

Staphylococcus Pyogenes: Still a Danger?

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MonteFiore, D., Coker, G. O., Adedeji, S. O. and Sogbetun, A. O. (1974)
Nigerian Journal of Paediatrics, 1 (1), 14. **Staphylococcus Pyogenes: Still a Danger?** A prospective study of sensitivity patterns of *Staph. pyogenes* strains isolated from samples sent to the diagnostic laboratory of the University College Hospital, Ibadan, has shown that penicillin resistance is frequent, and that 19 per cent of the penicillin-resistant strains obtained from in-patients were also resistant to methicillin. Most of the methicillin-resistant strains were isolated from adult patients; the strains do not appear to have become established at the moment in either the childrens' wards, or among the out-patient population.

Although the present study did not include very severe infections by such strains, experience elsewhere indicates that they are liable to occur. Malnourished or debilitated children might be expected to develop severe infections if nursed in an environment where such strains are established. The fact that methicillin-resistant *staph. pyogenes* is frequently resistant to a wide range of other antibiotics may render the treatment of severe infections caused by such organisms extremely difficult. Erythromycin and lincomycin appear to be the most useful of the currently available antibiotics for use in such cases. However, their general use should be restricted in order to minimise the chance of wide-spread resistance to these agents developing among staphylococcal strains.

STAPHYLOCOCCUS PYOGENES used to be regarded as one of the most dangerous of 'hospital pathogens', but despite the high hopes that arose following the introduction of penicillin and other antibiotics, that the danger of hospital-acquired infections due to this organism were a thing of the past, a substantial number of hospital infections are still caused by strains of *Staph. pyogenes* (Solberg, Bruun, and B ϕ e, 1972).

Hospital-acquired infections due to *Staph. pyogenes* derive initially from patients with septic lesions, and more importantly, from patients and

staff who carry the organism in the nose, throat, and perineum (Green 1961). The staphylococci can multiply in these sites, from where they are transferred to clothes, bedding and ward dust, which form the final vehicles for the infection of new patients (Solberg 1965). It is easy to appreciate, therefore, that where conditions exist which favour the emergence of antibiotic-resistant strains of *Staph. pyogenes*, as, for example in a semi-closed community such as a hospital, the establishment of a repeated cycle of infection by these organisms can readily occur. Similarly,

even in the outside community, antibiotic-resistant strains can readily be established, if there is widespread and uncontrolled use of antibiotics exerting a selection pressure favouring the maintenance of populations of antibiotic-resistant staphylococci in preference to the antibiotic-sensitive strains.

In a previous publication (Montefiore and Okubadejo, 1970), it was shown that only about 25 per cent of *Staph. pyogenes* strains isolated from in-patients, and about 30 per cent of those isolated from out-patients, attending the University College Hospital, (U.C.H.) Ibadan, were sensitive to benzyl penicillin. It was also shown that between 1963 and 1967, there had been a general decrease in the proportion of strains which were sensitive to the commonly available antibiotics. No information was included, however, on the sensitivity pattern shown by local strains of *Staph. pyogenes* towards the penicillinase-resistant penicillins.

Methicillin, the first of the penicillinase-resistant penicillins, became available in 1960, and it was generally hoped that this would prove to be the answer to the penicillin-resistant strains of *Staph. pyogenes*. However, it soon became apparent that naturally occurring methicillin-resistant strains of the organism did exist (Barber, 1961), and although at first they seemed to be extremely rare (Parker and Jevons, 1964), they later appeared to be increasing in frequency, although there were wide geographical variations in the proportions of resistant strains isolated (Bran, Levison, and Kaye, 1972; Finland, 1972; Jessen *et al.*, 1969).

Although at first it was thought that methicillin-resistant strains were of very low pathogenicity, and there are several reports which suggest that they are found more frequently in debilitated patients, possibly indicating some lowered virulence of the organism (Michel and Priem, 1971), there is no doubt that some strains can be highly virulent, and can be responsible for severe infection. Attempts to treat such infections with methicillin, or other penicillinase-resistant

penicillins, are likely to prove unsuccessful (Gilbert and Sanford, 1970; Editorial, 1967).

