

Chapter 22

Antifungals

FLUCYTOSINE (5-FLUOROCYTOSINE, 5-FC): in WHO Model list of Essential Drugs as complementary drug when drugs in main list are known to be ineffective or inappropriate for a given individual and as drug with limited applications or narrow spectrum of activity; oral (take with or after food; not registered in Australia) and parenteral; mode of elimination renal

Indications: mainly used in synergistic combination with amphotericin B against *Cryptococcus neoformans* (including cryptococcal meningitis); also severe *Aspergillus* infections; fungal brain and epidural abscess; *Candida* empyema, fungemia, chronic mucocutaneous infection, pneumonitis; chromoblastomycosis; disseminated *Blastoschizomyces capitatus* and *Trichosporon beigelii* infections; eumycetoma; *Histoplasma capsulatum* infections; fungal meningitis; *Mucor* infections; fungal osteomyelitis and osteochondritis; fungal peritonitis; fungal pneumonia (including diffuse interstitial); fungal postseptal cellulitis; fungal prostatitis and seminal vesiculitis; chronic fungal sinusitis; systemic *Blastoschizomyces capitatus*, *Exophiala dermatitidis* and *Pseudallescheria boydii* infections; torulopsosis; fungal urinary infections; mild zygomycosis

Side Effects: bone marrow toxicity (most commonly thrombocytopenia with high serum levels; monitoring advised; leucopenia also common; agranulocytosis rare), hepatic toxicity (elevated liver enzymes common; hepatic necrosis rare); nausea, vomiting, diarrhoea, anaemia, rash common; gastrointestinal haemorrhage, allergic reactions, epidermal necrolysis, convulsions, myocardial toxicity, ventricular dysfunction rare; dosage adjustment necessary in renal insufficiency (monitor serum levels, monitor peripheral blood count (neutropenia, thrombocytopenia), gastrointestinal tonus) and in dialysis; may falsely elevate serum creatinine measurement by certain assays; safety in pregnancy not established; toxic level

> 100 mg/L peak; amphotericin and other drugs that predictably reduce glomerular filtration rate produce accumulation of flucytosine; increased risk of neutropenia ? thrombopenia with cytotoxic agents; cytarabine may antagonise antifungal activity

Contraindications: avoid if pregnant or breastfeeding (insufficient data)

KETOCONAZOLE: imidazole; oral (variable, acid-dependent absorption, increased if taken with acidic drinks and food); in WHO Model List of Essential Drugs as drug for which specific expertise, diagnostic precision or special equipment required for proper use; mode of elimination hepatic, not significantly excreted in urine; active against *Blastomyces dermatitidis*, *Candida albicans*, *Candida krusei*, *Coccidioides immitis*, *Cryptococcus*, some strains of *Fusarium*, *Histoplasma*, *Paracoccidioides*, *Pseudallescheria boydii*, *Sporothrix schenckii*, *Trichosporon*; inactive against *Aspergillus*, *Candida tropicalis*, *Torulopsis*; usual dose 200-400 mg; peak serum concentration 1.7-3.6 mg/L; half life 8 h; protein binding 99%; CSF/serum concentration < 10; 50% absorption; 2% active drug in urine

Indications: first choice in blastomycosis (mild cases), chronic mucocutaneous candidiasis, nondisseminated extracutaneous coccidioidomycosis in immunocompetent host, entomophthoromycoses, histoplasmosis (nondisseminated extracutaneous disease in immunocompetent host), paracoccidioidomycosis, mild penicillosis, *Pseudallescheria boydii* infections and sporotrichosis; alternative in candidal oesophagitis, onchyomycosis, severe oropharyngeal candidiasis, chronic or unresponsive candidal paronychia, pityrosporiasis, superficial mycoses (dermatophytosis (unresponsive tinea corporis, pedis and cruris, tinea capitis, tinea unguium), vaginitis (recalcitrant and recurrent candidal, due to *Torulopsis glabrata*, *Saccharomyces cerevisiae*)) when intolerance or failure with classical treatment; in nonimmunosuppressed patients, alternative to amphotericin B in systemic mycoses (eg., treatment and prophylaxis of systemic candidiasis (including pneumonitis), coccidioidomycosis (including diffuse interstitial pneumonia, mild to moderate stable disease of bones, genitourinary tract, peritonitis, viscera), *Exophiala dermatitidis*, systemic protothecosis); in immunosuppressed patients, no evidence of efficacy of treatment in curing infection except in treatment of oesophagitis in granulocytopenia, but useful as prophylaxis against aspergillosis and candidiasis in chronic granulomatous disease and in cryptococcosis prophylaxis; also used in *Aspergillus* and *Mucor* infections,

chromoblastomycosis, eumycetoma, fungal endocarditis, zygomycosis, seborrhoeic dermatitis and dandruff (shampoo), tinea versicolor

