31 Infective endocarditis

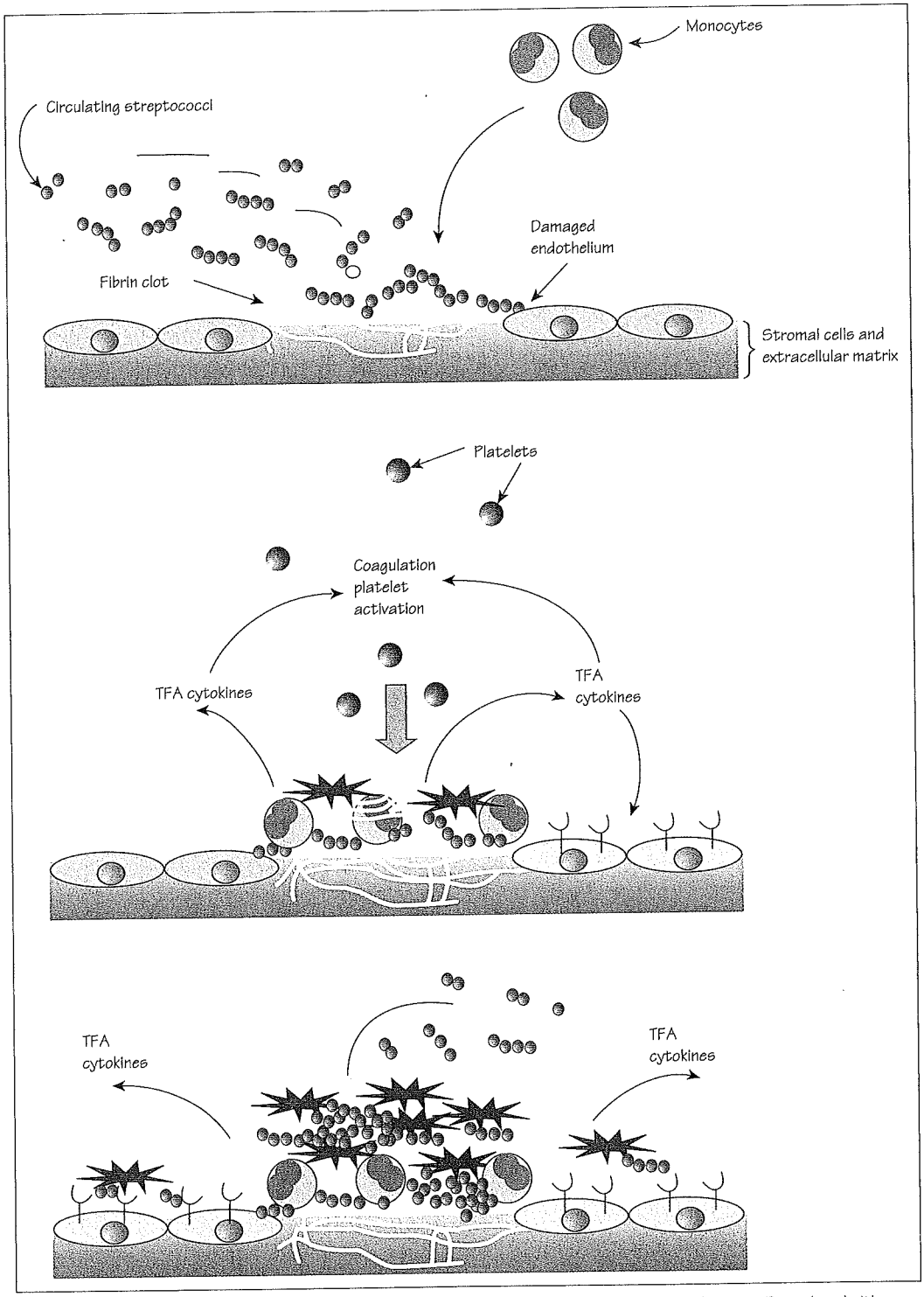

Figure 31.1 Growth of a thrombotic vegetation following bacterial attachment to damaged endothelial sites. Reproduced with permission from Moreillon P, Que Y-A Infective endocarditis. *Lancet* (2004), 363: 139–149.

Endocarditis is an inflammation of the inner layer of the heart, characterized by formation of a vegetation. This is a mass of platelets, fibrin, some inflammatory cells and microorganisms. Infective endocarditis (IE) has a low incidence rate (1 in 10–100,000, depending upon population) but high mortality. In the past, IE was divided into sub-acute (low virulence proceeding over weeks or months) or acute (a sudden illness over days or weeks). However, this terminology is no longer used. Altered blood flow around the heart valves is a risk factor for infective endocarditis. The valves may be damaged from surgery, autoimmune disease (e.g. rheumatic fever), or simply from old age. Vegetations result from bacteremia, the presence of bacteria in the blood. This occurs quite easily, for example by vigorous tooth brushing, also from urinary tract infections and in IV drug users. The latter tend to get their right side valves infected because the veins injected go into the right side of the heart. In rheumatic heart disease the aortic and mitral valves are affected in the left side of the heart. It is also important to distinguish between native valve and prosthetic valve disease. Early prosthetic valve endocarditis usually is due to operative or post-operative bacterial contamination.

Bacteria in IE

The viridans streptococci (most commonly *S. sanguinis*), and related but unidentified oral streptococci, account for about 50% of IE cases in the developing world. The streptococcal-like genera include *Gemella*, *Granulicatella* and *Abiotrophia*. Approximately another 30% of cases are due to *S. aureus*, and these develop more rapidly as *S. aureus* is more virulent than oral streptococci. *Enterococcus faecalis* and *Enterococcus faecium* (Lancefield group D organisms) are also frequent agents of IE, accounting for about 10% of cases. They are often derived from urinary tract infections and are hospital acquired. The most important diagnosis for IE is blood culture of the microorganisms combined with results of echocardiography. However, culture-negative endocarditis accounts for about 10% of cases, and some of the pathogens responsible are *Aspergillus*, *Brucella*, *Coxiella* and *Chlamydia*.

Mechanism of vegetation formation

Formation of a vegetation begins by bacteria becoming established at a site of injury on a heart valve, or on the wall of a blood vessel (endothelial site). Bacteria interact with the fibrin-platelet clot, and with fibronectin or collagen exposed as a result of damage. In experimental animals the fibronectin-binding proteins FnBPA and FnBPB are necessary for *S. aureus* to cause IE. Once attached to the host site (see Figure 31.1), bacteria interact with blood platelets by transiently trapping them and causing them to roll. This mimics the natural system for blood vessel repair whereby endothelial damage is recognized by von Willebrand factor, which is activated by collagen and traps circulating platelets. Tissue factor (TFA) is involved in the formation of thrombin. Once platelets are trapped by the bacteria, fibrinogen accumulates and is converted by thrombin protease to fibrin. The platelets become activated and aggregate in close association with the bacteria to form a thrombotic vegetation.

Bacterial virulence factors

Fibronectin binding proteins in *S. aureus*, and matrix-binding proteins in *E. faecalis* are involved in IE. However, platelet interactions are important in the generation of thrombi. *S. sanguinis* and *S. gordonii* produce cell-surface proteins GspB/Hsa (and homologs are present in other streptococci) that specifically recognize sialic acid residues on human platelet receptors. The sialic acid present on platelet glycoprotein Ib (GPIb) is bound by this streptococcal protein, effectively providing the means by which platelets are trapped in the circulation. GPIb is the platelet receptor recognized by von Willebrand factor, so the bacteria mimic the activity of a host protein. Subsequently, other proteins present on the bacterial cell surface may induce platelet aggregation and activation. This occurs in conjunction with binding of fibrinogen (*S. aureus* ClfA protein binds fibrinogen) and with antibody reacting with the platelet Fc receptor. Other specific virulence factors have been identified in streptococci and staphylococci. The metal ion binding proteins FimA, ScaA and SloA in viridans streptococci are virulence factors for IE, as is polysaccharide production by *S. mutans*. Animals vaccinated with SloA are partially protected against *S. mutans* induced IE, suggesting that vaccination of high risk groups could be beneficial.

Antibiotics in IE

In the past, bacteremia caused by certain dental procedures, e.g. tooth extraction was thought to be significant in IE. Consequently, patients with heart problems were given antibiotic prophylaxis in case of infection. This practice has now ceased in many countries as there is no firm evidence that dental treatment increases the risk for IE any more than simply brushing or flossing teeth. For subjects presenting with IE, high dose antibiotics are administered by the intravenous route, often for long periods (up to six weeks). This maximizes the diffusion of antibiotics into the vegetations. Viridans group streptococci are highly sensitive to pencillin, whereas treating for *S. aureus* might require oxacillin or vancomycin. Fungal endocarditis requires anti-fungal treatment such as with amphotericin B.

32 Oral mucosal, bone and systemic infections

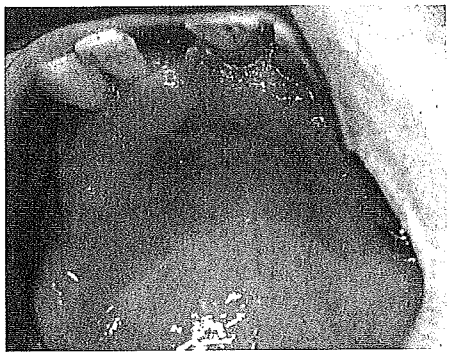

Figure 32.1 Denture stomatitis on upper palate. Inflammation has occurred underneath the denture and is delineated by the red line.

