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Double-Blind Study Comparing Erythromycin and Mupirocin for Treatment of Impetigo in Children: Implications of a High Prevalence of Erythromycin-Resistant *Staphylococcus aureus* Strains

RON DAGAN[1]* AND YAIR BAR-DAVID[2]

The Pediatric Infectious Disease Unit, Soroka University Medical Center and the Faculty of Health Sciences, Beer-Sheva,[1] and the Pediatric Clinics Mabuim and Ofakim, Negev,[2] Israel

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Staphylococcus aureus* has been consistently isolated from a high proportion of impetiginous lesions, and in several recent studies, it was present in the majority of the cases. Since recently a large proportion of *S. aureus* strains in our community showed erythromycin resistance, we undertook a prospective double-blind controlled study comparing topical mupirocin with oral erythromycin to determine (i) the prevalence of erythromycin-resistant *S. aureus* strains in impetigo and (ii) whether an increased rate of failure of erythromycin treatment was associated with such resistance. A total of 102 patients 3 to 185 months old (median = 49 months) were enrolled. Culture was positive for 97 of 102 (95%) patients, and *S. aureus* was present in 93% of the patients for whom cultures were positive. *S. aureus* was the single pathogen in 64% of these patients. Erythromycin-resistant *S. aureus* strains were present in 27 of 91 (28%) patients for whom cultures were positive. In all cases but one, *S. aureus* was resistant to penicillin, and in all cases it was sensitive to mupirocin. A marked difference was observed in favor of mupirocin in the clinical courses of the disease. However, only patients with erythromycin-resistant *S. aureus* strains had unfavorable courses compared with those treated with mupirocin (failure rate, 47 versus 2%, respectively). Patients with erythromycin-susceptible *S. aureus* strains who received erythromycin had a failure rate of 8%. In four patients, *S. aureus* strains initially susceptible to erythromycin became resistant during treatment. We conclude that erythromycin-resistant *S. aureus* strains are commonly isolated from impetigo in our region. In view of the increasing resistance of *S. aureus* to various antibiotic drugs, new therapeutic regimens should be sought for this common skin infection. In our setting, mupirocin seems an appropriate alternative.

There is mounting evidence that the predominant organism in impetigo, the most common skin infection of children, is changing. For many years, impetigo had been considered a streptococcal disease (9, 12, 13, 18, 21, 22). However, *Staphylococcus aureus* has been consistently isolated from a high proportion of impetiginous lesions, and in several recent studies it was present in the majority of the cases, whereas *Streptococcus pyogenes* was isolated in about one of three of the cases, usually with *S. aureus* (5, 7, 8, 14, 16, 20). We and others have recently shown that in areas where *S. aureus* strains are usually penicillin resistant, a high rate of failure may occur if antistaphylococcal coverage is not provided by the therapeutic regimen, thus suggesting the role of *S. aureus* as a causative agent in impetigo (8, 14).

Because of its activity against both streptococci and *S. aureus*, erythromycin is a widely used drug for impetigo and has been used as a "gold standard" for comparisons of topical and systemic treatments (3, 5, 11, 14–16). The susceptibility of *S. aureus* to erythromycin was not mentioned in most of these studies, but clinical response was adequate.

Recently, strains of *S. aureus* from pediatric patients with community-acquired infections in our region exhibited resistance to both penicillin and erythromycin (7), and at the same time we started to observe an increasing frequency of failure of erythromycin in the treatment of impetigo (unpublished data). Since the local strains were susceptible to mupirocin, we undertook a prospective double-blind controlled study comparing topical mupirocin with oral erythromycin in the treatment of impetigo to determine (i) the prevalence of erythromycin-resistant *S. aureus* in impetigo and (ii) whether failure of erythromycin is associated with erythromycin-resistant *S. aureus*, thus confirming its causative role in impetigo.

MATERIALS AND METHODS

Infants and children under 16 years of age presenting with impetigo at two pediatric clinics in the Negev region of Israel from July 1989 to October 1990 were enrolled. These clinics generally serve a population with crowded households that belong to the lower and middle socioeconomic classes. Excluded groups were (i) patients who had received topical or systemic antibiotics within the preceding 48 h, (ii) neonates (≤28 days old) (iii) immunocompromised patients, and (iv) patients on whom the total surface area of the lesions exceeded 50 cm^2.

The following data were recorded before the initiation of treatment: each patient's age, the presence of fever (temperature, ≥38°C), nature of lesions (bullous or nonbullous), number of lesions, diameters of the three largest lesions, and the presence of regional lymphadenopathy.

The three largest lesions were cultured as follows. The corner of the crust was lifted by a sterile procedure to reach the fresh exudate underneath. The lesion was then touched with a sterile cotton swab which was transferred to the

* Corresponding author.

laboratory in a transport medium (Culturette; Marion Scientific, Kansas City, Mo.).

