

# Updates in Pharmacotherapy

Cardiology, Diabetes, and Community-Acquired Infections

# Learning Objectives

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- ▶ 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)

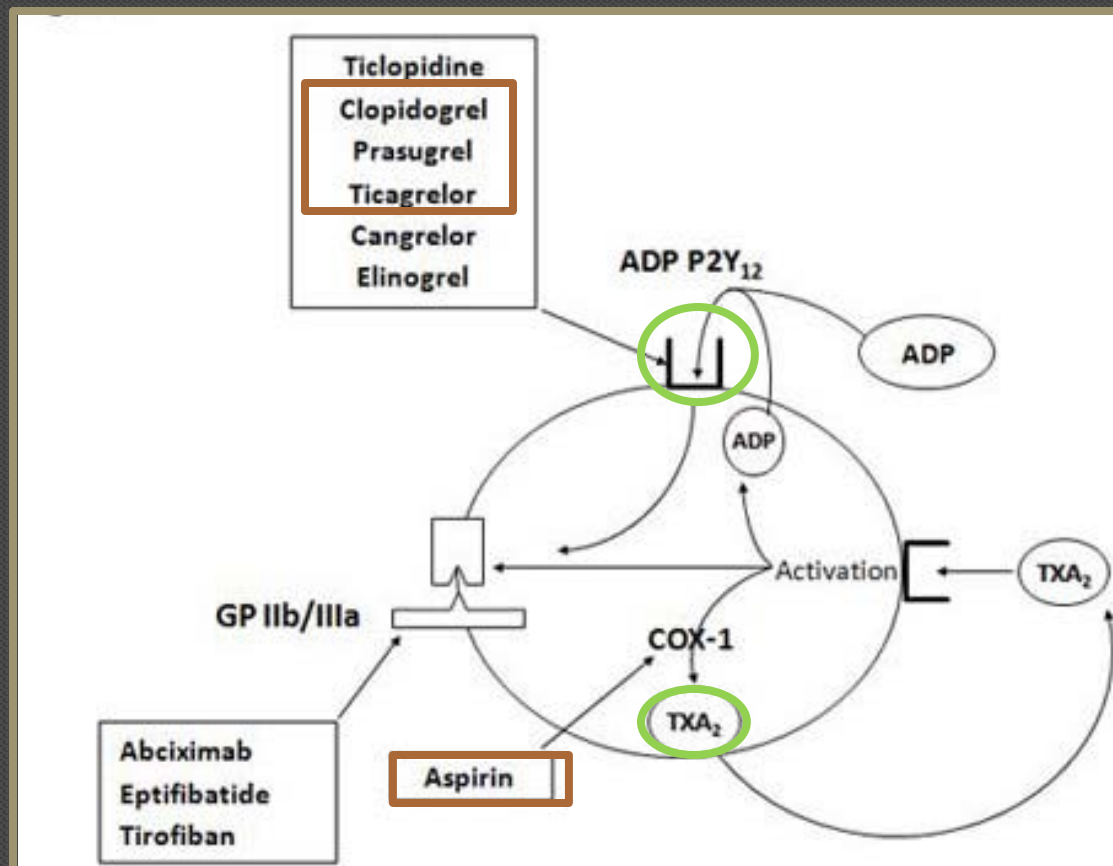


# New Drugs in Cardiology

Oral Antiplatelets and Anticoagulants

# Post-PCI Antiplatelet Therapy

- ▶ Endothelial dysfunction → plaque formation → plaque rupture → clot formation → **platelet activation**



