

Systematic Review

The Role of Routine Hearing Screening in Children With Cystic Fibrosis on Aminoglycosides: A Systematic Review

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Objective: To review the role of routine hearing screening for sensorineural hearing loss (SNHL) in children with cystic fibrosis (CF) who have been on aminoglycoside therapy.

Data Sources: PubMed, Cochrane, Scopus, and Ovid databases.

Review Methods: A systematic review of the literature was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive search was performed from 1970 to 2014. Randomized controlled trials, case-control studies, cohort studies, and case series including pediatric subjects with baseline auditory evaluations were included.

Results: Twelve studies (1979–2014) were reviewed. The study population included 762 children (5 months–20 years). Hearing screening measures included pure-tone audiometry (PTA) at standard \pm high frequency threshold (HFPTA) (12/12), distortion product otoacoustic emissions (DPOAE) (4/12), transient-evoked otoacoustic emissions (1/12), and automated auditory brainstem response (1/12). The overall prevalence of SNHL ranged from 0% to 29%. However, on subset analysis of children with greater than 10 courses of intravenous (IV) aminoglycosides, up to 44% had SNHL. Eight studies recommended hearing screening in CF children on aminoglycosides; of these, two studies recommended screening even without aminoglycoside exposure, and four studies made no recommendations. HFPTA was the most commonly recommended screening measure followed by DPOAEs.

Conclusion: This systematic review supports a recommendation for clinicians to perform routine hearing screening in children with CF during and after aminoglycoside exposure based on the high prevalence of SNHL in this population. Future studies should define the optimal timing for hearing screening during and after aminoglycoside therapy in children with CF.

Key Words: Cystic fibrosis, aminoglycosides, hearing loss, hearing screening, pediatric, systematic review.

Level of Evidence: NA

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INTRODUCTION

Patients with cystic fibrosis (CF) are often subject to pulmonary infections treated with antibiotics such as

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aminoglycosides. Generally, these antibiotics are highly effective against gram-negative organisms, particularly *Pseudomonas aeruginosa*, which is often the causative agent of disease in CF children.¹ By adolescence, 85% of patients with CF are thought to have chronic pseudomonas infections.² This colonization is a risk factor for further pulmonary deterioration and decreased survival.³ Additionally, pulmonary disease is the leading cause of morbidity and mortality in these patients, further necessitating the use of anti-pseudomonas antibiotics.^{4,5} Because children with CF have a greater volume of distribution and increased renal clearance of aminoglycosides,⁶ they are often treated with higher doses. However, aminoglycosides have also been associated with ototoxicity.^{7,8} Because children with CF are often on prolonged courses and/or higher doses of aminoglycosides, they are particularly at risk of ototoxicity.

Aminoglycoside-associated ototoxicity involves both vestibulotoxicity and cochleotoxicity.⁸ Vestibulotoxicity manifests as disequilibrium and oscillopsia, but is usually temporary.⁸ Permanent sensorineural hearing loss (SNHL) occurs at the level of cochlear hair cells secondary to the generation of reactive oxygen radicals from an

TABLE I.
Background and Demographics of Studies Included in the Systematic Review.

Author	Type of Study	Country	Year	No.	Age (Mean or Range)	Statistical Analysis on Outcome	Level of Evidence
Al-Malky et al. ¹⁸	Retrospective cohort study	United Kingdom	2014	70	10.7	Yes	3
Al-Malky et al. ¹⁹	Retrospective cohort study	United Kingdom	2011	45	10.9	Yes	3
Martins et al. ²⁰	Retrospective cohort study	Brazil	2010	120	5 months–18 years	Yes	3
Cheng et al. ²¹	Retrospective cohort study	United States	2009	50	11.4	Yes	3
Mulheran et al. ²²	Randomized control trial	United Kingdom	2006	125	—	Yes	1
Piltcher et al. ²³	Retrospective case series	Spain	2003	42	7.87	No	4
Stavroulaki et al. ²⁴	Prospective case control study	Greece	2002	31	5.2–14.1	Yes	2
Mulheran et al. ²⁵	Retrospective cohort study	United Kingdom	2001	72	—	No	3
Ozcelik et al. ²⁶	Retrospective cohort study	Turkey	1995	50	2 to 17	No	3
McRorie et al. ²⁷	Retrospective cohort study	United States	1989	40	11.3; 3+ overall	Yes	3
Forman-Franco et al. ²⁸	Retrospective case series	United States	1979	64	M: 14.5; F: 12.7	Yes	4
Thomsen et al. ²⁹	Retrospective case series	Denmark	1979	53	11.8	No	4