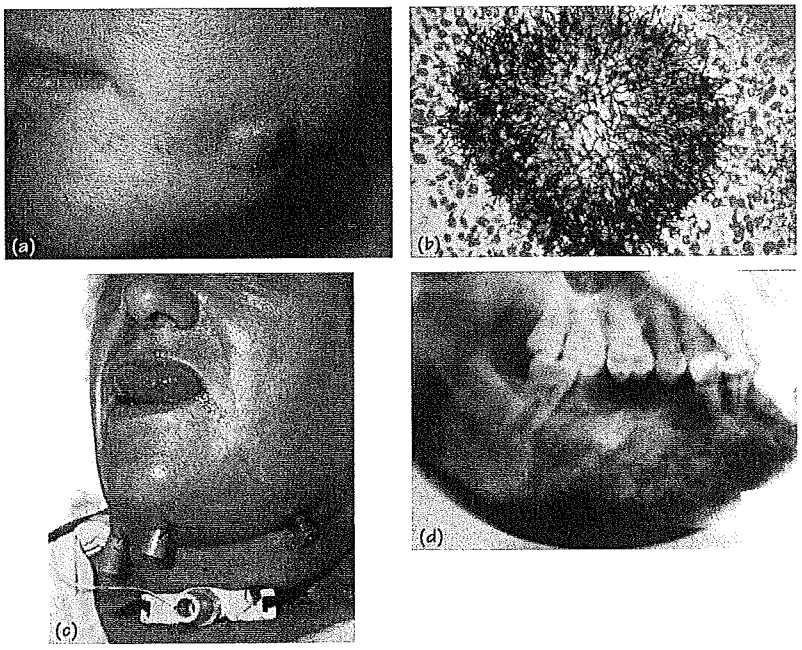

Figure 32.2 Examples of odontogenic infections associated with oral bacteria. (a) cyst typical of actinomycosis; (b) rosette of *Actinomyces israelii* within cyst; (c) Ludwig's angina, showing external drains for inflammatory exudate, and raised tongue due to swelling of sub-lingual space; (d) osteomyelitis of the jaw.

Table 32.1 Oral microbe-associated infections, the etiologic agents and their origins.

Disease	Agent(s)	Origin
Mucosal lesions	*S. aureus*, enterococci, *Neisseria*, enteric bacteria, *Candida*	Oral colonizers or transients
Halitosis	*Fusobacterium*, *Porphyromonas*, *Prevotella*, *Treponema*, *Eubacterium*	Oral colonizers of tongue
Angular cheilitis	*S. aureus*, *C. albicans*	Oral colonizers or transients
Osteomyelitis of lower jaw	*S. aureus*, *Pseudomonas*	Dentoalveolar
Actinomycosis	*Actinomyces israelii*	Oral colonizer
Osteonecrosis	Polymicrobial including *A. israelii*	Oral colonizers or transients
Submucosal abscess	Polymicrobial	Oral
Brain abscess	Polymicrobial (periodontal microflora)	Periodontitis, periapical abscess
Chronic sinusitis	Ill defined	Periodontitis
Ludwig's angina	Polymicrobial (periodontal microbiota and viridans streptococci)	Periapical abscess, periodontitis, dental caries
Lung abscess	*Actinomyces*, *Aggregatibacter*, *Prevotella*	Periodontitis
Chronic obstructive lung	*Pseudomonas aeruginosa*	Oral transient
Prosthetic joint infection	*Peptostreptococcus*, *Streptococcus*	Periodontitis, periapical abscess
Chronic meningitis	*Streptococcus*	Periapical abscess, dental caries
Acute meningitis	*Neisseria meningitidis*, *S. sanguinis*	Periodontitis, endodontic therapy

Most of oral microbiology is concerned with infections of the teeth and gums leading to dental caries and periodontal disease. There are, however, many disease conditions of the oral mucosa and submucosa and systemic conditions, in addition to infective endocarditis, that may result from mobilization of oral microbiota components. Infections of the mucosa are more usually associated with transient oral bacteria. For example, staphylococci are found in the saliva of approximately 30% individuals, but they are considered transients rather than components of the resident oral microbiota. Likewise Gram-positive enterococci, and Gram-negative facultatively anaerobic rods, e.g. *E. coli*, *Klebsiella*, *Pseudomonas*, are transient bacteria in saliva. However, all these microorganisms can play a significant role in oral and respiratory tract infections of a compromised host.

Mucosal infections

Epithelial cell desquamation prevents accumulation of microorganisms upon epithelial surfaces on the palate, on the floor of the mouth and on the inside buccae. By contrast, the dorsum of the tongue provides a surface of papillae and taste buds for rich microbial biofilms to develop. Halitosis can be caused by bacteria on the tongue processing proteins into: volatile sulfur compounds such as hydrogen sulfide, methyl mercaptan and dimethyl sulfide; phenyls, such as indole, skatole and pridine; diamines, such as putrescine and cadaverine; or short chain fatty acids such as butyric acid and propionic acid. Halitosis can also be caused by extra-oral and systemic conditions. The most common mucosal lesions are stomatitis (Figure 32.1) and angular cheilitis (see Chapter 33) which involve combinations of *Candida* fungi and bacteria. Microbes associated with lesions include *S. aureus*, enterococci, enterobacteriacae and *Candida* (see Table 31.1). Factors that pre-dispose to mucosal infections include mechanical injury, associated with impaired function of the tongue or impaired salivary flow, inadequate oral hygiene especially of dentures and faulty restorations, and systemic influences such as chemotherapeutics, impaired immune function and malnutrition.

Submucosal and bone infections

Submucosal infections, caused by bacteria penetrating the epithelial barrier and entering underlying tissues, usually form abscesses (Figure 32.2). Most of these infections are polymicrobial and anaerobic. In individuals with normal immune function, submucosal infections only occur as a result of local predisposing factors. These include necrotic pulp, dental calculus, deep periodontal pockets and soft tissue damage. A complication of subepithelial infections is spreads to the head and neck. Osteomyelitis may occur in the lower jaw and has similar microbiology to periodontal or endodontal conditions. Actinomycosis is a specific infection, developing in the head and neck and affecting the lower jaw. Infected root canals provide the point of entry for *Actinomyces* bacteria, which set up what is commonly a chronic infection. A hard swelling develops, often with formation of a granuloma in which aggregates of *Actinomyces* cells appear as grains (so called 'sulfur granules'). *Actinomyces israelii* is the most commonly isolated species from human actinomycosis. Osteonecrosis of the jaw is associated with bisphosphonates, a class of drugs that inhibit osteoclasts and bone resorption, and are used in the prevention and treatment of osteoporosis. Osteonecrosis of the jaw often follows high-dose intravenous administration as is used for some cancer patients. *A. israelii* is associated with this condition, most likely in a mixed biofilm with other oral organisms such as *Fuosbacterium*, *Treponema* and yeasts.

Oral manifestations of systemic infections

Many human infections at other body sites may manifest in changes within the oral cavity. These can be important in the diagnosis of non-oral conditions. For example, both gonorrhea and syphilis cause oral lesions, either as grayish areas on the tongue and soft palate (gonorrhea) or as hard chancres (primary syphilis) or small gray mucous syphilitic patches (secondary). Lepromas, containing *Mycobacterium leprae*, form on the tongue and palates in immunocompromised subjects with leprosy. Tularemia, caused by *Francisella tularensis*, is a febrile illness transmitted by insects into humans from rodents and birds. In humans, initial infections occur on the fingers, or as oral lesions, as a result of eating infected meat. These lesions can be mistaken for syphilitic lesions. Many forms of mucosal lesion indicate some degree of immune dysfunction that may be localized or systemic.

Systemic manifestations of oral infections

Brain infections and disorders may occur secondarily to bacteremias derived from the oral cavity. *Streptococcus*, *Peptostreptococcus*, *Prevotella* and *Fusobacterium* have all been isolated from brain abscesses. Periodontal and periapical infections can spread into tissues surrounding the oral cavity leading to maxillary sinusitis, Ludwig's angina and fascial plane infections. Lung abscesses may be caused by aspiration of salivary or dental plaque bacteria. Acute respiratory infections may follow aspiration during dental treatment. Chronic obstructive pulmonary infections in cystic fibrosis patients may be caused by mucoid variant strains of *Pseudomonas aeruginosa* colonizing the buccal mucosa and being aspirated into the lungs. Prosthetic joint infections involving *Peptostreptococcus* and viridans streptococci can occur following systemic spread. Chronic meningitis has been related to periapical abscesses and dental caries. A case of osteomyelitis of the ulna caused by *P. gingivalis* has been reported. For more on systemic conditions possibly associated with periodontal pathogens see Chapter 27.

33 *Candida albicans* and fungal infections

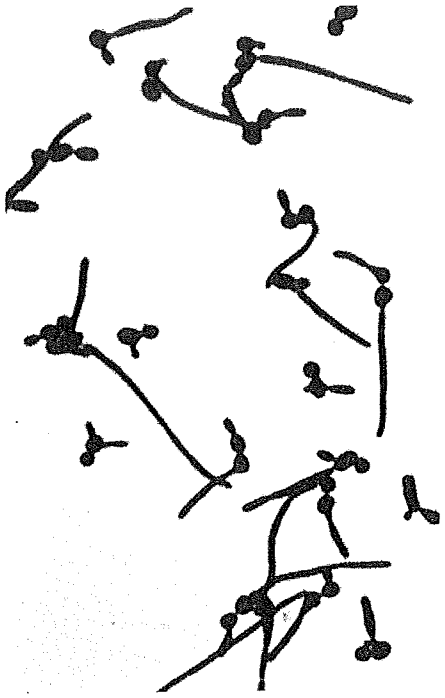

Figure 33.1 Image of *Candida albicans* showing yeast cells (blastospores), pseudohyphae (small projections) and true hyphal filaments.

Figure 33.2 Co-adhesion between *Candida* and oral streptococci.

Table 33.1 *Candida* species infections in humans.

Superficial candidiasis	Disseminated candidiasis
Cutaneous	Candidemia
Perianal	Chronic disseminated
Submammary	Urogenital
Granuloma	Endocarditis
Mucocutaneous	Meningitis
Glossitis	Encephalitis
Stomatitis	Phlebitis
Cheilitis	
Bronchitis	
Esophagitis	
Pneumonia	
Enteritis	

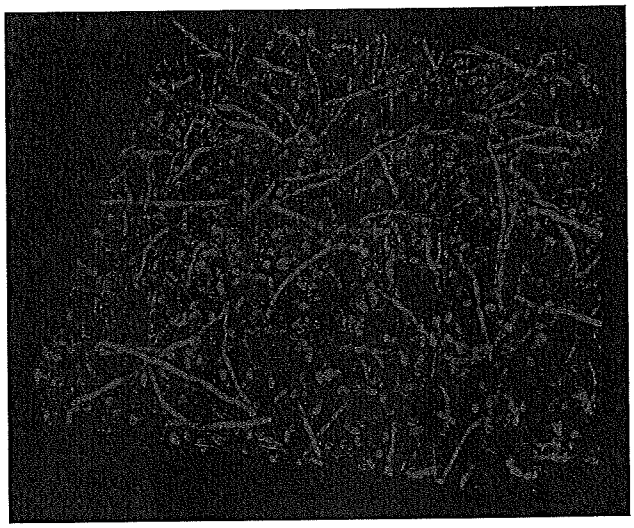

Figure 33.3 Confocal scanning laser microscope 3D image of *C. albicans* biofilm formed on salivary pellicle, showing hyphal filaments intertwined with yeast forms.