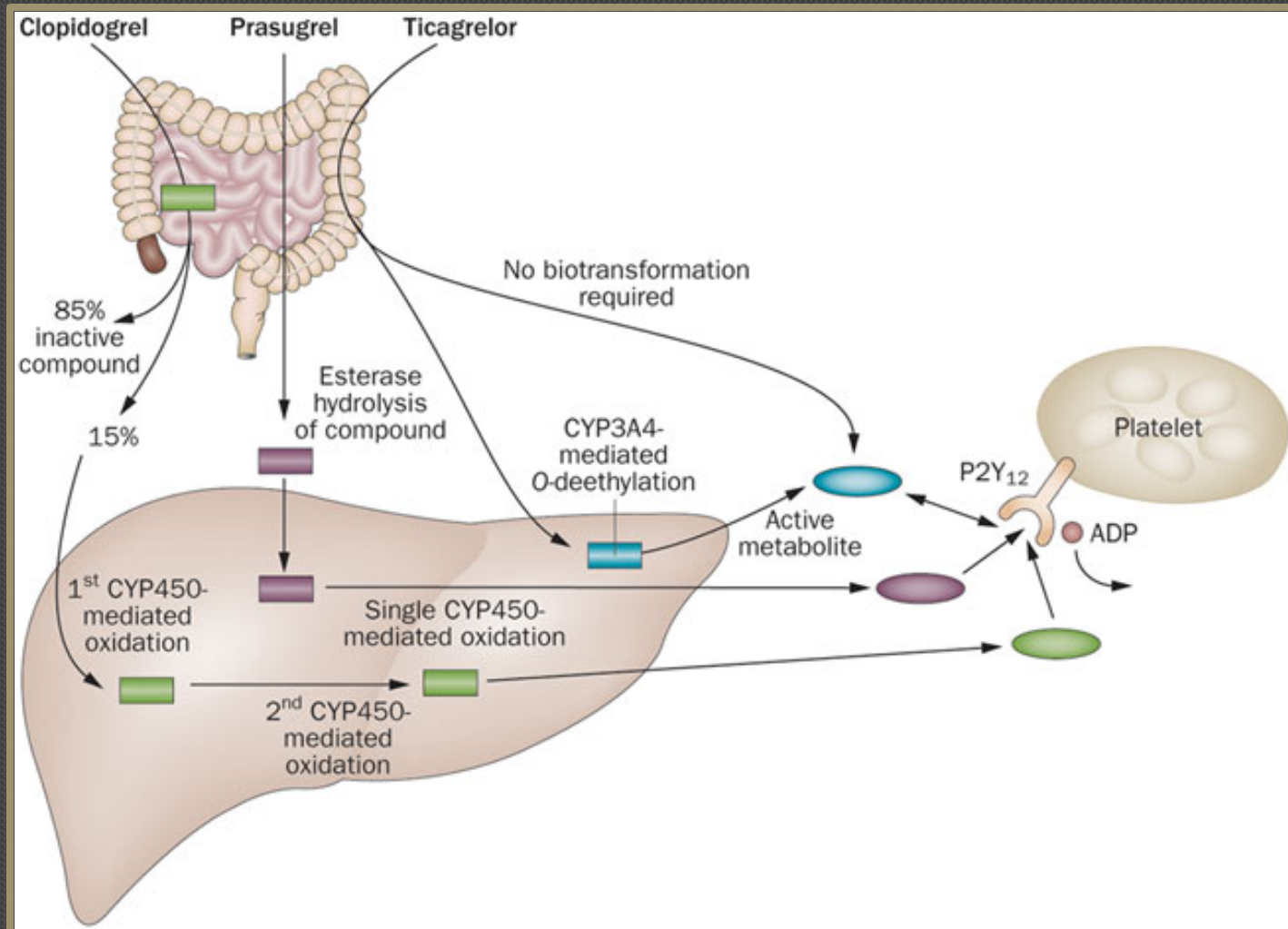
# Available Agents

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

## Duration of therapy:

- Drug Eluting Stent (DES) = 1 year
- Bare Metal Stent (BMS) = 30 days; up to 1 year

# Pharmacology



# Compared to Clopidogrel

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- ▶ 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

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## 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

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- ▶ Age and weight for prasugrel
  - ▶  $\geq 75$  years – NOT recommended
  - ▶  $< 60$  kg (132lbs) – consider dose reduction (5mg daily)
- ▶ Ticagrelor reversibility
  - ▶ Reversible binding to P2Y<sub>12</sub> receptor
  - ▶ Major bleed management more difficult
- ▶ Ticagrelor/aspirin DAPT
  - ▶ Maximum dose aspirin 81mg



# Patient Case

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- ▶ 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

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- ▶ Know patients' stroke and bleeding history
- ▶ Ticagrelor and aspirin dosing

