Updates in Pharmacotherapy

Cardiology, Diabetes, and Community-Acquired Infections
Learning Objectives

- Discuss new antiplatelet and oral anticoagulants and their practical uses
- Review the 2013 American Diabetes Association Diabetes Care guideline and new oral agents
- Review appropriate antimicrobial regimens for common outpatient infections (CA-MRSA, UTI, CAP)
New Drugs in Cardiology

Oral Antiplatelets and Anticoagulants
Post-PCI Antiplatelet Therapy

- Endothelial dysfunction $\rightarrow$ plaque formation $\rightarrow$ plaque rupture $\rightarrow$ clot formation $\rightarrow$ platelet activation

Image credit: http://www.escardio.org/communities/councils/ccp/e-journal/volume8/PublishingImages/ej-vol8n21-fig1.jpg
### Available Agents

<table>
<thead>
<tr>
<th>P2Y12 Inhibitors</th>
<th>Indication</th>
<th>Maintenance Dosing</th>
<th>Recommendation (Classification of Recommendation and Level of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel (Plavix®)</td>
<td>ACS managed medically or with PCI</td>
<td>75 mg PO daily</td>
<td>IB</td>
</tr>
<tr>
<td>Prasugrel (Effient®)</td>
<td>ACS with PCI</td>
<td>10 mg PO daily</td>
<td>IB</td>
</tr>
<tr>
<td>Ticagrelor (Brilinta®)</td>
<td>ACS managed medically or with PCI</td>
<td>90 mg PO BID</td>
<td>IB</td>
</tr>
</tbody>
</table>

**Duration of therapy:**
- Drug Eluting Stent (DES) = 1 year
- Bare Metal Stent (BMS) = 30 days; up to 1 year

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Compared to Clopidogrel

- Mortality benefit
- More potent
  - 40% vs 70-80% platelet inhibition
- Increased major bleeding – prasugrel
- Increased fatal intracranial bleeding – ticagrelor
- No CYP 2C19 interaction (omeprazole)
- Dyspnea associated with ticagrelor (adenosine analogue)

Important Contraindications

### Prasugrel
- History of TIA/stroke

### Ticagrelor
- History of intracranial bleeding
- Severe hepatic impairment

Other:
- Active pathological bleeding (e.g. peptic ulcer, intracranial bleed)
- Hypersensitivity
Considerations

- **Age and weight for prasugrel**
  - > 75 years – NOT recommended
  - < 60 kg (132lbs) – consider dose reduction (5mg daily)

- **Ticagrelor reversibility**
  - Reversible binding to P2Y12 receptor
  - Major bleed management more difficult

- **Ticagrelor/aspirin DAPT**
  - Maximum dose aspirin **81mg**
Patient Case

- A 63 year old male presents with crushing chest pain. PMH is significant for h/o NSTEMI s/p PCI with DES x1 to the left circumflex in 2012, HTN, HLD, and h/o CVA. The ECG reveals ST elevation. The patient is taken to cath lab where angiography reveals in-stent thrombosis of the left circumflex, and PCI is performed with a new DES.

- Home medications:
  - Aspirin 325 mg daily
  - Clopidogrel 75 mg daily
  - Atorvastatin 80 mg daily
  - Coreg CR 20 mg daily
  - Lisinopril 10 mg daily

What changes could be made to the antiplatelet regimen?
Summary and Pearls

- Know patients’ stroke and bleeding history
- Ticagrelor and aspirin dosing

Reserve for low bleeding risk or stent thrombosis
New Oral Anticoagulants (NOAC)

Direct Thrombin Inhibitor
- Dabigatran (Pradaxa®)

Factor Xa Inhibitors
- Rivaroxaban (Xarelto®)
- Apixaban (Eliquis®)

Image credit: http://www.neurology.org/content/78/7/501/F2.large.jpg
## FDA-Approved Indications and Dosing

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Indication</th>
<th>Standard Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1. Stroke prevention in nonvalvular AFib</td>
<td>1. 150 mg PO BID</td>
</tr>
<tr>
<td></td>
<td>2. Post-op hip/knee replacement surgery VTE ppx</td>
<td>2. 10 mg PO daily &lt;br&gt; • DOT 12-14 days (knee), 35 days (hip)</td>
</tr>
<tr>
<td></td>
<td>3. DVT/PE treatment</td>
<td>3. 15 mg twice daily with food for 3 weeks followed by 20 mg once daily with food</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1. Stroke prevention in nonvalvular Afib</td>
<td>1. 20 mg PO daily</td>
</tr>
<tr>
<td></td>
<td>2. Post-op hip/knee replacement surgery VTE ppx</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. DVT/PE treatment</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>1. Stroke prevention in nonvalvular AFib</td>
<td>1. 5 mg PO BID</td>
</tr>
</tbody>
</table>