Side Effects: nausea, vomiting, pruritis common; may cause serious hepatic disease (mild reactions (transient elevated transaminases) in 5-10%, serious injury (severe hepatotoxicity with hepatocellular damage) in 1 in 10 000 - 1 in 70 000; monitor liver function tests monthly); rash uncommon; blocks steroid synthesis and may cause adrenal suppression and adrenal crisis, and gynecomastia, azoospermia and loss of libido through reduction in testosterone levels; psychiatric reactions rare; single case report of tinnitus; dosage modification not required in renal dysfunction or in dialysis; safety in pregnancy not established; bioavailability reduced by antacids, cimetidine, didanosine buffered preparations (take ketoconazole 2 h before), H₂-receptor antagonists, proton pump inhibitors; significant interactions with many other drugs metabolised in liver: risk of cardiac arrhythmias due to high plasma levels of astemizole, cisapride and terfenadine (which have resulted in deaths), increased risk of myopathy with simvastatin (acute rhabdomyolysis and hepatotoxicity reported), atorvastatin, fluvastatin, pravastatin, increased sedative/amnesic effects with midazolam, triazolam, may increase plasma concentrations of alprazolam, buspirone, carbamazepine, cisapride (increased risk of QT prolongation), cyclosporin, methylprednisolone, nevirapine (with decrease in ketoconazole levels), sildenafil, warfarin, indinavir, saquinavir, enhances anticoagulant effect of coumarin, decreases plasma concentrations of theophylline, may cause hypoglycaemia in combination with oral antidiabetic agents, plasma levels remarkably reduced by cimetidine, isoniazid, phenytoin, rifabutin and rifampicin (80%; effect increased by isoniazid; rifabutin/rifampicin levels may increase or decrease), plasma levels and effects may be decreased by isoniazid, phenytoin, phenobarbitone, may decrease effect of amphotericin, lopinavir and ritonavir may increase plasma levels; very weak association with oral contraceptive failure; safety in pregnancy not established; caution in systemic treatment in breastfeeding (insufficient data)

MICONAZOLE: imidazole; interferes with production of ergosterols; i.v. and topical; in WHO Model List of Essential Drugs (topical); mode of elimination hepatic; active against *Blastomyces dermatitidis*, *Candida albicans*, *Candida krusei*, *Candida tropicalis*, *Coccidioides immitis*, *Cryptococcus*, *Histoplasma*, *Paracoccidioides*, *Sporothrix schenckii*, possibly *Fusarium* and *Trichosporon*; usual dose 0.6-1.8 g; peak serum concentration 7.5-10 mg/L; half life 24 h; protein binding 90%; CSF/serum concentration < 10; 50% absorption; 1% active drug in urine; no longer available in US or Europe

Indications: cutaneous, oropharyngeal and vulvovaginal candidiasis (topical); dermatomycoses including paronychia (topical); paracoccidioidomycosis; phaeohyphomycosis (topical); pityriasis versicolor (topical); fungal pneumonia (including diffuse interstitial); candidal local and generalised sepsis

Side Effects: oral: may induce hyponatremia; dosage modification not required in renal dysfunction or in dialysis; topical safe in pregnancy and breastfeeding; enhances anticoagulant effect of warfarin; oral hypoglycaemics, cyclosporin, phenytoin, phenobarbitone increase serum levels (monitor or reduce dose if necessary); isoniazid, rifampicin, carbamazepine, phenytoin may reduce levels by increasing metabolism; topical: infrequent burning, stinging, itching, redness, rare allergic reactions

ECONAZOLE: imidazole

Indications: cutaneous candidiasis (topical); candidal otitis externa (topical); paronychia (topical); dermatophytosis; tinea versicolor

Side Effects: burning and pruritis in 3%; safe in pregnancy and breastfeeding; enhanced anticoagulant effect of warfarin

CLOTTRIMAZOLE: imidazole; interferes with production of ergosterols

Indications: candidiasis in AIDS patients with CD4+ > 100; chronic mucocutaneous and vaginal candidiasis (gynaecology patients); candidal balanitis (topical); candidal oesophagitis (100% response); prophylaxis of oropharyngeal candidiasis in immunosuppressed patients; candidal otitis externa (topical); dermatomycoses including paronychia (topical); oesophagitis in granulocytopenia; pityriasis (tinea) versicolor (topical); vaginitis due to *Torulopsis glabrata*, *Saccharomyces cerevisiae* (topical)

