Fortnightly Review

Management of community acquired lower respiratory tract infection

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Lower respiratory tract infection incorporates a spectrum of disease from acute bronchitis to pneumonia. The division between bronchitis and pneumonia is not always clear, but patients with focal signs on clinical examination should be regarded as suffering from clinical pneumonia even if the chest radiograph is normal.

In otherwise healthy individuals, acute bronchitis is usually associated with a speedy recovery and few sequelae, but pneumonia remains a leading cause of death throughout the world. Infective exacerbations of chronic obstructive pulmonary disease lead to considerable morbidity, time off work, and days in hospital. This article reviews the diagnosis and management of community acquired lower respiratory tract infection. The management of patients with underlying diseases such as cystic fibrosis and bronchiectasis, and of immunocompromised patients, is not considered here.

Summary points

- Lower respiratory tract infection comprises a broad spectrum of disease from self limiting acute bronchitis to severe pneumonia
- *Streptococcus pneumoniae* remains the commonest bacterial cause of acute lower respiratory tract infection; bacterial resistance to penicillin remains low in the United Kingdom but is much higher in other parts of Europe and the United States
- When indicated, antibiotics should be used in adequate doses for a specified period of time, then stopped—the use of repeated courses of antibiotic is often unhelpful and encourages bacterial resistance
- Currently available laboratory diagnostic tests may not be of particular value to general practitioners, but newer tests based on molecular biology techniques may soon allow a more rapid and accurate diagnosis
- Preventive measures such as advice on stopping smoking and vaccination against influenza and pneumoccocus are important measures in reducing morbidity from respiratory disease

Box 1: Classification of pneumonia

- Community acquired
- Hospital acquired (nosocomial)
- Geographical pneumonia
- Aspiration pneumonia
- Pneumonia in the immunocompromised host

Epidemiology

Infections of the lower respiratory tract are responsible for 6% of all general practitioner consultations and form 4·4% of all hospital admissions.[1] They account for 3-5% of deaths in adults up to the age of 60. The best estimate from available data suggests that around 25 million prescriptions for antibiotics are written each year by general practitioners to treat respiratory infections.[2]

As with most diseases, the less severe types predominate. Acute bronchitis is common and usually self limiting, although the associated cough and sleep disturbance can be distressing. Children who develop croup or stridor during a viral respiratory infection may need to be admitted to hospital.

Community acquired pneumonia is potentially more serious, with elderly people and those with pre-existing illness at greatest risk of dying. Community acquired pneumonia is distinct from other types (box 1) in terms of epidemiology, causative organisms, management, and outcome. It occurs more commonly in those over 65, smokers, and those with other non-respiratory illnesses (particularly alcoholism), and the incidence doubles during the winter months. Most cases are managed by primary care teams—78-95% of adults with pneumonia are treated at home by general practitioners.[1] The remainder of patients with more severe illness will require hospital admission, including all those with adverse prognostic factors, severe pain, or breathlessness.

Organisms

Viruses account for most cases of acute bronchitis and up to a fifth of cases of pneumonia. Viral lower respiratory tract infection is most prevalent in autumn and winter. Common viruses causing respiratory disease include the influenza viruses, parainfluenza viruses, respiratory syncytial virus, and adenoviruses. A hospital survey by the British Thoracic Society of community acquired pneumonia in adults found influenza A virus in 7% of cases, the third most commonly isolated pathogen.[3] Viral infections are the commonest cause of acute bronchitis, bronchiolitis, and pneumonia in children, with parainfluenza viruses and respiratory syncytial virus predominating.[3,4] Outbreaks of lower respiratory tract infection caused by respiratory syncytial virus have been recorded in elderly people in nursing homes.[5] Viruses damage the respiratory epithelium, predisposing to bacterial superinfection, and impairment of mucociliary function may increase the severity of subsequent bacterial infection. Staphylococcal pneumonia during an influenza epidemic is the most common and severe example.