*ALL require RENAL adjustment*
Compared to Warfarin

- Rapid anticoagulation (no bridging)
- Fewer labeled indications
  - Prosthetic cardiac valves – dabigatran *contraindicated*
  - Hypercoagulable disease states
- No established reversal agents/antidotes
- No routine lab monitoring (risk vs benefit)

Dabigatran Considerations

- **Dosing**
  - 150 mg vs 75 mg

- **Renal function**
  - US labeling: CrCl < 15 mL/min = not recommended
  - Canadian labeling: CrCl < 30 mL/min = **contraindicated**
  - CHEST Guidelines: CrCl < 30 mL/min = **contraindicated**

- **Age**
  - ≥ 80 years – EXTREME caution

- **Bleeding**
  - GI bleeding
  - FDA Safety Announcements

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You JJ, et al. Chest 2012;141:e531s-75s
## Factor Xa Inhibitors and ACS

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATLAS-ACS</strong></td>
<td><strong>APPRAISE-2</strong></td>
</tr>
<tr>
<td><strong>ATLAS-ACS2-TIMI 51</strong></td>
<td></td>
</tr>
<tr>
<td>Dose: 2.5 mg BID or 5 mg BID</td>
<td>Dose: 5 mg BID</td>
</tr>
<tr>
<td>Increased major bleeding but not fatal bleeding</td>
<td>Terminated early</td>
</tr>
<tr>
<td>Reduction in cardiovascular events</td>
<td>Increased major bleeding, no benefit recurrent ischemic events</td>
</tr>
</tbody>
</table>

## Place in Therapy Pearls

### Conversion Between Anticoagulants

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Switching FROM warfarin</th>
<th>Switching TO warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D/C warfarin and start NOAC when…</td>
<td>D/C NOAC and start warfarin…</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>INR &lt; 2</td>
<td>Overlap based on CrCl:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &gt;50 mL/min: 3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 31-50 mL/minute: 2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 15-30 mL/minute: 1 day</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>INR &lt; 3</td>
<td>24h after last dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>INR &lt; 2</td>
<td>Next scheduled dose</td>
</tr>
</tbody>
</table>

**NOTE:** All three agents falsely elevate INR
Patient Case

- A 65 year old female with PMH significant for atrial fibrillation, HTN, CKD 3 (baseline SCr 1.5), and systolic heart failure (EF 40%). She has had difficulty with labile INRs and would like to consider switching to one of the new anticoagulants. She weighs 55kg and is 5’2”. INR is 3.2.

- Current medications:
  - Toprol XL 50 mg daily
  - Lisinopril 10 mg daily
  - Furosemide 20 mg BID
  - KCl 20mEq daily.

Which of the new anticoagulants would be reasonable to try? And what adjustments would be necessary?
Summary

- All NOACs
  - Affect INR
  - Require renal adjustment
  - Have fewer indications than warfarin
  - Lack antidotes
Diabetes Management Update

New Guidelines and Oral Medications
Standards of Medical Care in Diabetes: Treatment and Prevention Goals

- **A1c**
  - < 7% non-pregnant adults
  - < 6.5% long life-expectancy, no hypoglycemia, no CVD
  - < 8% hypoglycemia, short life-expectancy, significant co-morbidities

- **Blood Pressure**
  - 140/80

- **Lipids**
  - LDL < 100 (optional < 70)
  - HDL > 50
  - TG < 150

Initial Approach to Treating Hyperglycemia in Type 2 Diabetes

Markedly symptomatic and/or hyperglycemic

Metformin

Insulin

A1c at target in 3-6 months

Add another PO agent*, GLP-1 agonist, or Insulin

Continue therapy

PO Agent Options:
- Sulfonylureas
- Thiazolidinediones
- DPP-4 Inhibitors

Overview of Combination Therapy

Dipeptidyl Peptidase 4 (DPP-4) Inhibitors

- Block deactivation of GLP-1
  - Slow gastric emptying
  - Block glucagon release
  - Suppress appetite
  - Promote insulin secretion following absorption of food

- Monotherapy if intolerance or contraindication to metformin, sulfonylureas, or thiazolidinediones
New DPP-4 Inhibitors

- Alogliptin (Nesina®)
- Linagliptin (Tradjenta®)

Combination

- Linagliptin + metformin (Jentadueto®)
- Sitagliptin + simvastatin (Juvisync®)

Older DPP-4 Inhibitors:

