Antibiotics, sore throats and acute nephritis

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SUMMARY. A study was carried out of 274 children in Scotland aged 0 to 13 years recorded as having had acute nephritis over a four-year period (1976–79). The medical records for 223 of the patients were examined and 79 cases of post-streptococcal nephritis were identified, giving an estimated incidence of 2.1 episodes per 100,000 children per year. Using a number of assumptions, the authors sought the answers to two important questions: What is the risk that glomerulonephritis will develop after sore throat/inflamed throat illness? Is this risk influenced by the prescribing of an antibiotic for the original illness?

The risks of developing nephritis after an antibiotic-treated sore throat and after a non-antibiotic treated sore throat were assessed as being equivalent (1:13,000 and 1:17,000 respectively). Furthermore, it appears that, during his lifetime, a general practitioner has a chance of only one in six of seeing a child with post-streptococcal nephritis after a sore throat.

Introduction

ANYWHERE in the developed world, 'sore throats' are one of the two commonest symptoms seen by general practitioners, and the 'inflamed throat' is the commonest physical abnormality found. Although it would be reasonable to assume that general practitioners manage the sore throat/inflamed throat syndrome with a measure of uniformity, it is well known that this does not happen. Doctors seem to agree that tonsillitis and pharyngitis (terms used interchangeably) are conditions which merit prescription of an antibiotic, whereas for the 30 per cent of sore throats and inflamed throats not given these labels the decision to use or not to use an antibiotic appears to be almost random.

Despite recent work aimed at understanding and explaining antibiotic use by general practitioners,[1-4] two key and related questions remain unanswered. First, what is the risk that patients with the sore throat/inflamed throat syndrome will develop glomerulonephritis or rheumatic fever; and second, does prescribing an antibiotic (usually penicillin) for the original illness influence this risk? In attempting to answer these questions Weinstein and Le Frock[5] reviewed 11 studies and found insufficient reason to recommend antibiotic use as a prophylactic against nephritis, and in a more recent review of benefits and risks of different antibiotic treatment policies for sore throats[6] the issue has been rather uncritically dismissed in an otherwise excellent review. This study was an attempt to provide contemporary information to help answer these important questions.

Method

The study was carried out in Scotland, which has a population of 1,100,000 children aged 0–13 years. All 274 children in this age group admitted to hospital with a diagnosis of acute glomerulonephritis (ICD 580) or glomerulonephritis unqualified (ICD 583) during the four-year period 1976–79 were studied. Thirty patients with Henoch Schonlein purpura were excluded; the records for 223 (91 per cent) of the remaining 244 patients were found and studied. Glomerulonephritis was regarded as post-streptococcal if, as well as having the diagnostic features of acute nephritis, two of the following four features were also described: history of prodromal respiratory or skin infection; positive swab for group A β-haemolytic streptococcus; ASO titre greater than 250; depression of C_3 complement level. The records were searched for information about any prodromal illness, particular attention being given to previous sore throat/inflamed throat illness and to whether antibiotics had been prescribed. If necessary, additional information was collected from the referring general practitioner. The numbers of post-streptococcal sore throats/inflamed throats for which antibiotics had been prescribed and the numbers for which antibiotics had not been prescribed were noted. These were used as the numerators in the calculation of the risk of nephritis in antibiotic treated and non-antibiotic treated streptococcal sore throats in the study population.

To estimate the denominators for the calculation—the total numbers of streptococcal sore throats treated and streptococcal sore throats not treated with antibiotics in the whole population of children over the four-year period—a number of assumptions were used, derived mainly from the results of research carried out within Scotland.

Assumptions

1. The average child presents one respiratory illness to a general practitioner each year. (The consultation rate for children with respiratory illness in Livingston New Town in 1970 was estimated at 0.94 episodes per child per year;[7] a study

of 968 child-years of respiratory illness in Aberdeen noted 1,260 episodes, or 1.3 episodes per child-year in a population slightly weighted towards younger children;[2] the equivalent rate for the age distribution 0–13 years, calculated from the second (UK) National Morbidity Study for 'respiratory illness' and 'cough', is 0.78 for a population with a consultation rate three quarters of that prevailing in Scotland.)[8]

2. One respiratory illness in four presented has sore throat/inflamed throat as its major abnormality. (In a study of 7,515 episodes of respiratory illness reported by 62 doctors in north-east Scotland, 968 were tonsillitis, 591 pharyngitis and 578 minor illness with 'inflamed throat' as the major abnormality;[4] this represented 29 per cent of patients in a mixed age range.)