Ages are given in years unless noted otherwise.
F = female; M = male

iron-aminoglycoside complex.⁸ Hair cells located at the basal end of the cochlea responsible for high-frequency sound perception are impacted first.^{8–10} SNHL occurring as early as 4 hours from treatment has been reported.¹¹ Additionally, SNHL has been noted in patients with short and/or few courses of aminoglycosides, whereas many with prolonged courses have normal hearing. These observations support the theory that aminoglycoside-associated ototoxicity is multifactorial, and a genetic predisposition may be a contributing factor. Several mitochondrial gene mutations within the MT-RNR1 and MT-TS1 groups (including the highly studied mitochondrial 1555A>G mutation) are known to predispose to aminoglycoside ototoxicity and have been reported in patients with CF.¹²

Documenting aminoglycoside-induced SNHL by routine hearing screening in patients with CF has several key implications. First, appropriate interventions can be taken including the discontinuation of the offending agent and utilization of an alternative if feasible. Second, a protocol can be developed for routine hearing screening in this at-risk population implementing hearing tests during and after aminoglycoside therapy. Currently, no protocol exists specifically outlining appropriate hearing screening methods or the frequency of screening. The American Academy of Audiology has not advocated for a specific screening method, but has recommended screening “weekly or biweekly” during aminoglycoside therapy and also “a few months” after discontinuation.¹³ Last, a spotlight on this topic may appeal to the medical community-at-large for further research into the development and testing of antioxidant drugs that have shown to effectively inhibit ototoxicity in animal models.¹⁴ This review has three objectives: 1) to determine the prevalence of hearing loss in children with CF after exposure to aminoglycosides, 2) to determine the role of routine hearing screening in early detection of SNHL in these children, and 3) to determine the most appropriate hearing screening method in children with CF.

MATERIALS AND METHODS

Search Methodology, Inclusion Criteria, and Data Collection

A systematic review of the literature was performed in accordance with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.¹⁵ A literature search of the English-language literature for all indexed years was performed in PubMed (www.ncbi.nlm.nih.gov/pubmed) in May 2014. The following exploded MeSH (Medical Subject Heading) terms were used in the search including all their subheadings: cystic fibrosis, hearing loss, and aminoglycosides. This search strategy was then adapted to three additional databases—Cochrane, Scopus (including Embase), and Ovid—and verified by a medical librarian for accuracy (see Supporting Information, Appendix 1, in the online version of this article). References from the retrieved articles were also analyzed for the inclusion of any missed studies relevant to our review. Two authors independently reviewed the abstracts and all included articles; a consensus was achieved based on predetermined inclusion and exclusion criteria. Only randomized controlled trials, case-control studies, cohort studies, and case series with original data including pediatric subjects with initial baseline auditory evaluation were included. Exclusion criteria included: review articles, editorials, case reports, animal or biochemical studies, studies lacking measurable outcomes or impertinent to aminoglycoside-induced SNHL, and studies with inextricable pediatric data.

Data Extraction and Analysis

Data from the selected studies were extracted and reviewed by two investigators independently. A spreadsheet was used for this purpose accounting for authors, study titles, healthcare system (single vs. multi-institutional), study design, outcomes, type of hearing screening measure, and statistical analysis. When discrepancies in data extraction occurred, the two investigators discussed and reviewed the study together until a consensus was reached. A third investigator further verified the decision. Each article was assigned a “level of evidence” for its study design based on the Oxford Centre for Evidence-based Medicine-Levels of Evidence guidelines¹⁶ (Table I). Additionally, risk of bias was determined based on the

TABLE II.
Newcastle-Ottawa Quality Assessment Bias Grading for Nonrandomized Studies.

