Antimicrobial Drugs 2 :

Antifungals, Antimycobacterials, and Antiviral Drugs.

Learning Objectives.

At the end of this course, you should be able to :

1. **understand the ways in which these drugs bring about their effects**
2. **be able to give an example of drugs from each category, and explain their clinical application**
3. **have an appreciation of the challenges of managing these types of infection via drug therapies.**

Antifungal Drugs.

Antifungals can be classified, like antibacterials, by their target site and chemical groups :

Target	Chemical type	Mode of action	Drug	Spectrum
Cell membrane function	Polyenes	Membrane leakage via ergosterol binding	• Amphoteracin B • Nystatin	• Very wide • Local candidiasis
Cell membrane synthesis	Azoles	Inhibit ergosterol synthesis	• Clotrimazole • Ketoconazole • Fluconazole • Itraconazole • Voriconazole	• Medium, local • Broad, systemic • Broader, systemic • Broader, systemic • Broadest, systemic
Cell membrane synthesis	Allylamine	Inhibit ergosterol synthesis	• Terbinafine	• Skin and nail infections

Cell wall synthesis	Echinocandins	Inhibit glucan synthesis	• Capsofungin	• *Candida* spp, *Aspergillus* spp
Nucleic acid synthesis	Pyrimidines	Inhibits DNA synthesis	• Flucytosine	• Cryptococcus
	Benzofurans	Inhibit DNA synthesis	• Griseofulvin	• Dermatophytes

Amphotericin B is a major parenteral drug for systemic fungal infections, acting on cell membrane function. It is poorly distributed, but low concentrations in blood, CSF and urine do not correlate with efficacy. Excretion is biliary, and slow; renal toxicity is considerable. Formulation, dosage and administration are highly specialised and debatable. It is also used in amoebic meningoencephalitis and leishmaniasis.

Nystatin is a polyene, acting on fungal cell membrane function. It is not absorbed orally or parenterally so is only used locally on *Candida* spp. infections of skin, mouth, or vagina.

Terbinafine inhibits ergosterol synthesis in fungal cell membranes. It is well absorbed orally and locally. Being active against dermatophytes, moulds and yeasts, it is especially useful for skin and nail infections.

Azoles include clotrimazole, miconazole and econazole (used locally), and ketoconazole, fluconazole, itraconazole, voriconazole and posaconazole (used systemically for systemic disease). All inhibit ergosterol synthesis in fungal cell membranes. Additionally, they are well absorbed orally; fluconazole and voriconazole are also given intravenously. Ketoconazole is active against *Candida* spp., the four systemic mycotic fungi, but not *Cryptococcus, Aspergillus* or *Mucor* spp. Fluconazole is active against C. *neoformans,* whilst itraconazole also

has some activity against some *Aspergillus* and *Mucor* spp., exceeded by voriconazole with activity also against *Fusarium* spp. and *Scedosporium* spp. Toxicity is low, *but drug interactions with warfarin, isoniazid, rifampicin, ciclosporin or phenytoin can be dangerous.*

Caspofungin inhibits the synthesis of glucan in fungal cell walls of *Candida* spp. and *Aspergillus* spp. It is only given intra-vascularly, and penetrates tissues well. It has few side effects, and interacts only with ciclosporin. Renal impairment is not a contraindication.

Flucytosine is a pyrimidine, and its metabolite, 5-fluorouracil, inhibits fungal DNA synthesis. It is absorbed orally but also given parenterally. It is widely distributed, and largely excreted unchanged by the kidney. Activity is mainly against *Cryptococcus* and *Candida* spp. Dose-related toxicity includes gut intolerance, hepatotoxicity and marrow suppression, especially in AIDS and/or renal impairment.

Antimycobacterial drugs.

All mycobacterial infections need prolonged treatment with two or more drugs because:

- mycolic acids in their cell-wall make them impermeable to many drugs
- mycobacteria grow slowly, requiring long-term treatment
- some mycobacteria are intracellular pathogens so drugs must enter human cells
- antibiotic resistance is common, and most infections contain some resistant bacteria
- incidence is rising in the immunodeficient, whose natural defences are impaired or absent.

