

Common complications of antimicrobial drugs



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Penicillins

- The most important adverse effects of the penicillins are **hypersensitivity** reactions .
- **Anaphylactic reaction** (IgE) is characterized by fever, urticaria, joint pains, and angioneurotic edema .
- **Exfoliative dermatitis** and **Stevens-Johnson syndrome** allergic vasculitis with the development of cutaneous and visceral lesions .
- **Hematologic toxicity** is **rare**, although **neutropenia** has been encountered with the use of **all types of penicillins**, particularly when **large doses** are used.

Penicillins

- **Interstitial nephritis** is seen with **all penicillins** : fever, macular rash, eosinophilia, proteinuria, eosinophiluria, and hematuria.
- **hypokalemia**, owing to the **large dose** ...
- **CNS toxicity** in the form of **myoclonic seizures** can follow the administration of **massive doses** of **penicillin G** .
- Clostridioides difficile: diarrhea

Amoxicillin-Clavulanate

- **No major adverse reactions** to the use of clavulanic acid combined with amoxicillin have been reported.
- Delayed **hepatotoxicity** may occur, which usually follows a benign course.
- The incidence of **skin reactions** has been **similar to** that seen when **penicillin** is used alone.
- **Diarrhea** is the most common side effect.
- **Nausea** also accompanies use of these doses.
- In accordance, the oral dose of clavulanic acid is recommended not to exceed **125 mg two or three times** a day.

sulbactam plus ampicillin

- Clinical studies of the combination of sulbactam plus ampicillin have revealed **no major hematologic, renal, hepatic, or CNS reactions.**
- **Diarrhea** has **not** been a major problem after IV use.
- **Elevation of aminotransferase levels.**

Cephalosporins

- The frequency of **hypersensitivity reactions** to cephalosporins is **less than that for penicillins**.
- Various **cutaneous rashes**, often **associated with eosinophilia** and occasionally with **fever**, occur in 1% to 7% of patients receiving these drugs.
- More severe hypersensitivity reactions, **such as serum sickness, anaphylaxis, or angioedema**, occur very infrequently.
- These immunoglobulin E (IgE)-mediated reactions are estimated to occur in fewer than **1 in 100,000** patients.

Cephalosporins

- Because the cephalosporins have **broad-spectrum** activity, **superinfection** or **overgrowth of *Candida*** in the **gastrointestinal** and **vaginal** tracts can occur.
- Similarly, overgrowth of ***Clostridioides difficile*** (formerly *Clostridium difficile*) in the **gastrointestinal tract** with **diarrhea and colitis** has been associated with increased use of broad-spectrum cephalosporins.

Carbapenems are generally well tolerated.

- There seems to be no particular propensity for them to cause major adverse effects, *C. difficile*–associated colitis, coagulation abnormalities, nephrotoxicity, or hepatotoxicity.

Carbapenems are generally well tolerated.

- The **most common adverse** : nausea, vomiting, diarrhea, rash, headache, and phlebitis, occurring in 1% to 3% of patients.
- All carbapenems have been associated with **seizures**.
- the risk is elevated in patients with renal failure and neurologic comorbidities.
- Seizures are **more common with imipenem** (1%–2%) than ertapenem, meropenem, and doripenem (0.1%–0.3%).

Antibiotic Allergy

- **Four** main pathophysiologic mechanisms in allergic drug reactions :
- Type 1 : Immunoglobulin E (IgE)-mediated
- Type 2 : Cytotoxic reactions
- Type 3 : Immune complex reactions
- Type 4 : delayed-type hypersensitivity reactions

Antibiotic Allergy symptoms

- Type 1 : urticaria and angioedema or anaphylaxis
- Type 2 : hemolytic anemia or thrombocytopenia
- Type 3 : serum sickness–like reactions with rashes, fever, and arthralgias
- Type 4 : the most common manifestation of antimicrobial drug reactions as exemplified by the **maculopapular exanthem**

Antibiotic Allergy

Immediate (Immunoglobulin E–Mediated) Drug Reactions

- Immediate IgE-mediated reactions result from the interaction of **drug antigens** with preformed **drug-specific IgE**
- These reactions usually occur within **1 hour** of drug administration and clinically manifest as **urticaria, angioedema, rhinitis, bronchospasm, or anaphylaxis**

Antibiotic Allergy

Non Immediate Drug Reactions

- They occur more than **1 hour** and within **7 days** after the last drug administration.
- Although drug reactions can involve **multiple organs**, **cutaneous** reactions are the most common.
- Severe cutaneous adverse reactions (**SCARs**), including Stevens-Johnson syndrome (**SJS**) and toxic epidermal necrolysis (**TEN**), may include **internal organ** involvement.
- In other antibiotic allergic manifestations only in the presence of a specific underlying predisposing factor (e.g., **ampicillin-induced rash in Epstein-Barr** infection; increased risk for **sulfonamide-related rashes** in **HIV and CD4 lymphopenia**).

