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Erythromycin-resistant *Streptococcus pyogenes* in Riyadh, Saudi Arabia

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Introduction: *Streptococcus pyogenes* infections, and their sequelae such as acute rheumatic fever and acute glomerulonephritis, have long been considered as major illnesses in children. By the 1970s, however, these complications were rarely seen [1–3], although acute streptococcal infections continued to occur in their former pattern and with their former severity.

During the latter half of 1980s, there was a dramatic change, focusing attention again on infections caused by this organism and its sequelae. The resurgence of acute rheumatic fever and severe life-threatening *S. pyogenes* infections including toxic shock-like syndrome has been reported from North America, Europe and other parts of the world [2–5]. Many of the *S. pyogenes* isolates described in recent reports have had a mucoid-colony type similar to that associated with severe streptococcal disease in earlier years.

S. pyogenes has remained uniformly sensitive to penicillin, which has continued to be the drug of choice for these infections for more than five decades. For patients who are allergic to penicillin, erythromycin has been the treatment of choice. Although this drug often has gastrointestinal side-effects, it has been an effective and very safe antimicrobial agent. Drug resistance of *S. pyogenes* to erythromycin was first reported by Lowbury in 1958 [6]. Since then, there have been reports regarding its incidence in Canada [7], Japan [8], USA [9], Sweden [10], Spain [11], UK [12], Western Australia [13], Hawaii and Philippines [14], and Finland [15]. Most of these studies were conducted on isolates from adult and paediatric patients.

As far as we know, there have been no published data on the incidence of erythromycin-resistant *S. pyogenes* in Saudi Arabia. Therefore, we have evaluated the erythromycin resistance of *S. pyogenes* isolated recently from children with tonsilitis in King Khalid University Hospital (KKUH), Riyadh, Saudia Arabia. KKUH is a major teaching hospital and consists of 650 beds providing primary and tertiary health care.

Patients and methods: 250 isolates of *S. pyogenes* were isolated from children with tonsillitis during a period of 1 year from January to December 1993. The patients were derived mainly from paediatric outpatient clinics and paediatric accident and emergency departments. The isolates were identified by beta-haemolysis on blood agar, bacitracin sensitivity and by a commercial latex-agglutination test (Streptex, Wellcome, Dartford, UK). Patients' data were recorded in a standard proforma for details concerning demographic features, clinical manifestations, complications and the treatment regimens given.

Antibiotic susceptibility testing was carried out by disc diffusion using a rotating Stoke's technique [16]. Antibiotics included were penicillin (1 unit), ampicillin (10 μg), erythromycin (5 μg), clindamycin (2 μg), terracycline (10 μg) and cephradine (5 μg). In addition, a PDM Epsilometer (E-test, AB Biodisk, Solna, Sweden) was used to determine the minimum inhibitory concentration (MIC) of erythromycin to all isolates of *S. pyogenes*. MICs were also performed for penicillin, ampicillin and clindamycin for all erythromycin-resistant isolates.

After incubation of blood agar plates for 18 h at 37°C in an atmosphere of 5% CO_2, symmetrical drop-shaped inhibition zones were seen along the test strips. The MIC values were read at the points of intersection between the zone edges and the test carriers. Isolates were regarded as resistant to erythromycin if the MIC was ≥ 1 μg mL^{-1} [17]. The MIC_{50} and MIC_{90} were defined as the antimicrobial concentrations to inhibit growth of 50% and 90% of the isolates. *Streptococcus pyogenes* ATCC 10389, *Staphylococcus aureus* (Oxford) NCTC 6571 and a known resistant *S. pyogenes* to erythromycin were used as controls with each batch of susceptibility testing.

Results: Table 1 shows the age and sex distribution of the patients. There were 250 children with tonsillitis from whom *S. pyogenes* was isolated. Their age ranged from 1 to 14 years, with a mean (SD) of 7.14 ± 3.21. 150 were male and 100 female. The majority (60.4%) of these cases belonged to the age group 3 to < 9 years. Only 7.2% belonged to the age group less than three years.

Table 1: Age and sex distribution of children with streptococcal tonsillitis.

Age (years)	Males	Females	Total (%)
<3	12	6	18 (7.2)
3–<6	46	27	73 (29.2)
6–<9	46	32	78 (31.2)
9–<12	31	24	55 (22)
12–14	15	11	26 (10.4)
Total	150	100	250 (100)

Table 2: Clinical manifestations of children with streptococcal tonsillitis.

