Infectious Diseases Modules
1. Overview
2. Normal flora & innate immunity
3. Host defences in infection
4. Examples of infectious diseases
5. Bacterial pathogenesis- virulence
6. Bacterial pathogenesis- genetics
7. Viral pathogenesis- methods
8. Paradigms of microbe-host relationships
9. Viruses
10. Mycoses and animal parasites
11. Medicine and infection
12. Future challenges in infectious diseases

Overview of infectious Illness
• What is infectious illness?
• Agents of infection
• How infections occur
  - routes into the body
  - sources of infection
• Establishment of disease
• Course of Infection

Infection is not the only cause of illness
Illness may be caused by:

- Inborn defects
- Metabolic disorders
- Developmental changes
- Degenerative processes
- Malignant growths
- Nervous conditions
- Poisons
- Nutritional disorders
- Injuries

Illnesses we most expect to deal with in day to day life are infectious ones
Disease

Definition: A specific disorder that features a recognizable complex of physical signs, symptoms and effects

All diseases have a cause (known or unknown) that include:
- hereditary
- environment
- new growth (neoplasia)
- diet
- infection

Infection

Definition
- The process by which organisms capable of causing disease gain entry to the body and establish themselves
- The state of injury or damage to part of the body resulting from this process

Infection

- Successful invasion of a host by a microorganism
- Subclinical
- Clinical but self-limiting
- Clinical and associated with morbidity and mortality

Process of Infection

- The growth/multiplication of a microbe in a host
- Infection does not always result in injury of the host (disease)
- Two main classes - by site
  - Localised
  - Generalised (disseminated, systemic)

Infectious Diseases

Diseases caused by organisms that can be spread directly from person to person

Common infectious diseases include: chickenpox, diphtheria, glandular fever, tuberculosis, measles, meningitis, influenza, STD’s, gastroenteritis

Diseases requiring a vector (may be excluded)
- malaria
- leishmaniasis
- yellow fever

Leading causes of death

[Diagram showing leading causes of death]
Top 10 Infections - Mortality

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency (x 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>4,400</td>
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<tr>
<td>Diarrhea</td>
<td>3,100</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3,100</td>
</tr>
<tr>
<td>Malaria</td>
<td>2,100</td>
</tr>
<tr>
<td>AIDS</td>
<td>1,500</td>
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<tr>
<td>Hepatitis B</td>
<td>1,100</td>
</tr>
<tr>
<td>Measles</td>
<td>1,000</td>
</tr>
<tr>
<td>Neonatal tetanus</td>
<td>460</td>
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<tr>
<td>Pertussis</td>
<td>350</td>
</tr>
<tr>
<td>Worms</td>
<td>135</td>
</tr>
</tbody>
</table>

Why study infectious disease?

- Understand pathogenesis
- Aid in early diagnosis
- Develop effective therapeutic measures
- Disease control

Human Costs of Epidemics

- Loss of life
- Loss of health
- Cost of care
- Costs of lost productivity
- Costs of disability

Economic Impact of Plague Epidemic

India: 1994

- >45,000 travellers to India cancelled plans
- 20-60% decrease in hotel occupancy
- $66,000 loss by Air India per day
- $1 million loss by Indian Airlines per week
- 50% decrease in ships docking at Bombay
- $460 million loss in exports
- $23 million loss in diamond exports alone
- Total Loss = >$1.7 billion

Source: India Today

World Health Organisation
Economic impact of recent SARS outbreak
SARS virus outbreak Nov 2002-June 2003
Focused Beijing, Hong Kong, Canada
Eventually cases in 19 countries across 4 continents
Initial SARS related damage to regional GDP in Far East at US$ 10-15 billion
Hong Kong alone:
Retail sales 50% less since mid-March
Tourism arrivals dropped by 80%
Entertainment/restaurant 80% less
Travel restrictions lifted mid-June, 2003
Most disease contained early July, 2003