Antibiotic Allergy

Drug Rash With Eosinophilia and Systemic Symptoms (DRESS)

- is a **systemic reaction** that is distinguished from other antimicrobial reactions by a delayed appearance after a **2- to 10-week** exposure to several antibiotics, including **sulfonamides** and **vancomycin**.
- Clinical characteristics include **rash, fever, lymph node swelling, hepatitis, or involvement of other organs**.

DRUG ALLERGY TO SPECIFIC ANTIMICROBIAL AGENTS

Penicillins

- Recent literature suggests that up to **98%** of patients with a **history of penicillin allergy** have **negative** findings on investigation.
- The vast majority of patients with a **label of penicillin allergy** are **not allergic**.
- **Penicillin allergy testing** should be done routinely in patients with self-reported penicillin allergy .

DRUG ALLERGY TO SPECIFIC ANTIMICROBIAL AGENTS

Cephalosporins

- The majority of allergic reactions to cephalosporins are **delayed rashes**, but **IgE-mediated urticaria** and **anaphylaxis** can also occur.

DRUG ALLERGY TO SPECIFIC ANTIMICROBIAL AGENTS

Carbapenems

- Imipenem
- Meropenem
- Doripenem
- Ertapenem
- **hypersensitivity** less than 3%.

DRUG ALLERGY TO SPECIFIC ANTIMICROBIAL AGENTS

Sulfonamides

- **maculopapular exanthems** are the most common form of drug allergy with sulfonamides .
- **SJS** and **TEN** or **DRESS**
- **TMP-SMX** has also been observed to have a much higher reaction rate in the **HIV-infected population**, mostly in the form of **exanthems**.

DRUG ALLERGY TO SPECIFIC ANTIMICROBIAL AGENTS

Vancomycin

- One of the most common adverse reactions to **vancomycin** is the **infusion-related**.
- **Red man syndrome**, manifests as **pruritus** and erythematous **flushing**, particularly of the **face and neck**.
- In some cases, **urticaria**, **angioedema**, and even **hypotension** may also .
- These **pseudoallergic** reactions can be prevented by **slowing** the rate of infusion and premedicating with **H1 blockers**.

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DRUG ALLERGY TO SPECIFIC ANTIMICROBIAL AGENTS

Quinolones

- **Delayed exanthems** being a more common reaction.
- **Moxifloxacin** has been shown to increase the odds of immediate **hypersensitivity** by **fourfold** compared with other quinolones.

DRUG ALLERGY TO SPECIFIC ANTIMICROBIAL AGENTS

Aminoglycosides

- Although **topical aminoglycoside** antibiotics are common causes of allergic **contact dermatitis** .
- **systemic hypersensitivity** is **unusual** and descriptions have mostly been limited to isolated reports of **anaphylaxis** to various compounds such as **gentamicin** and **tobramycin**.

DRUG ALLERGY TO SPECIFIC ANTIMICROBIAL AGENTS

Macrolides

- A history of **allergic reactions** to macrolides is **rare**.
- These reactions develop in **0.4% to 3%** of the treated population.

Aminoglycosides complications : Nephrotoxicity

- The precise mechanisms of aminoglycoside-induced injury to renal proximal tubular cells remain incompletely understood.
- Neomycin is the most toxic aminoglycoside, and streptomycin is the least nephrotoxic .
- Thus for a given total daily dose of a specific aminoglycoside the magnitude of toxicity is greatest when the dose is divided into multiple small increments and least when it is given as a single daily dose.

