Chapter 84

Respiratory Tract Infections: A Clinical Approach

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INTRODUCTION

Respiratory tract infections (RTIs) are among the most common and important problems in clinical medicine. In developed countries, acute respiratory infections (ARI) account for the majority of antibiotic prescriptions written, 20% of all medical consultations and over 30% of lost days from work [1]. The situation is even more dramatic in developing countries where nearly 20% of mortality in children under the age of 5 years can be attributed to ARI [2]. When a patient is thought to have a respiratory infection, considering the disease features in a sequential manner can help focus the differential diagnosis and expedite specific diagnosis and treatment. The starting point is a basic understanding of the pathophysiology of the respiratory tract and ways in which innate and acquired immune systems interact with microbial pathogens. The physician then defines the clinical syndrome being evaluated, the medical characteristics of the affected patient and context in which the infection was contracted. This information guides laboratory testing, imaging and acquisition of other ancillary data needed to arrive at a final diagnosis and treatment plan. This chapter provides an overview of key concepts related to RTIs, with an emphasis on clinical and microbiological aspects.

PATHOPHYSIOLOGY OF RESPIRATORY TRACT INFECTIONS

In common with other infectious diseases, the outcome of RTIs is a complex interplay between the ability of the pathogen to infect, colonize and damage tissues and the capacity of the host to mount an effective immune response. The primary function of the respiratory tract is gas exchange between inspired air and circulating blood. The average human inhales approximately 28 000 breaths of air each day along with any contaminating bacteria, virus and fungal particles present as aerosols in the environment. Also, inadvertent microaspiration of oropharyngeal and/or gastric contents occurs not infrequently in normal hosts and is extremely common in critically ill, mechanically ventilated patients [3]. Despite these challenges, the lungs, bronchi and trachea below the larynx remain essentially sterile in normal individuals. Fortunately, the respiratory tract has evolved to withstand this onslaught of potential pathogens by a variety of innate and acquired immune defences. For example, infectious particles larger than 8–10 microns are efficiently trapped in a mucociliary blanket lining the nares, trachea and bronchi. A large amount of mucus is produced by goblet cells present in ciliated columnar epithelium; once an organism is trapped in this viscous layer, directional ciliary action transports it to the back of the throat where it can be swallowed or expectorated. Mechanical clearance is also facilitated by the normal flow of saliva, sloughing and regeneration of respiratory epithelial cells, and, for the oropharynx, competition between resident normal flora and invading pathogens. Importantly, the respiratory mucosa is the site of production of large amounts of IgA (10–15% of total protein in nasal secretions), which has both antibacterial and antiviral activity. Immunoglobulins G and M, along with complement are present in respiratory secretions through transudation from the blood, and serve to opsonize, agglutinate and neutralize pathogenic organisms, similar to their role in blood and other sites. Additionally, the surface liquid of the airways contains a wide variety of proteins and peptides with antimicrobial properties. These include lactoferrin, lysozyme, cathelicidins, secretory leukocyte proteinase inhibitor and beta-defensins. Beta-defensins are an important family of cationic antimicrobial peptides which greatly enhance the resistance of

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epithelial surfaces to microbial colonization. They interact with the negatively charged membranes of Gram-positive and Gram-negative bacteria, fungi and enveloped viruses by displacing Ca^{2+} and Mg^{2+} ions, thus altering the integrity of microbial membranes. Additionally, defensins are chemokines which attract macrophages, dendritic cells and other immune cells to the site of infection, thus serving a dual role in both the innate and acquired immune systems [4,5].

Most bacteria and viruses are so small that they can reach the terminal bronchioles and alveoli. Although there is no mucociliary function at this level, other cell-mediated and humoral host defences are present to make up for this deficit. For example, components of surfactant (a phospholipoprotein complex secreted by type II pneumocytes) have several important immune functions. SP-A and SP-D bind sugars on the surface of pathogens and opsonize them for enhanced uptake by phagocytes. They also interact with the adaptive immune response to enhance clearance of pathogens by alveolar macrophages and neutrophils [6]. Free fatty acids and various iron-binding proteins also act within the alveoli and terminal bronchioles as microbiocidal compounds.

Any congenital or acquired damage to the mucociliary defence system increases the risk that infection will develop. Primary ciliary dyskinesia (PCD) is a rare and heterogeneous group of genetic disorders characterized by mutations in genes coding for dynein arm, radial spoke and other proteins associated with cilia motility. Within the respiratory tract, impaired ciliary function reduces mucous clearance from the lungs, sinuses and middle ears and results in recurrent and progressive infections [7]. Cystic fibrosis is a common genetic defect that alters ciliary action and will be discussed in a separate section.

