

Other antifungals: polyenes, echinocandins and allylamines

Three mechanistically unrelated antifungal families grouped here by what they are not - not azoles - that between them cover the oldest systemic antifungal still in use (amphotericin B), the newest major mechanism to reach the fungal cell wall rather than its membrane (the echinocandins), and the drug of choice for nail and skin dermatophyte infections (terbinafine).

Online guide: <https://www.medguideglobal.com/pharmacology/antivirals-antifungals-antiparasitics/other-antifungals>

Content updated: 2026-09-15

Quick revision

One Liner: Amphotericin B punches pores straight through the fungal membrane by binding ergosterol, the echinocandins instead attack the fungal cell wall by blocking 1,3-beta-D-glucan synthase, and terbinafine blocks an earlier step of ergosterol synthesis than the azoles do - three separate mechanisms whose toxicity profiles (severe nephrotoxicity, a comparatively clean safety record, and hepatotoxicity respectively) are just as distinct as their targets.

1. Amphotericin B binds ergosterol in the fungal cell membrane and forms transmembrane pores, causing leakage of monovalent ions (Na⁺, K⁺, H⁺, Cl⁻) and cell death - a direct membrane-disrupting mechanism, not enzyme inhibition.

[1]

2. Liposomal amphotericin B formulations meaningfully reduce infusion-related reactions and nephrotoxicity compared with conventional amphotericin B deoxycholate, though a real risk of nephrotoxicity remains even with the liposomal form. [1][7]

3. The echinocandins (caspofungin, micafungin, anidulafungin) noncompetitively inhibit 1,3-beta-D-glucan synthase, an enzyme with no mammalian counterpart, blocking synthesis of an essential fungal cell-wall component rather than acting on the membrane at all. [2][5]

4. Echinocandins are fungicidal against most *Candida* species (including many azole-resistant strains) but only fungistatic against *Aspergillus*, and none of them is labelled for or effective against *Cryptococcus neoformans*. [5]

5. Echinocandins have a comparatively low incidence of adverse effects and minimal drug-drug interactions relative to the azoles, though caspofungin still requires dose reduction in moderate hepatic impairment and interacts with cyclosporine and tacrolimus. [2][5]

6. Terbinafine is a non-competitive inhibitor of fungal squalene epoxidase, an earlier step in ergosterol synthesis than the azoles' target, and it is the labelled treatment of choice for dermatophyte onychomycosis. [4][6]

7. Oral terbinafine carries a hepatotoxicity warning that includes reported liver failure, transplant and death, requiring baseline and periodic liver function testing, and it can cause taste and smell disturbance that is occasionally severe, prolonged or permanent. [4][6]

8. Micafungin's label discloses hepatic tumours (carcinomas and adenomas) seen in a rodent toxicology study, though whole-life carcinogenicity studies in animals have not been conducted for the drug. [3]

Overview

1. This class exists as a grouping of convenience as much as mechanism: polyenes, echinocandins and allylamines share no single molecular target with one another, and the only thing that truly unites them for teaching purposes is that none of them is an azole. That said, each has a genuinely distinct and testable mechanism, and together they cover ground the azoles do not: the oldest reliable systemic antifungal still in clinical use, the newest major antifungal mechanism to reach clinical practice, and the standard treatment for dermatophyte nail disease. [7]

2. Amphotericin B, a polyene first developed decades before the azoles, works by direct physical disruption rather than

enzyme inhibition. It binds ergosterol in the fungal cell membrane and assembles into transmembrane channels, and the resulting leakage of monovalent ions across the compromised membrane is what kills the cell. That same ergosterol-binding affinity is also amphotericin B's central liability, because ergosterol's mammalian counterpart, cholesterol, is structurally similar enough that some binding and membrane disruption occurs in human cells too - which is the mechanistic root of the drug's well-known nephrotoxicity. Liposomal formulations do not change the mechanism; they change delivery, reducing (without eliminating) both infusion-related reactions and nephrotoxicity relative to the older conventional deoxycholate formulation. [1]