After the cultures and informed consent from one of the parents were obtained, patients were randomized into two groups: (i) the erythromycin group, which received a placebo ointment (ointment containing polyethylene glycol only) and an oral erythromycin ethyl-succinate suspension (50 mg/kg of body weight per day up to 750 mg/day), and (ii) the mupirocin group, which received a 2% mupirocin ointment in polyethylene glycol and an oral placebo suspension. Both drugs were administered three times daily for 7 days.

The drugs and placebo were prepared by the manufacturers (mupirocin, Beecham Pharmaceuticals, Brentford, England; erythromycin, Teva Pharmaceutical Industries, Petah-Tikva, Israel). The randomized code was prepared by Beecham Pharmaceuticals and was not known to the investigators until after the raw data were tabulated.

The study was approved by the local and national Committees for Human Investigations.

The patients were monitored on days 3 and 4, 5 and 6, and 7 and 8 and evaluated for (i) the morphologic structure of the lesions (the grades were as follows: cured, improved, unchanged, and worse), (ii) the appearance of new lesions (the lesions were circled with a marking pen at the initial visit, and parents were instructed to look for new lesions, (iii) regional lymphadenopathy (the grades were as follows: disappeared, improved, unchanged, and worse), (iv) fever, and (v) adverse events (classified as mild, easily tolerated by the patient, causing minimal discomfort, and not interfering in everyday activities; moderate, sufficiently discomforting to interfere with normal everyday activities; and severe, incapacitating and preventing normal everyday activities and/or requiring therapeutic intervention such as the use of prescription drugs, hospitalization, or discontinuation of the study regimen).

The definitions for improvement were as follows: cured, lesions disappeared or became completely dry; improved, lesions were less extensive or some were dry, but at least some were still not completely dry. In addition, during each follow-up visit the physician had to decide whether a culture should be repeated (given that the lesion was not completely dry or the appearance of new lesions was observed).

Compliance was assessed at each visit by examining the amount of drug left in the bottles. The patient was contacted again by telephone 3 weeks after completion of treatment to determine the recurrence rate of the infection. When impetigo recurred (as defined by new lesions), the patient was seen in the clinic and treated with oral cephalexin. When the investigator decided that the case was a failure during treatment (on the basis of worsening of the lesions and/or the appearance of new lesions), the treatment was changed to oral cephalexin.

All swabs were plated on sheep blood agar and chocolate agar media. The presence of group A streptococci was screened by using a bacitracin disk (0.04 U) after incubation in 5% carbon dioxide at 35°C for 18 to 24 h. Confirmation was performed by specific serotyping (Wellcome Diagnostics, Dartford, England). Identification of *S. aureus* was based on colony structure, pigment, and hemolysin production. Confirmation was performed by the slide coagulase technique. Antibiotic susceptibility testing was performed by the method described by Bauer et al. (4).

Statistical analysis was performed by chi-square or Fisher's exact test. A P value of < 0.05 was considered significant.

TABLE 1. Comparison of children with impetigo assigned to erythromycin and mupirocin treatment groups

Characteristic or variable	Value for group	
	Erythromycin (n = 51)	Mupirocin (n = 51)
Age (mo)		
Range	3–132	11–185
Median	44	54
Male (%)	33 (65)	23 (45)
No. with bullous/no. with nonbullous impetigo	8/43	7/44
Duration of illness before treatment (days)		
Range	1–60	2–30
Median	7	7
No. of lesions		
Range	1–>10	1–>10
Median	5	4
Largest diam of lesions (mm)		
Range	4–35	5–50
Median	12	12
% with regional lymphadenopathy	22 (41)	21 (41)
% with temp of >38°C	5 (10)	1 (2)

RESULTS

During the study period, 102 patients were enrolled (51 in the erythromycin group and 51 in the mupirocin group). The two study groups differed slightly in age distribution (the mupirocin group was slightly older) and gender distribution (65 versus 45% males in the erythromycin and mupirocin groups, respectively), but the differences were not significant (Table 1).

Culture was positive for 97 of 102 (95%) of all enrolled children (Table 2). *S. aureus* was the organism most commonly isolated from both groups and was present in most patients (96 and 90% of the erythromycin and mupirocin groups, respectively). *S. aureus* was the single pathogen in 65 (64%) of the patients. Beta-hemolytic streptococci, mostly *S. pyogenes* (group A) strains, were present in about one of three of the patients. Other organisms, mainly gram-negative bacilli, were occasionally present. In 27 of 91 (28%) patients from whom *S. aureus* was isolated, the organism was resistant to erythromycin, and in 90 (99%) it was resistant to penicillin; it was susceptible to mupirocin in all patients. In 60 of 91 (66%) patients positive for *S. aureus*, the organism was isolated from more than one lesion. Close correlation was found in the patterns of susceptibility to erythromycin when cultures from multiple lesions were compared. In only one case, one isolate was susceptible and the other isolate was resistant to erythromycin. All staphylococci and streptococci were susceptible to cloxacillin and cephalexin, and all streptococci were susceptible to erythromycin, penicillin, and mupirocin.