Agents of Infection

Infectious illness occurs when certain microorganisms gain access or colonize the body
Symptoms of illness arise from their effects on the body
AND
from the body’s attempts to cope with them
The agents involved are usually single celled rather than multicellular and are mostly bacteria or viruses
Agents of infection:
- bacteria & their toxins
- viruses
- parasites
- funghi

Agents of infection: bacteria
A form of tiny (3-5μM thick) single celled organism
Consist simply of outer cell wall, inside mostly protoplasm and DNA
Most are capable of limited movement- flagella
Almost all divide simply into 2- binary fission (rapid)
Many form spores, seed like inactive state...enables survival
Preferred conditions vary:
- temperatures not too hot or too cold
- and moisture not too acidic
Agents of Infection: bacteria

Bacteria occur commonly in vast numbers in almost every corner of life including ON & IN the human body

Most bacteria are harmless to humans

Bacteria play a vital role in the body ....aid digestion, manufacture vitamins & destruct dangerous substances

All life depends on bacteria in the air and in the soil without which dead matter would not decay and return into the cycle of existence

“Microbes make the difference between a living planet and a dead one”.........Salyers and Whitt.

Endospores

• Resistant to heat, drying, etc.
• Survival, not procreation-
• Bacillus and Clostridium

Prokaryotes

• Absence of nucleus
• Singular circular chromosome
• Additional DNA in plasmids
• Transcription/Translation is simultaneous
• Thick protective cell wall
  – Gram-Positive = PeptidoGlycan
  – Gram-Negative = PG + LipoPolySaccharide

Gram Stain

<table>
<thead>
<tr>
<th>Step</th>
<th>Gram-positive organisms</th>
<th>Gram-negative organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unstained</td>
<td>Clear</td>
<td>Clear</td>
</tr>
<tr>
<td>2. Crystal violet</td>
<td>Violet</td>
<td>Violet</td>
</tr>
<tr>
<td>3. Iodine</td>
<td>Violet</td>
<td>Violet</td>
</tr>
<tr>
<td>4. Decolourisation (alcohol, acetone)</td>
<td>Violet</td>
<td>Clear</td>
</tr>
<tr>
<td>5. Carbol fuschin</td>
<td>Purple</td>
<td>Red</td>
</tr>
</tbody>
</table>

Bacterial cell wall-Gram stain

40-80% PG
Teichoic acids
Polyol phosphate polymers
Inner cell membrane

No teichoic acids
One layer PG (5% CWW)
Inner & outer membrane
LPS in OM
-Protects against C’ lysis
-Stimulates cytokine release
Microbial Growth

Physical requirements
- Temperature
- pH
- Osmotic pressure

Chemical Requirements
- Carbon
- Nitrogen
- Sulfur
- Phosphorus
- Trace elements
- Oxygen
  - Aerobic = requires O_2
  - Facultative anaerobic = use O_2 when present
  - Obligate anaerobic = unable to use O_2 as final electron acceptor
  - Microaerophiles = [O_2]<20% ie. surface of water

Bacteria

Normal flora
- Colonize the body and usually do not cause disease

Opportunistic pathogens
- Normally do not cause disease, but may under certain circumstances

Frank pathogens
- Always cause disease

Other
- Caused mostly by the ingestion of preformed toxins or when toxins are produced from bacteria during infection

Illness from bacteria arise in two ways

1. ENDOGENOUS: bacteria that normally exist in the body... get into the wrong part.

- Acne
- Pimples
- Boils
- UTI

Proprionibacterium acnes

- Normal skin flora gain entrance to sebaceous gland
- Skin wound
- Bacteria (E.coli) from anal area gain entry to UT (mainly in females)
2. EXOGENOUS: bacteria that are always harmful gain access to the body

Examples of illness carried by one specific organism:

- Scarlet fever: Streptococcus
- Tuberculosis: Mycobacterium tuberculosis
- Syphilis: Treponema pallidum
- Typhoid: Salmonella typhi
- Gonorrhoea: Neisseria gonorrhoea
- Diptheria: Corynebacterium diphtheriae

Illnesses that can be caused by a range of bacteria:

- Tonsilitis
- Dysentery/diarrhoea
- Pneumonia
- Food poisoning

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**Bacteria of Medical Importance**

**Gram-positive**

- **Gram-positive cocci**
  - Staphylococci
  - Streptococci

- **Gram-positive bacilli**
  - The genus Bacillus
  - Clostridia
  - Other Gram-positive bacilli

**Gram-negative**

- **Gram-negative cocci**
  - Neisseria sp.

