

Zidovudine, also known as azidothymidine (AZT), is in the nucleoside and nucleotide reverse transcriptase class of antiretroviral drugs. AZT is an analogue of the nucleoside thymidine in which the hydroxyl group on the ribose is replaced by an azido group. AZT is converted to zidovudine triphosphate by cellular kinases, which then acts as an inhibitor of, and substrate for, the viral reverse transcriptase. The azido group prevents the formation of phosphodiester linkages. Proviral DNA formation is blocked because AZT triphosphate is incorporated onto the DNA, resulting in chain termination. AZT is given orally. Adverse effects of AZT include; bone marrow suppression (macrocytic, anaemia, neutropenia, leukopenia), nausea, vomiting, headaches, myalgia, malaise, lactic acidosis, hyperlipidaemia, lipoatrophy, insulin resistance and diabetes mellitus. AZT is used in the treatment of HIV.

### Antifungal agents

The number of suitable antifungal agents is limited. Selective toxicity is more difficult to achieve in the eukaryotic fungal cells than in the prokaryotic bacteria. Additionally, antifungals have pharmacological problems including; solubility, stability, and absorption. Antifungal resistance is increasing. Invasive fungal infections are a significant cause of morbidity and mortality in patients undergoing chemotherapy, immunosuppression and transplantation. Thus the development of antifungals is a priority. The majority of antifungals act on the synthesis or function of the intracellular membranes. The exceptions are flucytosine and griseofulvin which interfere with DNA synthesis, and caspofungin which inhibits cell wall formation. There are currently no inhibitors of fungal protein synthesis that do not also inhibit the equivalent mammalian pathway.

#### Azole compounds

Azole antifungals act by inhibiting lanosterol C14-demethylase, an important enzyme in sterol biosynthesis. Clotrimazole and miconazole are useful as topical preparations. Itraconazole and fluconazole are used in the treatment of a variety of serious fungal infections. Fluconazole is used in the treatment of candida infections, however, resistant candida strains are increasing, possible resistance mechanisms include; point mutations in the gene encoding the lanosterol demethylase enzyme, and changes in the candida cell membrane resulting in rapid efflux of the drug out of the cell before it can become active. Newer azole compounds include posaconazole, which is used in aspergillosis unresponsive to amphotericin B, and itraconazole, which is used in the treatment of invasive mucormycosis.

#### Polyenes

Polyenes inhibit cell membrane function. Amphotericin B and nystatin act by binding to sterols in cell membranes, resulting in leakage of cellular contents and cell death. Their preferential binding to ergosterol over cholesterol is the basis for selective toxicity. Amphotericin is used in the treatment of serious fungal infections. Amphotericin can have serious toxic side effects, lipid formulations have lower toxicity. Nystatin is used in topical formulations.

### Antiparasitic agents

plant toxin ricin, the A subunit can be attached to a monoclonal antibody to make it a specific poison for tumour cells.

### Botulism

Botulism is a rare but serious disease caused by the exotoxin of *Clostridium botulinum*. Spores of *C. botulinum* are widespread in soil and contaminate vegetables, meat and fish. When foods are canned or preserved without adequate sterilization (often at home), contaminating spores survive and can germinate in the anaerobic environment leading to the formation of toxin. There are seven major botulinum neurotoxins, A-G, only A, B, E, and less frequently F are associated with human disease. While not destroyed by digestive enzymes the toxins are inactivated after 30 minutes at 80 degrees celsius. The toxins are ingested in food or produced in the gut after ingestion of the organism, the toxins are absorbed from the gut into the bloodstream and then reach their site of action: the peripheral nerve synapses. Botulinum toxins have a characteristic two subunit structure, a functional A domain and a binding B domain. Botulinum toxins enter the body by the intestine escaping digestion and crossing the gut wall. The toxin affects peripheral nerve endings at the neuromuscular junction, blocking presynaptic release of acetylcholine. This prevents muscle contraction. Botulinum toxins are extremely potent and active at low doses.

After an incubation period of 2-72 hours, botulism presents clinically with symmetric descending flaccid muscle paralysis, beginning with the cranial nerves causing diplopia, dysphagia, vomiting, vertigo, and slurred speech. Then respiratory and cardiac muscles are affected. There is no abdominal pain, diarrhea or fever.

There are three forms of botulism; food borne botulism, infant botulism, and wound botulism. In wound botulism the organisms are implanted in a wound and multiply and elaborate toxin *in vivo*. In infant botulism the organisms are ingested and multiply and elaborate toxin *in vivo*. Infant botulism has been associated with feeding babies honey contaminated with *C. botulinum* spores.

Considering botulism in the differential diagnosis is key and then confirmed by laboratory diagnosis. Laboratory diagnosis involves demonstrating the presence of toxin in clinical specimens or food or culturing the bacteria. A bioassay may be used if serum is available, whereby the serum would be injected into mice that have been protected with botulinum antitoxin or left unprotected. Culture of faces or wound exudate for *C. botulinum* as well as toxin detection by PCR-based assay for toxin sequences and ELISA tests for functional toxin activity.

Since the specific *C. botulinum* strain(s) responsible are normally unknown, trivalent antitoxin (for type A, B, and E toxins) is administered promptly as an adjuvant to intensive supportive therapy for botulism. Supportive therapy may include mechanical ventilation, due to difficulty in breathing, and intravenous and nasogastric nutritional support, due to dysphagia.

Prevention of botulism depends on preventing the germination of spores in food by; maintaining food at an acid pH, storing food at <4 degrees celsius, inactivating spores by

heating at 121 degrees celsius for 3 minutes before storage, and inactivating toxin by heating for 5 minutes at 80 degrees celsius.