3. Streptococci can be isolated from 30 per cent of patients presenting to the doctor with sore throats. (Ninety-two isolations of streptococci were obtained from 306 sore throats (30 per cent) in children aged up to 15 years in Edinburgh;[10] 125 isolations were obtained from 452 sore throats (28 per cent) in a study in the Tayside region of Scotland.)[11]

4. Streptococci will be present in at least 10 per cent of sore throats not presented to doctors. (The carrier rate in 411 Edinburgh schoolchildren was found to be 10.4 per cent.)[12]

5. Eighty per cent of patients seen by doctors with sore throat/inflamed throat as the major finding receive antibiotics. (Antibiotics were prescribed to 98 per cent of the patients with tonsillitis, to 88 per cent of the patients with pharyngitis and for 46 per cent of the minor illnesses with 'inflamed throat' in the study referred to in (2) above, giving a total for the whole group of 81 per cent.)[13]

It was also assumed that three illnesses are not presented to the doctor for every one that is. This is in line with the general illness-behaviour described by Horder and Horder[14] which suggests that exactly this proportion of illness is taken to doctors. The implication that children average four respiratory illnesses a year seems reasonable.

In calculating a risk factor in treatment with penicillin, the 1:38 prevalence of penicillin allergy calculated by Madden[15] was accepted (the *Drug and Therapeutics Bulletin* has estimated that 3.8 per cent of patients are affected,[16] and the Office of Health Economics (OHE) figure of approximately 20 million prescriptions of penicillin annually in England and Wales from 1970–1979 was used to infer an average of 0.4 penicillin prescriptions per patient per year).

Results

Seventy-nine cases of acute post-streptococcal nephritis were found, giving an incidence of 2.1 episodes per 100,000 children per year. Although one region had more cases than expected and one region had fewer, there was no evidence of clinically important clustering by time or geography.

'Sore throat/inflamed throat' was identified as a prodrome in 39 (49 per cent) of the 79 cases of nephritis. Antibiotics had been prescribed to 18 of these 39 children and had not been prescribed to 21 children, five of whom had consulted their general practitioners and 16 had not. (Of the 40 children who had not had a prodromal 'sore/inflamed throat', 15 had no prodrome described, 11 had had other respiratory infection, seven had had skin infections and seven had had other illnesses ranging from chickenpox to osteomyelitis.)

Using the assumptions described above, the risk of developing nephritis after an antibiotic-treated streptococcal sore throat/inflamed throat was assessed as 1:13,000; if no antibiotic had been prescribed, the risk was assessed as 1:17,000 (Figure 1).

Multiplying Madden's[15] prevalence of penicillin allergy of 1:38 by the calculation that each patient in the population receives 0.4 prescriptions for penicillin annually for an estimated life of 70 years could imply a risk of developing penicillin allergy of 1:38 × (0.4 × 70), or approximately 1:1,000 prescriptions.

Taking the figures for this four-year period in Scotland to make generalizations over the time span of a general practitioner's career, each doctor has a 1:3 chance of seeing a child with post-streptococcal nephritis during his working life and a 1:6 chance of seeing such an illness following a sore throat/inflamed throat. It does not appear that the 1:6 chance is influenced by decisions to treat or not to treat sore throats/inflamed throats with antibiotics. (The chances of looking after a child with leukaemia or having a child on one's list who is killed in a road accident are each 1:1.) One patient a year in a practice of 1,500 patients becomes allergic to penicillin.

Discussion

Validity of assumptions

Most of the assumptions were based on previous research carried out in the field of respiratory illness in Scotland, the country where the main study was based. Attempts were made to validate our assumptions, and two corroboratory studies are worth reporting. First, our estimate of sore throats/inflamed throats seen in the at-risk children (aged 0–13 years) by all general practitioners during the study period was 1,000,000: according to the second National Morbidity Study the expected total of diagnoses of pharyngitis/tonsillitis for the same age group would be 880,000.[8]

Second, in a series of papers describing attempts to estimate the incidence of streptococcal throat infection in the community, Valkenberg and his colleagues predicted in the early part of their report[18] that a child has one streptococcal throat infection every five years (a figure that would give 800,000 infections in our population) and their final estimation was 13.8 infections per 100 patients per year (a figure that would give 552,000 infections in our population). From our own projections the figure we arrived at was 600,000 infections, again a good approximation given the different age range and geographical locus of the two surveys.

It is not possible to comment on the relative severity of the streptococcal throats presented and the streptococcal throats not presented to the general practitioner. The first group will probably contain the more serious infections and the second group the less serious, and this probability may of course hide a protective role of penicillin in the treatment of the more serious episodes.

