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Clinical outcome and impact on health care utilisation of invasive pneumococcal disease in the era of antimicrobial resistance

Key Messages

1. Resistance to penicillins, macrolides, and fluoroquinolones was common among invasive pneumococci isolated from both children and adults. Most such isolates, including the majority of the antibiotic-resistant strains, were of serotypes targeted in the currently available 7-valent and 23-valent pneumococcal vaccines.
2. Bacteraemic pneumococcal infections conferred high mortality, especially in patients aged 65 years or above living in old-age homes. We suggest that these subjects be prioritised for pneumococcal vaccination.
3. At the current levels of penicillin resistance, bacteraemic pneumococcal infection (outside the central nervous system) caused by penicillin–non-susceptible strains were not associated with increased mortality and higher health care utilisation than infections by penicillin-susceptible strains, provided they are promptly and appropriately treated intravenously with β-lactams having good anti-pneumococcal activity.

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Introduction

Increasing rates of antimicrobial resistance in *Streptococcus pneumoniae* raised issues on how best patients should be treated and whether the currently available vaccines are relevant in Hong Kong.

Aims and objectives

This study evaluated the prevalence of penicillin and other antimicrobial resistance, among strains of *S pneumoniae* causing invasive infections, and the impact of such resistance on clinical outcomes and health care utilisation, in patients infected with invasive strains. The study also aimed to document the serotypes of *S pneumoniae* that cause invasive infection among adults and children.

Methods

This study was conducted from November 2002 to October 2004. Isolates of *S pneumoniae* obtained from the blood and cerebrospinal fluid of patients admitted to five hospitals in Hong Kong during 1995 to 2001 were studied with respect to their serotypes and susceptibilities to antimicrobial agents.[1] The patient records were reviewed. 'Underlying disease' was defined as a disease that predisposed to infection, altering defence mechanisms or causing functional impairment. Infection was classified as 'severe' when: the Pitt bacteraemia score was ≥4, the Pneumonia Severity Index was high risk (classes IV and V), intensive care unit (ICU) admission ensued, the underlying disease was rapidly fatal. Univariate and multivariate analyses were performed to identify variables associated with patient mortality.[2] Overall mortality was defined as death during hospital admission. Bacteraemia-related mortality was defined as death during 2 to 7 days following the first positive blood culture.

Results

Antimicrobial susceptibilities and serotype distribution

The numbers of isolates obtained from different age-groups were as follows: <2 years, 48; 2-5 years, 40; 6-15 years, 11; 16-49 years, 33; 50-64 years, 27; and ≥65 years, 106. In all, 256 (97%) of these isolates were from blood, 6 from cerebrospinal fluid, and 3 from brain abscesses. The susceptibilities of the corresponding 265 pneumococcal isolates to nine antimicrobial agents are summarised in Table 1.

In children (≤15 years), the rate of penicillin non-susceptibility was significantly higher than that in adults (49% vs 31%, P=0.004). In all, eight of these isolates could not be typed, and 34 different serotypes were identified among the remainder. Serotype 14 was the most common (25%). Four serotypes (6B, 14, 19F, and 23F) accounted for 93% of all penicillin–non-susceptible isolates and 85% of all clarithromycin–non-susceptible isolates. Serotypes targeted in the 7-valent pneumococcal conjugate vaccine formulations (4, 6B, 9V, 14, 18C, 19F, and 23F) provided cover against 90% and 91% of penicillin–