Management of Tuberculosis

Isoniazid (INAH) is synthetic isonicotinic acid hydrazide which has a

bactericidal action, probably by inhibiting mycolic acid synthesis. It is well absorbed orally and widely distributed, including the central nervous system. It is used only in mycobacterial infections, chiefly TB, and toxicity is neurological or hepatic.

Ethambutol is a synthetic mycobacteriostatic drug, probably inhibiting RNA synthesis. It is well absorbed and well distributed. It is used only in mycobacterial infections, chiefly TB. Toxicity includes optic neuritis, so it is essential that regular reviews are carried out.

Pyrazinamide is a synthetic tuberculocidal drug which is absorbed orally and penetrates both the CNS and cells, including macrophages. Liver toxicity was previously common with high doses, but safer, lower doses are effective and widely used.

Streptomycin is an aminoglycoside with bactericidal action via protein synthesis inhibition. It is not absorbed orally, penetrates the CNS poorly, is excreted by the kidney and has auditory toxicity. It is now little used as therapy is usually entirely oral.

Management of Leprosy

Dapsone is a synthetic sulphone, very similar to sulphonamides. It is cheap, given orally, usually well tolerated and was widely used alone for decades until widespread resistance brought about the development of combined therapy with rifampicin. It is also used in toxoplasmosis, usually with pyrimethamine.

Antiparasitic Drugs.

Parasites are eucaryotes, just like mammalian cells so it is harder to find drugs selectively toxic to them. The following table lists the major drugs used in this category:

Disease	Drug
Amoebiasis	Metronidazole, tinidazole, diloxanide
Giardiasis	Metronidazole, tinidazole, furazolidone, nitazoxanide
Trichomoniasis	Metronidazole, tinidazole,
Ameobic meningoencephalitis	Amphoteracin B
Cryptosporidiosis	Nitazoxanide, paromomycin
Malaria	Artemesinins, Cholorquine, doxyline, mefloquine, primaquin, quinine
Toxoplasmosis	Pyrimethamine, sulphadiazine, clindamycin
Pneumocystosis	Pentamidine, co-trimoxazole, atovaquone, dapsone
Leishmaniasis	Pentamidine, antimony compounds, amphoteracin B
Trypanosomiasis	• African – pentamide, antimony compounds • American – Benznidazole, nifurtimox

Antimalarials

The **Artemisinin** derivatives**,** artemether and artesunate, are the most rapidly parasiticidal antimalarials, especially combined with lumefantrine. Oral treatment is safe, effective and short, replacing quinine for uncomplicated falciparum malaria.

Chloroquine is a 4-aminoquinoline, well absorbed orally and also given intravenously. It concentrates so much in liver, spleen and CNS that loading doses are unnecessary. Resistance in *P.falciparum* is now so widespread that it is only useful in Central America and parts of the Middle East.

Mefloquine is a quinolinemethanol well absorbed orally,

concentrated in the liver and slowly excreted in the faeces, with a very long half-life of 17 days. Resistance is uncommon but is increasing in South East Asia. It has troublesome neurological and cardiac toxicity, so requires careful use.

Primaquine is an 8-aminoquinoline which is well absorbed orally, widely distributed (including the liver) and rapidly metabolised, being undetectable in 24 hours. It is used in a 14-day course for radical cure of P. *vivax* and P. *ovale* malaria.

Quinine, used for over 400 years, is a natural alkaloid. It is given orally or intravenously (not intramuscularly) and is metabolised in the liver, with some renal excretion and a half-life of 18 hours. It is schizontocidal only, so must be used with another drug such as doxycycline. Dosage is critical, and ECG and blood pressure should be monitored for cardiotoxicity.

Other antiprotozoal drugs

Antimonials include suramin (for prophylaxis and early treatment) and melarsoprol (for meningoencephalitis, 'sleeping sickness') in trypanosomiasis, and pentavalent compounds such as sodium antimony gluconate used in leishmaniasis. All are given by slow intravenous injection, are toxic and require special care and knowledge.

Nitazoxanide is a new oral drug used against cryptosporidiosis and giardiasis.

