Infectious disease pathology

	Infectious diseases	**Viruses** 20-30nm Obligate intracellular parasite Depend on host for replication Classified by nucleic acid content – RNA, DNA **Chlamydiae, Mycoplasmas, Rickettsiae** 100-1000nm Obligate intracellular parasite Similar to bacteria but lack essential characteristics. Chlamydia lack ATP synthesis. Mycoplasmas lack a cell wall. **Bacteria, spirochaetes, mycobacteria** 1-15um Prokaryotes that lack nuclei and ER. Synthesise own DNA/RNA and proteins. Depend on the host for favourable environment for reproduction **Gram negative** – 2 lipid bilayers with sandwiched peptidoglycan layer, covered by a cell wall Escherichia coli (anaerobic) Klebsiella (anaerobic) Enterobacter (anaerobic) Proteus (anaerobic) Serratia Pseudomonas Bacteroides (anaerobic) Shigella (facultative anaerobe) Salmonella Yersinia Cholera Legionella – Legionnaires disease Haemophilus ducreyi - chancroid Calymmatobacterium donovani - donovanosis **Gram postive** – single bilayer covered with peptidoglycan and a cell wall **Fungi** 2-200um Thick ergosterol cell walls *Candida* **Protozoa** 1-50um Single celled organisms with motility, pliable plasma membranes, complex cytoplasmic organelles. *Giardia* **Helminths** Highly differentiated multicellular organisms with complex life cycles. Roundworms – nematodes (ascaris, hookworms, strongyloides, trichinella) Flatworms – cestodes (tapeworms, cysticerci, hydatid cysts) Flukes – trematodes (schistosomes) **Ectoparasites** Arthropods – lice, ticks, fleas

	Host barriers to infection	Behavior modification Hand washing, general hygiene measures Skin Forms a continuous barrier Damaged skin more susceptible Respiratory tract Nasal hairs Tonsils and adenoids Mucociliary clearance Gastrintestinal tract Lysozyme IgA Gastric acid Viscous mucus covering gut wall. Pancreatic enzymes and bile detergents. Genitourinary tract Vaginal pH Mucosal surface Long urethra in males
	Immune evasion mechanisms	Evasion of barrier mechanisms *Gram-negative organisms* have fimbriae or pili that mediate adherance to specific cells of the host *Gram-positive organisms* have fibrillae that bind to the surface of all eukaryotic cells *Respiratory viruses* can attached to surface carbohydrates and evade mucociliary clearance. Some *respiratory viruses* can degrade mucus. *Haemophilius and bordetella* make toxins that paralyse cilia. Location in anatomical areas inaccessible to the immune system Gallbladder, lumen of the intestine, keratinised epithelium *Salmonella* Intracellular evasion - rapid entry of pathogen into cells offers protection *Malaria* Characteristics of organism Physical protection Dense fibrous capsule of *tapeworm cysts* Capsule of *pneumococcus and meningococcus* Immune system modification Resisting phagocytosis. *Mycobacterium TB* is resistant to phagocytosis. *Pseudomonas* secretes a leukotoxin that kills neutrophils. Immune evasion by varying or shedding antigens *Pneumococci* capable of 80 variations of their capsular polysaccharides. *Neisseria and borrelia* can vary their surface antigens Infection of cells of the immune system *HIV and EBV* directly infect cells of the immune system and reduce immune response Inhibition of complement *Staphylococci* are covered by protein A molecules which bind Fc and therefore inhibit phagocytosis Some *E coli* prevent complement activation

		Some *gram negative bacteria* have long polysaccharide chains which activate complement away from the cell membrane. Inhibition of cytokines *HBV* Suppression of MHC1 *Adenovirus* Inhibition of B cell activation *EBV* Inhibition of antibody *Neisseria, haemophilius, streptococcus* secrete proteases that degrade antibodies.
	How microorganisms cause disease	Contact/enter cell to cause cell death Inhibition of RNA/DNA Inhibition of protein synthesis Damage to cell wall. Cause destruction of cell by immune system Release of products that cause cell death or degrade tissue components. *Endotoxin* – lipopolysaccharide that is a structural component of the outer cell wall of gram negative bacteria. *Exotoxin* – enzymes (coagulases, fibrinolysins etc.) that act on a substrate – eg diphtheria toxin Induction of cellular response that may result in additional tissue damage <u>Mechanisms of viral injury</u> Contact/enter cell to cause cell death Inhibition of RNA/DNA Inhibition of protein synthesis *Poliovirus* Damage to cell wall *Measles virus* Cause destruction of cell by immune system Replication and destruction *Yellow fever virus* Release of products that cause cell death or degrade tissue components. *Respiratory viruses* damage respiratory epithelium and make secondary infection more likely Induction of cellular response that may result in additional tissue damage *RSV* causes release of cytokines which induce mast cell activation and eosinophil accumulation <u>Mechanisms of bacterial injury</u> Bacterial virulence Bacterial damage to host tissues depends on their ability to adhere to cells and invade tissues. A broad range of cells can be affected Contact/enter cell to cause cell death Inhibition of RNA/DNA Inhibition of protein synthesis *Diphtheria* Damage to cell wall. Replication and destruction