Aminoglycosides complications : Ototoxicity

- Aminoglycoside antibiotics can cause **cochlear** and **vestibular** damage.
- It is **unusual** to have **both** ototoxicity and nephrotoxicity in the same patient.
- **Prolonged therapy** beyond 10 days, **renal or hepatic impairment**, and prior **exposure to aminoglycosides** are **major risk factors**.
- Concomitant **loop diuretics**, **vancomycin**, and **loud ambient noise** increase the risk of cochlear toxicity.
- The use of **aspirin** reduced the incidence of ototoxicity **from 13% to 3%**.

Neuromuscular Blockade

- Neuromuscular blockade after aminoglycoside administration is a **rare** but serious and potentially ethal adverse effect.
- neomycin, streptomycin, kanamycin , tobramycin, gentamicin, amikacin , or netilmicin .

Tetracyclines

- **Gastrointestinal Side Effects :**
- Nausea , vomiting , diarrhea , heartburn , and epigastric pain
- Patients should drink at least **100 mL of water** while standing upright for at least **90 seconds**.
- Patients with **esophageal strictures** should not take **doxycycline**.
- **Diarrhea** may occur with **doxycycline**
- **Minocycline** also commonly causes nausea, but vomiting, diarrhea, and esophageal ulcerations .

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Tetracyclines : Photosensitivity and Hyperpigmentation

- A **photosensitive rash** commonly occurs in **sun-exposed** areas of patients taking **tetracyclines**.
- This reaction occurs as a result of **drug accumulation in the skin** and is **phototoxic**.
- This may occur **shortly after exposure to the sun** and can persist for a few days after the drug is discontinued.
- **Severe cases** may be associated with **edema, papules** .
- Hyperpigmentation of various body parts has been well described with the tetracyclines, particularly **minocycline**.

Tetracyclines : Teeth and Bone

- Tetracyclines deposit in teeth and bones as a result of chelation of tetracycline with calcium.
- The teeth can become stained owing to the formation of tetracycline-calcium orthophosphate complexes that darken with sun exposure.
- Enamel hypoplasia has been most commonly described in premature
- Children receiving tetracycline early in life tend to have deposition in their deciduous teeth.
- This can also occur in developing fetuses when their mother receives tetracycline during pregnancy, particularly after the 25th week of gestation.
- Tetracycline has also been noted to inhibit bone growth in infants receiving the drug.

Tetracyclines : Hepatotoxicity

- Hepatotoxicity is rarely associated with tetracycline use.
- Hepatotoxicity has been well described with highdose intravenous preparations of tetracycline.
- Rarely, acute symptomatic hepatitis requiring hospitalization may develop with prolonged use of oral tetracycline over a period of 10 days.
- Doxycycline does not appear to have the same side-effect profile and is rarely associated with significant liver toxicity.

Tetracyclines : Nephrotoxicity

- In the setting of **impaired renal function**, the tetracyclines can exacerbate renal malfunction by **inhibiting protein synthesis**.
- This causes a catabolic effect on amino-acid metabolism, leading to **azotemia, hyperphosphatemia, and acidosis**.

Tetracyclines : Neurotoxicity

- Central nervous system (CNS) effects have been described the most with minocycline.
- Minocycline has been noted to cause reversible dizziness, vertigo, tinnitus, and lack of concentration.
- Pseudotumor cerebri, or idiopathic intracranial hypertension, has been noted with prolonged use of minocycline, and with tetracycline and doxycycline.
- Symptoms may occur within 2 weeks to 6 months of therapy.

Tetracyclines : Hypersensitivity Reactions

- Hypersensitivity reactions are **uncommon** .
- Occur more frequently with **minocycline**.
- They can include **urticaria, facial edema, drug-induced autoimmune disease,** and **rarely anaphylaxis**.
- **Minocycline** has been associated with **drug-induced autoimmune disorders** .

Tetracyclines : Teratogenicity

- The **tetracyclines** are able to cross the **placenta into the fetus**.
- pregnancies exposed to **doxycycline** showed that there was **no increase in risk of fetal abnormalities**.
- The **tetracyclines** are still generally avoided in pregnancy owing to their potential to stain **teeth** and cause **enamel hypoplasia**.

Rifamycins

- **RIFAMPIN**
- **RIFABUTIN**
- **RIFAPENTINE**
- **RIFAXIMIN**

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RIFAMPIN

- The **rifampin-associated flulike syndrome** consists of fever, chills, malaise, myalgias, and headache several hours after dosing and usually resolves within several hours.
- The incidence of flulike syndrome escalates with **higher doses** (900–1200 mg) given weekly .

