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Respiratory tract infections and pneumonia

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Many organisms cause respiratory tract infections, and not all can be discussed in this review. Although many respiratory tract infections are nonlife-threatening, they are associated with a significant level of morbidity. The oral cavity acts as a portal of entry and as a reservoir for many bacterial, viral and fungal species. Here these microorganisms gain access to interlinked airways, composed of mucosal epithelia, which collectively comprise the respiratory tract. This large mucosal surface area acts as a reservoir for infectious particles that are inhaled. There is good evidence to show that improved oral hygiene and frequent professional healthcare can reduce the progression or occurrence of respiratory diseases, especially amongst high-risk patient groups (4).

A formidable host defence system protects the lower respiratory tract. Organisms must first negotiate the nonspecific mechanisms in the upper respiratory tract, which include a mechanical washing mechanism, the cough response, anatomic barriers and the mucociliary tree. Additional barriers in the lower respiratory tract include the frequent branching of the pulmonary tree (to effect aerodynamic filtration) and the restrictive size (0.3–5.0 μm) of the alveolus opening. Once microorganisms reach the alveolus they must resist the activity of phagocytes, immune response cells and other antimicrobial defence factors. If these microorganisms can overcome or subvert the innate host defences, such as the mucociliary system, bronchoconstriction, cough reflex or acquired immunity (mucosal immunoglobulin A), then the infectious process can begin. Infections may be acute or chronic, and lower respiratory tract infections may be limited to the bronchial tree (bronchitis) or the lung alveoli (pneumonia), or involve both (broncho-pneumonia).

Clinical syndromes

Common cold

Both viruses and bacteria cause pharyngitis and tonsillitis, but approximately 70% of acute sore throats are viral. Pharyngitis often occurs as part of the common cold or influenza, and is also caused by Epstein–Barr virus, herpes simplex virus and certain Coxsackie A viruses (herpangina, and hand, foot and mouth disease). The clinical presentation of upper respiratory tract infections is influenced by the infecting virus, but is also greatly affected by the age, physiological state and immunological experience of the host. This makes it difficult to define precisely the syndromes of 'common cold' and 'flu', because of the wide variation in severity, duration and types of symptoms.

Prevalence

The common cold is a very prevalent infection in humans, with adults having two to five colds each year and schoolchildren suffering between seven and 10 colds per year (34).

Microbiology

More than 200 different types of virus are responsible for human upper respiratory tract infections (34). The most common are rhinoviruses (30–50% of all colds), followed by coronaviruses (10–15% of all colds). Influenza viruses cause 5–15% of colds.

Pathophysiology

The symptoms of the common cold are a result of viral infection of the upper airway. The incubation

period is 2–4 days. A flow of virus-rich fluid from the nasopharynx is induced by the infection and, when sneezing is triggered, large numbers of virus particles are expelled into the air. Transmission by aerosol is therefore important but these viruses are also spread via contaminated hands. It is thought that the immune response to infection is the main factor in causing symptoms, in particular the release of a complex mixture of pro-inflammatory cytokines and mediators. Bradykinin is believed to have a major role in generating the local symptoms (e.g. sore throat) (80), whilst cytokines are responsible for the systemic symptoms, such as fever (27). A detailed review of the pathophysiological mechanisms underlying the common cold has been published recently (34).

Signs and symptoms

The common cold is typically a short, mild illness. Early symptoms include headache, sneezing, chilliness and sore throat. Later symptoms comprise nasal discharge, nasal obstruction, cough and malaise. The severity of symptoms increases rapidly to peak in 2–3 days, with a mean duration of symptoms of 7–10 days.

Diagnosis

The diagnosis is made clinically.

Treatment

No specific treatment is available for the common cold, and management focuses on symptom control. There is a large literature on both prevention and management of the common cold, but many of the published studies lack scientific rigor. The area has been reviewed recently (90).

Bronchitis

Acute bronchitis

Acute bronchitis is an inflammatory condition of the tracheobronchial tree that is characterized by cough without pneumonia (109). In otherwise healthy patients, the disease is often a mild complication of upper respiratory tract viral infections. The degree of damage to the respiratory epithelium varies with the infectious agent, and secondary bacterial infection with *Streptococcus pneumoniae* and *Haemophilus influenzae* (see below) may also play a role in pathogenesis. The disease often presents with a cough that is initially dry and painful, but later productive with the expectoration of greenish sputum. Treatment is largely symptomatic if the disease is mild. Antibiotics are frequently prescribed, although their value is uncertain unless the identity and sensitivity of the causative agent is known.

Chronic bronchitis

In chronic bronchitis, cough and excessive secretion of mucus are present in the tracheobronchial tree but are not attributable to specific diseases such as tuberculosis or asthma. Chronic bronchitis is defined as cough and phlegm for at least 3 months every year for at least 2 years (106). Etiological factors include infection, cigarette smoking and inhalation of toxic dust or fumes. Whilst infection does not initiate the disease, it is significant in prolonging it and producing acute exacerbations that cause progressive lung damage and may lead to death. Both bacteria (e.g. *H. influenzae, S. pneumoniae, Moraxella catarrhalis*) and viruses (e.g. influenza, coronaviruses) are commonly associated with acute bouts of infection. Treatment is complex, dependent on the severity of exacerbations and the causative agents.