Candida albicans is found as part of the human microbiota of the digestive tract, which includes the mouth. There are approximately 200 different species of *Candida* yeasts. *C. albicans* accounts for 75% of all fungal infections of humans. Up to 40% of healthy adults carry *C. albicans* in their mouths. In general, *Candida* grows and survives as a commensal. However, a slight modification of the host defenses, or of the commensal microbiota, can provide an opportunity for *Candida* to breach the protective barriers and become pathogenic. *C. albicans* is a good example of an opportunistic pathogen. It is a pleiomorphic (many forms) fungus, growing as an oval shaped budding yeast, or as pseudohyphae or true hyphae (Figure 33.1). The transition from yeast form to hyphal form is one of the many characteristics associated with virulence. Other microbial components involved in pathogenesis include: adhesins, such as HWP1 (hyphal wall protein), which promote colonization; hydrolytic enzymes, e.g. proteases, phospholipases, that cause tissue destruction; and molecules like CR3-like receptor and HSP90 (heat shock protein) that modulate immune system functions. Pathogenesis is facilitated by breakdown of host immunity by immunodeficiency diseases or by iatrogenic factors. The latter include chemical or physical therapeutic interventions that weaken the defenses at various levels.

C. albicans infections (Table 33.1)

Infections caused by *Candida* may be superficial or systemic. The superficial infections include those of the cutaneous or mucocutaneous tissues (Table 33.1). Systemic infections, which have high mortality rates, may involve multiple organs. Mucocutaneous candidiasis occurs in subjects who have cellular immune deficiency, are immunosuppressed, or have their protective commensal microbiota disturbed. The incidence of systemic candidiasis has increased over the past two decades, and *Candida* species such as *albicans*, *dubliniensis*, *tropicalis*, *parapsilosis* and *glabrata* are significant nosocomial (hospital-acquired) pathogens. The increase is due mainly to more invasive surgical techniques, the growing use of prosthetic devices such as intravascular catheters, and new drug therapies. Prosthetic devices provide new surfaces for microbial colonization, and *C. albicans* is efficient at forming robust biofilms.

Denture stomatitis

This is a *Candida* infection of the oral mucosa caused by a close-fitting upper denture. This cuts off the mucosa from the normal protective and lubricatory properties of saliva. It is rarely seen under a lower denture because this is more mobile and salivary flow is usually unrestricted. *Candida* hyphal forms may be seen microscopically as having grown between the denture and mucosa. Bacteria are also present in this condition, such as *Streptococcus*, but also *S. aureus* and *E. coli*, and may enhance inflammation in the palatal mucosa.

Angular cheilitis

This is frequently associated with denture stomatitis and involves leakage of *Candida* infected saliva at the angles of the mouth where there is erythema, crusting and cracking. It is a general sign of candidiasis and may indicate systemic disorders including HIV infection and diabetes mellitus. Bacteria such as *S. aureus*, *E. coli* and *Pseudomonas* may also play a role in maintenance of the labial lesion.

Gingivitis and periodontal disease

Forms of gingivitis that involve acute inflammation with ulceration, which are promoted by heavy cigarette smoking or immunosuppression, often contain *Candida*, enteric bacteria and staphylococci. In addition, in persistant root canal infections, *C. albicans* is frequently isolated with oral streptococci, to which it can adhere (Figure 33.2), and with *Peptostreptococcus* and *Fusobacterium*.

Prosthetic implants

Infectious failures of dental implants are associated with complex microbial etiologies (see Chapter 28). After prolonged use of systemic antibacterial agents, or chlorhexidine mouth rinses, overgrowth of atypical periodontal organisms such as *C. albicans*, *S. aureus* and *Pseudomonas* may occur. In patients with surgical laryngectomies, a voice prosthesis acts as a shut valve between the trachea and esophagus. The medical-grade silicone rubber within the voice prosthesis are subject to microbial colonization. Mixed species biofilms comprising mainly of *Candida*, staphylococci, oral streptococci and enterococci form on the esophageal side, causing the valve mechanism to malfunction and the prosthesis fails. Central venous catheters, endotracheal tubes and urinary catheters become colonized by a range of microbes, and *Candida* species often feature in these polymicrobial infections.

Biofilms and antifungal drugs

Candida biofilms (Figure 33.3) are more resistant to antifungal compounds, including amphotericin B, fluconazole and nystatin, as well as to chlorhexidine. The reasons for this are still not entirely clear, but several genes encoding anti-fungal drug export pumps are up-regulated in biofilms. Recently, it has been shown that adherence initiates production of multi-drug tolerant persister cells within *C. albicans* biofilms. These slowly metabolizing or dormant cells probably confer reduced susceptibility to antifungal agents. This explains why *Candida* infections often cannot be eliminated with current antifungal drugs. The search for new antifungal agents has led to the discovery of echinocandins, such as caspofungin, that attack the glucan components of the *Candida* cell wall. Because of low bioavailability, echinocandins are given intravenously.

34 Oral virology I, herpes, papillomavirus and parvovirus

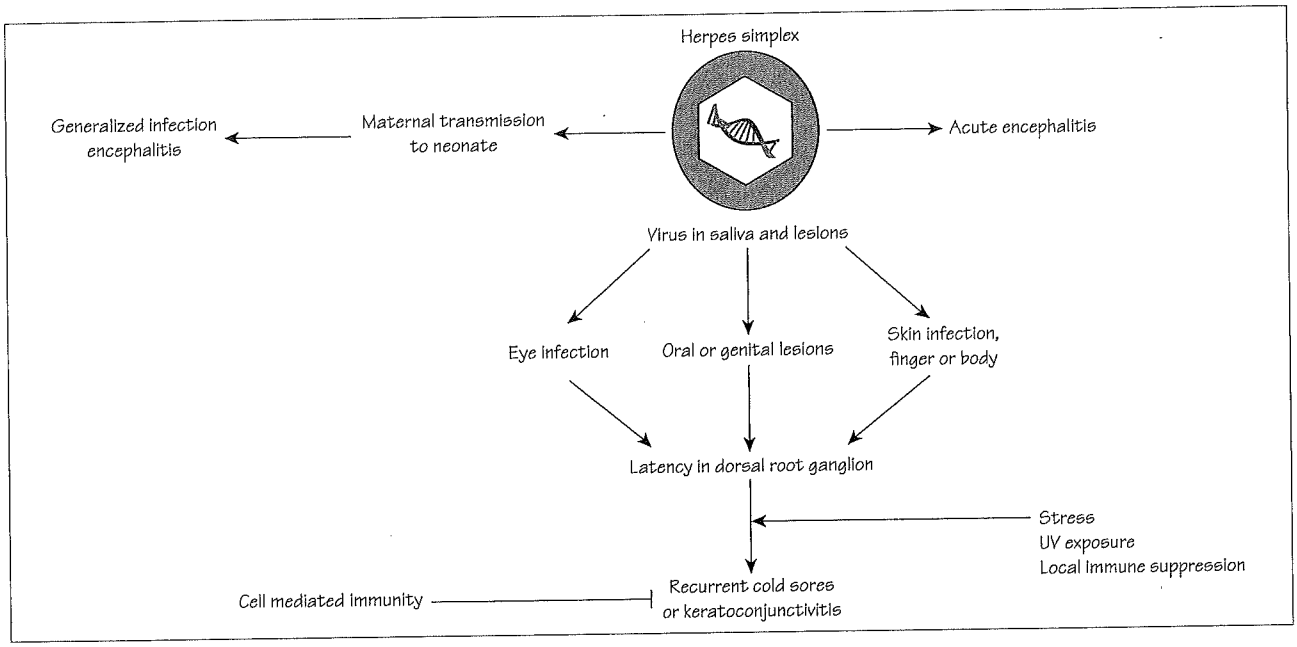

Figure 34.1 Progression and manifestations of herpes simplex infection.

Table 34.1 Characteristics of human herpes viruses.

Name	Common designation	Major disease(s)	Site of Latency	Transmission
HHV1	Herpes simplex 1	Stomatitis (cold sores) on oral epithelium	Neuron	Close contact, saliva
HHV2	Herpes simplex 2	Genital lesions	Neuron	Sexual and close contact
HHV3	Varicella zoster (VZV)	Chickenpox, shingles (after reactivation)	Neuron	Respiratory and close contact
HHV4	Epstein Barr (EBV)	Infectious mononucleosis, B-cell lymphomas, hairy oral leukoplakia	B-cell	Saliva
HHV5	Cytomegalovirus (CMV)	Congenital defects, opportunistic in immunocompromised patients	Monocyte, lymphocyte	Close contact, transfusion, congenital
HHV6	Herpes lymphotropic virus	Exanthema subitum (roseola or sixth disease)	T-cell	Respiratory, saliva and close contact
HHV7	Human herpesvirus 7	Unknown	T-cell	Unknown
HHV8	Kaposi's sarcoma-associated herpes virus (KSHV)	Kaposi's sarcoma, primary effusion lymphoma (PEL) and multicentric Castelman's disease (MCD)	Lymphocyte	Sexual, saliva, close contact

Many viruses can be acquired by mouth and are present in whole saliva. Viruses can also be present in the oral cavity following spread from other tissues. Herpes viruses, hepatitis B virus, rubella virus, measles virus, mumps virus and respiratory viruses such as influenza can all be spread by aerosols. Dentists are therefore at risk both of contracting viral infections and spreading viral infections among patients. In the next two chapters we shall discuss those viruses with most significance to dentistry.

Herpes viruses

Herpes viruses are large (150–200 nm), enveloped, icosahedral viruses containing double stranded linear DNA that replicate in the host cell nucleus. Herpes viruses can establish latency and cause persistent infections (Table 34.1).

(1) Herpes simplex virus 1 and 2 (HSV-1, HSV-2; human herpes virus 1, human herpes virus 2) (Figure 34.1)

HSV-1 is transmitted by contact with saliva and is usually acquired in early childhood. Primary infection is often asymptomatic, but bilateral stomatitis in the epithelium of the oral mucosa can occur for 2–3 weeks. Following primary infection, HSV-1 is transported up the trigeminal ganglia where it remains latent. Reactivation (brought about by stress, UV exposure, local immune suppression), results in transport of the virus back down the axon where infection and replication in epithelial cells occurs, causing unilateral stomatitis (cold sores).

