Emergence of *Streptococcus pneumoniae* with high-level resistance to cefotaxime in Hong Kong

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We report on two cases of pneumococcal infection caused by strains demonstrating high-level cefotaxime resistance (minimal inhibitory concentration, 4 μg/mL). One patient had acute community-acquired meningitis with bacteraemia and the other had bacteraemia probably as a result of nosocomial pneumonia. Both patients died despite treatment with third generation cephalosporins. This is the first report from Hong Kong of infection with *Streptococcus pneumoniae* with high-level cefotaxime resistance that resulted in death. The emergence of high-level resistance to third-generation cephalosporins will result in treatment failure when these agents or penicillin are used alone, especially in cases of severe infection, such as meningitis, in which drug penetration of the blood-brain barrier is critical. The treatment of severe infections due to these isolates is problematic. Indiscriminate use of life-saving third-generation cephalosporins as out-patient treatment of minor infections or as first-line therapy for uncomplicated community-acquired infections in the hospital and in the community should be discouraged.

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Introduction

Infection with *Streptococcus pneumoniae* is one of the most common causes of community-acquired acute bacterial pneumonia and meningitis worldwide. The standard therapy with penicillin G (benzylpenicillin) has been challenged in the past decade by the emergence of strains that have moderate to high levels of penicillin resistance. Penicillin-resistant *S pneumoniae* was first isolated in Hong Kong in 1989.[1] Since then, the prevalence of pneumococci demonstrating moderate to high levels of penicillin resistance has been increasing in Hong Kong.[2] The treatment of choice for severe infections that are caused by penicillin-resistant pneumococci has been to prescribe the cephalosporins ceftriaxone and cefotaxime. Of all cephalosporins, these two drugs possess the best activities against pneumococci.[3] In this article, they are referred to as third-generation cephalosporins with anti-pneumococcal activity (CAPA). We report on two fatal cases of pneumococcal infection in Hong Kong that demonstrated a high level of resistance to third-generation CAPA. This is the first report of the isolation of *S pneumoniae* isolates with such a high level of CAPA resistance in Hong Kong. The therapeutic options for treating pneumococcal infections in different clinical situations and their rationale are discussed.

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Case reports

Case 1

A 47-year-old man was admitted to the Queen Mary Hospital because of a 1-week history of fever and prostration. The patient was mentally retarded owing to an episode of paediatric meningitis and he was living at home. He had a cough and was producing mucopurulent sputum; he had been treated by a general practitioner for a chest infection. On the day of hospital admission, the patient's condition suddenly deteriorated and mental dullness increased. The oral temperature was 39°C and he was tachycardic (pulse rate, 110 beats per minute). There was clinical evidence of dehydration and marked neck stiffness. The score on the Glasgow coma scale was 9; computed tomography of the brain showed evidence of bilateral hydrocephalus. External ventricular drainage