Side Effects: topical safe in pregnancy and breastfeeding, infrequent burning, stinging, itching, redness, rare allergic reactions

BIFONAZOLE: imidazole; active against dermatophytes, *Malassezia furfur* and *Candida*, safety in pregnancy not established

Indications: mucocutaneous candidiasis, dermatophytosis, tinea versicolor

FLUCONAZOLE: triazole; good tissue penetration, including CNS; well absorbed following oral administration (relationship of dose to food doesn't matter); relatively expensive; i.v. and oral; usual dose 100-400 mg; peak serum concentration 2.5-6.7 mg/L; half life 20-30 h; protein binding 11%; CSF/serum concentration > 60; excretion renal; 85% absorption; 66% active drug in urine; active against *Candida albicans*, *Candida tropicalis*, *Coccidioides immitis*, *Cryptococcus*, *Histoplasma*, *Paracoccidioides*, *Sporothrix schenckii*, *Trichosporon*, ? *Blastomyces dermatitidis*, ? *Pseudallescheria boydii*; variable activity against *Fusarium*; inactive against *Aspergillus*, *Candida krusei*, *Torulopsis*

Indications: chronic mucocutaneous candidiasis in AIDS (CD4+ > 100); treatment and prophylaxis of systemic candidiasis; mild to moderate coccidioidomycosis of bones, genitourinary tract, peritonitis, viscera; cryptococcosis (induction, maintenance, prophylaxis); fungal endocarditis; less severe fungal endophthalmitis; fungemia; meningitis (cryptococcal; induction in mild and maintenance in coccidioidal); candidal oesophagitis (85% response); severe oropharyngeal candidiasis in immunocompromised and when failure of response to other treatment; systemic *Exophiala dermatitidis* and *Pseudallescheria boydii* infections; fungal urinary infections; recalcitrant candidal vaginitis

Side Effects: nausea (4% in AIDS), headache (2% in AIDS), skin rash (2% in AIDS), abdominal pain (2% in AIDS), vomiting (2% in AIDS), diarrhoea (2% in AIDS); pruritis, constipation common; asymptomatic liver function tests elevations in 1-2%; renal complications in renal dysfunction; serious adverse blood events (thrombocytopenia, neutropenia, leucopenia)

2.8/100 000 prescriptions; hypokalemia, hepatitis, peripheral neuropathy, adrenal suppression uncommon; alopecia, allergy rare; dose interval adjustment required in renal failure and in dialysis; increased risk of QT prolongation with cisapride; may increase plasma levels and effects of clarithromycin, cyclosporin, glibenclamide, glipizide, phenytoin, rifabutin (may cause uveitis), theophylline, warfarin; bioavailability reduced by rifampicin; possible interaction with astemizole and terfenadine; very weak association with oral contraceptive failure; safe in breastfeeding

Contraindications: pregnancy

ITRACONAZOLE: triazole; oral (capsules: take with or after food (absorption enhanced by food and acidic drinks, decreased by proton pump inhibitors or histamine H₂-receptor antagonists); oral solution: take 1 h before food); usual dose 200 mg; peak serum concentration 0.1 mg/L; half life 15-40 h; protein binding 99.8%; CSF/serum concentration < 10; excretion hepatic; 99% absorption; 1% active drug in urine; improved activity against filamentous fungi, eg. *Aspergillus*; also active against *Blastomyces dermatitidis*, *Candida albicans*, *Candida tropicalis*, *Candida krusei*, *Cryptococcus*, *Histoplasma*, *Paracoccidioides*, *Sporothrix schenckii*, *Trichosporon*, ? *Pseudallescheria boydii*; variable activity against *Fusarium*

Indications: mild or moderate systemic aspergillosis; mild cases of blastomycosis; oesophageal and oropharyngeal candidiasis; chromoblastomycosis; mild to moderate stable coccidioidomycosis of bones, genitourinary tract, peritonitis, viscera; less severe fungal endophthalmitis; histoplasmosis (induction and maintenance); fungal meningoenzephalitis; myocarditis and pericarditis due to *Aspergillus*; candidal oesophagitis (71% response); oropharyngeal candidiasis in immunosuppressed; fungal osteomyelitis and osteochondritis; malignant otitis externa due to *Aspergillus*; fungal pneumonia; penicilliosis (mild, maintenance); scedosporiosis; local and generalised sepsis due to *Alternaria*; sporotrichosis (cutaneous lymphatic, maintenance)