Of the 15 patients with bullous impetigo, an organism was isolated from 13 (87%). *S. aureus* was present in all 13 patients for whom cultures were positive (1 of 13 was

TABLE 2. Organisms isolated from 97 patients with impetigo and their patterns of susceptibility to penicillin, erythromycin, and mupirocin[a]

Organism(s)	Erythromycin group (n = 49) No. (%) infected	% Susceptible to: Ery	Pen	Mup	Mupirocin group (n = 48) No. (%) infected	% Susceptible to: Ery	Pen	Mup
S. aureus	47 (96)	64	2	100	43 (90)	77	0	100
Streptococci	17 (34)	100	100	100	19 (40)	100	100	100
Group A	10				17			
Group B	1				2			
Group C	2				0			
Group G	2				0			
Enterococcus faecalis	2				0			
Acinetobacter spp.	4 (8)	ND	ND	ND	10 (21)	ND	ND	ND
Others[b]	6 (12)	ND	ND	ND	3 (6)	ND	ND	ND

[a] All gram-negative organisms were isolated from patients infected with at least one gram-positive pathogen. Abbreviations: Ery, erythromycin; Pen, penicillin; Mup, mupirocin; ND, not determined.
[b] *Klebsiella* spp. (5), *Streptococcus pneumoniae* (2), *Enterobacter* spp. (1), *Escherichia coli* (1).

erythromycin resistant). Streptococcus groups B, C, and G were each isolated from one patient with bullous impetigo.

A marked difference between the clinical courses of the disease in the erythromycin and mupirocin groups was noted. This could be observed at the first follow-up visit (Table 3). Improvement was significantly greater in the mupirocin group than in the erythromycin group, as judged by all variables shown in the table. A total of 18 (78%) of the 23 cultures obtained from the erythromycin group at the first follow-up visit were positive, compared with only 4 of 13 (31%) from the mupirocin group ($P < 0.05$). A total of 14 of the 18 (78%) positive cultures from the erythromycin group were resistant to erythromycin, compared with none of the 4 positive cultures from the mupirocin group.

A total of 13 patients did not complete the study; 1 patient in the erythromycin group because of side effects and 12 (7 in the erythromycin group and 5 in the mupirocin group) because of their refusal to continue treatment or to return for the follow-up visit.

TABLE 3. Clinical courses of 89 patients with impetigo at first follow-up visit (days 3 and 4 of treatment)

Variable	Value for group: Erythromycin (n = 45)	Mupirocin (n = 44)	P^a
Day of treatment (mean ± SD)	3.6 ± 0.5	3.6 ± 0.5	NS
No. (%) with regional lymphadenopathy:			
Improved or disappeared	4 (9)	7 (16)	NS
Worse	6 (13)	0	<0.05
No. (%) with:			
Cured or improved lesions	33 (73)	42 (95)	<0.05
Worse lesions	11 (24)	1 (2)	<0.05
Appearance of new lesions	9 (20)	3 (7)	NS
Need for swab	23 (51)	13 (30)	NS
Swabs with positive culture	18 (78)[b]	4 (31)[b]	<0.05
Erythromycin-resistant organisms	14 (78)[c]	0 (0)[c]	

[a] NS, not significant.
[b] Of those needing swab.
[c] Of those with positive swab cultures.

At the end of the study, 89 patients, 43 in the erythromycin group and 46 in the mupirocin group, were available for evaluation. Failure was observed for 10 of 43 (23%) of the patients in the erythromycin group compared with 1 of 46 (2%) in the mupirocin group ($P < 0.05$).

To determine the role of the erythromycin-resistant *S. aureus* strains in causing failure, the patients in both groups were divided into two groups, those infected with erythromycin-resistant *S. aureus* and those infected with erythromycin-susceptible *S. aureus*. The failure rate among the patients with erythromycin-susceptible strains was not different for the two groups (2 of 26 [8%] versus 1 of 36 [3%] in the erythromycin and mupirocin groups, respectively). In contrast, 8 of 17 (47%) of the patients infected with erythromycin-resistant *S. aureus* in the erythromycin group failed compared with 0 of 10 in the mupirocin group ($P < 0.05$ when the failure rate with erythromycin-resistant strains in the erythromycin group was compared with that of any other group; $P < 0.01$ when the failure rate was compared with that of all other groups combined). Thus, erythromycin resistance was the main cause of failure of the treatment.

