Clinical Infectious Diseases

MAJOR ARTICLE

Quinolone Ear Drops After Tympanostomy Tubes and the Risk of Eardrum Perforation: A Retrospective Cohort Study

Adel Alrwisan,[1,2] Patrick J. Antonelli,[3] and Almut G. Winterstein[1,4]

[1]Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville; [2]Saudi Food and Drug Authority, Riyadh, Saudi Arabia; [3]Department of Otolaryngology, College of Medicine, and [4]Department of Epidemiology, College of Public Health and Health Professions and College of Medicine, University of Florida, Gainesville

Background. This study investigated whether quinolone ear drops, with or without corticosteroids, increase the risk of perforation requiring tympanoplasty following tympanostomy tube (TT) placement in children.

Methods. This was a retrospective cohort study using Medicaid encounter and pharmacy billing data from 29 US states between 1999 and 2006. Children <18 years old without predisposing factors for perforation during a 6-month look-back period entered the cohort after TT placement and first dispensing of antibiotic ear drops. Included ear drops were quinolones (ofloxacin, ciprofloxacin plus hydrocortisone, or ciprofloxacin plus dexamethasone) or neomycin plus hydrocortisone. Children were followed until end of 2006, end of Medicaid enrollment, or occurrence of study outcome. A Cox regression model, adjusted for age, sex, race/ethnicity, initial TT indication, reinsertion of TT, adenoidectomy, and number of ear drop prescriptions was used to compare the rate of perforation between quinolone and neomycin plus hydrocortisone ear drop–exposed children. Perforation was defined by its diagnosis code followed by a tympanoplasty code.

Results. A total of 96 595 children entered the study cohort. Patients exposed to quinolone ear drops had a higher risk of perforation, with an adjusted hazard ratio of 1.61 (95% confidence interval [CI], 1.15–2.26). The adjusted hazard ratios were 1.49 (95% CI, 1.05–2.09) for ofloxacin, 1.94 (95% CI, 1.32–2.85) for ciprofloxacin plus hydrocortisone, and 2.00 (95% CI, 1.18–3.41) for ciprofloxacin plus dexamethasone.

Conclusions. Exposure of children with TT to quinolone ear drops is associated with increased risk of perforations requiring tympanoplasty, which appears to be further exaggerated by corticosteroids. Clinicians should consider the risk of perforation and counsel patients/families accordingly when prescribing quinolone ear drops.

Keywords. tympanic membrane; perforation; tympanostomy tube; quinolone.

Tympanostomy tube (TT) placement is the most commonly performed ambulatory surgery in children [1]. Serious complications related to TTs, such as tympanic membrane perforations (TMPs), have historically been considered uncommon, on the order of 2% [2]; however, recent studies have reported post-TT TMP rates in excess of 10% [3]. Most patients with TTs suffer from at least 1 bout of otorrhea [4], which has also been associated with post-TT TMP [3]. Antibiotic ear drops are recommended for post-TT otorrhea [5], with preference for quinolones over aminoglycosides [6], in large part because of the potential for ototoxicity with aminoglycosides [7, 8].

Systemic use of quinolones has been linked to detrimental effects on collagenous tissue in humans [9]. Following several observational studies [10, 11], the US Food and Drug Administration (FDA) requested a class labeling change for oral quinolones to include a black box warning about the risk of tendon rupture in 2008 [12]. In 2015, the FDA convened an advisory committee meeting to review new safety concerns with oral fluoroquinolones. The committee concluded an unfavorable risk-benefit for their use in acute sinusitis, uncomplicated urinary tract infections, and acute exacerbations of chronic bronchitis and recommended that topical fluoroquinolone preparations should be reviewed as well [13].

Quinolone ear drops have not been linked to post-TT TMP, but clinical trials have been limited by small sample size and short follow-up periods [14, 15]. Animal studies on quinolone ear drops have focused on the effects of combined corticosteroids on healing of the perforated eardrum (tympanic membrane [TM]) and ignored the potential impact of quinolones [16]. A recent cell culture study showed that treatment of TM fibroblasts with ciprofloxacin, at concentrations similar to those achieved with ear drops in humans, led to marked cytotoxicity and depression in collagen synthesis, which is necessary for

Received 6 July 2016; editorial decision 24 December 2016; accepted 17 January 2017; published online February 27, 2017.

Correspondence: A. G. Winterstein, University of Florida, 1225 Center Dr, HPNP 3226, Gainesville, FL 32611 (almut@cop.ufl.edu).