Side Effects: asymptomatic liver function tests elevations in 2-3%; serious liver problems, some resulting in transplantation or death, reported; single case report of vestibular symptoms; others as for **FLUCONAZOLE**; increased sedative/amnesic effects with alprazolam, oral midazolam, triazolam; may increase plasma levels and effects of astemizole, cisapride (increased risk of QT prolongation) and terfenadine (risk of cardiac arrhythmias, which have resulted in deaths), buspirone, cyclosporin, digoxin, felodipine, indinavir, nifedipine, norethisterone, oral hypoglycemics, prednisolone, quinidine, saquinavir, sildenafil, vincristine, warfarin; plasma levels and effects may be decreased by amphotericin (amphotericin may also not be as effective; may be antagonistic), carbamazepine, isoniazid, phenytoin, phenobarbitone, rifabutin and rifampicin; bioavailability reduced by antacids, didanosine buffered formulations (take itraconazole 2 h before), H₂-receptor antagonists and proton pump inhibitors; increased risk of myopathy with simvastatin (acute rhabdomyolysis and hepatotoxicity reported), atorvastatin, fluvastatin, pravastatin; reduces clearance of busulphan; levels almost doubled by clarithromycin; plasma levels increased by amprenavir, lopinavir, ritonavir; very weak association with oral contraceptive failure; dosage modification not required in renal failure or in dialysis; safety in pregnancy and breastfeeding not established

VORICONAZOLE: triazole; structurally related to fluconazole; spectrum similar to itraconazole; tablets (take 1 h before or 1 h after food), powder for injection

Indications: invasive aspergillosis, serious infections with *Candida*, *Scedosporium*, *Fusarium*

Side Effects: as for **FLUCONAZOLE** + common transient visual changes (in 30%) and hallucinations and uncommon hepatotoxicity (including fatal liver failure), Stevens-Johnson syndrome; increased plasma levels of alprazolam, midazolam, triazolam may lead to prolonged sedation; may increase plasma levels of atorvastatin, simvastatin; likely enhanced warfarin effect; safety in pregnancy not established

Contraindications: coadministration with carbamazepine, ergotamine, pimozide, cisapride; avoid in breastfeeding (insufficient data)

CASPOFUNGIN: echinocandin; inhibits β -(1,3)-D-glucan in cell wall; slow i.v. infusion

Indications: salvage therapy in invasive aspergillosis; *Candida* oesophagitis and candidaemia

Side Effects: nausea, vomiting, fever, flushing, pain or redness or phlebitis at site of infusion, decrease in haemoglobin, increase in liver enzyme concentrations common; anaphylaxis rare; cyclosporin increases levels; decreases tacrolimus levels; plasma levels reduced by carbamazepine, dexamethasone, efavirenz, nelfinavir, nevirapine, phenytoin, rifampicin

Contraindications: concomitant cyclosporin

CICLOPIROXOLAMINE

Indications: oral: more serious fungal infections; topical: tinea pedis

GRISEOFULVIN: fungistatic; inhibits dermatophyte invasion of keratin structures; effective orally (take with or after food (absorption enhanced)) but has to be taken for prolonged periods; may also be effective topically; in WHO Model List of Essential Drugs as drug for which adverse effects diminish benefit/risk ratio

Indications: kerion; recalcitrant tinea due to *Microsporum*, *Trichophyton*, *Epidermophyton*; unresponsive tinea corporis, pedis and cruris; tinea capitis; tinea unguium

Side Effects: headache, dry mouth, nausea, vomiting common; neuritic pains, arthralgia, mental confusion, diminished motor coordination (doses > 1 g daily), skin sensitivity reactions, urticaria, photosensitivity, petechial rash, exacerbation and/or precipitation of lupus erythematosus, fixed drug eruption, blurred vision, paraesthesia, myelosuppression, menstrual irregularities uncommon; hepatic toxicity, epidermal necrolysis rare; ? precipitates acute attacks in porphyria, ? intolerance of alcohol (tachycardia, flush); unpredictable marked decrease in effect of warfarin due to induction of metabolism; absorption impaired by phenobarbitone; dose adjustment not required in renal failure or in dialysis; safety in pregnancy not established; very weak association with contraceptive failure

Contraindications: liver failure, porphyria; avoid if breastfeeding (insufficient data)

