- Flucytosine is available for oral or parenteral use.
  - It is mainly used for its synergistic effect, in combination with amphotericin, against Cryptococcus neoformans.
  - High plasma levels, which often occur with renal impairment, are associated with bone marrow toxicity, and monitoring of plasma concentrations is advised.
- Monitoring
  - Toxicity is associated with peak flucytosine plasma levels above 100 mg/L.
  - Monitoring is recommended in patients with renal impairment and in all patients receiving concomitant amphotericin.
  - trough levels should be kept above 25 mg/L to maintain efficacy.
  - Because of concerns about bone marrow suppression, full blood counts should also be regularly monitored in all patients receiving flucytosine.
- Ketoconazole, fluconazole, itraconazole, posaconazole and voriconazole are used systemically to treat fungal infections.
- Fluconazole has activity against Cryptococcus.
- Itraconazole has a broader spectrum, also being active against Aspergillus species.
- Voriconazole is active against Aspergillus species, Scedosporium apiospermum and Fusarium species.
- Posaconazole is active against Candida and Aspergillus species; it also has activity against Coccidioides immitis, Fusarium, Histoplasma, Zygomycetes and phaeohyphomycetes.

Pharmacokinetics
- Fluconazole has good tissue penetration, including penetration into the CNS. It is well absorbed following oral administration, but is expensive.
- Liver function monitoring should be considered.
- Itraconazole absorption requires an acidic stomach pH. Absorption is decreased in patients on proton pump inhibitors or histamine H2-receptor antagonists and an alternative antifungal is more appropriate in these patients.
- Itraconazole has been associated with reports of congestive heart failure and should therefore be used with caution in patients with a history of congestive heart failure. Liver function monitoring should be considered.
- Ketoconazole, an imidazole, was the first orally active azole. It has similar acid-dependent oral absorption to itraconazole which precludes its use in achlorhydric patients, and in those patients taking proton pump inhibitors, unless it is administered in an acidic vehicle.
- It is not significantly excreted in the urine.

Systemic azoles
- Common adverse effects include gastrointestinal upset, gynaecomastia and irregular menses.
- Hepatotoxicity and hypoadrenalism can occur. All patients on ketoconazole should have their liver function monitored before starting therapy, at two weeks and then monthly.
- Ketoconazole is a potent inhibitor of the CYP3A4 system and should not be administered with 3A4 substrates (more than 400 drugs always check the product information).
- Enzyme inducers (e.g. rifampicin, phenytoin) significantly reduce the bioavailability of ketoconazole.
- Ketoconazole may enhance the anticoagulant effect of warfarin and the INR requires frequent and careful monitoring.
- Posaconazole is a CYP3A4 inhibitor but is not as extensively metabolised by the other CYP enzymes as the earlier azoles. Posaconazole is a new drug and previously unrecognised adverse drug reactions and interactions may occur. Posaconazole’s safety and efficacy in children have not yet been established.

Amphotericin remains the treatment of choice for most serious systemic fungal infections.
- It is a toxic drug. The patient should be closely observed during the first dose, but daily incrementation of the dose is not necessary. Regular monitoring of serum electrolytes, renal function and Full Blood Count is essential.
- Amphotericin B desoxycholate is the conventional form of amphotericin.
- Amphotericin is also available as a lipid complex and in a liposomal formulation which provide different dosing schedules and infusion rates.
- Serious adverse events have occurred when the dosage and infusion rate have not been appropriate for the product. Conventional amphotericin B desoxycholate doses should not exceed 1.5 mg/kg/day. If products other than amphotericin B desoxycholate are chosen, appropriate doses and infusion rates for the preparation must be calculated.
- Hydrocortisone, antihistamines, antiemetics, opioids or an antipyretic may provide symptomatic relief.
- If severe immediate reactions continue, or renal impairment develops rapidly, or the patient fails to respond, and fluconazole is not appropriate, then a liposomal or lipid formulation of amphotericin can be substituted with fewer toxic effects but much greater cost.

Caspofungin inhibits glucan synthesis in the cell wall in a novel way.
- It is used in the treatment of invasive aspergillus infections in patients who are refractory to or intolerant of other therapies such as amphotericin or itraconazole.
- It is also active against Candida, and can be used for treatment of candida oesophagitis and candidaemia.
- It is administered by slow intravenous infusion.

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- Ketoconazole, fluconazole, itraconazole, posaconazole and voriconazole are used systemically to treat fungal infections.
  - Spectrum of activity
    - Ketoconazole is active against a variety of fungal infections, particularly yeasts. It is also used as a steroidogenesis inhibitor.
    - Fluconazole has activity against Cryptococcus.
    - Itraconazole has a broader spectrum, also being active against Aspergillus species.
    - Voriconazole is active against Aspergillus species, Scedosporium apiospermum and Fusarium species.
    - Posaconazole is active against Candida and Aspergillus species; it also has activity against Coccidioides immitis, Fusarium, Histoplasma, Zygomycetes and phaeohyphomycetes.