At a purely mechanical level, alterations in levels of consciousness from drug intoxication, anaesthesia, neurologic impairment and even normal deep sleep can result in aspiration of oropharyngeal or gastric contents into the lower respiratory tract [8]. Acquired damage to the mucociliary apparatus is extremely common and can result from a wide variety of insults to the respiratory tract. The effects of alcohol have been studied extensively and the damage to host defences occurs at multiple levels. In addition to suppressing cough and epiglottic reflexes, consumption of alcohol has been associated with increased colonization of the oropharynx with Gram-negative bacilli. It also impairs cellular immune responses to infection by decreasing recruitment and mobilization of neutrophils to the lung, blocking the TNF response to endotoxin, and increasing production of IL-10, a cytokine with anti-inflammatory properties [9,10]. Tobacco smoke and other air pollutants are detrimental to pulmonary defence mechanisms by interfering with mucociliary action and macrophage activity [11].

DELINEATING THE CLINICAL SYNDROME

It is useful to divide RTIs into those involving the upper and the lower tracts. The clinical syndromes involving the upper tract include otitis media, mastoiditis, sinusitis and pharyngitis, while infections of the lower tract can be divided into tracheobronchitis, bronchiolitis and pneumonia. Most of these conditions can exist in acute and chronic forms. Acute disease is usually caused by viral or bacterial infections, and chronic disease is usually caused by fungi, slow-growing bacteria such as mycobacteria, bacteria adapted to persist in biofilms and occasional less common pathogens such as parasites. Chronic infections can also develop when structural changes (e.g. bronchiectasis, nasal polyps, and cavities) occur as a result of recurrent or especially severe acute infections, surgical intervention or other processes which alter the structural integrity of the respiratory tract.

Otitis media refers to infections or inflammation of the middle ear and is extremely common, especially in children. The middle ears, mastoid cavities, and sinuses are connected to the nasopharynx and the pathogenesis of otitis media often relates to obstruction of the eustachian tube, resulting in fluid retention and suppuration. Bacterial biofilm formation may be important in the pathogenesis of chronic infections [12]. Clinical manifestations typically include otalgia (ear pain) and decreased hearing – the presence of fever is variable. Many patients with otitis media experience a viral upper respiratory tract infection or exacerbation of allergic rhinitis in the days or week before onset of symptoms. Diagnosis is based on clinical history and examination of the tympanic membrane. The tympanic membrane is normally translucent but becomes cloudy or opaque in response to infection. Studies have documented the microbiology of acute otitis media based on needle aspiration and culture of middle ear fluid. *Streptococcus pneumoniae* and *Haemophilus influenzae* predominate, while *Streptococcus pyogenes*, *Staphylococcus aureus* and *Moraxella catarrhalis* are less frequently isolated [13,14]. It is interesting that of the many known serotypes of *S. pneumoniae*, a relatively small number account for the majority of cases, and some regional differences in predominant serotypes have been noted [15]. Respiratory viruses can be isolated from nearly half of all children with acute otitis media. The most frequently isolated viruses include influenza A, respiratory syncytial virus (RSV) and rhinoviruses [16].

Mastoiditis involves inflammation and infection of the mastoid air cells and is relatively uncommon. The clinical significance is high because of the close proximity to the brain and large cerebral blood vessels. Almost all patients with acute mastoiditis have concurrent otitis media. Fever, severe pain behind the ear that worsens at night and persistent otorrhoea beyond 3 weeks' duration are

signs and symptoms of developing mastoiditis. Because acute mastoiditis is an extension of an ongoing otitis media, the microbiological features are very similar with *S. pneumoniae*, *H. influenzae* and *S. pyogenes* being the most commonly isolated pathogens [17]. An important epidemiologic observation has been the increasing frequency with which multidrug-resistant *S. pneumoniae* is being isolated. Approximately 40–50% of isolates are resistant to penicillin, 30–35% are resistant to macrolides, and 25% resistant to ceftriaxone [18]. *S. aureus*, including meticillin-resistant strains have become increasingly important as a cause of mastoiditis since the routine use of pneumococcal vaccination. Chronic mastoiditis commonly occurs in the background of chronic suppurative otitis media and cholesteatoma formation. The most frequently isolated organisms include *Pseudomonas aeruginosa*, enteric Gram-negative bacilli, *S. aureus*, and a variety of anaerobic bacteria. Polymicrobial infections are common.