AMPHOTERICIN B: polyene; oral (take with or after food) and parenteral; fungistatic and fungicidal in high concentrations; decreased fungicidal effect under anaerobic conditions; in WHO Model List of Essential Drugs; liposomal and lipid formulations less toxic but much more expensive

Indications: treatment of choice for most serious systemic fungal infections; consultation with infectious disease physician or clinical microbiologist advised; invasive severe aspergillosis (including arteritis, burn infections, myocarditis and pericarditis, skin lesions, upper airways, rhinosinusitis prophylaxis in neutropenics (nasal spray)); systemic *Bipolaris* infections; blastomycosis (including splenic abscess); disseminated and systemic *Blastoschizomyces capitatus* infection; fungal brain and epidural abscess; candidiasis (bronchopulmonary, chronic mucocutaneous, myocarditis and pericarditis, resistant oesophagitis, mild oropharyngeal (topical)); fungal cellulitis; fungal chorioretinitis; chromoblastomycosis; disseminated coccidioidomycosis; cryptococcosis treatment (including pancreatitis and pulmonary); empiric therapy in neutropenia, AIDS and acute myelogenous leukemia patients; chronic fungal empyema; fungal endocarditis; systemic *Exophiala dermatitidis* infection; severe fungal endophthalmitis; eumycetoma; fungemia; fungal genitourinary infections; geotrichosis; systemic *Hansenula* infections; fungal hepatic granuloma; fungal hepatitis; histoplasmosis (anterior uveitis, bone marrow infection, disseminated, oronasopharyngeal, induction of treatment in severe); meningitis (candidal, coccidioid, cryptococcal); mucormycosis; oesophagitis in granulocytopenics; ophthalmic mycoses; fungal osteomyelitis and osteochondritis; paracoccidioidomycosis; severe penicilliosis; fungal peritonitis; phaeohyphomycosis; fungal pneumonia (disseminated aspergillosis, blastomycosis, coccidioidomycosis, pulmonary cryptococcosis, pulmonary histoplasmosis, diffuse interstitial pneumonia) and pneumonitis; fungal postseptal cellulitis; fungal prostatic abscess; fungal prostatitis and seminal vesiculitis; systemic protothecosis; invasive *Saccharomyces*

cerevisiae infections; chronic fungal sinusitis; skin lesions due to *Dreschlera*; disseminated and pulmonary sporotrichosis; tinea nigra; toruloposis; disseminated *Trichosporon beigelii* infection; zygomycosis

Side Effects: minimised by alternate day therapy, 0.5-1 L 0.9% sodium chloride prior to infusion; hydrocortisone, antihistamines, antiemetics, opiates, antipyretic may provide symptomatic relief; i.v.: chills and fever (ameliorated by ibuprofen), nausea, vomiting, malaise, muscle and joint pain, hypotension (minimised by aspirin + antihistamine or 50 mg hydrocortisone), local thrombophlebitis (1000 U heparin added to infusion may be helpful), anaemia (normocytic normochromic), nephrotoxicity (in 80%; not with methyl ester; lower incidence with lipid complex or liposomal; dose dependent and largely reversible; decreased creatinine clearance, isothermia, decreased excretion of H⁺, abnormal urine sediment, renal tubular, acidosis, nephrocalcinosis, probable increased risk in renal insufficiency (avoid use unless absolutely indicated, monitor renal function); increased risk with aciclovir, aminoglycosides, cyclosporin, frusemide, vancomycin) common; urinary retention, anuria, oliguria, malignant hypertension, cardiac arrest, unusual arrhythmias, blood dyscrasias, gastrointestinal bleeding, rash, neurological effects, acute hepatic failure, jaundice and hepatocellular dysfunction (methyl ester), headache uncommon; hypersensitivity reactions, hypokalemia (may increase risk of digoxin toxicity), hypomagnesia, severe loss of body weight (not with methyl ester), hearing loss, anaphylaxis, bronchiolitis obliterans rare; intrathecal: pain along distribution of lumbar nerves, paresthesias, nerve palsies (foot drop), chemical meningitis, ? impaired vision, red man syndrome, topical: pruritis, burning in intertriginous areas, rare sensitisation; oral: diarrhoea; liposomal: cardiopulmonary toxicity; causes neutropenia by myelosuppression; toxic level > 2 ? mol/L (1.5 mg/L); increases nephrotoxicity of cyclosporine; miconazole may antagonise antifungal activity; plasma levels decreased by phenobarbitone; may significantly reduce warfarin activity; probably safe in pregnancy; dose adjustment not needed in renal failure or in dialysis

Contraindications: avoid i.v. in breastfeeding (insufficient data)