The closely related HSV-2 virus is usually sexually transmitted and causes lesions in the genital area. However, HSV-2 can also cause disease in the oral cavity. Other sites of infections for HSV viruses include the throat (pharyngitis), eye (keratitis), finger (whitlow), and body (gladiatorum). In rare cases, usually associated with immune suppression, both HSV-1 and -2 can cause severe and fatal encephalitis.

TH-1 associated delayed type hypersensitivity cytotoxic T-cells are necessary to kill infected cells. Both HSV-1 and -2 can be treated with acyclovir, a drug that is activated by HSV thymidine kinase and blocks viral DNA polymerase.

(2) Varicella zoster virus (VZV, human herpes virus 3)

VZV causes varicella (chickenpox), after which virus becomes latent in ganglia along the entire neuraxis. Virus reactivation produces zoster (shingles). The virus is present in saliva and is spread by respiratory droplet and by direct contact.

(3) Epstein Barr virus (EBV, human herpes virus 4)

EBV is transmitted in saliva, and infection usually occurs in early childhood when it is asymptomatic. In later life, primary infection can cause infectious mononucleosis ('mono', kissing disease) with fever, swollen adenoid glands and fatigue. This disease is usually benign and self-limiting. EBV replicates primarily in B-cells and can cause B-cell transformation. EBV is thus associated with B-cell lymphomas such as Burkitt's lymphoma in Africa. EBV also infects epithelial cells and is associated with nasopharyngeal lymphoma in China. Hairy oral leukoplakia, that occurs mainly in AIDS patients, is a manifestation of EBV infection of epithelial cells in the oral cavity. EBV can remain latent in B-cells. T-cells are required for controlling infection.

(4) Cytomegalovirus (CMV, human herpes virus 5)

CMV infections can be spread by saliva and are usually asymptomatic, but primary infection in early pregnancy can lead to severe complications for the fetus. In immunocompromised (diminished cell-mediated immunity) patients, more severe symptoms occur such as retinitis, hepatitis and encephalitis. CMV infects many lymphocyte types, including macrophages. The virus can remain latent in lymphocytes and in tissue, and infected tissues show a characteristic 'owl's-eye' nuclear inclusion body.

(5) Human herpes viruses 6, 7 and 8 (HHV6, HHV7, HHV8)

HHV6 is associated with a common childhood disease, exanthema subitum (roseola, sixth disease). The virus replicates in the salivary glands and is secreted into saliva. Most infections are subclinical, and almost all adults are seropositive. HHV7 is detected in saliva but as yet has no known disease association. HHV8 is present in the saliva and is associated with the etiology of Kaposi's sarcoma.

Papillomaviruses

Papillomaviruses are small (50–55 nm) icosahedral, non-enveloped viruses containing double stranded DNA. They are members of the papovavirus family. Human papillomaviruses (HPV) cause warts on the skin and mucosal surfaces, including the oral soft tissues. There are several types of HPV that are based on DNA homology and these have different tropisms for epithelial cells. Some HPV possess oncogenes such as the E6 and E7 proteins of HPV-16 and HPV-18 that can cause cervical carcinoma and are also linked to oral cancer. HPV-6 and HPV-11 are associated with benign head and neck tumors.

Parvoviruses

Only one parvovirus, B19, is associated with human disease. B19 causes erythema infectiosum (fifth disease, slapped cheek syndrome) in children. In adults with sickle-cell disease or similar types of chronic anemia, B19 can cause an acute, severe anemia. B19 can also cause abortion if infection occurs during pregnancy. Parvoviruses are small (18–26 nm in diameter) with a non-enveloped icosahedral capsid. B19 has one linear, single strand DNA. Large numbers of virus are released into saliva.

35 Oral virology II, hepatitis and HIV

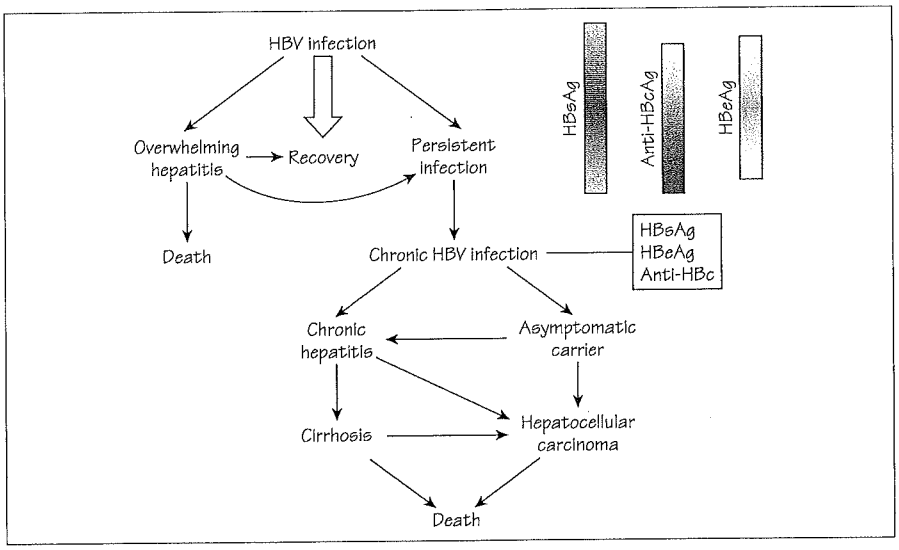

Figure 35.1 Outcomes of HBV infection and concentration changes in HBV antigens and antibodies.

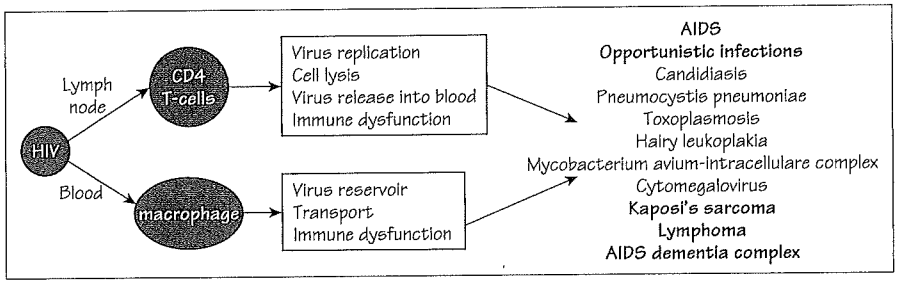

Figure 35.2 Major pathogenic mechanisms of human immunodeficiency virus (HIV) and disease outcomes.

Table 35.1 Vaccines against Hepatitis viruses

Vaccine and duration	Recommendations
Hepatitis A	Recommended for all children over one year
Inactivated virus	People age 12 months or older who are traveling to or working in areas of the world where Hepatitis A is endemic, or there is a known outbreak (fecal to oral transmission, usually by water). Vaccine or IgG to the virus can be given when exposure is suspected. Infants under 12 months can also receive IgG
Two dose series protects for at least 20 years in adults	People whose sexual activity puts them at risk
	People receiving clotting factor concentrates
Hepatitis B	Recommended for all newborns in many countries
Recombinant Surface	Health care workers, and research laboratory staff and students working with human tissues e.g. blood, saliva
Antigen S component	People exposed to blood contaminated body fluids through work, drug use or sexual activity
Three dose series protects for at least 20 years	Babies born to mothers with active hepatitis B infections. IgG to the virus should also be given
Hepatitis C	No current vaccine although promising future with development of a new animal model of infection
Hepatitis D	Not possible to acquire Hepatitis D unless subject already has Hepatitis B. Therefore, most effective approach against Hepatitis D is to get the Hepatitis B vaccine
Hepatitis B Vaccine	
Hepatitis E	Vaccine close to production. Will be recommended for travelers to sub-Saharan Africa, Central America, India and SE Asia (fecal to oral transmission, usually by water).

Hepatitis B virus (HBV)

HBV is a small (42 nm) enveloped virus, and a member of the hepadnavirus family. Genetic material is circular, partially double-stranded DNA. However, the virus produces a reverse transcriptase and replicates through an RNA intermediate. Surrounding the DNA and enzymes is the core antigen (HBcAg) and an envelope containing the surface antigen (HBsAg). HBeAg is related to HBcAg and is a minor component of the virion (Dane) particles, but is secreted into the serum. HBsAg is also secreted in filamentous (Australia antigen) or spherical particles. HBsAg includes three glycoproteins (L, M and S) encoded by the same gene but translated from different start codons.

HBV is transmitted by contact with contaminated blood and other human fluids such as saliva. The virus targets hepatocytes in the liver, and disease can be symptomatic or asymptomatic, and acute or chronic. The incubation period is about 2–6 months when inflammation of the liver, usually without high fever, occurs. During the latter half of the incubation period very high numbers of virions and surface antigen particles are present in the blood, and blood and saliva become infectious. The acute phase lasts about two months and then the numbers of virions and HBsAg particles drop, and antibodies to the core antigen develop. Antibodies to HBsAg do not develop until a number of weeks after the surface antigen is no longer detectable in the blood, but they can persist for several years. About 30% of infections are subclinical. In 10% of cases in adults, but up to 95% in neonates following vertical transmission, a chronic carrier state develops, with continued viral replication and no obvious symptoms. Of these, about 2% die of cirrhosis and 0.5% die of primary hepatocellular carcinoma (Figure 35.1).

Detection of HbsAg and HBeAg indicates active viral replication. Chronic infection can be distinguished by the continued presence of these antigens in the absence of detectable antibody. A vaccine for HBV comprises recombinant HBsAg S component (Table 35.1).

Hepatitis D virus (HDV, delta agent)

HDV is a defective virus that requires HBV to replicate. HDV has a small RNA genome surrounded by a delta antigen core and an HBsAg envelope. The requirement for HbsAg means that HDV either co-infects with HBV or superinfects chronic HBV carriers. In either case a fulminant hepatitis with high mortality is likely to occur.

Other hepatitis viruses

These are of less concern in a dental context. Hepatitis A (HAV, a picornavirus) and hepatitis E virus (HEV, a calcivirus) are spread by the fecal-oral route. HEV is more common in developing countries and can cause a fulminant hepatitis in pregnant women. Hepatitis C (HCV) and Hepatitis G (HGV) are flaviviruses that are transmitted through contaminated blood. HCV was a major cause of transfusion hepatitis before routine screening of donated blood. There is a possible association of hepatitis C with Sjögren's syndrome and with lichen planus.

