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Antibiotic-resistant pneumococci in hospitalized children

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SUMMARY

A search for nasopharyngeal carriers of *Streptococcus pneumoniae* was conducted in 573 children hospitalized in Durban, South Africa. Study subjects were divided into two groups, comprising 305 new admissions and 268 patients who had been hospitalized for more than 24 h. Of the 573 children 178 (31 %) yielded pneumococci on nasopharyngeal culture; 99 (32 %) and 79 (29 %) children in the new admission and in-patient categories respectively. Twenty-one (12 %) pneumococci were resistant to penicillin, including 11 strains that were resistant to more than one antibiotic. Resistant pneumococci belonged exclusively to serotypes 6 and 19 (Danish nomenclature), which were also the commonest serotypes among penicillin-sensitive strains. Factors that correlated with carriage of penicillin-resistant pneumococci were hospitalization for more than 24 h, young age and recent exposure to beta-lactam antibiotics.

INTRODUCTION

Streptococcus pneumoniae is a frequent cause of pneumonia, bacteraemia, otitis media and meningitis (Mufson, 1981). For many years, penicillin has been the mainstay of antipneumococcal therapy, but the emergence in many parts of the world of penicillin-resistant strains has necessitated a re-evaluation of its position (Ward, 1981).

During 1977, strains of *S. pneumoniae* resistant to penicillin and chloramphenicol were recovered from patients with meningitis and bacteraemia in Durban, South Africa (Appelbaum *et al.* 1977). Subsequent searches in Durban and Johannesburg for patients and carriers of antibiotic-resistant pneumococci revealed strains with higher levels of resistance to penicillin G (minimum inhibitory concentrations of 2–10 mg per litre) than had previously been reported (Jacobs *et al.* 1978; Koornhof *et al.* 1978, 1979; Ward *et al.* 1979; Ward, 1981). In many cases these bacteria were also resistant to several other antimicrobial agents, including cephalosporins,

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chloramphenicol, clindamycin, erythromycin, tetracycline and trimethoprim-sulphamethoxazole (Jacobs *et al.* 1978).

Epidemiological studies of penicillin-resistant pneumococci in the major urban centres of South Africa revealed that these bacteria colonized black children in only a few hospitals, chiefly in Johannesburg and Durban, and suggested that infections were nosocomially acquired. Surveys of hospital staff and individuals in the community disclosed only a few carriers of resistant strains, many of whom reported a recent association with one of the involved hospitals.

Efforts to limit the spread of pneumococci by isolating patients and carriers and by attempting to cure them of the carrier state met with partial success (Koornhof *et al.* 1979; Ward, 1981), but proved too costly of time and labour to be pursued in the long term. Accordingly, surveillance has been restricted to the routine performance of antibiotic susceptibility tests on pneumococci associated with systemic infection, in particular bacteraemia and meningitis.

During 1980 and 1981, although only five penicillin-resistant pneumococci were recovered from blood or cerebrospinal fluid cultures at university-associated laboratories in Johannesburg, Pretoria, Cape Town and Bloemfontein, nine such strains were identified in the microbiology laboratory of the University of Natal in Durban. These bacteria represented 5% (8 of 168) and 1% (1 of 99) of all pneumococci obtained respectively from samples of blood and cerebrospinal fluid cultures examined during the same period.

In view of the continued presence of penicillin-resistant pneumococci in Durban, and the suggestion that some patients may have been infected outside hospital, we undertook a survey of pneumococcal carriers among black children attending a large teaching hospital in Durban. The results are presented in this paper.

MATERIALS AND METHODS

Study subjects

During the two-week period from 22 June to 5 July 1981 (midwinter), a search for nasopharyngeal carriers of pneumococci was conducted amongst all in-patients less than 12 years old and new paediatric admissions to King Edward VIII Hospital in Durban.