		Shigella Release of products that cause cell death or degrade tissue components. *Endotoxin* Lipopolysaccharide that is a structural component of the outer cell wall of gram-negative bacteria. Causes release of cytokines IL1 and TNF that activate macrophages and induce fever *Enzymes and toxin production* Staphylococci – lipases Clostridium - tetanus toxin Induction of cellular response that may result in additional tissue damage
	Spectrum of inflammatory response to infection	Acute suppurative inflammation Neutrophils are attracted by secreted bacterial peptides, and via endotoxin which stimulates macrophages to release IL1 and TNF Chronic inflammation Granulomatous inflammation Necrosis Clostridium perfringens secrete toxins that cause tissue destruction. Cytopathic-cytoproliferative inflammation Focal cell damage leads to the formation of blisters Proliferation of epithelial cells can cause warty lesions Viruses can cause dysplastic changes

Infection	Epidemiology	Aetiology	Pathogenesis	Morphology	Clinical features
Haemophilus influenzae	Major cause of upper and lower respiratory tract infections, epiglottitis, meningitis	Pleomorphic, gram-negative organism Encapsulated and unencapsulated forms Type B (encapsulated) causes most severe disease	Pili increase adherance Exotoxin reduces ciliary function Protease degrades IgA Capsule prevents opsonisation		

Infection	Epidemiology	Aetiology	Pathogenesis	Morphology	Clinical features
Tuberculosis	Infects one third of world population Kills 3 million per year. Associated with poverty and overcrowded living conditions. Increased incidence in association with HIV and AIDS.	Mycobacterium tuberculosis Aerobic non-spore forming, non motile bacilli with a waxy coat which retains red dye in acid fast stains.	Droplet spread **Evasion mechanisms** Evasion of phagocytosis by macrophages by production or cord factor and LAM that inhibit macrophage activation Induction of delayed type IV hypersensitivity by secretion of heat shock proteins Induction of macrophages to secrete TNF resulting in fever, weight loss and tissue damage Inhibition of T cell proliferation by secretion of IL10 **Primary infection** Inhalation of mycobacteria. Phagocytosed by macrophages but not lysed. Transported to hilar lymph nodes. Mycobacterium multiplies and is phagocytosed by further macrophages – dissemination may occur. Delayed type IV hypersensitivity is demonstrated by CD4 T cell secrete gamma interferon which activate macrophages to kill mycobacteria via activated nitrogen intermediates CD8 T cells cause mycobacteria lysis T cells (CD4 and CD8 negative) lyse macrophages without killing mycobacteria. These mechanism result in the formation of a *granuloma* (subpleural, usually just above or below interlobar fissure) and eventually to the formation of calcified scar in lung parenchyma and hilum – *ghon complex*. **Secondary and disseminated tuberculosis** May occur due to reinfection, reactivation or direct progression of primary disease. Multiple granulomas form – most commonly in apex of lung, also in kidneys, meninges, other organs. Miliary TB represents massive haematogenous spread. Caseous necrosis and cavities may form and therefore produces more damage than does primary TB.		