**Reserve for low bleeding risk or  
stent thrombosis**



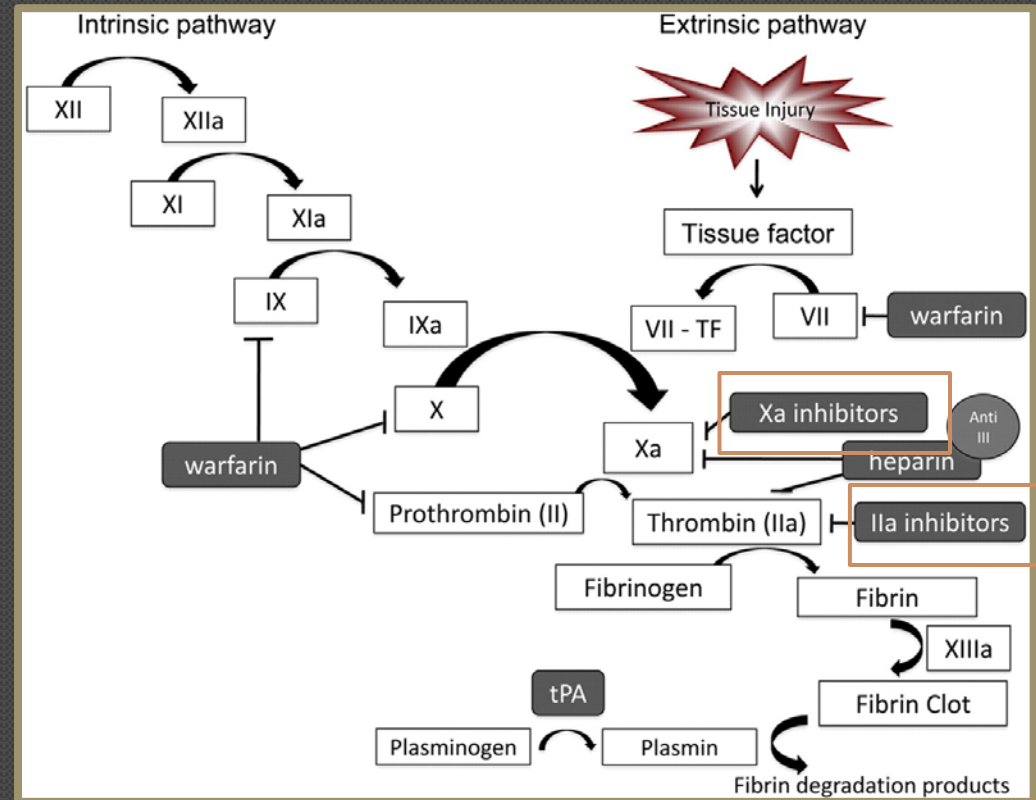
# New Oral Anticoagulants (NOAC)

## Direct Thrombin Inhibitor

- ▶ Dabigatran (Pradaxa<sup>®</sup>)

## Factor Xa Inhibitors

- ▶ Rivaroxaban (Xarelto<sup>®</sup>)
- ▶ Apixaban (Eliquis<sup>®</sup>)



# FDA-Approved Indications and Dosing

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

***ALL require RENAL adjustment***

# Compared to Warfarin

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- ▶ 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

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## ▶ 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

# Factor Xa Inhibitors and ACS

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## Rivaroxaban

- ▶ ATLAS-ACS
- ▶ ATLAS-ACS2-TIMI 51
  - ▶ Dose: 2.5 mg BID or 5 mg BID
  - ▶ Increased major bleeding but not fatal bleeding
  - ▶ Reduction in cardiovascular events

## Apixaban

- ▶ APPRAISE-2
  - ▶ Dose: 5 mg BID
  - ▶ Terminated early
  - ▶ Increased major bleeding, no benefit recurrent ischemic events



# Place in Therapy Pearls

## Conversion Between Anticoagulants

NOAC	Switching FROM warfarin D/C warfarin and start NOAC when...	Switching TO warfarin D/C NOAC and start warfarin...
Dabigatran	INR < 2	Overlap based on CrCl: <ul style="list-style-type: none"><li>• &gt;50 mL/min: 3 days</li><li>• 31-50 mL/minute: 2 days</li><li>• 15-30 mL/minute: 1 day</li></ul>
Rivaroxaban	INR < 3	24h after last dose
Apixaban	INR < 2	Next scheduled dose

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

# Patient Case

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- ▶ 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

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- ▶ 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