- Sitagliptin (Januvia®)
- Saxagliptin (Onglyza®)
### Comparison of DPP-4 Inhibitors: Place in Therapy

<table>
<thead>
<tr>
<th>DPP-4 Inhibitor</th>
<th>Standard Dosing</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin (Januvia®)</td>
<td>100 mg PO daily</td>
<td>Renal</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza®)</td>
<td>2.5 – 5 mg PO daily</td>
<td>Renal</td>
</tr>
<tr>
<td>Alogliptin (Nesina®)</td>
<td>25 mg PO daily</td>
<td>Renal</td>
</tr>
<tr>
<td>Linagliptin (Tradjenta®)</td>
<td>5 mg PO daily</td>
<td><strong>NONE</strong></td>
</tr>
</tbody>
</table>

#### Adverse Effects to Consider
1. Nasopharyngitis
2. URI
3. Pancreatitis (sitagliptin, alogliptin, linagliptin)
Patient Case

- A 56 year old woman with DM2, HTN, HLD, and CKD3 (baseline SCr 1.7) presents to diabetes clinic for follow-up. A1c 8%. She states she has been compliant with lifestyle modifications.

- Current medications:
  - Metformin 1000 mg BID
  - Lisinopril 20 mg daily
  - Simvastatin 40 mg daily
  - Amlodipine 5 mg daily

Which DPP-4 inhibitor would be ideal for this patient?
Hot off the Press: Canagliflozin (Invokana®)

- Sodium-glucose co-transporter 2 (SGLT2) inhibitor
- Blocks renal reabsorption of glucose
  - Increases urinary concentration glucose
  - Risk of yeast infection
- Lowers HbA₁c levels by 0.5–1.5%
- Dosing: 100-300 mg PO daily
  - Requires renal adjustment

Summary

- New BP goal = 140/80
- DPP-4 inhibitors are just another option for combination therapy with metformin
  - All but linagliptin require renal adjustment
- Look out for more about SGLT2 inhibitors
Outpatient Infectious Diseases Review

Community Acquired MRSA Skin Infections, Urinary Tract Infections, and Community Acquired Pneumonia
Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

- Common pathogens
  - *Staphylococcus aureus*
  - *Streptococcus pyogenes*
- Less common – gram negatives, anaerobes (unless risk for polymicrobial infections)
- Becoming more prevalent:
  - **Community acquired MRSA (CA-MRSA)**
  - Most common strain in the US: USA300

Image credit: http://microbewiki.kenyon.edu/images/3/3d/Just_staphylococcus_aureus.jpg
Treatment Guideline Recommendations

1. I&D

2. Antibiotics:
   - Severe/extensive disease or rapid progression of symptoms
   - Signs/symptoms systemic illness
   - Immunosuppression
   - Extremes of age
   - Difficult to drain area (face, hand, genitalia)
   - Septic phlebitis
   - Failure of initial I&D

3. Duration of therapy: 5-10 days

Empiric Therapy

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Dose</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>300-450 mg PO TID</td>
<td>• Significant GI effects may limit dose&lt;br&gt;• Higher risk of C diff</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (TMP-SMX)</td>
<td>1-2 DS tab PO BID</td>
<td>• Pregnancy category C/D&lt;br&gt;• Contraindicated in:&lt;br&gt;  • 3rd trimester&lt;br&gt;  • Age &lt; 2 months</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg PO BID</td>
<td>• Pregnancy category D&lt;br&gt;• Contraindicated in:&lt;br&gt;  • Age &lt; 8 years</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg PO BID</td>
<td>• Expensive</td>
</tr>
</tbody>
</table>

Urinary Tract Infections

**Complicated**
- Catheter-associated
- UTIs in males

**Uncomplicated**
- Cystitis
- Pyelonephritis
Uncomplicated Cystitis and Pyelonephritis in Women

- **Common pathogens**
  - *Escherichia coli*
  - *Proteus mirabilis*
  - *Klebsiella pneumoniae*
  - *Staphylococcus saprophyticus*


Image credit: http://2.bp.blogspot.com/-sWt9ln87erY/TkQmiKPAcYI/AAAAAAAAAFU/-vA1oN8zrYY/s1600/E_coli_.jpg
### Empiric Treatment Guidelines: Cystitis

