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Effect of β lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study

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Abstract

Objective To examine the relation between use of antibiotics in a cohort of preschool children and nasal carriage of resistant strains of pneumococcus.

Design and participants Prospective cohort study over two years of 461 children aged under 4 years living in Canberra, Australia.

Main outcome measures Use of drugs, respiratory symptoms, and visits to doctors were documented in a daily diary by parents of the children during 25 months of observation. Isolates of pneumococci, which were cultured from nasal swabs collected approximately six monthly, were tested for antibiotic resistance.

Results From the four swab collections 631 positive pneumococcal isolates from 461 children were found, of which 13.6% were resistant to penicillin. Presence of penicillin resistant pneumococci was significantly associated with children's use of a β lactam antibiotic in the two months before each swab collection (odds ratio 2.03 (95% confidence interval 1.15 to 3.56, $P = 0.01$)). The odds ratio of the association remained > 1 (though did not reach significance at the 0.05 level) for use in the six months before swab collection. The association was seen in children who received only penicillin or only cephalosporin antibiotics in that period. The odds ratio was 4.67 (1.29 to 17.09, $P = 0.02$) in children who had received both types of β lactam in the two months before their nasal swab. The modelled odds of carrying penicillin resistant pneumococcus was 4% higher for each additional day of use of β lactam antibiotics in the six months before swab collection.

Conclusions Reduction in β lactam use could quickly reduce the carriage rates of penicillin resistant pneumococci in early childhood. In view of the propensity of these organisms to be spread among children in the community, the prevalence of penicillin resistant organisms may fall as a consequence.

Introduction

The worldwide increase in pneumococcal resistance to antibiotics is worrying.^{1,2} An important contributor to antibiotic resistance is the excessive use of antibiotics in

young children with respiratory symptoms.³ It is widely accepted that antibiotic resistance is related to both the extent and amount of antibiotics used. However, there are few prospective data to support these presumptions. Carriage of resistant pneumococci in childhood has been associated with younger age, attendance at daycare centres, and previous use of antibiotics.^{4–6} In our two year prospective study in a community setting we studied the nasal carriage of pneumococci, their sensitivity profile, and the intake of antibiotics by preschool children in Canberra, Australia.

Methods

A cohort of 484 children from Canberra participated in the study from September 1997 to September 1999. General practitioners were first recruited into the study, then these doctors were asked to recruit the first 15 children who visited their practice for any reason. The parents of all participants kept a daily diary of the children's respiratory symptoms, visits to the doctor, and use of drugs, with detailed information on antibiotic use, including the name of the drug, duration of use, and the reason for taking it. Informed consent was obtained from the parents during recruitment. Nasal swabs were collected from the children up to four times over the 25 months of the study. Pneumococci were identified by colony characteristics and were tested for susceptibility to penicillin.⁷ The study period was divided into 12 periods of 60 days each. To limit misclassification of antibiotic use we considered only those children whose diary observations were complete for at least 75% of observation days. We also excluded from the main analysis swabs that were collected from children who were receiving continuous antibiotic therapy.

We defined penicillin as including penicillin V, amoxicillin, and amoxicillin clavulate. Cephalosporin refers also to cefalexin and ceclor. The term β lactam refers to either penicillin or cephalosporin.

We used two sided Fisher's exact tests for our univariate analyses and multiple logistic regression models to model the odds of carriage of a resistant organism. We accounted for correlation between repeated observations on the same child.^{8,9} We assessed a range of covariates as possible confounders of the association between antibiotic use and carriage

of a resistant organism. A potential confounder was entered into the logistic model if adjustment for the variable resulted in a distortion of the odds ratio of $\geq 10\%$.¹⁰

