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# Randomized Clinical Trial of Topical Mupirocin versus Oral Erythromycin for Impetigo

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**The safety and efficacy of a new topical antiinfective agent, mupirocin, was compared with that of oral erythromycin ethylsuccinate in the treatment of impetigo in children. Sixty-two children aged 5 months to 13 years with impetigo were assigned to be treated with either mupirocin in three daily applications or erythromycin ethylsuccinate (40 mg/kg of body weight per day divided into four doses) according to a randomized treatment schedule. On the initial visit, exudate or cleansed infected sites or both were cultured and therapy was begun. All patients were treated for 8 days. Patients were seen again on days 4 to 5 of therapy, at the end of therapy, and 7 days after the end of therapy. Sites of infection were comparable between the groups, as were bacteriologic responses. At the first visit, 24 of 30 children in the mupirocin group and 14 of 32 children in the erythromycin group were cured or had at least a 75% reduction in size of the lesions. At the end of the study, all 29 of the children in the mupirocin group who came to follow-up, compared with 27 of 29 in the erythromycin group, were cured. Side effects were few. Five children in the erythromycin group developed mild diarrhea. Thus, mupirocin appears to be safe and effective in treating impetigo in children. Our data show a trend toward more rapid clinical response with mupirocin than with erythromycin.**

Impetigo is a highly contagious superficial skin infection which shows a marked seasonal incidence (17). It is classically thought to have a streptococcal etiology (3, 6, 10); however, evidence is accumulating to suggest that the pathophysiology may be changing (2, 21). It is now clear that *Staphylococcus aureus*, along with *Streptococcus pyogenes*, must be considered a true pathogen in this illness (1).

Most therapy for impetigo is administered on an empiric basis since cultures are seldom obtained. Thus, it is essential that the bacterial causes be well recognized and that empiric therapy be effective against both pathogens. In the past, a number of therapeutic approaches have been used. These have included antiseptic scrubs (19), topical antibiotics (3, 7, 14), parenteral antibiotics (4, 7), and oral antibiotics (3, 5, 6, 11, 14, 15).

The efficacy of antiseptic scrubs is of only historical importance. We now know that antimicrobial therapy, not the antiseptics, is the key to curing the disease (4, 19). It is also clear from our experience with topical therapy that the drug used must have significant gram-positive activity (4, 7, 14, 19). The purpose of this study was to compare topical mupirocin therapy versus conventional systemic therapy with oral erythromycin in the treatment of impetigo.

Mupirocin is a new topical antibiotic with a unique chemical structure unrelated to those of other antimicrobial agents (22). The drug is produced by a particular strain of *Pseudomonas fluorescens* (18, 22) and appears to inhibit bacterial protein and RNA synthesis (12, 13). Its spectrum of activity includes *S. aureus*, the streptococci, and some gram-negative enteric bacteria (22). When applied as an ointment, mupirocin is delivered to the outer layers of the skin without systemic absorption (22). In preliminary trials, mupirocin had been effective in treating superficial skin infections with cure rates in excess of 90% (8, 16, 20). This information has prompted a reconsideration of topical therapy for impetigo.

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## MATERIALS AND METHODS

Children 3 months of age and older who were seen at Rainbow Babies and Childrens Hospital with the diagnosis of impetigo were eligible for our study. This study was approved by the Institutional Review Board for Human Subject Investigation of University Hospitals of Cleveland. Written consent was obtained for each enrolled child from a parent or legal guardian.

Impetigo was defined as a primary superficial infection of previously normal skin. Lesions had honey-colored drainage with crusting on a red base. Children were excluded if there was evidence of cellulitis or extensive skin involvement (more than 15 discrete lesions) or if they had been given antibiotic therapy within the preceding 24 h. Also excluded were children with acute or chronic dermatoses or hypersensitivity to mupirocin, polyethylene glycol ointment, or erythromycin.

Enrolled children were randomly assigned to groups that received either mupirocin topical therapy in a 2% polyethylene glycol ointment or oral erythromycin ethylsuccinate. Before treatment was begun, lesions were cultured. Swab cultures were obtained from representative sites after the skin lesions were washed with soap and water to remove any crusts and the washed area was dried. More than one culture was obtained if multiple body sites were involved. A representative lesion from each site was cultured. Lesions were counted and mapped to evaluate responses.

