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Association of Outpatient Oral Macrolide Use With Sensorineural Hearing Loss in Children, Adolescents, and Young Adults

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IMPORTANCE Prior publications have reported the sporadic development of sensorineural hearing loss (SNHL) after intravenous or high-dose macrolide therapy for adults with comorbid conditions, but investigations of the auditory effect of oral outpatient dosing for children, adolescents, and young adults have been limited.

OBJECTIVE To determine whether broad-based outpatient use of oral macrolide therapy is associated with increased risk of pediatric SNHL through nationally representative analyses.

DESIGN, SETTING, AND PARTICIPANTS A retrospective case-control study of 875 matched pairs of children, adolescents, and young adults was performed, matching on age, sex, and the time elapsed since prescription date. All eligible pediatric patients were included, with matched control participants from the TRICARE US military health insurance system who were evaluated between October 1, 2009, and September 30, 2014.

EXPOSURES Oral outpatient macrolide treatment compared with penicillin use among pediatric patients.

MAIN OUTCOMES AND MEASURES The clinical outcome of interest was SNHL in children, adolescents, and young adults. Multivariable conditional logistic regression was used to compare the risk of prior macrolide exposure with penicillin exposure, adjusted for other risk factors and potential confounders. Four time frames between exposure and diagnosis were additionally assessed.

RESULTS There were 875 eligible matched pairs of children, adolescents, and young adults included. The mean (SD) age of the participants was 5.7 (4.9) years; 1082 participants were male (62%), 58 were Asian (3%), 254 were Black (15%), 1152 were White (66%), and 286 were of Native American and other (no further breakdown was available in the TRICARE database) race and ethnicity (16%). In multivariable analysis, participants who had SNHL had increased odds of having received a macrolide prescription compared with a penicillin prescription when all time frames from exposure were included (adjusted odds ratio, 1.31; 95% CI, 1.05-1.64). There were significantly higher odds of macrolide exposure than penicillin exposure when diagnosis and testing occurred more than 180 days after antibiotic exposure (adjusted odds ratio, 1.79; 95% CI, 1.23-2.60).

CONCLUSIONS AND RELEVANCE In this case-control study of a nationally representative patient population, findings suggest that children, adolescents, and young adults with SNHL had increased odds of outpatient oral macrolide use compared with penicillin use, particularly when having received a diagnosis more than 180 days after exposure. Further study of the association of macrolides with SNHL in children, adolescents, and young adults is warranted.

Invited Commentary

Supplemental content

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The prevalence of hearing loss increases as children age, such that 19% of US children, adolescents, and young adults may be affected.[1] Epidemiologic data suggest that 23% of these cases may be attributable to genetic causes, 20% may be attributable to acquired causes, and 56% may be idiopathic.[2] The substantial proportion of cases of unknown origin suggests the possibility of unrecognized but ongoing, broad-based exposures in the population whose associations have yet to be elucidated. Identification and awareness of any such exposures are crucial because sensorineural hearing loss (SNHL) can be irreversible, particularly if the inciting agent is not discontinued or if appropriate treatment is not initiated soon.[3]

Macrolides are among the most frequently prescribed medications for children, adolescents, and young adults[4] because they can be used to manage common conditions, such as otitis media, pneumonia, and sinusitis.[5] Among patients aged 3 to 24 months, approximately 50% of acute otitis media, 10% of pneumonia, 3% of pharyngitis, 3% of sinusitis, and 8% to 16% of respiratory infections are treated with outpatient macrolide therapy.[6] The potential association with SNHL has been described in case reports and small case series for adults and has often been focused on participants who had significant comorbid conditions or received intravenous or atypically high doses.[7-13] In these instances, macrolide-associated hearing impairments have been clinically significant and, in some cases, irreversible. For children, 1 case series demonstrated a 7% prevalence of hearing loss with long-term use for nontuberculous mycobacteria.[14] No publications, to our knowledge, however, have investigated the risk of potential SNHL in association with large-scale, routine oral macrolide use among children, adolescents, and young adults.

Our objective was to determine whether SNHL was associated with macrolide use in a national study population of children, adolescents, and young adults. More specifically, while adjusting for the presence of potentially associated diagnoses, we hypothesized that there would be no difference in exposure to macrolide or penicillin agents between children, adolescents, and young adults with SNHL and those without it.