Human immunodeficiency virus (HIV)

HIV is a member of the retrovirus family that are enveloped (80–120 nm in diameter) and contain two copies of positive strand RNA. Retroviruses encode an RNA-dependent DNA polymerase (reverse transcriptase) and thus replicate through a DNA intermediate that is integrated into the host cell chromosome. The HIV reverse transcriptase lacks proof reading capabilities and so the mutation rate for HIV is high, which contributes to immune avoidance and resistance to therapeutic agents (see below). HIV mainly infects cells expressing CD4 such as T helper cells, macrophages, dendritic cells and some neural glia cells. Co-receptors such as CXCR4 on T-cells and CCR5 on macrophages are also important for binding and infection. HIV causes proliferation and lysis of T-cells resulting in immune suppression, and there is also a persistent low level infection of macrophages. Immune suppression increases susceptibility to secondary infections and to tumor proliferation. In the oral cavity, HIV infection is associated with oral candidiasis (thrush), necrotizing ulcerative gingivitis (NUG) and hairy oral leukoplakia (Figure 35.2). HIV is present in body fluids such as blood, vaginal secretions and semen, however, transmission by saliva has not been demonstrated, possibly because of the anti-viral activity of some salivary molecules (Chapter 7).

Several treatment options are now available for HIV/AIDS. Reverse transcriptase inhibitors can be nucleoside analogs such as AZT, which are activated by phosphorylation, or non-nucleoside such as nevirapine. Protease inhibitors such as indinavir, block cleavage of the gag and gag-pol polyproteins which prevents virion morphogenesis. Current therapy calls for a cocktail of drugs with different mechanisms of action, termed highly active antiretroviral treatment (HAART).

36 Antibiotics and antibiotic resistance

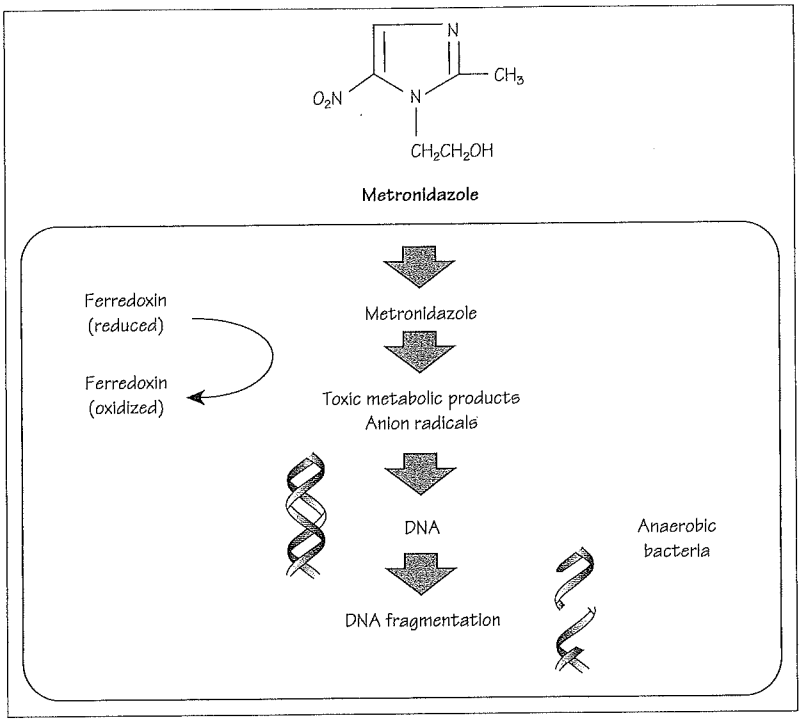

Figure 36.1 Mechanism of action of metronidazole.

Table 36.1 List of commonly-used antibiotics in clinical practice, their modes of action and some usually susceptible organisms.

Antibiotic	Principal mode of action	Susceptible organisms
Penicillin G and V, ampicillin, amoxicillin, cloxacillin	Cell wall biosynthesis (peptide cross-linking)	*Streptococcus, Neisseria, Actinomyces*
Augmentin	Cell wall biosynthesis (contains β-lactamase inhibitor)	*Neisseria, Clostridium*
Cephalosporins (cefotaxime)	Cell wall biosynthesis (peptide cross-linking)	*Gram-negatives*
Cycloserine	Cell wall biosynthesis (analog of D-alanine)	*Staphylococcus, Mycobacterium*
Vancomycin	Cell wall biosynthesis (peptidoglycan backbone)	*Gram-positives*
Aminoglycosides (streptomycin, gentamicin, kanamycin)	Protein synthesis (30S sub-unit detachment)	*Gram-negatives Enterobacteriacae, Shigella*
Tetracyclines (minocycline, doxycycline)	Protein synthesis (30S sub-unit tRNA acceptor site)	*Haemophilus, Chlamydia, Bacteroides*
Macrolides (erythromycin)	Protein synthesis (translocation)	*Streptococcus, Gram-positives bacteria*
Lincomycin, clindamycin	Protein synthesis (bind to 50S ribosomal sub-unit)	*Gram-positives*
Chloramphenicol	Protein synthesis	*Neisseria, Enterococcus*
Nitroimidazoles (metronidazole)	Nucleic acid synthesis (converted to compound that disrupts DNA helix)	*Anaerobic bacteria*

Antibiotic refers to any substance naturally produced by a microorganism that is inhibitory for another. It now also includes synthetic compounds that are antibacterial. Substances that kill sensitive organisms are bactericidal, while those that inhibit growth are bacteriostatic. The latter therefore rely on the host immune system to actually kill the infectious organism. Many bacterial species that were previously sensitive to antibiotics have acquired resistance (or reduced sensitivity). The important factor in this is the selection pressure imposed by antibiotic usage for less antibiotic-sensitive organisms. It is generally agreed, therefore, that unnecessary usage of antibiotics only fuels the development of antibiotic resistance. Although many antibiotics are taken orally, the levels of antibiotics such as penicillins and erythromycin present in saliva are much less than those achieved in serum. The reverse is true for the macrolide azithromycin. Commonly-used antibiotics are described in Table 36.1.

Antibiotics in dentistry

The most commonly prescribed antibiotics in dentistry are β-lactams (penicillins and cephalosporins), clindamycin, tetracyclines (especially local delivery in periodontal disease) and metronidazaole. Production of β-lactamases, which destroy penicillins and some cephalosporins, by streptococci is very rare. Hence streptococci generally have retained sensitivity to amoxicillin, and this is a frontline antibiotic administered by dental clinicians. However, levels of resistance are increasing amongst α-hemolytic streptococci, e.g. *S. pneumoniae*, and interspecies transfer of resistance determinants by DNA-mediated transformation is of major concern. Resistance is determined by mutations in a penicillin-binding protein (PBP2B) such that enzymic activity in cell wall biogenesis is unaffected by the antibiotic. Generally bacteria such as *P. gingivalis* remain relatively penicillin sensitive. However, in one study about 30% of *F. nucleatum* isolated from odontogenic infections were shown to produce β-lactamase enzymes. In view of this, there are recommendations for using clindamycin (active against most Gram-positives and Gram-negative anaerobes) in endodontic infections. Clindamycin is also the first-line agent in patients with penicillin allergy, but can cause antibiotic-associated colitis. Metronidazole, which also inhibits anaerobic bacteria, is particularly useful in periodontal disease (Figure 36.1). Emergence of resistance is not of major concern at the moment, partly because metronidazole is often used in combination with another antibiotic in order to counteract less anaerobic organisms. However, increasing resistance to metronidazole amongst *Helicobacter pylori* isolates is evident.

Resistance to anti-microbial agents

S. pneumoniae, and enterococci isolated from root canal infections, show high levels of resistance to cephalosporins. Cefotaxime resistance is easily transferred across α-hemolytic streptococci. The general level of resistance in the oral microbiota is not clear, but the potential for commensal bacteria to pass resistance on to more pathogenic species is of concern. A relatively high incidence of resistance to tetracycline is found in the oral microbiota. Up to 50% of oral isolates have been found to carry one or more of the tet resistance genes that confer resistance by ribosomal protection, tetracycline efflux, enzymatic inactivation, or modification of the ribosomal target. Often tetracycline resistance is linked with genes encoding penicillin, vancomycin or erythromycin resistance on the same transposable element. Tetracyclines are now used less frequently in dental practice because of the side effects of these drugs, one of which is to affect tooth color.

Transfer of anti-microbial resistance

Antibiotic resistance determinants can be spread by transformation and conjugation, and can be carried on transposons and integrons. Conjugation of plasmids and conjugative transposition can result in acquisition of multiple drug resistance genes. Oral microbial biofilms provide a means for microbes to exist in close proximity, facilitating genetic exchange between the bacteria by conjugative plasmids or by conjugative transposons. For example, high transfer frequencies of tetM, by a Tn916-like element, between *Veillonella* and *Streptococcus* have been found. These organisms grow together in an inter-nutritional relationship (Chapter 14). There is also concern about the increasingly high prevalence of antibiotic resistance genes within ingested bacteria, especially probiotic preparations. Organisms in foods carrying anti-microbial resistance determinants have the potential to transfer those determinants to the oral microbiota.

Curtailing anti-microbial resistance

New guidelines in the UK and USA do not recommend prophylatic administration of antibiotics as coverage for dental procedures in most patients. This represents a major effort to reduce what is considered the unnecessary usage of antibiotics. New antibacterial approaches, such as biomimetics for inhibition of biofilm development, natural plant products and biological interference, provide alternatives to antibiotic usage. These may help contain the development and spread of antibiotic resistant organisms. A major future challenge will be to identify potential antibiotic resistance determinants within the ~50% oral bacterial species that have not yet been cultivated. This may reveal new resistance genes for current antibiotics, as well as possibly new anti-microbials.