- **Gram-negative bacilli**
  - Enterobacteriaceae
  - Pseudomonads
  - Curved, Gram-negative rods
  - Other Gram-negative bacilli

**Others**

- Mycobacteria, Spirals

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**Rickettsia**

- Obligatory intracellular parasite, spread by arthropods (ticks, lice)

**Chlamydia**

- Obligatory intracellular Gram-Negative

**Mycoplasma**

- Lack a cell wall

**Erlichia**

- Obligate intracellular Gram-Negative organism, spread by ticks

**Bartonella**

- Non-contagious, Gram-Negative motile, bacillus-like, spread by sandflies

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**Agents of Infection: Viruses**

Viruses are most primitive form of life we know - each a minute quantity of nucleic acid wrapped in a protein sheath

Viruses are the ultimate parasites

Exist in most conditions but only active inside a host cell to exploit the cellular enzymes they lack

- **Virus enters cell**
- Takes over cells chemical processes
- Uses it to produce hundreds of new virus
- Cell breaks open....lyses....dies
- Liberates new virus
- Released virus infects new cells
Illnesses caused by viruses fall into two groups:

- Attack particular organs
  - respiratory system: influenza, SARS
  - salivary glands: mumps
  - nervous system: poliomyelitis
  - immune system T cells: HIV

- Cause general symptoms with skin rash
  - measles
  - rubella
  - chickenpox
  - smallpox

Eukaryotes

- DNA on several chromosomes in a nucleus
- Separate cytoplasm
- Transcription of DNA into mRNA which moves to the cytoplasm
- Cytoplasm is rich with organelles
  - Mitochondria
  - ER
  - Golgi
  - Lysosomes

Other agents of infection

Protozoans, single celled organisms and much larger than bacteria cause infection
mostly in tropical/sub-tropical parts of the world
often develop into fatal infections
Examples: Amoebic dysentery, Malaria, Sleeping sickness

Protozoans

- Amoebae
  - Move via pseudopods
- Flagellates
  - Move via flagellae
- Sporozoites, merozoites, trophozoites
  - No locomotive organelles
Parasites

Infectious agents which have developed a life cycle that depends on passing part of their existence in another creature & part in man.
- Malaria parasite: mosquito and man
- Bilharzia parasite: snail and man
- Toxoplasmosis: cat and man

Infectious Diseases

Top 10 Infections - Frequency

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency (x 1000)</th>
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</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>4,000,000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1,900,000</td>
</tr>
<tr>
<td>Worms</td>
<td>1,400,000</td>
</tr>
<tr>
<td>Malaria</td>
<td>500,000</td>
</tr>
<tr>
<td>Hepatitis (HBV &amp; HCV)</td>
<td>450,000</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>395,000</td>
</tr>
<tr>
<td>Sexually transmitted diseases</td>
<td>330,000</td>
</tr>
<tr>
<td>Measles</td>
<td>42,000</td>
</tr>
<tr>
<td>Pertussis</td>
<td>40,000</td>
</tr>
<tr>
<td>HIV (new infections)</td>
<td>3,100</td>
</tr>
<tr>
<td>Meningococcal meningitis</td>
<td>350</td>
</tr>
</tbody>
</table>

Macroparasites

- Worms, Arthropods
- Require metabolic nutrients = ingest and digest host cells, tissue fluids, intestinal contents
- Rapid spread through extracellular fluids and over surfaces
- Sheer size renders them insusceptible to host defences normally used on smaller organisms