Clinical Infectious Diseases® 2017;64(8):1052–58

DOI: 10.1093/cid/cix032

the TM healing process [17]. The eye, especially the cornea, is similarly frequently treated with ophthalmic quinolones [18]. Quinolone preparations have been reported to have toxic effects on corneal cells in vitro [19], in vivo [20], and in clinical trials [21]. Given the widespread use of otic quinolones following TT placement and the known association between TT placement and TMP [2], we sought to investigate whether otic quinolones would increase the risk of TMP compared to otic neomycin plus hydrocortisone preparations.

METHODS

Data Source and Cohort Set-up

This retrospective cohort study was conducted using Medicaid Analytical eXtract (MAX) files made available for research by the Centers for Medicare and Medicaid Services (CMS). MAX includes billing data for inpatient and outpatient encounters with detail on diagnoses and procedures as well as pharmacy dispensing claims. MAX data are extensively used for drug safety and effectiveness research and are particularly valuable for pediatrics, with approximately 50% of US children enrolled in Medicaid [22].

We included patients aged 18 years or younger and eligible for Medicaid fee-for-service benefits in 29 US states between 1999 and 2006 (detail on states is available in Supplementary Appendix A). This study time period was used to maximize exposure to neomycin, as preferences for antibiotic ear drops have shifted heavily toward quinolone preparations in recent years [6]. Children entered the cohort at the first dispensing of either quinolone or neomycin ear drops following their first TT placement, which was identified from inpatient or outpatient encounter records with Current Procedural Terminology (CPT) code 69433 or 69436. All patients had to have at least 6 months continuous eligibility for Medicaid services prior to TT surgery and throughout the first ear drop dispensing, which had to occur within 12 months after TT placement. This time period was chosen because TTs extrude and the TM commonly heals between 12 and 18 months after insertion [23]. This study focused on the effect of quinolones on this healing process.

We excluded patients with conditions that might predispose to TMP or other TM pathology requiring surgery, based on inpatient or outpatient encounter diagnoses within the 6-month look-back period prior to TT insertion and throughout follow-up. These conditions included cholesteatoma, human immunodeficiency virus, severe combined immunodeficiency, organ transplant, cancer, craniofacial anomalies, cleft palate, burns, ear trauma, failure to thrive, cachexia, exposure to chemotherapeutic agents, head and neck radiation, and >2 weeks of systemic steroid exposure. Patients with the study outcome 6 months prior to cohort entry were also excluded. Definitions of excluded conditions are in Supplementary Table 1.

Study Outcome

We defined persistent TMP as an inpatient or outpatient encounter associated with TMP (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 384.20, 384.21, or 384.23–384.25) followed by a tympanoplasty (CPT codes 69631–69633, 69635–69637, or 69641–69646). Tympanoplasty is routinely delayed until children are older to improve the likelihood of success [24]. Though we knew the requirement for surgical TM repair would severely underestimate the true incidence of TMP in children who received TTs, we elected to use this more restrictive definition to maximize specificity for detecting permanent perforation. To preclude reverse causation, where the plan for tympanoplasty resulted in otic antibiotic initiation to eliminate ear infections prior to surgery, we excluded cases of perforation occurring within 30 days after the cohort entry date.

Exposure

We considered neomycin plus hydrocortisone as active comparator because neomycin has no known adverse effects on collagen tissues and it has historically been used following TT placement [6]. In a previous study, we found that neomycin and quinolone ear drops accounted for nearly all of the ototopical agents prescribed to children with TTs [6], effectively limiting our study to these 2 categories. Quinolone preparations included in this study were ofloxacin, ciprofloxacin plus hydrocortisone, and ciprofloxacin plus dexamethasone. Ear drops containing ofloxacin with a steroid and ciprofloxacin without a steroid were not commercially available during the study period and could therefore not be evaluated. Based on the first pharmacy dispensing record, patients were classified as either quinolone or neomycin plus hydrocortisone users. When a patient in either of the study groups was later prescribed a consecutive otic antibiotic other than the initial one, then follow-up was terminated at this point. This was done because effects on collagenous tissue may be irreversible and decisions to undergo tympanoplasty may be delayed, especially in young children. Accordingly, patients were followed after initial otic antibiotic use until a switch to different ear drops, end of 2006, end of Medicaid enrollment, or occurrence of the study outcome, whichever occurred first.

