Pathogenesis of infection

2.1 Stages of infectious disease

Learning objectives
You should:
• know the mechanisms that microorganisms use to cause infection
• understand infection as a staged biological process

The process through which microorganisms cause disease involves several or all of the following stages:
1. encounter
2. colonisation
3. penetration
4. spread
5. damage
6. resolution.

Encounter with microorganisms
The initial contact with a given microbial species is critically important. The indigenous microbial flora is already present on the body surface. Infections acquired from this pool of organisms are said to be ‘endogenous’, e.g. urinary tract infection. Organisms acquired as a result of transmission from an external source are said to be exogenous. The major routes of transmission are:
• direct contact (including intimate sexual contact), e.g. soft tissue infections, gonorrhoea, genital herpes
• inhalation/droplet infection, e.g. common cold, pneumonia
• ingestion/faecal–oral route, e.g. gastroenteritis
• inoculation or trauma, e.g. tetanus, malaria
• transplacentally, e.g. congenital toxoplasmosis.

Colonisation
The initial encounter with a new microbial species may result in nothing more than short-lived contact with an external body surface. The microorganism needs to survive and multiply under local conditions (e.g. of temperature and pH) to establish itself in its new habitat. It must successfully compete against an established indigenous microbial flora and resist local defence mechanisms. Some species are capable of producing mucolytic enzymes to help them penetrate the layer of mucus coating internal body surfaces. Other species have specific adhesins that enable binding with receptor sites on human cells (e.g. gonococcal pili attachment to urethral epithelium and influenza virus adherence to glycoprotein receptors on upper respiratory mucosal cells). Locally active IgA produced by some mucosal surfaces can be inactivated by bacteria such as Haemophilus influenzae, Streptococcus pneumoniae and Neisseria meningitidis, which produce IgA protease. Once established on a body surface, an organism is said to have colonised that site. However, not all organisms...
that colonise will go on to invade and damage underlying host tissues.

**Penetration of anatomical barriers**

In order to invade living human tissues, a microorganism must breach surface barriers. In the case of the skin, bacteria probably do not penetrate intact surfaces. Infection thus requires a break in the epithelial cover due to trauma, surgical wounds, chronic skin disease or insect bites. Some parasites (e.g. schistosomes, the cause of bilharzia) can penetrate intact skin. The respiratory tract is continuously exposed to air-borne organisms. However, the upper respiratory tract functions as an inertial filtration system and protects the more delicate lungs from exposure to inhaled particles. The cough reflex and the mucociliary escalator provide back-up, expelling any particles inhaled into the airways. Infective particles (e.g. droplet nuclei, less than 5 μm in diameter) may reach the alveoli and establish infection. In the gastrointestinal tract, some disease-causing organisms damage the mucosal surface by releasing cytotoxins (e.g. those causing dysentery), while others (*Salmonella typhi*) are taken up by the M cells overlying gut-associated lymphoid tissue in Peyer’s patches. The fetus is not normally exposed to microorganisms in utero. Only a small group of organisms cause infection in the mother during pregnancy and can also traverse the placenta to cause intrauterine infections such as toxoplasmosis, rubella, syphilis and cytomegalovirus infection. If an organism is capable of intracellular infection (e.g. tuberculosis, chlamydial disease or viral infection), it must also be capable of cell penetration and survival in an intracellular habitat. At this stage, evasion or subversion of host defences becomes important to microbial survival.

**Spread**

An invading microorganism may spread by one or more routes: direct extension through surrounding tissues, along tissue planes or via the veins and lymphatic vessels. The vascular route of spread is a particularly effective means of delivering organisms from an initial focus to distant sites around the body. Organisms may play an active part in spread by destroying cells, or even by self-propulsion. As the organisms spread, evasion of host defences becomes increasingly important.

**Mechanisms of damage**

Microorganisms damage tissues by a variety of mechanisms:

- bulk effect
- toxin mediated
- altered function of host systems
- host response to infection.

**Bulk effect**

The sheer bulk of organisms may obstruct a hollow organ, e.g. some helminth infections of the intestine. Swelling of infected tissues can cause pressure on adjacent hollow organs or neurovascular bundles.

**Toxins**

Toxin-mediated disease may also be caused by production of microbial substances that damage cells. Most bacterial toxins (Table 1) are proteins released by the organism or a lipopolysaccharide complex located in the cell wall and liberated during cell growth or lysis. A number of specific toxins have been shown to play an essential role in corresponding diseases. They include:

- tetanospasmin: tetanus
- botulinum toxin: botulism
- cholera toxin: cholera
- diphtheria toxin: diphtheria.