Pneumonia

In pneumonia, the lung alveoli become filled with edema fluid, accompanied by inflammation in the lung parenchyma. Bacteria may enter the lungs by inhalation or through aspiration of oropharyngeal fluid. The latter is thought to be the most common route for bacterial pulmonary infections. Aspiration pneumonia is prevalent in community-acquired pneumonia as well as in hospital-acquired pneumonia (89). Pneumonia may be classified as lobar (consolidation of lung tissue limited to one lobe or segment), broncho-pneumonia (consolidation scattered throughout the lung but concentrated mainly at the bases) or atypical (patchy consolidation).

Common clinical features of pneumonia include fevers, rigors, malaise, shortness of breath, cyanosis, productive cough and lung consolidation. Most cases (about 90%) of pneumonia are acquired in the community, and less commonly in hospitals, although ventilator-associated pneumonia is an important problem (82). A wide range of microorganisms may be implicated. In otherwise healthy individuals, most pneumonia is caused by *S. pneumoniae,* viruses or *Mycoplasma pneumoniae*. Patients with underlying disease may develop community-acquired

pneumonia from a wider range of organisms, including *Staphylococcus aureus, H. influenzae, Klebsiella pneumoniae,* or *Pneumocystis jiroveci*. Hospital-acquired pneumonias are commonly associated with aerobic or facultative gram-negative bacilli, or with *S. aureus*, and can be transmitted via the contaminated hands of healthcare workers, or through instruments and equipment.

Specific infections

Streptococcus pneumoniae

Prevalence

S. pneumoniae (also designated pneumococci) is a leading cause of morbidity and mortality worldwide, especially in the very young, the very old and the immunocompromised (75, 77). In Scotland, the overall incidence of invasive pneumococcal disease is 11 cases per 100,000, with 21 per 100,000 in infants under 1 year of age and 45 per 100,000 in elderly patients (> 65 years of age) (62). There are more than 90 recognized serotypes of *S. pneumoniae*, 23 of which cause 96% of the cases of invasive pneumococcal disease (70). Serotype 14 pneumococci are most prevalent, accounting for 18.5% of the cases of pneumococcal disease in England and Wales from 1995 to 1997 (93). It has also been recognized that important relationships exist between common serotypes of *S. pneumoniae* and emerging resistance to erythromycin (23).

Microbiology

S. pneumoniae is a gram-positive coccus, normally appears in pairs and is α-hemolytic. Both George Sternberg and Louis Pasteur independently discovered the 'pneumococcus' in 1881. It was an important organism in the early experiments which demonstrated that genetic material consists of DNA (48).

Pathophysiology

Pneumococcal pneumonia occurs when pneumococci are aspirated into the lungs but not cleared. Infection activates complement proteins, stimulates cytokine production and attracts neutrophils. However, pneumococci adhere to and invade different epithelial and endothelial cells using cell-specific mechanisms for internalization (1, 30). The polysaccharide capsule is significant for the pathogenesis of the infection because it renders the pneumococcus resistant to complement-mediated opsonophagocytosis and plays a key role in systemic dissemination (3). Variation in capsule morphology has been associated with reduced expression of the capsular polysaccharide (58). In addition to the capsule, pneumococci employ other significant virulence factors, such as pneumolysin, neuraminidase, hyaluronic acid, autolysin, hydrogen peroxide, choline-binding protein A and protective antigen (PspA) (25).

Signs and symptoms

Symptoms of pneumococcal pneumonia can begin suddenly with severe chills, which are usually followed by high fever, cough, shortness of breath, rapid breathing and chest pains. A serious complication of pneumococcal infection is meningitis, presenting as severe and persistent headache, stiff neck, nausea and vomiting.

Diagnosis

Rapid, noninvasive diagnosis of pneumococcal pneumonia can be carried out by performing a sputum gram stain (6), although this is dependent on obtaining a representative sample from the patient. Urinary antigen tests have been developed as an alternative, early noninvasive diagnostic method but have limited sensitivity despite high specificity (86). Microbiological diagnosis requires culture of the organism. Pneumococci will display α-hemolysis on blood agar within 48 h when incubated under aerobic conditions at 35 °C. Optochin sensitivity distinguishes *S. pneumoniae* from possible viridans group streptococci. Serotyping is conducted using co-agglutination methods (94). In addition to these methods, multilocus sequence typing can be conducted for enhanced surveillance of the relationships between sequence types and serotypes of pneumococci (114).

Treatment

The increasing prevalence of resistance to penicillin and other drugs among pneumococci has considerably complicated the empirical treatment of community-acquired pneumonia. Penicillin resistance has become widespread globally. Resistance to other classes of antibiotics traditionally used as alternatives in the treatment of pneumococcal infections has also increased markedly during recent years. In some areas of the USA, Europe and East Asia a prevalence of macrolide resistance as high as 35% has recently been reported (45, 76). Serotype 14 is one of the most common serotypes of invasive pneumococci and its resistance to erythromycin has been shown to be highly related to clonal type (24).

To combat developing resistance, vaccines have become important in the prevention of invasive pneumococcal disease. A 23-valent polysaccharide vaccine is available, but because it elicits a T-cell-independent response, it is ineffective in children under 2 years of age (38). The licensed 7-valent conjugate vaccine contains the polysaccharide of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to a nondiphtheria variant carrier protein and induces high antibody concentrations to these serotypes. Initial studies have assessed the molecular epidemiology of the pneumococcus prior to vaccine implementation and immediately afterwards (110). These studies have revealed that the use of the vaccine has reduced the burden of disease in young children and may be effective in preventing disease in adults by conferring herd immunity to the unvaccinated population (71).