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## ▶ A1c

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

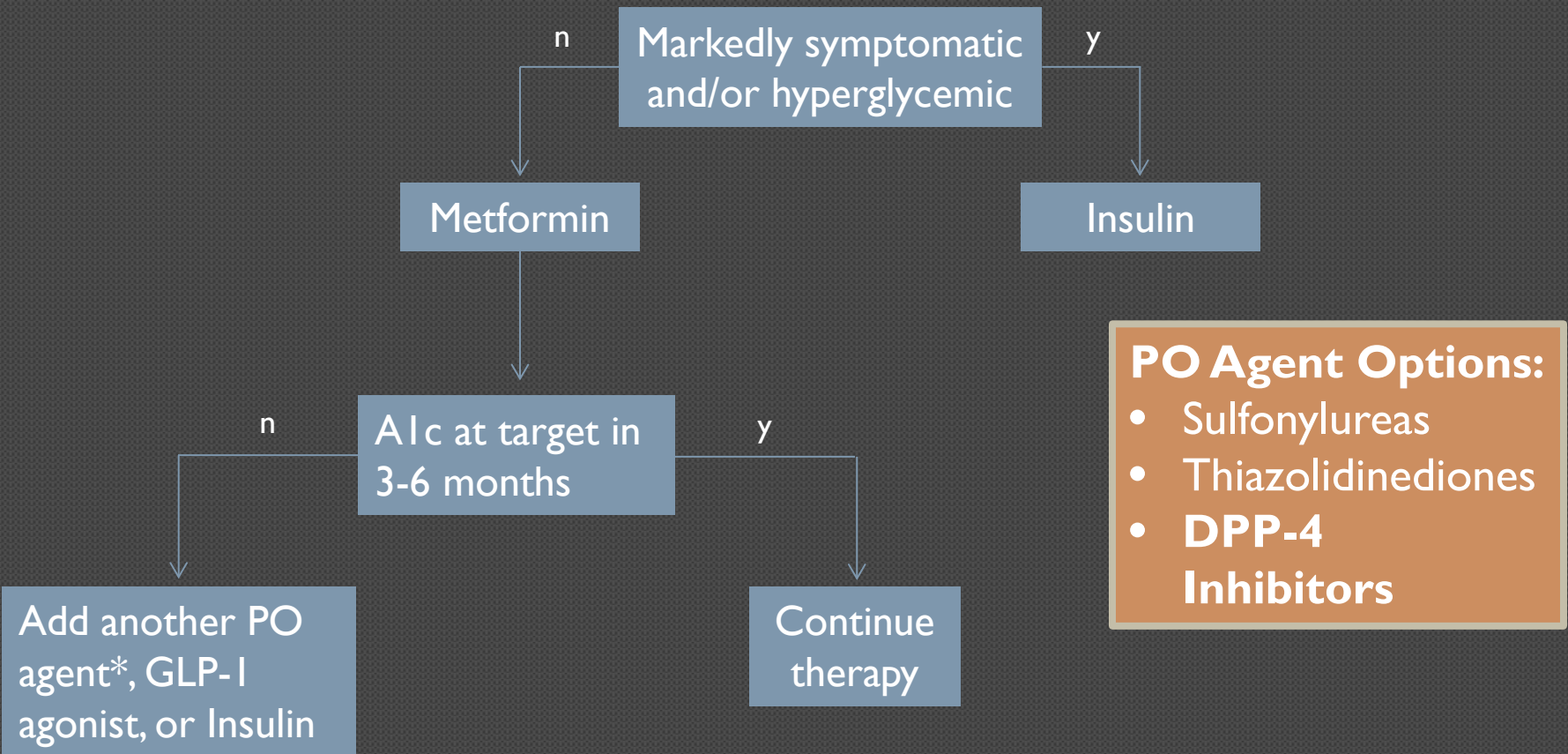
## ▶ Blood Pressure

- ▶ 140/80

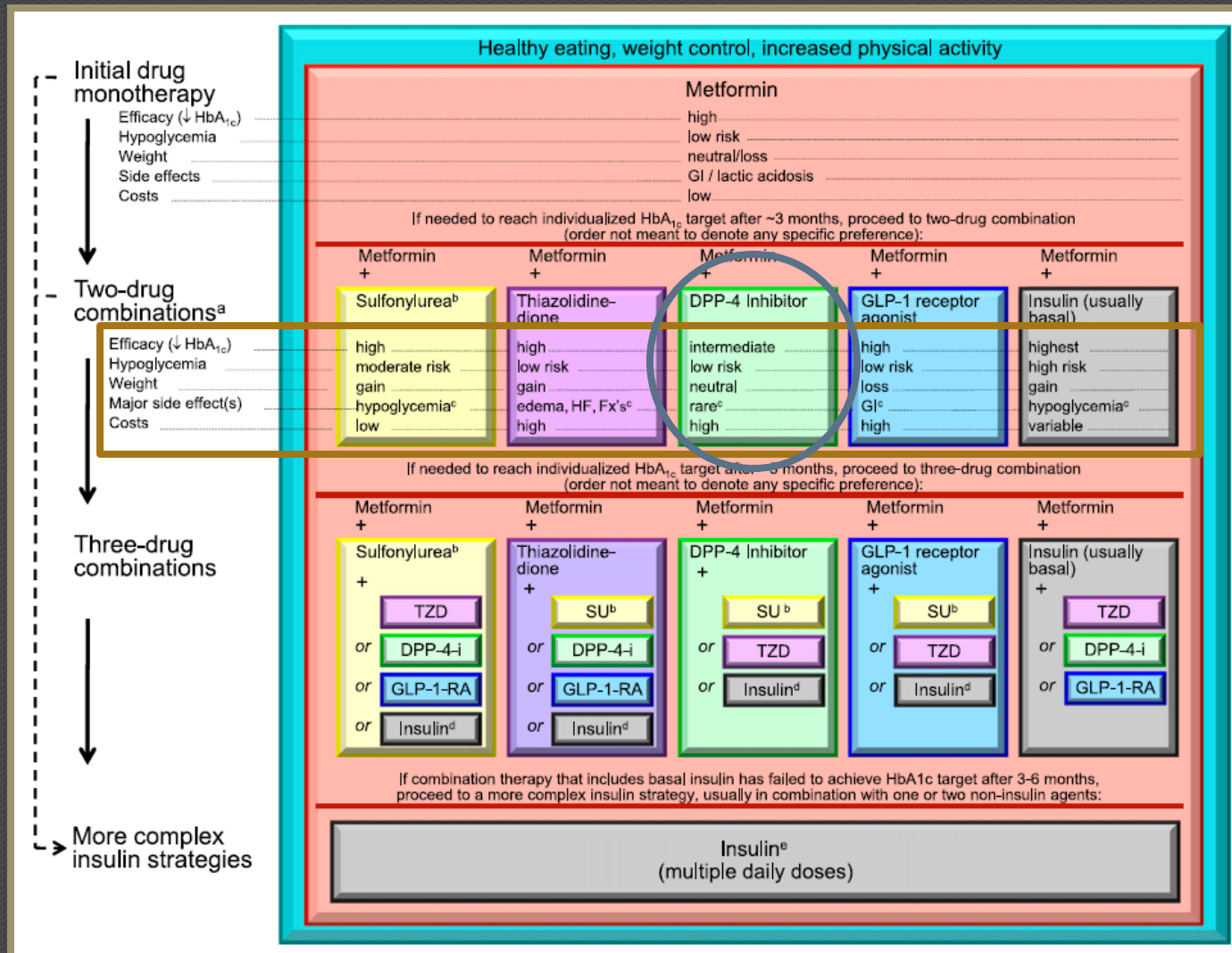
## ▶ Lipids

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

# Initial Approach to Treating Hyperglycemia in Type 2 Diabetes



# Overview of Combination Therapy



# Dipeptidyl Peptidase 4 (DPP-4) Inhibitors

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- ▶ Block deactivation of GLP-I
  - ▶ 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

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- ▶ Alogliptin (Nesina<sup>®</sup>)
- ▶ Linagliptin (Tradjenta<sup>®</sup>)
- ▶ Combination
  - ▶ Linagliptin + metformin (Jentaduetto<sup>®</sup>)
  - ▶ Sitagliptin + simvastatin (Juvisync<sup>®</sup>)
- ▶ Older DPP-4 Inhibitors:
  - ▶ Sitagliptin (Januvia<sup>®</sup>)
  - ▶ Saxagliptin (Onglyza<sup>®</sup>)




# Comparison of DPP-4 Inhibitors: Place in Therapy

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DPP-4 Inhibitor	Standard Dosing	Adjustments
Sitagliptin (Januvia <sup>®</sup> )	100 mg PO daily	Renal
Saxagliptin (Onglyza <sup>®</sup> )	2.5 – 5 mg PO daily	Renal
Alogliptin (Nesina <sup>®</sup> )	25 mg PO daily	Renal
Linagliptin (Tradjenta <sup>®</sup> )	5 mg PO daily	<b>NONE</b>