Infectious gastroenteritis					
Infection	Epidemiology	Aetiology	Pathogenesis	Morphology	Clinical features
Rotavirus *(other viral gastroenteritis caused by Norwalk-like viruses, coronaviruses, adenoviruses, astroviruses)*		Encapsulated DS-RNA genome.	Faecal-oral transmission Invades and destroy mature epithelial cells in the middle and upper villus. Diarrhoea caused by reduced absorption of sodium and water from the lumen.		
Campylobacter	Most common cause of bacterial gastroenteritis	Campylobacter jejuni. Flagellated gram negative.	Faecal-oral transmission. Associated with ingestion of chicken. Flagellae necessary for penetration of mucus. Invades epithelial cell. Associated with reactive arthritis in HLA B27 individuals Also associated with Guillain Barre syndrome		Variable depending on the degree of invasiveness – varies from mild diarrhoea to dysentery to enteric fever.
Shigella – bacillary dysentery		Shigella dysenteriae, flexneri, boydii, soneii. Gram negative facultative anaerobe.	Faecal-oral transmission. Tiny number of organisms required. Invades intestinal mucosa but does not go beyond the lamina propria. Bacteria multiply and causes cell death. Shiga toxin causes haemorrhagic colitis, HUS and Reiter's syndrome. Associated with reactive arthritis in HLA B27 individuals	Mucosa becomes hyperaemic and oedematous. Enlargement of lymphoid follicles. Fibrinosuppurative exudate forms a pseudomembrane. Mucosa becomes soft and friable with superficial ulceration.	Dysentery – diarrhoea with blood, pus and mucus plus abdominal cramping.
Salmonella		Flagellated gram negative bacteria. Salmonella typhi, enteritidis, typhimurium.	Salmonella enteritidis and typhimurium transmitted via infected meat. Humans are the only host for salmonella typhi. Invades damaged mucosa and results in systemic infection		Samonella typhi – protracted illness characterised by fever, rash and profuse bloody diarrhoea. Hepatosplenomegaly is common. Gallbladder colonization may result in a carrier state.
Cholera	Regular pandemics in undeveloped countries	Vibrio cholerae. Comma shaped. Gram negative. 140 serotypes.	Faecal-oral transmission. Flagellae result in penetration of mucous layer Multiply underneath the mucous layer Remain in the lumen and secrete enterotoxin – cholera toxin – very similar to E. coli enterotoxin. Cholera toxin results in persistent activation of adenylate cyclase, high levels of intracellular cAMP and massive secretion of chloride, sodium, bicarbonate and water.	No invasion therefore minor histopathological changes.	Rice-water stool

Parasitic intestinal infections

Infection	Epidemiology	Aetiology	Pathogenesis	Morphology	Clinical features
Amoebiasis	Common in developing countries	Entamoeba histolytica	Cysts are resistant to gastric acid. In the *colon*, cysts release trophozoites that then reproduce. Trophozoites attach to and invade colon wall to cause dysentery.	Amoebae mimic macrophages in appearance. Invade ctypts of colonic glands. Burrow through tunica propria, then create a broad based ulcer. Uncommonly an amoeboma is created which is a ring like area of granulaton tissue	10% of those affected develop dysentery. 40% of those with dysentery develop liver abscess
Giardiasis	Most prevalent intestinal protozoan worldwide.	Giardia lamblia	Cysts resistant to chlorine in water supplies. Faecal-oral transmission. 2 forms – trophozoites and cysts. Trophozoites multiply in duodenum and adhere to epithelial cells but do not invade. Trophozoites form cysts again as they move away from cholesterol rich areas in the duodenum.	Trophozoites are pear shaped and binucleate. Cause clubbing of villi	Infection often subclinical. Causes variable acute, chronic diarrhoea, steatorrhoea, constipation

Gram positive pyogenic bacterial infections

Infection	Epidemiology	Aetiology	Pathogenesis	Morphology	Clinical features
Staphylococcal *Pyogenic gram positive coccus*	Common cause of infection including skin and respiratory infections, endocarditis, gastroenteritis and toxic shock syndrome.	Staphylococcus aureus. Staphylococcus epidermidis Pyogenic, gram positive cocci which tend to form grape-like clusters.	Several factors contribute to the virulence of the staphylococcus *Surface molecules* - bind to endothelial cells, extracellular matrix and artificial materials and increase adherence. *Secreted enzymes* - lipase degrades skin lipids and allows tissue invasion. *Production of toxins* *Haemolytic toxins* including alpha, beta, delta and gamma toxins that cause cell disruption and lysis. *Enterotoxins* Food poisoning – toxin stimulates vomiting centres in GIT. Enterotoxin also acts as a 'Superantigen' – atypical binding to MHC II causes massive stimulation of T cell and release of cytokines that cause systemic effect. *Exfoliative toxins* – cells in granular layer of epidermis detach from each other – scalded skin syndrome. *Toxic shock syndrome toxin* – resembles enterotoxin in effect and causes massive release of cytokines	Regardless of site of infection, staphylococcus aureus causes locally destructive pyogenic infection.	Common infections Wound Impetigo Focal skin infections Respiratory Endocarditis Food poisoning Scalded skin syndrome Toxic shock syndrome
Streptococcal	Common cause of skin and respiratory infections, endocarditis and post-streptococcal immune mediated syndromes such as GN, rheumatic fever and erythema nodosum	Facultative anaerobes. Gram postive cocci. Grow in pair or chains Beta haemolytic Group A – streptococcus pyogenes Group B – streptococcus agalactaie Group D - enterococcus faecalis Streptococcus pneumoniae Alpha haemolytic Streptococcus viridans	*Capsule* – pneumococci have a polysaccharide capsule that prevents phagocytosis. *Surface molecules* – M protein inhibits phagocytosis, lipoteichoic acid binds to extracellular matrix. *Secreted enzymes* – C5a peptidase degrades C5a, pneumolysin inserts into target cell membranes and lyses them (and also activates complement, making less complement available for bacterial lysis). *Production of toxins* *Pyrogenic exotoxin* – causes fever and rash in scarlet fever, erysipelas. Rheumatic fever results from production of anti M protein antibodies that cross-react with cardiac myosin.	Diffuse interstitial neutrophilic infiltrates.	Erysipelas – caused by pyogenic exotoxin from Group A streptococcus – characterised by a rapidly spreading erythematous cutaneous swelling, typically in a butterfly distribution. Scarlet fever Impetigo Wound Focal skin infections Pharyngitis Pneumonia