3. The echinocandins represent a genuinely newer idea: rather than targeting the fungal membrane at all, they target the fungal cell wall, specifically by noncompetitively inhibiting 1,3-beta-D-glucan synthase, the enzyme that builds an essential glucan polymer found in fungal but not mammalian cells. That mammalian-cell absence is a large part of why this subclass has a comparatively favourable safety profile and relatively few drug interactions next to the azoles or amphotericin B. Their spectrum, however, is uneven by design: they are reliably fungicidal against *Candida* species, including many that are azole-resistant, but only fungistatic against *Aspergillus*, and they have no meaningful activity against *Cryptococcus neoformans* at all - a gap worth remembering precisely because it is easy to assume a modern, well-tolerated antifungal must be broad-spectrum. [2][5]

4. Terbinafine, an allylamine, sits apart from both of the above because its primary clinical role is dermatological rather than systemic-invasive-disease treatment: it is the labelled treatment for onychomycosis of the toenail or fingernail caused by dermatophytes. Mechanistically it acts earlier in the same ergosterol biosynthesis pathway the azoles interrupt later, by non-competitively inhibiting squalene epoxidase, the enzyme that converts squalene to squalene epoxide. The consequence is twofold: ergosterol synthesis falls, but squalene itself also accumulates inside the fungal cell to a degree that is directly toxic, which is part of why terbinafine can be fungicidal against the dermatophytes it targets rather than merely fungistatic. Its own defining risk is hepatotoxicity, serious enough that the label requires liver function testing before starting oral therapy and periodically during it. [4][6]

Classification and drug examples

Intro: Three subclasses, three mechanisms, three very different typical clinical roles: membrane-disrupting polyenes for severe invasive and disseminated disease, cell-wall-targeting echinocandins mainly for invasive candidiasis, and the allylamine terbinafine mainly for dermatophyte nail and skin infection.

1. Name: Polyenes

1. Note: Bind ergosterol directly and form membrane pores; broad-spectrum but limited clinically by nephrotoxicity, mitigated substantially (not eliminated) by liposomal formulation.

Name: Amphotericin B (liposomal)

AmBisome

Route: Intravenous

Note: Indicated for empirical therapy in febrile neutropenic patients, cryptococcal meningitis in HIV-infected patients, refractory *Aspergillus*/*Candida*/*Cryptococcus* infections, and visceral leishmaniasis. [1] [1]

2. Name: Echinocandins

2. Note: Inhibit fungal cell-wall glucan synthesis; strong against *Candida* (fungicidal), weaker against *Aspergillus* (fungistatic), inactive against *Cryptococcus*.

1. Name: Caspofungin

Cancidas

1. Route: Intravenous

1. Note: Indicated for empirical therapy in febrile neutropenia, candidaemia and other *Candida* infections, oesophageal candidiasis, and invasive aspergillosis refractory to or intolerant of other therapy. [2]

2. Name: Micafungin

Mycamine

2. Route: Intravenous

2. Note: Indicated for candidaemia and disseminated candidiasis, oesophageal candidiasis, and Candida-infection prophylaxis in haematopoietic stem cell transplant recipients; label discloses hepatic tumours in a rodent toxicology study. [3]

3. Name: Anidulafungin

3. Route: Intravenous

3. Note: Shares the class mechanism and general spectrum pattern (Candida-fungicidal, Aspergillus-fungistatic, no Cryptococcus activity) described for the class generally. [5] [2][5]

3. Name: Allylamines

3. Note: Inhibit squalene epoxidase, an earlier step of ergosterol synthesis than the azoles' target; the class's main clinical role is dermatophyte infection, particularly onychomycosis.

Name: Terbinafine

Lamisil

Route: Oral or topical

Note: Oral terbinafine is indicated for onychomycosis of the toenail or fingernail due to dermatophytes; requires pre-treatment and periodic liver function testing. [4] [4][6]

Mechanism of action

Summary: The three subclasses here interrupt fungal survival at three different structural levels. Polyenes act directly on the finished fungal membrane by binding the ergosterol already embedded in it and physically punching pores through the lipid bilayer. Echinocandins act on the fungal cell wall, a structure fungi have and mammalian cells do not, by blocking the enzyme that synthesises one of its essential polymers. Terbinafine acts upstream in ergosterol biosynthesis itself, at an earlier enzymatic step than the azoles, so that both ergosterol depletion and toxic squalene accumulation contribute to fungal cell death.