Symptom/sign	Total (%)
Fever	233 (93.2)
Sore throat	187 (74.8)
Nausea/vomiting	79 (31.6)
Headache	50 (20)
Cough	43 (17.2)
Abdominal pain	37 (14.8)
Rhinorrhoea	19 (7.6)
Arthralgia	8 (3.2)
Congested tonsils with/without exudates	230 (92)
Enlarged cervical lymph nodes	138 (55.2)
Erythematous skin rash*	18 (7.2)

** 12 of the 18 children with skin rashes had other signs of scarlet fever.*

Table 3: Minimum inhibitory concentration ranges of erythromycin to Streptococcus pyogenes

Isolates	Number	Range ($\mu g\ mL^{-1}$)	MIC_{50} ($\mu g\ mL^{-1}$)	MIC_{90} ($\mu g\ mL^{-1}$)
Erythromycin-sensitive	194	0.032–0.125	0.064	0.094
Erythromycin-resistant	8	2–16	4	8

Table 2 shows the clinical features of the patients. The majority of the children had fever with congested tonsils with or without exudates. Slightly over half had enlarged cervical lymph nodes. 18 children (7.2%) had skin rashes, 12 (4.8%) of them also had other signs of scarlet fever.

Non-suppurative complications of acute tonsillitis were found in four (1.6%) of the children. They included acute rheumatic fever (1 case), acute glomerulonephritis (1 case) and reactive arthritis (2 cases).

Table 3 shows the MICs of erythromycin to *S. pyogenes*. MIC_{50} and MIC_{90} for erythromycin sensitive isolates were 0.064 and 0.094 $\mu g\ mL^{-1}$ respectively. Only 3.2% (8/250) of isolates were resistant to erythromycin. MIC_{50} and MIC_{90} being 4 and 8 $\mu g\ mL^{-1}$ respectively. However, these isolates were sensitive to penicillin (MIC_{50} and $MIC_{90} < 0.016$), ampicillin (MIC_{50} and $MIC_{90} < 0.016$) and clindamycin ($MIC_{50} = 0.032$, $MIC_{90} = 0.094$).

All isolates were sensitive to penicillin, ampicillin, cephradine and clindamycin by disc diffusion test (DDT). However, 2.8% (7/250) were resistant to erythromycin and 11.7% to tetracycline. The MIC of the erythromycin-resistant isolate not detected by DDT was 2 $\mu g\ mL^{-1}$.

The majority of children were given oral penicillin (Biochemie GmbH, Vienna, Austria) followed by oral amoxycillin (SPIMACO, Al-Qassim, Saudi Arabia) whereas only 2.8% (7/250) were given erythromycin (Abbott Laboratories, Chicago, USA). All eight patients with erythromycin-resistant *S. pyogenes* were treated with oral penicillin.

Discussion: Reports on the antibiotic resistance of strains of *S. pyogenes* to erythromycin started to appear in 1958. The impression of a progressive increase in resistance to erythromycin has been confirmed recently [10–15]. 3% of our isolates showed resistance to erythromycin. This figure is comparable to those in USA (5%) and UK (3%) [9, 12] but higher than those in Canada (1.4%) and Spain (0.7%) [7, 11]. However, our figure is much lower than those in Japan (61.8%), Western Australia (17.6%) and Finland (up to 54%) [8, 13, 15].

This high incidence may be due to excessive use of erythromycin. This was confirmed by both Japanese [8] and Finnish workers [15]. In Japan, patients with streptococcal sore throats were treated routinely with erythromycin and other macrolides during the period from 1974 to 1975 as these antibiotics were considered to be of low toxicity [8]. In addition, the use of macrolide group of antibiotics increased rapidly since 1972 in Japan, and the total consumption amounted to almost 160 tons of macrolide antibiotics, including 50 tons of erythromycin in 1976 [8]. This practice probably exerted a selective pressure.

However, the frequency of erythromycin-resistant *S. pyogenes* decreased after the use of erythromycin was reduced [8]. There was a similar experience in Finland [15] where use of erythromycin in 1988 and 1989 was approximately three times that in 1978. In 1988, erythromycin accounted for 15% of total consumption of antibiotics, and its use was surpassed only by that of tetracycline (28%) and penicillin V (21%). Indiscriminate use of erythromycin was further highlighted by a study from Western Australia where a majority of erythromycin-resistant isolates were derived from wounds since this drug has been used as a first line treatment for superficial skin infections in outpatients for reasons of cost [13]. In our case, although the level of consumption of erythromycin was not known countrywide, only 3,500 g of the drug were used in our hospital in 1993. This may explain the low resistance of the drug to *S. pyogenes* in this country.

Slightly over half of our patients were treated with penicillin and more than one fifth received oral amoxycillin. The treatment of patients with streptococcal pharyngitis has been reviewed extensively by various authors [18, 19]. They concluded that oral penicillin is still the drug of choice, a regimen of 250 mg twice daily for children younger than 12 years of age and 500 mg twice daily for older children and adults appears optimal and is recommended [18]. Antibiotics other than penicillin play a more prominent role in the management of penicillin treatment failures [20].

Ideally, amoxycillin should be reserved for situations in which it affords added benefit. It may be preferred for individuals who have concomittant acute otitis media where this drug provides additional coverage of *Haemophilus influenzae*. Tetracycline is not indicated for treating streptococcal pharyngitis because of its side effects and the high resistance of these organisms.

Resistance of *S. pyogenes* to erythromycin is a serious matter, because this drug is currently considered the first alternative to penicillin V for oral treatment of patients with streptococcal pharyngitis. Physicians choose erythromycin to treat streptococcal infections in patients who are allergic to penicillin. If treatment with erythromycin is excluded, the only drug available for these patients are the oral cephalosporins and clindamycin.

