Fortnightly Review

The pneumococcal problem

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Streptococcus pneumoniae remains an important cause of morbidity and mortality. Despite the advent of powerful antibiotics and other medical advances, mortality associated with bacteraemic pneumonia has remained unchanged at 25% over the past 40 years.^{1 2} Moreover, although *S pneumoniae* used to be readily killed by high doses of penicillin, it is now rapidly becoming drug resistant.^{3 4} It is therefore not difficult to envisage a time when strains causing bacteraemic disease become multidrug resistant, leading to increased morbidity and mortality from pneumococcal infection. The cost of managing increased numbers of patients with drug resistant invasive infection would erode the health resources of communities, particularly in communities with high percentages of patients at increased risk of pneumococcal infections.

In this article we review the current epidemiology of pneumococcal infections; the protective host response and factors predisposing to severe pneumococcal infections; and current methods of diagnosis, prevention, and management of pneumococcal infections.

Epidemiology of pneumococcal infection

In the United Kingdom pneumococcus is responsible for 30-50% of community acquired and 8% of nosocomial pneumonia,⁵ and it may be the cause of most cases

Summary points

- Mortality from bacteraemic pneumonia has remained unchanged at 25% over the last 40 years
- Globally, *Streptococcus pneumoniae* causes over 1 million deaths in children under the age of 5 years
- Antibiotic resistant strains of *S pneumoniae* are increasing world wide. In Spain over 50% of isolates are resistant to one or more antibiotics
- Patients at increased risk of severe pneumococcal infection should be:
Informed
Immunised
Given prophylactic antibiotics

of pneumonia with no identifiable causative organism.⁶ The overall mortality from community acquired disease has been estimated at 3% but rises to over 11% with bacteraemic disease.⁶ In developing countries such as the Gambia the attack rate of pneumococcal disease is high, particularly in children, and an estimated 60-90% of lower respiratory tract infection in children under 5 years of age is caused by *S pneumoniae*.⁷ Similar or even higher attack rates have been recorded in crowded communities of adults such as the mining communities of South Africa, in whom the attack rate may be as high as 100 per 1000 population per year.⁸ Globally, the pneumococcus accounts for over 1 million deaths each year in children under 5 years of age, and preventing such deaths should be a high priority in the health development policies of developing countries.^{9 10}

S pneumoniae causes a wide variety of other infections, from meningitis, sinusitis, osteomyelitis, bronchitis, and otitis media to comparatively benign soft tissue infection. It is one of the leading causes of acute bacterial meningitis with bacteraemia, which is often most severe in preschool children, elderly people, alcoholic patients, and asplenic patients. In the United States the overall incidence of pneumococcal meningitis is 1.1 per 100 000 population, but in infants under 5 months old the incidence is 30 in 100 000 with a 10% mortality.¹¹ In developing countries pneumococcal bacteraemia with meningitis in children under the age of 2 years has a 30-35% mortality, a rate which has remained unchanged since the introduction of penicillin.¹² There is seasonal variation in the incidence of pneumococcal infections: in temperate climates infections are most frequent in winter but in the tropics they occur mostly at the end of the dry season.¹³

The pneumococcus and pneumococcal infection

Pneumococci are Gram positive diplococci. More than 84 distinct serotypes have been identified

Streptococcus pneumoniae: still a scourge of humanity

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according to differences in the antigenic composition of their capsules. Serotyping of pneumococci can be determined by the quellung (Neufeld's) reaction; specific antibodies react with capsular antigens on the surface of the organism being tested, causing capsular swelling. More than 80% of severe pneumococcal infections are caused by 23 of the 84 different serotypes.¹⁴ Virulence of pathological strains is determined by the chemical composition and size of their polysaccharide capsules which protect the organisms from phagocytosis.¹⁵

Although the carriage rate in a given community may be high, the incidence of invasive disease is usually comparatively small. Surface defence mechanisms that suppress penetration of the bacteria and changes in the host that allow defences to be breached are still not fully understood.