Target: Ergosterol in the fungal cell membrane (polyenes); fungal 1,3-beta-D-glucan synthase (echinocandins); fungal squalene epoxidase (terbinafine)

Cidal Static: Amphotericin B is generally fungicidal; echinocandins are fungicidal against Candida but only fungistatic against Aspergillus; terbinafine is fungicidal against the dermatophytes it targets

Kill Kinetics: Amphotericin B and the echinocandins act relatively directly once bound to their target (membrane or cell wall integrity fails quickly); terbinafine's effect builds as intracellular squalene accumulates over the course of therapy

1. Step: 1

1. Title: Amphotericin B binds ergosterol already present in the fungal membrane

1. Detail: Unlike the azoles or terbinafine, amphotericin B does not block a synthesis enzyme; it binds the finished sterol molecule directly wherever it sits in the membrane. [1]

2. Step: 2

2. Title: Bound amphotericin B molecules assemble into transmembrane pores

2. Detail: Multiple amphotericin B molecules aggregate around bound ergosterol to form channels spanning the membrane. [1]

3. Step: 3

3. Title: Monovalent ions leak through the pore and the cell dies

3. Detail: The label states this directly: the channels lead 'to alterations in cell permeability through which monovalent ions (Na⁺, K⁺, H⁺, and Cl⁻) leak out of the cell resulting in cell death.' [1]

4. Step: 4

4. Title: Echinocandins instead block synthesis of a cell-wall component before it is ever built

4. Detail: Caspofungin noncompetitively inhibits beta-(1,3)-D-glucan synthase, the enzyme responsible for synthesising an essential glucan polymer of the fungal cell wall; because this enzyme has no counterpart in mammalian cells, the mechanism is highly fungus-selective. [2][5]

5. Step: 5

5. Title: Terbinafine blocks an earlier ergosterol-pathway enzyme, squalene epoxidase, causing both ergosterol depletion and toxic squalene buildup

5. Detail: Terbinafine is a non-competitive inhibitor of squalene epoxidase, the enzyme that converts squalene to squalene epoxide; blocking it both starves the pathway of ergosterol downstream and lets squalene accumulate intracellularly to levels that are themselves toxic to the fungal cell. [4][6]

Spectrum of activity

Intro: Spectrum here is where the practical differences between these three subclasses become sharpest, particularly the echinocandins' well-defined gap against *Cryptococcus* and terbinafine's dermatophyte focus.

1. Subclass: Amphotericin B (liposomal)

1. Covers: A genuinely broad range: *Candida*, *Aspergillus* and *Cryptococcus* species (including cryptococcal meningitis), and the protozoan agent of visceral leishmaniasis; used empirically in febrile neutropenia.

1. Gaps: Broad activity is offset by dose-limiting nephrotoxicity, which is what actually restricts its first-line use in many settings rather than any spectrum gap. [1]

2. Subclass: Echinocandins

2. Covers: *Candida* species, including many strains resistant to azoles, with fungicidal activity; fungistatic activity against *Aspergillus* species, supporting use as therapy for aspergillosis refractory to or intolerant of other agents.

2. Gaps: No meaningful activity against *Cryptococcus neoformans*, a specific and testable gap distinct from their otherwise broad *Candida* coverage. [5][2]

3. Subclass: Terbinafine

3. Covers: Dermatophytes (*Trichophyton*, *Microsporum*, *Epidermophyton* species) causing onychomycosis and other dermatophyte infections.