Haemophilus influenzae

Prevalence

The environmental niche of the respiratory tract provides a favourable environment for *H. influenzae* colonization and the potential for infection. Of the six capsular antigenic types of *H. influenzae*, capsulate strain type b is responsible for more than 90% of human infections and is an important cause of pneumonia and meningitis, although many nonencapsulated strains also cause disease. In developing countries such as Bangladesh, Chile and The Gambia, deaths from *H. influenzae* pneumonia greatly outnumber deaths from meningitis. The disease burden of *H. influenzae* is estimated at 3,000,000 serious illnesses per year and 386,000 deaths (111). The majority of victims are less than 5 years of age, and following the decline of maternal antibodies, children 4–18 months of age are most vulnerable. Epidemiologic studies have documented that *H. influenzae* nasopharyngeal colonization rates vary between 25 and 80% in humans (103), with higher rates for children than for adults. Anticapsular antibodies are good opsonins, allowing bacteria to be phagocytosed and killed. These antibodies are T-cell independent and are not produced until the child is 2–3 years of age.

Microbiology

H. influenzae is a small gram-negative rod, frequently coccobacilliary. It is a nonmotile, nonspore-forming facultative anaerobe. There are six antigenically distinct capsular types recognized (a-f), and also nonencapsulated, nontypeable organisms. The presence or absence of a polysaccharide capsule determines the morphology of its colonies and its pathogenicity. Encapsulated bacteria secrete a capsular polymer that makes the colony appear umbilicated. *H. influenzae* requires hematin (X factor) and NADP (V factor) for growth and can be differentiated from other species by culture on enriched media containing these factors.

Pathophysiology

H. influenzae is primarily transmitted by respiratory droplets from the infected individual or a carrier and adapts well to limited ecological niches in humans. *H. influenzae* is less likely to rely on environmental sensing strategies (46); it uses fitness selection and clonal expansion of those population members that express phenotypic characteristics important for survival. Selective pressures include host immune responses (13), nutritional resources in the respiratory mucosa (104) and bloodstream (50), host factors for bacterial adherence (83), cellular penetration and host-to-host transmission (10). *H. influenzae* will also employ virulence factors such as the immunoglobulin A protease, pili, endotoxin and outer membrane to establish infection.

Signs and symptoms

Symptoms of *H. influenzae* infection include those typically associated with pneumonia, such as fever, a cough that produces sputum, and shortness of breath. Diagnosis may be difficult because of these nonspecific symptoms. Complications include meningitis, sepsis and arthritis.

Diagnosis

Diagnosis of *H. influenzae* in the laboratory requires culture on chocolate agar to provide X and V factors for these fastidious organisms. Collection of specimens for blood culture can be difficult, especially in very young children. This has highlighted the need for nonculture methods such as the polymerase chain reaction (PCR). BexA is an appropriate gene for the detection of encapsulated *H. influenzae* (types a to f), as bexA is a conserved capsular gene involved in exportation of capsular material (28).

However, in many countries where vaccination is routine, nonencapsulated strains are the predominant cause of disease. Precise methods for characterizing isolates of bacterial pathogens are required to understand the transmission, track the spread of virulent or antibiotic-resistant strains and to monitor the impact of vaccination on the bacterial

populations (73). Multilocus sequence typing, a nucleotide sequence-based approach for the unambiguous characterization of isolates of bacteria, offers precise and accurate characterization of encapsulated and nonencapsulated *H. influenzae*, which will be of value for continuing surveillance.

Treatment

H. influenzae infection is entirely preventable because *H. influenzae* type b vaccines are highly effective and have been available since the early 1990s in the majority of the developed world. Systematic vaccination has virtually eliminated *H. influenzae* type b in industrialized nations, with disease resulting only from other capsular types or vaccine failures. Prior to vaccine availability in the USA, 40–200 per 100,000 children less than 5 years of age became infected with *H. influenzae* type b; this has now decreased to 1.3 per 100,000 (figures are per year) (15). Eighty-nine countries have an infant vaccination scheme, and 92% of these populations were vaccinated by 2003.

However, vaccination has not fully resolved the problem of *H. influenzae* infection in humans. There is only 42% coverage in developing countries and 8% coverage in the least developed countries (sub-Saharan Africa) (102). Political and financial issues prevent blanket immunization, as the cost of the Hib vaccine is approximately seven times higher than measles or polio vaccines. Thus, meningitis remains a serious problem in children under 7 years of age in areas where the Hib vaccine is not used. Similarly, strains of nontypeable *H. influenzae*, for which vaccines are not available, continue to pose a problem for adults (102) and it is essential that antimicrobial drugs are used with care to avoid significant emergence of resistance (85, 102).

Legionella pneumophila

Prevalence

Ninety per cent of all legionellosis is associated with aerosol-generating devices such as water-cooling towers, showers and spa pools (41). The key reservoir is fresh water (42) with the exception of *Legionella pneumophila*, which is found in potting soil (96). It remains a highly under-reported organism, but it has been estimated that 8000 to 18,000 cases of legionella infection occur each year in the USA (68). The reasons for under-reporting are that *L. pneumophila* is not part of the usual spectrum of diagnostic tests and current empirical therapy negates the requirement to identify the etiology. In many cases, fear of litigation would prevent this bacterium from being reported.

Legionellosis follows no trend or seasonal predilection, although there is a twofold increase in cases associated with cooling towers in the summer months (9). Legionellosis, or Legionnaire's Disease, is so-called in reference to the first recorded outbreak, in a travelling group of members of the American Legion (43). As this organism is mainly associated with travel, detection of outbreaks is difficult. Relatively low attack rates, long incubation periods and dispersal of affected persons away from the source of infection all contribute to the under-reporting of this disease.