Study	Newcastle-Ottawa Scale Bias Grading			Total Grade [†]
	Selection Grade (Maximum 4 Stars)	Comparability Grade (Maximum 2 Stars)*	Exposure Grade (Maximum 3 Stars)	
Al-Malky et al. ¹⁸	***	**	*	*****
Al-Malky et al. ¹⁹	***	**	*	*****
Martins et al. ²⁰	***	*	*	*****
Cheng et al. ²¹	****	**	*	*****
Mulheran et al. ²²	N/A	N/A	N/A	N/A
Piltcher et al. ²³	***	N/A	*	****
Stavroulaki et al. ²⁴	****	**	***	*****
Mulheran et al. ²⁵	***	**	*	*****
Ozcelik et al. ²⁶	***	**	*	*****
McRorie et al. ²⁷	***	**	*	*****
Forman-Franco et al. ²⁸	**	N/A	*	***
Thomsen et al. ²⁹	***	N/A	*	****

*In case series, the comparability grade for control comparison is not applicable.

[†]Maximum total score achievable for case control, cohort, and case series is 9, 9, and 4, respectively.

N/A = not available.

Newcastle-Ottawa Quality Assessment Scale for nonrandomized studies composed of 3 different grades including selection, comparability, and exposure (Table II).¹⁷

RESULTS

A schematic flow diagram detailing the systematic search and study selection is included (Fig. 1). The literature search yielded 66 studies, whereas a citation review resulted in an additional nine studies. Of these initial 75 studies, 63 studies did not meet inclusion criteria

and were excluded. A total of 12 articles were included in the final review (Table I).^{18–29} Three of the 12 articles also studied adult CF patients. The total number of subjects was 994, of whom 762 were children (range, 5 months–20 years) and were the final study population. A meta-analysis was not conducted due to the heterogeneity of the data analyzed.

The study design of the articles was as follows: eight retrospective cohort studies, two retrospective case series, one randomized control trial, and one prospective

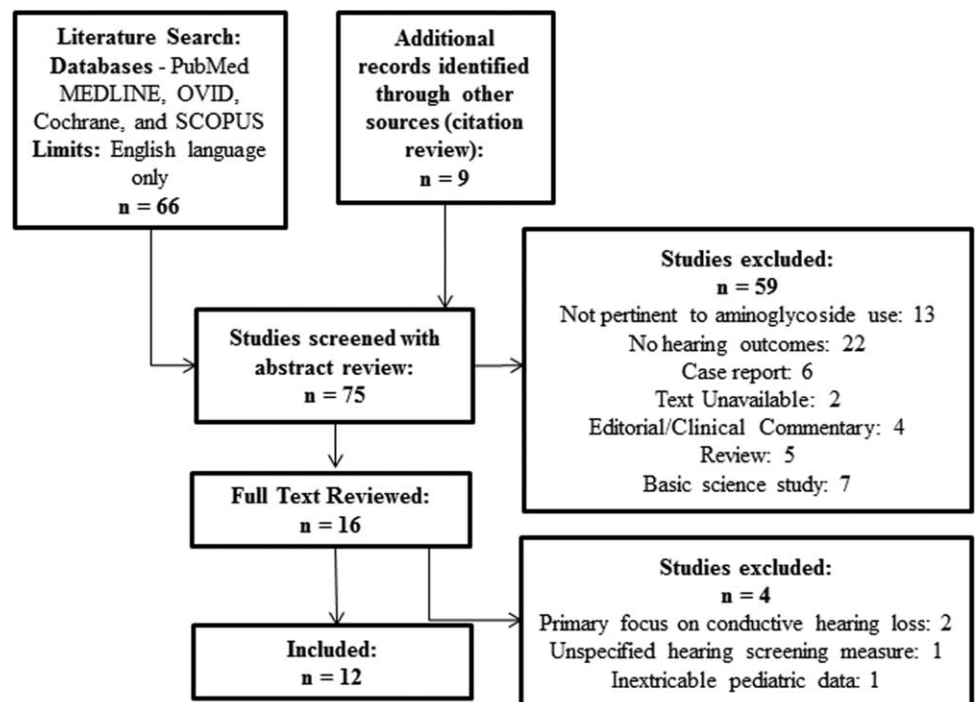


Fig. 1. Flow schematic diagram for studies included and excluded in the systematic review search.

case control study. All studies were carried out at single institutions except for Mulheran et al.,²² which was a multicenter study. Eight of 12 studies (66.7%) utilized statistical analysis.^{18–29} A comprehensive overview of the studies is presented in Table III. Hearing screening measures included pure-tone audiometry (PTA) up to 8 kHz thresholds (12/12), distortion product otoacoustic emissions (DPOAEs) (4/12), transient-evoked otoacoustic emissions (1/12), and automated auditory brainstem response (AABR) (1/12). Five studies (41.7%) also measured high frequency thresholds in addition to PTA at standard thresholds; the highest frequencies tested were 16 kHz^{18,22,25} and 20 kHz^{19,27} in three and two studies each, respectively.