Study data			
Population of children in Scotland aged 0–13 years		1,100,000	
Number of children covered by study (91 per cent)		1,000,000	
Number of patient-years 1976–79		4,000,000	
		Seen by GPs	Not seen by GPs
*Assumptions**			
1. Number of respiratory illnesses experienced		4,000,000	12,000,000
2. Twenty-five per cent are sore throat/inflamed throat as major symptom		1,000,000	3,000,000
3.] Number of cases where 4.] streptococci present		300,000 *(30)*	300,000 *(10)*
5. a) Number treated with antibiotic		240,000 *(80)*	—
b) Number not treated with antibiotic		60,000 *(20)*	300,000
Estimation of risk			
a) Acute nephritis after streptococcal sore throat treated with antibiotic**	$\frac{18}{240,000}$	=	1:13,000
b) Acute nephritis after streptococcal sore throat not treated with antibiotic**	$\frac{21}{360,000}$	=	1:17,000

*Denominator based on 'assumptions' explained under Method in text.
**Numerator as described under Results in text.

Figure 1. *Estimation of risk of developing acute nephritis after (a) antibiotic treatment and (b) non-antibiotic treatment of streptococcal sore throat/inflamed throat of Scottish children aged 0-13 years. (Percentages in parentheses.)*

On the other hand, the estimate of a 10 per cent streptococcal isolation rate in non-consulting patients was deliberately placed low to avoid artificial inflation of the denominator used to calculate the risk of developing nephritis after non-treatment with antibiotics (which would decrease the apparent risk). The estimate of three non-consulting patients to one consulting patient is also low for the same reason. It might even be possible that a denominator for the risk of developing nephritis after non-antibiotic treatment of a streptococcal throat based on a higher likelihood that patients with sore throats do not attend doctors,[19] would allow the reader to conclude that penicillin treatment of the prodrome actually increases the chances of developing nephritis—an interesting hypothesis for further debate.

Accuracy of conclusions

The accuracy of the estimated incidence of nephritis relies on all patients with the disease being referred to hospital; at present this seems a reasonable assumption. Our estimate of incidence (2.1 episodes per 100,000 children) is, however, lower than that of the most comparable UK study, in which the figure presented was 3.5 per 100,000.[20] That study was carried out a decade before ours, and the general belief is that the incidence of nephritis has fallen in the intervening years. Whichever figure of incidence is preferred, it is clear that post-streptococcal glomerulonephritis is now an uncommon sequel to sore throats, no matter how they are treated. Even if the risk estimated in this study is approximate, the direct observation that almost equal numbers of nephritic illnesses have followed antibiotic treatment and non-antibiotic treatment of prodromal sore throat/inflamed throat illness is likely to be accurate. Substantial errors in our assumptions would need to be present to question the general conclusion that penicillin treatment of the prodrome does not protect against subsequent development of nephritis. Furthermore, even if it is argued that only a small proportion of prescribed penicillin is taken, the secondary morbidity of the complete population of sore-throat sufferers remains exceedingly low and would clearly be an acceptable risk under most circumstances.

Other issues

The estimate of incidence of allergy after penicillin prescribing is only intended for crude comparison with the risks of developing nephritis. Clearly, many factors relating to the pathogenesis of penicillin allergy remain to be discovered before more precise estimates could have epidemiological substance.

Because rheumatic fever is a different illness to glomerulonephritis, there must be caution in applying inferences from this study to rheumatic fever. In the same age group over the same period covered by this study, hospital admissions classified as being due to rheumatic fever were 30 per year compared with 60 per year for acute glomerulonephritis; even if the prodromal illnesses had a different chance of being sore throats/inflamed throats and penicillin had a different

ability to protect, the risk to patients from non-use of prophylactic penicillin must again be very low. Studies in countries where the prevalence of rheumatic fever is higher (for example, Saudi Arabia) would be of great interest.

At the time of this study 69 of the 79 patients with post-streptococcal nephritis had recovered completely. Of the remaining 10 patients: one died (with a congenital cardiac lesion); one was in renal failure and one had a hemiplegia (these three had received antibiotics for their prodromal illness); five had persisting haematuria and two patients had been lost to follow-up.

Conclusions

On the basis of an objective study of clinical records, it appears that, at present, the incidence of acute post-streptococcal glomerulonephritis in children in Britain is low and the outcome is generally favourable. Using significant but defensible projections from the objective data, it is concluded that treatment of streptococcal sore throats/inflamed throats with antibiotics does not protect against development of acute glomerulonephritis. It is suggested that anyone wishing to argue an opposite case, or to make estimates of risk based on different assumptions from those we have used, should do so using the data in the first part of our report as a starting point.

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