Treatment of Recurrent Otitis Media After a Previous Treatment Failure

Which Antibiotics Work Best?

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BACKGROUND. Recurrent infection after an episode of otitis media is common in pediatric patients. If a patient experienced primary treatment failure in a preceding episode, physicians often feel pressured to prescribe a broad-spectrum, second-line agent for the next episode rather than a first-line drug. The purpose of our study was to determine whether using a second-line drug resulted in fewer treatment failures in a recurrent otitis episode following an episode of apparent resistance.

METHODS. The Practice Partner Research Network database, a national research network of practices that use the same electronic medical record, was reviewed to identify all primary episodes of otitis media over a 2-year period (N = 7807). From this, 1416 pediatric patients with presumed treatment failures were identified. The subset of those with a second otitis media episode more than 90 days after the index episode (N = 343) was selected for study. Of this group, 236 (69%) received first-line antibiotics (amoxicillin, ampicillin, penicillin, or sulfamethoxazole-trimethoprim) and the remaining 107 received a broader-spectrum, second-line antibiotic. The primary outcome was the need for an additional antibiotic for otitis media within the next 45 days.

RESULTS. Patients receiving first- and second-line antibiotics did not differ in sex or age. However, those receiving second-line antibiotics had a shorter duration between episodes (231 vs 280 days, $P = .007$). Failure rates for first- and second-line antibiotics in recurrent episodes were not significantly different (13% vs 19%, $P = .20$). Because the duration between episodes could have affected failure rates, we stratified the time between episodes into short, intermediate, and long duration. Second-line antibiotics were not superior to first-line drugs in any stratum.

CONCLUSIONS. For a new otitis media episode in a patient with a previous treatment failure, first-line drugs (amoxicillin, ampicillin, penicillin, or sulfamethoxazole-trimethoprim) are just as effective as broader-spectrum, more expensive, second-line antibiotics.

KEY WORDS. Antibiotics; otitis media; drug resistance. *(J Fam Pract 1999; 48:43-46)*

Acute otitis media is one of the most common pediatric conditions seen in primary care. In 1990, there were 12.8 million episodes of acute otitis media in children younger than 5 years in the United States, with total estimated costs of $3.5 billion, including $240 million spent on antibiotics.[1] Despite extensive clinical experience in the management of otitis media, there is no consensus regarding which antibiotics are most appropriate for initial or recurrent therapy, the optimal duration of therapy, or even whether antibiotics are of any significant benefit at all. The variation in management of otitis media is typified by a study of 9 countries in the mid-1980s.[2] In that study, antibiotics were used over a wide range of episodes (31% to 98%) with similar variation in the types of antibiotics used and the duration of therapy.

One of the most common and costliest complications of otitis media is primary treatment failure; that is, persistent illness or early recurrence of disease following the initial treatment of an episode.[3] A meta-analysis of 33 randomized trials supports initial antibiotic use (94% primary treatment success vs 81% with placebo)[4]; however, there were no significant differences in failure rates when comparing standard or first-line antibiotics (penicillin, amoxicillin, ampicillin, erythromycin, and sulfamethoxazole-trimethoprim [SMX-TMP]) with extended-spectrum or second-line antibiotics and no difference in the duration of therapy. The only factor that appears to be consistently linked to a higher likelihood of primary treatment failure is a child's age,[5,6] with children younger than 2 years having treatment failures in 26% to 37.5% of the cases. For older children, treatment failures occur in 2% to 19% of episodes.[5,6]

One option that physicians may choose to manage primary treatment failure is to switch from a narrow-spec-

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trum to a broader-spectrum agent until symptoms are clear. This change in drug classes may be prescribed because physicians and parents perceive that a specific antibiotic or class of antibiotic will no longer work for that patient. In reality, though, the correlation between bacteriologic resistance and clinical response is not very strong. In fact, one review[4] concluded that 89% of bacteria from primary treatment failures were susceptible to the antibiotic prescribed, and in 13% of the clinical successes, the bacteria were not susceptible to the antibiotic prescribed. Also, most clinical recurrences after therapy are due to infection with a new bacteriologic species and thus may not indicate failure of initial therapy.[7] Confusion about the bacteriology of otitis media and reinfection may contribute to the observed rise in the use of expensive, broad-spectrum agents for the treatment of otitis media.[8-10] The goal of our study was to determine how often physicians use second-line agents as primary therapy in recurrent otitis media and to assess whether broader-spectrum drugs are more likely than first-line agents to result in primary treatment success.