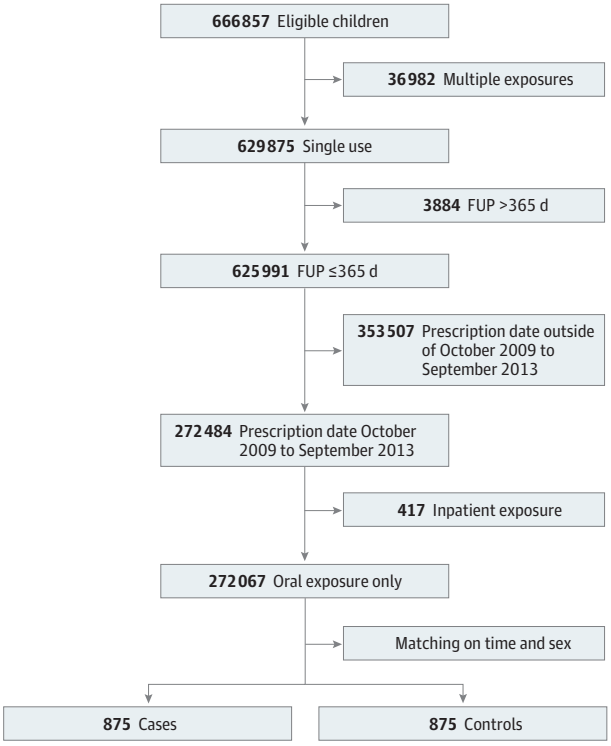
Key Points

Question Is outpatient oral macrolide therapy associated with pediatric sensorineural hearing loss in a nationally representative patient population?

Findings In this case-control study with multivariable analyses of 875 matched pairs of children, adolescents, and young adults, a diagnosis of sensorineural hearing loss was associated with increased odds of macrolide exposure compared with penicillin exposure. Odds of macrolide exposure were significantly higher when 181 to 365 days had elapsed before testing and diagnosis.

Meaning In an environment in which 56% of pediatric sensorineural hearing loss is idiopathic, the data from this study suggest that macrolides warrant further study as a potential risk factor, but the findings may help direct parent counseling and the monitoring of exposed children, adolescents, and young adults.

Figure. Development of the Case-Control Study Sample



FUP indicates follow-up period.

Methods

Database Selection and Entry

This case-control study used the database of the US Department of Defense Military Health System (TRICARE), the health care program for uniformed service members, retirees, and their families. This administrative claims data set includes records of diagnostic codes, outpatient prescriptions, and diagnostic tests, such as audiograms for children of eligible military beneficiaries at both military and civilian facilities. The planned protocol was reviewed by the Mass General Brigham institutional review board, who deemed the deidentified data exempt from oversight. The informed consent process was established by the curators of the TRICARE database.

Study Design

A case-control approach was planned, given the observed prevalence of SNHL among children, adolescents, and young adults and the expected potential latency between onset and diagnosis of hearing loss in children, adolescents, and young adults, who may not immediately understand, notice, or report a hearing deficit. The case-control design is suited for studies related to common precursors of less frequent disease and was thus well matched for this assessment. The study population included all outpatient encounters for all eligible pediatric patients 18 years of age or younger within the TRICARE database between October 1, 2009, and September 30, 2014 (**Figure**). We included consecutive outpatient children, adolescents, and young adults whose SNHL status and antibiotic

exposure status could be analyzed. We excluded children, adolescents, and young adults who had received macrolides within the preceding 12 months or had any diagnosis of any type of hearing loss. Patients who had concurrent inpatient encounters were excluded to prevent concurrent association with intravenous medication use and to maintain focus on oral exposure only.

SNHL, Case, and Control Definitions

Sensorineural hearing loss was identified via the presence of indicative clinical diagnostic codes (eTable 1 in the Supplement) and a required audiogram within the 90 days preceding the SNHL diagnosis. A concurrent *International Classification of Diseases, Ninth Revision (ICD-9)* diagnostic code of sudden hearing loss, "unspecified" hearing loss, or "other" hearing loss was allowed along with the diagnosis of SNHL as long as the defining sensorineural-specific diagnosis was present and formal audiometry had been performed. However, SNHL was deliberately not defined by any unspecified or other hearing loss diagnostic codes in isolation (eTable 1 in the Supplement) to avert misclassification of instances of non-SNHL (eg, conductive hearing loss from middle ear fluid).

