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ARTICLE

Effectiveness of Trimethoprim/Sulfamethoxazole for Children With Chronic Active Otitis Media: A Randomized, Placebo-Controlled Trial

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ABSTRACT

OBJECTIVE. The goal was to determine the clinical effectiveness of prolonged outpatient treatment with trimethoprim/sulfamethoxazole for children with chronic active otitis media.

METHODS. We performed a randomized, placebo-controlled trial with 101 children (1–12 years of age) with chronic active otitis media (defined as otorrhea for ≥12 weeks). In addition to a short course of steroid and antibiotic eardrops, children were assigned randomly to receive 6 to 12 weeks of orally administered trimethoprim/sulfamethoxazole (18 mg/kg, 2 times per day) or placebo and were monitored for 1 year.

RESULTS. At 6 weeks, 28% of children in the trimethoprim/sulfamethoxazole group and 53% of children in the placebo group had otomicroscopic signs of otorrhea. At 12 weeks, these values were 32% and 47%, respectively. At 1 year, the numbers of children with otorrhea were similar in the 2 groups (25% and 20%, respectively). One child in the trimethoprim/sulfamethoxazole group developed a skin rash. Vomiting or diarrhea was reported for 9% of the trimethoprim/sulfamethoxazole group and 2% of the placebo group. Pure-tone hearing levels and health-related quality of life improved during the study but did not differ between the trimethoprim/sulfamethoxazole group and the placebo group. *Pseudomonas aeruginosa* was the most frequently isolated bacteria in the otorrhea samples from both groups.

CONCLUSIONS. A 6- to 12-week course of high-dose, orally administered trimethoprim/sulfamethoxazole therapy is beneficial for children with chronic active otitis media. The treatment effect is most pronounced with the shorter course and disappears if administration of the medication is discontinued.

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Key Words
chronic suppurative otitis media, children, drug therapy, trimethoprim/sulfamethoxazole combination

Abbreviations
COM— chronic active otitis media
NNT—number needed to treat
RD—rate difference
CI— confidence interval

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CHRONIC ACTIVE (MUCOSAL) otitis media (COM) is a common infectious disease, affecting children in both developing and industrialized countries.[1–3] It causes considerable morbidity and is a major global cause of hearing impairment in children. Moreover, it may lead to serious extracranial and intracranial complications, such as mastoiditis and meningitis.[4–8] An active approach in the management of COM is therefore important.[6] Evidence regarding the most effective medical or surgical treatment of COM is incomplete; few randomized, controlled trials have been performed, and inclusion criteria, outcome measures, and follow-up methods in those studies vary considerably.[9–16]

Trimethoprim/sulfamethoxazole has been used for many years for the treatment of upper respiratory tract infections in children. It is an inexpensive antimicrobial drug and is well tolerated by children. When used for prophylaxis for recurrent acute otitis media, it was found to be effective.[17,18] A retrospective analysis of data for children with COM treated with trimethoprim/sulfamethoxazole for a prolonged period at our hospital showed promising results. We therefore initiated a randomized, placebo-controlled trial of a 6- to 12-week course of orally administered trimethoprim/sulfamethoxazole in addition to a short course of steroid and antibiotic eardrops for children with COM who had experienced failure of conventional management with topical medications and/or short-term systemic antibiotic treatment. In this article, we report on both the clinical effectiveness and bacteriologic findings.

METHODS

Patients

We conducted a randomized, placebo-controlled trial between February 2003 and June 2006. Otorhinolaryngologists and pediatricians from across the Netherlands referred potential participants (ie, children with COM who had experienced failure of conventional management with topical medications and/or short-term systemic antibiotic treatment) to the pediatric otorhinolaryngology department of the University Medical Center Utrecht. Inclusion criteria were age of 1 to 12 years and a documented history of ≥3 months of continuous otorrhea through either a tympanic membrane perforation or a tympanostomy tube. We excluded children with (1) cholesteatoma, (2) known immunodeficiency other than for IgA or IgG subclasses, (3) Down syndrome, (4) craniofacial anomalies, (5) cystic fibrosis, (6) primary ciliary dyskinesia, (7) allergy to trimethoprim/sulfamethoxazole, or (8) continuous use of antibiotics for >6 weeks in the past 6 months. The medical ethics committee of the University Medical Center Utrecht approved the study protocol.