At any given time up to 60% of people in the community may carry pneumococci in the nasopharynx, which is the normal ecological niche of the bacterium in humans.¹⁶ A high rate of carriage of virulent strains within a population is associated with an increased rate of pneumococcal infection.¹⁷ Although the carriage rate in a given community may be high, the incidence of invasive disease is usually comparatively small. Surface defence mechanisms that suppress penetration of the bacteria and changes in the host that allow defences to be breached are not fully understood. The bacteria may gain access to the lung by aspiration and there adhere to alveolar type II cells.¹⁸ Additional factors favouring the progression of disease are viruses and cytokines, which enhance bacterial adherence in vitro.¹⁹ In animal experiments inhalation of infected aerosol particles containing pneumococcus induces an inflammatory reaction and removal of the pathogen is initiated by alveolar macrophages and neutrophils.²⁰ Occasionally, some bacteria enter the lymphatic system and then pass into the systemic circulation through the thoracic duct, causing bacteraemia. An intact immune system is required for effective clearance of invasive pneumococci from the lungs and blood.

Host immunity to pneumococcus

S pneumoniae is an extracellular pathogen that needs to be ingested by phagocytic leucocytes to be effectively killed and removed.^{20 21} This process (phagocytosis) occurs most efficiently in the presence of specific antibody for capsular antigens and other serum opsonins—for example, complement and C reactive protein. Although antibody to the cell wall polysaccharide is virtually universal, protection is widely believed to be mediated by serotype specific anticapsular antibodies of IgG class, particularly the IgG₂ subclass.²² In the lung, alveolar macrophages are the first line of cellular defence. Interaction of pneumococcus with these cells induces an inflammatory response, which results in the accumulation of neutrophils and increased concentrations of serum opsonins at the site of invasion.

Pneumococci entering the blood stream are removed by cells of the reticuloendothelial system.²³ Splenic macrophages can remove bloodborne pneumococci effectively even without opsonising capsular antibodies. After the loss of these macrophages, as in asplenic states, bloodborne pneumococci can be removed by other cells of the reticuloendothelial system such as Kupffer's cells of the liver, but these cells need the pneumococci to be coated with high concentrations of specific capsular antibodies to remove them efficiently.²⁴ The spleen may also be an important site of production of these antibodies.²³

Therefore, in assessing immunity most laboratories now measure antibody to capsular polysaccharide in different solid phase assays and after adsorption of non-specific antibody to pneumococcal cell wall polysaccharide. It is assumed, but not proved, that a concentration of antibody nitrogen of 300 mg/l equates to protection from invasive disease in a healthy adult.⁷ Interestingly, however, infants (who have a notoriously poor immune response to polysaccharide antigens) seem to have benefited in Papua New Guinea from the widespread use of the pneumococcal polysaccharide vaccine, which induced an antibody concentration about a 100th that of the "protective level in adults."²⁵ Only recently has there been a move to standardise solid phase assays for the determination of serotype specific antibody concentration, and even more crucial is the fact that there are still no established serological correlates of protection. Although components of the pneumococcal bacterial cell such as pneumolysin and pneumococcal surface protein A have known pathogenic effects, the role of antibody raised against these components in protecting against invasive disease in humans is not clear.²⁶

Abnormalities of host defence in vulnerable patients

Key elements of host defence against pneumococcus may be identified by considering immune and non-immune defects which increase susceptibility to pneumococcal infections (box).

Risk factors associated with pneumococcal infection

- Physiological
 - Very young age (<2 years of age)
 - Old age
- Non-immunological defects
 - Skull fracture
 - Disruption of bronchial epithelium—for example, influenza, noxious chemicals, smoking
 - Obstruction of eustachian tube
 - Decreased vascular perfusion—for example, sickle cell anaemia, congestive heart failure
- Immunological defects
 - Primary and secondary antibody deficiencies—for example, hypogammaglobulinaemia, IgG subclass deficiencies, specific antibody deficiency, B cell malignancies
 - Phagocyte abnormalities—for example, neutropenia, hyposplenism, cirrhosis of the liver
 - Complement deficiencies—for example, of C2 or C3

Disruption of natural barriers, such as skull fracture, can act as a route of entry for pneumococcus, leading to recurrent and severe pneumococcal infections. Damage to bronchial epithelium, as occurs with influenza viral infection or after inhalation of noxious substances, is associated with an increased incidence of secondary pneumococcal pneumonia.²⁷ Underperfusion and oedema of the lung as seen in sickle cell infarction, congestive heart failure, and the nephrotic syndrome also predispose to an increased incidence of pneumococcal pneumonia.²⁷

Patients with an inherited or acquired antibody deficiency, particularly IgG₂ subclass deficiency, fail to make adequate quantities of opsonising antibodies.²⁸ Children under the age of 2 years old do not make adequate IgG₂ antibody and respond poorly to encapsulated bacteria such as pneumococci.²⁹ This may account for the increased incidence of encapsulated bacterial otitis media and pneumococcal bacteraemia in this age group.