In these infections, the toxin causes the main features of the disease. However, toxins do not have to

<table>
<thead>
<tr>
<th>Species</th>
<th>Toxin</th>
<th>Type</th>
<th>Gene location</th>
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<tbody>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>Botulinum toxin</td>
<td>Neurotoxin</td>
<td>Bacteriophage</td>
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<tr>
<td><em>Clostridium tetani</em></td>
<td>Tetanospasmin</td>
<td>Neurotoxin</td>
<td>Plasmid</td>
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<tr>
<td><em>Corynebacterium diphtheriae</em></td>
<td>Diphtheria toxin</td>
<td>A-B ADP ribosylating</td>
<td>Bacteriophage</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Heat-labile toxin</td>
<td>A-B ADP ribosylating</td>
<td>Plasmid</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Cholera toxin</td>
<td>A-B ADP ribosylating</td>
<td>Chromosome</td>
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destroy cells to cause damage. They can cause sub-lethal damage or alter cellular function, adding to the disease process in more subtle ways. Many exotoxins have two principal subunits: A (active) and B (binding). The B subunit determines tissue specificity, while the A subunit causes cellular damage after binding by the B subunit and subsequent penetration of the cell membrane.

Altered function of organs, tissues or cells
Microbial invasion can change the function of organs, tissues or cells. These changes can be the result of physiological mechanisms acting to remove the infective agent, e.g. increased bowel motility leading to diarrhoea, or coughing and sneezing.

The host response to infection
The host response usually begins with an inflammatory reaction, and is followed by a humoral or cell-mediated immune response. This may cause damage due to swelling, increased fragility of tissues, formation of pus, scarring or necrosis. Chronic intracellular infection may cause formation of fibrous nodules and a state of latency from which acute infection can be re-established at a much later stage.

2.2 Pathogenicity

Learning objectives
You should:
- know the principal contributors to infection-related tissue damage and the factors that might limit this damage
- understand the balance between the microorganism, the human recipient and the intervening environment in determining the outcome of an infection.

Individual species or strains vary in their ability to cause disease. A prerequisite of microorganism-induced damage is microbial growth. Microorganisms have a great variety of strategies to enable continued growth in a hostile environment. They compete for substrates such as iron (an important growth-limiting factor) and other trace elements. Many species have defences against phagocytic cells (e.g. the polysaccharide capsule of *S. pneumoniae*, and antiphagocytic toxins such as staphylococcal leukocidin) and some have a capacity to survive inside macrophages (such as *Mycobacterium tuberculosis*).

Some organisms change their surface antigenic makeup intermittently to evade the host immune system (e.g. borrelia and trypanosomes).

The genetic determinants of microbial pathogenicity are complex. In bacteria, the genes coding for toxin production may be on the chromosome, on the plasmids (extrachromosomal DNA) or even in a bacteriophage. Expression of 'virulence factors' in most cases is a response to an environmental trigger. Work with laboratory animals resulted in the development of a promoter gene trap for the study of bacterial pathogenesis. The system, known as in vitro expression technology (IVET), led to the identification of the structural and controller genes responsible for promoting disease. The products of the disease-promoting genes have been placed in six categories: adhesins, invasins and toxins, and cloaking, shielding and scavenging factors. The genetic switching on and off in response to environmental triggers allows the bacterium to survive mechanical, non-specific and immune defences. Post-transcriptional regulation via sigma factors provides a molecular link between the microbial genome and the organism’s physiological response to its immediate environment. Whole groups of proteins can be up- or downregulated as the microbe adapts to its environment. Proteins under the control of a single, unified mechanism constitute a regulon.

Many aspects of bacterial physiology are specific to a particular phase of growth. If also dependent on microbial density, they are said to be subject to quorum sensing, a process in which a group of low-molecular-weight compounds known as acyl homoserine lactones (AHLs) are expressed in a simple system of intercellular communication.