Randomization

Children whose parents gave informed consent were assigned randomly to receive either trimethoprim/sulfamethoxazole (18 mg/kg, administered orally, 2 times per day) or placebo for 6 to 12 weeks. A computer-generated randomization list was prepared by an independent data manager and sent to the hospital pharmacist, who then provided numbered boxes with bottles filled with a blinded suspension of either trimethoprim/sulfamethoxazole or placebo, with identical taste, bottle appearance, and fluid appearance. At entry into the trial, the investigator responsible for seeing the study participants allocated the next available number on the randomization list and the corresponding box with blinded suspension to each participant. The investigators remained blinded to the randomization until the end of the study.

When otorrhea was found to be present in either ear at the first control visit after 6 weeks, study medication administration was continued for another 6 weeks. Administration of the study medication was discontinued if both ears were found to be free of otorrhea and parents confirmed that they had seen no signs of otorrhea during the previous week. Parents were instructed to start study medication treatment again if symptoms of otorrhea recurred between the follow-up visits at 6 and 12 weeks. At inclusion and if otorrhea was present at the 6-week and 12-week follow-up visits, hydrocortisone/bacitracin/colistin eardrops were prescribed in addition to the study medication for 7 to 10 days, in both the trimethoprim/sulfamethoxazole group and the placebo group. These eardrops were chosen because they are widely used in the Netherlands and are generally considered safe.[6] From July 2004 onward, hydrocortisone/neomycin/polymyxin B eardrops were prescribed because the former combination was no longer available in the Netherlands. During the first 12 weeks, local otorhinolaryngologists and pediatricians were allowed to prescribe additional medication, except for trimethoprim/sulfamethoxazole, to the participants according to their regular practice. After the second control visit at 12 weeks, administration of the study medication was discontinued irrespective of the presence or absence of otorrhea. At that time, children were referred back to their local doctors. Treatment was unblinded for an independent doctor, who informed the parents and local doctors about the assigned treatment by letter. The letter also included a treatment recommendation in case otorrhea was still present or recurred, that is, trimethoprim/sulfamethoxazole (18 mg/kg, 2 times per day, for 6–12 weeks) for the placebo group and azithromycin (5 mg/kg, once per day, for 6–12 weeks) for the trimethoprim/sulfamethoxazole group. At that stage, local otorhinolaryngologists and pediatricians were free to follow the recommendations or to manage symptoms of otorrhea according to their regular practice.

