Formoterol inhaler 1 cap BID
- C. Salmeterol/fluticasone 50/500 1 puff BID
- D. Salmeterol/fluticasone 50/500 1 puff BID plus roflumilast (Daliresp) 500mcg PO once daily

## GOLD Guidelines: Assessment of Severity and Risk

![GOLD Guidelines Table]

## Pharmacotherapy for Stable COPD (GOLD)

![Pharmacotherapy Table]
### Treatment Guidelines

(ACP/ACCP/ATS/ERS)

- In patients with respiratory symptoms and I/E, between 0.0% and 90.0% of predicted, treatment with long-acting inhaled bronchodilators is suggested.
- For patients with respiratory symptoms and I/E, between 90.0% and 110.0% of predicted, treatment with long-acting inhaled bronchodilators is recommended.
- Monotherapy using long-acting inhaled anticholinergics or LABAs is recommended for symptomatic patients with FEV<sub>1</sub> < 60% of predicted. The choice of specific monotherapy should be based on patient preference, cost, and adverse effect profile.
- Combination therapy using long-acting inhaled anticholinergics, LABAs, or ICS may be used for symptomatic patients with FEV<sub>1</sub> < 40% of predicted.

### GOLD Guidelines: Assessment of Severity and Risk

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Characteristics</th>
<th>Symptomatic GOLD Classification&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Exacerbations per Year</th>
<th>Symptom Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low risk</td>
<td>1 Mild (FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 80% of pred) or 2 Moderate (50% &lt; FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 80% of pred)</td>
<td>≤ 1</td>
<td>mMRC 0–1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAT &lt; 10</td>
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<tr>
<td>B</td>
<td>Low risk</td>
<td>1 Mild (FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 80% of pred) or 2 Moderate (50% &lt; FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 80% of pred)</td>
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<td></td>
<td></td>
<td>CAT &lt; 10</td>
</tr>
<tr>
<td>C</td>
<td>High risk</td>
<td>3 Severe (30% &lt; FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 50% of pred) or 4 Very severe (FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 30% of pred)</td>
<td>≤ 2</td>
<td>mMRC 0–1</td>
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<td></td>
<td></td>
<td>CAT &gt; 10</td>
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<tr>
<td>D</td>
<td>High risk</td>
<td>3 Severe (30% &lt; FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 50% of pred) or 4 Very severe (FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 30% of pred)</td>
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<td>mMRC 0–1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>CAT &gt; 10</td>
</tr>
</tbody>
</table>

### Pharmacotherapy for Stable COPD (GOLD)

**Patient Case 14**

- K.R. is a 60 y/o man with COPD. Smokes ½ ppd. Gradual worsening of SOB over 1-2 years. FEV<sub>1</sub>/FVC: 55%; FEV<sub>1</sub>: 63%. CAT score: 10. Never had an exacerbation; no OCS in past 2 years. Meds: tiotropium (Spiriva<sup>®</sup>) QD and albuterol HFA prn. Which is most appropriate according to GOLD?
  - A. Add salmeterol 1 puff BID
  - B. Add long-term azithromycin 250 mg QD
  - C. Add fluticasone 110 mcg 2 puffs BID
  - D. D/C tiotropium & start Advair 250/50

### Roflumilast (Daliresp)

- Oral phosphodiesterase-4 inhibitor
- Anti-inflammatory; no direct bronchodilator activity
- Indicated as a chronic treatment to reduce the risk of COPD exacerbations in patients with severe COPD (FEV<sub>1</sub> < 50% pred) associated with chronic bronchitis and a history of exacerbations
- Studies show a reduction in exacerbations, and a reduction in the composite end-point of moderate exacerbations treated with oral or systemic corticosteroids or severe exacerbations requiring hospitalization or causing death. (Evidence: B)
- Also shown when roflumilast is added to long-acting bronchodilators. (Evidence: B) No comparison has been done with ICS.

### Chronic Azithromycin for Prevention of Exacerbations

- Recent study in patients with COPD at risk of exacerbations
- Azithromycin 250mg daily vs. placebo x 1 year
- Results:
  - Longer time to exacerbation (266 vs. 174 days; 90 days difference; p < 0.001)
  - Decreased rate of exacerbations (1.48 vs. 1.83; p = 0.01)
  - NNT to prevent one exacerbation of COPD: 28.6
  - QOL improved more with azithro vs. placebo (p=0.03)


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Chronic Azithromycin for Prevention of Exacerbations

- **Adverse effects:**
  - Hearing decrements were more common with azithromycin vs. placebo (25% vs. 20%, p=0.04) (NNH=20)
  - Increased incidence of colonization with macrolide-resistant organisms (81% vs. 41%, p<0.001)
- **However:**
  - The most recent GOLD guidelines still do not recommend treatment with antibiotics, except for when indicated during acute exacerbations.

Patient Case 15

- M.J. is a 56 y/o man with COPD (patient group A) who presents to clinic with several days of worsening SOB, coughing & production of “cloudy” sputum (much more sputum than usual). Pulse ox 95%. In addition to nebulized albuterol/ipratropium q 1-4 hours, what else should be added?
  - A. No additional therapy needed
  - B. Add oral prednisone 40 mg once daily for 10 days
  - C. Add TMP/SMX DS 1 tablet BID for 7 days
  - D. Add oral prednisone 40 mg once daily for 10 days and TMP/SMX DS 1 tablet BID for 7 days.

Managing Exacerbations

- Short-acting albuterol is preferred (Evidence C)
  - 2.5mg via nebulizer every 1-4 hours or
  - 4-8 puffs via MDI/holding chamber every 1-4 hr
  - Generally, short acting ipratropium is also given
- Systemic corticosteroids are effective (Evidence A)
  - Use in most exacerbations
  - GOLD guidelines no longer provide criteria
  - Dose in outpatients: 30-40 mg QD prednisolone or equivalent QD x 10-14 days (Evidence D)

- Antibiotics should be given if:
  - COPD exacerbation with all **THREE** cardinal symptoms (Evidence B)
  - COPD exacerbation with **TWO** cardinal symptoms, if one is increased **sputum purulence** (Evidence C)
  - **Severe** COPD exacerbation requiring mechanical ventilation (Evidence B)

Managing Exacerbations

- Empiric antibiotics are used to cover the most common pathogens: *Streptococcus pneumonia*, *Hemophilus influenzae* and *Moraxella catarrhalis*.
  - In Gold 3 and 4 patients, *Pseudomonas aeruginosa* is more prevalent
- Recommended antibiotic duration is 5 – 10 days (Evidence D)
### Antibiotics for COPD Exacerbations

<table>
<thead>
<tr>
<th>Uncomplicated COPD</th>
<th>Azithromycin, clarithromycin, doxycycline, TMP/SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated COPD with risk factors</td>
<td>Amoxicillin/clavulanate, levofloxacin, moxifloxacin</td>
</tr>
<tr>
<td>Risk of Pseudomonas Infection</td>
<td>High dose levofloxacin (750mg) or ciprofloxacin</td>
</tr>
</tbody>
</table>

Risk factors: comorbid diseases, severe COPD, > 3 exacerbations/year, antibiotic use in past 3 months.