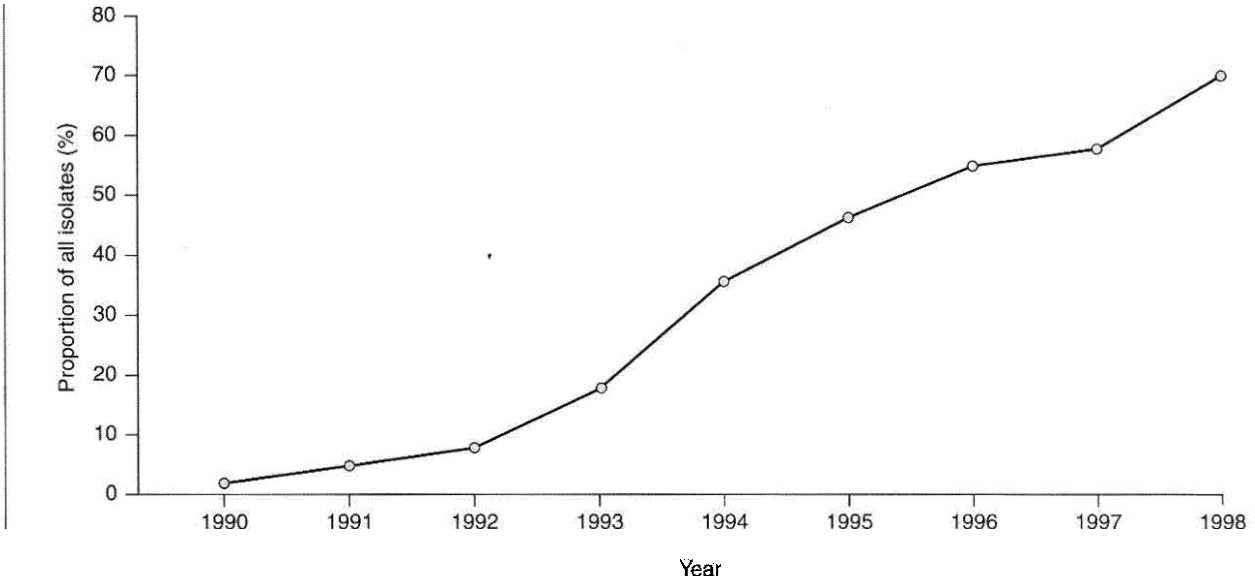

Fig. Isolation of penicillin-resistant *Streptococcus pneumoniae* in Hong Kong

of the cerebrospinal fluid (CSF) was performed immediately. Gram smearing of the CSF showed numerous leukocytes and Gram-positive diplococci. The total cell count of the CSF was 520 x 10^6/L (97% neutrophils, 1% lymphocytes, 2% mononuclear cells); the glucose concentration in the CSF was <1.1 mmol/L (blood glucose, 6.9 mmol/L) and the protein concentration was 3.7 g/L. Intravenous ceftriaxone 2 g every 12 hours was given as empirical therapy for bacterial meningitis. However, the patient died 2 days after hospital admission. Blood and CSF cultures yielded *S pneumoniae*; the minimal inhibitory concentration (MIC) of penicillin was 2 μg/mL and that of cefotaxime was 4 μg/mL.

Case 2

An 84-year-old man was admitted to the Queen Mary Hospital for the management of a stage III sacral pressure sore. He had a history of dementia, epilepsy due to previous cerebrovascular accidents, atrial fibrillation, and congestive heart failure. At the time of hospital admission, culture of the pus from the sacral sore yielded various bacteria, which indicated possible infection of the sacral sore. The patient was given intravenous cefuroxime 750 mg every 8 hours for 10 days and cloxacillin 500 mg every 6 hours for 8 days. Oral co-amoxiclav and metronidazole were also given. The patient's condition remained stable but was complicated by episodes of nosocomial pneumonia. A low-grade fever (temperature, 38.2°C) developed on day 35 of hospital admission. Blood culture was performed on day 40, when increased lower-lobe haziness of the right lung was visible on the chest X-ray. A course of intravenous cefoperazone-sulbactam 1 g every 12 hours was commenced. Hypotension developed on that evening, and the blood culture was found to positive for *S pneumoniae* the following day. The patient died on day 43. The isolate of *S pneumoniae* was subsequently found to have a penicillin MIC of 1 μg/mL and a cefotaxime MIC of 4 μg/mL.

Discussion

Clinically important infections caused by *S pneumoniae* include community-acquired pneumonia, acute sinusitis, acute otitis media, bacteraemia, and meningitis. Multiresistant *S pneumoniae* infection is characterised by the reduced susceptibility of the bacterium to penicillin and sometimes the CAPA; isolates are usually simultaneously resistant to multiple antibiotics such as macrolides, clindamycin, co-trimoxazole, and sometimes quinolones. Hong Kong is second to South Korea in the prevalence of penicillin-resistant pneumococci in Asia (69.0% versus 79.7%).[4] The speed at which penicillin-resistant *S pneumoniae* has emerged in Hong Kong is alarming (Fig). Since the first isolation of penicillin-resistant pneumococci in Hong Kong in 1989,[1] the percentage of moderately to highly resistant pneumococci has risen to 70% in 1998.[2,5] A recent territory-wide study found that 31%, 15%, and 54% of *S pneumoniae* isolates were found to be susceptible, moderately resistant, and resistant to penicillin G, respectively.[4]