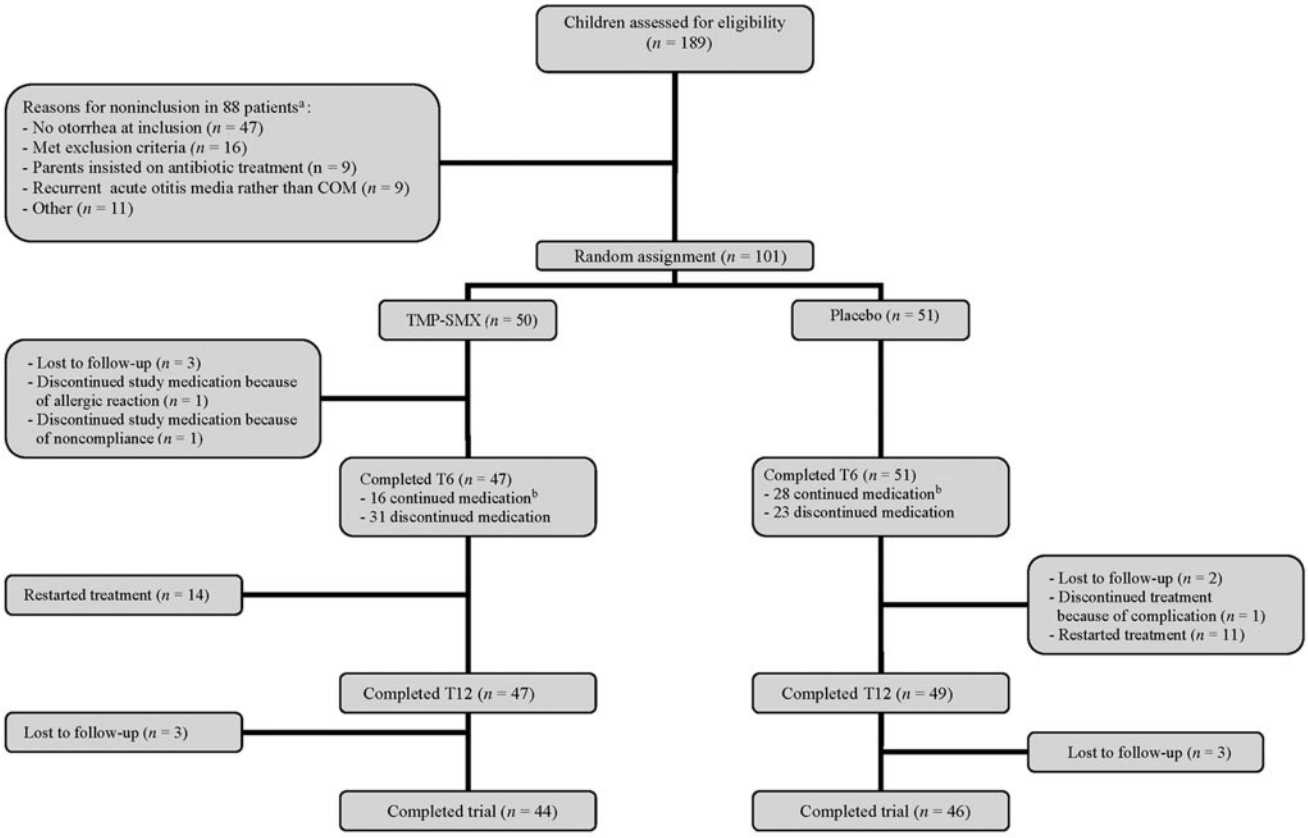

FIGURE 1

Flow of participants through the trial. TMP-SMX indicates trimethoprim/sulfamethoxazole; T6, 6-week follow-up; T12, 12-week follow-up. [a] The number exceeds 87 because >1 reason could be indicated. [b] Administration of the study medication was discontinued if both ears were found to be free from otorrhea and parents confirmed that they had seen no signs of otorrhea during the previous week.

Inclusion and Follow-up Monitoring

At inclusion, disease-specific questionnaires, including information on potential risk factors for ear disease, duration of otorrhea before study entry, and previous treatments, were completed. At inclusion and at the 3 follow-up visits at 6 weeks, 12 weeks, and 1 year, parents completed 1 generic and 2 disease-specific questionnaires on health-related quality of life, namely, the Child Health Questionnaire parental form,[19] a 6-item otitis media questionnaire,[20] and a visual analog scale measuring ear-related quality of life.[20] At these visits, the ears of the children were examined with an otomicroscope. The following features were noted: tympanostomy tube, tympanic membrane perforation, otorrhea, and middle ear effusion. If otorrhea was present, then a swab was taken from the otorrhea before suction cleaning was performed. To test for adverse reactions to the study medication, venous samples were taken for complete blood counts and hepatic (aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltranspeptidase) and renal (urea and creatinine) function tests at inclusion, at 6 weeks, and at 12 weeks. For children >3 years of age, pure-tone air conductive hearing levels were measured at frequencies of 500, 1000, 2000, and 4000 Hz.

Parents kept a diary of study medication and additional medication used for their child's' ear disease, including eardrops. These data were collected at the follow-up visits. During those visits, adverse effects of the study medication were noted and the empty and full bottles of study medication were weighed, to determine compliance rates.

Microbiologic Investigation

At inclusion and at the follow-up visits, study physicians took otorrhea samples by using flexible, sterile, rayon-tipped swabs (Medical Wire & Equipment Co, Corsham, Wiltshire, United Kingdom). The samples were immediately stored in Stuart's transport medium at room temperature. Samples were transported to the microbiology laboratory and plated, within 18 hours after sampling, onto sheep blood (5%), *Haemophilus*, and MacConkey agar plates for the isolation of potential aerobic pathogens. The culture plates were incubated aerobically at 37°C (MacConkey agar) and <5% carbon dioxide (blood and *Haemophilus* agars). They were examined at 24 and 48 hours. Colonies suspected to be *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, or aerobic Gram-negative bacteria were identified with previously described methods.[21]

Study Outcomes

The primary end point was otomicroscopic signs of otorrhea in the presence of a tympanostomy tube or tympanic membrane perforation at follow-up times of 6 weeks, 12 weeks, and 1 year. Secondary outcome measures were use of medication other than the study medication for ear disease, adverse effects of the study medication, ear/nose/throat operations, health-related quality of life, pure-tone hearing levels, and bacteriologic findings for the otorrhea samples.