Pentamidine is a diamidine which binds to DNA. It is given intramuscularly or intravenously to treat Gambian trypanosomiasis and P. *jirovecii* pneumonia (PCP), or by inhalation for PCP prophylaxis. As it does not enter the CNS it is useless for the neurologic stage of trypanosomiasis. Common toxic effects include hypoglycaemia, hypotension, renal impairment and rashes.

KEY LEARNING POINTS.

1. **Superficial mycoses are treated with nystatin or an azole, while invasive, systemic or disseminated mycoses need amphotericin B, and/or a newer azole.**
2. **Azoles tend to interact with a number of other drugs, so care is needed when advising patients about purchasing over-the-counter preparations.**
3. **Terbinafine is useful in skin and nail infections, but care is required as side-effects can be problematic.**
4. **The major anti-tuberculous drugs are isoniazid, rifampicin, ethambutol and pyrazinamide: treatment usually begins with three drugs (four if resistance is likely), then decreases to two for many months. Resistance is an increasing problem.**

Antiviral drugs

The steps in viral replication are the basis for antiviral drug action, and should be reviewed. In summary, they are:

1. **Early stage** - Recognition, Attachment, Penetration (entry) and Uncoating.
2. **Central stage** - mRNA Synthesis, Protein synthesis and Genome (nucleic acid) replication. Enzymes involved include DNA polymerase.
3. **Final stage** - Assembly and Release (with or without Enveloping).

Early Stage drugs

Attachment **– Enfuvirtide** is the first fusion inhibitor for HIV infection, a peptide that binds to part of gp41 envelope glycoprotein, inhibiting viral entry. It is only given by injection, and local reactions can be a problem.

Uncoating - **Amantadine** and **rimantadine** block the M2 protein ion channel of the influenza virus envelope, preventing uncoating. As they only act on Influenza A, have considerable cerebral side-effects, and resistance emerges rapidly, they are little used.

Central Stage Drugs

DNA polymerase inhibitors of nucleic acid synthesis

Group 1 – nucleoside reverse transcriptase inhibitors (NRTIs)

These include abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), tenofovir (TDF), and zidovudine (ZDV, formerly AZT). All inhibit DNA synthesis by inhibiting reverse transcriptase, causing chain termination, and so blocking DNA provirus production. Emtricitabine and lamivudine are also used against Hepatitis B. All are used in HAART (Highly Active Anti-Retroviral Therapy) which uses three (or more) drugs, commonly two NRTIs, with either an NNRTI or

a PI (Protease Inhibitor, see below). Dosage, combinations, side-effects, resistance development and interactions with other drugs are complex and common.

Group 2 - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Nevirapine, delavirdine and efavirenz inhibit viral DNA synthesis not by chain termination but by binding near the active site of reverse transcriptase of HIV-I (not HIV-2). They are only used in combination with NRTIs, otherwise resistance and cross-resistance rapidly develop. Delavirdine is little used due to dosing problems, but the other two are useful and enter CSF well, but have CNS, liver and skin side-effects.

Group 3 - Nucleoside inhibitors

Aciclovir (prodrug famciclovir) and penciclovir (prodrug valaciclovir) are guanosine nucleoside analogues. They are phosphorylated by viral thymidine kinase, then cellular enzymes, to triphosphate forms which selectively inhibit viral DNA poly-merase rather than host (human) DNA polymerase. They have good activity against Herpes Simplex Virus – 1 (HSV-1) and -2, lesser activity (so need higher dose and concentrations) against Varicella-zoster virus, and no activity against cyto-megalo virus (CMV). All are available for oral use, but aciclovir has poorest absorption and shortest half-life, so now is not used orally. However only aciclovir is given intravenously. They are used to treat acute attacks, and at times prophylactically for frequent relapses or in immunocompromised patients. Side effects are rare.

Ganciclovir and valganciclovir are also guanosine analogues. They are activated by CMV-encoded and host phosphokinases, and then inhibit CMV DNA polymerase, so are used to treat CMV infections including retinitis, colitis, oesophagitis, pneumonitis and CNS infections, especially in AIDS and other immunocompromised

patients. Ganciclovir is usually given intravenously at first, followed by oral valganciclovir. They may also be used prophylactically before immunosuppression. Side-effects include bone marrow suppression with thrombocytopenia and/or leucopenia.