NYSTATIN: polyene; fungistatic and fungicidal in high concentrations; poorly absorbed from gastrointestinal tract (timing to food does not matter); not absorbed through skin or mucous membranes; creams, gels, vaginal pessaries, lozenges, tablets

Indications: bronchopulmonary candidiasis (aerosol); cutaneous candidiasis (topical); oropharyngeal candidiasis (lozenge); paronychia (topical); 'swimmer's ear' (topical); systemic infection prophylaxis in cell-mediated immunity disorders, granulocytopenia; candidal vaginitis (topical; gynaecology and obstetric patients and male partners)

Side Effects: nausea, vomiting, diarrhoea; safe in pregnancy and breastfeeding

TERBINAFINE: allylamine; interferes with the production of ergosterols; fungicidal for many dermatophytes; oral (well absorbed from gut; relationship of dose to food doesn't matter) and topical (73% efficacy in tinea pedis)

Indications: unresponsive tinea corporis, pedis and cruris; tinea unguium

Side Effects: oral: gastrointestinal effects (abdominal pain, nausea), mild allergic skin reactions, taste disturbances including loss of taste, transient elevated transaminases common; toxic epidermal neurolysis, hepatitis, neutropenia, Stevens-Johnson syndrome rare; isolated cases of hepatobiliary dysfunction, cholestatic jaundice, dizziness, tiredness, sedation, light-headedness, chest pain; asymptomatic liver function tests elevations in 1-2%; serious liver problems, some resulting in transplantation or death, reported; probably safe in pregnancy; dose adjustment required in renal failure, not in dialysis; rifampicin and other enzyme inducing agents may decrease levels and effects; cimetidine may block metabolism, increasing plasma levels; topical: redness, itchiness, stinging, some reports of menstrual disorders in women taking oral contraceptives, rare allergic reactions

Contraindications: avoid if breastfeeding (insufficient data); caution in hepatic disease

UNDECENOIC ACID

Indications: tinea pedis (67% efficacy)

TOLNAFTATE

Indications: tinea pedis (74% efficacy)

AMOROLFINE: morpholine

Indications: tinea unguium (nail lacquer)

Side Effects: safety in pregnancy not established

PENTAMIDINE ISETHIONATE: mechanism of action poorly understood; in WHO Model List of Essential Drugs as main list drug to improve compliance

Indications: pneumocystosis treatment and prophylaxis

Side Effects: i.v.: immediate hypotension, nausea and vomiting; later, local pain at injection site, abscess formation, neutropenia (frequent in AIDS), thrombocytopenia, rash (rare), nephrotoxicity (mild azotemia to severe tubular necrosis; increased risk (including acute renal failure) with amphotericin, cidofovir, foscarnet), hepatitis with abnormal liver function tests, hypoglycaemia and hyperglycaemia, cardiotoxicity in 23% of patients treated for antimony-resistant kala azar, hypomagnesia, hypokalemia, acute pancreatitis, ventricular arrhythmias; severe hypocalcaemia with foscarnet; possible potentiation of toxic effects on rapidly growing cells (bone marrow, spermatogonia, germinal layers of skin and gastrointestinal mucosa) with ganciclovir; increased risk of QT prolongation with all drugs prolonging QT interval; diabetes in 20% of patients treated for 3 weeks; dose adjustment required in renal failure, not in dialysis (except continuous venovenous or arteriovenous haemodialysis); aerosolised: bronchospasm, acute pancreatitis, mild hypoglycaemia, increased risk of spontaneous pneumothorax; safety in pregnancy not established

DAPSONE

Indications: *Pneumocystis jiroveci* pneumonia prophylaxis in HIV positive that cannot tolerate cotrimoxazole

Side Effects: see Chapter 21

TRIMETHOPRIM-DAPSONE

Indications: diffuse interstitial pneumonia due to *Pneumocystis jiroveci*

Side Effects: skin rash in 10%, nausea and vomiting in 7%, methaemoglobinemia in 3%, haemolytic anaemia (particularly in patients with G6PD deficiency); safety in pregnancy not established

PYRIMETHAMINE: selectively inhibits dihydrofolate reductase; half life 96 h; oral (take with or after food); in WHO Model List of Essential Drugs