Case patients were defined as those who had an SNHL diagnosis as defined earlier. Control participants were defined as those who did not have diagnostic codes for SNHL, sudden hearing loss, unspecified hearing loss, or other hearing loss at any point during the study. *Current Procedural Terminology* codes were used to determine the status of audiometric testing.

Exposure Definitions

To determine macrolide exposure status, we identified systemic macrolide prescriptions for erythromycin, azithromycin, clarithromycin, fidaxomicin, and telithromycin while excluding topical therapy. The penicillin class of medication was selected as a control exposure because it has an expected nonassociation with hearing loss. The penicillin group included amoxicillin, amoxicillin-clavulanate, ampicillin, ampicillin-sulbactam, phenoxymethylpenicillin, benzylpenicillin, cloxacillin, dicloxacillin, carbenicillin indanyl sodium, oxacillin, and penicillin G potassium. Database prescription codes were used to assign exposure and medication status.

Case-Control Analysis

Cases and controls were matched on age group, sex, and the time elapsed since the date of prescription to generate risk-set sampling in a 1:1 ratio. Age group strata were 0 to 2 years, 3 to 6 years, 7 to 12 years, and 13 to 18 years. In comparing cases with controls, the primary analysis assessed the odds ratio (OR) of exposure to oral macrolide agents compared with exposure to penicillin agents. The analysis focused on patients who had a single administration of either antibiotic class, meaning that only these patients were included. In accordance with this plan, participants with multiple exposures to 1 or multiple antimicrobial agents were excluded to provide a targeted analysis.

The analysis was designed to allow for delayed diagnosis of SNHL because children and families may not notice mild and unilateral cases immediately, and formal audiometric testing may be delayed until after a school screening finding or subsequent symptom revelation. Within the planned assessment periods, we categorized the time between antibiotic exposure and hearing outcome into 4 periods: 0 to 30 days, 31 to 90 days, 91 to 180 days, and 181 to 365 days.

In addition to the abovementioned criteria, because a variety of potential causes of SNHL exists,[15] the assessment included other covariates that could also be associated with the key variables (outcome and exposure), meaning we considered potentially confounding conditions as well. More specifically, we assessed any family history (ie, at any time in the database preceding the date of prescription) of hearing loss or genetic variants, meningitis, noise exposure, premature birth or low birth weight, cytomegalovirus, hypoxemia, and/or hyperbilirubinemia within the first 6 months of life. We also included head trauma, varicella virus, acute and chronic otitis media, acute and chronic rhinosinusitis, acute and chronic pharyngitis, pneumonia, and nutritional deficiencies identified within the year preceding the antibiotic prescription date as potential concurrent confounders. The multivariable conditional logistic regression analysis incorporated variables that were found to be significant in bivariable analyses, along with demographic factors, region (Midwest, Northeast, West, and South), race and ethnicity (African American or Black, Asian, White, and other, which included Native American [no further breakdown was available in the TRICARE database]), and income (**Table 1**). Race and ethnicity were categorized by the designers of the TRICARE database. Noise exposure and cytomegalovirus were also assessed in univariate analysis, although the low number of patients with a formal diagnosis did not support their inclusion in stable multivariable analyses. *ICD-9* clinical diagnostic codes were used to determine the status of these potentially relevant covariates (eTable 1 in the Supplement). This study protocol was designed to follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Statistical Analysis

Bivariable and multivariable analyses were performed. Bivariable assessment spanned all time frames, using conditional logistic regression, and then proceeded to multivariable assessments that accounted for potentially confounding conditions (as listed individually earlier), as well as the 4 periods since exposure. Bivariable analysis assessed the association between case-control status and antibiotic exposure status. Multivariable analysis assessed the association between case-control status and antibiotic exposure status while adjusting for the presence of potentially confounding conditions. A standard interaction term was used to examine time-specific associations, with the a priori plan to proceed with time frame–specific subanalyses if the interaction was significant.