Helminth infections

- Roundworms
  - Nematodes
  - Flatworms
  - Trematodes eg. flukes
  - Cestodes eg. tapeworms

Helminthes

- Two groups
  1. Nematoda
     - Non-segmented roundworm
     - Most are parasites
  2. Platyhelminthes
     - Flatworms
     - Trematodes eg. flukes
     - Cestodes eg. tapeworms

Helminth infections - Host Types

1. Definitive host
   - Adult or sexually mature parasite
2. Intermediate host
   - Immature or larvae stages
3. Reservoir host
   - Other animal species act as host for species that are parasites for humans
Infectious Diseases

Intestinal Round Worms

• Round worms (nematodes) are extremely common infestations in the Third World
• Most intestinal worms cause little pathology (they don’t eat much) except that they may cause obstruction with heavy infestation
  – Hookworms (Necator americanus) often cause anemia, depending upon worm load
  – Strongyloides stercoralis may proliferate and disseminate in the body

Infectious Diseases

Pinworms - Enterobius vermicularis

• One of the most common parasitic roundworms in humans
• Found in the colon
• At night, they come through the anus to lay their eggs on the perianal skin
• Common in children who reinfect themselves

Infectious Diseases

Pinworm - Morphology

Infectious Diseases

roundworm-Ascaris lumbricoides

• Adult worms are 10-14 inches long
• Larvae hatch in the gut, then migrate through tissue to the lung – are swallowed, then mature in the gut
• Eggs are passed in the faeces, where they may infect another human via faecal-oral contamination

Infectious Diseases

Ascaris lumbricoides - Pathology

• Rarely cause obstruction of the colon, appendix, or biliary tree
• Larvae migration may induce an eosinophilic pneumonitis
• Rarely, larval or even adult worms may be expectorated

Infectious Diseases

Appendicitis - Ascaris
Infectious Diseases
Colonic Obstruction - Ascaris

Infectious Diseases
Characteristics of Parasitic Flatworms
1. Dorso-ventrally flat
2. Incomplete digestive system with one opening
3. Very simple nervous system
Two Groups
- Trematodes - Flukes are leaf shaped and non-segmented
- Cestodes - Tapeworms that are ribbon shaped and can be as long as 30 ft with segments called proglottids

Infectious Diseases
Cestodes - Tapeworms
- Live as mature organisms in the intestines of the definitive host
- Hosts include cats, dogs, cows, whales, and humans
- Human infections occur when uncooked, infected meat is eaten, or by ingesting the eggs
- Human infection with the common dog tapeworm is transmitted by the ingestion of infected fleas - most commonly seen in children

Infectious Diseases
Funghi
A type of plant that has no chlorophyll and so derive nourishment from Organic matter
- Unicellular yeasts
- Filamentous multicellular moulds
Diphasic (both) forms
- Immunocompetent: Infections tend to be limited to the skin epidermis and mucous membranes of the genital tract
- Malnourished & poor living - deeper penetrating infections to feet + other
- Immune deficiency allows widespread opportunistic fungus infections of all Parts of the body (AIDS, transplants, cancer, diabetes, TB)
- Common infections: "ringworm" tinea thrush candidiasis (yeast fungus of mouth & vagina)

Fungal Infections
- Opportunistic pathogens - usually systemic infections
- Superficial mycoses – infections limited to outermost/keratinous layers of skin and hair
- Cutaneous mycoses – infections which extend deeper into the epidermis as well as invasive diseases of the hair and nails
- Subcutaneous mycoses – infections involving dermis, subcutaneous tissue and fascia
- Systemic (deep) mycoses – infections
Fungal Infections - Tinea

Infectious Diseases
Pharynx - Candidiasis

Infectious Diseases
Candidiasis - AIDS

Routes into the body
**Sources of Infection:**

Inhalation—most frequent source of common infections

Breathing, speaking, coughing & sneezing all liberate droplets of saliva, sputum or secretion into the air