Streptococcus pneumoniae remains the most commonly identified organism in community acquired pneumonia (fig 1), isolated in 20-30% cases.[3,7-9] It probably also accounts for most of the third of cases in which no causative organism is found.[10]

Other agents commonly found are *Mycoplasma*

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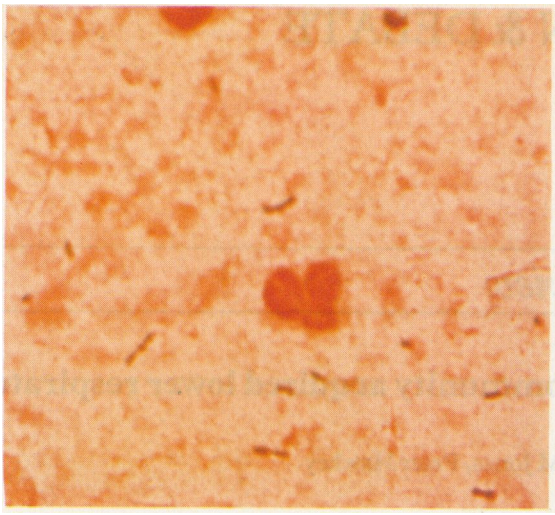

FIG 1—*Streptococcus pneumoniae in a Gram stained film of sputum*

pneumoniae, Haemophilus influenzae, Legionella spp and *Staphylococcus aureus* (fig 2). Mycoplasma infection occurs in three to four year cycles in temperate climates and often affects children and young adults.[11] In children over 4 years of age pneumococcal and mycoplasma infections account for most non-viral cases of lower respiratory tract infection.[4] *H influenzae* is the commonest cause of bacterial exacerbation of chronic obstructive pulmonary disease and accounts for 5-10% of cases of pneumonia.

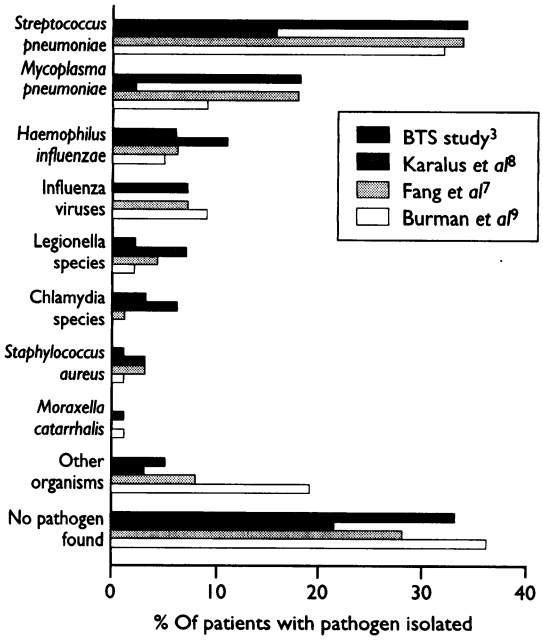

FIG 2—*Pathogens in community acquired pneumonia isolated in four large studies*

Legionella infection remains rare in the United Kingdom; half of cases are acquired abroad. It occasionally occurs in clusters of patients with no history of foreign travel—a source of infection (such as cooling towers) should be sought in such circumstances.

Other organisms may be isolated from the sputum but their causative role in lower respiratory tract infection is unclear. *Moraxella* (previously *Branhamella*) *catarrhalis* is often found in those with underlying chronic obstructive pulmonary disease but its significance is disputed; in the context of an infective exacerbation of chronic obstructive pulmonary disease it should be treated.[12,13] It is occasionally identified as the likely cause of acute pneumonia.[7,9] The role of *Chlamydia pneumoniae* is unclear.[14] It has been identified as the cause of up to 6% of cases of community acquired pneumonia, but limited laboratory diagnostic tests make assessment of pathogenicity difficult. Recent work suggests that it may be a more common respiratory pathogen than previously thought—positive serological results initially thought to suggest infection with *C trachomatis* and *C psittaci* may in fact be due to cross reaction with antibodies due to *C pneumoniae*.[15]