Pathogenesis of viral infection
As obligate intracellular parasites, viruses require effective mechanisms of transmission, adherence and cellular penetration to establish infection. Many viruses have specific preferences for certain host tissues (e.g. rhinoviruses for the upper respiratory epithelium and human immunodeficiency virus (HIV) for CD4 T lymphocytes). Viruses can spread by lysis of the primary infected cell and secondary viraemia, or by formation of bridges (syncytia) between cells. Human cells need not be destroyed. Viral penetration of the host cell cytoplasmic membrane without cell rupture is a complex process in which the virus may use cell surface molecules to subvert normal membrane and cytoskeletal functions. Viruses can be continually formed at the cell surface or the genome can even be integrated into
the host cell's own genome. The long-term survival of viruses within human cells as obligate intracellular parasites places them beyond the reach of immune defences. Some viruses integrate into the host cell genome to produce a latent state. Viral damage is caused by the cytotoxic effects of the virus or by host immune attack. Mechanisms of late-stage viral damage include autoimmune, immune-complex or neoplastic disease.

Pathogenesis of viral infection

Fungal disease, particularly its life-threatening extreme, is relatively rare despite the many species of fungi present in the environment and on the human body surface. Most fungal infections appear to require a breach in host defences in order to become established. Yeasts often cause mucosal inflammation following alteration of either vaginal or gastrointestinal flora. Dermatophytic fungi cause a variety of skin conditions but rarely cause more invasive disease in immunocompetent patients because they are restricted to the skin. There is no good evidence for the involvement of toxins in fungal disease. Most damage is probably caused by the host response.

Pathogenesis of parasitic infections

Protozoal and helminth infections have a complex pathogenesis, which is best understood by referring to the parasite's life cycle. Some protozoal and helminth infections require transmission by a disease vector. The vector is often an arthropod. The development of disease depends on a three-way relationship between microorganism, vector and human victim in these infections. The ecology of the vector (sometimes known as the 'intermediate host') is critical to the long-term survival of the parasite within a human population. In developed countries, parasitic infections are most common in international travellers, the sexually active, immunocompromised patients and poor people. The application of novel molecular parasitology techniques has provided new insights into the mechanisms of parasite disease.

Opportunistic infections

If an organism is capable of causing disease in an apparently healthy individual, it is clearly aggressively pathogenic. If it is normally incapable of causing disease but can do so only when the human body is compromised in some way, it is said to be opportunistic. Opportunistic infections are of particular importance in hospital patients and in people whose immune systems are depressed by drugs or infection, particularly by HIV.

Infection and the environment

The model mechanism of infection that we inherited from Robert Koch places its emphasis on an identifiable microbial pathogen; the presumed external agent of disease. This emphasis may have been useful in the early days of the germ theory of disease. However, a preoccupation with the microorganism to the exclusion of all other factors misses the wider context of the discoveries made by the early pioneers of microbial disease research. Koch provided a rule of thumb to establish the role of a given microorganism as the causal agent of a given disease. Unfortunately, Koch's postulates, as they are known, are only rarely fulfilled, despite attempts to bring them up to date with a molecular biological slant.

The early immunologists recognised the fundamental importance of the infected person's response in the development of infectious disease. Accepting the contribution of humoral and cellular immunity, tissue reaction and immune compromise to the course of an infection leads to a more sophisticated model of infection as an interactive process between human and microbe with destructive consequences.

Until very recently, the environment in which the initial interaction between microbe and host occurs was seen as little more than a passive backdrop to infection, with the possible exception of some vector-borne parasitic infections. The critical role of the environment in mediating the encounter with a potentially infective microorganism, and thereby influencing the outcome, is a more recent idea.

The emerging picture of infectious disease pathogenesis is one in which the outcome is determined by a three-way tussle between microorganism, human recipient and the intervening environment. The complex cellular and molecular events that determine the final outcome of each encounter are likely to throw more light on the origins of disease. This multilayered picture of infection as a process encompassing molecular events, cellular events, tissue, whole organism, habitat and geography is known as ‘biocomplexity’.

Dynamic biological processes

The dynamics of the interaction between microorganism and human cells are beginning to open up to mechanistic analysis. The application of mathematical modelling to theoretical biology now allows
us to predict the consequences of introducing a new disease-causing microbe to a human population. The perturbations from the initial steady-state populations of microorganisms and humans resemble a discordant state that demands resolution before harmony can be restored. Infection can be thought of as the unsought consequence of an accidental encounter between two populations attempting to restore biological order—a noisy negotiation for a peaceful settlement. This newer way of looking at pathogenesis (the origins of disease) complements mainstream germ theory, and has taken our understanding of infectious disease processes into unfamiliar multidisciplinary territory.
Extended matching questions

The following is a list of questions:

1. What is an example of a vertical infection?
2. What is the best example of an infection that requires initial colonisation of a body surface?
3. Which infection listed is most likely to result from inhalation?
4. Which one of these infections is most often transmitted in air?
5. Which infection needs an initial breach in the body surface?
6. In which infection does a leukocidin play a role?
7. Which infection is caused by an obligate intracellular organism?
8. Which infection is entirely due to the action of a toxin?
9. In which infection is droplet size a critical factor?
10. Which infection does not require microbial penetration of the body surface?