### ANTICOAGULATION

**Patient Case 16**

J.J. is a 30 y/o woman receiving warfarin for a proximal DVT. She was taking oral contraceptives at the time her DVT was diagnosed; they have since been discontinued. Which of the following is correct with regards to the recommended duration of warfarin?

- A. 3 months
- B. 6 months
- C. 1 year
- D. Indefinite

---

### Anticoagulation for VTE

<table>
<thead>
<tr>
<th>TYPE OF VTE EVENT</th>
<th>INR</th>
<th>DURATION</th>
<th>EVIDENCE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT/PE with reversible risk factors</td>
<td>2 – 3</td>
<td>3 months</td>
<td>1A</td>
<td>Initiate warfarin together with LMWH or fondaparinux (preferred) or UFH and continue for ≥ 5 days &amp; until INR ≥ 2 for at least 24 hr</td>
</tr>
<tr>
<td>First unprovoked proximal DVT/PE</td>
<td>2 – 3</td>
<td>At least 3 months, then extended VKA if low-mod bleeding risk (2B); or 3 mo. total VKA if high bleeding risk (1B)</td>
<td>1A</td>
<td>First unprovoked isolated distal DVT: 3 months is sufficient. Treat recurrence of unprovoked VTE with extended therapy if low (1B) or moderate (2B) bleeding risk; or 3 months total VKA if high bleeding risk (2B)</td>
</tr>
</tbody>
</table>

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### Risk factors for bleeding (depends on severity, time interval, and if RF was corrected):

- **Low**: 0 risk factors
- **Moderate**: 1 risk factor
- **High**: ≥ 2 risk factors

- Anticoagulant control, comorbidity & functional capacity, recent surgery, frequent falls, EtOH abuse
Patient Case 17

M.H. is a 63 y/o woman with mechanical mitral valve replacement, HTN, dyslipidemia. Meds: warfarin 8 mg/d, aspirin 81 mg/d, lisinopril, atorvastatin. What is M.H.’s goal INR?

- A. 1.5 – 2.5
- B. 1.8 – 2.6
- C. 2 – 3
- D. 2.5 – 3.5

Patient Case 18

If M.H. had an aortic mechanical valve replacement (63 y/o woman with HTN, dyslipidemia, on warfarin, aspirin, lisinopril, atorvastatin), which of the following best represents her INR goal?

- A. 1.5 – 2.5
- B. 1.8 – 2.6
- C. 2 – 3
- D. 2.5 – 3.5

Patient Case 19

B.D. is a 79 y/o man taking warfarin 5 mg daily for a. fib. H/O depression and GERD. Meds: fluoxetine (started 1 mo. ago) & omeprazole (started 6 mo. ago). Has warfarin 5, 2 and 1 mg. Denies any signs/symptoms of bleeding. Last INR 6 wk ago (in range).

INR today: 8

Which of the following is the best way to deal with B.D.’s high INR?

- A. Hold warfarin x 1 day then restart at lower dose (do not check INR)
- B. Hold warfarin x 2 days then restart at a lower dose (do not check INR)
- C. Hold warfarin x 2 days, recheck INR, and restart warfarin at a lower dose when INR approaches 3
- D. Hold warfarin, give po vitamin K 2.5 mg x 1 then restart at lower dose when INR approaches 3
Warfarin Reversal Guidelines

<table>
<thead>
<tr>
<th>INR Range</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 - 5.0</td>
<td>No need to reverse anticoagulation. Monitor INR closely.</td>
</tr>
<tr>
<td>&gt; 5.0</td>
<td>Reversal with vitamin K. Cautiously, reinitiate warfarin at low dose when INR falls into therapeutic range.</td>
</tr>
<tr>
<td>No evidence of bleeding</td>
<td></td>
</tr>
<tr>
<td>&gt; 10.0 &amp; no evidence of bleeding</td>
<td>Consult medical management for decision.</td>
</tr>
</tbody>
</table>

Patient Case 20

- When warfarin is reinitiated in B.D., which of the following is the best dose to start (he was taking 5 mg daily)?

A. 5 mg 2 days/wk & 2.5 mg 5 days/wk
B. 2.5 mg/day
C. 4 mg/day
D. 4.5 mg 2 days/wk & 5 mg 5 days/wk

Adjusting Warfarin Dose

- For out-of-range INR, ▲ or ▼ cumulative weekly warfarin dose by 5%–20% depending on INR
- If INR is high, may hold 1-2 doses & resume at lower dose
- Usually do not need to adjust dose if INR is within 0.1 of goal (but monitor more closely)
- 2012 CHEST guidelines state that if INR stable/therapeutic and single out-of-range INR is ≤ 0.5 above or below goal, to continue current dose and recheck INR within 1-2 weeks (2C)
- Takes 5-7 days for dose change to reach full effect

Responding to INRs

- 2012 CHEST guidelines recommend against bridging with LMWH/UFH for a single subtherapeutic out-of-range INR in a normally stable patient (2C)
- 2012 CHEST guidelines suggest INR testing frequency of up to 12 weeks in patients who are consistently stable/therapeutic (2B)
- Previous testing frequency was every 4 weeks

Patient Case 21

- A 77 y/o man with atrial fibrillation, HTN, diabetes, and h/o TIA 3 years ago. Having major abdominal surgery in 1 week and will need to hold his warfarin. Which of the following is the most appropriate LMWH bridge therapy for him?