Multivariable conditional logistic regression was used to determine ORs associated with SNHL and macrolide or penicillin exposure, matching on age group, sex, and time frame and adjusting for comorbid, potentially confounding covariates. The association of each potentially confounding variable with SNHL was assessed by the Cochran-Mantel-

Table 1. Baseline Characteristics of the Study Population

Characteristic	Patients, No. (%)		Difference in percentage, % (95% CI)
	SNHL	No SNHL	
Total patients, No.	875	875	NA
Demographic characteristics			
Age, y			
0-2	340 (38.9)	340 (38.9)	0
3-6	248 (28.3)	248 (28.3)	0
7-12	161 (18.4)	161 (18.4)	0
13-18	126 (14.4)	126 (14.4)	0
Sex			
Male	541 (61.8)	541 (61.8)	0
Female	334 (38.2)	334 (38.2)	0
Race and ethnicity			
Asian	25 (2.9)	33 (3.8)	0.9 (−0.8 to 2.6)
Black	118 (13.5)	136 (15.5)	2.0 (−1.3 to 5.3)
White (reference)	594 (67.9)	558 (63.8)	4.1 (−0.3 to 8.5)
Other[a]	138 (15.8)	148 (16.9)	1.1 (−2.4 to 4.6)
Region			
South (reference)	542 (61.9)	498 (56.9)	5.0 (0.4 to 9.6)
Midwest	58 (6.6)	86 (9.8)	3.2 (0.6 to 5.8)
Northeast	83 (9.5)	63 (7.2)	2.3 (−0.3 to 4.9)
West	192 (21.9)	228 (26.1)	4.2 (0.2 to 8.2)
Socioeconomic status surrogate			
Enlisted	670 (76.6)	657 (75.1)	2.0 (−2.0 to 6.0)
Officer	205 (23.4)	215 (24.6)	2.0 (−2.0 to 6.0)
Environment of care			
Purchased	144 (16.5)	141 (16.1)	0.4 (−3.1 to 3.9)
Direct	731 (83.5)	734 (83.9)	0.4 (−3.1 to 3.9)
History elements			
Family history of hearing loss	12 (1.4)	2 (0.2)	1.2 (0.4 to 2.0)
Noise exposure	27 (3.1)	0	3.1 (2.0 to 4.2)
Head trauma	4 (0.5)	0	0.5 (0.0 to 1.0)
Meningitis	4 (0.5)	2 (0.2)	0.3 (−0.3 to 0.9)
Nutritional deficiency	15 (1.7)	9 (1.0)	0.7 (−0.4 to 1.8)
Low birth weight	24 (2.7)	3 (0.3)	2.4 (1.3 to 3.5)
Cytomegalovirus	1 (0.1)	0	0.1 (−0.1 to 0.3)
Hypoxemia	47 (5.4)	19 (2.2)	3.2 (1.4 to 5.0)
Hyperbilirubinemia	2 (0.2)	1 (0.1)	0.1 (−0.3 to 0.5)
Varicella	6 (0.7)	7 (0.8)	0.1 (−0.7 to 0.9)
Chronic otitis media	145 (16.6)	46 (5.3)	11.3 (8.4 to 14.2)
Acute otitis media	630 (72.0)	539 (61.6)	10.4 (6.0 to 14.8)
Chronic sinusitis	107 (12.2)	109 (12.5)	0.3 (−2.8 to 3.4)
Acute sinusitis	170 (19.4)	182 (20.8)	1.4 (−2.4 to 5.2)
Pneumonia	128 (14.6)	135 (15.4)	0.8 (−2.5 to 4.1)
Acute pharyngitis	414 (47.3)	485 (55.4)	8.1 (3.4 to 12.8)
Chronic pharyngitis	32 (3.7)	27 (3.1)	0.6 (−1.1 to 2.3)
Antibiotic use	2 (0.2)	6 (0.7)	0.5 (−0.1 to 1.1)
Aspirin use	1 (0.1)	2 (0.2)	0.1 (−0.3 to 0.5)

(continued)

Table 1. Baseline Characteristics of the Study Population (continued)

Characteristic	Patients, No. (%)		Difference in percentage, % (95% CI)
	SNHL	No SNHL	
NSAID use	1 (0.1)	1 (0.1)	0.0 (−0.3 to 0.3)
Tobacco exposure	8 (0.9)	11 (1.3)	0.0 (−0.9 to 0.9)
Ototoxin exposure	1 (0.1)	1 (0.1)	0.0 (−0.3 to 0.3)
Antibiotic exposures			
Macrolide use	609 (69.6)	546 (62.4)	1.37 (1.12 to 1.67)[b]
Penicillin use	266 (30.4)	329 (37.6)	

Abbreviations: NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; SNHL, sensorineural hearing loss.

[a] Other included Native American, but no further breakdown was available in the TRICARE database.

[b] Odds ratio (95% CI).