- **Rifampin** can cause **changes in liver function**, but serious injury is usually confined to patients with underlying **liver disease** due to alcohol, viral hepatitis, and other hepatotoxins , such as isoniazid , which often is coprescribed .

- **Rifabutin** has a unique toxicity profile, including uveitis, leukopenia, and polyarthralgias.
- The most common event was leukopenia, followed by GI symptoms, abnormal liver enzymes, a diffuse polyarthralgia .
- Uveitis was seen in patients receiving clarithromycin and is likely secondary to a drug interaction that raises rifabutin serum concentrations.

- **Uveitis** has been seen in HIV-infected patients receiving 300mg dosing for **prophylaxis** as late as **14 months** after initiation, often in combination with **fluconazole** or **azithromycin** or **both**.

- **Rifapentine** is **better tolerated** than rifampin, likely due to higher protein binding.
- **Once-weekly** dosing has a lower incidence of the **flu-like syndrome** ; however, cases with **hemolysis** and **renal failure** have been reported.
- The incidence of **hepatotoxicity** is **similar to rifampin**.
- **Hyperuricemia** has been reported with rifapentine .

- Rifaximin is associated with few adverse effects.
- An unusual case of rifaximin-associated neutropenia was described in a patient receiving 1200 mg daily with severe ulcerative colitis .

Metronidazole

- Metronidazole is generally **well tolerated**.
- Nausea , diarrhea , dry mouth , metallic taste , candidal vaginitis , and stomatitis .
- Serious **CNS** adverse effects (ataxia , encephalopathy , dysarthria , seizure , aseptic meningitis , and peripheral neuropathy) have been reported most commonly with **prolonged therapy** but are **reversible**.
- Other **mild CNS** effects have been reported , including dizziness , headache, confusion , vertigo , and insomnia.

Macrolides

- Erythromycin, azithromycin, and clarithromycin
- Although frequently used specifically for its motility effects, **gastrointestinal** adverse effects are the **most common adverse** effects caused by **erythromycin**.
- Symptoms including **abdominal pain** , **nausea and vomiting** , and **diarrhea** occur more commonly **in children** .
- **Pseudomembranous colitis** caused by **erythromycin**.

Macrolides

- **Ototoxicity** has been reported rarely in association with the use of **large intravenous doses** of erythromycin lactobionate or large doses of oral **erythromycin**.
- This may occur **more commonly in older adults** , in **patients with hepatic or renal insufficiency**, with receipt of **higher doses**, and with concurrent use of ototoxic medications.
- **Symptoms** are usually **reversible**; however, **irreversible tinnitus and hearing loss** have been reported.
- Polymorphic ventricular tachycardia (torsades de pointes) with **QT prolongation** has been reported in association with treatment with intravenous and oral **erythromycin**.

Macrolides

- Superinfection, especially of the gastrointestinal tract or vagina, with *Candida* species or gram-negative bacilli may occur, as with other antibiotics.
- Infantile hypertrophic pyloric stenosis has been epidemiologically linked to early exposure to erythromycin in children.

clarithromycin and azithromycin

- Adverse reactions to clarithromycin and azithromycin at the usual doses have been rare.
- The most common complaints are gastrointestinal (diarrhea, nausea, abdominal pain) .
- Acute psychosis or “mania” has been noted in a few patients receiving clarithromycin.
- High doses of clarithromycin in animals have been associated with teratogenic effects, and therefore that drug is not recommended for use in pregnancy.
- Azithromycin is classified as pregnancy category B.

Azithromycin

- Abnormalities in liver function are occasionally encountered in patients treated with azithromycin.
- With the high doses of these drugs used in the treatment of *M. avium* complex, tinnitus, dizziness, and reversible hearing loss have been reported.
- Rarely, severe allergic reactions have occurred with the use of azithromycin.
- The risk of macrolide-associated torsades de pointes (a polymorphic ventricular tachycardia) has been associated with increasing age, female sex, chronic use, and concomitant drug use, especially with cisapride.

Clindamycin

- **Cutaneous reactions** are common adverse responses to clindamycin, including delayed **maculopapular eruptions**, **urticaria**, **erythema multiforme**, **fixed drug eruptions**, drug rash with eosinophilia and systemic symptoms (**DRESS**), **Stevens-Johnson syndrome**, **toxic epidermal necrolysis**, and acute generalized exanthematous **pustulosis**.