Prevalence of Sensorineural Hearing Loss Secondary to Aminoglycosides

The prevalence of SNHL ranged from 0% (Thomsen et al.²⁹ and Mulheran et al.²²) to 28.6% (Piltcher et al.²³). Of note, Mulheran et al.²² reported a 0% prevalence following a single 14-day course of intravenous (IV) tobramycin only, whereas Thomsen et al.²⁹ reported 0% prevalence following a mean of 3.2 courses of 10- to 14-day IV or intramuscular courses of tobramycin. Piltcher et al.²³ reported a prevalence of 28.6%, but without reporting the mean number of antibiotic courses per patient. Three studies (Al-Malky et al.^{18,19} and Cheng et al.²¹) divided patients into tiers of aminoglycoside exposure and reported the prevalence of SNHL per subsets. Al-Malky et al.¹⁸ reported a prevalence of 21% in patients on more than five courses of IV aminoglycosides. In 2014, the same group¹⁹ reported the overall prevalence to be 24%. In their high-exposure group consisting of patients who had received >10 courses of aminoglycosides, the prevalence was 44%. Cheng et al.²¹ reported an overall 14% prevalence of SNHL, and a 43% prevalence in subjects who had received more than 10 courses of IV aminoglycosides.

Recommendations for Routine Hearing Screening

Eight studies^{18–21,23–25,27} (66.7%) recommended routine hearing screening in CF patients on aminoglycosides. Piltcher et al.²³ made the most specific recommendation: patients should be screened with audiometry before, during, and after treatment as well as at least every 6 to 12 months thereafter for an unknown length of time. Two studies^{20,21} recommended hearing screening in all CF patients including those without aminoglycoside exposure. Mulheran et al.²⁵ and Al-Malky et al.¹⁸ recommended against screening patients exclusively with surveys and other subjective means, because patients included in their studies were unaware of hearing loss even after considerable progression. Of the four studies that made no recommendations,^{22,26,28,29} three primarily involved short courses of aminoglycoside. For example, the majority of patients studied by Ozcelik et al.²⁶ had received aminoglycosides for less than 2 months. The subjects studied by Mulheran et al.² received only one 14-day

course, whereas Forman-Franco et al.²⁸ followed patients through one hospitalization only.

Hearing Screening Measures

From the five studies that utilized high-frequency pure-tone audiometry (HFPTA) in addition to standard PTA, three recommended HFPTA in addition to standard PTA as a means of screening.^{18,19,27} Of the four studies that utilized otoacoustic emissions (OAEs), all found DPOAEs to be at least as useful for screening as PTA.^{18–20,24} Three of these studies formally recommended DPOAEs as a screening measure.^{19,20,24} Ozcelik et al.²⁶ utilized AABRs with or without PTA, but made no statement regarding the usefulness of AABRs for screening.

DISCUSSION

Hearing Screening Recommendations

Based on the high prevalence of SNHL in children with CF with a history of aminoglycoside exposure, routine hearing screenings should be implemented.^{18–21,23–25,27} The articles that made no recommendation either studied patients with low levels of exposure or reported no hearing loss over a short duration.^{22,26,28,29} Additionally, all four studies published in the last 5 years recommended hearing screening, possibly reflecting higher emphasis placed on the surveillance aspect of current patient-care paradigms.^{18–21} This need for screening is paramount, especially because children are less reliable than adults in recognizing and reporting hearing loss.^{18,25} Detecting SNHL early could result in the prompt discontinuation of the offending aminoglycoside if an alternative is available. Screening during and after treatment would be appropriate, and results should be compared to a pretreatment baseline. However, future studies should help define the specific point(s) in time to screen during therapy and the appropriate timeframe for the post-treatment screening. With regard to screening during treatment, a previous article studying aminoglycoside ototoxicity in adults recommended testing every 2 to 3 days to detect ototoxicity closest to when it first occurs.³⁰