Gram positive spore-forming anaerobes					
Infection	Epidemiology	Aetiology	Pathogenesis	Morphology	Clinical features
Clostridium *Obligate anaerobic gram positive spore-forming bacillus producing spores that are frequently present in soil.*	Clostridium tetani *Tetanus* Uncommon due to immunization and education. Common in undeveloped nations especially neonatal tetanus. Clostridium botulinum. *Botulism* Uncommon due to controls on heat processing of food. Clostridium perfringens *Cellulitis and gas gangrene* Uncommon due to wound management procedures and antibiotics Clostridium difficile *Pseudo membranous colitis.*	Clostridium tetani Clostridium botulinum Clostridium perfringens Clostridium difficile	Clostridium tetani Transmission most commonly occurs from soil-contaminated wounds. *Clostridium tetani neurotoxin* – Extremely potent toxin Binds to gangliosides on peripheral nerves, transported to the nucleus via the axon, is released from the nucleus to be taken up by inhibitory neurons where it *cleaves synaptobrevin*, destroying the ability of inhibitory synaptic vesicles to fuse. Clostridium botulinum Spores are heat resistant and and are able to survive in improperly heat-processed foods to cause food poisoning. Results from ingestion of preformed toxin. *Clostridium botulinum neurotoxin* Acts at peripheral nerve endings, cleaves synaptobrein, SNAP 25 and syntaxin, prevents vesicles from fusing. Mostly affects NMJ and autonomic system. Clostridium perfringens Infection usually results from traumatic injury and contaminated wound. Clostridium perfringens is able to produce various enzymes (collagenase and hyaluronidase degrade extracellular matrix) and toxins able to destroy tissue within anerobic wounds Clostridium difficile Normal inhabitant of gastrointestinal tract that proliferates if antibiotics reduce other flora. Secreted toxins cause local bowel damage (toxin A is an enterotoxin and granulocyte chemoattractant, toxin B causes cytopathic effects) characterized by fibrinous pseudomembranes.		Clostridium tetani *Tetanus* Symptoms 4-10 days (up to several months) after exposure. No tissue damage. Early symptoms include muscle stiffness then spasms. Death from respiratory complications. Neonatal tenanus Clostridium botulinum *Botulism* Symptoms include weakness, dizziness, diplopia, dysphagia, paralysis of respiratory muscles, death. Mortality 20-70% Clostridium perfringens *Cellulitis and gas gangrene.* Swollen tissues have dark yellow discolouration and foul smelling exudates. Gas produced by the bacteria causes distension. Clostridium difficile *Pseudomembranous colitis.* Common in neonates. Causes abdominal pain and severe diarrhoea.