Statistical Aspects

Assuming a spontaneous recovery of 25% and a treatment effect of trimethoprim/sulfamethoxazole of 50% (based on a retrospective study of children treated with trimethoprim/sulfamethoxazole for COM at our hospital) and using an α of .05 and a power of 0.80, we calculated that each group should consist of 50 children. Rate differences (RDs) with 95% confidence intervals (CIs) were calculated at the 3 control visits, to compare the 2 groups for otomicroscopic results, use of medication other than the study medication for ear disease, and adverse effects of the study medication. To detect possible effect modification, subgroup analyses were performed according to age (≤3 years or >3 years) and duration of otorrhea before study entry (≤6 months or >6 months), as prespecified in the trial protocol. Health-related quality-of-life instrument scores were transformed linearly onto scales of 0 to 100. The differences between the scores at the follow-up visits and at study entry were calculated and presented for each domain. Differences in domain scores between the groups at follow-up times of 0 weeks, 6 weeks, 12 weeks, and 1 year were tested with the Mann-Whitney *U* test, because these scores were not normally distributed. Box and whisker plots were used to compare the pure-tone hearing levels (air conduction at 500, 1000, 2000, and 4000 Hz) between the 2 groups. Percentage differences with 95% CIs were calculated for the bacteriologic findings. All analyses were performed on an intention-to-treat basis.

RESULTS

Study Group

Between February 2003 and November 2005, 101 children were enrolled; 50 were allocated to the trimethoprim/sulfamethoxazole group and 51 to the placebo group. The flow of the participants through the trial is presented in Fig 1. At baseline, clinical characteristics did not differ significantly between the 2 groups (Table 1). The median age of the study participants was 50 months (interquartile range: 55 months). The compliance rates for both the trimethoprim/sulfamethoxazole group and the placebo group were good (ie, >90% of the prescribed study medication was used).

TABLE 1 **Characteristics of Patients With COM in the Trimethoprim/Sulfamethoxazole Group and the Placebo Group**

Characteristics	Trimethoprim/Sulfamethoxazole ($n = 50$)	Placebo ($n = 51$)
Male, *n* (%)	28 (56)	26 (51)
Age, median (range), mo	48 (12–144)	51 (15–143)
Duration of otorrhea before study entry, median (range), mo	8 (3–113)	5 (3–116)
Previous treatment, *n* (%)		
Ototopical drops	50 (100)	50 (98)
Systemic antibiotic therapy	48 (96)	46 (90)
Surgery		
Adenoidectomy and/or tonsillectomy	30 (60)	36 (71)
Tympanostomy tubes	45 (90)	46 (90)
Tympanoplasty and/or mastoidectomy	5 (10)	7 (14)
No. of siblings, median (range)	2 (0–6)	1 (0–3)
Family history of otitis media (parents or siblings), *n* (%)	29 (58)	28 (55)
No. of upper respiratory tract infections in 6 mo before study entry, median (range)	6 (0–8)	6 (0–7)
Day care or school in year before study entry, *n* (%)	45 (90)	47 (92)
Parental smoking, *n* (%)	16 (32)	13 (26)
Use of systemic antibiotic therapy during past 2 wk, *n* (%)	3 (6)	2 (4)
Unilateral/bilateral COM, *n* (%)[a]	25 (50)/25 (50)	30 (59)/21 (41)
Tympanostomy tubes, *n* (%)[a]	32 (64)	29 (57)
Tympanic membrane perforation,[a] *n* (%)	24 (48)	27 (53)

Eleven children (6 in the trimethoprim/sulfamethoxazole group and 5 in the placebo group) had a tympanostomy tube in one ear and a tympanic membrane perforation in the other.
[a] At inclusion.