Dental unit water lines in dental surgery equipment are at risk of developing biofilms, an environment conducive to colonization with *Legionella* species (100). *L. pneumophila,* together with other *Legionella* species, has been detected in dental unit water in several studies in the USA, Austria, England and Germany (100). For example, in one American study, *L. pneumophila* was detected in 8% of water samples taken from the dental units in 28 offices distributed over a four-state area (2). There is a theoretical risk of infection during dental treatment, and indirect evidence from published serological studies of dental staff tends to support this conclusion. However, there is no scientific evidence to date that water from a dental unit has ever caused Legionnaire's Disease.

Microbiology

L. pneumophila is a gram-negative, catalase-positive bacterium that possesses polar or lateral flagella, which allow these rod-shaped organisms to be motile. There are 48 identified species, comprising 70 distinct serogroups within the *Legionella* genus. There are 15 serogroups of *L. pneumophila*, and 79% of the confirmed cases of *L. pneumophila* are caused by serogroup 1 (7).

Legionellae are capable of intracellular growth in host cells. They will grow at 25–42 °C, but optimally at 35 °C (56). Legionellosis is attributed to man-made water environments with increased ambient temperatures that upset the balance of protozoa and bacteria. Legionellosis may be described as a disease that has resulted from human intervention.

The nutrients required for growth are not found in the usual water environments. Thus, legionellae survive as intracellular parasites of free-living protozoa (e.g. ameba, ciliated protozoa and slime mold) (40).

Pathophysiology

Microscopic observations have shown that legionellae multiply intracellularly in protozoa and human macrophages. Horwitz's experiments demonstrated cell entry by phagocytosis, but the phagosome does not fuse with the lysosome and thus the bacteria are protected. The bacteria initiate multiplication and become motile within the cell, eventually leaving it by lysis or remaining encysted. Stationary-phase genes are expressed to facilitate infection into the new host cell (54).

The macrophage infectivity potentiator (*Mip*) gene encodes a surface protein required for the efficient infection of host cells. The exact mechanism is not known, but *mip* proteins exhibit peptidyl-prolyl-cis/trans isomerase activity (19). Legionellae use type IV secretion systems to encode factors involved in the assembly and activation of conjugal transfer of plasmid DNA (99). These operons may deliver virulence factors required for entering the host cell and initiating the infectious process.

Signs and symptoms

There are three key syndromes associated with legionellae.

- Legionnaire's Disease: severe pneumonia and multisystem failure (43). The clinical symptoms of initial Legionnaire's Disease (e.g. fever, nonproductive cough, headache, myalgias) are very difficult to distinguish from other pneumonia-causing organisms.
- Pontiac Fever: a self-limiting, flu-like illness (47).
- subclinical seroconversion: asymptomatic (11).

Diagnosis

Legionellae can be identified by growth on buffered charcoal yeast-extract agar, appropriate colony morphology and the requirement for L-cysteine. Isolates that react with specific antisera against known *Legionella* species are confirmed legionellae. Species within *Legionellacae* can be distinguished by biochemical analysis, fatty acid profiles, protein-banding patterns, serology and nucleic acid analysis (8). The gold standard diagnosis of legionellosis remains culture from serologically positive patients: specificity is 100% and sensitivity 60% (35). Legionellae can be isolated from blood, lung tissue, lung biopsy specimens, respiratory secretions (sputum, bronchial alveolar lavage, bronchial aspirates) and stool samples (35).

Legionellae can be detected in respiratory secretions by direct fluorescence antibody for several days after the start of antimicrobial therapy. Urine antigen detection will permit outbreaks to be recognized and allow a rapid public health response (65). The capture antibodies used in the majority of assays are specific for *L. pneumophila* serogroup 1, but this may miss up to 40% of the cases of legionellosis, impacting on the number of reported cases. The PCR is one of the few diagnostic tests with the potential to detect infections caused by all known *Legionella* species, by detecting the 16S rRNA gene (66) or the *mip* gene (67).

Treatment

Empirical therapy for patients hospitalized with community-acquired pneumonia should include coverage for Legionnaire's Disease (6). Erythromycin is the drug of choice, although azithromycin and levofloxacin are licensed by the US Food and Drug Administration and are considered preferable (36).

Tuberculosis

Prevalence

Tuberculosis has affected humans for at least 10,000 years, but despite advances in modern medicine, it still causes more deaths worldwide than any other infectious disease. According to the World Health Organization report in 2007 on Global Tuberculosis Control (http://www.who.int/tb/publications/global_report/2007/pdf/full.pdf), the worldwide epidemic is on the threshold of decline, but in 2005 there were an estimated 8.8 million new cases of tuberculosis and 1.6 million people died of tuberculosis, including 195,000 with human immunodeficiency virus (HIV). Of these new cases, 7.4 million were in Asia and sub-Saharan Africa. It is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis* and it is fortunate that only about 10% of those infected actually develop tuberculosis during their lifetime. However, this percentage increases if high-risk factors are involved. For example, the risk for a person infected with HIV of developing tuberculosis changes from 10% in a lifetime to 8% per year of life.

