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Efficacy of topical 2% mupirocin ointment for treatment of tympanostomy tube otorrhea caused by community-acquired methicillin resistant *Staphylococcus aureus*

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ABSTRACT

Objective: To demonstrate the safety and effectiveness of topical 2% mupirocin ointment as an adjunctive therapy for tympanostomy tube otorrhea (TTO) caused by methicillin-resistant *Staphylococcus aureus* (MRSA).
Methods: We treated children with community-acquired MRSA TTO by aural suctioning and culture-directed systemic antibiotics (+/− ototopical drops) alone (control group) or with the addition of single 1 ml dose of mupirocin ointment applied to the tube and ear canal (mupirocin group). Patient age, laterality, response to treatment, associate hearing loss, duration of follow-up, and recurrence of infection by MRSA or by other organisms were compared.
Results: 29 children (37 ears) with MRSA TTO were included. 8 children (12 ears) received adjunctive topical mupirocin ointment – 21 children (25 ears) did not. 8 of 12 ears in the mupirocin group received concomitant systemic antibiotics – 4 ears were treated with topical mupirocin alone. The mean duration of follow-up of the mupirocin group was 7 months (with 95% C.I of 7 ± 7). The control group was 24 months (with 95% C.I of 24 ± 9). Recurrence of MRSA TTO in the mupirocin and control groups were 0/12; 0% and 10/25; 40%, by ear, respectively ($p = 0.015$). Recurrence of non-MRSA TTO in the mupirocin and control groups were 6/12; 50% and 9/25; 36%, by ear, respectively ($p = 1.0$). There were no sensorineural hearing losses in the mupirocin-treated children.
Conclusion: In this small series, a single application of topical mupirocin in combination with mechanical debridement, controlled infection by CA-MRSA without evidence of local reaction or subsequent hearing loss. Its role in treatment of MRSA TTO merits further investigation.

1. Introduction

Otorrhea is the most common adverse sequela of tympanostomy tube insertion, with a mean incidence of 26% (range, 4%–68%) in observational studies and up to 83% with prospective surveillance [1]. In children less than 3 years of age, tympanostomy tube otorrhea (TTO) is caused by the usual pathogens of acute otitis media -*Streptococcus pneumoniae, Hemophilus influenzae* and *Moraxella catarrhalis*. In older children and those who have been treated with antibiotics, *Staphylococcus aureus* and *Pseudomonas aeruginosa* grow more commonly in cultured otorrhea discharge [2].

Methicillin-resistant *S. aureus* (MRSA) was first reported as a cause of otorrhea in the last decade of the 20th century [3]. With the rise of MRSA as a cause of community acquired skin and respiratory infections, similar increases in MRSA otorrhea have been reported [4–6]. In a recent series, community acquired methicillin-resistant *S. aureus* (CA-MRSA) was recovered from 16% of 1079 pediatric TTO cultures [7]. There is no standard treatment for MRSA otorrhea. Currently, only fluoroquinolone drops are United States Food and Drug Administration (FDA) approved for topical treatment of acute TTO. Systemic fluoroquinolones are no longer recommended as monotherapy for invasive MRSA infections given high rates of resistance and emergence of resistance during treatment [8]. While some have argued that the high concentration of fluoroquinolones in ototopical preparations should overcome resistant strains [9], fluoroquinolone drops fail in more than 50% of MRSA –TTO [10].

Encouraged by early reports of efficacy in treatment of adult chronic otorrhea [11] and animal studies demonstrating lack of ototoxicity

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[12], we began routine use of topical mupirocin as an adjunct to culture-directed systemic therapy in 2014. We report our experience with the safety and efficacy of this approach in children with MRSA TTO.

2. Methods

Our treatment protocol for MRSA TTO prior to 2014 included aural suctioning using an operating microscope, culture of the tympanostomy tube orifice, and systemic treatment with an antibiotic for 10–14 days based on microbiological sensitivities. Ototopical fluoroquinolone drops were used if the MRSA was sensitive to them. After January 2014, all children with MRSA TTO received similar treatment with the addition of single application of 1 ml of 2% mupirocin ointment to the tympanostomy tube, tympanic membrane and external auditory canal with a 3-ml syringe and 18-gauge intravenous catheter under microscopic guidance.

After receiving an exemption from Temple University's Human Research Protection Program (IRB protocol 24709), a computerized collection of patient office notes and operative reports was queried using the Microsoft Word "find" feature. The data collection was done in a manner that protected patient identity and privacy. Children with MRSA TTO were identified using the search terms "MRSA" "methicillin-resistant *Staphylococcus aureus*" and "mupirocin". Patient age at time of first treatment, laterality, MRSA sensitivities, prior treatments, concomitant use of systemic antibiotics, response to treatment, associate hearing loss, duration of follow-up, and recurrence of infection by MRSA or by other organisms were recorded. Patients over the age of 18 years and those with incomplete records were excluded.

Probabilities and confidence intervals were calculated using the Fisher exact test. A p-value less than 0.05 was considered significant when comparing recurrence rates and a 95% confidence interval was used with respect to follow up duration.