- Ordinary breathing > 1m
- Loud speaking > 1.5m
- A sneeze spreads 20000 droplets > 4m

Droplets can be breathed in or ingested with food by others

Inhalation of dried bacterial spores in dusty air eg anthrax
Other sources of infection:  

<table>
<thead>
<tr>
<th>Source of infection</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct physical contact with infected person</td>
<td>STD's, skin infections</td>
</tr>
<tr>
<td>Contact with fomites</td>
<td>colds, hepatitis</td>
</tr>
<tr>
<td>Ingesting infected food or drinks</td>
<td>hepatitis, food poisoning</td>
</tr>
<tr>
<td>Entry of soil or dust into a wound</td>
<td>tetanus, gas gangrene</td>
</tr>
<tr>
<td>Bites of parasitic insects</td>
<td>malaria, bubonic plague</td>
</tr>
<tr>
<td>Bites/contact infected animals</td>
<td>rabies, toxoplasmosis</td>
</tr>
<tr>
<td>Unsterile medical procedures</td>
<td>hepatitis</td>
</tr>
<tr>
<td>Infection carried by mother's bloodstream</td>
<td>rubella, CMV</td>
</tr>
<tr>
<td>Self infection-poor hygiene</td>
<td>UTI, staphylococci</td>
</tr>
</tbody>
</table>

Sources of Infection - Exogenous

- **Inhalation**: common cold, flu, meningitis, Legionnaire's disease, diphtheria, TB, and more
- **Ingestion**: typhoid fever, tapeworm, cryptosporidium, hepatitis A
- **STD**: gonorrhea, HIV, syphilis
- **Wound**: tetanus, rabies
- **Insect Bite**: malaria, yellow fever, dengue

Sources of Infection - Endogenous

- **Gut**: E. coli
- **Skin**: staphylococcus
- **Throat**: streptococcus
- **Blood**: EBV
- **Lungs**: Candida, CMV, streptococcus

Pathogen Reservoirs

**Reservoir** - A site where a microorganism can survive and multiply as a source of infection.

1. **Human**
   - (a) Passive carrier - Show no symptoms of the disease but release microbes eg. Typhoid Mary
   - (b) Active carrier - Recovery from a disease in the ending stages example of carrier diseases eg. hepatitis (viral), pneumonia (bacterial), Staphylococcus aureus (food poisoning)

2. **Animal**
   - Zoonoses - Animals which transmit pathogens to humans eg. rabies

3. **Nonliving**
   - Soil - Many microbes tolerant to drying ie. spores (bacterial and fungal) eg. Clostridium tetani, Clostridium botulinum,
   - Histoplasmosis (flu-like symptoms), Skin fungi (dermatophyte)
   - Water - eg. polio virus
   - Fomite - inanimate objects example spoon, fork and pencils

Congenital Infections

- **T =** toxoplasmosis, treponema (syphilis)
- **O =** other (varicella, Venezuelan equine encephalitis, mumps, coxsackie, parvovirus)
- **R =** rubella
- **C =** cytomegalovirus
- **H =** herpes, HIV, HBV

**Consequences**

- Birth defects (teratogenesis)
- Abortion
Establishment of Disease

How Microorganisms Cause Disease

1. Contact/Enter host cells and directly kill them
2. Release factors that indirectly kill cells
3. Induce a host response that harms the host as well as the microorganism

A framework for understanding infectious diseases

- The following steps take place in all infectious diseases:
  - Encounter: the pathogen meets the host
  - Entry: the pathogen enters the host
  - Spread: the pathogen spreads from the site of entry
  - Multiplication: the pathogen multiplies in the host
  - Damage: the pathogen or the host response or both cause damage
  - Outcome: the pathogen or the host win, or they coexist

- The manner in which each pathogen combats host defenses at each step distinguishes one pathogen

Establishment and Outcome

- Encounter
  - time from first encounter
  - exogenous (colonisation)
  - endogenous (normal flora)