Side effects were noted with 22 (22%) of the 98 patients, 15 of 47 (32%) in the erythromycin group and 7 of 51 (14%) in the mupirocin group, who received treatment for 5 days or more ($P < 0.05$). Gastrointestinal side effects (diarrhea, vomiting, or both) were noted for 11 (23%) in the erythromycin group and 4 (8%) in the mupirocin group. Of the 11 patients with systemic side effects in the erythromycin group, the symptoms of 3 were considered moderate and those of 1 (diarrhea and vomiting) were considered severe, thus necessitating discontinuation of the study regimen. All side effects in the mupirocin group were judged to be mild.

A total of 80 patients were available for a follow-up visit at least 1 week after the cessation of treatment. Of those, 11 (14%) had a relapse within 1 week. Of the 35 children in the erythromycin group, 7 (20%) had a relapse (after 1 to 7 days; median, 3 days), and of the 45 children in the mupirocin group, 4 (9%) had a relapse within 1 week (after 2 to 7 days; median, 4 days) (not significant). Of the seven children in the erythromycin group who had a relapse, one was infected with an erythromycin-resistant *S. aureus* strain and for one the *S. aureus* strain, initially susceptible to erythromycin, became resistant during treatment. In the other five patients in the erythromycin group in whom relapses occurred, *S. aureus* strains were erythromycin susceptible.

During a 6-month follow-up period, none of the patients in the study was seen at the hospital for any potential late or early sequelae of impetigo, such as glomerulonephritis, osteomyelitis, septic arthritis, or any other systemic streptococcal or staphylococcal infections.

In four cases, *S. aureus* strains initially susceptible to erythromycin became resistant during treatment. In one case, this was associated with a worsening of the morphology of the lesions on day 7 and a full relapse on day 1 after the cessation of treatment; in the second case, a resistant *S. aureus* strain was isolated from a lesion judged to be worse on day 4, but the patient was cured. With two other patients, complete cures were observed.

DISCUSSION

Before the last decade, impetigo, especially the nonbullous type, was considered a streptococcal disease (9, 12, 13, 18, 21, 22). More recently, many studies from various parts of the world showed that the predominant organism in the disease was *S. aureus*, isolated alone or with streptococci from 65 to 98% of the patients (1, 5, 7, 8, 14, 16, 19, 20). Furthermore, failure rates with penicillin and amoxicillin were unacceptably high, ranging from 20 to 47% (1, 7, 8) and suggesting that *S. aureus* was not just an innocent bystander but rather played an important role in the disease as either a primary or a secondary pathogen.

Erythromycin is considered an appropriate drug for impetigo, since it is a nontoxic, relatively inexpensive drug active against both staphylococci and streptococci (1, 6, 10, 17). In fact, it was even claimed that erythromycin may be the preferred drug on the basis of cost effectiveness (2, 8). During the last decade, the sensitivity to erythromycin of *S. aureus* strains isolated from impetigo was approximately 90% or higher (8, 10, 14, 20). However, two recently published articles from Israel (7) and Australia (19) reported erythromycin resistance rates of 32 and 48%, respectively. Although in these two studies no attempt to correlate resistance and failure rate was made, Carruthers, in a recent review, proposed an algorithm which suggested the use of flucloxacillin or cephalexin in districts where much erythromycin resistance is found (6).

The present report not only confirms the high erythromycin resistance rate of *S. aureus* strains isolated from impetigo in Israel, but it also demonstrates a clear correlation of the resistance with the failure of erythromycin treatment. In a previous study by our group (7), erythromycin resistance did not affect the cure rate with amoxicillin plus clavulanic acid, and in the present study, it did not affect the cure rate with topical mupirocin. These findings suggest that resistance to erythromycin is not associated with a different disease and emphasize the causative role of *S. aureus* in impetigo in children and the importance of continuous epidemiological studies before the choice of appropriate antibiotic drugs for impetigo is made in each community.

Our study confirms the finding by others that mupirocin is an efficacious drug against impetigo in children (3, 5, 11, 14–16). In the presence of extensive penicillin resistance among *S. aureus* strains and in view of its efficacy, mupirocin is a promising drug that may be cost effective in areas where erythromycin resistance is widespread.

We conclude that erythromycin-resistant *S. aureus* is commonly isolated from impetigo in our region. In areas like ours, erythromycin should not be the drug of choice for impetigo. In view of the increasing resistance of *S. aureus* to various antibiotic drugs, continuous epidemiological studies should be made and new therapeutic approaches should be investigated.

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