Covariates

We considered patient sex, race, the calendar year at study entry, and diagnoses at the time of TT placement as fixed covariates. In addition, we adjusted for TT reinsertion, adenoidectomy, and number of ear drop prescriptions as time-varying covariates during follow-up (covariate definitions are available in Supplementary Table 2). We noted a difference in timing of ear drops relative to TT insertion, especially in more recent study years where quinolones were used earlier than neomycin. We interpreted this as potential confounding by severity, where quinolones were increasingly used for more minor effusion at TT

insertion, whereas neomycin ear drops were more often initiated when otorrhea or otitis media developed during follow-up. To account for this difference, we also adjusted the analysis for the time difference between TT placement and ear drop initiation.

Statistical Analysis

We used a time-dependent Cox regression model to estimate the unadjusted and adjusted hazards ratios (HRs) of TMP comparing exposure to quinolones and neomycin plus hydrocortisone. We further examined the association between different quinolone-containing ear drop formulations to neomycin plus hydrocortisone using a categorical exposure variable that identified the initial antibiotic dispensation as neomycin plus hydrocortisone, ofloxacin, ciprofloxacin plus hydrocortisone, or ciprofloxacin plus dexamethasone.

To challenge the study assumptions, we conducted 2 sensitivity analyses. First, we did not exclude cases of tympanoplasty occurring within 30 days of the first antibiotic exposure. Second, we allowed patients to switch between exposure groups and ear drops were modeled as time-varying exposure with cases attributed to the last exposure. SAS software version 9.4 (SAS Institute, Cary, North Carolina) was used for data management and analysis. All tests were 2-sided, with an α level of .05 indicating statistical significance. The study protocol was approved by the CMS and our center's institutional review and privacy boards.

RESULTS

We identified 300 173 children with encounter claims for TT procedures. After applying the exclusion and inclusion criteria, the number of patients included in the cohort was 96 595. Of these, 78 275 were exposed to quinolones; the remainder were neomycin plus hydrocortisone–exposed children (Figure 1). Children who were started on otic neomycin were slightly older. All other baseline characteristics showed <1 percentage point differences between groups (Table 1).

The distribution between children initiated on otic neomycin or quinolone was similar at the beginning of the study period but changed rapidly to predominant use of quinolones in later study years (Table 2). Of note, the proportion of children who had ear drops dispensed at the same day as tube placement increased steadily among the quinolone users from 18% to 58%, whereas it remained steady for neomycin users at about one-quarter.

A total of 364 TMPs occurred during follow-up, resulting in an incidence rate of 11 TMPs/10 000 patient-years for neomycin plus hydrocortisone–exposed children and 17 TMPs/10 000 patient-years for children with exposure to otic quinolone. The unadjusted HR for TMP for patients who were exposed to any otic quinolone preparation compared with children exposed to neomycin was 1.44 (95% confidence interval [CI], 1.04–2.00). When we adjusted for demographics and other covariates, the HR was 1.61 (95% CI, 1.15–2.26; Table 3). Each year increase in patients' age was associated with a 21% increase in the hazard of TMPs (95% CI, 18%–24%). An increased frequency of ear drop prescriptions was also associated with higher risk of TMPs (HR, 1.14 [95% CI, 1.11–1.17]). Comparisons of ofloxacin,

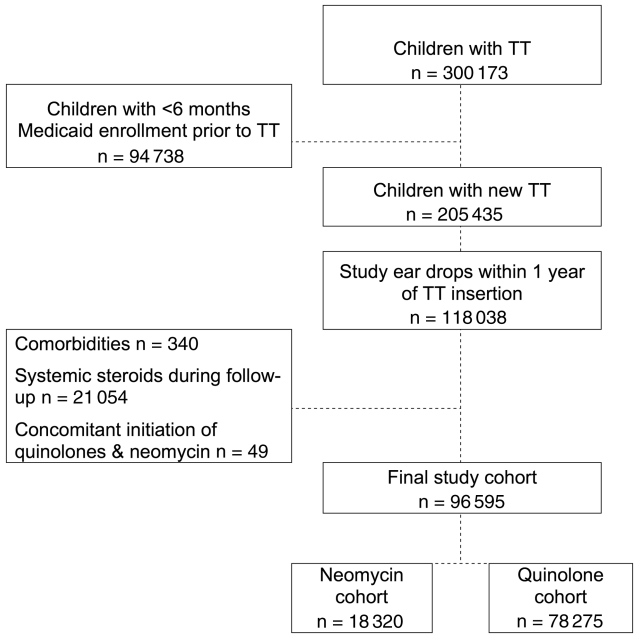

Figure 1. Study enrollment and details of exclusion. Abbreviation: TT, tympanostomy tube.