Table 2. Risk of Sensorineural Hearing Loss: Macrolides Compared With Penicillin (Conditional Logistic Regression)[a]

Time frame	Patients, No. (%)		Multivariable analysis	
	Cases	Controls	OR (95% CI)	aOR (95% CI)
All patients, all time frames				
Macrolides	875 (50)	875 (50)	1.37 (1.13-1.67)	1.31 (1.05-1.64)
Penicillin				
Time frame interaction			1.14 (1.04-1.25)	1.39 (1.14-1.69)
At 0-30 d				
Macrolides	163 (19)	163 (19)	0.78 (0.48-1.27)	0.70 (0.37-1.34)
Penicillin				
At 31-90 d				
Macrolides	178 (20)	178 (20)	1.19 (0.79-1.79)	1.11 (0.70-1.77)
Penicillin				
At 91-180 d				
Macrolides	217 (25)	217 (25)	1.61 (1.07-2.41)	1.44 (0.87-2.37)
Penicillin				
At 181-365 d				
Macrolides	317 (36)	317 (36)	1.76 (1.25-2.46)	1.79 (1.23-2.60)
Penicillin				

Abbreviation: aOR, adjusted odds ratio.

[a] Percentages of the total sample are shown in parentheses in the case and control columns. The multivariable models showed an association with increased odds of macrolide exposure while adjusting for chronic otitis, hypoxia, low birth weight, family history, acute otitis, acute pharyngitis, region, race and ethnicity, and income in the analysis of patients who received a diagnosis of hearing loss more than 180 days after exposure to macrolides.

Haenszel test for matched data in initial bivariable analyses. Variables were included in the multivariable analysis if the bivariable assessment demonstrated a 2-sided *P* value of less than .05. We additionally assessed whether the duration of antibiotic exposure (in days) was associated with the probability of SNHL. To achieve a power of 0.9, with an expected prevalence of exposure of 0.624 in the control group, 831 cases were required to determine a 0.4-point increase in odds. All primary analyses were performed at the .05 significance level with SAS (SAS Institute). We additionally performed a sensitivity analysis, which followed the protocol and matched on age in years rather than age group.

Results

The study included 1750 matched observations from 875 cases and 875 controls selected by risk-set sampling. A total of 1082 participants were male (62%), 668 were female (38%), 58 were Asian (3%), 254 were Black (15%), 1152 were White (66%), and 286 were Native American or other (no further breakdown was available in the TRICARE database) race and ethnicity (16%). Baseline characteristics were as delineated in Table 1 and confirmed that cases and controls were matched according to age, sex, and months elapsed since prescription date. The mean (SD) age of the participants was 5.7 (4.9) years. The SNHL (case) group had a higher proportion of family history of hearing loss, head trauma, noise exposure, prematurity or low birth weight, acute and chronic otitis media, and hypoxemia. Family history of hearing loss, head trauma, and low birth weight occurred infrequently (<3% of cases) (Table 1). The most frequent duration of macrolide exposure was 5 days of supplied therapy (905 of 1148 [79%] macrolide recipients).

In bivariable analysis of all matched observations, patients with SNHL had 1.37 times the odds of exposure to macrolides than to penicillin agents compared with controls without SNHL. The association of time frame in bivariable analysis was also significant (OR, 1.14; 95% CI, 1.04-1.25) (**Table 2**), suggesting the association differed according to time frame. The OR of exposure within each time frame was significantly higher (OR, 1.76; 95% CI, 1.25-2.46) at 181 to 365 days (Table 2).

Within the multivariable analyses across all time frames, patients with SNHL had 1.31 (95% CI, 1.05-1.64) times the odds of exposure to macrolides compared with those without SNHL. The association with time frame was additionally assessed in a multivariable model with an interaction term and also found to be significant (adjusted OR, 1.39; 95% CI, 1.14-1.69) (Table 2), suggesting that the odds of antibiotic exposure varied across

time frames. In accordance with these results, we performed a stratified analysis of patients by time frame (Table 2). In these analyses, there was no difference between macrolide and penicillin exposure at 0 to 30 days, 31 to 90 days, or 91 to 180 days before SNHL diagnosis. However, when antibiotic exposure occurred 181 to 365 days before diagnosis, odds of macrolide exposure compared with penicillin exposure were higher (adjusted OR, 1.79; 95% CI, 1.23-2.60) (Table 2). This observed association was statistically significant while adjusting for potential confounders, such as known risk factors for pediatric hearing loss and otitis media diagnoses. The point estimate of the OR was associated with an increase within each of the 4 successive time frames (eFigure 1 in the Supplement). Observations of the possible association between the duration of macrolide therapy and SNHL (eFigures 2 and 3 in the Supplement) suggested a potential increase in the probability of SNHL among patients who had macrolides prescribed for 5 days or longer.