Therefore, if methicillin-resistant strains of *Staph. pyogenes* are relatively common in any given population, it is clearly desirable to have other effective agents readily available to treat severe infections should they occur. The choice of such drugs must be based on a knowledge of the actual sensitivity patterns shown by the locally occurring strains of the organism; many of the commonly available antibiotics may not be of value, since it is recognised that methicillin resistant strains are frequently also resistant to a wide range of other antibiotics. Even some of the less usual agents, e.g. cephalosporins, are often not satisfactory for the treatment of severe infections by such organisms (Barber, 1964; Gilbert and Sanford, 1970; Parker and Hewitt, 1970; Stokes *et al.*, 1972).

It therefore, seemed worthwhile to review the antibiotic sensitivity patterns of *Staph. pyogenes* strains isolated from patients attending the hospital, with particular reference to their methicillin sensitivity. A strain which is resistant to methicillin will also be resistant to all the other penicillinase-resistant penicillins. Although these have not been widely used in Nigeria up to the present time, there is evidence that the occurrence and spread of methicillin-resistant strains may show little correlation with the use of these agents (Parker and Hewitt, 1970).

Materials and Methods

All strains of *Staph. pyogenes* isolated from samples sent to the diagnostic laboratory during August and September 1972, were included in the study. Identification of organisms was carried out by routine methods, and all strains were confirmed as *Staph. pyogenes* by the tube coagulase method.

Isolated strains were broadly classified as originating either from in-patients or from out-patients, and also into those isolated from adults, or from children 10 years of age or under.

Sensitivity tests were carried out using Oxoid Multodiscs and Mast sensitivity discs, on Oxoid Sensitivity Test Agar, and were incubated at 30°C. for 18 hours (Hewitt, Coe, and Parker, 1969). The discs contained the following agents:

Penicillin G	1.5 units
Streptomycin	10.0 mcg
Tetracycline	10.0 mcg
Chloramphenicol	10.0 mcg
Methicillin	10.0 mcg
Lincomycin	10.0 mcg
Erythromycin	10.0 mcg

Preliminary experiments with 65 strains of *Staph. pyogenes* established that 'sensitivity' or 'resistance' to methicillin, as determined by the disc diffusion method, gave complete correlation with the results of the tube dilution method. 'Resistant' strains were those able to grow in the presence of 12.5 mcg/ml. or more of methicillin (Gilbert and Sanford, 1970).

Results

A total of 286 strains of *Staph. pyogenes* were examined during the period of the survey.

Table I shows the proportion of strains isolated from either in-patients or out-patients, or from children or adults, and the percentage frequency of strains sensitive to the range of antibiotics tested. In only two cases were there significant ($P < 0.05$) differences between isolates obtained from adults and those obtained from children; strains isolated from children were less likely to be sensitive to benzyl penicillin, while the percentage of methicillin-resistant strains obtained from children was significantly less than that obtained from adult patients. In both cases, only in-patients showed these differences.

Table I also shows that the differences between in-patients and out-patients are significant ($P < 0.05$) in the case of adults only, in respect to the percentage sensitivities to tetracycline

TABLE I

Sensitivity Pattern of Staph. pyogenes strains isolated in U.C.H., Ibadan

	Out-Patients			In-Patients		
	No. Tested	Per cent		No. Tested	Per cent	
		Sens	S.E.D.		Sens	S.E.D.
<i>Penicillin</i>						
Children:	40	12.5		30	3.3	
Adults:	52	26.9	8.1	164	15.2	4.3
<i>Streptomycin</i>						
Children:	40	25.0		30	33.3	
Adults:	52	30.8	9.3	164	23.8	9.3
<i>Tetracycline</i>						
Children	40	51.6		30	46.7	
Adults	52	57.7	10.4	164	41.5	9.9
<i>Chloramphenicol</i>						
Children	40	70.0		30	70.0	
Adults	52	78.8	9.2	164	57.3	9.2
<i>Erythromycin</i>						
Children	40	92.5		30	86.7	
Adults	52	83.4	6.1	164	95.7	6.2
<i>Lincomycin</i>						
Children	34	100.0		25	100.0	
Adults	43	97.7		151	96.8	-
<i>Methicillin</i>						
Children	35	97.2		29	93.1	-
Adults	38	97.4	3.8	139	77.6	5.9

Note: Figures are calculated as percentages of penicillin resistant strains.

chloramphenicol and methicillin; in each instance sensitive strains were less frequent among in-patients. Only six strains were found to be resistant to lincomycin; these were all isolated from adult patients, and five of the six strains were also resistant to methicillin. Many strains of *Staph. pyogenes* were resistant to more than one antibiotic.