Clindamycin

- **Diarrhea** occurs in up to **20% of clindamycin-treated** patients and is more common with oral administration.
- However, the **major toxicity** of **lincomycin and clindamycin** that now appreciably limits their use is the occurrence of **pseudomembranous colitis** caused by toxins secreted by *C. difficile* that overgrows in the presence of these antibiotics.
- ***C. difficile* infection** has been reported after the use of **clindamycin vaginal** cream in a patient being treated for bacterial vaginosis.

Clindamycin

- Hypotension and electrocardiographic changes have occasionally been reported.
- Cardiopulmonary arrest has occurred rarely, when large intravenous doses of lincomycin were given rapidly.
- These effects have not been reported with clindamycin.

Vancomycin

- vancomycin-related **ototoxicity** was a **rare** reaction.
- **Nephrotoxicity** associated with vancomycin has been reported since the beginning of its clinical use, thought to be related, at least in part, to impurities in the early preparations.
- **Red-Man Syndrom**
- **Severe hypotension** and even **cardiac arrest** have also been reported during **vancomycin infusion**.
- **Neutropenia** is also observed with vancomycin in patients with **longterm vancomycin therapy**.
- **Thrombocytopenia** associated with vancomycin use is very **rarely** reported, although it may be unrecognized.

Vancomycin

- Presumptive vancomycin-induced **maculopapular or erythematous rash** and drug-related.
- Vancomycin has been associated with a series of immune-mediated reactions, or **hypersensitivity reactions** that include maculopapular rash, drug rash eosinophilia and systemic symptoms (**DRESS**) syndrome, linear immunoglobulin A bullous dermatosis, and **Stevens-Johnson syndrome** , **toxic epidermal necrolysis**.
- Despite the clinical efficacy of oral vancomycin for treating *C.difficile*–related diarrhea, cases of ***C. difficile colitis*** attributed to the use of **IV vancomycin** have been reported.

Linezolid

- Both linezolid and tedizolid are relatively **well tolerated**, with **headache, diarrhea, nausea, and vomiting** predominating in larger clinical trials.
- **Reversible myelosuppression**, including pure **red blood cell aplasia**, **pancytopenia**, and especially **thrombocytopenia**, has been clearly documented and related to linezolid use .

Linezolid

- Linezolid is a reversible, nonselective monoamine oxidase inhibitor and has been associated with the development of **serotonin syndrome** (fever, agitation, mental status changes, tremors) in patients receiving concurrent serotonergic agents.
- Small increases in systolic blood pressure have been documented in patients receiving tyramine concurrently with linezolid, leading to recommendations for dietary restriction.
- Similarly, blood pressure monitoring is recommended for patients taking adrenergic agents such as pseudoephedrine and phenylpropanolamine.

Linezolid

- **Peripheral neuropathy** may begin with dysesthesias in the hands and is poorly reversible.
- **Optic neuropathy** causes gradual onset of blurring and can lead to permanent loss of useful visual acuity if the drug is not discontinued; when detected early, **visual loss** has generally been reversible.
- **Lactic acidosis**, including fatal cases, has been reported most commonly during prolonged durations of linezolid therapy but can develop within the **first week**.

Sulfonamides

- Sulfonamides can cause **nausea, vomiting, diarrhea, rash, fever, headache, depression, jaundice, hepatic necrosis, drug-induced lupus** , and a serum sickness–like syndrome.
- Sulfadiazine used in excessively **high doses** is associated with **crystalluria** and tubular deposits of sulfonamide crystals.
- These complications can be minimized by maintenance of high urine flow and alkalization of the urine.
- **Tubular necrosis, interstitial nephritis, and necrotizing angiitis** may be associated rarely with sulfonamide sensitivity.

Sulfonamides

- Acute hemolytic anemia sometimes related to G6PD , aplastic anemia, agranulocytosis, thrombocytopenia, and leukopenia.
- During the last month of pregnancy : increasing the risk of kernicterus.

Sulfonamides

- Significant **hypersensitivity reactions** can occur with sulfonamides administered via any route.
- The most important of these reactions are **erythema nodosum, erythema multiforme (including Stevens-Johnson syndrome), fixed-drug eruption, vasculitis** similar to periarteritis nodosa, and **anaphylaxis**.