Table 1. Patient Characteristics According to First Otic Antibiotic Exposure

Characteristic	Quinolones	Neomycin
No. of patients	78 275	18 320
Male sex	44 390 (56.71)	10 510 (57.37)
Race		
White	54 057 (69.06)	12 721 (69.44)
Other	24 218 (30.94)	5599 (30.56)
Age, y, mean (SD)	3.32 (2.97)	3.60 (3.17)
Diagnosis at TT		
AOM	4462 (5.7)	1008 (5.5)
COME	52 836 (67.5)	12 513 (68.3)
AOM and COME	11 115 (14.2)	2455 (13.4)
Nonspecific OM	8532 (10.9)	2052 (11.2)
Other[a]	1330 (1.7)	292 (1.6)
Adenoidectomy	8939 (11.42)	2252 (12.29)
Reinsertion of TT	407 (0.52)	95 (0.52)
Mean No. of antibiotic ear drop dispensing during follow-up (SD)	2.42 (1.91)	1.42 (0.83)
Mean time from TT to first ear drop, d (SD)	71 (97)	90 (104)
Median follow-up time, d (IQR)	731 (656)	533 (887)
Median days from cohort entry to study outcome (IQR)	764 (769)	669 (539)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: AOM, acute otitis media; COME, chronic otitis media with effusion; IQR, interquartile range; OM, otitis media; SD, standard deviation; TT, tympanostomy tube.

[a]Diagnoses other than otitis media include miscellaneous middle ear indications, such eustachian tube dysfunction, conductive hearing loss, and mastoiditis; external ear diseases, such as otitis externa and impacted cerumen; nose and throat disorders; and disorders unrelated to ear, nose, and throat.

Table 2. Days between Initial Antimicrobial Ear Drop Dispensing and Tympanostomy Tube Placement

Antimicrobial	TT Year	1999	2000	2001	2002	2003	2004	2005
Quinolone	No.	3064	7902	10 100	12 000	15 747	16 465	12 988
	Median (IQR)	11 (42)	48 (145)	46 (152)	34 (145)	18 (126)	5 (108)	1 (77)
	% at day of TT	18	21	25	29	38	45	58
Neomycin	No.	2524	2555	3918	2827	2351	1434	711
	Median (IQR)	3 (34)	43 (151)	46 (164)	69 (186)	56 (176)	72 (189)	84 (190)
	% at day of TT	25	47	27	24	28	20	27

P value for trend <.001.

Abbreviations: IQR, interquartile range; TT, tympanostomy tube.

ciprofloxacin plus hydrocortisone, and ciprofloxacin plus dexamethasone against neomycin plus hydrocortisone showed an increased hazard for each individual quinolone preparation (HRs, 1.49 [95% CI, 1.05–2.09]; 1.94 [95% CI, 1.32–2.85]; and 2.00 [95% CI 1.18–3.41], respectively, Table 4). The sensitivity analyses yielded results comparable to the main analysis (Supplementary Tables 3 and 4).

DISCUSSION

The literature is replete with studies documenting the deleterious effects of quinolones on soft tissues [16, 25, 26]. Implicated mechanisms include increased apoptosis of extracellular matrix–producing cells [27], increased degradation of extracellular matrix via enhanced matrix metalloproteinase activity [28], and decreased levels of intact collagen [29]. The structural integrity of the TM is derived from its middle layer (lamina propria), which is composed largely of fibroblasts and collagen [30]. As the concentrations of quinolones in otic preparations—what is reaching the TM—can be roughly 1000 times the plasma concentrations achieved with oral administration [31], the soft tissue toxicity of quinolones would be expected to manifest in the quinolone-exposed TM. In cell culture, TM fibroblasts have shown increased cytotoxicity and markedly lower levels of collagen after quinolone exposure [17]. Consistent with the suggested mechanisms, our findings indicate an increased risk of TMPs associated with otic quinolone use after TT placement in children.