The MIC cut-off levels for various classes of susceptibility of *S pneumoniae* to penicillin according to the United States National Committee for Clinical Laboratory Standards are as follows[6]: sensitive,

Table. Recommended treatment regimens for different diseases caused by *Streptococcus pneumoniae*[3]

Disease	Treatment* if bacterial isolate is:		
	Susceptible to penicillin	Moderately resistant to penicillin	Resistant to penicillin
Acute sinusitis and otitis media†	Amoxycillin (oral) (250 mg three times daily)	Amoxycillin (oral) (500-750 mg three times daily)	Amoxycillin (oral) (750-1000 mg three times daily)
Pneumonia	Penicillin G (1-2 megaunits every 4-6 h)	Penicillin G (3-4 megaunits every 4 h)	CAPA‡ (if susceptible or moderately resistant to CAPA) or vancomycin (if resistant to CAPA; 500 mg every 6 h)
Bacteraemia	Penicillin G (1-2 M megaunits every 4-6 h)	Penicillin G (3-4 megaunits every 4 h)	CAPA (if susceptible to CAPA) or vancomycin (if moderately resistant or resistant to CAPA; 500 mg every 6 h)
Meningitis	Penicillin G (1-2 megaunits every 4-6 h)	Ceftriaxone (2 g every 12 h) or cefotaxime (3-4 g every 4 h) + vancomycin + rifampicin; specialist advice from clinical microbiologist is recommended	

* Intravenous unless otherwise stated; dosages as for a 70-kg adult with normal renal function
† Alternative agents can be considered if isolate is susceptible, eg macrolides, quinolones, or co-trimoxazole
‡ CAPA cephalosporins with anti-pneumococcal activity (eg ceftriaxone 1 g every 12 h and cefotaxime 1 g every 6-8 h)

≤0.06 μg/mL; moderately resistant, 0.12 to 1 μg/mL; and resistant, ≥2 μg/mL. The corresponding MIC values for the bacterium's susceptibility to ceftriaxone and cefotaxime are ≤0.15 μg/mL, 1 μg/mL, and ≥2 μg/mL. The MIC of cefotaxime of 4 μg/mL in the two cases presented in this report show that *S pneumoniae* isolates that are highly resistant to cefotaxime have now been detected in Hong Kong. The MIC of *S pneumoniae* to β-lactams carries more than academic interest; it bears considerable clinical significance in terms of the choice of antibiotics in different clinical situations with respect to the achievable antibiotic concentrations in blood and body fluids. The choice of a rational regimen against multiresistant pneumococcal infections depends on two key considerations: the site of infection (eg central nervous system [CNS] or non-CNS infection) and the level of resistance to the β-lactam antibiotics (in particular, penicillin, and CAPA). The recommended regimens in different situations are listed in the Table.[3] Owing to the different patterns of resistance to different groups of antibiotics, it is important for clinicians to communicate with clinical microbiologists in difficult cases, regarding the interpretation of the MIC data and the potential use of alternative agents. For example, infections due to isolates that are fully susceptible to penicillin can be treated with penicillin G if the infection is severe, or with oral amoxycillin in uncomplicated respiratory tract infections such as acute otitis media and sinusitis. For uncomplicated respiratory tract infections that are caused by penicillin-resistant *S pneumoniae*, oral amoxycillin given in higher than usual doses is often effective. This is due to the fact that the amoxycillin MIC is generally lower than the penicillin MIC by two-fold. Oral amoxycillin is preferable to ampicillin because the former has a higher bioavailability (74%-90% versus 30%-50%, respectively).[8]