Sinusitis (also called rhinosinusitis) refers to inflammation of the nasal cavity and paranasal sinuses. It occurs along a wide temporal continuum ranging from acute (symptoms less than 4 weeks) to chronic (symptoms lasting more than 12 weeks). Recurrent acute sinusitis is generally defined as four or more episodes per year with interim resolution of symptoms. In the US, it is estimated that more than 30 million adults are affected with acute or chronic sinusitis with an economic impact of $3 billion annually [19].

The vast majority of cases of acute sinusitis are due to respiratory viruses (e.g. rhinovirus, influenza virus and parainfluenza virus) in the clinical context of the 'common cold'. Respiratory viruses inoculated onto the conjunctiva or nasal mucosa of a susceptible individual replicate very rapidly and symptoms begin within a day or two thereafter. Fever, myalgia, headache, facial pain and nasal discharge are the predominant clinical features and the illness is almost always self-limiting. Acute bacterial infection is a complication of viral sinusitis in only a small minority (1–2%) of cases. Despite that statistic, a large percentage of patients with symptoms of uncomplicated viral sinusitis receive prescriptions for antibiotics, thus contributing to the development of resistance. Factors which predispose to bacterial sinusitis include allergies, obstruction of sinus drainage, mucociliary dysfunction and immune suppression. Organisms commonly associated with acute bacterial sinusitis in outpatients include *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. In contrast, hospitalized patients who develop acute bacterial sinusitis are most commonly infected with enteric Gram-negative bacilli such as *P. aeruginosa* and *Klebsiella pneumoniae* along with Gram-positive organisms, usually *S. aureus* [20–23].

Fungal sinusitis is an important subgroup of infection that must be distinguished from colonization of the respiratory tract due to inhalation of fungal spores. In most cases simple colonization of the sinuses is of little or no clinical significance. Patients most at risk of developing symptomatic disease include those with impaired sinus drainage from chronic inflammatory conditions, nasal polyps or structural abnormalities of the nasal septum or sinus ostia. Many species of fungus have been reported as colonizers of the sinuses, with *Aspergillus* spp. being among the most common. In the setting of poor sinus drainage, fungal hyphae can grow as dense intertwined collections referred to as 'fungus balls'. As the size of the ball increases there can be erosion of the wall of the sinus due to mass effect and surgical excision is needed to remove the fungus ball and relieve the obstruction [24]. Of greater clinical concern is fungal sinusitis occurring in the context of immune suppression. In these instances the infection is much more aggressive with invasion of the fungus into the sinus mucosa, and underlying bone and vascular structures. The tempo of disease is generally dependent on the level of immune suppression; the most profoundly immune-compromised patients experience acute disease with rapid progression of symptoms over several days, while patients with a more intact immune function show a more chronic course over several weeks or months. Epidemiologically, invasive fungal sinusitis has risen in parallel with the increased number of patients receiving bone marrow transplants, chemotherapy and solid organ transplants. Diabetic ketoacidosis and high-dose glucocorticoid therapy are also significant risk factors for the development of invasive fungal sinusitis, especially due to *Rhizopus* and other zygomycetes. Although cultures are useful in determining the aetiologic agent of infection and helping to guide antifungal therapy, biopsy is often necessary to document whether invasive infection is present rather than colonization of the sinus cavity [25].

Pharyngitis is typically manifested by a sore throat exacerbated by swallowing. Some patients have fever along with other constitutional signs and symptoms such as headache, malaise and swollen cervical lymph nodes. The clinical syndrome of pharyngitis is one of the most common reasons for seeking medical care, accounting for over 12 million outpatient visits each year in the US [26]. Non-infectious causes include seasonal allergies, exposure to smoke and other pollutants and poorly humidified air. Infectious causes include a wide variety of viral and bacterial pathogens. Essentially all of the respiratory viruses (rhinovirus, coronavirus, influenza virus, etc.) cause pharyngitis as well as herpes simplex virus, Epstein–Barr virus and human immunodeficiency virus [27]. Bacterial pharyngitis due to group A streptococcus (GAS) presents as the sudden onset of sore throat, tonsillar swelling, fever and cervical lymphadenitis. It is important to treat GAS pharyngitis in order to prevent suppurative and non-suppurative complications such as sinusitis,

retropharyngeal abscesses, rheumatic fever and acute glomerulonephritis [28]. Other beta-haemolytic streptococci (e.g. groups C and G) are not typically associated with the development of rheumatic fever and the role of antimicrobial therapy is less certain. Less common bacteria associated with pharyngitis include *Neisseria gonorrhoeae*, *Chlamydophila pneumoniae*, *Arcanobacterium haemolyticum*, *Mycoplasma pneumoniae* and *Corynebacterium diphtheriae* [29].