Specimen collection and processing

Nasopharyngeal secretions were collected pernasally by means of calcium alginate swabs on flexible aluminium shafts (Inolex Corporation), and streaked for single colonies on 1% (wt/vol) Columbia agar (Inolex Corporation) plates supplemented with 5% horse blood. To facilitate preliminary identification of pneumococci, a filter paper disk containing 5 μg optochin (Mast Laboratories Ltd) was placed on the surface of each plate (Robins-Browne, Kharsany & Ramsaroop, 1982). After 24–48 h incubation at 37 °C in an atmosphere of air containing 5% carbon dioxide, plates were examined for colonies resembling pneumococci. Putative pneumococci (at least two colonies per plate) were examined for bile solubility and susceptibility to optochin (Facklam, 1980). Most strains were also serotyped by capsular swelling using serum from the Statens Seruminstitut, Copenhagen, Denmark.

Table 1. *Antibiotic resistance patterns of* 21 *strains of penicillin-resistant* Streptococcus pneumoniae

Resistance pattern*	No. of strains	Serotype†		
		6	19	ND
P	10	4	2	4
PR	2	1	1	—
PC	2	—	1	1
PCR	1	—	1	—
PE	1	—	1	—
PT	1	1	—	—
PCTECl	3	—	2	1
PCTEClR	1	—	1	—
Total	21	6	9	6

* Drug resistance symbols. C, chloramphenicol, Cl, clindamycin, E, erythromycin, P, penicillin, R, rifampicin, T, tetracycline.

† Danish nomenclature; ND, not determined.

Bacteria identified as pneumococci were screened for their susceptibility to penicillin G by means of a filter paper disk containing 5 μg methicillin (Mast Laboratories) (Jacobs *et al.* 1979). Minimum inhibitory concentrations of penicillin G were determined for bacteria showing zones of inhibition less than 25 mm (Jacobs *et al.* 1979). Penicillin-resistant pneumococci were examined further for their susceptibility to chloramphenicol, clindamycin, erythromycin, rifampicin and tetracycline by means of disk susceptibility tests. The laboratory methods and criteria used to categorize pneumococci as sensitive or resistant to these agents have been reported previously (Jacobs *et al.* 1979).

Clinical and epidemiological data

The hospital files of all carriers of pneumococci were examined and the following information recorded: age, sex, location within the hospital, period of hospitalization (at the time of the investigation), major diagnosis, underlying disease, history of previous illnesses and hospital attendance, present therapy and antibiotic usage in the previous month.

Statistical analysis

Data pertaining to carriers of penicillin-resistant pneumococci were compared with those obtained from carriers of sensitive strains by using appropriate statistical tests (Armitage, 1971; Siegel, 1956). For all tests, values of P less than 0·05 were taken to denote statistical significance.

RESULTS

Pneumococcal carriers and antibiotic resistance

During the period under review 573 children, all but three of whom were black Africans, were investigated for their pneumococcal carrier status. Study subjects were divided into two groups comprising 305 new admissions and 268 patients who

Table 2. *Serotypes of* Streptococcus pneumoniae *obtained from children hospitalized in Durban, South Africa*

	Penicillin-sensitive		Penicillin-resistant	
Serotype*	No.	(%)	No.	(%)
6	37	(28)	6	(40)
19	25	(19)	9	(60)
14	14	(11)	—	—
1	10	(8)	—	—
4	9	(7)	—	—
9	7	(5)	—	—
5	5	(4)	—	—
7	5	(4)	—	—
23	4	(3)	—	—
2	3	(2)	—	—
8	3	(2)	—	—
10	3	(2)	—	—
15	3	(2)	—	—
20	2	(2)	—	—
3	1	(1)	—	—
11	1	(1)	—	—
13	1	(1)	—	—
Total	133†	—	15†	—

* Danish nomenclature.

† Totals exclude 17 penicillin-sensitive pneumococci and six penicillin-resistant strains whose serotype was not determined.

had been hospitalized for more than 24 h. Patients in these groups were comparable in terms of age and sex distribution, and nature of their underlying illness.

Pneumococci were obtained from the nasopharynx of 178 (31 %) of all 573 children. Twenty-one (12 %) of the bacteria isolated were resistant to penicillin G, including 11 strains that were resistant to more than one antibiotic. In keeping with previous reports (Jacobs *et al.* 1978; Koornhof *et al.* 1978; Ward *et al.* 1979), bacteria fitted into distinct patterns of antibiotic resistance (Table 1).