Infection	Epidemiology	Aetiology	Pathogenesis	Morphology	Clinical features
Herpes simplex		Herpes simplex-1 Herpes simplex-2 DS DNA viruses	Spread by body fluids Replicate in the skin and mucous membranes. Cause primary and recurrent infections. Primary infection resolves after a few weeks but virus remains latent in neurons. Reactivation may occur repeatedly with or without symptoms. May causes conjunctivitis and corneal infection, and encephalitis.	HSV typically forms Cowdry inclusions – pink/purple virions that push host cell chromatin to the edge of the cell.	Cold sores Gingivostomatitis Genital herpes Keratitis (HSV1) Encephalitis (HSV1)
Varicella zoster		VSV DSDNA	Droplet spread **VZV** infects mucous membranes, skin and neurons Disseminates haematogenously In neurons, primarily infects dorsal root ganglia and can be reactivated years later to result in shingles Usually reactivates in elderly or immunocompromised		Chicken pox Initial respiratory type illness. Rash appears after 2 weeks Rash is typically vesicular Vesicles crust and resolve Shingles Involve sensory nerves of one or more dermatomes May cause facial nerve paralysis due to the Ramsey Hunt syndrome **Complications** Interstitial pneumonia Encephalitis Transverse myelitis
Syphilis		Treponema pallidum Spirochaete detectable by silver stain, darkfield examination and immunofluoescense	Treponemes bind to endothelial cells and cause an obliterative endarteritis followed by delayed hypersensitivity. Host humoral and cellular response is insufficient to clear the spirochaetes – either due to poor antigenic stimulus or direct down-regulation of CD4 cells.		**Primary syphilis** 3 weeks after contact. Single, firm, raised, red, non-tender chancre at site of invasion. Chancre heals spontaneously. **Secondary syphilis** 2-10 weeks after primary chancre. Palmer/solar rash, fever, lymphadenopathy, headache, arthritis. **Tertiary syphilis** Years after primary lesion. *Neurosyphilis* – paresis, meningovascular, tabes dorsalis *Aortitis* – aneuryms, aortic regurgitation. *Gummas* – liver, bones and skin. **Congenital syphilis** Typically causes stillbirth, skin sloghing, saber shin, liver and lung (plus other organs) fibrosis, keratitis, Hutchinson teeth, eighth nerve lesions

Infection	Epidemiology	Aetiology	Pathogenesis	Morphology	Clinical features
Infectious mononucleosis		Epstein barr virus Herpes virus.	EBV transmitted via saliva. Virus penetrates upper respiratory tract epithelial cells and B cells. Infection results in immune response including humoral and cellular response. Cytotoxic T cell form atypical lymphocytes which are typical of the disease. Latent EBV remains in B cells and is linked with later development of Burkitts lymphoma.	Lymphocytosis with atypical lymphocytes. Enlargement of lymph nodes and spleen.	Infectious mononucleosis – benign self limiting lymphoproliferative disease characterised by fever, generalized lyphadenopathy, splenomegaly and sore throat. Rarely progresses to hepatitis, menoingoencephalitis, pneumonitis.
Pseudomonas	Opportunistic gram negative organism, important cause of morbidity and mortaility in cystic fibrosis, bums, neutropenia Third most common cause of hospital acquired infection	Pseudomonas aeruginosa Gram negative	Corregated pili and adherance proteins mediate adherance to epithelial cells Colonies secrete a alginate covering that protects them from phagocytosis Secrete exotoxin A that is similar to diphtheria toxin Secrete enzymes that inhibit host cell growth, lyses red cells, degrades surfactant and degrades extracellular matrix Secretes toxic iron containing compounds that damage endothelial cells		
Legionnaires disease		Legionella pneumophila Facultative intracellular parasite of macrophages	Droplet spread Resistant to cooling Associated with cooling and air conditioning systems Bacteria are phagocytosed by macrophages then inhibit oxidative burst and phagosomal fusion	Infection tends to affect peripheral respiratory tract and spare bronchi and proximal bronchioles Small abscesses are common	Healthy individuals usually develop self limiting Pontiac fever Smokers, elderly, immunocompromised develop legionnaires disease charcaterised by severe pneumonia
Malaria	Affects 100 million/year. Kills 1 million/year	Plasmodium falciparum Plasmodium vivax Plasmodium ovale Plasmodium malariae	Transmitted by 12 different anopheles mosquito types. Life cycle *Sporozoites* transmitted by mosquito bite. Bind to and invade liver cells then multiply. Hepatocyte ruptures, releasing *merozoites* into blood. Merozoites bind to and invade red blood cells Some merozoites from *gametocytes* that infect the next mosquito Most merozoites multiply, resulting in red cell rupture and infection of further red cells The red cell stage is initially called a *trophozoite*, then a *schizont*	Congestion and enlargement of the spleen – spleen may become fibrotic over time. Cerebral malaria characterised by vascular plugging with localized haemorrhages and hypoxic changes.	Falciparum Fever, severe anaemia, renal failure, pulmonary oedema, cerebral symptoms, death. Cerebral malaria is the cause of 80% of deaths in children Vivax, malariae Mild anaemia, rare splenic rupture and nephritic syndrome