Tracheobronchitis is a usually self-limited inflammation of the trachea and bronchi due to infection. Patients with bronchitis present with cough and sputum production but usually lack fever, tachycardia and tachypnoea. Acute bronchitis can be differentiated from chronic bronchitis based on the duration of symptoms. For example, chronic bronchitis in patients with chronic obstructive pulmonary disease is characterized by a cough lasting at least 3 months in each of two successive years. Viral infections are the most common cause of acute bronchitis with influenza A and B, parainfluenza, RSV, rhinovirus and human metapneumovirus being isolated most frequently [30]. It is especially important to recognize influenza infections because of the relatively higher morbidity and because specific antiviral therapy is available. It is controversial whether or not bacterial organisms commonly associated with pneumonia in adults (e.g. *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, etc.) can cause isolated acute bacterial bronchitis. However, three other organisms, *M. pneumoniae*, *C. pneumoniae* and *Bordetella pertussis* (the agent of whooping cough), have been shown to cause acute bacterial bronchitis. Treatment of pertussis is indicated to reduce both the duration of symptoms and transmissibility of infection.

Bronchiolitis is an inflammatory condition that affects primarily the bronchioles (small airways less than 2 mm in diameter). It is a complex disorder that differs significantly between paediatric and adult populations. Most children that are affected are younger than 2 years old and have had common cold symptoms for several days. The disease progresses to involve the lower airways, resulting in persistent cough, wheezing and rapid breathing. Infants and young children are at increased risk of developing laboured breathing resulting in cyanosis and apnoeic episodes requiring hospitalization. The disease can also be especially severe in children with underlying pulmonary or cardiac disease. The cause of bronchiolitis is usually viral with RSV being the most common aetiology. RSV infections occur in epidemics which peak in January and February in the northern hemisphere and in June and July in the southern hemisphere [31]. Although infectious bronchiolitis can occur in adults, it is rare compared to what is seen in children. RSV, adenovirus and *M. pneumoniae* have been reported as infectious aetiologies. More often it arises from inhalation injury from toxic fumes, drug ingestion or is idiopathic with no identifiable precipitating cause [32].

Pneumonia is characterized by inflammation of the lung parenchyma with infiltration of the alveolar spaces and pulmonary interstitium with fluid, inflammatory cells and fibrinous debris. The histologic pattern of inflammation varies depending on the pathogen involved and can be neutrophilic, lymphocytic, granulomatous or a combination of the three (Fig. 84.1). The list of infectious agents associated with pneumonia is extensive and includes a wide variety of viruses, bacteria, fungi and parasites. Pneumonia is associated with significant