Outcomes

At the 6-week follow-up visit, otorrhea was present for 28% of children in the trimethoprim/sulfamethoxazole group and 53% in the placebo group (RD: −25%; 95% CI: −44% to −6%; number needed to treat [NNT]: 4 children) (Table 2). At 12 weeks, the RD was still −15% (95% CI: −34% to 4%; NNT: 7 children) in favor of the trimethoprim/sulfamethoxazole group. At 1 year, there was no difference between the 2 groups (RD: 5%; 95% CI: −12% to 22%). At follow-up times of 6 weeks, 12 weeks, and 1 year, more children in the trimethoprim/sulfamethoxazole group had bilateral intact tympanic membranes and aerated middle ears than did those in the placebo group.

Otomicroscopic results were also analyzed according to age and duration of otorrhea before study entry. At

TABLE 2 **Otomicroscopic Results at Follow-Up Visits**

Otoscopy	6 wk			12 wk			1 y		
	No. (%)		RD (95% CI), %	No. (%)		RD (95% CI), %	No. (%)		RD (95% CI), %
	TMP/SMX ($n = 47$)	Placebo ($n = 51$)		TMP/SMX ($n = 47$)	Placebo ($n = 49$)		TMP/SMX ($n = 44$)	Placebo ($n = 46$)	
Otorrhea (in either ear)	13 (28)	27 (53)	−25 (−44 to −6)	15 (32)	23 (47)	−15 (−34 to 4)	11 (25)	9 (20)	5 (−12 to 22)
In the presence of									
Tympanostomy tube	6 (13)	11 (22)	−9 (−24 to 6)	9 (19)	10 (20)	−1 (−17 to 15)	5 (11)	2 (4)	7 (−4 to 18)
Tympanic membrane perforation	7 (15)	16 (31)	−16 (−32 to 0)	6 (13)	13 (28)	−15 (−31 to 1)	4 (9)	6 (13)	−4 (−17 to 9)
Bilateral intact tympanic membrane and aerated middle ear	2 (4)	0 (0)	4 (−2 to 10)	4 (9)	0 (0)	9 (1 to 17)	7 (16)	5 (11)	5 (−9 to 19)

TMP/SMX indicates trimethoprim/sulfamethoxazole.

the 6-week follow-up visit, otorrhea was present in 8 children (29%) with >6 months of otorrhea before study entry who were treated with trimethoprim/sulfamethoxazole and 14 (67%) who were treated with placebo (RD: −38%; 95% CI: −64% to −12%; NNT: 3 children). For the children with 3 to 6 months of otorrhea before study entry, these values were 5 (26%) versus 13 (43%) (RD: −17%; 95% CI: −44% to 10%; NNT: 6 children). At the 12-week follow-up visit, these numbers were 11 (39%) versus 15 (71%) (RD: −32%; 95% CI: −59% to −5%; NNT: 3 children) and 4 (21%) versus 8 (29%) (RD: −8%; 95% CI: −33% to 17%; NNT: 13 children), respectively. At the follow-up time of 1 year, the treatment effect was no longer affected by the duration of otorrhea before study entry. Age did not influence the effectiveness of trimethoprim/sulfamethoxazole.

During the first 6 weeks, 38 (83%) of the children in the trimethoprim/sulfamethoxazole group and 39 (77%) of the children in the placebo group used antibiotic eardrops (RD: 6%; 95% CI: −10% to 22%). After the first 6 weeks, antibiotic eardrops were used slightly more often in the placebo group than in the trimethoprim/sulfamethoxazole group; 21 (55%) in the trimethoprim/sulfamethoxazole group and 26 (67%) in the placebo group (RD: −12%; 95% CI: −34% to 10%) used eardrops between follow-up times of 6 weeks and 12 weeks. Between follow-up times of 12 weeks and 1 year, these figures were 78% and 82% (RD: −4%; 95% CI: −22% to 14%), respectively. Systemic antibiotics other than the study medication (mostly amoxicillin) were used by 4 children (11%) in the trimethoprim/sulfamethoxazole group and 7 children (18%) in the placebo group between inclusion and the follow-up time of 12 weeks (RD: −7%; 95% CI: −23% to 9%). Between 12 weeks and 1 year, these figures were 23 (62%) and 18 (47%), respectively (RD: 15%; 95% CI: −7% to 37%), and trimethoprim/sulfamethoxazole and azithromycin were used most frequently. Ear/nose/throat surgery (tympanostomy tube insertion or removal, $n = 13$; adenotonsillectomy, $n = 7$; tympanomastoidectomy and/or tympanoplasty, $n = 5$) was performed for similar numbers of children in the 2 groups between follow-up times of 12 weeks and 1 year, that is, 13 (30%) in the trimethoprim/sulfamethoxazole group and 11 (24%) in the placebo group (RD: 6%; 95% CI: −12% to 24%).