Chocolate agar and 5% sheep blood agar plates were inoculated and aerobically incubated. Plates were examined at 24 and 48 h. A selective streptococcus agar (GIBCO Laboratories, Grand Island, N.Y.) was also inoculated and incubated anaerobically. Staphylococci were identified by subculture on mannitol salt agar and by coagulase reaction. Beta-hemolytic streptococci were subcultured on blood agar, identified by absence of growth around a bacitracin disk (9), and typed by the latex agglutination test, using a Streptex kit (Wellcome Diagnostics, Research Triangle

TABLE 1. Demographic information

| Characteristic | Mupirocin group | Erythromycin group |
|---|---|---|
| No. in group | 30 | 32 |
| Age | | |
| Mean | 4.2 yr | 3.2 yr |
| Range | 5 mo–7 yr | 6 mo–13 yr |
| Male/female | 17/13 | 14/18 |
| Site(s) of infection[a] | | |
| Face, neck | 19 | 14 |
| Extremities | 7 | 8 |
| Trunk | 6 | 7 |
| Genitalia | 4 | 8 |

[a] In some children, more than one site was involved.

Park, N.C.). Gram-negative organisms were tested for oxidase reaction and subcultured on triple sugar agar. Enteric bacteria were identified by using a rapid E APT biochemical strip. All isolates were tested for susceptibility to erythromycin and to mupirocin by agar dilution (MIC) and by the Kirby-Bauer method of disk diffusion.

Parents or legal guardians of the children in the mupirocin group were instructed to apply the 2% mupirocin ointment three times per day, using the cotton swabs provided. Parents or legal guardians of children in the erythromycin group were given instructions and medication to administer erythromycin ethylsuccinate at 40 mg/kg of body weight per day in four doses. Both groups were given Dial soap and instructed to wash lesions three times per day. All children were to continue therapy for 8 days.

Children were seen on days 4 to 5 of therapy, at the end of therapy, and 7 days after the end of therapy. Clinical responses were scored at each visit on the basis of the number of lesions and involved areas. Bacteriologic response was judged by culturing persisting or recurrent lesions at each visit. Compliance was judged by history and by collecting and measuring unused medication.

## RESULTS

There were a total of 62 children enrolled in the study, 30 in the mupirocin group and 32 in the erythromycin group. Mean ages were 4.2 years for the mupirocin group and 3.2 years for the erythromycin group. Demographics and sites of infection of the treatment groups are described in Table 1.

Bacteriologic analysis of lesions revealed mostly pure cultures of *S. aureus* (Table 2). Group A streptococci or cultures containing both organisms were found for 11 children. Gram-negative enteric bacteria were isolated from two children. Both *Klebsiella pneumoniae* and group A streptococci were isolated from one child in the mupirocin group, and *Enterobacter cloacae* was isolated from one child in the erythromycin group. From two children in the erythromycin group, both group B streptococci and *S. aureus* were isolated.

TABLE 2. Bacteriologic findings

| Isolate(s) | No. of children | |
|---|---|---|
| | Mupirocin group | Erythromycin group |
| *Staphylococcus aureus* | 26 | 23 |
| *Streptococcus pyogenes* | 1 | 1 |
| *Staphylococcus aureus* and *Streptococcus pyogenes* | 2 | 7 |
| *Streptococcus agalactiae* | 0 | 2[a] |
| Gram negative (enteric) | 1[b] | 1[c] |
| None | 1 | 0 |

[a] With *Staphylococcus aureus*.
[b] *K. pneumoniae* with group A streptococci.
[c] *E. cloacae*.

TABLE 3. Results

| Determination | Clinical response (no.) | |
|---|---|---|
| | Mupirocin group ($n$ = 30) | Erythromycin group ($n$ = 32) |
| First visit | | |
| Cure or excellent response | 24 | 14 |
| Good response | 4 | 11 |
| Fair response | 1 | 6 |
| Lost to follow-up | 1 | 1 |
| End of therapy | | |
| Cure, excellent | 29 | 27 |
| Failure | 0 | 2 |
| Lost to follow-up | 0 | 2 |
| Follow-up | 25 | 27 |
| Cure | 25 | 25 |
| Failure | 0 | 2 |
| Relapse | 0 | 0 |
| Lost (total for study) | 5 | 5 |
| Adverse reactions | 0 | 5 |

At the first return visit (after 4 to 5 days on therapy), 24 of 29 children in the mupirocin group who returned had either a cure or excellent response, compared with 14 of 31 children in the erythromycin group who came to the first follow-up visit (Table 3). One child from each group did not return for the first visit. At the end of therapy, 29 of 29 children in the mupirocin group who completed the treatments were cured, compared with 27 of 29 in the erythromycin group. Two children, both from the erythromycin, did not return for this follow-up visit. There were no failures in the mupirocin group. The two failures of therapy in the erythromycin group involved children who had persisting lesions and bacterial cultures for pathogens at the end of therapy. There were no relapses in the 50 children reporting for the final visit, 1 week after therapy. Three more children in the mupirocin group and two in the erythromycin group failed to return for the last (follow-up) visit, all of whom had previously shown clearing of all lesions. Statistical analysis by the chi-square test showed no significant differences in outcome between the groups.