A sensitivity analysis was also performed, matching on age in years rather than age group. These results also showed a statistically significantly higher rate of macrolide exposure in cases with hearing loss (31-90 days: OR, 1.58 [95% CI, 1.02-2.44]; 91-180 days: OR, 1.65 [95% CI, 1.11-2.44]; 181-365 days: OR, 1.69 [95% CI, 1.19-2.38]) (eTable 2 in the Supplement). In this sensitivity analysis, however, the time interaction was not significant because macrolides were statistically more likely to have been prescribed across 3 of the 4 time frames studied.

Discussion

In multivariable analyses spanning all time frames in this study, children, adolescents, and young adults with SNHL had 1.31 times the odds of exposure to macrolides compared with those without SNHL. The time frame was a significant factor, and pediatric patients with a diagnosis of SNHL more than 180 days after exposure had 1.79 times the odds of having received macrolides rather than penicillin-related medications. Although the association was not statistically significant within the 3 periods shorter than 180 days, the point estimate of the OR was larger in each successive period elapsed since exposure (eFigure 1 in the Supplement). In addition, when observing the probability of hearing loss and the number of days supplied in macrolide prescriptions, we observed an association with increasing point estimates (eFigures 2 and 3 in the Supplement). Altogether, these findings suggest a potential association between SNHL and macrolides compared with penicillin agents.

Macrolides are one of the most commonly used medications for children.[4-6] Azithromycin is the most commonly prescribed outpatient antibiotic in the United States, with 54.1 million prescriptions per annum, or 174 prescriptions per 1000 persons.[16,17] Surveys of randomly selected households have shown that 0.6% of children have used this medication within the last 7 days alone.[4] Furthermore, macrolide use among children, adolescents, and young adults aged 4 to 18 years may be increasing.[6] Because of this large-scale use, if even a small proportion of macrolide users has associated SNHL, the potential association with public health may still be substantial. For example, for every 1 million macrolide prescriptions, if a risk difference of just 0.7% is estimated, it could affect 7000 individuals; because there are more than 54 million prescriptions, 378 000 patients could be affected each year. Also, when sudden SNHL occurs, the treatment window may be limited.[3] The suspected agent is ideally discontinued with alacrity, and in circumstances in which steroid treatment is indicated, it may be best administered within the first 14 days after hearing is lost.[18] Thus, clinician and parent awareness and early recognition are key.

This large-scale, nationally representative case-control study assessed whether SNHL is associated with routine outpatient use of oral macrolides among children, adolescents, and young adults and can be viewed in the context of preceding literature. A systematic review described 3 prospective and 41 retrospective studies, which included 78 cases of audiometrically confirmed SNHL.[19] These publications have frequently assessed the association with intravenous or high-dose macrolide therapy for adults with major comorbid conditions,[7-11] but, to our knowledge, they have not evaluated the broad-based association with frequently used pediatric outpatient prescriptions. For example, 1 retrospective case series of 34 patients with kidney allografts found that 32% of patients treated with intravenous erythromycin developed "clinically significant" hearing loss; 53% of patients exposed to 4 g per day had measurable hearing loss compared with only 16% of patients treated with 2 g per day.[12] A prior nested case-control study compared erythromycin (n = 30) and alternative antibiotics (n = 15) for community-acquired pneumonia in adults and demonstrated that high serum peak concentrations were associated with a decrease in hearing of at least 10 dB in serial evaluation.[13] Another nested case-control study of adults showed increased risk of SNHL with both macrolides and other antibiotics and concluded that the association could be confounded by indications for antibiotic treatment.[13,20] One prior single-institution study examined 167 children who received long-term clarithromycin treatment for nontuberculous mycobacteria and demonstrated a 7% prevalence of hearing loss.[14] Children may have a different potential for adverse effects than adults, as evidenced through experience with tetracycline and quinolone therapy.[21-23] To help address these aforementioned issues, our multivariable analysis focused specifically on children, adolescents, and young adults and adjusted for frequent locoregional infections, which prompt the use of macrolides or penicillin therapy, to mitigate the potential confounding by indication for treatment.