There seems to be a small but increasing number of patients presenting with lower respiratory tract infection in whom *Pneumocystis carinii* is identified, prompting the diagnosis of unsuspected HIV infection. Recent studies show that pneumonia due to *Klebsiella pneumoniae* is much less common than older textbooks have suggested.[16]

The patient's history may give clues to the cause of the pneumonia. Mycoplasma is commonly associated with cough, sore throat, nausea, diarrhoea, headache, chills, and myalgia. It is occasionally associated with neurological features.[11] The knowledge that an epidemic is under way may raise the level of suspicion. Staphylococcal pneumonia may be suspected during an influenza epidemic, especially if the patient is unwell and has radiological evidence of cavitation. Injecting drug users have a greater risk of staphylococcal lung infection and abscess formation, often associated with right sided endocarditis.

Contact with birds (typically a sick parrot) might suggest psittacosis (due to *Chlamydia psittaci*), and contact with farm animals the possibility of Q fever (due to *Coxiella burnetii*). Travel abroad, particularly to Mediterranean countries, could raise the possibility of infection with legionella, especially if several travellers are ill and there is evidence of renal or hepatic impairment. Other unusual causes should be considered in patients returning from other parts of the world—histoplasmosis or coccidiomycosis in the United States, brucella in the tropics, tuberculosis in Africa and the Far East.

Clinical signs

Uncomplicated acute bronchitis is not associated with abnormal clinical signs. In pneumonia the classic signs of consolidation with bronchial breathing are present in less than a quarter of cases, the commonest auscultatory finding being the presence of inspiratory crackles.

Diagnostic tests

Chest radiography should be considered in all patients with lower respiratory tract infection who have focal signs (box 2). In some cases this can be done after treatment has started, with the aim of identifying underlying lung disease. About 60% of patients with uncomplicated lower respiratory tract infection will have a normal chest *x* ray despite focal signs on examination.[17] It should be remembered that radiological signs of consolidation can take up to six weeks to resolve, even in patients with no underlying lung disease.

Measurement of airflow obstruction (for example, of peak expiratory flow rate) may reveal unsuspected

Box 2—Common reasons for requesting chest radiography

- Patient with adverse prognostic signs
- Patient with focal signs on examination
- Failure to improve after a course of appropriate antibiotics
- Clinical deterioration
- Signs of effusion or empyema
- Doubtful diagnosis
- Persisting haemoptysis

airways disease. Such measurement should be performed in all patients with breathlessness or wheeze as well as those with established airways disease, including asthma.

Ideally, a satisfactory sample of purulent sputum should be sent for culture, preferably before antibiotics are started. This will help to identify a specific causative agent and to establish resistance patterns of the organisms involved. However, this should not be allowed to delay treatment with antibiotics. Culture for tuberculosis should be requested if there is a clinical suspicion, the patient is in a high risk group (box 3), or if symptoms fail to resolve.

In patients ill enough to require hospital admission chest radiography is mandatory. In addition, blood cultures, a blood count, biochemical profile, and blood gas analysis should be performed. A raised neutrophil count is usual in bacterial infection except for overwhelming or legionella infection. A normal count is often seen in atypical or viral infection, but this is not specific enough to be of diagnostic value in most cases.

Box 3—Common risk factors for tuberculosis

- Poor social circumstances
- Alcoholism
- Diabetes mellitus
- Immigrant population
- Travel to developing countries
- No previous BCG vaccination
- HIV infection

Blood samples analysed for cold agglutinins and serological studies (viruses, mycoplasma, coxiella, chlamydia, legionella) will occasionally help in the management of individual patients and will also give a clearer epidemiological picture of the prevalent organisms in the area. A search for pneumococcal antigen in the sputum, blood, or urine is a useful and underused test[18] and may rapidly identify the cause of infection even if subsequent cultures are negative. Risk factors for HIV or a clinical suspicion of AIDS should prompt a request for HIV antibody testing.

Advances in molecular biology have led to newer tests such as the polymerase chain reaction and DNA probes that can identify specific gene products from various organisms (chlamydia, mycoplasma, pneumocystis, and viruses).[19,20] The application of these tests to the routine management of patients with lower respiratory tract infection has yet to be defined, but there is a clear need for such rapid, sensitive, and specific tests.