Table 1. Susceptibilities of pneumococcal isolates to 11 antimicrobial agents

Antimicrobial agents	% of isolates		
	Susceptible	Intermediate	Resistant
Penicillin	62.6	20.0	17.4
Amoxicillin	99.6	0.4	0.0
Cefotaxime	97.0	2.6	0.4
Cefepime	76.2	21.9	1.9
Clarithromycin	36.6	0.4	63.0
Vancomycin	100.0	0.0	0.0
Levofloxacin	96.2	0.0	3.8
Gatifloxacin	96.2	0.8	3.0
Moxifloxacin	97.0	0.8	2.3

and clarithromycin–non-susceptible strains isolated from persons with age ≤5 years, respectively. Cover provided by the 7-valent conjugate vaccine for all isolates from young children (≤5 years) was 90% (79/88). Of the penicillin–non-susceptible pneumococci, 90% from children aged ≤5 years and 55% from persons of all ages were of serotypes that are targeted in the 7-valent pneumococcal conjugate vaccine. In all, 94% of the isolates from children aged ≤5 years and 93% from persons of all ages were of serotypes targeted in the 23-valent polysaccharide vaccine.

Clinical data for patients included in analysis

The medical records were not available for 49 patients, who were therefore excluded from the analysis. The excluded patients did not differ significantly from the remainder in terms of gender, age, and proportion of strains with penicillin non-susceptibility (data not shown). The final cohort included 216 episodes of bacteraemia from 214 patients (139 males), with a mean age of 40 (SD, 33.7) years. Bacteraemia was associated with pneumonia in 144 patients, meningitis in 18 patients, and with infection at other sites in 13 others (otitis media, peritonitis, arthritis or soft tissue infections). In two patients, bacteraemic pneumonia was complicated by meningitis. In the remaining 41 patients, bacteraemia was primary in origin. Most patients had an underlying condition; the most common being diabetes (8.8%), chronic lung disease (4.2%), chronic liver disease (4.2%), and chronic renal disease (3.2%). An immunosuppressive condition was present in 44 (20%) of the patients, including solid tumour (n=16), haematological malignancy (n=20), treatment with systemic steroids (n=11), human immunodeficiency virus infection (n=1), splenectomy (n=1) and congenital immunodeficiency (n=1). Of the 216 pneumococcal isolates, 135 (62%) were penicillin-sensitive, 45 (21%) displayed intermediate penicillin sensitivity and 36 (17%) were penicillin-resistant. Among the 216 patients, 79 (37%) were initially treated with an antibiotic from the penicillin group, 39 (18%) were given a broad spectrum β-lactam with high anti-pneumococcal activity, 20 (9%) were given combinations including a macrolide, and 69 (32%) received other antibiotics. No antibiotic therapy was administered to nine (4%) of the patients. In 20 patients, vancomycin was initially included in combination with another agent.

Table 2. Mortality among patients with pneumococcal bacteraemia by age, 1995-2001

Age-group (years)	No. of deaths/total, n=216
0-2	2/40 (5%)
3-5	2/34 (6%)
6-15	0/10 (0%)
16-49	6/29 (21%)
50-64	8/22 (36%)
≥65	41/81 (51%)

In the patients treated with the penicillin group, 49 (62%) received amoxycillin-clavulanate. In those treated with broad-spectrum β-lactams, 35 (90%) received cefotaxime, ceftriaxone, or cefepime. Admission to ICU ensued in 49 (23%) patients. The same number of patients required mechanical ventilation. Mortality rates stratified according to age are summarised in Table 2.

Table 3 compares the clinical characteristics of patients with bacteraemia caused by penicillin-susceptible (n=135) and penicillin–non-susceptible (n=81) strains. There were no significant differences in the initial antibiotic therapy between the two groups.

Univariate (data not shown) and multivariate mortality analyses were carried out to assess relevant variables. Although there was a trend for penicillin resistance to associate with bacteraemia-related mortality, this did not reach statistical significance. In multivariate analysis, variables independently predictive of overall mortality were admission from an old-age home (odds ratio [OR]=6.25, 95% confidence interval [CI]=1.05-37.2, P=0.04), severe disease (OR=48.6, 95% CI=4.6-512.4, P=0.001) and multilobar infiltrate (OR=30.6, 95% CI=3.1-307.8, P=0.004). In the analysis of bacteraemia-related mortality, admission from old-age home (OR=16.8, 95% CI=2.5-111.4, P=0.04), severe disease (OR=13.9, 95% CI=3.6-60.84, P<0.001) and infection by serotype 19F (OR=14.7, 95% CI=1.3-156.7, P=0.03) were the independent variables. Penicillin resistance (minimum inhibitory concentration [MIC] ≥2 μg/mL) was not a risk factor for bacteraemia-related mortality. Initial therapy with antibiotics from the penicillin group was not associated with increased mortality.