## Adverse Effects to Consider

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

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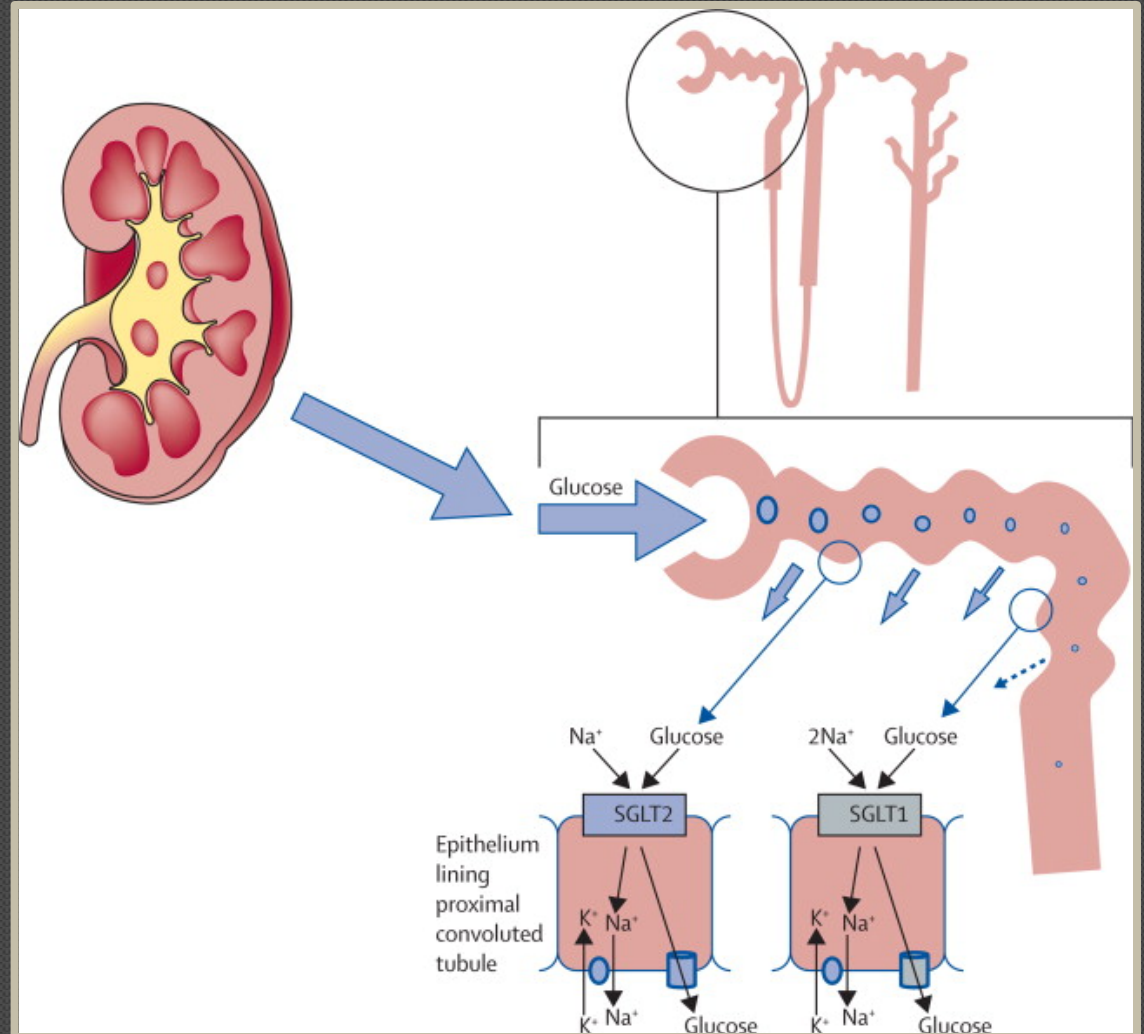
- ▶ A 56 year old woman with DM2, HTN, HLD, and CKD3 (baseline SCr 1.7) presents to diabetes clinic for follow-up. A1c 8%. She states she has been compliant with lifestyle modifications.
- ▶ Current medications:
  - ▶ Metformin 1000 mg BID
  - ▶ Lisinopril 20 mg daily
  - ▶ Simvastatin 40 mg daily
  - ▶ Amlodipine 5 mg daily

**Which DPP-4 inhibitor would be ideal for this patient?**



# Hot off the Press: Canagliflozin (Invokana<sup>®</sup>)

- ▶ Sodium-glucose co-transporter 2 (SGLT2) inhibitor
- ▶ Blocks renal reabsorption of glucose
  - ▶ Increases urinary concentration glucose
  - ▶ Risk of yeast infection
- ▶ Lowers HbA<sub>1c</sub> levels by 0.5–1.5%
- ▶ Dosing: 100-300 mg PO daily
  - ▶ Requires renal adjustment



# Summary

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- ▶ 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