Table II shows the incidence of multiple resistant strains, in terms of their resistance or sensitivity to penicillin and methicillin. It can be seen that strains that were resistant to methicillin were more likely to be resistant to a greater number of other agents, than were strains which were sensitive to this antibiotic.

It has been possible to compare the frequency of resistance of *Staph. pyogenes* strains to the four commonly used antibiotics, penicillin, streptomycin, tetracycline and chloramphenicol, over the

TABLE II

Resistance of Staph. pyogenes Strains to Multiple Antibiotics.

	<i>Pen: Sens: strains</i>	<i>Pen: resist: Meth: sens: strains.</i>	<i>Pen: resist: Meth: resist: strains.</i>
<i>No. strains tested:</i>	45	208	33
Per cent fully sens	35.6	—	—
Per cent resist 1 agent	26.7	19.2	—
Per cent resist 2 agents	20.0	32.2	0.0
Per cent resist 3 agents	15.5	18.8	6.1
Per cent resist 4 agents	2.2	27.9	24.2
Per cent resist 5 agents	0.0	1.9	54.5
Per cent resist 6 agents	0.0	0.0	12.1
Per cent resist 7 agents	—	0.0	3.1

period 1963 to 1972. The findings are shown in Table III, but the results for the two earlier years are taken from the paper by Montefiore and Okubadejo (1970). There has been a steady and

TABLE III

Antibiotic Sensitivities of Staph. pyogenes Strains Isolated in 1963, 1967, 1972

	<i>In-Patient Strains</i>			<i>Out-Patient Strains</i>		
	<i>No. tested</i>	<i>Per cent sensitive</i>	<i>S.E.D 1963/72</i>	<i>No. tested</i>	<i>Per cent sensitive</i>	<i>S.E.D 1963/72</i>
<i>Penicillin</i>						
1963	171	25.1		203	30.5	
1967	116	19.8		99	36.3	
1972	194	13.4	4.1	92	20.7	5.3
<i>Streptomycin</i>						
1963	171	45.6		203	74.9	
1967	133	36.1		108	77.8	
1972	194	25.3	4.9	92	28.3	5.6
<i>Tetracycline</i>						
1963	171	69.6		203	91.6	
1967	133	42.1		108	88.0	
1972	194	42.3	5.0	92	57.6	4.2
<i>Chloramphenicol</i>						
1963	171	81.3		203	93.6	
1967	133	93.2		108	96.2	
1972	194	59.3	4.6	92	75.0	4.8

significant reduction in the proportion of sensitive strains to most of these agents over the years; strains from adult in-patients appear to have changed more than strains obtained from children.

Discussion

Methicillin resistance is easily missed on routine testing of *Staph. pyogenes* strains (Hewitt, Coe, and Parker, 1969). The relative frequency of methicillin-resistant strains detected at U.C.H. suggests that it would be advisable that effective tests for methicillin resistance are carried out routinely. Incubation at 30°C. rather than the more usual 37°C. is probably the simplest and most effective way of demonstrating resistance, but in laboratories where a separate incubator is not available, one can also detect methicillin resistance either by incubating the test plates for 48 hours instead of the usual overnight period of about 18 hours. Alternatively, one can add five per cent NaCl to the medium, and incubate for 18 hours at 37°C. In the latter case, however, one should not test for sensitivity to other antibiotics on the high salt content medium, otherwise false results will be obtained.