A. No bridge LMWH is needed; just hold warfarin
B. Enoxaparin 30 mg BID
C. Enoxaparin 1mg/kg BID
D. Either enoxaparin 30 mg BID or 1 mg/kg BID are options

Interruption of Warfarin for Procedures

- First:
  - Determine bleeding risk during procedure (often determined by the surgeon)
- Next:
  - Determine thromboembolic risk of patient's underlying condition
  - For minor dermatologic procedures or cataract removal, continue VKA and use local measures (2C).
  - 2012 CHEST guidelines changed recommendation for minor dental procedures: now can either continue VKA and use oral prohemostatic agent (e.g., tranexamic acid) OR stop VKA 2-3 days before procedure (2C).
**CHADS₂ Score**

- Categorizes thromboembolic risk in atrial fibrillation; assigns points for risk factors
- CHF (any history) – 1 point
- HTN – 1 point
- Age ≥ 75 – 1 point
- Diabetes - 1 point
- Stroke, TIA, systemic embolism - 2 points each

**Patient Case 21**

- A 77 y/o man with atrial fibrillation, HTN, diabetes, and h/o TIA 3 years ago. Having major abdominal surgery in 1 week and will need to hold his warfarin. Which of the following is the most appropriate LMWH bridge therapy for him?

\[ \text{CHADS}_2 \text{ score } = 5 \]

**High Risk of Thromboembolism**

\( (>10\% \text{ annual risk}) \)

- **Mechanical heart valve:**
  - Any mechanical mitral valve, older aortic valve (caged ball, tilting disk), recent stroke/TIA (past 6 mo.)
- **Atrial fibrillation:**
  - CHADS₂ score of 5 - 6, recent stroke/TIA (past 3 mo.), rheumatic valvular heart disease
- **VTE:**
  - Recent VTE (past 3 mo.), severe thrombophilia (protein C, protein S or antithrombin deficiency, antiphospholipid antibodies, or multiple abnormalities)

**BRIDGE with therapeutic dose LMWH**

**Bridging with LMWH**

- Stop warfarin approximately 5 days before surgery
- In 2 days, start therapeutic dose LMWH
  - Last dose the AM prior to surgery: consider half dose if using once-daily LMWH
- Check INR day before surgery if feasible; give 1-2 mg vitamin K if INR ≥ 1.5
- Post-op, commence LMWH (24 hr after minor surgery; 48-72 hr if major surgery/high bleeding risk) and warfarin (12-24 hr after surgery)
- Continue LMWH until warfarin therapeutic

**Therapeutic dose subcutaneous LMWH:**

- Enoxaparin 1 mg/kg BID
- Enoxaparin 1.5 mg/kg once daily
- Dalteparin 200 IU/kg once daily
- Dalteparin 100 IU/kg BID
- Tinzaparin 175 IU/kg once daily

**Low-dose subcutaneous LMWH:**

- Was previously a bridging option for low-moderate thromboembolic risk; 2012 CHEST guidelines removed this option; only therapeutic dose LMWH is recommended.

**Moderate Risk of Thromboembolism**

\( (5-10\% \text{ annual risk}) \)

- Decision to bridge or not is based on individual risk factors

**Low Risk of Thromboembolism**

\( (<5\% \text{ annual risk}) \)

- Do NOT bridge
**Dabigatran (Pradaxa)**
- Oral direct thrombin inhibitor (BID)
- Indicated for the prevention of stroke/systemic embolism in nonvalvular atrial fibrillation
- Store in original container; good for **4 months**
- Compared with warfarin:
  - Lower rates of stroke and systemic embolism
  - Similar rates of major hemorrhage, lower intracranial bleeding and higher GI bleeding
- No known agent to reverse bleeding
  - Levels/effect drop fairly quickly (t ½ 12-17 hr)
  - For serious bleeding, is dialyzable

**Rivaroxaban (Xarelto)**
- Oral direct factor Xa inhibitor (QD)
- Indicated for the prophylaxis of VTE in patients undergoing THR or TKR surgery.
- Studies show superiority to enoxaparin with no difference in major bleeding events.
- Duration: 35 days for THR; 12 days for TKR
- Also indicated for the reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation
- **Preliminary** data showing possible reversal by PCC

**Desirudin (Iprivask)**
- Specific inhibitor of human thrombin; FDA approved (SQ injection; BID)
  - Similar structure to hirudin, from medicinal leeches
- Indicated for DVT prophylaxis after THR surgery

**ADULT IMMUNIZATIONS**

**Patient Case 22**
- E.V. is a 71 y/o woman with COPD. Her only med is tiotropium inhaled 1 capsule/day. She received the influenza vaccine last October, her last Td vaccine was at age 65, and her pneumococcal vaccine was at age 60. She now cares for her new grandson (age 3 months). Which one of the following vaccines should she receive at her October clinic appointment?
  - A. Only the influenza vaccine should be given.
  - B. Influenza and pneumococcal polysaccharide vaccines should be given.
  - C. Influenza, pneumococcal polysaccharide, and zoster vaccines should be given.
  - D. Influenza, pneumococcal polysaccharide, zoster and Tdap vaccines should be given.
Early pneumococcal vaccination

- Pneumococcal vaccine is indicated prior to age 65 in:
  - Chronic lung disease (e.g., COPD, asthma)
  - Chronic CV disease
  - Diabetes
  - Chronic liver disease, cirrhosis
  - Chronic alcoholism
  - Functional or anatomic asplenia
  - Immunocompromising conditions
  - Smokers (age 19 – 64)
  - Cochlear implants, CSF leaks
  - Nursing home/LTCF patients

Revaccination with Pneumococcal Vaccine

- One time re-vaccination with pneumococcal vaccine is indicated 5 years after 1st vaccine in:
  - Chronic renal failure or nephrotic syndrome
  - Functional or anatomic asplenia
  - Immunocompromising conditions

- For persons ≥ 65 y/o, one-time revaccination if they were vaccinated ≥ 5 years ago and were < age 65 at time of first vaccination

Zoster Vaccine

- Zoster vaccine (Zostavax) is indicated in:
  - All adults age 60 and older
    - Although FDA approved for age 50 and older, ACIP only recommends at age 60 and older
    - Should receive, whether or not they have had a prior episode of zoster
    - Confusion over whether it can be given concurrently with pneumococcal polysaccharide vaccine (Pneumovax) or if they should be separated by 4 weeks
      - HZV package insert states not to give concurrently, but CDC states they can be given concurrently

Tdap:

- Everyone age 11–64 not previously vaccinated with Tdap (or unknown status) should be vaccinated with a one-time dose of Tdap
- Tdap specifically indicated for:
  - Adults of any age with close contact with infants younger than age 12 months
  - Pregnant women > 20 weeks gestation
  - Health care personnel
- Adults > 65 y/o may receive a single dose of Tdap if not previously vaccinated
- Tdap can be administered regardless of the interval since the last Td vaccine.

Recommended Adult Immunization Schedule 2012

Patient Case 23

- S.C.: 20 y/o female going away to college; living in the dorm. Smokes ½ ppd; no other medical conditions.
  - She is up to date with all her routine childhood vaccines, but no vaccines in the past 11 years. Not sexually active.