37 Sterilization

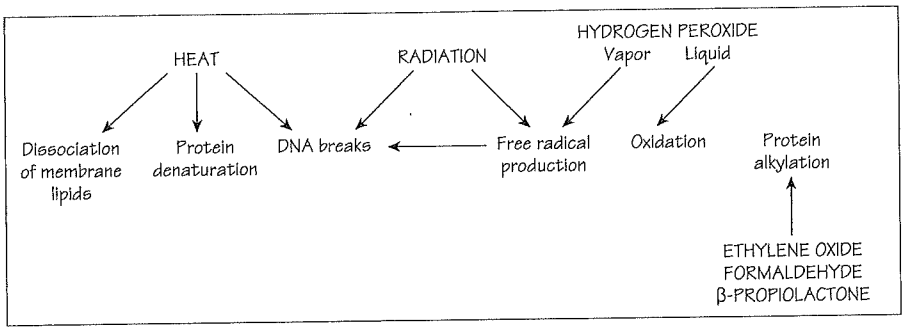

Figure 37.1 Mode of action of the major sterilization agents.

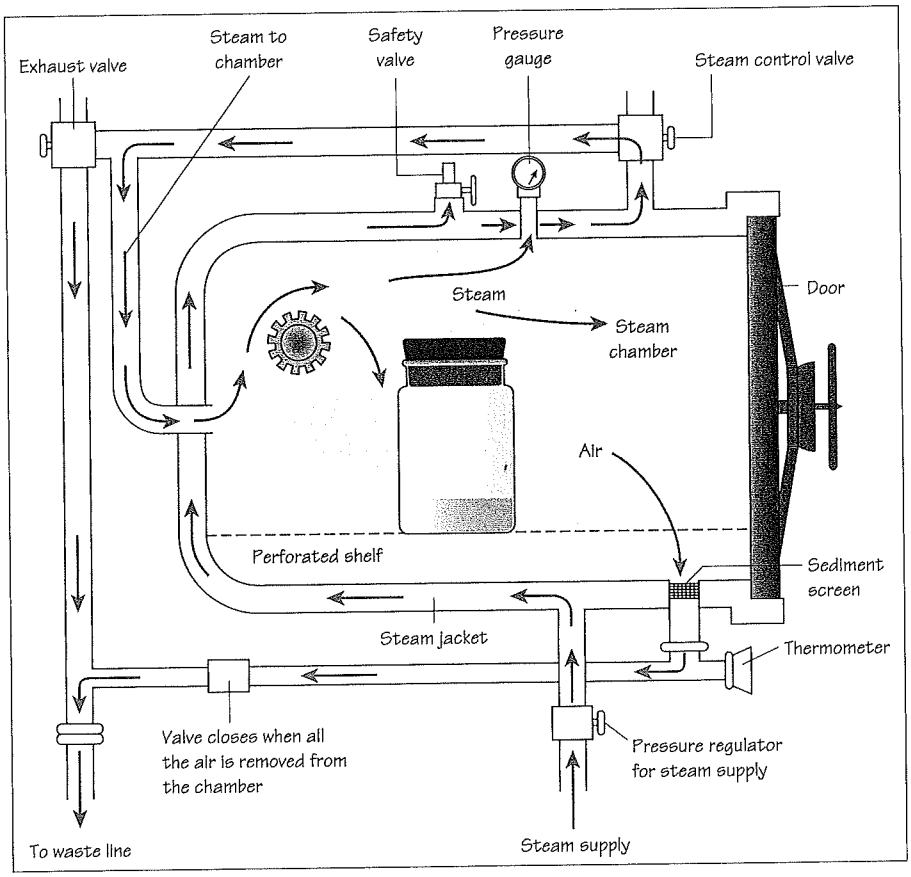

Figure 37.2 Moist heat sterilization in an autoclave.

Sterilization is the complete elimination of all forms of life, whereas disinfection is the reduction or removal of potential infectivity. Antisepsis refers to disinfection of living tissues. The mode of action of common sterilizing agents is shown in Figure 37.1.

Heat

Heat kills by denaturation of proteins, causing single strand breaks in DNA and dissociation of membrane lipids. Vegetative cells of bacteria, fungi and viruses are killed within a few minutes at 60–80°C. However, bacterial spores are more resistant to heat and sterilization requires temperatures over 120°C.

(1) Moist heat Steam is heated to 121–132°C by applying a pressure of 104 kPa (15 lb/in^2). Sterilization requires at least 15 minutes. Moist heat sterilization is accomplished in an autoclave (Figure 37.2). Parameters such as load/chamber volume ratio and flow rate of steam affect the time required for killing. It is important that no air pockets remain in the autoclave chamber as these prevent penetration of the steam. The temperature can be monitored with a thermocouple, and autoclave tape is useful to distinguish autoclaved from non-autoclaved material. However, biological effectiveness of sterilization should be monitored with a spore test. A strip or vial of *Bacillus stearothermophilus* spores is placed in the center of the load and tested for subsequent failure to germinate. Most instruments can be sterilized by autoclaving, although some metals corrode. Paper and other non-wettables cannot be autoclaved.

(2) Dry heat Hot air is heated at 160–180°C for 1–2 hours. This is not as efficient as moist heat as penetration of air is slower than steam, and lack of water makes hydrogen bonds more stable and reduces the rate of protein denaturation. Dry heat ovens are useful for materials that are damaged by water. Killing should be tested with spores of *Bacillus subtilis* which are more resistant to dry heat than spores of *B. stearothermophilus*.

Radiation

Ionizing radiation from X-rays or γ-rays with wavelengths less than 200 nm break chemical bonds and ionize molecules. Free radicals then cause damage to DNA. Radiation requires expensive equipment and shielding, so is more commonly used by commercial suppliers of disposables.

Chemicals

(1) Ethylene oxide This is an alkylating gas (transfers a CH_3 group) that causes protein denaturation. It does not require water for activity, but sterilization takes over three hours' exposure. It can be used on wrapped surgical materials such as sponges and plastics that cannot be sterilized by heat. Sterilized material should not be handled for at least 24 hours to allow any residual ethylene oxide to evaporate.

(2) Formaldehyde This is an alkylating agent. It is only effective over a narrow concentration range. A residue of pararformaldehyde can form on surfaces, which depolymerizes to formaldehyde and irritates the skin.

(3) Hydrogen peroxide At concentrations of 10–25% hydrogen peroxide is sterilizing. A more recent innovation is plasma gas sterilization using vaporized hydrogen peroxide. Radio-frequency energy is applied to create an electric field, which transforms the hydrogen peroxide vapor into a low-temperature gas plasma and generates free radicals.

(4) β-propiolactone This alkylating gas is very toxic to humans and rarely used.

(5) Chemical vapor (chemiclave) This uses a combination of formaldehyde, alcohols, acetone, ketones and steam at 138–176 kPa and 127–132°C for 30 minutes. It is useful in the dental setting as it does not corrode instruments or destroy heat sensitive materials, and is faster than dry heat sterilization. Adequate ventilation must be available to remove fumes released when the chamber is opened.

38 Disinfection

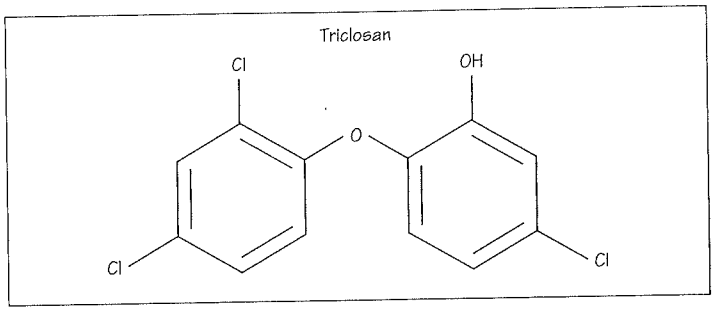

Figure 38.1 Structure of triclosan.

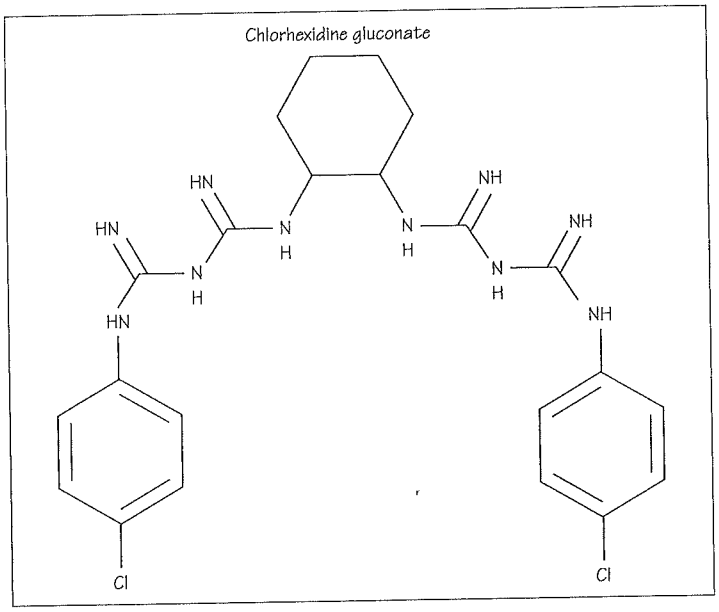

Figure 38.2 Structure of chlorhexidine.

Table 38.1 Common disinfectants and their principal mode of action.

Agent	Principal mode of action
UV light	Thymidine dimers in DNA
Laser light	Photothermal
Ultrasound	Cavitation waves
Phenols	Membrane disruption and protein denaturation
Halogens	Oxidation
Alcohols	Membrane disruption and protein denaturation
Aldehydes	Protein denaturation by alkyaltion
Surfactants	Membrane disruption
Diguanides	Membrane disruption
Oxidants	Oxidation, free radical generation and protein denaturation

The optimal disinfecting agent depends on the types of organism present, the physical nature of the material to be treated, and the amount of organic matter present. Common disinfectants are described in Table 38.1.

Physical

(1) Filtration This is useful for liquids. Pore size filters 0.22–0.45 μm remove most bacteria and fungi. Filtration does not remove viruses, mycoplasma and some small bacteria.

(2) Ultraviolet (UV) light Maximal killing by UV light occurs at 260 nm, the wavelength optimally absorbed by nucleic acids. UV light induces the formation of dimers between adjacent pyrimidine bases which block the progress of DNA and RNA polymerases. In addition, repair systems are activated, some of which are error prone and introduce mutations. The disadvantage of UV light is that it is poorly penetrating. UV light is produced by mercury vapor lamps which are used for control of airborne contamination or to disinfect surfaces when people are absent.