The CAPA were initially very effective against penicillin-resistant pneumococci. *Streptococcus pneumoniae* that was resistant to CAPA started to appear since the early 1990s.[3] Infections caused by pneumococci with low-level CAPA resistance may still be managed with high doses of these antibiotics, provided that the infections do not involve CNS. Treatment failure has been noted, however, and is especially common in cases of meningitis owing to the relatively lower levels of antibiotic in the CSF.[3,7,9] The penetration of most antibiotics through the normal meninges is poor, and even in the presence of inflammation, the CSF levels of penicillin G, ceftriaxone, cefotaxime, and vancomycin are only 8%, 16% to 32%, 27%, and 7% to 21% of the serum levels, respectively.[8] The poor penetration of most β-lactam antibiotics into the CSF is partly compensated by the use of higher doses of antibiotics. Nevertheless, in the presence of moderate to high levels of β-lactam resistance, the peak antibiotic levels in the CSF may be marginally above the MIC, and may even drop below the MIC when trough concentrations are reached. This effect probably accounts for treatment failure of the cephalosporins or even vancomycin alone when meningitis is caused by multiresistant pneumococci. Hence, even when the level of resistance to penicillins and cephalosporins is moderate by MIC criteria, meningitis caused by these strains of *S pneumoniae* must be treated very aggressively with antibiotic combinations (Table).

Infections that do not involve the CNS are generally less problematic because most β-lactam antibiotics can be given in relatively high doses, thereby ensuring that drug concentrations in the blood are many times greater than the MIC.

Apart from β-lactams, other groups of antibiotics may be considered in the treatment of multiresistant pneumococcal infections.[3,10] The only agents that *S pneumoniae* is universally sensitive to—at least for the time being—are the glycopeptides such as vancomycin. These drugs may be the only treatment in cases of severe infection that is caused by *S pneumoniae* with high-level resistance to CAPA. Their use as first-line agents in the treatment of uncomplicated pneumococcal infections that are caused by *S pneumoniae* with lower levels of β-lactam resistance is not recommended in view of the concern for the emergence of vancomycin-resistant Gram-positive bacteria, the potential toxicity of the drugs, and their poorer penetration into body fluids as compared with the β-lactams. The clinical efficacy of fourth-generation cephalosporins (eg cefepime and cefpirome) and meropenem has not been established, although the in vitro activities of these agents against local isolates are not superior to those of CAPA.[4] The other commonly used third-generation cephalosporins ceftazidime and cefoperazone-sulbactam are less effective than CAPA and are not recommended when pneumococcal infection is suspected. The macrolides erythromycin, clarithromycin, and azithromycin may be useful in managing uncomplicated respiratory tract infections; the latter two drugs are particularly valuable because they achieve very high tissue levels. Unfortunately, 78.5% and 75.1% of local isolates are resistant to erythromycin and azithromycin, respectively.[4] And for clindamycin, there is a 78.6% resistance rate locally.[4] The use of macrolides and clindamycin is limited by their relatively low levels in the CSF. Similarly, the prevalence of quinolone resistance in local isolates precludes their use in the treatment of pneumococcal infections.[4] Newer antibiotics that may be considered include the streptogramins and oxazolidinones; however, clinical efficacy data are scanty for these agents.

Inappropriate antibiotic usage, both in the community and in the hospitals, has spawned a host of multiresistant bacteria in recent years. Prominent examples are methicillin-resistant *Staphylococcus aureus*,[11] penicillin-resistant *S pneumoniae*, and the extended-spectrum β-lactamase–producing Enterobacteriaceae. The introduction of new antibiotics against these organisms lags far behind their appearance. *Streptococcus pneumoniae* is one of the few, if not the only, multiresistant bacteria for which an effective vaccine is available for prophylaxis. The use of pneumococcal vaccine has not been common locally. However, in view of the recent emergence of high-level penicillin and cephalosporin resistance, using a vaccine should be seriously considered for the high-risk population, such as patients who have functional or anatomical asplenia, or chronic respiratory and cardiovascular diseases, or who are immunocompromised. Ultimately, the only effective means of preventing further spread of multiresistant pneumococci is by the judicious use of antibiotics, because previous use of broad-spectrum antibiotics is strongly associated with the appearance of multiresistant bacteria. The inappropriate use of the third-generation cephalosporins is therefore strongly discouraged.

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