Discussion

This study reported high rates of penicillin, macrolide, and fluoroquinolone resistance among pneumococci that caused invasive diseases in Hong Kong. The majority of these invasive isolates, including the antibiotic-resistant strains were targeted in the 7-valent and 23-valent vaccine formulations. Therefore, wider use of the pneumococcal vaccines can be expected to have substantial benefit on the burden of pneumococcal resistance and invasive disease. In view of the high mortality in patients aged ≥65 years admitted from old-age homes, we suggest these groups be given

Table 3. Comparison of demographic and clinical information between patients with penicillin-susceptible (Pen-S) and penicillin–non-susceptible (Pen-NS) *Streptococcus pneumoniae* bacteraemia (univariate analysis)

Variable	Pen-S, n=135 (%)	Pen-NS, n=81 (%)	P value
Age (mean±SD)	43.9±32.8	35.3±34.7	0.07
Female sex	52 (40%)	25 (31%)	0.26
Charlson comorbidity index	1.5±1.7	2.2±1.8	0.028
Underlying disease	82 (61%)	44 (54%)	0.35
Severe infection	38 (28%)	24 (30%)	0.81
Meningitis	9 (7%)	9 (11%)	0.25
Pneumonia	96 (71%)	49 (61%)	0.11
Pitt bacteraemia score (mean±SD)	2.8±3.0	2.5±2.4	0.5
Use of computed tomography, magnetic resonance imaging, and/or ultrasonography	40 (29.6%)	28 (34.6%)	0.4
High usage of laboratory tests (>20)	43 (32%)	22 (27%)	0.6
Length of stay (days)	17.0±24.3	13.6±13.3	0.3
Suppurative complication	11 (8%)	3 (4%)	0.19
Intensive care unit admission	33 (24%)	16 (20%)	0.43
Mechanical ventilation	35 (26%)	14 (17%)	0.14
Overall mortality	38 (28%)	21 (26%)	0.72
Mortality during first 24 hours	15 (11%)	2 (3%)	0.04
Bacteraemia-related mortality (2-7 days)	12 (9%)	14 (17%)	0.07

priorities in vaccination programmes. For pneumococcal infections outside the central nervous system, evidence to date indicates that infection caused by pneumococci termed as having intermediate resistance or resistant to penicillin (MIC, 0.12 μg/L to 2 μg/mL) respond well to penicillin given in appropriate doses.[3] Despite the high proportion of penicillin-resistant strains we encountered, our outcome analysis did not find an independent association with mortality. Several other outcome indicators including length of stay, suppurative complications, admission to an ICU and utilisation of supporting services were also not significantly different between patients with infections by penicillin-susceptible and penicillin–non-susceptible strains. As suggested by the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group, the intermediate category for penicillin should be shifted upwards to include MICs up to 2 μg/mL in pneumonia and possibly also for other infections outside the central nervous system.[3] However, it should be pointed out that most of our patients were treated with intravenous antibiotics at high doses which were expected to yield T>MIC of 40% or more, a parameter that was shown to be important for efficacy.[4] In choosing therapies, agents with poor in-vitro activities against penicillin-resistant strains should be avoided because they may be associated with excessive treatment failures and breakthrough infections. Due to the high rates of resistance in this locality, monotherapy with a macrolide or a fluoroquinolone is not expected to provide sufficient cover in presumed or confirmed pneumococcal infections.

Conclusion

At the current levels of penicillin resistance, invasive pneumococcal infections caused by penicillin–non-susceptible strains were not associated with increased mortality and poorer outcomes; provided they were treated promptly and appropriately with intravenous β-lactams with good anti-pneumococcal activity.

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