Figure 2 shows box and whisker plots of the hearing levels for children >3 years of age. Pure-tone air conduction levels at 500, 1000, 2000, and 4000 Hz could be determined for 20 children in the trimethoprim/sulfamethoxazole group and 18 children in the placebo group. Although hearing levels generally improved, no differences between the groups were found.

During the study, the health-related quality-of-life scores improved substantially in both the trimethoprim/sulfamethoxazole and placebo groups (data not shown). Mean scores for the trimethoprim/sulfamethoxazole and placebo groups for the 6-item otitis media questionnaire, Child Health Questionnaire, and visual analog scale were the same at all visits.

Table 3 shows that, at follow-up times of 6 weeks, 12 weeks, and 1 year, there were no differences in the proportions of culture-positive otorrhea samples for the trimethoprim/sulfamethoxazole group and the placebo group (6 weeks: RD: 0%; 95% CI: −14% to 14%; 12 weeks: RD: 3%; 95% CI: −20% to 26%; 1 year: RD: −8%; 95% CI: −23% to 7%). At follow-up times of 6 and 12 weeks, *Pseudomonas aeruginosa* was the most frequently isolated microorganism in both groups and, in contrast to most other organisms, was found more frequently in the otorrhea samples of the trimethoprim/sulfamethoxazole group than in those of the placebo group, that is, 9 (56%) vs 12 (38%) at 6 weeks (RD: 18%; 95% CI: −12% to 48%) and 7 (50%) vs 9 (31%) at 12 weeks (RD: 19%; 95% CI: −12% to 50%). At the follow-up time of 1 year, no differences were found between the groups.

Adverse Effects

During the first 6 weeks, vomiting or diarrhea (potential adverse effects of the study medication) were reported for 9% of the trimethoprim/sulfamethoxazole group and 2% of the placebo group (RD: 7%; 95% CI: −2% to 16%; number needed to harm: 14 children). Between 6

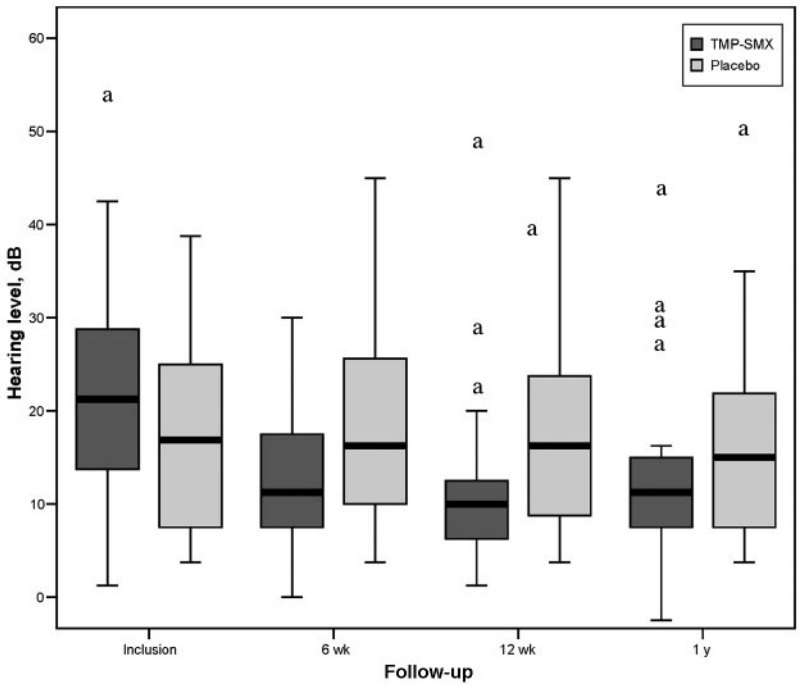

FIGURE 2
Box and whisker plots[22] of the average air-conduction levels at 500, 1000, 2000, and 4000 Hz at inclusion and at 6 weeks, 12 weeks, and 1 year. Values are expressed as the median (horizontal line in each box), with the quartiles (top and bottom of the box) and range (I bar), excluding out-of-range observations ([a] ≥1.5 times the interquartile range beyond the quartile). TMP-SMX indicates trimethoprim/sulfamethoxazole.