Of the 59 original *S. aureus* isolates, 58 were susceptible to erythromycin in vitro. All strains of *Streptococci* were susceptible to erythromycin and mupirocin. One child, from whom *S. aureus* had been isolated in pure culture and who had been assigned to the erythromycin treatment group, had a partial response to treatment but ultimately was one of the two children who failed erythromycin therapy. From the other child who failed erythromycin therapy, both group A streptococci and *S. aureus* had been isolated at the time of enrollment in the study. The original isolate of *S. aureus* was susceptible to erythromycin. A pure culture of *S. aureus* was obtained at the end of therapy and this isolate was resistant to erythromycin. Both of these children went on to respond to treatment with an oral cephalosporin. One mupirocin-resistant isolate was recovered at the end of therapy from a child treated with mupirocin. All of the child's skin lesions had cleared.

There were no adverse reactions in the mupirocin group. Parents were universally pleased with the outcome and ease

of using the ointment. The ointment is greasy but does not stain clothing. Although application is somewhat messy, there were no complaints. Five children in the erythromycin group had diarrhea. All episodes were mild, and none required a change in therapy.

## DISCUSSION

Although two types of impetigo have been recognized, conventional wisdom has been that most cases are streptococcal in origin. Convention has also dictated that impetigo be treated with oral or parenteral therapy, most often with penicillin or erythromycin. The recommendations are based on double-blind studies comparing systemic therapy (erythromycin or penicillin) with treatment with either neomycin or bacitracin ointment (3, 6, 14). Topical therapy with these agents was clearly less effective than systemic therapy.

Therapy of impetigo, however, seems in need of reexamination. Some data suggest that penicillin may no longer be adequate empiric therapy for many cases of impetigo. This finding appears to reflect the increased occurrence of staphylococcal infections and the almost universal penicillin resistance of community-acquired staphylococcal infections (21). The children who failed therapy in our study also appeared to have *S. aureus* infections. From one child an erythromycin-resistant isolate was initially cultured; the other child appeared to develop erythromycin resistance while on therapy. The clinical distinction between the thick, honey-colored crusted lesions of streptococcal impetigo and the bullous lesions of staphylococcal impetigo is not as clear as previously described (7). Most of the children in our study were infected with staphylococci alone, despite the presence of the classical lesions of streptococcal impetigo.

In our study, results after topical therapy with mupirocin were very encouraging. In this comparison of treatment with topical mupirocin ointment versus systemic oral therapy with erythromycin for mild to moderate cases of impetigo, topical therapy was as efficacious as the standard systemic therapy and was associated with fewer side effects. Therapy was well accepted by caretakers, and there was a trend toward an earlier response with mupirocin.

In all of the children in the mupirocin group, lesions had cleared by the end of therapy and most had cleared completely by days 4 to 5 of treatment. The rates of cure in both study groups were comparable with those described previously (3, 6, 14). An explanation of why mupirocin is more effective than other topical agents in treating impetigo is unclear. However, mupirocin is also effective in treating superficial skin infections and in eradicating nasal carriage of *S. aureus*, including methicillin-resistant species. The compound appears to reach superficial skin layers and to be a very effective antibacterial agent, especially against gram-positive organisms (20, 22).

Although side effects with mupirocin ointment have been described, these are rare and appear to be due to the polyethylene glycol vehicle and not the drug itself (22). None occurred in this small study. Avoidance of the complications of systemic therapy, which in this study included mild diarrhea, are a definite advantage of topical therapy. The treatment was easy to apply, and the promptness of response was often dramatic.

Disadvantages of topical therapy include difficulties in applying an ointment to large areas, especially the scalp. Children with extensive areas of impetigo were not evaluated. Systemic therapy may be easier to use in such cases.

Concern about the risk of glomerulonephritis with topical versus systemic therapy has been raised. The concern seems unfounded, since even systemic therapy does not appear to prevent glomerulonephritis in children with either group A streptococcal pharyngitis or skin infection (23). Obviously, systemic infections (fever or bacteremia) or deeper skin infections (cellulitis) will require systemic therapy.

In this trial, the standard systemic therapy for mild to moderate impetigo, erythromycin, was compared with topical mupirocin therapy. Similar cure rates occurred in the two groups. There was a trend toward a prompter response with topical mupirocin. These findings suggest that the previously standard regimen of systemic therapy only for impetigo should be reevaluated and that a return to topical therapy for most cases of impetigo may be forthcoming. Also, when oral therapy is required, the need to use agents effective against *S. aureus* is underscored by the clinical failures in our study.

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