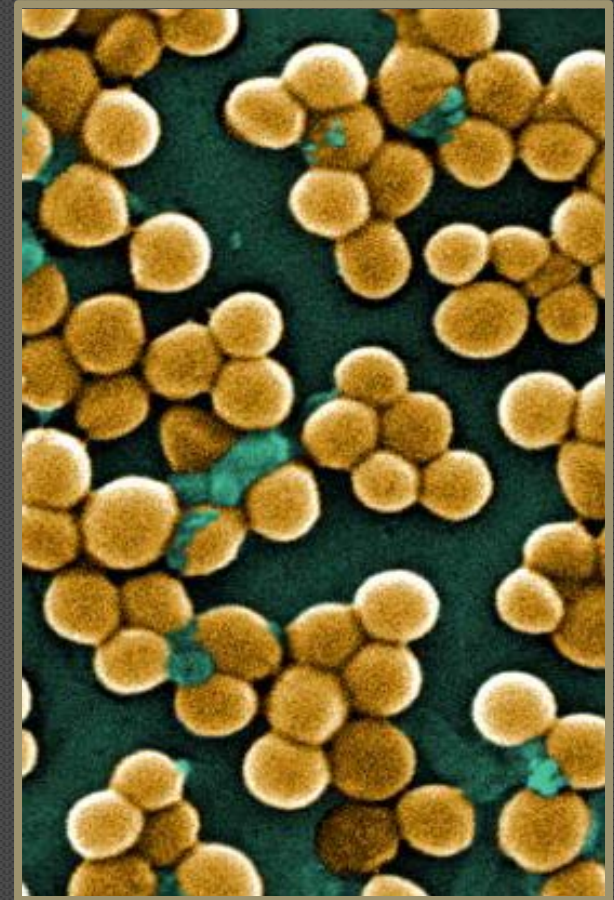
# Outpatient Infectious Diseases Review

Community Acquired MRSA Skin Infections, Urinary Tract Infections, and  
Community Acquired Pneumonia

# Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

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- ▶ 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



# Treatment Guideline Recommendations

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## 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

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Antimicrobial	Dose	Considerations
Clindamycin	300-450 mg PO TID	<ul style="list-style-type: none"><li>• Significant GI effects may limit dose</li><li>• Higher risk of <i>C diff</i></li></ul>
Trimethoprim-sulfamethoxazole (TMP-SMX)	1-2 DS tab PO BID	<ul style="list-style-type: none"><li>• Pregnancy category C/D</li><li>• Contraindicated in:<ul style="list-style-type: none"><li>• 3<sup>rd</sup> trimester</li><li>• Age &lt; 2 months</li></ul></li></ul>
Doxycycline	100 mg PO BID	<ul style="list-style-type: none"><li>• Pregnancy category D</li><li>• Contraindicated in:<ul style="list-style-type: none"><li>• Age &lt; 8 years</li></ul></li></ul>
Linezolid	600 mg PO BID	<ul style="list-style-type: none"><li>• Expensive</li></ul>

# Urinary Tract Infections

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## Complicated

- ▶ Catheter-associated
- ▶ UTIs in males

## Uncomplicated

- ▶ Cystitis
- ▶ Pyelonephritis



# Uncomplicated Cystitis and Pyelonephritis in Women

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



# Empiric Treatment Guidelines: Cystitis

Antimicrobial	Dose	Considerations
Nitrofurantoin*	100 mg BID x 5-7 days	<ul style="list-style-type: none"> <li>• Avoid use in <b>elderly</b></li> <li>• Ineffective if <b>CrCl &lt; 60</b></li> </ul>
Trimethoprim-sulfamethoxazole (TMP-SMX)	1 DS tab BID x 3 days	<ul style="list-style-type: none"> <li>• <b>Resistance</b></li> <li>• Pregnancy category C/D</li> <li>• Contraindicated in:               <ul style="list-style-type: none"> <li>• 3<sup>rd</sup> trimester</li> <li>• Age &lt; 2 months</li> </ul> </li> </ul>
Fosfomycin trometamol*	3 g x1	<ul style="list-style-type: none"> <li>• CDiff risk associated with long-term use</li> </ul>
Fluoroquinolone (levofloxacin or ciprofloxacin <b>ONLY</b> )	Levo: 250 mg daily Cipro: 500 mg BID X 3 days	<ul style="list-style-type: none"> <li>• <b>2<sup>nd</sup> line</b></li> <li>• Avoid coadministration with multivitamin (Ca, Mg, Al)</li> <li>• QTc prolongation</li> </ul>
Cephalexin	500 mg BID x 3-5 days	<ul style="list-style-type: none"> <li>• Adjust for CKD</li> </ul>