Pneumococcal bacteraemia also peaks in elderly people and may be due to the increased prevalence of diseases such as congestive heart failure, diabetes mellitus, and haematological malignancies. Defective phagocyte function has been reported in patients with poorly controlled diabetes and in hypogammaglobulinaemia, which may occur in haematological malignancies such as chronic lymphocytic leukaemia. Although impaired immune responses and loss of immune memory may occur in old age, healthy elderly people reportedly make adequate responses to pneumococcal immunisation.³¹

Asplenia, which causes a reduction in phagocytic mass, is arguably the commonest abnormality associated with undue susceptibility to *S pneumoniae*. This micro-organism accounts for about half of the cases of bacterial septicaemia in asplenic patients.²³ Pneumococcal sepsis after splenectomy is severe and rapid in onset. There are a few prodromal symptoms, typically nausea, vomiting, headache, or confusion. Thereafter, progression is rapid, with high fever, circulatory collapse, coagulopathy, coma, and death within a few hours. Septicaemia, if present, is overwhelming, with large numbers of circulating organisms and often no obvious focus of infection.³²

Other defects in the complement pathway occur in conditions such as sickle cell disease and asplenic disorders and may predispose to increased susceptibility to pneumococcal infections.²³ Complete deficiencies of complement components, such as C2 and C3, are associated with life threatening pneumococcal infections,³³ but fortunately these are rare. Recently, it has been reported that inheritance of certain receptor allotypes for the heavy chain of immunoglobulin G expressed by phagocytes is associated with defective ingestion of encapsulated organism and may predispose to pneumococcal pneumonia.³⁴

Diagnosing pneumococcal infection

Isolation of pneumococci from blood or other normally sterile sites such as cerebrospinal fluid or synovial or pleural fluids remains the ideal standard for diagnosis.

Isolation of pneumococci from blood or other normally sterile sites such as cerebrospinal fluid or synovial or pleural fluids remains the standard way of diagnosing pneumococcal infections. Establishing the diagnosis in non-bacteraemic disease can be problematic, especially in patients presenting with muted forms of pneumococcal infections such as infants, elderly people, or immunocompromised patients. Gram staining of "properly collected sputum specimens" (>25 phagocytes and <10 epithelial cells per microscopic field at 1000× magnification) has 62% sensitivity and 85% specificity for diagnosing pneumococcal pneumonia.³⁵ This method has the advantage of being inexpensive and of giving a presumptive diagnosis within minutes, but it is not applicable in young children, who are usually treated empirically. Newer techniques such as the use of the polymerase chain reaction for detecting *S pneumoniae* DNA in blood samples with negative results on culture is encouraging but awaits further clinical evaluation.³⁶ Pneumococcal serology as a tool for aetiological diagnosis, for epidemiological surveys, and for studies on the clinical efficacy of pneumococcal vaccines would be invaluable but little progress has been made on this.

Management of vulnerable patients

The morbidity and mortality from non-bacteraemic pneumonia is low (3%) but rises up to 25% in bacteraemic disease. Management strategies are aimed at

preventing bacteraemic disease in patients most at risk of pneumococcal infections. Though consensus on what constitutes optimal care of patients at high risk is poor, some general principles are useful.

PATIENT EDUCATION

Patients at risk of severe pneumococcal infections need to be educated about the risks and the importance of seeking medical help at the onset of any illness. Patient information leaflets are becoming more widely available in general practitioners' surgeries, in hospitals, and from self help groups such as the Splenectomy Trust (c/o Mrs P Boyer, Swinbrook Post Office, Swinbrook, Oxfordshire OX18 4EE). The use of a Medic Alert bracelet is also recommended.³⁷

IMMUNISATION WITH PNEUMOCOCCAL VACCINE

Routine monitoring of antibody concentrations after immunisation to ensure that the patient has mounted an immune response and to observe the rate of antibody decline may be beneficial, but there is a need to define serological correlates of protection to define when reimmunisation may be necessary.