Microbiology

Tuberculosis is caused by the obligate aerobic bacillus *M. tuberculosis*. This is one of the so-called *M. tuberculosis* complex of six species, including *Mycobacterium bovis*, the principal cause of tuberculosis in cattle and many other mammals. Members of the *M. tuberculosis* complex (also known as tubercle bacilli) are nonmotile, nonsporing, noncapsulate straight or slightly curved rods, about

3 × 0.3 μm (length × width) in size. They grow on a wide range of enriched culture media, the most widely used of which is Lowenstein–Jensen medium. Human tubercle bacilli produce visible growth on Lowenstein–Jensen medium in about 2 weeks, although on primary isolation from clinical samples, growth may take up to 8 weeks to appear. The optimal growth temperature for tubercle bacilli is 35–37 °C, and they fail to grow at temperatures of 25 °C or less or 41 °C or more.

Pathophysiology

M. tuberculosis is spread between humans by aerosols. Cases of occupational tuberculosis can occur in healthcare workers following exposure to patients with known active or unsuspected pulmonary infection with *M. tuberculosis* (74). Although transmission of tuberculosis to members of the dental profession has not been a particular problem, care is required. Patients with active disease should be treated in a hospital environment where isolation facilities exist. Patients become noninfectious within 2 weeks of the initiation of effective treatment.

Early in the course of the disease, cells of *M. tuberculosis* are engulfed by phagocytes, but the organism survives intracellular digestion and can even multiply within and destroy the phagocytes. However, the development of cell-mediated immunity produces 'activated' macrophages that can destroy the bacterium. The course of the disease is highly dependent on the individual host response. Most frequently, infection leads to asymptomatic cases of *M. tuberculosis* that are radiograph negative and skin-test positive, but in whom small numbers of *M. tuberculosis* may remain viable and be re-activated at a later date. Some infections lead to symptomatic primary tuberculosis that starts as exudative lesions in the lower respiratory tract and progresses to productive lesions as cell-mediated immunity (type IV hypersensitivity) develops, with the formation of tubercles. Healing may occur at this point, or the lesions may extend with caseation necrosis. This may heal or progress to massive destruction of lung tissue and cavity formation.

Hematogenous spread of *M. tuberculosis* from the lungs to other body sites occurs in about 15% of otherwise normal patients, but in 50–70% of HIV-infected patients. Such spread is facilitated by the ability of *M. tuberculosis* to establish intracellular infection. Tuberculosis can recur later in life from tubercle bacilli that remain viable, but inactive, in the body from a previous primary infection. The World Health Organization estimates that about two-thirds of all new active cases of tuberculosis actually result from re-activation of a healed primary infection.

Signs and symptoms

The clinical features of tuberculosis include malaise, headache and fever. There is a persistent productive cough, with blood in the sputum. Patients also suffer from weight loss and night sweats.

Diagnosis

The diagnosis of tuberculosis is based on the microscopic detection of acid-fast and alcohol-fast bacilli and the culture of *M. tuberculosis* from sputum, together with skin testing. Culture is undertaken on an agar called Lowenstein–Jensen medium, but is extremely slow (4–8 weeks). However, using the more modern BACTEC radiometric system (Becton Dickinson Microbiology Systems, Sparks, MD, USA), the detection time can be reduced to 9–16 days. Molecular biological methods have now been applied to laboratory diagnosis (16). DNA probes can identify *M. tuberculosis*, in pure cultures, within a few hours. In addition, the use of PCR-based diagnostics has made it possible to identify, within 24 h, *M. tuberculosis* in clinical specimens. This technology will become routine in the future.

The Mantoux test consists of an intradermal injection, in the arm, of purified protein derivative from cultures of *M. tuberculosis*. A positive test (a 'hard' lesion of 10 mm or more in diameter at the site of the injection after 48–72 h) indicates either active disease or past infection. A negative test does not definitively rule out tuberculosis, as some false-negative results may occur.

Treatment

Patients with tuberculosis are usually treated with three or four drugs to prevent the emergence of resistant strains during the prolonged period of treatment. In the UK, a 6-month regimen comprising isoniazid, rifampicin, pyrazinamide and ethambutol for two initial months, followed by rifampicin and isoniazid for a further 4 months, is recommended for adult respiratory tuberculosis. However, within the last decade, multiple drug-resistant strains of *M. tuberculosis* have emerged, about 20% of which are resistant to both isoniazid and rifampin (44). Secondary drugs (less effective and generally more toxic) include para-aminosalicylic acid, streptomycin, amikacin, ciprofloxacin and clarithromycin.

Of even more concern is the emergence of strains known as XDR TB, which are resistant to all first-line agents, an injectable agent and a fluoroquinolone

(44, 84). These strains are virtually untreatable and carry a mortality of 80–100%. Worryingly, in a recent Centers for Disease Control / World Health Organization study, these isolates comprised 2% of all those examined (37).

Immunization

Bacille Calmette–Guérin vaccination (a live, avirulent, bovine strain of *Mycobacterium*) has been used almost worldwide (but not in the USA) for vaccination against tuberculosis in purified protein derivative-negative persons. Unfortunately, protection is variable and is stronger in children than in adults. A significant research effort is underway to develop new and more effective vaccines (112).

Viral pneumonias

A range of viruses can cause pneumonia, particularly in children. In the absence of laboratory culture data it can be difficult to differentiate clinically between viral and bacterial pneumonias. In presumed cases of viral pneumonia, a specific viral agent is identified in only about 50% of patients.

Influenza

Prevalence

Influenza is a seasonal epidemic disease, which occurs during the colder months in temperate climes. Occasionally, following antigenic drift in the virus (see below), severe worldwide pandemics occur, historically at 10–40-year intervals. In the 20th century there were three pandemics. The Spanish influenza pandemic (1918–1919) claimed an estimated 50 million lives, whilst the Asian (1957) and Hong Kong (1968–69) outbreaks each resulted in 1–2 million deaths.

