



Principles of Antimicrobial Therapy for Exam: PK/PD, Drug-Drug Interactions, and Toxicities

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor, *The Sanford Guide to Antimicrobial Therapy*

Pharmacokinetics

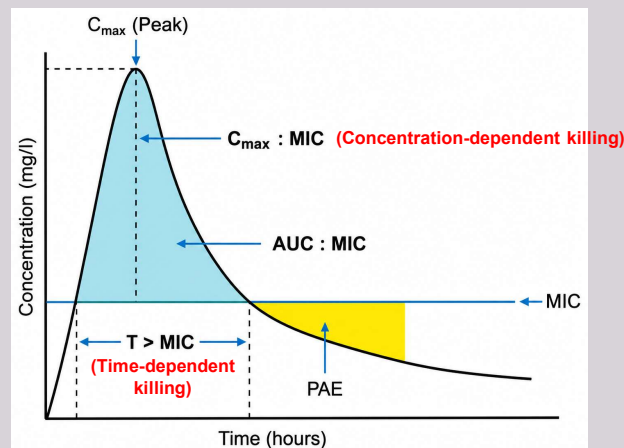
Describes the movement of a drug into, through, and out of the body over time. Summarized by ADME: absorption, distribution, metabolism, excretion.

Pharmacodynamics

Focuses on the biological and physiological effects of a drug, including its mechanism of action.

PK/PD

Establishes and evaluates dose-concentration-response relationships.



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50 Principles of Antimicrobial Therapy for Exam: What You Need to Know About Toxicities, PK/PD, Drug-Drug Interactions

Douglas Black, PharmD

Putting It All Together

Drugs	Activity	Killing	PAE	PD index
β-lactams	Bactericidal	Time-dependent	Minimal*	T>MIC
Aminoglycosides Colistin Daptomycin Fluoroquinolones Metronidazole	Bactericidal	Concentration-dependent	Prolonged	Cmax:MIC AUC:MIC
Clindamycin Linezolid Macrolides Tetracyclines Tigecycline Vancomycin**	Bacteriostatic	Concentration-dependent	Moderate to prolonged	AUC:MIC

*Exception: carbapenems (prolonged post-antibiotic effect vs. gram-negative bacilli)

**Vancomycin is bacteriostatic vs enterococci, bactericidal vs staphylococci and streptococci

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Here are 3 relevant clinical applications of PK/PD principles that you might get asked about...

- Extended-interval aminoglycoside dosing
- Extended-infusion piperacillin-tazobactam
- Vancomycin AUC monitoring

PK/PD Question #1

What is the primary rationale for using extended-interval aminoglycoside dosing instead of conventional dosing?

- Therapeutic drug monitoring is no longer necessary
- The duration of treatment is shortened
- The need for audiometry is eliminated
- Clinical cure rates are always improved
- Nephrotoxicity is generally reduced

Conventional vs. Extended-Interval Aminoglycoside Dosing

	Aerobic gram-positive infection	Aerobic gram-negative infection
Conventional	Preferred	Use in certain situations*
Extended-interval	OK for certain types of streptococcal endocarditis	Preferred

*Burns >20% BSA, cystic fibrosis, age <12 years, ascites, obesity, poor renal function

PK/PD Question #2

What is one documented benefit of extended-infusion piperacillin-tazobactam?

- A. Less *C. difficile* infection is observed
- B. Clinical outcomes are improved in some patients
- C. The emergence of resistant isolates is reduced
- D. The need for renal dosage adjustment is eliminated
- E. CNS penetration of piperacillin is improved

Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

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Background. Piperacillin-tazobactam is frequently used to treat *Pseudomonas aeruginosa* infections in critically ill patients. In an effort to improve clinical outcomes, an extended-infusion dosing scheme for piperacillin-tazobactam therapy was devised using a Monte Carlo simulation and was adopted into clinical practice at Albany Medical Center (Albany, New York). This study evaluates the clinical implications of extended infusion of piperacillin-tazobactam therapy for critically ill patients with *P. aeruginosa* infection.