Table 3. Adjusted Risk of Tympanic Membrane Perforation for Patients Exposed to Quinolone versus Neomycin Plus Hydrocortisone Ear Drops

Characteristic	Variable	Hazard Ratio	95% CI
Exposure	Neomycin	Reference	
	Quinolones	1.61	1.15–2.26
Age, y		1.21	1.18–1.24
Sex	Male	Reference	
	Female	1.23	1.00–1.52
Race	Nonwhite	Reference	
	White	0.90	.73–1.12
Diagnosis at TT	Other	Reference	
	AOM	1.53	.68–3.44
	COME	1.24	.61–2.52
	AOM and COME	1.22	.57–2.61
	Nonspecific OM	1.43	.68–3.04
Adenoidectomy		1.26	1.01–1.58
Reinsertion of TT		1.31	1.08–1.71
No. of antibiotic ear drop dispensings during follow-up		1.14	1.11–1.17
Calendar year	1999	Reference	
	2000	0.92	.52–1.61
	2001	0.97	.54–1.72
	2002	1.15	.64–2.05
	2003	1.15	.63–2.09
	2004	1.04	.55–1.95
	2005	0.48	.21–1.08
Time to first ear drop, d		1.001	1.000–1.003

Abbreviations: AOM, acute otitis media; CI, confidence interval; COME, chronic otitis media with effusion; OM, otitis media; TT, tympanostomy tube.

Choice of the appropriate comparator was an important consideration in this study. TMPs are known complications of both otitis media [32] and TT placement [2]. Post-TT otitis media, the primary indication for otic antibiotics, therefore, acts as confounder and precludes comparisons to patients without any treatment. Post-TT otitis media can be treated with oral antibiotics [33], but cure rates are less favorable [14]. Furthermore, oral antibiotics may be given for a myriad of indications, unrelated to the ear. Thus, given similar indications and efficacy profiles, and in absence of effective ear drops that contain neither quinolones nor steroids, our chosen neomycin plus hydrocortisone comparator established the most balanced comparison groups.

The neomycin ear drops used as the reference agent in our study have been associated with TM pathology [34], which has been linked to an excipient, propylene glycol [35]. These neomycin ear drops also contain hydrocortisone, which may independently increase the risk for TMPs. For example, experimental studies have reported delayed healing of TMs after myringotomy and topical treatment with hydrocortisone [36] and spontaneous TMPs following acute otitis externa treatment with neomycin plus hydrocortisone [37]. Thus, the probability for a slightly elevated risk of TMP in our reference group should be considered when interpreting the relative increase in risk attributed to otic quinolones.

Unfortunately, comparison of different quinolone formulations was compromised by small sample size. Furthermore, because preparations containing ofloxacin with a steroid and ciprofloxacin without a steroid were not commercially

Table 4. Association between Quinolones and Tympanic Membrane Perforations

Exposure	No. of Patients	No. of Cases	Person-time, y	Incidence per 10 000 PY	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Neomycin	18 320	42	36 862	11.4	Reference	
All quinolones	78 275	322	186 509	17.3	1.44 (1.04–2.00)	1.61 (1.15–2.26)
Ofloxacin	50 163	207	126 730	16.3	1.35 (.96–1.89)	1.49 (1.05–2.09)
Cipro/HC	11 649	79	31 344	25.2	2.17 (1.48–3.61)	1.94 (1.32–2.85)
Cipro/Dex	16 463	36	28 435	12.7	0.87 (.55–1.39)	2.00 (1.18–3.41)

Abbreviations: CI, confidence interval; Cipro, ciprofloxacin; Dex, dexamethasone; HC, hydrocortisone; HR, hazard ratio; PY, person-years.

[a]Adjusted for age, sex, race, adenoidectomy, tympanostomy tube reinsertion, calendar year of tube insertion, number of ear drop prescriptions, and time to first ear drop initiation.

available during the study period, we could not address 2 clinically important questions. First, does the addition of steroids to quinolones increase the risk for TMP? Synergistic effects of steroid/quinolone combinations have been described by others, including an increased risk of tendon rupture associated with concomitant use of systemic corticosteroids and quinolones [10]. Second, is the quinolone effect drug-specific or a class phenomenon? We did find independent effects of each quinolone preparation, but were unable to discern whether the magnitude of effect differs across agents. Our in vitro experiments with TM fibroblasts suggest more pronounced effects of ciprofloxacin compared with ofloxacin [38].

We chose a study period of the last decade when otic neomycin was commonly used to treat post-TT otitis media [6]. Addition of more recent years would have included an era when clinical guidelines started to discourage use of neomycin in children with non-intact TM [7], resulting in limited use and yielding it an inadequate comparator. Because preferences changed over the study period, we adjusted for study year to ensure comparisons were not confounded by other secular changes. We did note increasing use of otic quinolones (but not neomycin) at the time of tube placement, which was likely triggered by lesser pathology (such as middle ear effusion) than therapeutic use for otitis media later during follow-up. Because the predominant initiation time of neomycin remained consistently several weeks after TT placement, suggesting more frequent use when complications manifested, we adjusted our comparison for the difference between initiation time and TT placement. As expected, hazard ratios for quinolone exposure increased after adjustment, indicating a bias in favor of quinolones because they were likely used more frequently in absence of major complications.