Indications: infections with *Pneumocystis*, interstitial plasma cell pneumonia

Side Effects: anorexia, vomiting, folinic acid reversible megaloblastic anaemia, usually reversible leucopenia and other haematological toxicity with long term use, may be embryopathic; additional suppression of folate metabolism with cotrimoxazole, sulphonamides, trimethoprim and other folate antagonists (including cytostatic drugs) may result in serious pancytopenia and megaloblastic anaemia, rarely aplasia; convulsions in children with CNS leukemia treated with methotrexate; dose adjustment not required in renal failure or in dialysis but monitor for myelosuppression; safety in pregnancy not established; safe in breastfeeding

PYRIMETHAMINE-DAPSONE: interferes with folate metabolism; dapson half life 21 hours

Indications: *Pneumocystis* prophylaxis

Side Effects: agranulocytosis, cyanosis, allergic dermatitis, gastrointestinal disorders, acute haemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency; safety in pregnancy not established

Contraindications: avoid if breastfeeding G6PD deficient infants; monitor for haemolysis and jaundice if breastfeeding premature infant or < 1 mo old; avoid high doses if breastfeeding any infant (may interfere with folic acid metabolism)

PYRIMETHAMINE-SULPHADOXINE: interferes with folate metabolism; in WHO Model List of Essential Drugs as complementary drug for curative treatment of malaria when drugs in main list are known to be ineffective or inappropriate for a given individual; half life sulphadoxine 200 h; take with or after food

Indications: prophylaxis of diffuse interstitial pneumonia due to *Pneumocystis jiroveci*

Side Effects: erythema multiforme, orogenital lesions, pharyngitis, pruritis, rash, agranulocytosis, exfoliative dermatitis, serum reaction type reaction, urticaria, gastrointestinal disturbances, induction of folate deficiency; Stevens-Johnson syndrome (can be fatal), toxic epidermal necrolysis rare; much more common when taken in combination with chloroquine

Contraindications: pregnancy; neonatal period; avoid if breastfeeding premature infant or infant < 1 mo or with G6PD deficiency

PYRIMETHAMINE-SULPHADIAZINE

Indications: *Pneumocystis* prophylaxis

Side Effects: seen in 30-45% of patients; severe skin rash, leucopenia, thrombocytopenia, elevated levels of serum transaminases, bone marrow toxicity, pancytopenia, megaloblastic anaemia

CLINDAMYCIN

Indications: diffuse interstitial pneumonia due to *Pneumocystis jiroveci*

Side Effects: see Chapter 21

PRIMAQUINE: oral (take with or after food)

Indications: infections with *Pneumocystis jiroveci*

Side Effects: abdominal cramps and pain, epigastric distress, nausea and vomiting on an empty stomach common; haemolytic anaemia with large doses and in those with glucose-6-phosphate dehydrogenase deficiency, methaemoglobinemia and cyanosis uncommon; cardiac arrhythmias, hypertension, anaemia, leucopenia, agranulocytosis, fever, rash rare; risk of toxicity increased by quinacrine; increases plasma levels and adverse effects of mefloquine

Contraindications: pregnancy, glucose-6-phosphate dehydrogenase deficiency (including breastfed infants; monitor also for haemolysis and jaundice in breastfed premature infants and those < 1 mo)

ATOVAQUONE: take with or after food (absorption enhanced); absorption reduced in patients with severe diarrhoea; plasma levels significantly reduced by metoclopramide, rifampicin

Indications: *Pneumocystis jiroveci* infections in patients unable to tolerate other agents

Side Effects: occasional rash, fever, elevated liver function tests, abdominal pain, vomiting, nausea, diarrhoea, anorexia, headache, dizziness, myalgia; probably safe in pregnancy

Contraindications: avoid in breastfeeding (insufficient data)

CARBUTAMIDE

Indications: *Pneumocystis jiroveci* infections

EFLORNITHINE: in WHO Model List of Essential Drugs as complementary drug for use in rare disorders or in exceptional circumstances

Indications: diffuse interstitial pneumonia due to *Pneumocystis jiroveci*

TRIMETREXATE-LEUCOVORIN

Indications: diffuse interstitial pneumonia due to *Pneumocystis jiroveci*

Side Effects: bone marrow suppression (particularly neutropenia; alleviated by increasing dose of leucovorin)

CALCIUM FOLINATE

Indications: prevention of anaemia in trimetrexate therapy

ZIDOVUDINE

Indications: prophylaxis of diffuse interstitial pneumonia due to *Pneumocystis jiroveci* in AIDS

Side Effects: see Chapter 20

BENZOIC ACID + SALICYLIC ACID: antifungal dermatological drug; in WHO Model List of Essential Drugs

Indications: fungal skin infections (apply often)