The present findings that methicillin-resistant strains are relatively frequent among adult in-patients of UCH, Ibadan, but are rare among children, as well as out-patients, suggest that these strains are able to circulate freely among the hospital patients, and personnel, even though penicillinase-resistant penicillins are not widely used. At present, the strains do not appear to have established themselves in the children's wards, or in the general population outside hospital.

Parker and Hewitt (1970) have also noted that methicillin-resistant staphylococci could spread and circulate freely in hospitals where methicillin was used on only a small scale or not at all. These authors therefore, suggested that under certain circumstances other penicillins might select for methicillin-resistant strains. The fact that such strains are also resistant to many

other commonly used antibiotics, would suggest that a selection pressure in favour of the emergence of methicillin resistant strains might exist in circumstances where there is a widespread use of almost any antibiotic, irrespective of whether it is a penicillin or not.

During the period of the present study, none of the infections caused by methicillin-resistant *Staph. pyogenes* were of great severity. But the relatively high incidence of such strains, which are circulating among adult in-patients, would suggest that such infections might well occur in the future, as they have done in other parts of the world (Benner and Kayser, 1968). Indeed Stokes and co-workers (1972) regard these strain, as 'dangerous hospital pathogens'. While at the present time these strains are infrequent among children, the occurrence of severe malnutrition and other debilitating states among such patients might render them particularly liable to the development of severe infections should methicillin resistant *Staph. pyogenes* strains become established in the children's wards.

It is therefore, important to know what agents would be most suitable, in general, for the treatment of such infections should they arise. It is also important that such agents should, as far as possible, be kept 'in reserve' so as to reduce the likelihood that these too will lose their efficacy.

Vancomycin has previously been suggested as the drug of choice in the treatment of severe infections by methicillin-resistant *Staph. pyogenes*, but this is a toxic agent. It is also not readily available. The present results indicate that erythromycin or lincomycin would be suitable in the majority of cases under existing conditions although 14 per cent of the methicillin-resistant strains were also resistant to lincomycin.

Our findings also show the progressive decrease over the years in the proportion of strains of *Staph. pyogenes* sensitive to the four commonly used antibiotics (penicillin, streptomycin, chloramphenicol and tetracycline). The majority of both in-patient and out-patient strains were already resistant to penicillin by 1963, and there has been relatively little change since then, but

the frequency of strains resistant to the other antibiotics has increased markedly. Particularly noteworthy is the increase in the proportion of strains isolated from out-patients, which are resistant to tetracycline, particularly noticeable between 1967 and 1972. The increase in the proportion is not however paralleled by a comparable change among in-patient strains. This may reflect an increasingly frequent use, by self-prescription, of tetracycline among the general population. The main importance of this observation is the finding that tetracycline resistance is often associated with multiple resistance to other antibiotics (Stokes *et al.*, 1972). This is illustrated, with regards to local strains (Table IV) where a total of 457 *Staph. pyogenes* strains are considered (including the 286 strains considered in the other tables). It is clear from the figures that tetracycline-resistant strains are substantially more often resistant to multiple antibiotics than are strains which are sensitive to tetracycline.

TABLE IV

Relation of Tetracycline Resistance to Multiple Antibiotic Resistance Among Staph. pyogenes Strains.

No. Tested	Tetracycline	
	sensitive	resistant
	204	253
Per cent fully sensitive:	11.8	
Per cent resist 1 agent	40.2	1.6
Per cent resist 2 agents	35.3	8.3
Per cent resist 3 agents	8.3	23.3
Per cent resist 4 agents	2.8	41.5
Per cent resist 5 agents	2.5	18.2
Per cent resist 6 agents	-	7.1

Although Gram-negative infections have become increasingly important in recent years as a cause of hospital-acquired infections, particularly among debilitated patients, staphylococci still remains an important and dangerous pathogen. There is no complete answer to this organism

which is able to develop strains resistant to the various antibiotics, rapidly. Such strains may sometimes be of lowered virulence, but this is not always the case, and should methicillin-resistant strains become established in a children's ward, one might expect that some of the patients would develop severe infections due to these organisms. The increasing attention being paid to infection by Gram-negative organisms should therefore not lead to relaxation of precautions against infection by staphylococcus.

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