  What vaccines should she receive today?
  - A. Td and HPV vaccines.
  - B. Tdap, meningococcal and HPV vaccines.
  - C. Meningococcal, pneumococcal polysaccharide, and Td vaccines.
  - D. Meningococcal, pneumococcal polysaccharide, Tdap and HPV vaccines

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Meningococcal vaccine
- Two types: MCV4 (Menactra; quadrivalent); MPSV4 (Menomune)
- Age ≤ 57: MCV4 for age ≤ 55; MPSV4 for age ≥ 55
- First-year college students up through age 21 years who are living in residence halls should be vaccinated if they have not received a dose ≥ age 16
- No revaccination after 6 years even if still living in dormatory
- Functional asplenia
- Persistent complement component deficiencies
- HIV-infected persons
- Microbiologists exposed to isolates of Neisseria meningitidis
- Military recruits
- Persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic

HPV vaccine
- Recommended in both girls/women and boys/men
- Vaccinate at age 11-12, or between age 13-26 if not previously vaccinated
- For men, recommended up to age 21 but age 22-26 “may be vaccinated”; recommended up to age 26 in men who have sex with men (MSM)
- Ideally prior to sexual activity, but still give if sexually active
- Still administer to women with a h/o HPV, genital warts, abnormal pap, positive HPV DNA test
- Two different HPV vaccines available (HPV2-bivalent [Cervarix] & HPV4-quadrivalent [Gardasil])
- Either can be used for females; HPV4 recommended for males

Pneumococcal vaccine:
- Smoker age 19-64

Tdap:
- Everyone age 11–64 not previously vaccinated with Tdap (or unknown status) should be vaccinated with a one-time dose of Tdap

Recommended Adult Immunization Schedule 2012

2012 Updates in Therapeutics: The Pharmacotherapy Preparatory Review & Recertification Course

Endocrine and Metabolic Disorders
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Texas Tech University Health Sciences Center – School of Pharmacy
Conflict of Interest Disclosures

Dr Irons has no conflicts of interest to disclose.

Learning Objectives

- Focus on diabetes mellitus and disorders of the thyroid, adrenal, and pituitary glands
  - Diagnosis
  - Classification
  - Therapeutic agents
  - Treatment / Monitoring
- Review treatment of polycystic ovary syndrome and obesity
- Review treatment of diabetes-related complications

Thyroid Disorders

Focus on:

- Hyperthyroid Disorders
  - Graves' Disease (Autoimmune disorder)
    - Thyroid-stimulating antibodies mimic TSH
- Hypothyroid Disorders
  - Hashimoto's Disease (autoimmune-mediated)
  - Thyroid resection or ablative therapy

Thyroid Labs / Diagnosis

- Free T4 and TSH tell most of the story
- Hyperthyroid: Low TSH, elevated free T4
- Hypothyroid: High TSH (lack of negative feedback), suppressed free T4
  - TSH may be low or normal in secondary causes (e.g. pituitary cause)
- Thyroid antibodies
- Radioactive iodine uptake

Hyperthyroid Clinical Presentation

- Appetite increased
- Weight loss
- Goiter
- Heat intolerance
- Fine hair
- Palpitations / tachycardia
- Anxiety / insomnia / nervousness
- Moist skin / sweating
- Exophthalmos (bulging eyes)
Hypothyroid Clinical Presentation

- Weight gain
- Dry skin
- Cold intolerance
- Weakness / fatigue / lethargy
- Bradycardia
- Slow reflexes
- Coarse skin / hair

Thyroid Disorder: Goals

- Improve quality of life
- Minimize or eliminate symptoms
- Minimize long-term damage
- Normalize free T4 / TSH

Patient Case 1

63-year-old woman has Hashimoto’s disease.
Recent TSH = 5.6 mIU/L (0.5-4.5) and free T4 = 0.5 ng/dL (0.8-1.9).
Complains of dry skin and being rundown.
What is the best drug for initial treatment?

a) Levothyroxine
b) Liothyronine
c) Desiccated thyroid
d) Methimazole

Patient Case 2

43-year-old woman has diagnosis of Graves’ disease. Does not want to undergo ablative therapy and wants to try medications instead. TSH = 0.22 mIU/L (0.5-4.5), free T4 = 3.2 ng/dL (0.8-1.9). Complaints of feeling anxious and warm.
Which of the most appropriate initial option?

a. Lugol’s solution
b. Propylthiouracil
c. Atenolol
d. Methimazole

Treatment of Hyperthyroidism (Graves’)

- See references for updated 2011 guideline for hyperthyroidism (ATS/AACE)
- Treatment of choice: ablative therapy with radioactive iodine (surgical resection for most adenomas)
- Pharmacotherapy reserved for:
  - Awaiting ablative therapy or surgery (depletes stored hormone)
  - Not a surgical or ablative candidate (or refuses)
  - If ablative therapy or surgery fails to normalize thyroid function

Thioureas (aka Thioamides)

- Propylthiouracil (PTU) and Methimazole
- Inhibit iodination and synthesis of thyroid hormones
- Efficacy
  - Methimazole is preferred agent (based on ADR profile)
  - Monthly dose titrations (symptoms / TSH guide)
  - Low remission rate: 40-50% (1-2 years on therapy)
  - May take weeks for symptomatic improvement
  - 4-6 months for maximal effect
  - Neither drug appears more effective than the other
  - Mg-Mg: methimazole is 10x more potent
Thioureas (aka Thioamides): ADRs
- Hepatotoxicity with PTU (black box warning): Obtain baseline LFTs
- Arthralgias
- Fever
- Rash
- Transient leukopenia
- Agranulocytosis: Obtain baseline CBC

Other Agents used in Hyperthyroidism
- Beta-blockers: Primarily for symptomatic improvements (e.g. propranolol/nadolol) (tachycardia / anxiety / tremor / palpitations)
  - Recommended in elderly, symptomatic patients or those with heart rates > 90 bpm
- Iodines: (Lugol's solution / SSKI)
  - Block release (not synthesis) of hormone / May help in reducing size and vascularity of gland prior to surgery
  - Only used short-term (1-2 weeks): Gland will eventually begin to leach hormone

Hypothyroid Pharmacotherapy
- Drug of Choice: Synthetic T4 (levothyroxine)
  - Cost / antigenicity profile / potency / ADR profile
- Initial dose: 50-75 micrograms (lower in elderly or with CAD)
- Titrate based on T4/TSH and symptoms
  - 6 weeks to reach steady state (usual titration schedule)
- ADRs: Hyperthyroidism / angina / MI