and 12 weeks, no differences between the groups were found. One child in the trimethoprim/sulfamethoxazole group developed a skin rash; she was treated with cetirizine and administration of the study medication was discontinued, after which the rash disappeared. Treatment of COM was continued with azithromycin. Complete blood count and hepatic and renal function tests at inclusion and at follow-up times of 6 weeks and 12 weeks did not show any abnormalities in either group.

Two children developed mastoiditis during the first 12 weeks of follow-up monitoring, and their randomization codes were unblinded immediately. One child was allocated to trimethoprim/sulfamethoxazole; he was treated with a mastoidectomy and amoxicillin/clavulanic acid, administered intravenously for 7 days and orally for 14 days. The other child was allocated to placebo; he was treated with intravenously administered amoxicillin/clavulanic acid for 7 days, followed by 6 weeks of trimethoprim/sulfamethoxazole. Both children recovered well with this therapy.

DISCUSSION

This is the first placebo-controlled, randomized trial of systemic antibiotic treatment for patients with COM. It showed that a 6- to 12-week high-dose course of trimethoprim/sulfamethoxazole in addition to a short course of steroid and antibiotic eardrops had a cure rate of 68% at the follow-up time of 12 weeks and was clinically more effective than placebo for children with COM who had experienced failure of conventional management with topical medications or short-term systemic antibiotic therapy. This treatment effect was most pronounced during the first 6 weeks. Children with a history of otorrhea for >6 months benefited more from trimethoprim/sulfamethoxazole therapy than did those with a shorter history of otorrhea. Age did not influence the effectiveness of trimethoprim/sulfamethoxazole. Pure-tone hearing levels and health-related quality of life improved during the study but did not differ between the trimethoprim/sulfamethoxazole group and the placebo group.

The effect of treatment with trimethoprim/sulfamethoxazole for COM was studied in one previous trial, in which a 2-week course of trimethoprim/sulfamethoxazole was compared with a course of antibiotics based on culture results.[9] After a maximal follow-up period of only 14 days, otorrhea resolved for 75% of the trimethoprim/sulfamethoxazole group and 85% of the patients treated with culture-directed antibiotics. Other studies using various systemic antibiotics for COM found similar success rates of ~70%.[10–14,16] Inclusion and outcome criteria, route of drug administration, and follow-up periods in those studies varied considerably, and no study was placebo controlled.[2]

Our results need to be interpreted in light of several limitations. First, the children in our study had persistent symptoms of COM despite conventional management with topical medications, short-term systemic antibiotic therapy, and/or previous ear surgery. Because the majority of children with otorrhea seen by generalist physicians respond well to conventional management, our results should be applied to patients with similarly complicated COM.

Second, because the Netherlands is known for its

TABLE 3 **Bacteriologic Findings for the Otorrhea Samples of Children at Inclusion and During Follow-Up Monitoring (per Sample Taken)**