Methods. We performed a cohort study of patients who received piperacillin-tazobactam therapy for a *P. aeruginosa* infection that was susceptible to piperacillin-tazobactam during the period January 2000–June 2004. Prior to February 2002, all patients received intermittent infusions of piperacillin-tazobactam (3.375 g intravenously for 30 min every 4 or 6 h); after this time, all patients received extended infusions of piperacillin-tazobactam (3.375 g intravenously for 4 h every 8 h). Data on demographic characteristics, disease severity, and microbiology were collected, and outcomes were compared between groups.

Results. A total of 194 patients comprised the 2 study groups: 102 patients received extended infusions of piperacillin-tazobactam, and 92 patients received intermittent infusions of piperacillin-tazobactam. No differences in baseline clinical characteristics were noted between the 2 groups. Among patients with Acute Physiological and Chronic Health Evaluation–II scores ≥ 17 , 14-day mortality rate was significantly lower among patients who received extended-infusion therapy than among patients who received intermittent-infusion therapy (12.2% vs. 31.6%, respectively; $P = .04$), and median duration of hospital stay after collection of samples for culture was significantly shorter for patients who received extended-infusion therapy than for patients who received intermittent-infusion therapy (21 days vs. 38 days; $P = .02$).

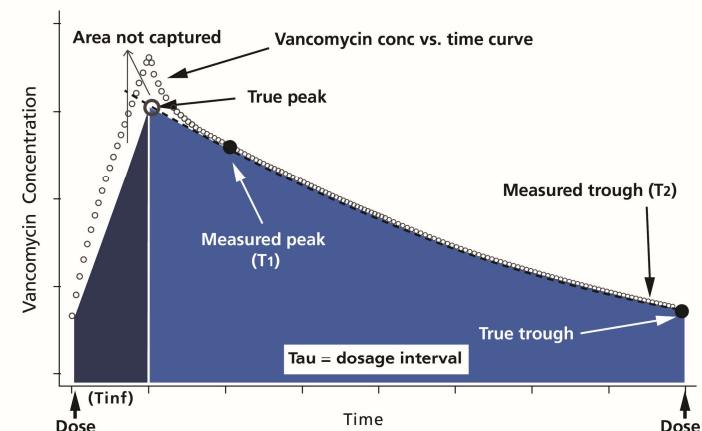
Conclusions. These results indicate that extended-infusion piperacillin-tazobactam therapy is a suitable alternative to intermittent-infusion piperacillin-tazobactam therapy, and they strongly suggest that improved outcomes may be realized by administering extended-infusion piperacillin-tazobactam therapy to critically ill patients with *P. aeruginosa* infection.

Clin Infect Dis 2007;44:357-63

PK/PD Question #3

What is the correct vancomycin AUC to target for treating MRSA pneumonia?

- A. 100-200 $\mu\text{g}\cdot\text{hr}/\text{mL}$
- B. 200-400 $\mu\text{g}\cdot\text{hr}/\text{mL}$
- C. 200-600 $\mu\text{g}\cdot\text{hr}/\text{mL}$
- D. 400-600 $\mu\text{g}\cdot\text{hr}/\text{mL}$
- E. 400-800 $\mu\text{g}\cdot\text{hr}/\text{mL}$



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Vancomycin AUC Monitoring Pearls

- For serious MRSA infections, an AUC of 400-600 should be targeted. MIC is assumed to be 1. This approach will minimize the risk of AKI and maximize efficacy, compared to trough-only monitoring.
- For other pathogens or infections, the routine use of AUC monitoring is not well established and requires further study.
- There are pros and cons to the two methods of determining AUC (trapezoidal equations vs. Bayesian methods).
- If administering vancomycin by continuous infusion, simply multiply steady-state concentration by 24 to calculate AUC₂₄.