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Dose</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin*</td>
<td>100 mg BID x 5-7 days</td>
<td>• Avoid use in elderly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ineffective if CrCl &lt; 60</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (TMP-SMX)</td>
<td>1 DS tab BID x 3 days</td>
<td>• Resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pregnancy category C/D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Contraindicated in:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 3rd trimester</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Age &lt; 2 months</td>
</tr>
<tr>
<td>Fosfomycin trometamol*</td>
<td>3 g x1</td>
<td>• CDiff risk associated with long-term use</td>
</tr>
<tr>
<td>Fluoroquinolone (levofloxacin or ciprofloxacin ONLY)</td>
<td>Levo: 250 mg daily Cipro: 500 mg BID X 3 days</td>
<td>• 2nd line</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Avoid coadministration with multivitamin (Ca, Mg, Al)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• QTc prolongation</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>500 mg BID x 3-5 days</td>
<td>• Adjust for CKD</td>
</tr>
</tbody>
</table>

### Empiric Treatment Guidelines: Pyelonephritis

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Dose</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| Fluoroquinolone                      | Levo: 750 mg daily x 5 days, Cipro: 500 mg BID x 7 days | • Avoid coadministration with multivitamin (Ca, Mg, Al)  
  • QTc prolongation                  |
| Trimethoprim-sulfamethoxazole (TMP-SMX) | 1 DS tab PO BID x 14 days                 | • Pregnancy category C/D  
  • Contraindicated in:  
  • 3rd trimester  
  • Age < 2 months                 |

**UTI vs Asymptomatic Bacteruria**

- **Definition:**
  - 2 consecutive urine samples
  - Same bacterial strain
  - Colony count $\geq 10^5$ CFU/mL
  - $+$ pyuria
  - **No symptoms**

- **Treatment**
  - **ONLY for pregnant females or recent bladder instrumentation**
  - DOT 3-7 days

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Patient Case

- An 80 year old female presents to urgent care with upper respiratory symptoms and general malaise. A urine sample is taken and is significant for pyuria. The patient is otherwise stable, afebrile, with normal vital signs. She is diagnosed with a viral URI.

Should the patient be sent home with antibiotic therapy?
Community Acquired Pneumonia (CAP)

- Common pathogens:
  - *Streptococcus pneumoniae*
  - *Mycoplasma pneumoniae*
  - *Haemophilus influenzae*
  - *Chlamydia pneumoniae*
  - Respiratory viruses*

*Use of oseltamivir (Tamiflu) is NOT recommended for uncomplicated influenza with sx for > 48h*

Image credit: http://24.media.tumblr.com/tumblr_lh3a3IS8UPIqgl0s1o1_500.gif
Treatment

Previously Healthy  
(no abx within last 3mo)

- Doxycycline
- Azithromycin

Comorbidities*  
(abx within last 3mo)

- Respiratory fluoroquinolone
- B-lactam + macrolide

*Comorbidities: chronic heart, lung, or renal disease; asplenia; immunosuppressing conditions or use of immunosuppressants

## Recommended Agents

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Dose</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>500 mg x1, then 250 mg PO daily x 4 days</td>
<td>• Some GI effects</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg PO BID x 7 days</td>
<td>• Pregnancy category D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Contraindicated in:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Age &lt; 8 years</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>750 mg PO daily x 5-10 days</td>
<td>• Avoid coadministration with multivitamin (Ca, Mg, Al)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg PO daily x 5-10 days</td>
<td>• QTc prolongation</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1 g PO TID x 5-10 days</td>
<td>• Diarrhea</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>2 g PO BID x 5-10 days</td>
<td></td>
</tr>
</tbody>
</table>

Empirically treat rhinosinusitis ONLY if:

- **PERSISTENT** non-improving symptoms for \( \geq 10 \) days
- **SEVERE** symptoms for 3-4 consecutive days
  - High fever \( \geq 39\text{C} \)
  - Purulent nasal discharge
  - Facial pain
- **WORSENING** symptoms after 5-6 days of typical viral URI
  - New onset
    - Fever
    - Headache
  - Increased nasal discharge

**Empiric Tx:**
- Amoxicillin-clavulanate 500/125 mg TID or 875/125mg BID
- PCN allergy: doxycycline 100 mg BID or 200 mg QD
- Failure of initial tx: respiratory FQ (levo/moxi) or high dose Augmentin

A 41 year old male presents to clinic complaining of chest pain, productive cough and subjective fevers for the past 2 days. CXR consistent with lower lobe infiltrate suggesting pneumonia. He has no significant past medical history, no recent illnesses/hospitalizations, and no known drug allergies.

**What would you prescribe to treat his CAP?**
Summary

- ABSSSI treatment
  - I&D first, may be sufficient

- UTI
  - Do NOT treat asymptomatic bacteruria
  - Fosfomycin and nitrofurantoin for cystitis ONLY

- CAP
  - Be aware of comorbidities that require broadened therapy

- Rhinosinusitis
  - Do NOT treat unless it meets criteria for ARBS
Thank You