Hypothyroid Pharmacotherapy
- Synthetic T3 (liothyronine): Less attractive alternative (higher CV ADR profile)
- Liotrix: T3/T4 mix – limited availability
- Desiccated thyroid: Not used much anymore

Patient Case 2
43-year-old woman has diagnosis of Graves' disease. Does not want to undergo ablative therapy and wants to try medications instead. TSH = 0.22 mIU/L (0.5-4.5), free T4 = 3.2 ng/dL (0.8-1.9). Complaints of feeling anxious and warm. Which if the most appropriate initial option?
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  a) Levothyroxine
  b) Liothyronine
  c) Desiccated thyroid
  d) Methimazole
Thyroid Storm Therapy

- Life-threatening thyrotoxicosis
- Infection / Trauma common causes
- Fever / Tachycardia / N-V / Dehydration / Delirium / Tachypnea / Coma
- PTU- 300-400 mg tid
- Iodide treatment: After PTU initiated
- Beta-blocker (e.g. esmolol / propranolol)
- APAP (avoid NSAIDs)
- Corticosteroid tx: 25-100 mg prednisone or equivalent

Pituitary Disorders

Acromegaly and Hyperprolactinemia

Patient Case 4

28-year-old woman with acne, facial hair growth, irregular menses for 6-7 months. Other diagnoses include HTN, depression (taking atenolol and fluoxetine). Both pituitary and thyroid tests are normal. Prolactin level today is 112 ng/mL (15-25). Which of the following is the most likely cause of her prolactin elevation?

a. Atenolol
b. Prolactin-secreting adenoma
c. Pregnancy
d. Fluoxetine

Acromegaly Therapy

- Somatostatin analog (octreotide): Blocks GH secretion
  - Commonly used agent
  - ADR: Lot of GI / hypothyroidism / arrhythmias / glucose abnormalities / biliary tract disorders
  - Good symptomatic relief (50-60% IGF-1 normalization)
- Dopamine Agonists (paradoxical decrease in GH production)
  - Bromocriptine / cabergoline
  - ADRs: Nervousness / fatigue / dizziness / GI
  - ~50% get symptom relief (10% obtain normal IGF-1)
- GH Receptor antagonist – pegvisomant
  - Very good IGF-1 normalization / long-term trials needed

Hyperprolactinemia Therapy

- Prolactinomas: Case where drug therapy may be better than surgery
  - Dopamine agonists
    - Cabergoline – More effective than bromocriptine
    - Bromocriptine
  - Drug-induced: SSRIs, anti-psychotics
  - DC offending agent
Patient Case 4
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a. Atenolol
b. Prolactin-secreting adenoma
c. Pregnancy
d. Fluoxetine

ADRENAL DISORDERS

Treatment Goals
- Reduce Morbidity and mortality
- Eliminate Cause (if known)
- Reverse clinical features
- Normalize biochemical changes
- Remission or long-term control without reoccurrence

Patient Case 5
44-year-old man with consistently elevated blood pressure (172/98) despite 2 BP agents. Complains of HA, thirst, fatigue. Urine free-cortisol is 45 mcg/24 hr (20-90) and plasma aldosterone:renin is 125 (<25). Which of the following is the most likely cause of his BP?

a. Cushing’s syndrome
b. Addison’s disease
c. Hyperprolactinemia
d. Hyperaldosteronism

Adrenal Disorders: Cushing’s Syndrome

- ACTH-Dependent: Excessive ACTH secretion via pituitary adenoma >> excessive cortisol secretion
- Clinical Presentation
  - Central obesity / facial rounding
  - Peripheral obesity / fat accumulation
  - Myopathies
  - Osteoporosis / back pain / fracture
  - Glucose intolerance / diabetes
  - HTN

Pharmacotherapy
- Ketoconazole (inhibits cortisol production)
  - Gynecomastia / GI discomfort / LFT increase
- Mitotane
  - Anorexia / Ataxia / GI discomfort / Lethargy
- Etomidate
  - IV only – reserved for rapid control or npo
- Metyrapone (compasionate use)
  - HTN / Hypoadrenalism / HA / GI / hirsutism / acne

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Adrenal Disorders: Hyperaldosteronism

- Primary aldosteronism
  - Bilateral adrenal hyperplasia: 70% of cases
  - Aldosterone-producing adenoma: 30% of cases
- Diagnosis / Clinical Presentation
  - Elevated plasma aldosterone
  - Hypernatremia / hypokalemia / hypomagnesemia
  - HTN / HA / Muscle fatigue or weakness / Polydipsia / Nocturnal polyuria

Treatment

- Aldosterone antagonists
  - Spironolactone (drug of choice) or Eplerenone
  - Hyperkalemia / Gynecomastia / GI discomfort
- Amiloride

Monitor

- BP
- Electrolytes
- Symptomatic relief

Plasma aldosterone:renin

Patient Case 5

44-year-old man with consistently elevated blood pressure (172/98) despite 2 BP agents. Complains of HA, thirst, fatigue. Urine free-cortisol is 45 mcg/24 hr (20-90) and plasma aldosterone:renin is 125 (<25). Which of the following is the most likely cause of his BP?

- a. Cushing’s syndrome
- b. Addison’s disease
- c. Hyperprolactinemia
- d. Hyperaldosteronism

Obesity

- Classification
  - Normal: 18.5-24.9
  - Overweight: 25.0-29.9
  - Class I: 30.0-34.9
  - Class II: 35.0-39.9
  - Class III: 40+

- Therapy
  - Diet / Exercise
  - Sibutramine (Meridia) pulled from market 2010
  - Orlistat – Inhibits gastric and pancreatic lipases >> reduced fat absorption
    - Rx (Xenical): 120 mg three times daily (up to 1 hour prior to meals)
    - OTC (Alli): 60 mg three times daily (up to 1 hour prior to meals)
    - LOTS GI ADRs: flatulence, oily stool, loose stool
**Obesity Therapy**
- Diethylpropion or Phentermine
  - Both scheduled meds (IV)
  - Should be used for limited duration (3 months)
  - HTN / tachycardia / dysrhythmias / constipation
  - Risk for abuse
- Phentermine/Topiramate – FDA Advisory
  - Committee approval February 2012
- Numerous ‘off label’ meds where weight loss is unintentional side effect (e.g. GLP-1 agonists, SSRIs, bupropion/naltrexone)