(3) Laser light Nd:YAG, Er:YAG, Er,Cr:YSGG, diode and KTP lasers can be used for photothermal disinfection, including in root canals, carious lesions and periodontal pockets. In addition, bacteria can be photosensitized with compounds such as tolonium chloride, toluidine blue or aluminum disulfonated phthalocyanine, and killed with low power lasers such as helium/neon or gallium aluminum arsenide lasers, by a photochemical reaction that produces reactive oxygen species, a technique termed photo-activated disinfection (PAD). Photodynamic therapy using PAD is less likely to damage host tissues.

(4) Ultrasound and sound Ultrasonic (and upper audible) waves with frequencies greater than 20 kHz will kill microorganisms. Sound waves in liquid produce cavitations which collapse violently and physically disrupt cell structures. Bacteria vary greatly in susceptibility; however, organic material is readily dislodged from contaminated surfaces. Sonic toothbrushes use sound waves around 6 kHz that create waves of pressure and shear forces that help dislodge plaque, along with cavitation waves. The long-term effects of these on host tissues are unknown.

Chemical

(1) Phenol-based compounds Phenol kills organisms primarily by disrupting lipid containing membranes, and hence is poorly active against spores and non-enveloped viruses. However phenolic compounds are active against mycobacteria due to the high lipid content of mycobacterial cell walls, and phenols are not easily inactivated by organic matter. Activity can be increased by emulsifying in detergent to improve solubility and penetration. In addition, substituting the organic ring with a halogen, alkyl or hydroxyl group increases activity, and two linked phenols (bis-phenols or diphenyls) are more active. Triclosan is a halogenated phenolic used in toothpastes and in plastics as a surface antimicrobial (Figure 38.1). Triclosan is also used as a skin disinfectant to control methicillin resistant *S. aureus*. Other examples of phenolics are Lysol and chloroxylenol (Dettol).

(2) Halogens Compounds based on iodine or chlorine are very effective disinfectants. Iodine combines irreversibly with some amino acids and is also an oxidant. It is useful for disinfecting skin or mucus membranes prior to surgery. Iodine is most active at pH less than 6, and kills most bacteria (including mycobacteria), viruses, and even shows some activity against bacterial spores. Iodine can be dissolved in alcohol (tincture) or complexed with a carrier such as a detergent (iodophor). Povidone iodine (iodine complexed with polyvinylpyrrolidone) is commonly used. Some individuals are allergic. Examples are Wescodyne and Betadine. Chlorine is generally used as a 5% solution of sodium hypochlorite. Chlorine is a strong oxidizing agent that is active against vegetative bacteria and viruses. Organic matter and alkaline detergents reduce effectiveness. Sodium hypochlorite is often used as an irrigant in root canal therapy. An example is Chlorox.

(3) Alcohols These disrupt lipid membranes and denature proteins. Activity is improved in aqueous solutions of about 70%, and activity increases with chain length, up to eight carbons when insolubility becomes a problem. Alcohols kill vegetative bacteria, some fungi and enveloped viruses. They are easily inactivated by organic matter. Ethanol (C2) and isopropanol (C3) are the most common.

(4) Aldehydes Glutaraldehyde is commonly used as a disinfectant although it is toxic to living tissues. Glutaraldehyde is optimally active at pH 8.5 which is attained by "activation" with sodium hydroxide/bicarbonate. Glutaraldehyde alkylates and denatures proteins and is active against most bacteria and viruses, and shows some activity against spores. Glutaraldehyde is easily inactivated by organic matter.

(5) Surface active agents (surfactants) These are compounds that contain both hydrophobic and hydrophilic regions and can thus solubilize lipid membranes. Among the more effective are the cationic quaternary ammonium compounds such as benzalkonium chloride, with four organic groups covalently linked to nitrogen. Activity is greatest against Gram-positives. They are easily inactivated by organic matter.

(6) Diguanides Chlorhexidine is used in mouthwash (at 0.2%, e.g. Peridex) for plaque control and at higher concentrations (2%) as a denture disinfectant (Figure 38.2). An advantage of chlorhexidine is the property of substantivity, whereby the compound binds to oral surfaces and remains active over extended time periods. Chlorhexidine is deactivated by anionic compounds, including SDS, commonly used as detergents in toothpastes. Thus, chlorhexidine mouth rinses should be used at least 30 minutes after other dental products. Chlorhexidine is active against bacteria (but not mycobacteria) and *Candida*, but is easily inactivated by organic matter.

(7) Oxidizing agents Hydrogen peroxide (3%) and potassium permanganate (1%) oxidize proteins and other cellular constituents and generate free radicals.

39 Infection control

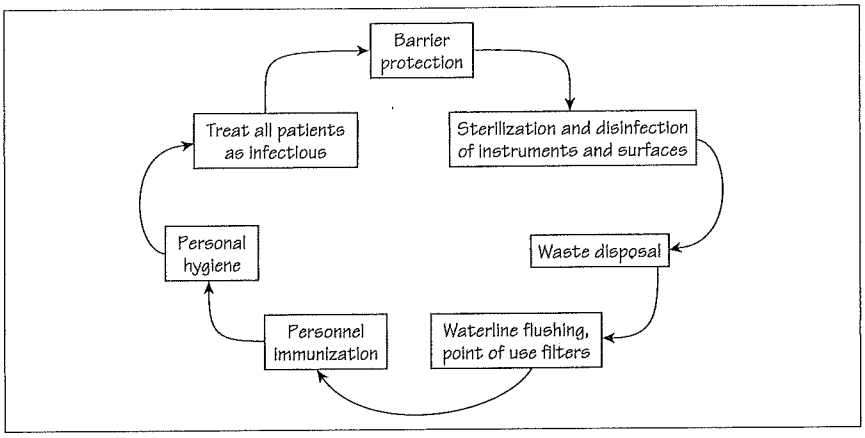

Figure 39.1 Major components of an effective infection control policy.

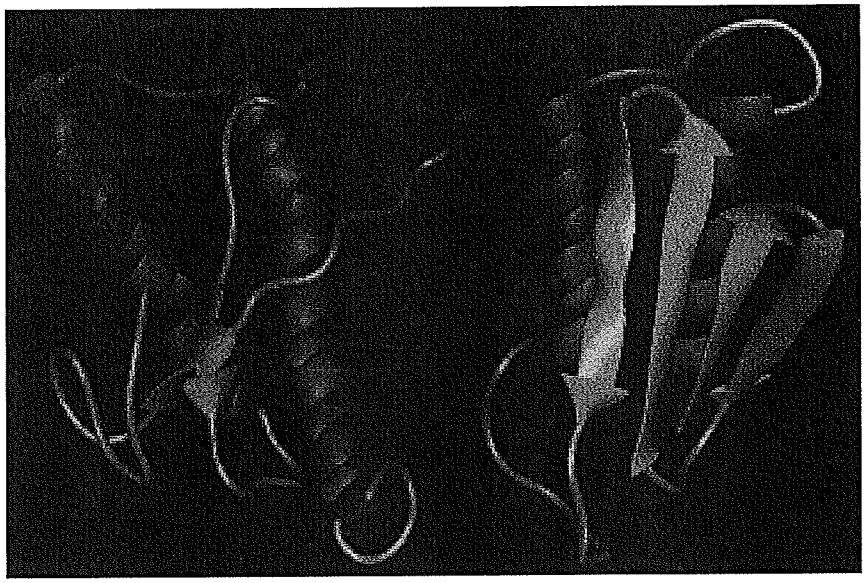

Figure 39.2 Prions. Normal prion protein (left) can change its own conformation to the misfolded infectious prion (right), and induce other prions to become abnormally folded. The misfolded prions aggregate into an amyloid structure containing densely packed beta-sheets, and damage tissues.

Infection control in the dental setting is designed to prevent transmission of infectious disease and is based on the assumption that *all patients are potentially infectious.*

There are several elements to an effective, universal infection control policy (Figure 39.1).

(1) Patient evaluation Medical history should be recorded and updated on each visit. This will reveal specific infectious diseases.

(2) Personal hygiene Hands should be washed with liquid anti-microbial soap. Open wounds should be covered. Hair should be short or tied up. Fingernails should be trimmed and jewelry should be removed.

(3) Personal protection Disposable covers should be placed on frequently handled surfaces. New gloves should be worn for each patient. Sterile gloves should be worn for surgical procedures. Heavy duty gloves should be worn when cleaning instruments. Gowns should be worn and changed at least daily. Eye shields and facemasks should be worn. A rubber dam should be used to isolate the tooth and minimize aerosol and splatter when appropriate. Sharps should be discarded in a puncture resistant sharps container.

(4) Sterilization and disinfection Instruments, materials and surfaces should be sterilized or disinfected as discussed in Chapters 37 and 38. Disposal of all clinical waste should follow local guidelines.

(5) Immunization Dental health care personnel should be immunized against hepatitis B, measles-mumps-rubella, varicella-zoster, polio, diphtheria-tetanus-pertussis and influenza (annually). In some countries the BCG vaccine against tuberculosis is recommended. A hepatitis A vaccine is available, but is not specifically recommended for dental personnel.

Prions

Prions are isoforms of a normal protein and are capable of self-propagation although they lack nucleic acid (Figure 39.2). Prion diseases have an incubation period of years and are usually fatal within one year of diagnosis. In humans, prions cause progressively fatal transmissible spongiform encephalopathies (TSEs) including kuru, Creutzfeldt-Jakob disease (CJD), and variant CJD (vCJD). There is no evidence linking dental procedures to infection with TSEs. However, such an association cannot be completely excluded. Moreover, prions are exceptionally resistant to physical and chemical sterilization. It is probably wise, therefore, when treating a patient with known prion disease to employ single-use instruments which are then incinerated, as far as is practicable. Disinfectants that can reduce the infectivity of prions include chlorine, guanidine thiocyanate and sodium hydroxide. Sterilization may require 121–132°C for 60 minutes or longer. Autoclaving at 134–138°C for 18 minutes or in six three-minute cycles followed by immersion in sodium hydroxide (2 M) or sodium hypochloride (20,000 ppm) has also been recommended.

Dental unit water lines (DUWL)

Biofilms form readily on the inside surfaces of DUWL. Bacteria can be shed from these biofilms and released in aerosols. Most of the bacteria in these biofilms are harmless (in immunocompetent individuals) environmental organisms, originating from the water source. However, opportunistic respiratory pathogens such as *Pseudomomas aeruginosa*, mycobacteria and *Legionella* have also been detected, as have oral bacteria that presumably originate from backflow from dental apparatus. While the risk of disease from bacteria in DUWL is small, American Dental Association guidelines are that water from DUWL contains fewer than 200 cfu/ml. To achieve these levels, DUWL should be flushed for two minutes at the beginning of each day and for 30 seconds between patients. DUWL should also have independent water reservoirs and be fitted with point of use filters to prevent backflow.