The Department of Health recommends immunisation with the 23 valent vaccine "for all those aged over two years in whom pneumococcal infection is likely to be common and/or dangerous" (box).³⁸

Diseases for which immunisation with pneumococcal vaccine is recommended³⁸

- Homozygous sickle cell disease
- Asplenia or severe dysfunction of the spleen
- Chronic renal disease or nephrotic syndrome
- Immunodeficiency or immunosuppression due to disease or treatment, including HIV infection
- Chronic heart disease
- Chronic lung disease
- Chronic liver disease, including cirrhosis
- Diabetes mellitus

Protection is thought to last for five years, after which antibody concentrations wane and people at risk should be reimmunised.²⁶ The overall efficacy of the vaccine in preventing pneumonia is 60-70%,³¹ but its efficacy is reduced in immunosuppressed patients, patients with haematological malignancies, HIV infection, and sickle cell disease, transplantation recipients, and possibly elderly patients with chronic obstructive lung disease.²⁶ Protection may last only two to three years in some patients at high risk^{39 40}; perhaps in these cases reimmunisation should be considered earlier. Since the response to immunisation in patients at high risk may be poor and unsustained, we believe that it is advisable to monitor antibody concentrations three to four weeks after immunisation and then annually to ensure that the patient has responded adequately to the vaccine and to determine the best time for reimmunisation. Several departments of immunology in the United Kingdom currently offer tests for measuring pneumococcal antibody concentrations. Sensitive enzyme linked or radioimmunoassays are commonly used. Methods vary between centres, but attempts are being made internationally to develop a standard test. The average cost of a test is about £10. In cases that fail to respond to immunisation the managing clinician must maintain a

vigilant approach and should consider antibiotic prophylaxis or protection with regular intravenous immunoglobulin when appropriate.

ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis is an essential part of the care of patients at risk of pneumococcal disease. However, the duration of prophylactic antibiotic cover remains controversial. For example, recommendations after splenectomy include antibiotic cover up to the age of 16 years in children, for the first two years in adult patients, and for a lifetime in both groups.^{41 42} Opponents of long term prophylactic antibiotics argue that the risk of invasive pneumococcal disease is small and that long term antibiotic use is excessive and may promote the emergence of antibiotic resistant strains.⁴³

Penicillin is still the mainstay of prophylaxis; in adults phenoxymethylpenicillin 500 mg twice a day is the recommendation. Erythromycin should be considered as an alternative for patients sensitive to penicillin.⁴² Long term drug use is not without problems, and even educated patients may become non-compliant. A more pragmatic approach may be to ensure that patients have ready access to at least a 48 hour supply of antibiotics to be taken at the onset of infection and that they seek medical attention as soon as possible thereafter. This approach would ensure that the start of treatment is not unavoidably or unnecessarily delayed.

ANTIBIOTIC RESISTANT PNEUMOCOCCI

The exquisite sensitivity of the pneumococcus to antibiotics has delayed the progress of development of other "weapons of warfare" against this micro-organism. Over the past two decades there has been a rapid emergence of antibiotic resistant pneumococci posing a formidable threat to health in developed and developing countries alike.

Antibiotic resistant strains of *S pneumoniae*—defined in terms of the lowest antibiotic concentration that inhibits microbial growth (minimal inhibitory concentration)—have been identified world wide, with evidence that the prevalence of resistant isolates is high in some areas.^{4 44} A report from Spain, which has a high prevalence of drug resistant pneumococci, showed that 57% of over 5000 isolates between 1979 and 1994 were resistant to one or more antibiotics. Resistance to a single drug was shown in 20%, to two drugs in 15%, and to three or more drugs in 22%.⁴⁴ In Britain drug resistant isolates seem to be less prevalent than in Spain, though more laboratories throughout the country have been reporting penicillin resistant pneumococci. Unfortunately, in Britain there is no consensus between laboratories for which antibiotics should be tested, indicating the need for a national standard so that the incidence of penicillin resistant strains can be calculated. However, the number of laboratories reporting resistant strains is an index of how widespread such strains are. These reports rose from 3% in 1989 to 21% in 1992.⁴⁵

Most penicillin resistance is associated with serotypes 6, 9, 14, 19, and 23. Epidemiological studies have shown that these five serotypes account for over 70% of isolates from infected children under 2 years of age and that they are associated with prolonged nasopharyngeal carriage and rapid reacquisition.⁴⁶ Unlike other Gram positive cocci that may be resistant to penicillin through the production of β lactamases, the mechanism of antibiotic resistance in the pneumococci is different. Penicillin resistance occurs through molecular changes in the bacterial target of β lactam antibiotics, the penicillin binding proteins.⁴⁷ In addition, penicillin resistant strains are likely to be resistant to many antibiotics.