HFPTA vs. Conventional PTA for Screening

Aminoglycoside-induced ototoxicity affects the basal turn of the cochlea resulting in high-frequency hearing loss. This suggests an important role for hearing testing at higher frequency thresholds. A prior study that compared the sensitivities of standard PTA and high frequency PTA in adults found that HFPTA identified 71.1% of ears with ototoxic change from aminoglycosides compared to only 37.8% when conventional PTA was used.³⁰ In fact, McRorie et al.²⁷ reported on the use of HFPTA in 1989, but HFPTA was not utilized again in studies in the CF patient population until 2001.²⁵ Interestingly, the study reporting the highest overall prevalence of SNHL at 28.6% (Piltcher et al.²³), and a study reporting a high percentage of hearing loss (43%) in a high exposure cohort (Cheng et al.²¹) did not carry out HFPTA, possibly underestimating the presence of

TABLE III.
Overview of Studies Included in the Systematic Review.

Author	Main Objectives	Patient Groups	Antibiotics	Hearing Screening	Follow-up	Results	Specific Recommendations
Al-Malky et al. ¹⁸	Determine ototoxicity in CF and most appropriate audiological tests; identify risk factors	CF: nonexposure, <10 courses, 10+ courses	IV amikacin, tobramycin, and gentamicin	Standard PTA and HFPTA; DPOAEs	N/A	24% with AG exposure had HL; 44% with high exposure had HL	HFPTA should be test of choice and performed at least annually
Al-Malky et al. ¹⁹	Determine prevalence of SNHL from AG use in CF patients	CF: nonexposure, <5 courses, 5+ courses	IV tobramycin and amikacin; possible prior gentamycin	Standard PTA and HFPTA; DPOAEs	N/A	21% with high exposure had HL; no HL in low exposure group	DPOAEs and HFPTA > standard PTA for high exposure patients on IV AGs
Martins et al. ²⁰	Determine prevalence of SNHL in CF; whether AGs play a role, and if DPOAEs are suitable tests for HL	CF: nonexposure, 1 course, 1-5 courses, >5 courses	IV or inhaled amikacin and gentamycin	Standard PTA; DPOAEs	N/A	11% had high frequency HL; 4% also had low frequency HL	Screening for CF patients (with or without aminoglycoside use); DPOAEs as useful as PTA
Cheng et al. ²¹	Determine prevalence of SNHL in CF; relationship of SNHL to antibiotic use (AGs and macrolides)	CF: IV-10 or fewer courses, >10 courses; nasal topical/inhaled/macrolides: 5 or fewer courses, >5 courses	IV, inhaled, and nasal topical unspecified aminoglycosides; macrolides	Standard PTA	N/A	14% had SNHL; 43% with >10 courses IV had HL; 23% with >5 courses topical nasal; 60% with >5 courses of macrolides	Routine and longitudinal evaluation in all CF patients with HFPTA and DPOAEs especially after receiving AGs and possibly after starting macrolides
Mulheran et al. ²²	Determine prevalence of SNHL after 2-week course of IV tobramycin; any difference in ototoxicity in daily vs. thrice-daily dosing; prevalence of SNHL at 6-8 weeks from treatment	CF: 1 course	IV tobramycin	Standard PTA and HFPTA	2 weeks; 6-8 weeks for a subset	0% HL; no difference in ototoxicity from daily or thrice-daily dosing	None
Piltcher et al. ²³	Determine prevalence of SNHL among patients with CF; factors associated with it including antibiotic use, and evaluation for need for a specific ENT-CF clinic	CF patients with or without AG use	Tobramycin, amikacin, gentamicin	Standard PTA	N/A	28.6% had SNHL	Screen with audiometry and consider OAE every 6-12 months as well as before and after treatment

TABLE III.
(Continued)