3. Gaps: Not a first-line systemic agent for invasive yeast or mould disease; its labelled role here is specifically dermatophyte infection. [4]

Major clinical uses

1. Drug: Amphotericin B (liposomal)

1. Organism: *Candida*, *Aspergillus*, *Cryptococcus* species; *Leishmania* (visceral)

1. Indication: Empirical therapy in febrile neutropenia; cryptococcal meningitis in HIV-infected patients; infections refractory to conventional amphotericin B or in patients with renal impairment; visceral leishmaniasis

1. Line: reserved for severe or refractory invasive disease given its toxicity profile

1. Note: Liposomal formulation reduces but does not eliminate nephrotoxicity and infusion reactions relative to conventional amphotericin B deoxycholate. [1]

2. Drug: Caspofungin

2. Organism: *Candida* species; *Aspergillus* species (refractory/intolerant disease)

2. Indication: Empirical therapy for presumed fungal infection in febrile neutropenic patients; candidaemia and *Candida* intra-abdominal abscess, peritonitis and pleural infections; oesophageal candidiasis; invasive aspergillosis refractory to or intolerant of other therapies

2. Line: an option when azole resistance, intolerance, or interaction concerns favour a different mechanism

2. Note: Dose reduced in moderate hepatic impairment (Child-Pugh 7-9). [2]

3. Drug: Micafungin

3. Organism: *Candida* species

3. Indication: Candidaemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses; oesophageal candidiasis; prophylaxis of *Candida* infection in haematopoietic stem cell transplant recipients

3. Line: prophylactic and treatment option in transplant and candidaemia settings

3. Note: Label discloses hepatic carcinomas and adenomas in a 6-month rat toxicology study; whole-life carcinogenicity studies in animals have not been conducted. [3]

4. Drug: Terbinafine

4. Organism: Dermatophytes (tinea unguium and other dermatophyte infections)

4. Indication: Onychomycosis of the toenail or fingernail due to dermatophytes

4. Line: labelled treatment of choice for dermatophyte onychomycosis

4. Note: Requires pre-treatment liver function testing given reported hepatotoxicity, including liver failure and death.

[4][6]

Pharmacokinetics

1. Drug: Amphotericin B (liposomal)

1. Route: Intravenous infusion

1. Absorption: Not applicable (IV administration)

1. Csf Penetration: See prescribing reference

1. Metabolism: Not extensively characterised; cleared from plasma via the reticuloendothelial system as intact liposomes

1. Elimination: See prescribing reference

1. Dose Adjust: Renal function is monitored during treatment because of nephrotoxicity risk rather than as a formal renal dose-adjustment schedule [1]

2. Drug: Caspofungin

2. Route: Intravenous infusion

2. Absorption: Not applicable (IV administration)

2. Csf Penetration: See prescribing reference

2. Metabolism: Hepatic, via hydrolysis and N-acetylation, not primarily via CYP450

2. Elimination: Hepatic and renal

2. Dose Adjust: Reduced maintenance dose in moderate hepatic impairment (Child-Pugh 7-9) [2]

3. Drug: Micafungin

3. Route: Intravenous infusion

3. Absorption: Not applicable (IV administration)

3. Csf Penetration: See prescribing reference

3. Metabolism: Hepatic

3. Elimination: Primarily faecal

3. Dose Adjust: See prescribing reference [3]

4. Drug: Terbinafine

4. Route: Oral or topical

4. Absorption: Well absorbed orally

4. Csf Penetration: See prescribing reference

4. Metabolism: Hepatic, and an inhibitor of CYP2D6

4. Elimination: Primarily renal, as metabolites

4. Dose Adjust: Contraindicated in chronic or active liver disease; caution with CYP2D6 substrates [4]

1. This page gives no dose regimens by design. Loading and maintenance dosing for the echinocandins, infusion protocols for liposomal amphotericin B, and treatment duration for terbinafine belong in a current prescribing reference used by the treating clinician.