Moving on to 8 Drug-drug Interactions you Might Get Asked About

Pharmacodynamic

Pharmacokinetic

- CYP450-mediated
- Transporter-mediated

DDI Question #4

- A 72-year-old woman presents to the ED complaining of lightheadedness and a fainting spell
- Increasing fatigue and palpitations over the last 3 days
- Recently diagnosed with an LRI, prescribed clarithromycin 500 mg po bid 4 days ago
- Other problems: atrial fibrillation, hypertension, hyperlipidemia, type 2 diabetes
- Meds: candesartan, amiodarone, metoprolol, atorvastatin, metformin

DDI Question #4

A drug-drug interaction between clarithromycin and which drug below best explains this patient's syncopal episode?

- A. Candesartan
- B. Amiodarone
- C. Metoprolol
- D. Atorvastatin
- E. Metformin

DDI Question #5

- A 67-year-old woman presents to her primary care provider with persistent dysuria and urinary frequency x 5 days
- Started ciprofloxacin 500 mg po bid by urgent care 3 days ago for presumed UTI
- Denies flank pain, fever, hematuria
- PMH: GERD, hypertension, osteoarthritis
- Meds: lisinopril, losartan, omeprazole, sucralfate, acetaminophen

DDI Question #5

Administration of which medication should be staggered, if possible, to avoid interacting with ciprofloxacin?

- A. Lisinopril
- B. Losartan
- C. Omeprazole
- D. Sucralfate
- E. Acetaminophen

DDI Question #6

- A 75-year-old man started TMP-SMX one DS tablet q12h five days ago for acute prostatitis
- Allergy: levofloxacin (tendon pain)
- He now reports new-onset bruising, bleeding gums, and blood in his stool this morning
- No recent trauma or prior bleeding issues
- Other problems: atrial fibrillation, hypertension, type 2 diabetes
- Meds: warfarin, metformin, amlodipine

DDI Question #6

What is the most likely explanation for these bleeding symptoms?

- A. Inhibition of warfarin metabolism
- B. Protein binding displacement
- C. Alteration of vitamin-K producing gut flora
- D. Myelosuppression from TMP-SMX
- E. Changes in the patient's diet

DDI Question #7

- A 38-year-old woman has focal epilepsy that is well controlled on phenytoin x3 years
- She presents with new-onset breakthrough seizures
- Two weeks ago, she began treatment for LTBI (rifampin 600 mg daily)
- Serum phenytoin level is 3.2 µg/mL (reference range: 10–20 µg/mL)

DDI Question #7

Which of the following best explains the cause of her breakthrough seizures?

- A. Rifampin reduces gastrointestinal absorption of phenytoin
- B. Rifampin induces hepatic enzymes, lowering phenytoin serum levels
- C. Rifampin displaced phenytoin from plasma proteins, increasing clearance
- D. Rifampin inhibits P-glycoprotein, reducing phenytoin CNS penetration
- E. Rifampin binds directly to phenytoin, inactivating it in the plasma

DDI Question #8

- A 42-year-old woman presents with acute agitation, diaphoresis, muscle stiffness, and tremors
- 24 hours ago, she began linezolid 600 mg po q12h for a community-acquired MRSA skin infection
- History of major depressive disorder, takes sertraline 100 mg po q24h
- Other problems: migraine (prn treatment with sumatriptan).
- VS: T 39.2°C, HR 124, BP 159/86, RR 22

DDI Question #8

What is the most appropriate initial management?

- A. Discontinue linezolid and sertraline, give IV fluids and benzodiazepines
- B. Switch from sertraline to fluoxetine
- C. Start cyproheptadine, continue linezolid with dose adjustment
- D. Observe without intervention unless seizures occur
- E. Continue linezolid and sertraline, add propranolol for symptom control

DDI Question #9

- A 67-year-old man presents with a 3-day history of increasing muscle pain and weakness in his thighs and calves, and dark colored urine this morning
- Problems: hyperlipidemia, hypertension, onychomycosis (recently diagnosed)
- Meds: simvastatin 40 mg qd (x4 years), metformin 1 gm bid, lisinopril 10 mg qd, itraconazole 200 mg qd (started 6 days ago)
- Labs: CK 12,400 U/L, SCr 1.4 mg/dL (baseline 1.0), mild AST/ALT elevation. UA: myoglobinuria

DDI Question #9

Which of the following is a recognized risk factor for statin myopathy in the setting of oral antifungal therapy?