However, resistance to erythromycin and clindamycin are often linked [15]. In our series, all the erythromycin resistant isolates were sensitive to clindamycin, which may not be clinically effective against these isolates despite their susceptibility *in vitro*. This may also be true for other new macrolides antibiotics because of possible cross resistance [15]. The exact molecular mechanisms of erythromycin-resistance in these isolates are not known [21]. Van Embden *et al.* [22] have shown *in vitro* that this transfer was by conjugation and was plasmid mediated. This may explain the appearance of resistance over a short period of time in different serogroups. However, further studies are needed to elucidate the mechanisms of erythromycin resistance in *S. pyogenes*.

97% of our isolates were sensitive to erythromycin. This is in accord with other workers [9]. Although the number of isolates were small in our study, there was a good correlation between the E-test and the disc diffusion test (DDT). The former detected eight isolates which were resistant to erythromycin; 7 of whom were also detected by DDT. The only isolate, missed by DDT, had a low MIC. This is in agreement with the work of Kruse *et al.* [23]. They found that the results from the E-test were highly reproducible and observed correlation of 98% when compared with the microtitre dilution method and DDT. This has been confirmed by other investigators [24]. In addition, the E-test is easy and simple to perform.

In conclusion, the incidence of erythromycin resistant *S. pyogenes* was low in our hospital. This may be due to judicious use of the drug in the selected cases. Overuse of this drug must be avoided. Physicians and clinical microbiologists

should be aware of this resistance and monitor it by frequent determination of susceptibility of *S. pyogenes*. It is no longer true that susceptibility testing for this organism is not required. Further studies are needed to know the incidence of such resistance throughout this country.

1. Land, M.A. and Bisno, A.L. 1985. *J.A.M.A.* **249**, 895–898
2. Kaplan, E.L. 1991. *Eur. J. Clin. Microbiol. Infect. Dis.*, **10**, 53–57
3. Bisno, A.L. 1991. *N. Engl. J. Med.*, **325**, 783–793
4. Chaprik, E.K., Gradon, J.D., Lutwick, L.I. *et al.* 1992. *Clin. Infect. Dis.*, **14**, 1074–1077
5. Maher, D. and Osurowski, J. 1993. *J. Infect.*, **26**, 195–197
6. Lowbury, E.J.L. 1958. *Proc. R. Soc. Med.*, **51**, 807–810
7. Dixon, J.M.S. and Lipinski, A.E. 1974. *J. Infect. Dis.*, **130**, 351–356
8. Maruyama, S., Yoshioka, H., Fujita, K. *et al.* 1979. *Am. J. Dis. Child.*, **133**, 1143–1145
9. Isaac, G.R., Welch, D.F., Marks, M.I. and Moyer, N. 1981. *Antimicrob. Agents Chemother.*, **20**, 244–246
10. Zackrisson, G., Lind, I., Roos, K. and Larson, P. 1988. *Scand. J. Infect. Dis.*, **20**, 419–420
11. Perez-Trallero, E., Garcia-Arenzana, J.M. and Urbieta-Ergana, M. 1989. *Lancet*, **II**, 444–445
12. Spencer, R.C., Wheat, P.F., Magee, J.T. and Brown, E.H. 1989. *Lancet* **1989**, **i**, 168
13. Stingemore, N., Graham, R.J., Francis, M.T. and McGeechie, D.B. 1989. *Med. J. Aust.*, **150**, 626–631
14. Wittler, R.R. Yamada, S.M., Bass, J.N. *et al.* 1990. *Am. J. Dis. Child.*, **144**, 587–589
15. Seppala, H., Nissinen, A., Jarvinen, H. *et al.* 1992. *N. Eng. J. Med.*, **326**, 292–297
16. Stoke, E.J. and Ridway, G.L. 1987. *Clinical Bacteriology*, pp. 204–221. Edward Arnold, London
17. National Committee for Clinical Standards. 1991. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically: approved standard.* Villanova, Pa, USA. NCCLS (NCCLS publication no. M7–A2)
18. Bass, J.W. 1991. *Pediatr. Infect. Dis. J.*, **10**, 843–849
19. Peter, G. 1992. *Clin. Infect. Dis.*, **14** (Supp 2): S218–S223
20. Denny, Jr., F.W. 1993. *Curr. Problems Pediatr.*, **23**, 179–185
21. O'Brien, R.F. 1992. *N. Eng. J. Med.*, **326**, 339–340
22. Van Embden, J.D.A., Soedirman, N. and Engel, H.W.B. 1978. *Lancet*, **i**, 655–656
23. Kruse, H., Kurtuki, S., Soli, N. and Olsvik, O. 1992. *Scand. J. Infect. Dis.*, **24**, 733–739
24. Baker, C.N., Stocker, S.A., Culver, D.H. and Thornsberry, C. 1991. *J. Clin. Microbiol.*, **29**, 533–538

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