Fibreoptic bronchoscopy has a role in the investigation of patients whose symptoms fail to show improvement on clinical or radiological examination. Bronchoscopy is usually done to search for any underlying lung disease such as a bronchial tumour but the procedure is occasionally used to obtain specimens from the lower respiratory tract in cases where the identification of a specific aetiological agent is important.

Prognostic factors

Several prognostic factors are associated with an increased mortality in pneumonia (box 4).[3,10] In addition, the presence of underlying disease may delay complete resolution of the infection (box 5). These diseases should be considered and actively excluded, preferably in a hospital setting.

Management

Patients with acute bronchitis should receive advice on relief of symptoms (for example, inhalations, gargles, analgesia). Careful explanation of the likely viral cause of the infection, and the problems associated with unnecessary treatment with antibiotics, may satisfy some patients who expect a course of antibiotics.

All patients with signs of lower respiratory tract infection should receive an adequate course of an appropriate antibiotic. Regular non-sedative analgesia should be given to those with pleurisy to aid deep inspiration and coughing. Dehydration is common, due to a combination of poor fluid intake, fever, and rapid mouth breathing. This may result in tenacious sputum that is difficult to expectorate, and rehydration is essential. Physiotherapy and nebulised saline may help those with difficulty in expectorating. The need for oxygen is determined by the clinical state and blood gas analysis. High flow oxygen should be given to all those who are unwell, cyanosed, or breathless on transfer to hospital unless there is a history of chronic obstructive pulmonary disease and carbon dioxide retention. Coexisting airflow obstruction should be treated in its own right.

Box 4—Adverse prognostic factors in pneumonia

- Age >60 years
- Respiratory rate ≥ 30/min*
- Diastolic blood pressure ≤ 60 mm Hg*
- Confusion
- Blood urea >7 mmol/l*
- Arterial oxygen tension <8 kPa
- Leucocyte count >20 or $<4\times10^9$/l
- Serum albumin <35 g/l
- Multiple lobes seen to be affected on chest x ray

*Presence of two or more of these factors is associated with a 21-fold increase in mortality

Box 5—Common underlying diseases predisposing to lower respiratory tract infection

- Chronic obstructive pulmonary disease
- Bronchiectasis
- Bronchial carcinoma
- Inhaled foreign body
- Alcoholism
- Diabetes
- Immunosuppression (drugs, disease, HIV)

Treatment with antibiotics

ACUTE BRONCHITIS

Although there is little evidence that antibiotics are beneficial in otherwise healthy patients with acute bronchitis, they are often used, especially if the patient has purulent sputum. If used, they should be oral and cover the likely bacteria which can cause bronchitis. Broad spectrum antibiotics should be used with care because of the likelihood of promoting bacterial resistance to antibiotics. The risk of overgrowth by resistant organisms is lessened by prescribing for a specified period of time only. Amoxycillin or a macrolide (for example, erythromycin) are commonly used.

PNEUMONIA

Oral ampicillin or amoxycillin are appropriate first choice antibiotics in most cases. An adequate dose (for example, amoxycillin 500 mg three times a day) should be given to ensure adequate penetration of sputum. A macrolide should be considered in patients sensitive to penicillin. Fortunately, penicillin and erythromycin resistance in pneumococci remains low in the United

Kingdom (box 6),[21] although resistance rates are far higher in other parts of Europe and the United States.[20]

In patients failing to respond to the above measures, particularly those with underlying chronic obstructive pulmonary disease, organisms producing β lactamase should be suspected (resistant *H influenzae* or *M catarrhalis*, for example) and treated with a quinolone, co-amoxiclav or a second generation cephalosporin (such as cefaclor). The resistance rate of non-encapsulated *H influenzae* to ampicillin is currently around 8% in the United Kingdom (box 6). The quinolones such as ciprofloxacin give inadequate cover against the pneumococcus and should not be used as empirical first line treatment. Severely ill or vomiting patients should receive intravenous treatment.