2. None of caspofungin's metabolism runs primarily through CYP450, which is a real and testable point of contrast with the azoles' heavy CYP450 dependence and is part of why this subclass has 'minimal drug interactions' relative to the azole class. [5]

3. Terbinafine's CYP2D6 inhibition is clinically real: its own label describes roughly a two-fold increase in peak concentration and a five-fold increase in AUC of desipramine, a CYP2D6 substrate, when co-administered. [4]

Adverse effects

1. Effect: Infusion-related reactions (chills, rigors, fever)

1. Detail: Reported with both conventional and liposomal amphotericin B, though liposomal amphotericin B caused chills/rigors in 18% of patients on day 1 versus 54% with conventional amphotericin B in labelled comparative data. [1]

2. Effect: Gastrointestinal effects and phlebitis

2. Detail: Common with caspofungin, including diarrhoea, nausea, vomiting and injection-site phlebitis, alongside chills and fever. [2][5]

3. Effect: Headache and gastrointestinal upset

3. Detail: Common with oral terbinafine, generally mild and self-limited. [6]

1. Effect: Nephrotoxicity

1. Detail: A defining risk of amphotericin B; the liposomal label defines nephrotoxicity as a doubling of creatinine over pretreatment levels and reports a materially lower incidence with the liposomal formulation than with conventional amphotericin B, without eliminating the risk.

1. Action: Renal function and electrolytes (potassium, magnesium) are monitored throughout treatment. [1]

2. Effect: Electrolyte disturbance (hypokalemia, hypomagnesemia)

2. Detail: Reported with amphotericin B; labelled comparative data show hypokalemia (potassium 2.5 mmol/L at any time) in 6.7% of liposomal amphotericin B patients versus 11.6% with conventional amphotericin B.

2. Action: Electrolytes are monitored and repleted as needed during treatment. [1]

3. Effect: Hepatotoxicity

3. Detail: Both echinocandins and terbinafine carry hepatotoxicity risk: caspofungin requires liver enzyme monitoring, particularly with concomitant cyclosporine; oral terbinafine has caused liver failure, sometimes leading to transplant or death, which is why pre-treatment and periodic liver function testing is required.

3. Action: Baseline liver function testing before starting oral terbinafine, with periodic monitoring during treatment, and prompt discontinuation if signs of liver injury develop. [2][4]

4. Effect: Hypersensitivity reactions, including anaphylaxis

4. Detail: Serious hypersensitivity reactions including shock have been reported with micafungin, and terbinafine is contraindicated in patients with a prior allergic reaction to it because of anaphylaxis risk.

4. Action: Discontinue the drug and treat appropriately if a hypersensitivity reaction occurs. [3][4]

5. Effect: Taste and smell disturbance (terbinafine)

5. Detail: Terbinafine's label describes taste disturbance, including taste loss, that can be severe, prolonged, or in rare cases permanent, and has been associated with reduced food intake and weight loss.

5. Action: This is discussed with patients before starting oral terbinafine and is a reason for reassessment if it develops. [4][6]

1. Drug: Amphotericin B (liposomal)

1. Effect: Nephrotoxicity and infusion reactions are reduced, not eliminated, by the liposomal formulation - a genuine but partial safety improvement over conventional amphotericin B deoxycholate. [1]

2. Drug: Micafungin

2. Effect: The only drug in this page whose label specifically discloses hepatic tumours (carcinomas and adenomas) observed in a rodent toxicology study, alongside the statement that whole-life carcinogenicity studies in animals have not been conducted. [3]

3. Drug: Terbinafine

3. Effect: The taste/smell disturbance and hepatotoxicity risk profile are specific enough to this drug within the class that they drive its own dedicated pre-treatment counselling and monitoring requirements. [4]

Contraindications, precautions and interactions

1. Terbinafine: chronic or active liver disease, and a history of allergic reaction to oral terbinafine because of the risk of

anaphylaxis. [4]

2. Micafungin: known hypersensitivity to micafungin sodium, any component of the product, or other echinocandins. [3]

1. Renal function and electrolytes are monitored throughout amphotericin B therapy given its nephrotoxicity and electrolyte-wasting effects. [1]

2. Liver function is monitored during caspofungin therapy, particularly with concomitant cyclosporine. [2]

3. Baseline and periodic liver function testing is required before and during oral terbinafine therapy given its hepatotoxicity risk. [4]