METHODS

DATABASE

Data for the study were drawn from the Practice Partner Research Network (PPRNet). PPRNet represents 57 practices that use the same electronic medical record (Practice Partner, Physician Micro Systems, Seattle, Wash). Each month the practices extract data from their electronic records using a self-running program that collects information regarding patient-specific reasons for visit, diagnoses, medications prescribed, laboratory and radiology use, and outside records, such as hospital or consultation reports. The extracted data are linked by a patient-specific code in the database that cannot be linked to a patient or care provider in the practice.

SAMPLE

The eligible patient population was limited to individuals younger than 12 years. A total of 7807 patients who were given a diagnosis of otitis media were identified between January 1, 1995, and March 31, 1998 (Table 1). Within the next 45 days, 1416 (18%) made a second visit for otitis media that included a prescription for a new antibiotic. These patients were presumed to have a primary treatment failure.

Using these 1416 patients as potential subjects, we searched for any subsequent diagnosis of otitis media that occurred at least 90 days after the final contact for otitis media. We selected a 90-day otitis-free window as assurance that this was a new episode and did not represent continued symptoms from the previous infection. Since 90% of serous effusions after an episode of otitis media are cleared by 90 days,[12,13] any diagnosis of otitis media after this time period is likely to represent a new infection. Using these criteria, we identified 343 children with new otitis media treated with antibiotics following a previous treatment failure.

TABLE 1

Episodes of Otitis Media in Study Sample of Children Younger than 12 Years

Episode	No.	(%)
Primary	7807	(100)
Treatment failures	1416	(18)
Recurrent	343	(24)
Treated with first-line antibiotics*	236	(69)
Treated with second-line antibiotics†	107	(31)

*First-line antibiotics included amoxicillin, ampicillin, penicillin, and sulfamethoxazole-trimethoprim.
†Second-line antibiotics included all others.

ANTIBIOTIC AND OUTCOME CLASSIFICATIONS

We classified all children who received amoxicillin, ampicillin, or SMX-TMP as receiving first-line antibiotics. Penicillin was also considered a first-line agent, although it was rarely used (<1% of cases). All other antibiotics were classified as second-line drugs.

A treatment success occurred when no additional antibiotics were prescribed in the 45 days following an episode. Epidemiologic data shows that 40% of all otitis media effusions are cleared by 30 days and 80% by 2 months.[12,13] The selection of 45 days represents a time when most complications from an effusion would be likely to occur. A treatment failure was defined as any subsequent visit within 45 days of the initial diagnosis for otitis media that included the prescription of a new antibiotic.

DATA ANALYSIS

Comparisons of continuous data were performed with *t* tests while noncontinuous variables were compared with chi-square tests. In the case of duration between episodes where data was stratified, a Mantel-Haenszel summary chi-square was used. A P value of <.05 was defined as statistically significant.

RESULTS

Of the 343 children who were seen with recurrent otitis media following a treatment failure, 69% received prescriptions for first-line antibiotics and the remaining children were prescribed a second-line drug. The characteristics of children who received first and second-line drugs are shown in Table 2. The only difference between the 2 groups is that second-line antibiotics appeared to be used when recurrences occurred soon after the resistant episode.

Table 2 also shows that the failure rates for first- and second-line antibiotics were similar. Children who received first-line antibiotics required another antibiotic in

TABLE 2

Patient Characteristics and Failure Rates for Recurrent Episodes of Otitis Media Treated with First- and Second-Line Antibiotics

Characteristic	Treated with First-Line Antibiotics* (N = 236)	Treated with Second-Line Antibiotics† (N = 107)	*P*
Mean age, years (SD)	3.25 (2.35)	2.97 (2.44)	.31
Sex, no. male (%)	132 (56)	59 (55)	.41
Mean duration between episodes, days (SD)	280 (168)	231 (178)	.007
Treatment failures (%)	31 (13)	20 (19)	.20

SD denotes standard deviation.
*First-line antibiotics included amoxicillin, ampicillin, penicillin, and sulfamethoxazole-trimethoprim.
†Second-line antibiotics included all others.

13% of episodes compared with 19% of those who received second-line agents ($P = .20$).

Because of the difference in the time to recurrence between those who received first- and second-line antibiotics, it was possible that the lack of a difference in failure rates between first- and second-line agents could have been due to a higher rate of resistance in early recurrences compared with late recurrences. To explore this possibility, we stratified recurrences into 3 categories: early (90 to 180 days between episodes), intermediate (181 to 270 days), and late (more than 270 days). When antibiotic failures were examined in each stratum, there appeared to be no relationship between the time to recurrence and antibiotic failures (Table 3). Overall, first-line and second-line antibiotics had similar failure rates ($P = .28$).