Microbiology

Influenza viruses are RNA viruses, classified in the genus *Orthomyxovirus* (49). There are two types (A and B) that cause serious infections in humans. The influenza viruses have two major surface glycoprotein antigens: hemagglutinin, which is responsible for cell attachment; and an enzymically active neuraminidase, which assists virus maturation and release. These two surface antigens undergo gradual, progressive antigenic variation as a result of spontaneous mutation, with minor changes in the hemagglutinin (antigenic drift) that allows the viruses to escape host immunity and cause further outbreaks, typically of mild disease in the winter months. Pandemics involve the emergence of new influenza A subtypes in the human population, caused by major genetic re-assortment of the RNA segment that codes for the viral surface hemagglutinin (antigenic shift), creating a new virus to which human populations have little or no protection (49).

Pathophysiology

Recent evidence suggests that transmission of influenza occurs over short distances rather than over long distances, predominantly by the droplet and contact routes, rather than by aerosol (12). The viral particles attach to sialic acid receptors on superficial epithelial cells of the upper and lower respiratory tract, which they infect and kill. Cytokine release from host cells causes chills, malaise, fever and muscular aches. Influenza A rarely causes primary pneumonia, and damage to the lung is usually caused by secondary bacterial infection with *S. pneumoniae, S. aureus* or *H. influenzae*. However, in human disease caused by H5N1 (see below), primary viral pneumonia and multi-organ failure are common.

Signs and symptoms

Fever, cough, malaise and myalgia are the most frequently described symptoms. Influenza can be difficult to differentiate from other viral respiratory infections, but several studies have shown the importance of fever and nonproductive cough in distinguishing influenza, particularly when the infection is known to be present in the community (34).

Diagnosis

Testing should be undertaken early in a suspected outbreak to confirm that influenza is circulating in the community (51). Testing should also be undertaken whenever necessary to confirm the diagnosis in cases that are atypical. However, it does not need to be carried out in all patients who present with a typical clinical picture of influenza during an outbreak.

Viral cultures on nasopharyngeal specimens are the most sensitive and specific tests, but the results can take 3–10 days or longer, which limits their value clinically. Rapid tests for influenza are available, (http://www.cdc.gov/flu/professionals/diagnosis/labprocedures.htm) and can be helpful for individual patients when results will contribute to diagnostic and treatment decisions.

Treatment

Hydration is important to replace the large fluid losses associated with fever. Antipyretics, such as ibuprofen, can reduce fever and other associated symptoms, but there is no evidence that their use affects the duration of illness. If prescribed within 48 h of onset of symptoms in uncomplicated cases, a 5-day course of the neuraminidase inhibitors oseltamivir or zanamivir can reduce the duration of illness by 1–2 days. Both drugs could be used as prophylactic agents in the event of a future pandemic.

Vaccines are available but need to be reviewed annually in relation to the genetic changes that have occurred in viruses circulating the previous year. The vaccines provide protection in up to 70% of vaccinees and are valuable for protecting high-risk individuals, especially the elderly, those with chronic cardiopulmonary disease and healthcare workers.

A/H5N1

In recent times, the A/H5N1 strain of influenza has developed into an epizootic of domestic poultry (22). Associated human infections were observed first in Hong Kong in 1997 (17). There have subsequently been cases of A/H5N1 influenza across South-East Asia, Russia, Europe, Africa, India and the Middle East. The total number of human cases of A/H5N1 to date is low, because the current strain is not efficiently transmitted from human to human. By October 2007, the World Health Organization had confirmed 331 cases from 12 countries, of which 109 were in Indonesia and 100 were in Vietnam. Of these 331 cases, 202 patients died, a case fatality rate of 61%. Thus, human disease caused by H5N1 follows an aggressive course, in which primary viral pneumonia and multi-organ failure are common. Furthermore, most cases to date have been in previously healthy children and adults. Therefore, the concern is for major mortality globally if, through genetic reassortment, a strain emerges that is readily transmitted between humans, resulting in a pandemic. The combination of vaccines (20, 57) and the anti-viral drugs oseltamivir and zanamir (21) will be utilized in an attempt to reduce the impact of a pandemic, but case numbers and deaths are still expected to be extremely high, with massive social and societal impact.

Severe acute respiratory syndrome

In November 2002, an outbreak of a severe respiratory disease with no recognized etiology was reported from Guandong Province in China. The agent spread widely across East and Southeast Asia and to some other parts of the world, notably Toronto in Canada. By the time the outbreak was controlled in July 2003, cases had been identified in 30 countries. By August 2003, more than 8400 cases of severe acute respiratory syndrome and 916 deaths had been reported worldwide.

The disease was named severe acute respiratory syndrome (SARS) (39). Symptoms included high fever, cough, shortness of breath and difficulty breathing. Chest radiographs were consistent with pneumonia. Close contact with an infected person posed the greatest transmission risk, and many family members and healthcare workers became infected.

The causative agent is now known to be a new coronavirus, named the SARS-associated coronavirus. It can be detected by PCR and serology. There is no specific treatment, and infected patients with severe symptoms require mechanical ventilation in intensive care units. The mortality rate may be as high as 50% in the elderly.