Side Effects: may cause discomfort

BORIC ACID

Indications: otitis media due to *Aspergillus*, vaginitis due to *Saccharomyces cerevisiae*, *Torulopsis glabrata*

CANDICIDIN

Indications: candidal vulvitis (topical)

COTRIMOXAZOLE

Indications: non-disseminated extracutaneous histoplasmosis in immunocompetent host; *Pneumocystis jiroveci* infections

Side Effects: see Chapter 21

DESENSITISATION

Indications: candidal vaginitis involving hypersensitisation

DEXAMETHASONE

Indications: severe fungal endophthalmitis

DIAMTHAZOLE: topical antifungal

Side Effects: irritation and sensitisation

DRAINAGE

Indications: candidal pancreatic abscess; perinephric abscess; prostatic abscess; chronic sinusitis

FENTICLOR: topical antifungal

Side Effects: photosensitivity

GENTIAN VIOLET (METHYLOSANILINE CHLORIDE): anti-infective dermatological drug; in WHO Model List of Essential Drugs

Indications: oropharyngeal candidiasis (topical)

GRANULOCYTE INFUSIONS

Indications: fusariosis; systemic *Exophiala dermatitidis* infection

GRANULOCYTE MACROPHAGE COLONY STIMULATORY FACTOR

Indications: fusariosis

HALOGENATED SALICYLANILIDES: topical antifungal

Side Effects: photosensitivity

HYPERBARIC OXYGEN

Indications: zygomycosis

HYDROCORTISONE

Indications: induction of treatment in severe coccidioid meningitis

HYDROXYQUINOLINES: topical antifungal

Side Effects: irritation and sensitisation, yellow staining of fabrics

HYDROXYSTILBAMIDINE ISETHIONATE

Indications: blastomycosis if amphotericin B fails; cutaneous blastomycosis

INTERFERON-GAMMA

Indications: prophylaxis and treatment of pulmonary aspergillosis in chronic granulomatous disease

NATAMYCIN (PIMAFUCIN)

Indications: cutaneous, oral and vulvovaginal candidiasis (topical); fungal keratitis and iritis (topical); rhinosporidiosis

Side Effects: nausea, diarrhoea

POTASSIUM IODIDE: in WHO Model List of Essential Drugs

Indications: cutaneous-lymphatic sporotrichosis

Side Effects: gastrointestinal upset, metallic taste, rash

POVIDONE IODINE: in WHO Model List of Essential Drugs

Indications: *Rhizopus* isolated skin lesions

PREDNISOLONE

Indications: bagassosis and farmer's lung; hypoxia in early diffuse interstitial pneumonia due to *Pneumocystis jiroveci*

SELENIUM SULPHIDE: in WHO Model List of Essential Drugs as complementary drug for use in rare disorders or in exceptional circumstances

Indications: dandruff (shampoo); tinea versicolor (topical)

SHAVING

Indications: piedra; trichosis axillaris

SODIUM IODIDE

Indications: arteritis due to *Pythium*

SODIUM THIOSULPHATE: antifungal dermatological drug; in WHO Model List of Essential Drugs

Indications: tinea versicolor (topical)

STEROIDS

Indications: anterior uveitis due to *Histoplasma capsulatum*, fungal chorioretinitis

SULPHONAMIDES

Indications: paracoccidioidomycosis

Side Effects: see Chapter 21

SULPHUR

Indications: erythrasma; piedra; trichosis axillaris

SURGERY

Indications: fungal arteritis; brain abscess due to *Bipolaris*, *Rhinocladiella atrovirens*; *Aspergillus* burn infections; chromoblastomycosis; severe or potentially severe coccidioidomycosis of bones, genitourinary tract, peritonitis, viscera; cutaneous histoplasmosis; fungal endocarditis; epidural abscess; fusariosis; fungal keratitis and iritis; fungal meningoencephalitis; candidal myocarditis and pericarditis; phaeohyphomycosis; fungal pneumonia (localised pulmonary

aspergillosis, extensive pleural disease); fungal prostatitis; scedosporiosis; local and generalised sepsis due to *Alternaria*, *Aspergillus*, skin lesions due to *Dreschlera*, *Rhizopus*; splenic abscess; sporotrichosis; systemic *Exophiala dermatitidis* infection; zygomycosis

THIABENDAZOLE

Indications: chromoblastomycosis

Side Effects: see Chapter 23

TOPICAL DRY HEAT

Indications: phaeohyphomycosis

TRANSFER FACTOR

Indications: chronic mucocutaneous candidiasis; candidal vaginitis in anergy; cryptococcal meningitis (investigational)