Box 6—Some useful antibiotics for specific respiratory pathogens

Figures in parentheses represent resistance rates, when known for the United Kingdom, determined from various surveys; starred items are suitable for patients allergic to penicillin; caution must be exercised when using cephalosporins as 10% of patients will also be allergic to cephalosporins.

Streptococcus pneumoniae—penicillin (0-0·5), erythromycin* (0-2), ampicillin (0-0·5), ceflaclor (0·1).* Isolates acquired outside Britain may be resistant to one or all agents.

Haemophilus influenzae—ampicillin (7-12), cefaclor (5)*, cefixime (0·2)*, co-amoxiclav (0-5), tetracycline (4)*, ciprofloxacin

Staphylococcus aureus—flucloxacillin (0·2), fusidic acid (1-5)*, co-amoxiclav, rifampicin*

Moraxella catarrhalis—co-amoxiclav (0), ciprofloxacin,* cefaclor (1-3)*

Legionella spp—erythromycin*, rifampicin*, ciprofloxacin*

Mycoplasma spp—erythromycin*, tetracycline*

Coxiella burnettii and Chlamydia pscittaci—tetracycline*, chloramphenicol*, rifampicin*

Chlamydia pneumoniae (formally TWAR)—erythromycin*

Pneumocystis carinii—co-trimoxazole*, pentamidine*

If staphylococcal infection is suspected, flucloxacillin should be added. A suspicion of mycoplasma should prompt the use of erythromycin as first line treatment; similarly erythromycin (with rifampicin in severely ill patients) should be used if legionella is suspected. Tetracyclines are the treatment of choice for psittacosis and Q fever. Their lack of use over the past few years has allowed resistance rates in *H influenzae* to fall, and they may now be more useful in adults than previously thought. Trimethoprim and co-trimoxazole achieve low sputum concentrations, and several common organisms now have considerable resistance to these agents.

Other measures

Influenza and pneumococcal vaccination are useful preventive measures that are recommended for high risk groups of patients. There is some hope for more effective vaccines in the future.[22] Smokers should be identified and strongly encouraged to stop—older patients with respiratory infection are often concerned about underlying lung cancer (particularly if they are sent for chest radiography) and may be more amenable to help with stopping smoking at this time. There is current interest in a possible link between air pollution (including passive smoking) and acute respiratory infection, especially in children.[23]

Box 7—Differential diagnosis of lower respiratory tract infection

- Tuberculosis
- Asthma
- Pulmonary infarction
- Pneumothorax
- Pulmonary eosinophilia
- Alveolitis
- Organising pneumonitis
- Pulmonary oedema
- Subdiaphragmatic collection

Failure to respond

Failure to respond to an adequate course of an appropriate antibiotic should lead to a reassessment of the possible organism involved, consideration of an alternative disease process (box 7), underlying disease (box 5), or the development of complications (see below). Further investigation of these patients is required, including a chest radiograph and possible referral to a respiratory physician.

Complications of lower respiratory tract infection

The overall mortality from community acquired lower respiratory tract infection is not known but in patients requiring hospital admission the mortality is 5-15%.[3,7,8] Complications are uncommon but include localised bronchiectasis, abscess formation and empyema (box 8). A pleural effusion is often seen on the chest radiograph; it is usually sterile but should always be tapped for Gram staining and culture. Empyema is often related to staphylococcal infection or the presence of an underlying bronchial tumour. Sometimes when pneumonia occurs as part of a septicaemia there may be coexisting sites of infection—for example, endocarditis, osteomyelitis, septic arthritis, and cerebral abscess. Severe pneumonia can lead to rapid respiratory failure requiring intensive care and ventilation. In patients with chronic obstructive pulmonary disease, cor pulmonale and respiratory failure can be precipitated by trivial infection.