Fungal infections

There are a number of fungi that affect the lower respiratory tract and lungs, through colonization, allergy or direct infection (113). These microorganisms are acquired by inhaling pathogenic fungal spores or yeast cells. Most cases are asymptomatic or undiagnosed, but some may involve serious manifestations. Infectious fungal respiratory diseases can be divided into those that occur in generally healthy individuals and those that occur opportunistically in immunosuppressed patients (31). In healthy individuals, fungi causing respiratory disease include organisms such as *Histoplasma capsulatum, Coccidioides immitis* and *Blastomyces dermatitidis*, which are pathogens in certain geographical regions (26). Infectious fungal respiratory diseases remain important causes of morbidity and mortality in immunocompromised individuals, especially in those receiving immunosuppressive therapy, those undergoing bone marrow transplantation or solid-organ transplant and those with HIV infection. Fungi that affect immunosuppressed individuals are frequently species of *Aspergillus* and *Candida*, as well as *Cryptococcus neoformans* and *P. jiroveci* (61). Other, rarer, fungi are *Fusarium* spp, *Zygomycetes*, *Pseudallescheria boydii* and *Penicillium marneffii*, and those newly recognized as causative agents of pulmonary fungal

infections, such as *Pythium insidiosum*, *Absidia corymbifera*, *Phialemonium obovatum*, *Enterocytozoon bieneus*, *Hormographiella aspergillata* and *Irpex lacteus* (14, 63, 72, 87, 95, 98, 105). Some of the key fungi related to respiratory infections are now discussed.

Aspergillosis

Pathophysiology

Aspergillus spp affect immunocompromised patients, such as those with leukemia, those undergoing chemotherapy or treatment with steroids, transplant patients, those with cystic fibrosis, HIV or acquired immunodeficiency syndrome (AIDS), chronic obstructive pulmonary disease, chronic granulomatous disease, severe asthma with fungal sensitivity, and many others (52). *Aspergillus fumigatus*, the most pathogenic species, is responsible for about 90% of all cases of invasive aspergillosis (64). There are three main clinical syndromes caused by *A. fumigatus*, which has the greatest predilection of all species for the respiratory tract (60). Allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to the colonization of the airways / sinuses / lungs with *Aspergillus* spp, which predominantly affects patients with asthma, cystic fibrosis and bronchiectasis. The clinical syndrome of allergic bronchopulmonary aspergillosis affects approximately 1% of those with asthma and 5–10% of those with cystic fibrosis (92). Aspergilloma is an infection of a pre-existing pulmonary cavity with a mycetoma (fungal ball) of *Aspergillus* species. This has a variable prevalence depending on the amount of cavitating lung disease affecting the population in question (33). Invasive aspergillosis is a disseminated infection affecting immunocompromised individuals that often starts in the lungs but may involve other organs and tissues by hematogenous spread. Invasive aspergillosis is extremely rare amongst immunocompetent patients. However, its prevalence is rising as a result of the increasing number of patients undergoing intensive chemotherapy to treat neoplasms and those receiving organ transplants (69).

Microbiology

Aspergillus are opportunistic, filament-forming molds from a genus comprising over 180 spp, of which *A. fumigatus* is responsible for the majority of human *Aspergillus* infections (53). *Aspergillus* spp are universally distributed and are found in soil and other organic matter. Four other *Aspergillus* spp cause most of the remaining cases of aspergillosis, namely *Aspergillus terreus*, *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus nidulans*. *A. terreus* is associated with high mortality. *A. flavus* may cause sinusitis more commonly. *A. niger* is a more frequent colonizing species and is commonly associated with external otitis. *A. nidulans* is particularly associated with infection in chronic granulomatous disease (5). *A. fumigatus* is a ubiquitous saprophytic fungus with a worldwide distribution, which is a result, in part, of the production of small spores called conidia that have an average size of 2–3.5 μm. These are easily dispersed into the air and remain in the atmosphere for prolonged periods of time, but are dependent upon the external environment, such as temperature, humidity and seasonal variations (108). The spores of *A. fumigatus* have a hydrophobic protein-coat layer, which may enable them to withstand host defences and harsh environments. In addition, their very small size enables penetration deep into the lung, particularly *A. fumigatus*. All *Aspergillus* spp also form hyphae, which are septate and hyaline. This is one of the key virulence factors of *Aspergillus* and is required for tissue invasion. *A. fumigatus* grows the most rapidly, is extremely thermotolerant, and binds laminin and fibrinogen more efficiently than other species of *Aspergillus*, making it a-well adapted pathogen. The morphology and colour of the conidiophores vary between species (59).

Signs and symptoms

Allergic bronchopulmonary aspergillosis most frequently presents with wheezing, pulmonary infiltrates and fever. Cough may be severe, resulting in expectoration of large mucous plugs and hemoptysis, which may be coupled with generalized malaise and severe headache. Aspergilloma may present with hemoptysis, which can be life-threatening. Cough and / or fever are less frequent. The condition may be asymptomatic, and can be detected after radiographic changes in patients with pre-existing cavitating lung disease. Invasive aspergillosis presents with a cough combined with a fever, shortness of breath and pleuritic chest pain. Pneumonic consolidation may develop with a rapidly worsening clinical condition and severe hypoxia, including hemoptysis. The fungus may spread in the blood and affect the kidneys, brain, heart, spleen, liver, thyroid, gastrointestinal tract and eyes (52).