# Empiric Treatment Guidelines: Pyelonephritis

Antimicrobial	Dose	Considerations
Fluoroquinolone	Levo: <b>750 mg</b> daily x <b>5 days</b> Cipro: 500 mg BID x <b>7 days</b>	<ul style="list-style-type: none"><li>• Avoid coadministration with multivitamin (Ca, Mg, Al)</li><li>• QTc prolongation</li></ul>
Trimethoprim-sulfamethoxazole (TMP-SMX)	1 DS tab PO BID x <b>14 days</b>	<ul style="list-style-type: none"><li>• Pregnancy category C/D</li><li>• Contraindicated in:<ul style="list-style-type: none"><li>• 3<sup>rd</sup> trimester</li><li>• Age &lt; 2 months</li></ul></li></ul>

# UTI vs Asymptomatic Bacteruria

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## ▶ Definition:

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

## ▶ Treatment

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

### Classic Symptoms of True UTI:

- Urinary frequency
- Urgency
- Dysuria

## Patient Case

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- ▶ 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.

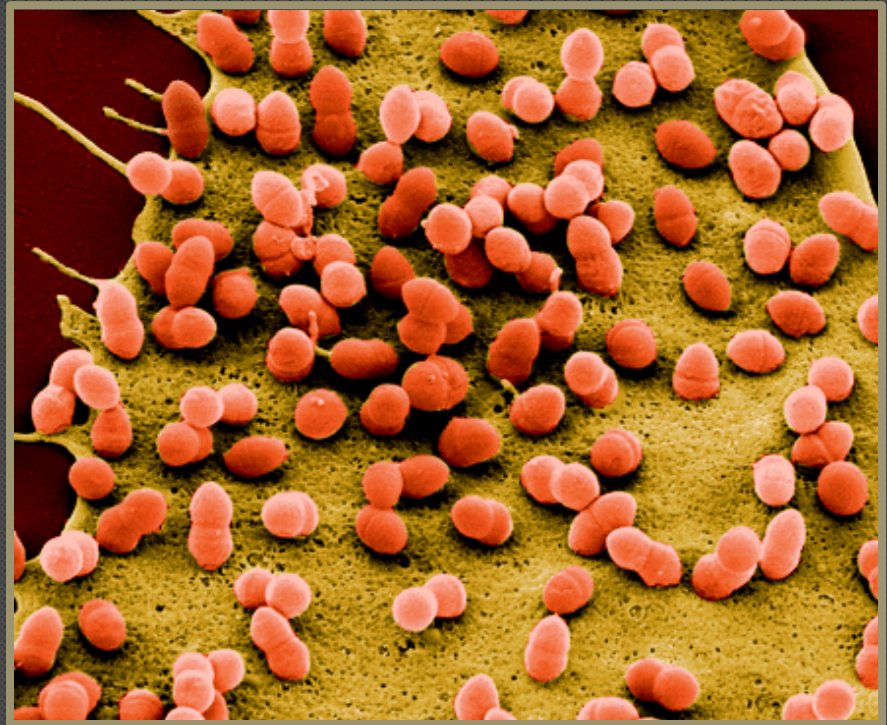
**Should the patient be sent home with antibiotic therapy?**



# Community Acquired Pneumonia (CAP)

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- ▶ 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



# Treatment

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## 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

Antimicrobial	Dose	Considerations
Azithromycin	500 mg x1, then 250 mg PO daily x 4 days	<ul style="list-style-type: none"><li>• Some GI effects</li></ul>
Doxycycline	100 mg PO BID x 7 days	<ul style="list-style-type: none"><li>• Pregnancy category D</li><li>• Contraindicated in:<ul style="list-style-type: none"><li>• Age &lt; 8 years</li></ul></li></ul>
Levofloxacin	750 mg PO daily x 5-10 days	<ul style="list-style-type: none"><li>• Avoid coadministration with multivitamin (Ca, Mg,Al)</li><li>• QTc prolongation</li></ul>
Moxifloxacin	400 mg PO daily x 5-10 days	
Amoxicillin	1 g PO TID x 5-10 days	
Amoxicillin-clavulanate	2 g PO BID x 5-10 days	<ul style="list-style-type: none"><li>• Diarrhea</li></ul>

# CAP $\neq$ Rhinosinusitis

- ▶ Empirically treat rhinosinusitis **ONLY** if:
  - ▶ **PERSISTENT**, non-improving symptoms for  $\geq 10$  days
  - ▶ **SEVERE** symptoms for **3-4 consecutive days**
    - ▶ High fever  $\geq 39^{\circ}\text{C}$
    - ▶ 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

## Patient Case

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- ▶ 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

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- ▶ 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

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