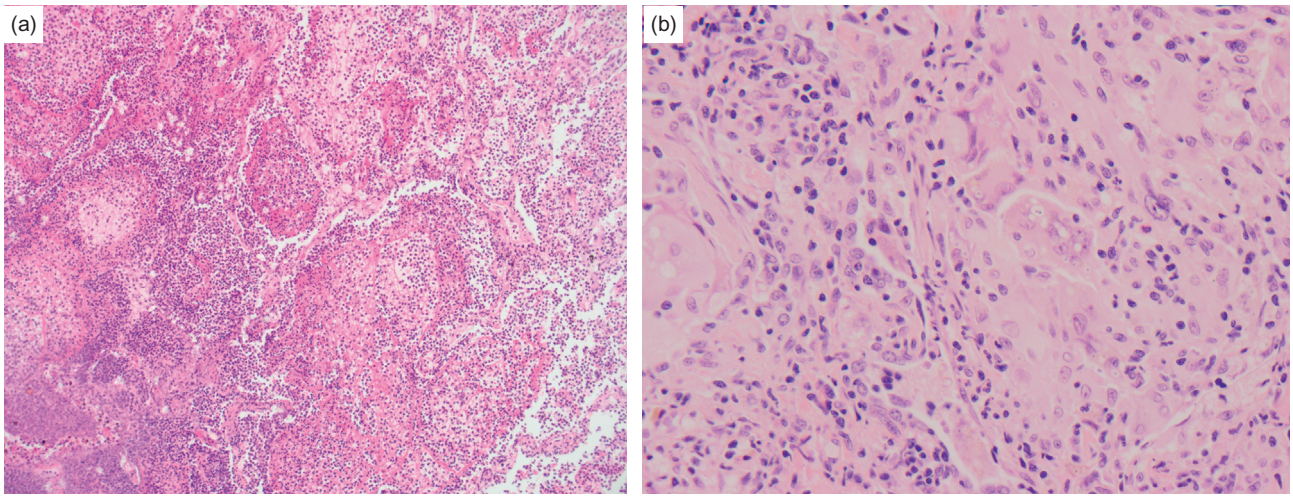

FIGURE 84.1 (a) Lung biopsy of early bacterial pneumonia. The alveolar septae are preserved but congested. Air spaces are filled with numerous neutrophils, mononuclear cells and red cells held together by a meshwork of fibrin. (b) Lung biopsy of fungal pneumonia. Air spaces have been replaced by granulomatous inflammation characterized by aggregates of epithelioid histiocytes, multinucleated giant cells and scattered small lymphocytes.

morbidity and mortality in all age groups. In developing countries, pneumonia is a major cause of mortality in young children. Physicians define specific pneumonia syndromes based on factors such as clinical presentation, epidemiologic considerations and laboratory results. For individual patients, the goal is to narrow down the list of organisms that might be causing disease so that targeted therapy can be provided in a timely and cost-effective manner.

Community-acquired pneumonia (CAP) is defined as pneumonia that develops in the outpatient setting or within 48 hours of admission to a hospital. Illness is often heralded by a sudden onset of fever and chills associated with chest pain, cough and production of purulent sputum. Constitutional symptoms such as fatigue, anorexia, sweats and nausea are common. On physical examination patients are often febrile, tachypnoeic and tachycardic, although this can vary greatly depending on the age of the patient and other factors. Clinical evidence of pulmonary consolidation can be confirmed by radiographic imaging (Fig. 84.2). The white blood cell count is often elevated in the range of 15 000−35 000/mm^3, when leukopenia is present it is a poor prognostic sign. Haematocrit and haemoglobin values are usually normal. Microscopic examination of sputum by Gram stain reveals numerous neutrophils and bacteria. When a single bacterial morphology predominates it can be helpful in establishing a diagnosis. However, caution should be applied because colonizing organisms can be present in large numbers and contaminating oral flora can confuse interpretation. Blood cultures are positive in a minority of cases of CAP but can be very useful in establishing the aetiologic agent. It is important to recognize that even with extensive evaluation, microbiologic diagnosis can only be made in 25−70% of cases [33].

FIGURE 84.2 Chest radiograph of an adult patient with community-acquired pneumonia. Patchy infiltrates are seen in both lungs and are especially prominent in the lower lobes.

The spectrum of pathogens associated with CAP is quite varied and depends, at least in part, on whether or not the patient is otherwise healthy or has co-morbidities. Nonetheless, most studies show that pneumococcus accounts for the majority (50−70%) of cases of CAP [33,34]. Co-morbidities that put patients at risk for severe pneumococcal disease include surgical or functional asplenia and immunoglobulin deficiencies. *H. influenzae* causes pneumonia with features similar to pneumococcus, but is less frequent, accounting for 3−38% of cases. Overall, S. *aureus* has traditionally been associated with CAP in a small percentage of cases. However, it has increased significance in the elderly and as a co-infection in patients with influenza virus. In the last decade there has been increasing concern about the global spread of CA-MRSA strains. Although they are most often associated with skin and soft tissue infections, when CA-MRSA pneumonia does occur it can be quite severe and is associated with a high mortality rate [35,36]. Pneumonia due to enteric Gram-negative bacilli, such as *Klebsiella*, *Pseudomonas* and *Enterobacter*, occur in the elderly and debilitated patients with alcoholism, chronic obstructive pulmonary disease and cystic fibrosis. They should be especially considered in patients who have been recently hospitalized. *Atypical pneumonia* is a somewhat confusing term, but generally refers to CAP due to less common agents such as *Legionella*, *Chlamydophila* or *Mycoplasma*. The incidence of *Legionella* infection seems to vary greatly based on geographic location. *Mycoplasma* tends to infect younger individuals and has occurred as epidemics in enclosed populations such as colleges and military bases [37].