Cidofovir is a nucleotide cytidine analogue lacking ribose. Although active against most herpes viruses, it is mainly used as a reserve drug against CMV infections. It is given weekly, but is commonly nephrotoxic, and also causes iritis. It can also be used in severe papilloma virus and poxvirus infections such as molluscum contagiosum or vaccinia in immunocompromised patients or smallpox.

Trifluorotbymidine (trifluridine) is a thymidine nucleoside analogue. It is too toxic for systemic use, but sometimes used for herpes simplex kerato-conjunctivitis.

Group 4 - Non-nucleoside inhibitors

Foscarnet is not a nucleoside analogue but a pyrophosphate analogue which inhibits herpesvirus DNA polymerases directly, without activation by intracellular kinases like the nucleoside analogues. It is used in HSV or CMV infections with resistance or intolerance to the aciclovir group or ganciclovir respectively.

Group 5 - Nucleoside inhibitors

Ribavirin is a guanosine nucleoside analogue which after phosphorylation inhibits synthesis of mRNA and early transcription in both DNA and RNA viruses. It is now available for aerosol, oral and IV use. It is used in severe Respiratory Syncitial Virus (RSV) pneumonitis, some viral haemorrhagic fevers, and with interferon in Hepatitis C. Its many troublesome side-effects include bronchospasm, hypotension, rash, fits and haemolytic

anaemia. Adefovir is a nucleotide analogue of AMP which is used in chronic active hepatitis B as it inhibits the DNA polymerase.

Integrase inhibitors, preventing integration of viral into cell DNA

This new class of anti-retroviral drugs act after reverse transcriptase produces viral DNA from viral RNA, preventing its integration into human DNA. Interferon-alpha blocks both viral RNA transcription and protein synthesis in many viruses. It is used in acute or chronic hepatitis B with lamivudine, in chronic hepatitis C with ribavirin, and at times in papillomavirus infections or Kaposi's sarcoma from HHV8 in AIDS. Side-effects are common and unpleasant, and response is not universaL relapse common and cure rare.

Fomiversen is the first anti-sense drug, i.e. a single-strand DNA with base sequence complementary to viral mRNA. It therefore binds to mRNA and blocks translation to viral protein. It is used to treat CMV retinitis.

Methisazone inhibits the protein synthesis of pox viruses by blocking translation of late mRNA. It has been used to treat smallpox, or disseminated vaccinia from smallpox vaccine.

Final Stage Drugs

Protease inhibitors (PIs), preventing structural protein formation

These include saquinavir, indinavir, ritonavir, nelfinavir, fosamprenavir, atazanavir and lopinavir (with ritonavir). They act by inhibiting the proteases which normally split polyproteins to produce retroviral nucleocapsid proteins. Proviral DNA remains integrated so the cell is still infected, but infectious virus is not released. They are only used in combination with NRTIs with or without NNRTI to delay resistance developing. Low-dose ritonavir is also used to boost the levels of a second co-administered PI by inhibiting its metabolism by hepatic cyto-

chrome P450 enzymes. Side-effects are seldom severe, but include gut and liver enzyme disturbance, possibly lipodystrophy, and urinary crystalluria, and kidney stones from indinavir.

Viral release inhibitors

Zanamivir and oseltamivir inhibit the viral neuraminidase and hence the release of influenza A or B virus from infected cells, thus limiting spread to other cells and other people. Zanamivir is given by aerosol and may cause bronchospasm, while oral oseltamivir may cause nausea, diminished by food. If given early for therapy they reduce the severity and duration of illness by about 30%, and also the frequency of complications. They can also be used in short-term prophylaxis of contacts (80% effective) or longer term for 4-6 weeks during epidemic peaks. They appear effective against early strains of avian influenza, but further mutations may cause resistance.

KEY LEARNING POINTS.

1. **These drugs can act at any stage of the viral replication cycle:**
    a. **Early – drugs that prevent attachment or uncoating.**
    b. **Central – drugs that inhibit protein synthesis**
    c. **Final – drugs that prevent assembly or release**
2. **Many viral infections still lack effective antiviral drugs.**