40 Bioterrorism

Table 40.1 Highly infectious or pathogenic microorganisms that have been considered bioterrorism agents, the diseases and symptoms, exposure and dosage, and treatment or prevention.

Agent	Disease	Transmission	Exposure	Infectious dose	Incubation/onset	Symptoms	Treatment and prevention
Bacterial *Bacillus anthracis*	Anthrax	Infected animal tissue	Skin	Unknown	2–5 days	Cutaneous: insect bite-like mark developing into blister/skin necrosis. Fever and headache	Numerous effective antibiotics available (intravenously for inhalational anthrax) Vaccine available to high risk workers
		Contaminated soil, animal hides	Inhalation	2.5–50 k cells		Inhalational: sore throat, fever, difficulty breathing, shock/meningitis or pneumonia	
		Contaminated undercooked meat	Ingestion	Unknown		Gastrointestinal: sore throat, loss of appetite, vomiting/fever, fluid filled abdomen – shock/death	
Yersinia pestis	Plague (pneumonic, bubonic, septicemic)	Exposure to infected animals	Inhalation	100–20,000 cells	Pneumonic: 2–4 days Bubonic: 1–8 days	Pneumonic: severe cough, bloody sputum, difficulty breathing Bubonic: fever/malaise, buboes, headache, seizures	Antibiotics available, must be given within first 24 hours of infection Vaccine available to high risk workers
		Flea bites	Skin	Unknown	Septicemic: 2–6 days post pneumonic or bubonic infection	Septicemic: abdominal pain, blood clotting problems, low blood pressure, vomiting, organ failure	
Francisella tularensis	Tularemia (pneumonic, ulceroglandular, oropharyngeal, typholdal)	Contaminated dust	Inhalation	5–10 cells	3–5 days	Pneumonic: cough, chest pains, difficulty breathing	Effective antibiotics available Vaccine not currently available
		Handling infected animals	Skin	10–50 cells		Ulceroglandular: ulcer at site of infection, swollen lymph glands, fever/chills, headache, exhaustion	
		Arthropod bite				Oropharyngeal: vomiting	
		Contaminated food or water	Ingestion	10^6–10^8 cells		Typholdal: (rare) fever, extreme exhaustion, weight loss	
Burkholderia pseudomallei	Melioldosis	Contaminated soil or water	Inhalation	Unknown	2–9 days	Pneumonic: fever, headache, chest pains, mild bronchitis to severe pneumonia	Numerous effective antibiotics available No vaccine
		Handling infected animals	Skin			Cutaneous: abscess/ulcer at site of infection, regional lymphadenopathy	
						Chronic infection may affect the heart, brain, liver, kidneys and eyes	
						Septicemia/bacteremia may occur in immunocompromised individuals	
Brucella spp.	Brucellosis	Contaminated meat/dairy products	Ingestion	Unknown	5–60 days	Undulant fever, chills, weight loss, headache, abdominal/back pain, swollen glands; can become chronic	Effective antibiotics available No human vaccine
			Inhalation (rare; mainly vets, slaughterhouse workers and lab workers)	10–100 cells			
		Handling infected animals	Skin	Unknown			
Toxins *Clostridium botulinum* toxin	Botulism (flaccid paralysis)	Food borne	Ingestion	Unknown in humans; estimated to be between 1.2–12 ng/kg	12–72 hrs by any route of exposure	Dysphagia, blurred/double vision, dry mouth, nausea, abdominal cramps, muscle weakness, difficulty breathing/respiratory failure, descending paralysis (flaccid paralysis)	Anti-toxin available May require surgical intervention Intensive care
			Inhalation (in weaponised or aerosolised form)				

Table 40.1 (*Continued*)

Agent	Disease	Transmission	Exposure	Infectious dose	Incubation/onset	Symptoms	Treatment and prevention
Clostridium perfringens (epsilon toxin)	Clostridial myonecrosis (gas gangrene)	Contaminated water or soil	Inoculation into open wounds	Undefined for humans	10–12 hrs (after ingestion of whole cells)	Gas gangrene: tachycardia, moderate/high fever, severe pain around site of injury/infection, blisters/air under skin, drainage from tissues; can result in shock and organ failure	Gas gangrene: intravenous antibiotics or surgical debridement
	Food poisoning	Food borne	Ingestion		Onset following ingestion/inhalation of toxin is unknown	Food poisoning: vomiting and diarrhea	Food poisoning: self-limiting, usually not treated
			Inhalation (in weaponised or aerosolised form)				
Staphylococcal enterotoxin B	Food poisoning	Food borne	Ingestion	Estimated to be 20 ng/kg	3–12 hrs by any route of exposure	Food poisoning: nausea, vomiting and diarrhea	Food poisoning: self-limiting and not usually life-threatening.
			Inhalation (in weaponised or aerosolised form)			Inhalational: sudden onset of fever, chills, headache, non-productive cough, chest pain, respiratory distress, hypotension, shock/death	
Viral							
Orthopox virus (variola)	Smallpox	Person to person (virus is confined to human host only)	Inhalation	Estimated to be 10–100 virions	10–17 days	High fever, fatigue, severe headache, backache, malaise, raised pink rash (pus-filled lesions; day 8–9) vomiting, diarrhea, excessive bleeding, delirium	Vaccinia based live vaccine available
			Contact with skin lesions or secretions				No effective anti-virals
Filoviruses (Ebola)	Hemorrhagic fever	Person to person (natural reservoir unknown)	Contact with infected blood, secretions or organs	Undefined for humans; less than ten virions for non-human primates	5–12 days	Fever, sore throat, weakness, severe headache, joint/muscle ache, vomiting, dehydration, dry cough, rash, liver and kidney failure, inability to clot/internal and external hemorrhage, death in second week of infection (intractable shock)	No vaccine No effective anti-virals
Arenaviruses (Lassa)	Hemorrhagic fever	Person to person	Inhalation	Unknown	7–21 days	Fever, chest pains, sore throat, back/abdominal pain, cough, vomiting and diarrhea, conjunctivitis, facial swelling, mucosal bleeding.	No vaccine No effective anti-virals
		Handling infected animals	Skin			Neurological symptoms may include hearing loss, tremors and encephalitis	
Alphaviruses (Venezuelan equine encephalitis virus)	Encephalitis	Mosquito bite	Skin	One virion	2–6 days	Low grade/moderate fever, headache/retro-orbital pain, nausea/vomiting, dehydration leading to hypotension, altered mental status, paralysis, coma	No vaccine No effective anti-virals
			Inhalation (in weaponised or aerosolised form)				

Biological agents (Table 40.1) have been used in war to incapacitate and kill for hundreds of years. An early recorded example in which biological warfare was employed dates back to the fourteenth century when during a conflict between Mongols and Italian traders the corpses of plague victims were catapulted into the city of Kaffa, resulting in a devastating outbreak of the plague. Similarly in 1763, following numerous hostilities between the British and Native Americans, smallpox-laced blankets were distributed to the Native Americans under the guise of a gesture of goodwill, leading to outbreaks of smallpox. The development and employment of biological weapons became more sophisticated and during both World Wars numerous bacterial, viral and toxin based weapons were developed and tested. This continued into the Cold War which saw extensive stockpiling of biological weapons, followed by the introduction of treaties to encourage disarmament.

Anthrax

The use of anthrax as a biological weapon emerged during the First World War, initially by Germany and later the UK, as a means of killing livestock and subsequently causing starvation. German agents planned anthrax and glanders attacks in a number of countries during World War I. World War II saw further development towards a weapon designed to incapacitate and kill humans. Extensive testing of anthrax bombs was carried out on Gruinard Island (off the coast of Scotland). *Bacillus anthracis* spores persisted in the soil for thirty years, after which time the land was decontaminated using a mixture of seawater and formaldehyde. In 2001, letters containing anthrax spores were delivered to news media offices and the US Congress, killing five people.

Botulism

Clostridium botulinum toxin was developed as a biological weapon over 60 years ago in Japan. During the Cold War years the USSR produced many thousands of liters of botulinum toxin, which was later destroyed as part of a disarmament program. The toxin can be produced in abundance and with relative ease; approximately 19,000 liters was produced by Iraq in the 1980s, much of which was incorporated into missiles and bombs. This amount is enough to kill the entire human population on earth.

Smallpox

Smallpox is regarded as the greatest threat if acquired by dissident organizations and used as a biological weapon. Only two repositories exist in the world, in Atlanta (USA) and Novosibirsk (Russia). If aerosolised, smallpox could easily be disseminated throughout a population and would spread rapidly from person to person. Worldwide reserves of the smallpox vaccine are limited, and during the 1970s when endemic smallpox was officially eradicated stringent vaccine programs were relaxed, meaning that there is a potentially vulnerable population.

Salmonella

Although not considered a significant bioterrorism agent, *Salmonella* was used in the first confirmed bioterrorism attack in the USA. In 1984, in an attempt to control local elections, followers of the Bhagwan Shree Rajneesh infected salad bars in The Dalles, Oregon, with *Salmonella enterica* Typhimurium. Over 700 people contracted food poisoning, but there were no fatalities.

Biological Weapons Convention

The Biological Weapons Convention was built upon the Geneva protocol of 1925, and was implemented in 1975. This prohibits the development, stockpiling and use of biological and toxin-based weapons. Initially 22 governments joined, and this number has risen in subsequent years. Consequently, numerous disarmament programs have been implemented worldwide.

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Oral Microbiology at a Glance

Richard J. Lamont and Howard F. Jenkinson

Oral Microbiology at a Glance is the new title in the highly popular *at a Glance* series. It provides a concise and accessible introduction and revision aid. Following the familiar, easy-to-use *at a Glance* format, each topic is presented as a double-page spread with key facts accompanied by clear diagrams encapsulating essential information.

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- Oral microbial origins of health or disease
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- Local and systemic extensions of oral infections
- Sterilization, disinfection, infection control methods, and bioterrorism

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Richard J. Lamont is Professor of Oral Microbiology at the University of Florida at Gainesville.

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Cover image shows a fluorescent confocal image of a multispecies oral biofilm. Image provided by Masae Kuboniwa, Osaka University.

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