### Tetanus

Tetanus is caused by the bacteria *Clostridium tetani*. *C. tetani* produce endospores within their cells, enabling them to survive in adverse conditions. Spores are formed when the cells are unable to grow, eg. when environmental conditions change or when nutrients are exhausted. Spores possess a multilayered coat, which surrounds the bacterial cell, consisting of dipicolinic acid and calcium, which confers the endospores extreme resistance to heat and chemicals.

Tetanus spores are widespread in soil and originate from the faeces of domestic animals. The spores enter a wound, and if necrotic tissue or presence of a foreign body permits local and anaerobic growth of bacteria, the toxin tetanospasmin is produced. Tetanus toxins are extremely potent and active at low doses. Tetanus toxins have the characteristic function A domain and binding B domain. The B subunit binds to ganglioside receptors on nerve cells. The internalised A subunit of tetanus toxin is carried by axonal transport from the point of production to the central nervous system, where it interferes with synaptic transmission in inhibitory neurons by blocking neurotransmitter release. This allows the excitatory transmitter to continuously stimulate the motor neurons, causing spastic paralysis.

After an incubation period of 3-21 days, tetanus presents clinically with exaggerated reflexes, muscle rigidity, uncontrolled muscle spasms, dysphagia, risus sardonicus, trismus (due to contraction of the jaw muscles), and neck stiffness and opisthotonos (especially in neonatal tetanus).

The diagnosis of tetanus is clinical.

Human anti tetanus immunoglobulin should be given as soon as tetanus is suspected clinically. The wound should be excised if necessary. Penicillin should be given to inhibit bacterial replication. Muscle relaxants are used. Respiratory support in an intensive care unit may be necessary. Tetanus is a vaccine preventable disease.

### Cholera

Cholera is an acute infection of the gastrointestinal tract caused by the comma-shaped Gram-negative bacterium *V. cholerae*. Cholera flourishes in communities with inadequate clean drinking water and sewage disposal. The disease remains endemic in South-East Asia, parts of Africa, and South America. *V. cholerae* is a free-living inhabitant in fresh water, and only causes infection in humans. Asymptomatic human carriers are a major reservoir. The disease is spread via contaminated food. Natural disasters can result in a breakdown of public health facilities and cause cholera epidemics. *V. cholerae* is classified into more than 200 serogroups based on somatic (O) antigens of the lipopolysaccharide. Only O1 and O139 serogroups cause epidemic cholera. O1 is further divided into two biotypes; classical and El Tor. El Tor differs from classical *V. cholerae* in several ways; it causes only mild diarrhea, it has a higher ratio of carriers to cases than classic cholera, carriage is more prolonged, and the organisms survive better in the host. The O139 strain

measles specific IgM assay is helpful in confirming the diagnosis either on blood or saliva samples. Complicated measles infection can be treated with ribavirin. There is a live attenuated measles vaccine.

The measles, mumps and rubella (MMR) vaccine combines the live attenuated vaccines for measles, mumps and rubella in one vaccination. The MMR vaccine was introduced into the UK childhood vaccination programme in 1988. All children were immunised at 18 months of age. The MMR vaccine requires 90% vaccine cover to provide effective herd immunity. Between 2000-2015, there was an estimated 79% drop in measles deaths worldwide, with an estimated 20 million deaths from measles prevented by vaccination. Nevertheless, WHO has estimated that >134 000 people died from measles in 2015, most of whom were children under 5. Cases of measles increased in the UK after 2001. Following reduced vaccine uptake. This resulted from the suggestion that the MMR vaccine caused autism, as there was an apparent rise in autism in both California and the UK that seemed to coincide with the introduction of the vaccine. However, further studies have failed to show an increased risk of autism after MMR.

#### Rotavirus vaccine

Rotavirus causes the most serious gastrointestinal disease in infants. Trials of an earlier vaccine were stopped when it caused intussusception, a rare cause of bowel obstruction. Two new live oral vaccines are now in use: the RV5 vaccine (RotaTeq) contains five restaurant rotavirus developed from human and bovine parent strains, while the RV1 vaccine (Rotarix) contains one live attenuated rotavirus strain. The vaccine gives 74-87% efficacy against any rotavirus gastroenteritis and 85-98% protection against severe gastroenteritis. Studies from a number of countries have demonstrated marked reductions in hospital admissions and in GP visits for all cause acute gastroenteritis in children after rotavirus vaccine was introduced.

#### **Tuberculosis**

Tuberculosis is one of the most serious infectious diseases of the resource-poor world. Mycobacterium tuberculosis causes tuberculosis (TB), which is one of the top 10 causes of death globally. TB affects the apparently healthy as well as being a serious disease of the immunocompromised and is one of the AIDS-defining illnesses. TB is primarily a disease of the lungs, but may spread to other sites or proceed to a generalized infection, miliary TB. infection is acquired by inhalation of M.tuberculosis in aerosols and dust. Airborne transmission of TB is efficient because infected people cough up enormous numbers of TB mycobacteria, projecting them into the environment, where their waxy outer coat allows them to withstand drying and therefore survive for long periods of time in air and house dust.

#### Pathogenesis

In primary infection the organisms are engulfed by the alveolar macrophages, in which they can both survive and multiply. Non-resident macrophages are attracted to the site, ingest the mycobacteria and carry them via the lymphatics to the local hilar lymph nodes. In the lymph nodes, the immune response, predominantly a cell mediated immune response, is