1. With: Cyclosporine

1. Effect: Increases caspofungin AUC by approximately 35%; liver enzyme monitoring is recommended during concurrent use. [2]

2. With: Tacrolimus

2. Effect: Caspofungin reduces tacrolimus blood concentrations, so tacrolimus levels are monitored during concurrent use. [2]

3. With: CYP2D6 substrates (e.g. desipramine)

3. Effect: Terbinafine inhibits CYP2D6 and meaningfully raises exposure to CYP2D6 substrates, shown in its own label as roughly a two-fold rise in peak concentration and a five-fold rise in AUC of desipramine. [4]

4. With: Other nephrotoxic agents

4. Effect: Concomitant use with other nephrotoxic drugs raises the risk of renal impairment during amphotericin B therapy and is a general caution addressed in the prescribing reference. [7]

Resistance mechanisms

Intro: Resistance mechanisms differ across these three subclasses just as sharply as their targets do, and the echinocandins' specific inactivity against *Cryptococcus* is a spectrum gap rather than an acquired-resistance phenomenon and is treated separately in the spectrum section above.

1. Mechanism: Reduced ergosterol content or altered membrane sterol composition

1. Organism: Some *Candida* and other fungal species, described generally in antifungal-mechanism literature

1. Impact: Because amphotericin B's mechanism depends on binding membrane ergosterol directly, fungal strains with reduced ergosterol content or altered sterol composition can show decreased susceptibility, though clinically significant resistance to amphotericin B is comparatively uncommon relative to the azoles. [7]

2. Mechanism: FKS gene mutations altering glucan synthase

2. Organism: *Candida* species, particularly some *Candida glabrata* isolates

2. Impact: Mutations in the FKS genes encoding the glucan synthase target can reduce echinocandin binding and confer resistance, which is why echinocandin susceptibility testing is relevant in refractory candidaemia even though echinocandin resistance overall remains less common than azole resistance. [5]

3. Mechanism: Squalene epoxidase target alteration

3. Organism: Some dermatophyte species with reported terbinafine resistance

3. Impact: Alterations in the squalene epoxidase target reduce terbinafine binding in resistant dermatophyte isolates, a phenomenon increasingly documented in some regions and relevant when standard therapy fails clinically. [6]

Comparison tables

Title: Three unrelated mechanisms, three different risk profiles

Caption: Grouped together mainly by what they are not (azoles), these three subclasses differ in target, spectrum gap, and defining toxicity.

1. Key: subclass

1. Label: Subclass

2. Key: target

2. Label: Target

- 3. Key: spectrum_gap
- 3. Label: Notable spectrum gap
- 4. Key: defining_toxicity
- 4. Label: Defining toxicity
- 1. Subclass: Polyenes (amphotericin B)
- 1. Target: Ergosterol in the fungal membrane (direct binding, pore formation)
- 1. Spectrum Gap: None major, but toxicity limits use
- 1. Defining Toxicity: Nephrotoxicity, electrolyte wasting, infusion reactions [1]
- 2. Subclass: Echinocandins
- 2. Target: 1,3-beta-D-glucan synthase (fungal cell wall)
- 2. Spectrum Gap: No activity against *Cryptococcus neoformans*; only fungistatic against *Aspergillus*
- 2. Defining Toxicity: Comparatively low; hepatic monitoring still relevant [5][2]
- 3. Subclass: Allylamines (terbinafine)
- 3. Target: Squalene epoxidase (ergosterol synthesis, upstream of the azole target)
- 3. Spectrum Gap: Dermatophyte-focused; not first-line for invasive yeast/mould disease
- 3. Defining Toxicity: Hepatotoxicity; taste/smell disturbance [4]