Results

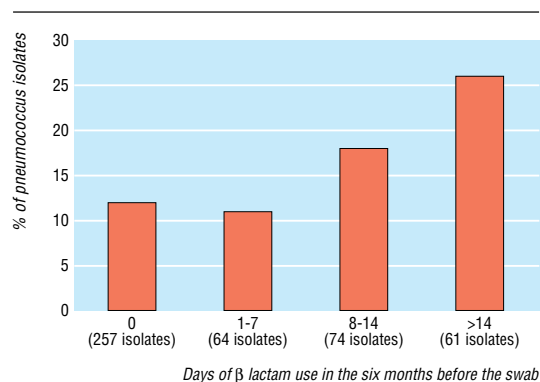
From the four nasal swab collections 631 pneumococcal isolates from 461 children were found—37%, 46%, 39%, and 46% of the swabs collected on each occasion (the higher percentages were from the swabs collected in winter). Of the 631 pneumococcal isolates, 86 (13.6%) were resistant to penicillin, and six isolates were highly resistant.

Elsewhere we have described in detail the pattern of antibiotic resistance in the isolates collected from these children.¹¹ Over half (334 (52.9%)) the isolates were resistant to at least one of the six antibiotics for which sensitivity was tested (penicillin, erythromycin, co-trimoxazole, tetracycline, chloramphenicol, and cefotaxime); 119 (18.9%) were resistant to two or more antibiotics; and 5 (0.8%) were resistant to all six.

Of the 631 pneumococcal isolates, 456 were collected from the children whose diary records of drug treatment and medical visits were at least 75% complete in the six months before collection of the swab. Of these isolates 68 (14.9%) were resistant to penicillin. These children took β lactam antibiotics for 0 to 85 days. Of the 456 isolates, 199 (43.6%) were from children with at least one day of β lactam use in the previous six months. Over three quarters of the children (355 (76.9%)) received an antibiotic at some point in the two year study period, and the overall mean period of antibiotic use per child per year was 17.6 days.

To consider the relation between antibiotic use and resistance, we used a logistic model to assess the odds of carrying a penicillin resistant pneumococcal isolate against β lactam use in each two month period before swab collection over the 24 months of the study. Age, sex, number of siblings, type of day care, duration of day care, and any hospital admission were assessed for their possible confounding effects. The use of β lactam antibiotics in the two months before swab collection was significantly associated with isolation of a penicillin resistant pneumococcus, and the relation was not confounded by the variables tested (adjusted odds ratio 2.03 (95% confidence interval 1.15 to 3.56; $P=0.01$)). The odds ratio adjusted for the clustering effect of multiple swabs in any one child was slightly >1 for β lactam prescriptions in the penultimate and last two month periods before swabbing (odds ratios of 1.27 and 1.25, respectively), but the 95% confidence intervals of these estimates included 1. If children had received both a penicillin and a cephalosporin preparation in the two month period before swabbing, the odds ratio of carrying a resistant organism was 4.67 (1.27 to 17.09; $P=0.02$).

The percentages of penicillin resistant isolates were similar in the group that had no β lactam use (12% (32/257)) and the group that had only a relatively short course of β lactam (11% (7/64)), but this percentage increased as the number of days of use increased beyond seven days, to 26% (16/61) in children who had >14 days' use (figure).



Penicillin resistance in pneumococcus isolates taken from children, and β lactam use in the six months before swab collection

Effect on penicillin resistance in pneumococcus isolates ($n=456$) of duration of β lactam use in the six months before swab collection. No β lactam use is the reference group

No of days of β lactam use	Odds ratio	95% CI	P value
1-7	0.86	0.37 to 2.02	0.73
8-14	1.50	0.73 to 3.06	0.27
>14	2.50	1.30 to 4.82	0.006

Although the children who received β lactam antibiotics for >7 days in the six months before swab collection were more likely to carry a penicillin resistant pneumococcus than the children who had not received β lactam preparations in that period, this association was significant only in children who had received >14 days of β lactam (table).

We further explored the association between duration of β lactam use and penicillin resistance by using duration of use as a continuous rather than a categorical variable. Using a logistic regression model adjusted for the effect of clustering within children, we found that for each additional day of use in the six months before the swab collection, the odds of a child carrying a penicillin resistant pneumococcus increased by 4% (adjusted odds ratio 1.04 (1.01 to 1.06; $P=0.001$)).