Within these diagnoses, chronic otitis media has been particularly associated with SNHL in both children and adults.[24] An assessment of 124 pediatric patients demonstrated a modest but significant increase in bone conduction thresholds in ears affected by unilateral chronic otitis media compared with the contralateral ear, with increasing effect sizes at higher audiometric frequencies.[25] Bone conduction thresholds at 500 to 1000 Hz may be particularly susceptible in children.[26] Our investigation showed an association between chronic otitis media and SNHL across all intervals studied, corroborating this existing evidence. Even with adjusting for this association, however, higher odds of exposure to macrolides were noted in SNHL cases than in controls.

Adverse effects associated with macrolides can extend beyond potential associations with hearing and are also important to consider. Gastrointestinal disturbances occur most commonly[27]; azithromycin is associated with abdominal symptoms in 15% to 20% of patients, whereas erythromycin is associated with abdominal symptoms in 30% to 40% of patients.[28] Other highly associated but rarer adverse effects of macrolides include cardiac QT-interval prolongation, hepatic and renal toxicity, and anaphylaxis.[29] Whereas many clinicians are aware of and counsel patients regarding these potential occurrences, when these medications are prescribed, SNHL has not been a routine consideration either in counseling or when longer durations of therapy are considered.

We examined multiple time frames in this study. Although adults with a history of normal hearing are readily able to communicate any new auditory deficits, children may not notice or articulate such symptoms, especially initially. Consequently, there may be delays in detection of new-onset SNHL in the pediatric population, especially in age groups in which detection relies primarily on mass screening.[30] In fact, the known potential for missing a timely SNHL diagnosis has formed the basis for routine hearing screening for children (the American Association of Pediatrics has recommended hearing screening at birth and at 4, 5, 6, 8, and 10 years of age).[31] For children with limited awareness or who are unable to report their symptoms, reliance on screening alone could delay the diagnosis of SNHL for more than 180 days because the intervals between routine testing exceed 6 months. From a physiologic standpoint, a delay in diagnosis could theoretically represent a risk within a multihit progression that predisposes to hearing loss but does not directly manifest in it, akin to similar theories in oncologic disease.[32] This postulation is based on a theoretic concept, as just noted, and may warrant further study.

Strengths and Limitations

The case-control approach was a strength of this study, which examined less common adverse effects (disease) and common interventions (exposures); the design of this study was also helpful when evaluating multiple risk factors while assessing drug toxicities. A limitation of this study, however, is that case-control groups cannot directly generate incidence data.[33] Although we can evaluate indirect incidence rates (eg, cumulative hazard curves) within the matched sample, this incidence exists among the case-control study sample in which macrolide-exposed children, adolescents, and young adults were more frequent than penicillin-exposed counterparts in those with SNHL. Thus, such probabilities are valid for this matched sample but are not representative of incidence within the general population. We also did not exclude patients with kidney, liver, or metabolic conditions. Macrolides are metabolized through the liver before excretion through bile and urine. Accordingly, patients with concurrent dysfunction of the hepatic, biliary, or urinary systems may have a risk for higher exposure. There may also be interethnic differences in the pharmacokinetics and in cytochrome P450 activity; for example, a comparison of Korean and White healthy participants after a single dose of erythromycin found that curves for the area under the concentration time were 65% higher for Korean patients.[34,35] Other limitations of this study include the retrospective use of administrative claims data, which may be subject to the quality of coding and missing data. The reliability and validity of reporting *ICD-9* diagnostic and procedure codes in TRICARE have previously been validated in a number of works,[36] and no patients were excluded based on missing data. The database lacks direct information on weight-based dosing to support a formal dose-response curve. Consequently, these data describe the association between risk of SNHL and the duration of exposure (ie, days of prescribed therapy) rather than weight-adjusted calculations, although weight-based dosing may have been calculated at prescribing.

Conclusions

The data in this case-control study suggest that pediatric patients with SNHL had increased odds of having received a macrolide prescription compared with a penicillin prescription. Children, adolescents, and young adults receiving a diagnosis of SNHL more than 180 days after exposure were more likely to have received macrolides than penicillin-related medications. These findings suggest that further study of the association of macrolide use with SNHL in children, adolescents, and young adults is warranted and that the indiscriminate or overly liberal use of antibiotics may have adverse effects.

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