High-yield exam pearls

- 1. Pearl: Amphotericin B is the only drug on this page that acts by direct physical membrane disruption rather than inhibiting an enzyme.
- 1. Why: It is what makes amphotericin B mechanistically distinct not just from the echinocandins and terbinafine here, but from the azoles too, and it directly explains why its toxicity (nephrotoxicity from cross-reaction with cholesterol-containing human membranes) looks so different from an enzyme-inhibitor's toxicity. [1]
- 2. Pearl: Echinocandins target a fungal cell-wall enzyme with no mammalian counterpart - that is the direct, mechanistic reason for their comparatively clean safety profile.
- 2. Why: It is a clean cause-and-effect exam link: no human enzyme homolog, so no analogous human toxicity mechanism, unlike amphotericin B's cholesterol cross-reactivity or the azoles' CYP450 cross-reactivity. [5]
- 3. Pearl: No echinocandin covers *Cryptococcus neoformans* - a specific, high-yield spectrum gap, not a general weakness.
- 3. Why: It is the exact opposite pattern from amphotericin B and fluconazole, both of which do cover cryptococcal disease, so an exam question testing 'which drug would you NOT use for cryptococcal meningitis' should point straight at this subclass. [5]
- 4. Pearl: Terbinafine's target, squalene epoxidase, sits upstream of the azoles' target (lanosterol 14-alpha-demethylase) in the same ergosterol pathway.
- 4. Why: Confusing the two enzymes is a common error; the pathway position also explains terbinafine's dual mechanism of harm - both ergosterol depletion and toxic squalene accumulation. [6]
- 5. Pearl: Liposomal amphotericin B reduces nephrotoxicity, it does not remove it.
- 5. Why: Labelled comparative data still show a real, just smaller, incidence of renal and electrolyte abnormalities with the liposomal form, which is why renal monitoring continues even when the 'safer' formulation is chosen. [1]

Common exam traps

- 1. Trap: Assuming echinocandins are broad-spectrum simply because they are well tolerated and modern.
- 1. Correction: Tolerability and spectrum are separate questions here: echinocandins have no activity against *Cryptococcus neoformans* and are only fungistatic, not fungicidal, against *Aspergillus*, despite their favourable safety profile against *Candida*. [5]
- 2. Trap: Treating amphotericin B's nephrotoxicity as fully solved by using the liposomal formulation.
- 2. Correction: Liposomal amphotericin B's own labelled comparative data show a lower, not zero, incidence of

nephrotoxicity and electrolyte disturbance relative to conventional amphotericin B; renal monitoring remains standard practice. [1]

3. Trap: Assuming terbinafine and the azoles inhibit the same enzyme because both act in the 'ergosterol pathway.'

3. Correction: Terbinafine inhibits squalene epoxidase, an earlier step than the azoles' target, lanosterol 14-alpha-demethylase; the two mechanisms are adjacent in the same pathway but are not the same enzyme and are not cross-resistant by the same mutation. [6][8]

4. Trap: Assuming oral terbinafine is essentially risk-free because it is commonly used for a cosmetic-seeming indication like toenail fungus.

4. Correction: Its label describes hepatotoxicity serious enough to require pre-treatment and periodic liver function testing, including reported cases of liver failure, transplant and death, and it is contraindicated outright in patients with chronic or active liver disease. [4]

Self-test questions

1. Question: What is the immediate cause of fungal cell death after amphotericin B binds ergosterol in the membrane?

1. Inhibition of glucan synthase
2. Formation of transmembrane pores causing leakage of monovalent ions
3. Inhibition of squalene epoxidase
4. Blockade of the fungal ribosome

1. Explanation: Amphotericin B forms transmembrane channels after binding ergosterol, and leakage of ions such as Na⁺, K⁺, H⁺ and Cl⁻ through these channels causes cell death, a direct physical mechanism rather than enzyme inhibition. [1]

2. Question: Which enzyme do the echinocandins inhibit?

1. Lanosterol 14-alpha-demethylase
2. Squalene epoxidase
3. 1,3-beta-D-glucan synthase
4. Dihydropteroate synthase

2. Explanation: Echinocandins such as caspofungin noncompetitively inhibit beta-(1,3)-D-glucan synthase, blocking synthesis of an essential fungal cell-wall polymer that has no mammalian counterpart. [2][5]

3. Question: Which organism is NOT covered by echinocandin therapy?

1. Candida albicans
2. Candida glabrata
3. Cryptococcus neoformans
4. Candida krusei

3. Explanation: Echinocandins have no meaningful activity against Cryptococcus neoformans, despite being fungicidal against most Candida species including some azole-resistant strains. [5]

4. Question: What enzyme does terbinafine inhibit, and how does its position in the ergosterol pathway compare with the azoles?