**Polycystic Ovary Syndrome (PCOS)**

**Polycystic Ovary Syndrome**
- Androgen excess or hyperandrogenism
- May be result of insulin resistance (regardless of body mass)
- Difficult consensus on classification and diagnosis
- Common signs: Hirsutism, acne, pattern alopecia
- Increased LH/FSH ratio (>2) and serum testosterone

**PCOS Therapy Goals**
- Improve fertility (if desired)
- Normalize menses / ovulation
- Minimize clinical signs
- Limit progression to Type 2 DM (mainly in those with obesity)

**PCOS Therapy Options**
- Clomiphene citrate
  - Selective estrogen receptor modulator (improves LH-FSH secretion)
  - ADRs: Flushing, GI discomfort, vaginal dryness, multiple pregnancies
- Recombinant FSH or GRH (+/- clomiphene)
  - May result in multiple pregnancies
- Metformin (commonly used with clomiphene)
- Symptomatic improvement with: Pioglitazone, spironolactone, estrogen-progesterone

**Diabetes Mellitus**
Diabetes Classification

- **Type 1 Diabetes Mellitus** (5-10% of DM)
  - Pancreatic beta-cell destruction / insulin required
- **Type 2 Diabetes Mellitus** (90-95% of DM)
  - Insulin resistance + decreased pancreatic insulin output
- Gestational diabetes
- Maturity-onset diabetes of the young (MODY)
- Others (pancreatitis, drug induced, genetic defects)

---

Patient Case 6

64-year-old AAF with a 27 pound increase in weight over the last year due to poor diet and activity. BMI = 44 kg/m². Both her mother and sister have type 2 diabetes. Fasting glucose today = 212 mg/dL. Which of the following is the best course of action?

a. Diagnose type 2 diabetes and begin to treat
b. Diagnose type 1 diabetes and begin to treat
c. Obtain another glucose concentration today
d. Obtain another glucose concentration another day

---

Screening for Diabetes

**Type 1 DM**

- If symptomatic (polyuria / polyphagia / polydipsia / weight loss)
- High risk asymptomatic (family history / transient hyperglycemia)

**Gestational DM**

- Previously dependent on risk (high / average / low)
- Recommendations by ADA
  - 24-28 weeks of gestation
  - 75 gram Oral Glucose Tolerance Test

---

Screening for Type 2 Diabetes

- Every 3 years starting at age 45
- Earlier if BMI ≥ 25 kg/m² and any of the below:
  - h/o CVD
  - IGT / IFG / mild increase in A1c (aka prediabetes)
  - Polycystic ovary syndrome
  - Low HDL or elevated TG
  - Hypertension
  - h/o gestational DM (or delivery of large baby)
  - High-risk ethnicity
  - First-degree relative with DM
  - Physically inactive

---

Type 1 and 2 DM Diagnosis (Based on glycemia)

- **Fasting Plasma Glucose** ≥ 126 mg/dL
- **Random Plasma Glucose** ≥ 200 mg/dL and symptomatic
- **Hemoglobin A1c** ≥ 6.5% (new in 2010)
Type 1 and 2 DM Diagnosis

- Elevated Plasma Glucose Post-OGTT
  - 2 hours after 75 g oral glucose ingestion
  - > 200 mg/dL
- Plasma Glucose if abnormal should be repeated on subsequent day (same test preferred)

Patient Case 6

64-year-old AAF with a 27 pound increase in weight over the last year due to poor diet and activity. BMI = 44 kg/m². Both her mother and sister have type 2 diabetes. Fasting glucose today = 212 mg/dL. Which of the following is the best course of action?

- a. Diagnose type 2 diabetes and begin to treat
- b. Diagnose type 1 diabetes and begin to treat
- c. Obtain another glucose concentration today
- d. Obtain another glucose concentration another day

Patient Case 7

56-year-old man with recent type 2 DM diagnosis. Has no other chronic diseases or h/o CVD. Which of the following sets of values is the best selection of goals for his sugar/BP/LDL?

- a. A1c < 6%, BP < 120/80, LDL < 70 mg/dL
- b. A1c < 7%, BP < 130/80, LDL < 100 mg/dL
- c. A1c < 6.5%, BP < 140/90, LDL < 130 mg/dL
- d. A1c < 8%, BP < 150/85, LDL < 160 mg/dL

Goals of Therapy in DM

- PREVENT ACUTE AND CHRONIC COMPLICATIONS!
- Acute: Hypoglycemia / DKA / HHNS
- Chronic:
  - Microvascular: Retinopathy / Neuropathy / Nephropathy
  - Macrovascular: Cardiovascular / Cerebrovascular / Peripheral vascular disease

ADA’s Glycemic Goals (non-pregnant adult)

- Fasting/Pre-meal Plasma Glucose: 70-130 mg/dL
- A1c: < 7.0% (< 6.5% per AACE/ACE)
  - Obtain every 3 months if uncontrolled
  - Obtain every 6 months if at goal
  - Can be less stringent in some patients
- Post-prandial (1-2 hours after meal): < 180 mg/dL
- Glycemic goals in gestational DM much more aggressive

Other Goals of Therapy

- Blood Pressure < 130/80 mm Hg
- LDL-C < 100 mg /dL
  - < 70mg/dL an ‘option’ with CVD
- Triglycerides < 150 mg/dL
- HDL > 40 (men), > 50 (women)
Benefits of Good DM Control

- **Glycemic Control**
  - Reduces microvascular complications

- **Cholesterol Control**
  - Reduces macrovascular complications

- **Blood Pressure Control**
  - Reduces both microvascular and macrovascular complications

---

Patient Case 7

56-year-old man with recent type 2 DM diagnosis. Has no other chronic diseases or h/o CVD. Which of the following sets of values is the best selection of goals for his sugar/BP/LDL?

a. A1c < 6%, BP < 120/80, LDL < 70 mg/dL
b. A1c < 7%, BP < 130/80, LDL < 100 mg/dL
c. A1c < 6.5%, BP < 140/90, LDL < 130 mg/dL
d. A1c < 8%, BP < 130/85, LDL < 160 mg/dL

---

Patient Case 8

52-year-old woman with newly diagnosed Type 2 DM. A1c = 7.8% and FBG today is 186 mg/dl. No other chronic disease states / CAD. Which of the following would be the best initial treatment of choice for this patient?

a. Implement lifestyle changes (diet/exercise)
b. Implement lifestyle changes plus metformin
c. Implement lifestyle changes plus sitagliptin
d. Implement lifestyle changes plus glargine