- A. Use of a statin metabolized by CYP1A2
- B. Rosuvastatin use
- C. Co-administration with metformin
- D. Young age
- E. Concomitant use of a moderate to strong CYP3A4 inhibitor

DDI Question #10

- A 72-year-old female complains of progressive weakness, lightheadedness, and occasional palpitations x3 days
- No chest pain or SOB
- Yesterday completed a five-day course of TMP-SMX (1 DS tab bid) for a UTI
- PMH: hypertension, CKD (CrCl $\approx$ 50), type 2 diabetes
- Meds: losartan 100 mg qd, amlodipine 5 mg qd, metformin 500 mg bid
- Labs: K⁺ 6.4 mEq/L, SCr 1.5 mg/dL
- ECG: peaked T waves, bradycardia

DDI Question #10

Which of the following prescribing practices would have been the best way to avoid this situation?

- A. Use nitrofurantoin instead of TMP-SMX
- B. Hold the metformin during the course of TMP-SMX
- C. Prescribe TMP-SMX at a reduced dose
- D. Replaced losartan with lisinopril
- E. Discontinue the amlodipine

DDI Question #11

- A 27-yo woman presents with a severely infected dog bite on her right hand
- You plan to prescribe a course of amoxicillin-clavulanate
- She is taking an oral contraceptive that contains 35 µg of ethinyl estradiol and 0.25 mg of norgestimate
- She asks if she should use condoms while taking the antibiotic

DDI Question #11

Which of the following antimicrobial agents is most clearly associated with reducing the efficacy of oral contraceptives?

- A. Amoxicillin-clavulanate
- B. Doxycycline
- C. Rifampin
- D. Azithromycin
- E. Ciprofloxacin

Drug-Drug Interactions Key Messages (Questions 1-4)

- Beware of drugs that **prolong the QTc interval**. Both PK and PD interactions can cause problems. Crediblemeds.org is a good website for QT-prolonging drugs.
- When prescribing FQs, always check for **polyvalent cation-containing** medications.
- TMP-SMX increases the bleeding risk from warfarin primarily by **inhibiting its metabolism**. At least four other mechanisms may or may not contribute.
- Rifampin is a **powerful inducer** of most of the major CYP enzymes. It affects many important drug classes, such as antiepileptics. Induction is a slow process.

Drug-Drug Interactions Key Messages (Questions 5-8)

- Linezolid added to an SSRI can cause **serotonin syndrome**, not by affecting the SSRI directly but by inhibiting the enzyme that metabolizes serotonin (monoamine oxidase).
- Always review for CYP450 interactions when prescribing an antimicrobial to someone on a **statin**. Simvastatin and lovastatin are most vulnerable; rosuvastatin or pravastatin are safer.
- Trimethoprim plus an ARB or ACEI can result in **hyperkalemia**, particularly in older patients and those with reduced renal function.
- Rifampin can diminish OC effectiveness, no question. However, available evidence suggests that **non-rifamycin antibiotics do not**, especially if the OC contains at least 30 µg of ethinyl estradiol.

- Enter the drugs in question
 - https://www.drugs.com/drug_interactions.html
 - <https://reference.medscape.com/drug-interactionchecker>
 - <https://www.webmd.com/interaction-checker/default.htm>
- The Liverpool sites
 - www.hiv-druginteractions.org
 - www.hep-druginteractions.org
 - www.covid19-druginteractions.org
- *The Sanford Guide to Antimicrobial Therapy*

Finally, 6 Antimicrobial Toxicities You Might Get Asked About

Toxicity Case #1

- A 72-year-old man with a history of CKD and hypertension is admitted with sepsis secondary to a UTI
- Cefepime 2 gm IV q12h + vancomycin 1 gm IV q12h are begun
- After 5 days of treatment, he begins to exhibit confusion, agitation, and tremors. His family reports that he has become increasingly disoriented and has had difficulty recognizing familiar faces.
- His SCr, previously stable, is found to be elevated

Cefepime-induced Neurotoxicity (CIN)

- Factors associated with CIN: age, renal function, total dose administered, cefepime trough concentration (>20 µg/mL).
- Mechanism: GABA inhibition.
- Median duration from drug initiation to onset of CIN: 4 days.
- Manifestations: altered mental status, myoclonus, non-convulsive status epilepticus.
- EEG may be helpful, although there are no specific findings.
- Prognosis favorable. Most cases improve within 3 days of drug discontinuation.