Discussion

Our results show that the likelihood of children carrying a resistant organism is in the short term related to the amount of β lactam recently taken. Therefore if the amount of β lactam prescribed could be reduced, it follows that selection and transmission of resistant strains would occur less often.

Antibiotics are being overused in children of this age group in Australia. We found that 47% of all episodes of respiratory symptoms resulted in a visit to the general practitioner and that up to 48% of children who visited their general practitioner received an antibiotic on their first visit. Elsewhere we have examined the severity of symptoms in children who received antibiotics and those who did not receive them, and we did not find any difference between the two groups.¹¹ This accords with the growing evidence from randomised controlled trials that the benefits of antibiotics in most early childhood respiratory illnesses are trivial or non-existent.¹²⁻¹³ The likelihood that antibiotic use will, in the short term, result in carriage of a resist-

What is already known on this topic

Resistance to pneumococcal antibiotics is increasing worldwide

One possible cause of resistance is the excessive use of antibiotics in children with respiratory symptoms

Few cross sectional studies have looked at the association between antibiotic use and subsequent carriage of organisms resistant to penicillin

What this study adds

Carriage of pneumococcus is high in preschool Australian children throughout the year and highest in winter

The likelihood of carrying penicillin resistant pneumococcus is doubled in children who have used any β lactam antibiotic in the two months before testing

The likelihood of a child carrying a penicillin resistant pneumococcus is increased by 4% for each additional day of β lactam use in the six months before testing

ant organism needs to be built into clinical decision making.

A substantial reduction of β lactam use in preschool children could quickly result in reduced carriage of penicillin resistant pneumococci. A recent randomised trial compared dosages of 90 mg/day of amoxicillin for five days and 40 mg/day for 10 days in children and found that the higher dose of shorter duration was associated with lesser subsequent carriage of resistant pneumococci.¹⁴ This supports our findings on the duration of β lactam use. If these drugs are to retain their clinical usefulness, new prescribing policies are needed in community practice.

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Domiciliary visit

The services that general practitioners provide for their elderly patients sometimes stray outside the boundaries of medical practice. I have changed a few light bulbs, carried in buckets of coal, and once repaired a lavatory seat. All these tasks were within my competence, but now and then I have received more challenging requests. Harriet was in her late 80s, a spinster long retired from a musical career. Her voice was still remarkably strong and true, but her Erard harp stood silent in the corner of her living room, the arthritis in her hands and feet now preventing her from playing it. Nevertheless, it was still her treasured possession: "My harp is my husband," she used to say.

One of her recurrent problems was shortage of money, usually the result of charitable donations which she could not really afford to make. The latest episode was more serious, however: it followed the death of her elder sister, for whom Harriet had provided an expensive funeral. Nothing less than the sale of her harp would appease her bank manager. "A dealer from London is coming to look at my harp," she told me. "Could you be here when he comes and see that I get a fair bargain?"

Knowing nothing about harps and being poor at business transactions, I didn't think I would be much help, but I could hardly refuse. A few days later I rang Harriet's doorbell and settled down for the usual wait while she would shuffle down the hall pushing ahead of her the tea trolley that she used as a zimmer frame. To my surprise, the door was opened promptly by a man whom I took to be the London dealer, presumably arrived early. I was mistaken: Harriet had managed to recruit the principal harpist of the City of Birmingham Symphony Orchestra. He finished tuning the harp and then gave us an impromptu recital while we waited for the man from London. When two men arrived, my saviour from the orchestra took charge and dealt with them very firmly. He knew what was a fair price for the harp, refused to be beaten down, and insisted that Harriet be given a certified cheque before they were allowed to take the instrument away.

It was a performance he could be proud of, and one for which Harriet was very grateful. We should sometimes be glad when patients arrange their own specialist care.

John Lester *retired general practitioner, Walsall*