DISCUSSION

In the practices in this network, physicians prescribed second-line antibiotics for new episodes of otitis following a treatment failure in nearly one third of the cases. The use of second-line agents was more common when less time elapsed between the resistant episode and the new case. However, our data suggest that regardless of the duration between episodes, there is no benefit in using a broad-spectrum antibiotic instead of a first-line agent, such as amoxicillin or SMX-TMP, for recurrent otitis media after a previously resistant episode.

The use of second-line antibiotics when a first-line agent will suffice creates 2 problems. First, in most cases the use of broad-spectrum drugs adds significant expense to therapy. Other authors have reported that the use of second-line agents compared with amoxicillin or SMX-TMP adds 16% to the overall cost of the episode.[3] Since the results of our study show comparable failure rates for first- and second-line antibiotics, there appears to be no justification for this additional cost.

Second, the injudicious use of broad-spectrum antibiotics may increase the potential for future development of antibiotic resistance. Overuse of antibiotics has been proposed as one reason for the observed growth in antibiotic resistance in common childhood organisms such as *Streptococcus pneumoniae*. Several reports have shown large reservoirs of resistant *S pneumoniae* in children from various states in both urban and rural settings.[14-17] Antibiotics are frequently prescribed for children with otitis media, and broad-spectrum antibiotics may be used unnecessarily. Limiting the use of broad-spectrum drugs to situations in which they have been proven beneficial (eg, managing a resistant case of otitis media) may help reduce further development of drug resistance in children.

LIMITATIONS

Limitations to our study design must be considered. Because we did not review each diagnosis individually, we had to rely on the diagnoses made by the physicians and, therefore, cannot verify that otitis media was present in the subjects. Data suggest that when studies have attempted to confirm the clinical diagnosis of otitis media by tympanocentesis, physicians may overdiag-

TABLE 3

Treatment Failures, by Antibiotic Choice and Duration Between Resistant and Recurrent Episodes

Days Between Episodes	First-Line Antibiotics* Failures	First-Line Antibiotics* Number Treated	First-Line Antibiotics* (%)	Second-Line Antibiotics† Failures	Second-Line Antibiotics† Number Treated	Second-Line Antibiotics† (%)
90 to 180	12	86	(14)	11	53	(21)
181 to 270	8	57	(14)	4	24	(17)
More than 270	11	93	(12)	5	30	(17)

Note: Mantel-Haenszel summary chi-square = .28.
*First-line antibiotics included amoxicillin, ampicillin, penicillin, and sulfamethoxazole-trimethoprim.
†Second-line antibiotics included all others.

nose the condition. Results from 2 studies showed that in primary care settings, the percent of patients with a diagnosis of otitis media who had either a positive tympanocentesis result (considered the gold standard) or about whom the physician felt very confident in his or her diagnosis ranged from 58% to 73% in one study[2] and was 85% in another.[5] It is possible that physicians used first-line agents more often for equivocal cases, when in fact otitis media did not exist. This could have led to a spurious finding of more success for first-line agents.

Second, our definition of treatment failure could include instances where antibiotics were changed for drug intolerance or reasons other than treatment failure. However, it is unlikely that this would occur at a higher rate for second-line agents compared with the first-line agents. Therefore, misclassification of treatment failure is unlikely to hide any difference between drug classes. For second-line agents to have a statistically significant lower failure rate than first-line agents, 60% or more of the changes in second-line drugs would have to be for reasons other than primary treatment failure.

Third, the broad classification of drugs into first-line and second-line may obscure subtle treatment changes between episodes. If physicians substituted a different first-line drug for subsequent episodes, that would not be detected by our classification. Thus, our study shows that first-line drugs in general remain effective, but this study does not necessarily imply that the same drug was used on both occasions.

Last, a post-hoc power analysis shows that our sample size allows only limited statistical power (approximately 30% using a 2:1 assignment). This raises the possibility of a type II error, indicating that the 2 treatments are not equally effective. However, if this is the case, the first-line agents would be superior to the second-line drugs, which is unlikely since the latter agents are effective therapy for nearly all the bacteriologic species covered by the first-line drugs.

CONCLUSIONS

Following presumed treatment failure of acute otitis media, amoxicillin, ampicillin, penicillin, and SMX-TMP have success rates that are at least equal to those of broad-spectrum drugs. Given that there are more than 13 million episodes of acute otitis media each year with primary failure rates reported between 2% and 38% depending on age, and that roughly 50% will have further episodes of acute otitis media,[5] the use of less expensive agents for recurrences after a resistant episode may have substantial financial impact.

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