1. Lanosterol 14-alpha-demethylase, the same target as the azoles
2. Squalene epoxidase, an earlier step in ergosterol synthesis than the azoles' target
3. 1,3-beta-D-glucan synthase, a cell-wall target unrelated to ergosterol
4. Dihydrofolate reductase, unrelated to fungal membranes

4. Explanation: Terbinafine non-competitively inhibits squalene epoxidase, which acts earlier in the ergosterol biosynthesis pathway than the azoles' target, lanosterol 14-alpha-demethylase. [6]

5. Question: What is required before starting oral terbinafine, given its labelled risk profile?

1. An ECG for QT monitoring
2. Baseline liver function testing
3. A renal biopsy

4. HIV testing

5. Explanation: Oral terbinafine's label requires pre-treatment evaluation of liver function given reported hepatotoxicity, including liver failure, transplant and death, with periodic monitoring during treatment. [4]

6. Question: Does the liposomal formulation of amphotericin B eliminate its nephrotoxicity risk?

1. Yes, liposomal amphotericin B carries no renal risk

2. No, it reduces but does not eliminate nephrotoxicity relative to conventional amphotericin B

3. No, liposomal amphotericin B is actually more nephrotoxic

4. Nephrotoxicity is not associated with any amphotericin B formulation

6. Explanation: Labelled comparative data show a lower, but still present, incidence of nephrotoxicity and electrolyte disturbance with liposomal amphotericin B compared with the conventional deoxycholate formulation, which is why renal monitoring continues regardless of formulation. [1]

Frequently asked questions

1. Question: Why would a clinician choose an echinocandin over amphotericin B for invasive candidiasis?

1. Answer: Echinocandins are fungicidal against most *Candida* species, including many azole-resistant strains, and their labelled and real-world adverse-effect burden is comparatively lower than amphotericin B's, particularly around nephrotoxicity and infusion reactions. Amphotericin B remains relevant chiefly where echinocandin coverage is inadequate (for example, suspected *Cryptococcus*) or in specific refractory or severe scenarios. [5][1]

2. Question: Can an echinocandin be used for cryptococcal meningitis?

2. Answer: No. None of the echinocandins has meaningful activity against *Cryptococcus neoformans*, so they are not an appropriate choice for cryptococcal disease regardless of how well tolerated they are for *Candida* infections; amphotericin B and fluconazole are the antifungals actually labelled and used for cryptococcal meningitis. [5]

3. Question: Is terbinafine's liver risk why toenail fungus treatment sometimes seems like 'a big deal' for a cosmetic-seeming problem?

3. Answer: Yes, essentially. Oral terbinafine's benefit for onychomycosis is real and it is the labelled and generally most effective option for dermatophyte nail infection, but its own label requires liver function testing before and during treatment because of reported hepatotoxicity that has, in rare cases, been fatal or required transplantation - which is exactly why a clinician weighs a cosmetic-feeling indication against a genuine systemic risk before prescribing it. [4][6]

4. Question: Why does liposomal amphotericin B still require monitoring if it's the 'safer' version?

4. Answer: Because the liposomal formulation changes drug delivery, not the underlying mechanism that causes nephrotoxicity - amphotericin B still binds cholesterol-containing human membranes to some degree wherever it reaches them. Labelled comparative data show a real reduction, not elimination, of nephrotoxicity and electrolyte disturbance versus conventional amphotericin B, so renal function and electrolytes are still tracked throughout treatment. [1]

References

[1] AMBISOME (amphotericin B liposomal) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f7be6506-4d20-401e-a0ff-02ad7c33158a>

[2] CANCIDAS (caspofungin acetate) - prescribing information. DailyMed, U.S. National Library of Medicine . <https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=3bad23a6-09a6-4194-9182-093ed61bc71c>

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