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J Antimicrob Chemother 2022;77:2908-2921

Antimicrobials Associated with Neurotoxicity

Beta-lactams (seizures, encephalopathy)

Ethambutol (optic neuritis, peripheral neuropathy)

Fluoroquinolones (confusion, seizures, peripheral neuropathy, exacerbation of myasthenia gravis)

Isoniazid (peripheral neuropathy, encephalopathy, psychosis, seizures)

Linezolid (peripheral/optic neuropathy, serotonin syndrome)

Metronidazole (peripheral/optic/autonomic neuropathy, encephalopathy)

Nitrofurantoin (peripheral neuropathy)

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Toxicity Case #2

- A 64-year-old woman presents to the ED with a painful left arm at a previous IV sit
- PMH: atrial fibrillation, type 2 diabetes
- She is diagnosed with superficial thrombophlebitis and sent home. She returns 7 days later with fever and hypotension. Piperacillin-tazobactam + vancomycin are begun.
- BC: positive for MSSA. TTE: no vegetations. She is switched to nafcillin 2 gm IV q4h, planned duration 2 weeks.
- On day 9, routine lab work shows SCr to be 2.1 mg/dL (baseline 0.8), with eosinophilia. A rash on her chest and back is also observed.

Acute Interstitial Nephritis

- Usually due to drug-induced hypersensitivity. Some infections (HIV, hepatitis) and immune disorders (lupus) have also been implicated
- Typically presents after 2-3 weeks of drug therapy
- Non-oliguric renal dysfunction ($\uparrow$ BUN, $\uparrow$ Scr) often gets our attention first
- The "classic" triad (fever, rash, eosinophilia) is seen in <33% of patients. Some say the triad includes arthralgia instead of eosinophilia. Patients may complain of flank pain.
- Definitive diagnosis requires kidney biopsy (generally not done)
- Full recovery usually occurs after the offending drug is stopped. Oral steroids have no established role.
- The patient's allergy history should be correctly labeled. Probably drug specific (not class).

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Drugs Associated with Acute Interstitial Nephritis

Beta-lactams (penicillins, cephalosporins)

Rifampin

TMP-SMX

Allopurinol

Immune checkpoint inhibitors

NSAIDs

Proton pump inhibitors

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Toxicity Case #3

- A 45-year-old man with a history of type 2 diabetes and recent diagnosis of MRSA bacteremia started daptomycin therapy 7 days ago.
- He presents with acute onset of dyspnea, dry cough, and fever, which has worsened over the past 24 hours.
- Exam: febrile, tachypneic, and has bilateral crackles on lung auscultation.
- Chest X-ray shows bilateral infiltrates consistent with pneumonia.
- Lab: elevated eosinophil count.

Daptomycin-induced Eosinophilic Pneumonia (DIEP)

- Rare but potentially severe
- Pathogenesis unestablished
- Unclear if DIEP is dose-related
- Onset typically 2-4 weeks
- Clinical features: new-onset fever, progressive dyspnea, cough (usually non-productive), diffuse bilateral pulmonary infiltrates, hypoxemia
- Also observed: peripheral eosinophilia, elevated inflammatory markers (ESR, CRP)
- BAL: >25% eosinophils, or eosinophilic pneumonia at lung biopsy
- Clinical improvement after discontinuation of daptomycin, corticosteroid administration

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Toxicity Case #4

- A 44-yo woman with AML undergoes allogeneic HSCT
- Course is complicated by severe GVHD with liver and intestinal involvement, treated with high-dose corticosteroids and infliximab
- Develops disseminated *Scedosporium apiospermum* infection with multiorgan involvement
- Treated with IV voriconazole, then oral voriconazole adjusted to maintain a trough concentration of 1.5-5 µg/mL
- 9 months after starting therapy, she complains of severe, disabling bone pain, arthralgias, and swelling of her hands and fingers