Viral infections are an important cause of CAP, especially in the young and the elderly but can be difficult to distinguish clinically from bacterial pneumonia. Recent studies aided by the availability of sensitive molecular detection systems show that around 15−30% of hospitalized patients with pneumonia have a viral infection. Influenza virus, RSV and human metapneumovirus are the most common, followed by parainfluenza viruses, enteroviruses and coronavirus. In recent years novel strains of coronaviruses and avian influenza viruses have been recognized that are of great concern because of the associated high morbidity and mortality [38−40].

Hospital-acquired pneumonia (HAP) has been defined as pneumonia occurring 2 days or more after admission to a hospital for an unrelated illness. However, recent changes in healthcare delivery have resulted in substantial amounts of sophisticated and intensive care (e.g. chemotherapy, dialysis and wound care) being delivered in an outpatient setting. This practice has blurred the distinction between CAP and HAP and a more appropriate

designation might be healthcare-associated pneumonia (HCAP) [41]. Several factors contribute to substantial differences between the microbiology of CAP and HCAP. First, antimicrobial pressure in hospitals and nursing homes has driven sharp rises in the incidence of multidrug-resistant bacteria. Also, hospitalized patients in intensive care units rapidly colonize their oropharynx with enteric Gram-negative bacilli and the widespread use of antacids and histamine type 2 blockers promotes stomach colonization with similar organisms [42]. Patient-related risks of HCAP include advanced age, multisystem organ failure, malnutrition and the numerous neurologic and other factors contributing to overt or silent aspiration. Infection control practices, such as hand hygiene and proper decontamination of medical equipment, also substantially affect the risk of infection. The single biggest risk of acquiring HCAP is the use of mechanical ventilation. Studies have documented up to a 20-fold increase in risk of infection compared to unventilated patients. Strategies to reduce the incidence of ventilator-associated pneumonia are currently topics of intense research interest [43].

Given these differences it is not surprising that half of cases of HCAP are due to enteric Gram-negative bacilli, with *Pseudomonas* being especially common. *S. aureus* (including MRSA) and polymicrobial infections due to aspiration of mixed aerobic and anaerobic flora are also frequently reported. Finally, viral pneumonia due to nosocomial acquisition of respiratory viruses is a frequent occurrence in nursing homes and hospitals [33].

MEDICAL CHARACTERISTICS OF THE AFFECTED PATIENT

The immune status of the patient is a crucial piece of clinical and epidemiologic information when evaluating RTIs. Patients with asplenia or congenital or acquired deficiencies in antibody and/or complement are predisposed to infection with encapsulated bacteria such as *S. pneumoniae*, *Neisseria meningitidis* and *H. influenzae*. Individuals with impaired inflammatory responses from chronic steroid use or deficient cell-mediated immunity from advanced HIV, chemotherapy or organ transplantation are particularly challenging because they are predisposed to infection with essentially all of the agents of CAP and HCAP along with reactivation of latent infections such as cytomegalovirus (CMV).

A wide variety of medical conditions predispose patients to respiratory infections. A classic example is cystic fibrosis, a genetic defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. More than 1500 possible mutations have been identified and the disease occurs in approximately 1 in 2500 live births. It is recessively inherited and results in defective chloride ion transport across epithelial cell surfaces. In the lower respiratory tract this interferes with mucociliary clearance of inhaled pathogens and leads to early recruitment of neutrophils and other inflammatory defence mediators. Additionally, the high salt content in the surface liquid of the airways decreases the activity of beta-defensins, lysosome and other innate immune mechanisms. The end result is chronic colonization and recurrent infections with *P. aeruginosa*, *S. aureus*, *H. influenzae* and the *Burkholderia cepacia* group of bacteria [44]. Although survival rates for cystic fibrosis have improved dramatically over the past several decades, no effective treatment is available currently to reverse the underlying genetic defect that results in infection. Other well-known associations between underlying disorders and increased risk of pneumonia include chronic obstructive pulmonary disease, heart failure, diabetes mellitus and alcoholism.