---

Areas of Action for DM Meds

- Glucosidase Inhibitors
  - Colesevelam

- GLP-1 Analogs
  - Bromocriptine

- Metformin
- TZDs
- Meglitinides
- DPP-4 Inhibitors

- GLP-1 Analogs
- Amylin Analog

---

Metformin

- **Initial Drug of Choice per leading guidelines**

- **Side Effect Profile**
  - Common
    - Gastrointestinal: Cramping, Diarrhea, N/V
  - Severe (but rare)
    - Lactic acidosis
  - Other
    - Hypoglycemia (uncommon with monotherapy)
    - Weight Loss
    - Triglyceride reduction
Metformin

**Precautions**
- High cardiovascular risk / Hypoxic state
- Elderly (80+): Potential for impaired renal function despite normal creatinine
- Heart failure (h/o significant exacerbations / unstable status)

**Contraindications**
- Increased serum creatinine
  - 1.4+ in women, 1.5+ in men

**In-Patient Metformin Issues:**
- Hold if undergoing radiological study using IV iodinated contrast dye (hold x 48 hr and get Cr before restarting)
- Hold if undergoing surgery (>minor)

---

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---

Type 2 DM Treatment Concepts

- Build upon existing therapy (unless significant ADRs or contraindications appear)
- The higher the baseline A1c the larger the drop in expected A1c with any therapy
- Additions to metformin (or in lieu of)
  - How high is the A1c
  - Fasting and / or post-prandial hyperglycemia
  - What precautions / contraindications exist
  - Cost
  - Oral vs injection preferences

---

Patient Case 9

A 66 yo man with T2DM x 4 years. History of pancreatitis. A1c today 7.7%. Current using diet/exercise (compliant) and 1000 mg bid metformin. Which of the following would be the best option for him?

a. Continue current therapy + improve diet/activity
b. Stop metformin, start exenatide 5 mcg bid
c. Add sitagliptin 100 mg daily
d. Add glyburide 5 mg bid

---

Patient Case 10

A 66 yo man with new diagnosis of T2DM. A1c = 8.2%, SCr 1.8 mg/dl. History of HF (NYHA class III), HTN, dyslipidemia. 2+ edema bilat. In addition to diet/exercise, which of the following would be the best option?

a. Metformin
b. Pioglitazone
c. Glipizide
d. Sitagliptin
### Sulfonylureas
- May affect both fasting and post-prandial glucose
- **Side Effect Profile**
  - Weight gain
  - Hypoglycemia
  - Rash
  - HA
  - GI complaints
  - SIADH (rare)

---

### Meglitinides
- Better Focus on Post-prandial BG than sulfonylureas
- Repaglinide likely better than nateglinide
- **Side Effect Profile**
  - Hypoglycemia (less than with sulfonylureas)
  - Weight Gain
  - URI
- **Precautions**
  - Concurrent use of gemfibrozil (increases repaglinide levels)

---

### Thiazolidinediones (TZDs)
- **Side Effect Profile**
  - Hypoglycemia (uncommon with monotherapy)
  - Weight gain
  - Peripheral edema
  - HDL increase / TG decrease (pioglitazone)
  - Bone fracture risk (women)
  - Heart failure risk (both agents): Black Box Warning
  - MI / Cardiovascular death (rosiglitazone – REMS)
  - Bladder cancer ? (pioglitazone)

---

### Alpha Glucosidase Inhibitors
- **Post-prandial glucose focus**
- **Side Effect Profile**
  - LOTS of GI side effects: Flatulence, diarrhea, cramping, pain, etc
  - Reason for slow titration
  - Increased LFTs at higher doses
- **Precautions / Contraindications**
  - Lower dosage in patients with renal impairment
  - Inflammatory bowel disease, ulcerative colitis, intestinal obstruction

---

### Colesevelam
- Mild reductions in A1c
- **Side Effects**
  - Constipation / dyspepsia / nausea / myalgia
- **Precautions / Contraindications**
  - Elevated triglycerides
  - Bowel obstruction
  - Difficulty swallowing
Bromocriptine

- Small reductions in A1c
- Side Effects
  - Fatigue / dizziness / nausea / vomiting / headache
  - Hypotension / syncope
- Precautions/Contraindications
  - h/o syncopal migraines
  - Nursing mothers
  - Limits effectiveness of antipsychotics

DPP-4 Inhibitors

- Sitagliptin / Saxagliptin / Linagliptin / Alogliptin / Vildagliptin
- Side Effect Profile (well tolerated)
  - GI complaints
  - Hypersensitivity (angioedema, exfoliative skin conditions, anaphylaxis)
- Precautions
  - Renal impairment (dose adjust except linagliptin)
  - History of pancreatitis

Incretin Mimetics

- GLP-1 analog (in Type 2 DM)
  - Exenatide
    - Byetta – Twice daily
    - Bydureon – Once weekly
  - Liraglutide (Victoza) – Once daily
- Amylin analog (in Type 1 and 2 DM)
  - Pramlintide (Symlin) – Three times daily pre-meals / initially reduce insulin doses
- None should be mixed with insulins

Exenatide and Liraglutide

- Side Effect Profile
  - Hypoglycemia (increased with sulfonylurea)
  - Weight Loss
  - Nausea
  - Vomiting
  - GI discomfort
  - Injection site discomfort
  - Pancreatitis risk

- Precautions
  - Existing gastroparesis
  - History of pancreatitis
  - Exenatide: Moderate renal impairment (<50 ml/min)
- Contraindications
  - Exenatide: CrCl<30 ml/min
  - Liraglutide: Medullary thyroid carcinoma

Exenatide and Liraglutide

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug Name</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Rapid-Acting</td>
<td>Aspart</td>
<td>5-15 minutes (10-20)</td>
<td>1-2 hours</td>
<td>4-6 hours</td>
</tr>
<tr>
<td></td>
<td>Lispro</td>
<td>5-15 minutes (15-30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glulisine</td>
<td>5-15 minutes</td>
<td>1-2 hours</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Short-Acting</td>
<td>Regular</td>
<td>0.5-1 hour</td>
<td>1-5 hours</td>
<td>6-10 hours</td>
</tr>
<tr>
<td>Intermediate</td>
<td>NPH</td>
<td>1-2 hours</td>
<td>4-8 hours</td>
<td>10-20 hours</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Detemir</td>
<td>2-4 hours</td>
<td>6-8 hours</td>
<td>3-4h (0.2-0.4)</td>
</tr>
<tr>
<td>Long-Acting</td>
<td>Glargine</td>
<td>1-2 hours</td>
<td>Not significant</td>
<td>~24 hours (Flat)</td>
</tr>
</tbody>
</table>
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d. Sitagliptin