Box 8—Complications of lower respiratory tract infection

- Respiratory failure
- Recurrent pneumonia
- Postpneumonic effusion
- Abscess or empyema
- Pneumatocele formation
- Postinfective bronchiectasis
- Infection elsewhere—septic arthritis, endocarditis, etc

Conclusion

Community acquired lower respiratory tract infection remains an important cause of morbidity and mortality worldwide. Rapid and sensitive diagnostic tests should help in the management of such patients in the future, but until then initial treatment with antibiotics will be empirical in most cases. Knowledge of the likely pathogens and their resistance patterns can aid in the choice of antibiotic therapy and improve the outcome. Preventive measures such as influenza and pneumococcal vaccines and counselling regarding smoking habit are important strategies in the reduction of respiratory disease in the community.

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Current Issues in Cancer

Is there an epidemic of cancer?

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This is the first in a series of articles examining developments in cancer and updating what we know about the disease.

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Trends in cancer mortality in England and Wales are dominated by a slowly evolving epidemic of lung cancer attributable to smoking. When the substantial effects of tobacco are discounted there is no evidence that the overall incidence of cancer is rising, but striking trends are apparent for several specific tumours. These may offer important clues to aetiology.

Among members of the general public the incidence of cancer is widely perceived to be rising. It is true that many more people die from the disease now than 100 years ago, but this is largely attributable to reductions in mortality from other causes. Cancer is for the most part an affliction of old age, and as longevity increases so will the number of cancer cases. To get a clearer picture we need to look at trends in death rates at different ages.

Not all cancers are fatal, and for those in which treatment has improved (for example, lymphoma and testicular cancer) mortality statistics must be interpreted with care. Also, allowance must be made for advances in diagnostic methods. For example, new imaging techniques may have led to better recognition of pancreatic tumours and thereby contributed to an apparent increase in mortality. Nevertheless, death rates are a good starting point for examining whether we really face a cancer epidemic.

Trends in death rates at different ages

Figure 1 shows the trends in overall cancer mortality in England and Wales during 1950-89 for five year age groups. In both males and females rates increased in elderly people but declined at younger ages. It turns out that this divergent pattern was determined mainly by changes in mortality from lung cancer, which contributes more deaths than any other tumour in men, and in women is second only to cancer of the breast.

Figure 2 shows age specific death rates from lung cancer, in this case plotted not against year of death but against year of birth (calculated simply by subtracting age at death from year of death). When the data are viewed thus it becomes clear that the generation of men born just after the turn of the century has experienced peak mortality from lung cancer at all ages. In women the pattern is similar but displaced to the right, so that the highest death rates occur in those born during the 1920s. The rise in mortality in the early generations can be attributed to the growing uptake of smoking, which

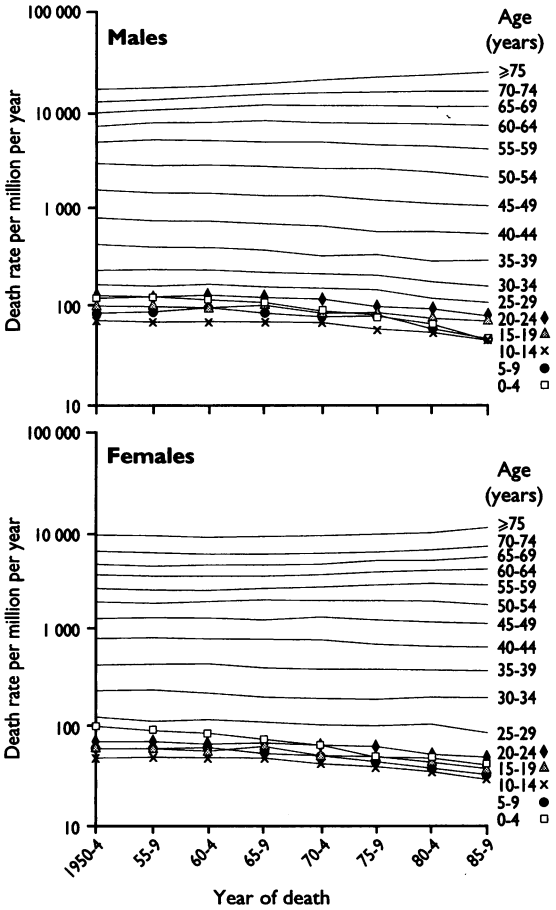

FIG 1—*All cancer death rates by year of death, age, and sex*