CIRCUMSTANCES OF INFECTION

Epidemic or Sporadic

When other patients appear to have the same condition during the same time period (i.e. an epidemic), a virus is the usual cause, but common source exposure to bacterial pathogens is also possible. Examples of the latter include environmental exposures to *Legionella* and epidemics of *M. pneumoniae* and pertussis that occur in schools and other closed populations [45]. Seasonality is a major factor in respiratory viral illnesses. Although the first patients in a viral epidemic are often treated for bacterial disease, information from the clinical laboratory allows for less aggressive and more appropriate treatment of subsequent cases.

Geography and Exposures

Geographic location, travel history and living conditions can be important considerations in developing a differential diagnosis. For example, the endemic thermally dimorphic fungi (*Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis/posadasii, Paracoccidiodes braziliensis* and *Penicillium marneffi*) are frequent causes of CAP in defined geographic areas [46,47]. However, without knowledge of potential exposure to these agents, diagnosis is often delayed until there is no response to empiric antibacterial therapy or extrapulmonary symptoms become apparent. Similarly, recent travel to, or immigration from, a developing country could increase the possibility of tuberculosis in a patient that otherwise might be considered at low risk. Finally, vocational or recreational exposure to wild and domestic animals can result in exposure to uncommon infections such as anthrax, brucellosis, Q fever and psittacosis.

LABORATORY TESTING

The approach to laboratory testing is highly dependent on the severity of illness, the clinical syndrome being evaluated and the availability of specimens for analysis. Relatively mild infections in otherwise healthy individuals are often diagnosed clinically and treatment is empiric. In contrast, for more severe illness, laboratory confirmation of the aetiologic agent may be valuable when there is significant likelihood that a pathogen is present that is not being covered by empirical therapy or when the result allows narrowing of antimicrobial coverage.

A complete blood count may give some indication of the chronicity of disease or the presence of an underlying haematological disorder. Leukopenia or absence of leukocytosis may indicate viral or granulomatous disease, but in the appropriate clinical setting can be a sign of severe sepsis. Lymphocytosis, particularly atypical lymphocytosis, suggests a viral cause. Thrombocytopaenia may indicate sepsis, disseminated intravascular coagulation or underlying bone marrow disease. Hyperglobulinaemia can result from either a chronic inflammatory disease (HIV, chronic infection, connective tissue disease) or a plasma cell or lymphocytic disorder with associated antibody deficiency or dysfunction. Abnormalities of liver or renal function imply a multisystem disease and should prompt a search for disseminated infection.

Some fungal and bacterial pathogens are present in low concentrations (e.g. *Mycobacterium tuberculosis*), and multiple smears and cultures may be requested on a single specimen. When this occurs it is important for clinicians to work with the laboratory to prioritize testing so that the diagnostic yield is optimized. Similarly, if unusual infections (e.g. anthrax, plague or Hantavirus) are a consideration, consultation with the laboratory will allow the most appropriate method of detection to be used. During community outbreaks of RTIs, the agent should be fully identified from at least the first patients identified in the epidemic and the results provided to public health officials.

Serologic studies to detect organism-specific antibodies may complement culture results. For example, serum antibody tests for *Legionella* species, *Coxiella burnetii*, *C. pneumoniae* and *M. pneumoniae* have been widely used for clinical diagnosis. In general, a positive IgM or a four-fold rise in IgG titre is considered diagnostic. Reference laboratories provide serologic testing for a wide variety of other pathogens associated with RTIs. However, diagnostic criteria are less certain and the sensitivity and specificity of the assays are variable [33].

The detection of antigens in blood and urine has proven useful for a number of respiratory tract pathogens. Enzyme immunoassays are available to detect soluble antigens of *L. pneumophila* serogroup 1 and polysaccharide cell wall and pneumolysin antigens found in all serogroups of *S. pneumoniae*. Although there are some limitations to these assays, they are widely used in hospitalized patients [48,49]. Similarly, blood and urine antigen tests are available for pulmonary and disseminated infections with *H. capsulatum* and *B. dermatitidis*. Negative results do not rule out infection with those pathogens but a positive result has a high positive predictive value. Significant cross-reactivity between the two fungi limits the utility of the test to provide a specific diagnosis [50].

There is increasing use of molecular methods to provide rapid and specific diagnosis in RTIs. The increased sensitivity and specificity of these tests has greatly enhanced diagnosis of respiratory viral infections, and numerous organism-specific assays are available for other pathogens [51]. The current costs of these tests prohibit the effective use of them in a shotgun approach. Consultation with the clinical laboratory is recommended when difficult cases are encountered so that testing is performed in an efficient and cost-effective manner.

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