Treating Type 1 DM

Patient Case 11
T2DM patient with A1c 7.6%. Insulin only regimen: Insulin detemir 60 units at bedtime
Insulin lispro 6 units before breakfast, 5 before lunch, and 8 before dinner.
Morning FBGs are consistently elevated (~160) and pre-meal BGs are all good (~125)
Denies hypoglycemia. Which of the following would be the best selection:

a. Increase dinnertime lispro to 10 units
b. Decrease his dinnertime lispro to 6 units
c. Increase his bedtime detemir to 65 units
d. Decrease his bedtime detemir to 55 units

Patient Case 12
Patient with T1DM is to start basal/bolus insulin therapy. Patient weighs 110 lb. MD wishes to start total daily insulin needs at 0.4 units/kg/day. Which of the following would be the most appropriate basal insulin regimen?

a. 20 units insulin glargine once daily
b. 20 units insulin detemir once daily
c. 10 units of insulin aspart once daily
d. 10 units of insulin glargine once daily

Patient Case 13
Patient with T1DM on basal/bolus insulin tx. Detemir 13 units once daily
Insulin lispro 4 before breakfast, 3 before lunch, and 4 before dinner (and stable)
Implement correctional dosing strategy – Which is the best estimate of the # of mg/dL decrease BG with 1 unit of lispro?

a. 25 mg/dL
b. 50 mg/dL
c. 75 mg/dL
d. 85 mg/dL
Natural Insulin Secretion

Plasma Insulin (µU/mL)

Breakfast Lunch Dinner

0:00 12:00 16:00 20:00 24:00 0:00

Time

Treating Type 1 DM

- Basal / Bolus Insulin Regimens (mimic nature)
  - Basal to prevent ketosis and control fasting BG
  - Detemir / Glargine / (NPH)
  - Bolus to control post-prandial glucose excursions
  - Glulisine / Aspart / Lispro / (Regular)

Assessing Therapy and Dosage Adjustment

- Know your goal fasting and post-prandial BGs
- Identify where in the day problems occur
- Determine which insulin(s) can affect problem areas
- Adjust medication (or behavior)

Treating Type 1 DM

- Initial treatment often weight-based estimate
  - e.g. 0.6 units/kg/day = total daily insulin (TDI) needs
- Basal is 50% of total daily insulin needs
- Bolus is 50% of total daily insulin needs split three ways and given prior to each meal
- "Correctional Dosing": 1800/TDI = # mg/dL estimate decrease by 1 unit of rapid insulin

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- Insulin lispro 6 units before breakfast, 5 before lunch, and 8 before dinner.
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Patient with T1DM is to start basal/bolus insulin therapy. Patient weighs 110 lb. MD wishes to start total daily insulin needs at 0.4 units/kg/day. Which of the following would be the most appropriate basal insulin regimen?

50 kg x 0.4 = 20 units (TDI) /2 = 10

1. a. 20 units insulin glargine once daily
   b. 20 units insulin detemir once daily
   c. 10 units of insulin aspart once daily
   d. 10 units of insulin glargine once daily
Patient Case 13

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Insulin lispro 4 before breakfast, 3 before lunch, and 4 before dinner (and stable)

Implement correctional dosing strategy – Which is the best estimate of the # of mg/dL decrease BG with 1 unit of lispro?

a. 25 mg/dL
b. 50 mg/dL
c. 75 mg/dL
d. 85 mg/dL

Treatment of Diabetes Complications

Hypoglycemia
- Treatment depends on degree of hypoglycemia
- Plasma glucose < 70 mg/dl (+/- symptoms)
- Mild-moderate low BGs: 15-20 gm oral glucose or equivalent
- Severe (cognitive impairment, requires help):
  - 1 mg IM glucagon
  - IV Dextrose

Diabetic Ketoacidosis
- Significantly elevated BG / ketoacidosis / dehydration
- Signs/symptoms: Thirst, abdominal pain, mental status changes, fruity breath, tachycardia, low Na / high K, ketones in urine/serum
- Most common causes: infection/acute illness or inappropriate/inadequate insulin therapy

DKA-Treatment (see ADA statement)
- Find and fix underlying cause (if known)
- NOT about normalizing blood glucose
- Fluid Replacement (IV Na% depends on serum Na)
- IV insulin: 0.1 unit/kg bolus, 0.1 unit/kg/hr drip (double drip rate if minimal response)
  - Hold if baseline serum K < 3.3 meq/L until corrected
- Potassium supplementation: Depends on baseline K

DKA Treatment Goals
- Serum glucose < 200 mg/dL and at least 2 of the following:
  - pH > 7.3
  - Serum bicarbonate ≥15 meq/L
  - Anion gap ≤ 12 mEq/L
- Convert IV drip to subcutaneous insulin
Screening for DM Microvascular Complications

- Type 2 DM: At diagnosis
- Type 1 DM: At 5 years post-diagnosis
- Screen yearly thereafter

<table>
<thead>
<tr>
<th>Urine albumin / creatinine (mg/g or mcg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>Macroalbuminuria (Proteinuria / overt nephropathy)</td>
</tr>
</tbody>
</table>

Diabetic Nephropathy

Diabetic Neuropathic Pain

- TCAs (smaller doses than in depression)
  - Desipramine / Nortriptyline / Amitriptyline
- Anticonvulsants
  - Gabapentin / Lamotrigine / Pregabalin
  - May be better tolerated than TCAs
- SSRIs / SSNRI
  - Duloxetine
- Tramadol/APAP

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- TCAs (smaller doses than in depression)
  - Desipramine / Nortriptyline / Amitriptyline
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  - May be better tolerated than TCAs
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  - Duloxetine
- Tramadol/APAP

Cardiovascular Disease Prevention

- Blood pressure control:
  - Regimen ideally contains an ACE-Inhibitor or ARB (goal < 130/80)
  - Take 1+ BP med at bedtime
- Cholesterol control: Statin therapy regardless of baseline LDL-C (goal < 100 mg/dL)
  - In established heart disease patients (LDL < 70 is ‘option’)
  - > 40 years old with other CVD risk factors
  - If LDL-C still not below 100 mg/dL, despite statin therapy, 30-40% reduction is alternative

Cardiovascular Disease Prevention

- Aspirin Therapy (75-162 mg daily)
  - Secondary prevention: All unless contraindicated
  - Primary prevention
    - 2010 ADA Changes
      - 10-year risk for cardiovascular event is > 10%
      - Will include most men > 50 and women > 60 with at least one other CVD risk factor
    - Clopidogrel is alternative in ASA allergy/intolerance