Bacterial Species	Inclusion		6 wk			12 wk			1 y		
	No. (%)		No. (%)		RD (95% CI), %	No. (%)		RD (95% CI), %	No. (%)		RD (95% CI), %
	TMP/SMX ($n = 74$)	Placebo ($n = 70$)	TMP/SMX ($n = 16$)	Placebo ($n = 32$)		TMP/SMX ($n = 14$)	Placebo ($n = 29$)		TMP/SMX ($n = 13$)	Placebo ($n = 11$)	
Positive culture	68 (92)	59 (84)	15 (94)	30 (94)	0 (−14 to 14)	12 (86)	24 (83)	3 (−20 to 26)	12 (92)	11 (100)	−8 (−23 to 7)
Streptococcus pneumoniae	10 (14)	7 (10)	0 (0)	5 (16)	−16 (−29 to −3)	0 (0)	4 (14)	−14 (−27 to −1)	1 (8)	1 (9)	−1 (−23 to 21)
Hemolytic streptococci, group A	4 (5)	1 (1)	0 (0)	2 (6)	−6 (−14 to 2)	1 (7)	3 (10)	−3 (−20 to 14)	1 (8)	0 (0)	8 (−7 to 23)
Haemophilus influenzae	13 (18)	23 (33)	0 (0)	6 (29)	−29 (−45 to −13)	1 (7)	9 (31)	−24 (−45 to −3)	2 (15)	1 (9)	6 (−20 to 32)
Staphylococcus aureus	15 (20)	14 (20)	2 (13)	6 (19)	−6 (−27 to 15)	1 (7)	6 (21)	−14 (−34 to 6)	2 (15)	1 (9)	6 (−20 to 32)
Pseudomonas aeruginosa	32 (43)	22 (31)	9 (56)	12 (38)	18 (−12 to 48)	7 (50)	9 (31)	19 (−12 to 50)	6 (46)	6 (55)	−9 (−49 to 31)
Moraxella catarrhalis	1 (1)	6 (9)	0 (0)	1 (3)	−3 (−9 to 3)	0 (0)	3 (10)	−10 (−21 to 1)	0 (0)	0 (0)	0 (0 to 0)
Other organisms	53 (72)	23 (33)	10 (63)	12 (38)	25 (−4 to 54)	4 (29)	10 (34)	−5 (−34 to 24)	7 (54)	9 (82)	−28 (−63 to 7)
Total No. of species	128	95	21	44		14	44		19	18	

TMP/SMX indicates trimethoprim/sulfamethoxazole.

restrictive policy regarding systemic antibiotic treatment for otitis media, it is possible that before study entry the participants had received fewer courses of systemic antibiotics and more courses of topical antibiotics than would be expected in other countries. A meta-analysis by Macfadyen et al,[16] however, showed that topical antibiotics, such as those used by our participants before study entry, were more effective than short courses of systemic antibiotic therapy in resolving otorrhea. Therefore, we think that our results can be extrapolated to countries where short-term systemic antibiotic therapy is used more frequently for the management of COM.

Third, children in our study all received suction cleaning and topical treatment, in addition to the study medication, when otorrhea was present. Antibiotic eardrops were used slightly more frequently in the placebo group than in the trimethoprim/sulfamethoxazole group between follow-up times of 6 and 12 weeks. This might have influenced the high cure rate in the placebo group at 12 weeks, which might have resulted in an underestimation of the real treatment effect of trimethoprim/sulfamethoxazole. Other important factors for the small treatment effect with the longer course might have been the natural course of COM and regression to the mean.

Fourth, at the follow-up time of 12 weeks, the parents and the local otolaryngologist or pediatrician were informed about the assigned treatment, and doctors were free to manage additional symptoms of COM in both groups either according to our advice (with a 6-week course of antibiotics) or according to their own practice. Our follow-up data revealed that 10 children in the placebo group and 7 children in the trimethoprim/sulfamethoxazole group indeed received a prolonged course of antibiotics after the follow-up period of 12 weeks. This might have added to the dilution of the effect after 12 weeks.

Fifth, the choice of trimethoprim/sulfamethoxazole for COM could be questioned, because *P aeruginosa*, which is the most common organism in COM and was present in 54 (38%) of otorrhea samples at inclusion, is known to be unsusceptible to trimethoprim/sulfamethoxazole. This is reflected by our culture results; during treatment with trimethoprim/sulfamethoxazole, the proportion of otorrhea samples positive for *P aeruginosa* did not change, whereas that of bacteria that are not intrinsically resistant to trimethoprim/sulfamethoxazole, such as *H influenzae* and *S pneumoniae*, decreased. Because trimethoprim/sulfamethoxazole was effective during the first 6 to 12 weeks of our study, *P aeruginosa* seems to be a secondary microorganism in COM, rather than the causative microorganism.

CONCLUSIONS

A 6- to 12-week course of high-dose, oral, trimethoprim/sulfamethoxazole therapy is beneficial for children suffering from COM. The treatment effect is

most pronounced with the shorter course and disappears if administration of the medication is discontinued.

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Effectiveness of Trimethoprim/Sulfamethoxazole for Children With Chronic Active Otitis Media: A Randomized, Placebo-Controlled Trial

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