Carriers of pneumococci occurred with approximately equal frequency in the in-patient and the newly admitted patient categories (29 % and 32 % respectively). Penicillin-resistant strains, however, were obtained significantly more frequently from in-patients (15 of 268) than from children who were investigated within 24 h of admission (6 of 305). $\chi_1^2 = 4{\cdot}3$, $P < 0{\cdot}05$.

Pneumococcus serotypes

The pneumococci isolated in this study belonged to a broad range of serotypes. Although altogether 17 serotypes were identified, types 6, 19 and 14 (Danish nomenclature) accounted for approximately 50 % of the strains (Table 2). Penicillin-resistant pneumococci, however, occurred exclusively within serotypes 6 and 19. Where the serotype was known, serotype 6 was found with similar frequency among penicillin-resistant and pencillin-sensitive strains (40 % and 29 % respectively). $\chi_1^2 = 0{\cdot}5$, not significant. Serotype 19, on the other hand, occurred significantly more frequently amongst resistant pneumococci (60 %) than among penicillin-sensitive strains (19 %). $\chi_1^2 = 10{\cdot}7$, $P < 0{\cdot}01$.

Table 3. *Clinical and epidemiological features of carriers of* Streptococcus pneumoniae *hospitalized for less than 24 h*

Clinical feature	Penicillin-susceptibility of pneumococcus: Sensitive $n = 76$	Penicillin-susceptibility of pneumococcus: Resistant $n = 5$
Median age (and range); years	1·3 (0–10·5)	1·1 (0·4–2·0)
Sex (% boys)	53	20
Nature of underlying illness		
Medical	55	5
Infective	42	4
Non-infective	13	1
Surgical	21	0
Malnourished	18	2
Hospitalized during previous year	9	1
Antibiotic treatment within previous month		
Any antibiotic	22	3
Beta-lactam	20	3

Differences between carriers of sensitive and resistant pneumococci are not significant for any of the criteria examined.

Clinical findings.

Complete clinical details were not available for 25 patients: 23 of whom were carriers of penicillin-sensitive pneumococci and two who were colonized with resistant strains. These patients were excluded from further consideration. Preliminary analysis of the clinical and epidemiological data obtained from the remaining 153 carriers of pneumococci revealed that those who carried sensitive strains had been hospitalized for a significantly shorter period (median < 1 day) than carriers of resistant strains (median 5·5 days). Accordingly, patients were divided into two groups depending on whether they had been hospitalized for more or less than 24 h. The chief clinical and epidemiological findings in these two groups of patients are summarized in Tables 3 and 4.

Among the patients hospitalized for less than 24 h, differences between carriers of sensitive and resistant pneumococci were not significant for any of the criteria examined (Table 3). This may be because of the small number of carriers of resistant pneumococci who fell into this category. Among children hospitalized for more than 24 h, carriers of resistant pneumococci were younger and more likely to have received beta-lactam antibiotics in the previous month than carriers of sensitive strains (Table 4). The latter two parameters, namely, age and exposure to beta-lactam antibiotics, were not entirely independent of each other. Thus of all children colonized with penicillin-sensitive pneumococci, those exposed to beta-lactams were younger (mean age 2·3 years) than those not exposed (mean age 2·9 years). Nevertheless, of all children less than three years of age, those who had received beta-lactams were 3·4 times more likely to be colonized with resistant pneumococci than those who had not received antibiotics ($\chi_1^2 = 6·3$, $P < 0·05$).

Factors that did not appear to influence colonization with resistant pneumococci were the patients' sex, underlying illness, nutritional status, history of previous hospitalization and location within King Edward VIII Hospital.