Unlike many drug safety concerns where the adverse effect follows exposure immediately, this study was challenged by the delay in diagnosis and treatment of tympanic perforation. The requirement of tympanoplasty in the definition of TMP focused our assessment on cases that were deemed to require surgical repair and reduced bias from the use of potentially unreliable *ICD-9-CM* codes. Guidelines recommend that tympanoplasty should not be performed for at least 1 year after TMP identification to allow spontaneous healing [5]. Therefore, unlike most clinical trials, we followed patients for an extended time, which was necessary to identify the delayed effects of quinolones. This "extended" follow-up—relative to clinical trials of quinolone ear drops—will still likely be insufficient to fully demonstrate the rate of TMP based on requirement for tympanoplasty. Tympanoplasty is often delayed beyond 1 year, as younger children are thought to have a lower surgical success rate [24]. These factors will underestimate the absolute incidence of TMPs in young children using our chosen criteria. The relative comparison of incidence rates in the reported HRs would, however, be unbiased unless the decision to perform tympanoplasty differed based on prior antibiotic exposure, and that is highly unlikely. Although the study outcome has not been validated, using the algorithm of TMP diagnosis code plus charge for tympanoplasty has been shown to yield similar rates of permanent perforation requiring surgical repair as those reported by prospective studies [39]. Of note, neither procedure codes used to identify tympanoplasties nor the ear drop dispensing charges are ear specific, which may have resulted in capturing some patients whose TMP did not occur in the ear with prior TT placement or with ear drop exposure. Bias resulting from exposure misclassification (eg, patients not taking the dispensed ear drops) would move the results toward the null hypothesis (ie, no difference between quinolone and neomycin treatment) if such measurement error was similar between groups.

Lack of randomization in this study comes with concerns about residual (ie, unmeasured) confounding. To focus our analysis on TMPs following TTs and ear drop exposure, we excluded patients with risk factors that may predispose to TMP. Review of risk factors that were measured in this study and their effect on hazard ratios in multivariate adjustment suggest that quinolones were slightly channeled toward children with lesser risk, which is likely explained by their increasing use right after tube insertion. Risk factors that we were not able to account for include the type of TT used, whether the tube extruded spontaneously, use of water precautions, and otorrhea severity, but these are not expected to differ across comparison groups and thus are not expected to create bias. This observation is also supported by a previous study in which we used similar exposure groups, and found an increased risk for sensorineural hearing loss (SNHL) associated with neomycin

use [8]. Imbalances related to more severe ear disease would need to be differential to explain an increased risk of SNHL for neomycin on one hand, and of TMP for quinolone exposure, on the other.

Our study raises important questions for further research. First, it was confined to children with a TM defect following TT placement. Studies evaluating quinolone effects in indication with intact TM, such as otitis externa, are needed. Second, while most drug safety effects are generalizable across socioeconomic classes, the background risk for TMP in children with private insurance may be lower than for those enrolled in Medicaid. Overall, precise quantification of risk-benefit of otic antibiotic use in various indications will greatly enhance evidence-based otologic practice. Finally, new quinolone preparations, which we were not able to examine within the selected study period, should be evaluated to fully understand the contribution of each preparation to TMP risk.

Evaluation of the benefits and risks of otic quinolones following TT placement should also consider the safety profile of the alternative treatment options, because otic aminoglycoside use is associated with SNHL [8]. Unlike a TMP, which can be repaired, SNHL is usually irreversible. Ideally, treatment that is neither toxic to the inner ear nor damaging to the TM would be used. Absent novel treatment options that meet both criteria, an important consideration is to avoid overuse of ear drops, which has been reported to be a common occurrence [40, 41].

In conclusion, use of quinolone ear drops in children with TTs is associated with an increased risk of persistent TMPs. Combination with corticosteroids may potentiate the risk for persistent TMPs. These risks must be balanced against the risk of SNHL with otic aminoglycosides in the presence of a TT.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. A.: Study conception and design, data analysis, drafting and revising the manuscript, and final approval for the manuscript to be submitted. P. J. A.: Substantial contributions to the conception and design, data interpretation, editing the manuscript critically for important intellectual content, and final approval of the version to be published. A. G. W.: Study conception and design, help with acquiring the data, data analysis and interpretation, editing the manuscript for important intellectual content, and final approval of the version to be published.