In patients infected with penicillin sensitive pneumococci, penicillin remains the preferred treatment. However, there are few guidelines for managing patients infected with penicillin resistant strains. This subject was extensively reviewed recently by Lister.⁴⁸ Third generation cephalosporins are the preferred initial treatment in pneumococcal meningitis caused by antibiotic resistant pneumococci. However, there have been increasing reports of clinical failures, mainly because of infection with highly resistant organisms. In such cases combination treatment such as ceftriaxone and vancomycin has been used with good effect. Chloramphenicol, which has a long history of efficacy in children with meningitis and is a commonly used antibiotic in developing countries, is not recommended because of clinical failures in penicillin resistant pneumococcal infections.

High dose penicillin is still the preferred treatment in cases of pneumococcal bacteraemia and pneumonia without meningitis as the concentrations in serum and soft tissues are many times greater than the minimal inhibitory concentrations for these organisms.⁴⁸ In acute otitis media, a less serious condition, a stepwise approach to antibiotic treatment is advised, starting with amoxycillin.

The future

Globally, the pneumococcus accounts for over 1 million deaths each year in children less than 5 years old. Prevention of such deaths should be a high priority in the formulation of health policies of developing countries.

S pneumoniae has always been a clinically significant cause of morbidity and mortality but never more so than now because of the emergence of strains resistant to many antibiotics. One approach to this problem is to improve host protective immunity to the organism by immunisation. Current vaccines have a good safety record but limited efficacy, especially in the patients most in need of protection.

This may be overcome by the development of conjugated vaccines. Briefly, the pneumococcal polysaccharide capsules are attached to a protein carrier in the same way as the highly successful conjugated *Haemophilus influenzae* type b vaccine. The conjugation step renders the vaccine more immunogenic to the immune system⁴⁹ and higher concentrations of antibody to capsular antigens are attained. However, these vaccines will contain a limited number of pneumococcal capsules as only seven to nine capsular polysaccharides can be attached to the protein carrier. While such conjugated vaccines will provide effective protection to strains contained within the vaccine, patients at risk may remain susceptible to strains not contained in the vaccine.

Safety and immunogenicity of conjugated pentavalent pneumococcal vaccines have been reported in a few trials. The clinical efficacy remains to be tested as well as the effect of such vaccines on pneumococcal carriage and the pattern of pneumococcal disease. A decrease in carriage will be important epidemiologically, as this will imply protection even for those not vaccinated in the community. Furthermore, since systemic vaccination with polysaccharide vaccines does not induce a protective immune response to *S pneumoniae* in the groups most vulnerable to invasive disease such as infants, elderly people, and immunocompromised patients, another route of immunisation may be worth exploring. Mucosal immune responses develop early in life and function well in elderly people, so mucosal vaccination by the oral, intratracheal, or intranasal routes are options worth considering.

Despite 100 years of pneumococcal research our knowledge of this organism is far from complete—it

remains a formidable, worldwide threat to health, particularly to children in poor populations. Clearly, this is an international problem requiring new approaches to combating an old foe, who once again is winning the battle.

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Lessons from international experience in controlling pharmaceutical expenditure II: influencing doctors

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This is the second of three papers that review international policies to control spending on drugs and to improve the efficiency of drug use. This paper reviews policies influencing doctors' prescribing of drugs—particularly the use of budgetary restrictions, information and feedback, and guidelines—and evaluates the impact of these policies. Studies evaluating incentive systems are limited, but evidence suggests that providing information on its own will not lead to substantial changes in practice and that more active strategies should be evaluated

In Britain several initiatives have been introduced with the aim of improving the efficiency of general practitioners' prescribing behaviour. These include providing data on prescribing analysis and cost (PACT), indicative prescribing budgets, and general practice fundholding. The impact of these policies on prescribing costs has been inadequately evaluated, but it seems to have been limited.¹ Can British policy makers learn from other countries' initiatives?

In this paper we examine the impact of policies aimed at directly influencing doctors' prescribing practice. Details of our literature search are in the first paper in this series.

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