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Table 4. *Clinical and epidemiological features of carriers of* Streptococcus pneumoniae *hospitalized for more than 24 h*

Clinical feature	Penicillin-susceptibility of pneumococcus: Sensitive $n = 58$	Resistant $n = 14$
Median age (and range); years	2·4 (0·1–9·1)	1·4 (0·3–4·4)*
Sex (% boys)	61	57
Nature of underlying illness		
Medical	39	12
Infective	22	8
Non-infective	17	4
Surgical	19	2
Malnourished	8	3
Median no. of days in hospital (range)	8 (3–114)	9 (3–83)
Hospitalized during previous year	23	9
Antibiotic treatment within previous month		
Any antibiotic	20	8
Beta-lactam	11	8*

* Difference between carriers of sensitive and resistant pneumococci is statistically significant ($P \leqslant 0{\cdot}01$).

DISCUSSION

Although pneumococcal carriage and disease have been the subject of a number of epidemiological studies (Loda *et al.* 1975; Gray, Converse & Dillon, 1980; Klein, 1981), comparatively few investigators have addressed the question of antibiotic-resistant pneumococci. The findings that carrier rates in the community generally are low and that infection is uncommon except in association with institutions suggest that these bacteria are acquired in hospital (Jacobs *et al.* 1978; Ward, 1981). This suggestion was borne out in the present study, which showed that the carrier rate of penicillin-resistant pneumococci was three times higher in patients hospitalized for more than 24 h than in those who had been admitted more recently ($\chi^2_1 = 4{\cdot}3$, $P < 0{\cdot}05$).

Other factors that influenced colonization by resistant pneumococci were age and a history of recent exposure to beta-lactam antibiotics (mainly penicillin G or cephalothin). All but one of 19 children in this investigation who carried penicillin-resistant pneumococci were under three years of age, compared with 84 of 134 carriers of penicillin-sensitive strains ($\chi^2_1 = 6{\cdot}3$; $P < 0{\cdot}02$). The increased susceptibility of young children to colonization by penicillin-resistant pneumococci may be connected with the fact that the immune response to pneumococcal polysacchrides 6 and 19 is poorly developed before the age of two years (Cowan *et al.* 1978; Mäkelä *et al.* 1980; Gray *et al.* 1981). Thus it is conceivable that children whose resident upper respiratory tract flora is suppressed as a consequence of anitibiotic therapy are particularly liable to colonization with penicillin-resistant strains if they have no pre-existing immunity to these bacteria. Older children, previously exposed to the penicillin-resistant serotypes 6 and 19, which are the

most prevalent serotypes among all pneumococci in Durban (Table 2), would generally have preformed antibodies to these types and thus would resist colonization. The finding that serotype 19 pneumococci were more likely to be acquired in hospital than serotype 6 may indicate that some pneumococcal strains become established in hospitals more readily than others. As this investigation lasted only two weeks, however, this finding could also be explained by a temporary increase in the prevalence of type 19.

In a case-control study of children and adults infected with penicillin-resistant pneumococci, Saah *et al.* (1980) concluded that antibiotic use did not enhance the risk of infection with resistant pneumococci. This conclusion is at variance with that of this study as well as with those of other workers (Radetsky *et al.* 1981; Ward, unpublished data). The reasons for these differences are not clear, but it should be possible to resolve them by undertaking a prospective cohort study of children admitted to King Edward VIII Hospital or a similarly affected institution.

Gray *et al.* (1980) have demonstrated that approximately one in six children who acquire new pneumococci will develop disease, usually within one month. In the case of antibiotic-resistant pneumococci, this could give rise to serious therapeutic difficulties. It is important therefore to reduce the likelihood of pneumococcal acquisition by hospitalized patients. Regrettably little is known of the means whereby cross-infection with pneumococci occurs, and attempts to limit their spread have met with difficulty. This is because the antibody response of young children to immunization with pneumococcal polysaccharide is weak and unpredictable and the treatment of carriers with antibiotics such as vancomycin and rifampicin is costly and not always successful (Ward, 1981; Koornhof, unpublished data). With regard to the latter, it is noteworthy that four of the 21 penicillin-resistant pneumococci recovered during this investigation were also resistant to rifampicin. Accordingly, we believe that in institutions where penicillin-resistant pneumococci have become established, the most useful control measures are to identify and, where possible, to isolate infected patients and carriers, and to reduce antibiotic use in young children as much as possible.

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