Select the single answer from the list below that best matches each one of the questions in the list above.

Any one answer can be used once, more than once or not at all.

- A. Cholera
- B. Gonorrhoea
- C. Pneumonia
- D. Staphylococcal skin infection
- E. Fetal (intrauterine) rubella
- F. Viral gastroenteritis

Short notes questions

Write short notes on the following:

1. How microorganisms cause damage in human disease
2. A comparison of pathogenesis of bacterial and viral infections
3. The main routes for transmission of infectious diseases and how microorganisms penetrate the respective anatomical barriers

Viva questions

1. What is the difference between colonisation and infection?
2. Can microorganisms be divided into pathogens and non-pathogens?
Extended matching answers

1. F:
Fetal rubella is transmitted from the mother to the fetus in utero and is therefore an example of a vertical infection. All others listed are exogenous infections due to external agents, with the possible exception of some staphylococcal skin infections, which can be caused by inoculation of bacteria from the endogenous skin flora.

2. B:
Gonorrhoea requires initial colonisation of the urethral mucosa and adhesion to the epithelial surface via pili. Cholera and viral gastroenteritis require ingestion, pneumonia requires inhalation and staphylococcal skin infection can result from direct inoculation.

3. C:
Pneumonia is usually caused by bacteria or viruses that have been inhaled into the smaller airways.

4. C:
Pneumonia is transmitted by inhalation of infective droplet nuclei. Gonorrhoea requires intimate body contact. Cholera requires a major breakdown in sewage disposal and other hygiene failures. Viral gastroenteritis is transmitted by the faecal–oral route, involves unwashed hands and may sometimes be spread via the air to those in close proximity.

5. D:
Staphylococcal skin infection usually requires at least a microscopic breach in the skin surface. Pneumonia results from inhalation. Gastroenteritis and cholera result from ingestion, and intrauterine infection results from transplacental spread.

6. D:
Leukocidin plays a part in the invasion stage of some of the more severe staphylococcal skin infections. It is not a feature of pneumonia, cholera, viral gastroenteritis or intrauterine infection.

7. F:
All viruses are obligate intracellular parasites. A few bacteria are obligate intracellular organisms, e.g. chlamydias, and a larger number are facultative intracellular organisms (e.g. Legionella, Listeria and Salmonella). The vibrio that causes cholera is extracellular and staphylococci can be both intra- and extracellular.

8. A:
The profuse diarrhoea seen in patients with cholera is almost entirely due to the extracellular action of cholera toxin.

9. C:
Inhaled droplet size is of critical importance in the pathogenesis of pneumonia, where droplets must be of the right diameter to reach the smaller air spaces where the bacteria or viruses that they contain can establish infection. Particle size is of lesser or no importance in all the other infections listed.

10. A:
Cholera is due to the effect of a toxin that acts on the intestinal mucosal surface and therefore does not require penetration of intestinal epithelial cells. Intrauterine rubella requires entry of the virus, first into the mother’s circulation, and then into the fetal bloodstream. The other listed infections all depend on penetration of an epithelial surface.

Short notes answers

1. The main topic areas of bulk effect, altered function, toxin-mediated effects and host response should be covered, with examples.

2. Could be tackled as a table. Follow the sequence of acquisition, colonisation, penetration, spread and damage. Give examples of bacteria and viruses.

3. Follow principal routes of transmission and means of penetration; probably best done using a system-based approach.
**Viva answers**

1. Briefly define the two terms, then give specific examples and discuss how confusion of the two terms can cause problems in clinical practice.

2. Some microbes have not yet been shown to cause human infection. Mention the spectrum of virulence from opportunist to those that can be highly lethal in the previously healthy patient. Refer to the balance between patient and microbe and its modification by host defences, antibiotics and environmental factors. Give specific examples of how concepts of pathogenesis have changed recently through developments in molecular and cell biology and now challenge a simplistic pathogen–non-pathogen dichotomy.