Establishment of Disease

2. Entry

- ingress ie. inhalation/ingestion
- mucous membrane
- penetration

Establishment of disease

3. Multiplication and Spread

- physical factors
- microbial nutrition
- anatomic factors
- microbial sanctuary
- microbial virulence
Establishment of Disease

4. Injury
- mechanical
- cell death
- microbial product induced
- host induced
  ie. inflammation, immunity, mediator

Establishment of Disease

5. Course of infection
- mild
- life-threatening
- acute
- subacute
- chronic

Establishment of Disease

6. Outcome of infection
- resolution
- chronic ie. carrier state, latent, reactivation
- death

Eight Steps in Infection (8 Rs)

1. Reservoir
   • Source
2. Route
3. Rupture
   • The first line of defense
4. Redeployment
   • Spread within the body; the second line of defense
5. Replication
6. Response
   • The third line of defense incl. tissue damage
7. Result
   • Disease, recovery and health or death
8. Release

Bacterial Virulence Mechanisms - EAT RICE

- Enzymes eg. streptokinase
- Adherence
- Toxins ie. endotoxin, exotoxins, by-products of growth eg. gas, acid
- Resistance to antibiotics
- Invasion of tissues
- Circulation to other areas of the body
- Evasion of immune response eg. superantigen, capsule, catalase,

Factors Influencing Infection - Host

Opportunities for host exposure
- Transmission routes
- Host availability

Susceptibility factors
- Dosage (quantity) and 'quality' of infectious organisms, including their ‘virulence’
- Age
- Social determinants
- Immunity, immunocompetence and health status
- Nutritional status
- Genetics
- Behaviour (personal habits)
Factors influencing infection: pathogen

- Virulence of micro-organism
  - Resistance to natural defences
  - Motility and invasiveness
  - Production of toxins (endotoxin or exotoxin)
- Failure of defence system
  - Physical and chemical barriers
  - Cellular or humoral deficiency
  - Immune deficiency states

Course of Infection

Stages-course of disease

- **Incubation**
  
  *Time depends on:*
  - specific microbe
  - number in inoculum
  - resistance of host
  - distance from portal of entry to target cells

2. **Prodromal (early warning signs)**
   - short period
   - early mild symptoms eg. malaise, general aches and pains

3. **Invasive**
   - acute symptoms
   - specific/general symptoms
   - 2nd/3rd line of host immune response
   - recovery or death

4. **Critical**
   - most intense symptoms
   - most intense battle
5. Decline
- Signs/symptoms decrease
- Secondary infections possible
- 24 hours to several days

6. Convalescence
- Microbe birthrate < death rate
- Person regains strength

Factors contributing to the emergence of infectious diseases

<table>
<thead>
<tr>
<th>Factor</th>
<th>Circumstance</th>
<th>Example</th>
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<tbody>
<tr>
<td>Ecological changes</td>
<td>Increased forestation</td>
<td>Lyme disease</td>
</tr>
<tr>
<td>Human behavior</td>
<td>IV drug use</td>
<td>AIDS</td>
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<tr>
<td>International travel</td>
<td>Transport of mosquitoes</td>
<td>‘Airport’ malaria</td>
</tr>
<tr>
<td>Technology</td>
<td>Mass food production</td>
<td>Enterohemorrhagic E. coli</td>
</tr>
<tr>
<td>Microbial adaptation</td>
<td>Use of antibiotics</td>
<td>Antibiotic resistance</td>
</tr>
<tr>
<td>Breakdowns in</td>
<td>Inadequate waste treatment</td>
<td>Cryptosporidium outbreaks</td>
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<tr>
<td>public health systems</td>
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</tr>
</tbody>
</table>

Goals of the CDC

Centres for Disease Control and Prevention
1. Surveillance and Response
   - Detect, investigate, monitor
   - Factors influencing emergence
2. Applied Research
   - Integrate lab science and epidemiology
3. Infrastructure and training
   - Strengthen public health surveillance
   - Support the planning, delivery and evaluation of public health activities and practice
4. Prevention and control
   - Prompt implementation and enhance communication