Quinolones

- Gastrointestinal tract:
- In most patients, anorexia, nausea, vomiting, and abdominal discomfort are mild when they occur.
- Symptoms of mild headache and dizziness have predominated, followed by insomnia and alterations in mood.
- Hallucinations, delirium, psychosis, and seizures are rare.

- With **gemifloxacin**, **rashes** developed in 2.8% of patients in clinical trials .
- **Hypersensitivity** cross-reactivity among different fluoroquinolones .
- **Phototoxicity** reactions are uncommon with currently used quinolones but can occur in some patients **after exposure** to **ultraviolet** .

- Acute interstitial nephritis, with eosinophiluria but generally not crystalluria.
- Infiltrates of lymphocytes and eosinophils have been found in the renal interstitium on renal biopsies.
- Arthropathy with cartilage erosions and noninflammatory effusions .
- Tendinitis with acute onset of pain, swelling, and inflammatory skin changes .
- The risks are highest in patients older than 60 years, patients on corticosteroids, and organ transplant recipients.

Quinolones

- retinal detachment
- Prolongation of the **QT interval**
- **Leukopenia and eosinophilia** generally occur in less than **1%** of patients

Quinolones

- Hypoglycemia associated with the use of ciprofloxacin, levofloxacin, and moxifloxacin
- Safety in pregnancy has not been established .
- Studies of babies born to women exposed to norfloxacin or ciprofloxacin during the first trimester identified no increase in major malformations, stillbirths, or premature births.
- Because quinolones can be excreted in breast milk, they should be avoided for nursing mothers.

Nitrofurantoin

- **Pulmonary reactions** have been classified into **acute and chronic** forms .
- Acute reactions occur **within hours to weeks** of drug exposure and are characterized by a **reversible hypersensitivity** phenomenon.
- The reaction comprises the **rapid onset** of **fever, cough, dyspnea, myalgia, and rash**. **Peripheral blood eosinophilia** (83% of cases),
- lower lobe infiltrates (94% of cases), and pleural effusions (20% of cases) .
- Sputum production, rash, pruritus, and chest discomfort may also occur.
- Most reports in **women** than in men, and most cases occur in patients **older than 40 years** .

Nitrofurantoin

- Chronic pulmonary reactions are 10 to 20 times less common.
- These reactions occur after 1 to 6 months of therapy and are characterized by nonproductive cough, dyspnea, interstitial infiltrates, and usually fever.
- Eosinophilia is less common than in patients with acute reactions.
- Abnormal results of liver enzyme studies (40%)
- Improvement can occur with discontinuation of the drug, but about half of the affected persons have persistent mild signs of pulmonary fibrosis.

Nitrofurantoin

- **Gastrointestinal Reactions** : nausea and vomiting
- **Cutaneous reactions** : Sweet syndrome, antineutrophilic cytoplasmic antibody-associated vasculitis, and **lupus**.
- Prolonged use of nitrofurantoin has been associated with **chronic active hepatitis, cirrhosis, and death**.
- **Hemolytic anemia** in patients receiving nitrofurantoin is most commonly associated with **glucose-6-phosphate dehydrogenase (G6PD) deficiency** .
- **Eosinophilia** has been described in patients with pulmonary and hepatic reactions.
- A **peripheral sensorimotor neuropathy** has been reported **uncommonly** .

Antifungal Drugs: Azoles

- Adverse effects from **itraconazole** may occur, including **hepatotoxicity and QTc prolongation**.
- **Gastrointestinal distress** is common with the oral suspension.
- More severe side effects include development of **hypertension, hypokalemia, and peripheral edema**.
- **Heart failure** has also been described secondary to the negative inotropic effects of **itraconazole**, and it should be used with caution in patients with a history of ventricular dysfunction of congestive heart failure.

Antifungal Drugs: Azoles

- Adverse effects from **fluconazole** are generally benign; however, **both hepatotoxicity and cardiac toxicity** due to **prolongation of the QTc interval** can occur with any of the triazoles.
- **Headache, alopecia**, are the most frequent side effects of **fluconazole** and are reversible after discontinuation of therapy.
- **Neurotoxicity** has been reported with very high doses (**2000 mg daily**) before the availability of alternative triazoles.
- Anaphylaxis and Stevens-Johnson syndrome have been rarely observed.