Potential conflicts of interest. P. J. A. has received research support from Alcon Laboratories and Otonomy and remuneration for advisory board service from Otonomy. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. Natl Health Stat Report **2009**: 1–25.
2. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. Otolaryngol Head Neck Surg **2001**; 124:374–80.
3. O'Connell Ferster AP, Tanner AM, Karikari K, Roberts C, Wiltz D, Carr MM. Factors related to persisting perforations after ventilation tube insertion. Int J Pediatr Otorhinolaryngol **2016**; 81:29–32.
4. van Dongen TM, van der Heijden GJ, Freling HG, Venekamp RP, Schilder AG. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. PLoS One **2013**; 8:e69062.
5. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg **2013**; 149 (1 suppl):S1–35.
6. Winterstein AG, Castillo JM, Xu D, Liu W, Antonelli PJ. Ototopical neomycin exposure in children with nonintact tympanic membranes. Laryngoscope **2012**; 122:2529–32.
7. Roland PS, Stewart MG, Hannley M, et al. Consensus panel on role of potentially ototoxic antibiotics for topical middle ear use: introduction, methodology, and recommendations. Otolaryngol Head Neck Surg **2004**; 130(3 suppl):S51–6.
8. Winterstein AG, Liu W, Xu D, Antonelli PJ. Sensorineural hearing loss associated with neomycin eardrops and nonintact tympanic membranes. Otolaryngol Head Neck Surg **2013**; 148:277–83.
9. Bailey RR, Natale R, Linton AL. Nalidixic acid arthralgia. Can Med Assoc J **1972**; 107:604 passim.
10. van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HM, Rowlands S, Stricker BH. Increased risk of achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. Arch Intern Med **2003**; 163:1801–7.
11. Corrao G, Zambon A, Bertù L, et al. Evidence of tendinitis provoked by fluoroquinolone treatment: a case-control study. Drug Saf **2006**; 29:889–96.
12. US Food and Drug Administration. FDA requests boxed warnings on fluoroquinolone antimicrobial drugs seeks to strengthen warnings concerning increased risk of tendinitis and tendon rupture. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116919.htm. Accessed 2 December 2016.
13. US Food and Drug Administration. November 5, 2015 joint meeting of the Antimicrobial Drugs Advisory Committee (AMDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiInfectiveDrugsAdvisoryCommittee/ucm424449.htm. Accessed 9 November 2016.
14. Dohar J, Giles W, Roland P, et al. Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea through tympanostomy tubes. Pediatrics **2006**; 118:e561–9.
15. Giles W, Dohar J, Iverson K, Cockrum P, Hill F, Hill N. Ciprofloxacin/dexamethasone drops decrease the incidence of physician and patient outcomes of otorrhea after tube placement. Int J Pediatr Otorhinolaryngol **2007**; 71:747–56.
16. Antonelli PJ, Winterstein AG, Schultz GS. Topical dexamethasone and tympanic membrane perforation healing in otitis media: a short-term study. Otol Neurotol **2010**; 31:519–23.
17. Orobello NC, Dirain CO, Schultz G, Milne-Davies BA, Ng MR, Antonelli PJ. Ciprofloxacin decreases collagen in mouse tympanic membrane fibroblasts. Otolaryngol Head Neck Surg **2016**; 155:127–32.
18. Fiscella RG, Lewis CC, Jensen MK. Topical ophthalmic fourth-generation fluoroquinolones: appropriate use and cost considerations. Am J Health Syst Pharm **2007**; 64:2069–73.
19. Bezwada P, Clark LA, Schneider S. Intrinsic cytotoxic effects of fluoroquinolones on human corneal keratocytes and endothelial cells. Curr Med Res Opin **2008**; 24:419–24.
20. Mah FS, Romanowski EG, Dhaliwal DK, Yates KA, Gordon YJ. Role of topical fluoroquinolones on the pathogenesis of diffuse lamellar keratitis in experimental in vivo studies. J Cataract Refract Surg **2006**; 32:264–8.
21. Patel GM, Chuang AZ, Kiang E, Ramesh N, Mitra S, Yee RW. Epithelial healing rates with topical ciprofloxacin, ofloxacin, and ofloxacin with artificial tears after photorefractive keratectomy. J Cataract Refract Surg **2000**; 26:690–4.
22. Hennessy S, Leonard CE, Palumbo CM, Newcomb C, Bilker WB. Quality of Medicaid and Medicare data obtained through Centers for Medicare and Medicaid Services (CMS). Med Care **2007**; 45:1216–20.
23. Weigel MT, Parker MY, Goldsmith MM, Postma DS, Pillsbury HC. A prospective randomized study of four commonly used tympanostomy tubes. Laryngoscope **1989**; 99:252–6.
24. Jesic SD, Dimitrijevic MV, Nesic VS, Jotic AD, Slijepcevic NA. Temporalis fascia graft perforation and retraction after tympanoplasty for chronic tubotympanic otitis and attic retraction pockets: factors associated with recurrence. Arch Otolaryngol Head Neck Surg **2011**; 137:139–43.
25. Buyten J, Kaufman G, Ryan M. Effects of ciprofloxacin/dexamethasone and ofloxacin on tympanic membrane perforation healing. Otol Neurotol **2007**; 28:887–90.