Diagnosis

Diagnosis of pulmonary aspergillosis is difficult, and requires a high index of suspicion. Histopathology of lung biopsies remains the ‘gold standard’. The

presence of acute dichotomous branching septate filamentous forms invading tissue combined with a pure culture is diagnostic (115). Chest radiographic features are also important, but not in the early stages of disease. Signs include bronchopneumonia, consolidation, segmental pneumonia, multiple nodules, masses, cavitary lesions and pleural effusion. Computed tomography scans of the chest reveal multiple nodules and the characteristic halo sign. Culture from bronchoalveloar lavage often provides a useful indicator of infection and adjunct to other diagnostic tests (5). More recent advances have seen the use of galactomannan detection by enzyme-linked immunosorbent assay. Galactomannan is a cell wall polysaccharide that can be detected in blood at levels as low as 0.5 ng/ml, and prior to the development of clinical signs. However, although it provides a high negative predictor of infection, it is limited by a poor positive predictive value as a result of cross-reactivity with other species and/or foodstuffs. Beta-D-glucan is another recent antigenic detection test that appears a promising addition to the diagnostic arsenal. Prospective clinical trials are necessary to evaluate this technology further. The PCR is a further test that is currently under development, which may offer both high specificity and sensitivity (53). However, distinguishing infection from colonization, and optimizing specimen collection, are problematic.

Treatment

Oral long-term high-dose steroids are the mainstay of management of allergic bronchopulmonary aspergillosis, coupled with treatment with itraconazole (55). Aspergilloma may be treated surgically, but this has been associated with high morbidity and mortality. For an aspergilloma, percutaneous administration with amphotericin B may be performed, but some studies show no apparent benefit. Conversely, itraconazole shows limited success because of its high tissue penetration. In terms of invasive aspergillosis (IA), amphotericin B has been the first-line therapy for aspergillosis for many years, but is associated with serious side effects, such as nephrotoxicity. However, liposomal formulations of these have been introduced that have fewer side effects (29). Voriconazole, a broad-spectrum triazole, has recently been approved for the treatment of IA because it has more favourable outcomes than amphotericin B and fewer side effects. Other azoles include posaconazole, which may be used as salvage therapy when conventional antifungals fail. The echinocandins such as caspofungin, which are cell wall inhibitors, have been introduced and used for salvage therapy (32). Although limited clinical study data are currently available, there is potential for combination therapy of the echinocandin with liposomal amphotericin B or the triazoles (91). Prophylaxis of high-risk patient groups is preferential, as itraconazole can be used with relative effectiveness. In addition, there are reports of immunotherapy for managing patients with invasive aspergillosis. These include colony-stimulating factors, such as granulocyte colony-stimulating factor, granulocyte–macrophage colony-stimulating factor, or interferon-γ (81). The most recent guidelines for the treatment of aspergillosis are a valuable resource for the management of this infection (107).

Cryptococcus neoformans

Of all 37 species of *Cryptococcus* described to date, *C. neoformans* is the most pathogenic (18). It is a ubiquitous encapsulated round-to-oval yeast-like fungus measuring 4–6 μm. It is initially inhaled prior to causing the disease coccoccosis, affecting immunocompromised individuals such as those with AIDS, immune deficiencies, cancer, steroid use and diabetes (88). It possesses a characteristic polysaccharide capsule of variable thickness (up to 30 μm) that surrounds the yeasts. Within the environment the capsule is thinner and the yeast smaller, while thicker capsules tend to be found in infected tissues. The polysaccharide capsule, the phenoloxidase enzyme and the organism's ability to grow at 37 °C, are its major virulence factors (78). Respiratory manifestations of the disease can be both acute and chronic. Acute forms of the disease are rare, occurring in patients with AIDS and presenting as severe acute respiratory distress. Chronic pulmonary forms are associated with the production of nodules or masses (usually in the upper lobes), cavities, segmental pneumonia, pleural effusion, or lymphadenopathy. Histologically, these infections appear with inflammation of a gelatinous appearance (88). This is composed of yeast cells that become granulomatous. Diagnoses can be made directly through visualization of the yeast cells in biopsy samples or from isolation. Indirect diagnosis can be made from detection of the cryptococcal polysaccharide antigen using commercially available latex agglutination assays (79).

Pneumocystis jiroveci

P. jiroveci (formerly *Pneumocystis carinii*) (97) is an atypical fungus that commonly invades the respiratory tract, usually causing asymptomatic infections. Some data on the measurement of specific antibody

levels to *P. jiroveci* suggest that about 80% of children are colonized by the age of 4 years. A few cases of *P. jiroveci* pneumonia occur in otherwise healthy children, but by far the most important expression of the disease is in the immunocompromised, especially in patients with AIDS (101). Diagnostic methods for *P. jiroveci* include demonstration of the microbe in sputum or lung-biopsy tissue using indirect immunofluorescent staining with monoclonal antibodies. Treatment involves trimethoprim-sulfamethoxazole or pentamidine.

Summary

This article reviews respiratory tract infections and pneumonia in the context of our current knowledge of the bacteria, viruses and fungi responsible for these diseases. A number of respiratory tract infections (including legionellosis and tuberculosis) can potentially be transmitted during dental treatment. Aspiration pneumonias associated with members of the oral flora are common among hospitalized, debilitated patients. In tuberculosis, there is global concern about antibiotic resistance, particularly among those strains known as XDR TB, which are virtually impossible to treat with chemotherapeutic agents. The influenza virus H5N1A is causing widespread concern, because of the potential for a pandemic if a strain develops that can transmit readily between humans. On a more positive note, improved understanding of the genetics and epidemiology of two important bacterial pathogens, *S. pneumoniae* and *H. influenzae*, have resulted in significant advances in prevention, through improved vaccine availability and effectiveness. Respiratory tract infections will continue to be prevalent in all human populations and provide an ongoing challenge for modern medicine.

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