Voriconazole-associated Periostitis

- Prevalence not known
- Features: generalized bone pain, ↑alkaline phosphatase, evidence of periostitis and/or exostoses on x-ray
- Any bones can be affected, but the most common are ribs, forearms, legs, and shoulders
- Takes a long time to occur, at least six weeks but often much longer
- Cause: excess fluoride exposure
- Related to voriconazole dose
- CYP2C19 ultrarapid metabolizers may have increased generation of free fluoride (as well the need for a high voriconazole dose)
- Resolves within 2 months of drug discontinuation

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Toxicity Case #5

- A 78-year-old woman being treated for UTI presents with recent symptoms of dyspnea, fatigue, and productive cough
- VS normal, no rash
- PMH: history of recurrent *E. coli* UTI, including an episode 4 months ago (treated with nitrofurantoin)
- Non-smoker
- Started another course of nitrofurantoin 3 days ago (100 mg bid x5 days)
- Chest X-ray: bilateral interstitial infiltrates, patchy ground-glass opacities, pleural effusion
- Lab: WBC 13,500/ μ L, eosinophils 10%. Other labs WNL.

Acute Nitrofurantoin Pulmonary Toxicity

- Occurs in about 1 in 5000 patients
- Typically presents about 9 days after a short course of therapy in women, age 60-70. Onset is shorter in repeat exposures.
- Think of as a hypersensitivity reaction (type I or III)
- Common symptoms: fever, dyspnea, cough, rash
- PE: inspiratory crackles
- Lab: eosinophilia, leukocytosis, elevated ESR
- Imaging: Diffuse parenchymal changes, pleural effusions
- Treatment: stop drug, document as allergy, avoid re-exposure. Steroids of unproven benefit.
- Improvement within 24-48 hours, full recovery in a few weeks

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Chronic Nitrofurantoin Pulmonary Toxicity

- Develops after several months or years of long-term therapy (women, age 60-70)
- A cell-mediated or toxic response, possibly to drug metabolites
- Common symptoms: Dyspnea, dry cough, fatigue. Fever uncommon. Overall, symptoms less intense than in an acute reaction.
- PE: dry crackles
- Lab: elevated serum gamma globulins, eosinophilia, elevated transaminases, elevated ESR. Maybe ANA+
- Imaging: Parenchymal opacities. Ground glass opacities on CT. Pleural effusion uncommon.
- Higher risk of parenchymal injury
- Treatment: stop drug. Steroids of unproven benefit. Clinical improvement in weeks to months, may not fully resolve.

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Toxicity Case #6

- A 68-yr female presents with complaints of dizziness and palpitations
- PMH: hypertension, type 2 diabetes
- One week ago, prescribed levofloxacin 500 mg po q24h for CAP
- VS stable, physical exam unremarkable
- ECG: QTc 520 ms. Baseline (6 months earlier) is 430 ms
- Lab: electrolytes WNL. Troponins negative, echo shows normal LV function

FQ-induced QTc Interval Prolongation

- Increases risk of serious ventricular arrhythmias (e.g., torsade de pointes)
- Mechanism: blockade of potassium channels
- Risk factors
 - Older age
 - Female
 - Congenital long QT syndrome
 - Bradycardia
 - CHF
 - Hypokalemia, hypomagnesemia
 - Other QT-prolonging drugs
- Symptoms: palpitations, lightheadedness or dizziness, fatigue, syncope
- Likelihood: moxifloxacin > levofloxacin > ciprofloxacin
- Consider ECG monitoring in high-risk patients

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Antimicrobial Classes Associated with QTc-interval Prolongation

Anti-parasitics: antimony, antimalarials, fexinidazole

ARVs: atazanavir, efavirenz, rilpivirine

Azole antifungals

Fluoroquinolones

Macrolides

Other antibacterials: gepotidacin, lefamulin

Pentamidine

Good Internet source: [crediblemeds.org](https://www.crediblemeds.org)

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Thank you for listening!