26. Hebda PA, Yuksel S, Dohar JE. Effects of ciprofloxacin-dexamethasone on myringotomy wound healing. Laryngoscope **2007**; 117:522–8.
27. Tan Y, Lu K, Deng Y, et al. The effects of levofloxacin on rabbit fibroblast-like synoviocytes in vitro. Toxicol Appl Pharmacol **2012**; 265:175–80.
28. Sendzik J, Shakibaei M, Schäfer-Korting M, Stahlmann R. Fluoroquinolones cause changes in extracellular matrix, signalling proteins, metalloproteinases and caspase-3 in cultured human tendon cells. Toxicology **2005**; 212:24–36.
29. Bujor AM, Haines P, Padilla C, et al. Ciprofloxacin has antifibrotic effects in scleroderma fibroblasts via downregulation of Dnmt1 and upregulation of Fli1. Int J Mol Med **2012**; 30:1473–80.
30. Knutsson J, Bagger-Sjöbäck D, von Unge M. Collagen type distribution in the healthy human tympanic membrane. Otol Neurotol **2009**; 30:1225–9.
31. Begg EJ, Robson RA, Saunders DA, et al. The pharmacokinetics of oral fleroxacin and ciprofloxacin in plasma and sputum during acute and chronic dosing. Br J Clin Pharmacol **2000**; 49:32–8.
32. Kalu SU, Ataya RS, McCormick DP, Patel JA, Revai K, Chonmaitree T. Clinical spectrum of acute otitis media complicating upper respiratory tract viral infection. Pediatr Infect Dis J **2011**; 30:95–9.
33. Ruohola A, Heikkinen T, Meurman O, Puhakka T, Lindblad N, Ruuskanen O. Antibiotic treatment of acute otorrhea through tympanostomy tube: randomized double-blind placebo-controlled study with daily follow-up. Pediatrics **2003**; 111(5 Pt 1):1061–7.
34. Masaki M, Wright CG, Lee DH, Meyerhoff WL. Effects of otic drops on chinchilla tympanic membrane. Arch Otolaryngol Head Neck Surg **1988**; 114:1007–11.
35. Vassalli L, Harris DM, Gradini R, Applebaum EL. Inflammatory effects of topical antibiotic suspensions containing propylene glycol in chinchilla middle ears. Am J Otolaryngol **1988**; 9:1–5.
36. Spandow O, Hellström S, Schmidt SH. Hydrocortisone delay of tissue repair of experimental tympanic membrane perforations. Ann Otol Rhinol Laryngol **1990**; 99:647–53.
37. Roland PS, Pien FD, Schultz CC, et al; Ciprodex Otic AOE Study Group. Efficacy and safety of topical ciprofloxacin/dexamethasone versus neomycin/polymyxin B/hydrocortisone for otitis externa. Curr Med Res Opin **2004**; 20:1175–83.
38. Milne-Davies BA, Antonelli PJ, Orobello NC, Dirain CO. Collagen and α-tubulin of mouse tympanic membrane fibroblasts treated with quinolones and aminoglycosides. Otolaryngol Head Neck Surg **2016**. pii:0194599816672627.
39. Alrwisan A, Winterstein AG, Antonelli PJ. Epidemiology of persistent tympanic membrane perforations subsequent to tympanostomy tubes assessed with real world data. Otol Neurotol **2016**; 37:1376–80.
40. Agius AM, Reid AP, Hamilton C. Patient compliance with short-term topical aural antibiotic therapy. Clin Otolaryngol Allied Sci **1994**; 19:138–41.
41. Lancaster J, Mathews J, Williams RS, Thussey C, Kent SE. Comparison of compliance between topical aural medications. Clin Otolaryngol Allied Sci **2003**; 28:331–4.