3. Results

Thirty children younger than 18 years of age (38 ears) with culture-proven CA-MRSA TTO were treated between 2001 and 2017. One child in the mupirocin group was excluded when lost to follow-up. Of the 29 remaining patients (37 ears), 8 children (12 ears) received adjunctive topical mupirocin ointment (mupirocin group). Twenty-one children (25 ears) were not mupirocin treated (controls). Six of the 8 children (8 ears) in the mupirocin group received concomitant systemic antibiotics – 2 children (4 ears) were treated with topical mupirocin alone or mixed with triamcinolone 0.1% cream. The 21 control children (25 ears) were treated with oral antibiotics with or without ototopical drops based on MRSA sensitivities. One child in each group has a tube surgically removed during treatment.

The average age was 5.3 years in the mupirocin-treated group and 3.5 years in the control group. MRSA otorrhea was eventually controlled in all children in both groups. One child in the control group was found to have a mild bilaterally symmetric sensorineural hearing loss after treatment with linezolid. There were no sensorineural hearing losses in the mupirocin-treated children. The mean duration of follow-up of the mupirocin group was 7 months (with 95% C.I of 7 ± 7) and that of the control group was 24 months (with 95% C.I of 24 ± 9). Recurrence of MRSA TTO in the mupirocin and control groups were 0/12; 0% and 10/25; 40% by ear, respectively ($p = 0.015$). Recurrence of non-MRSA TTO in the mupirocin and control groups were 6/12; 50% and 9/25; 36%, by ear, respectively ($p = 1.0$).

4. Discussion

Staphylococcus aureus has evolved multiple mechanisms to resist competition by other members of the microbiome during colonization and to defeat host defenses during invasive infection [13]. These mechanisms include biofilm formation and expression of antibiotic resistance genes. MRSA emerged from methicillin-sensitive organisms by acquisition of the staphylococcal cassette chromosome element that can include genes that encode resistance to several antibiotics. Plasmid and transposon derived genes can confer resistance to penicillins, macrolides, aminoglycosides, tetracyclines, chloramphenicol, mupirocin, and linezolid [14].

Staphylococcus aureus has become notorious for causing chronic infections due to its ability to resist therapeutic treatment by forming biofilms on indwelling medical devices, including implanted artificial heart valves, catheters, joint prosthetics [15] and tympanostomy tubes [16]. In order to form biofilms, bacteria generate a self-produced extracellular matrix composed of proteins, carbohydrates and/or extracellular DNA which encases the cells within a sticky matrix that facilitates survival in hostile or extreme environments [17]. These biofilms are thought to play an important role in persistent otorrhea as they isolate bacteria from circulating systemically-administered antibiotics increasing resistance 10–1000 fold when compared to planktonic (free-swimming) form [18]. They have been identified both on tympanostomy tubes and in biopsies of middle ear mucosa in chronic TTO [19]. Among the proposed mechanisms for defeating biofilms are the use of antibiotic combinations with different mechanisms of antimicrobial action, exposure to very high concentrations of antibiotics, mechanical disruption of biofilms by electricity, scrubbing or detergents, and removal of prosthetic materials whose surfaces support biofilms [20].

Empirically-chosen ototopical drops are considered the first line of treatment for acute TTO. When these fail, culture-directed therapies are preferred. These include topical and systemic antibiotics chosen based on *in vitro* sensitivities [21]. When MRSA is cultured from TTO, the "drug-bug" paradigm sometimes fails. Emergence of resistance during therapy is common with the two FDA-approved topical antibiotics (ciprofloxacin and ofloxacin) accounting for 39% rates of treatment failure in one series [10].

Oral antibiotics for pediatric MRSA TTO include clindamycin, trimethoprim-sulfamethoxazole, and linezolid [22]. While hospital-acquired MRSA infections are frequently resistant to these agent (resistance rates to trimethoprim-sulfamethoxazole is 61.5% and clindamycin is 42.3%) [23], community-acquired MRSA remain susceptible in North American studies [24]. The addition of oral rifampin to clindamycin or trimethoprim-sulfamethoxazole is sometimes recommended to help clear MRSA colonization. Tetracyclines are effective, but not used in children < 8 years of age because of the potential for tooth enamel discoloration and decreased bone growth. The use of intravenous antibiotics becomes necessary in complicated/persistent CA-MRSA. MRSA remains highly sensitive to intravenous vancomycin, daptomycin, tigecycline and teicoplanin. These parenteral medications are expensive and usually require hospitalization or maintenance of long-term intravenous access, so are seldom used for MRSA TTO.

Tympanostomy tube removal improves the rate of resolution in MRSA TTO [10]. However, as biofilms affect the middle ear mucosa as well as the tympanostomy tube surface, persistent otorrhea is common after tube removal without additional therapy.

Mupirocin, a mono-carbolic acid, was purified from *Pseudomonas fluoresce* in the late 1960s and introduced into clinical practice in 1985 [25]. It has a unique mechanism of action binding reversibly to the isoleucyl t-RNA synthetase thus inhibiting protein synthesis of the bacteria it affects. It is widely used as a topical antibiotic to treat skin and soft tissue infections and to eliminate nasal carriage of MRSA. As with other naturally-derived antimicrobials, resistance among Staphylococcus strains has emerged. In children treated in an urban dermatology clinic, 19% of patients had mupirocin-resistant *Staphylococcus aureus* isolates at the time of their first culture. This increased to 31% in children previously treated with topical mupirocin [26]. Fortunately, most mupirocin resistance is low-level - due to point mutations in the native isoleucyl-tRNA synthetase gene. High level resistance remains in the 1–5% range in North American hospital isolates of MRSA [27].