Author	Main Objectives	Patient Groups	Antibiotics	Hearing Screening	Follow-up	Results	Specific Recommendations
Stavroulaki et al. ²⁴	Determine if transient-evoked and distortion-product OAEs are more sensitive than PTA for SNHL in patients with CF	CF with exposure, CF without AG exposure, and healthy controls	Gentamicin; remote history of other AGs	Standard PTA; Transient evoked and DPOAEs	11–29 days	TEOAEs and DPOAEs were significantly affected at higher frequencies whereas PTA was normal	Screen with OAEs, particularly DPOAEs, regularly
Mulheran et al. ²⁵	Establish the incidence and severity of auditory deficit in CF patients	CF with exposure, CF without AG exposure, and healthy controls	Tobramycin, gentamicin	Standard PTA and HFPTA	N/A	3.7% pediatric subjects with SNHL	Screen but no specific method indicated
Ozcelik et al. ²⁶	Establish if hearing is affected in CF	CF with AG use up to 3 months, healthy controls	IV or inhaled amikacin, gentamicin, netilmicin, tobramycin	Standard PTA; AABRs	N/A	1/30 (3.3%) CF patients had SNHL per ABR and PTA	None
McRorie et al. ²⁷	Establish the utility of HF audiometry in detecting AG-induced elevation in pure-tone thresholds	CF with exposure, CF without AG exposure, and healthy controls	Amikacin, gentamicin, netilmicin, tobramycin	Standard PTA and HFPTA	N/A	Statistically significant elevation for PTA > 16 kHz in patients age < 19 years	High frequency audiometry may serve as useful measure of SNHL in CF
Forman-Franco et al. ²⁸	Assess overall incidence of HL—conductive and sensorineural—in CF patients (with and without AGs)	CF with AG in most recent hospitalization and CF nonexposure	Gentamicin, tobramycin	Standard PTA	N/A	1/42 patients had SNHL; no conductive HL; no greater incidence of HL in CF	None
Thomsen et al. ²⁹	Determine clinical ototoxicity of tobramycin and serum concentrations in CF patients	CF: 1 course	IV or IM tobramycin; history of inhaled tobramycin	Standard PTA	N/A	No conductive or SNHL; serum concentrations were within normal limits	None

AABR = automated auditory brainstem response; ABR = auditory brainstem response; AG = aminoglycosides; CF = cystic fibrosis; DPOAEs = distortion product otoacoustic emissions; ENT = ear, nose, throat; HF = high frequency; HFPTA = high-frequency pure-tone audiometry; HL = hearing loss; IM = intramuscular; IV = intravenous; N/A = not available; OAE = otoacoustic emissions; PTA = pure-tone audiometry; SNHL = sensorineural hearing loss.

SNHL. This may also be true for three of the studies^{26,28,29} that evaluated patients with standard PTA and did not detect significant hearing loss or remark on hearing screening recommendations.

Future Direction for Screening

HFPTA and DPOAEs are the most sensitive and reliable measures for hearing screening. The correlation between HFPTA and DPOAEs has been well-described and also demonstrated in two of the studies included in this review.^{18,19,31} Because both DPOAEs and HFPTA have been equally recommended by preexisting literature, recommending one method over the other is difficult without further evaluation and comparison of both methods in new screening protocol development studies. Regarding the feasibility of these options, Cheng et al.²¹ noted that DPOAE equipment is much more readily available in clinics than audiometers that are calibrated to high frequency. In addition, DPOAEs can be used in younger children and those who are unable to cooperate with audiometry.

The use of sensitive screening methods is essential for identifying hearing loss at its earliest stage, especially because even children with minimal hearing impairment (15–40 dB hearing loss) are considered to be at high risk for communicative and academic disabilities.^{32,33} In the study by Bess et al.,³³ the majority of children found to have minimal SNHL were not previously diagnosed with hearing loss during regular auditory screenings at school. As such, the most sensitive hearing screening method should be utilized in the CF patient population to prevent missing the children with mild SNHL, which may not be picked up on routine PTA.

Additional Observations

The studies highlighted several main risk factors for SNHL. High exposure to aminoglycosides was the most commonly reported major risk factor associated with SNHL.^{18,19,21} However, this relationship must not be overemphasized, because other key factors are at play, evidenced by the patients with no SNHL following many courses of aminoglycosides or those experiencing ototoxicity with fewer aminoglycoside courses.¹⁹ Most studies did not test for genetic mutations to fully evaluate if patients were, in fact, more susceptible to ototoxicity with fewer courses. Screening patients for mutations predisposing to aminoglycoside-induced ototoxicity should be explored separately, as it may also have an important role in prevention. Previously, a high penetrance of the mutated mitochondrial 1555A>G gene has been described in those with concurrent aminoglycoside exposure.³⁴ Screening for this gene was shown to be cost-effective, particularly in a population of European descent with a mutation frequency of 0.19% when compared to the cost of cochlear implantation and lifelong follow-up.³⁵ Screening for predisposing genes may lead to the avoidance of aminoglycosides if alternatives are available.

Several areas require further study. For example, the possible association of exposure of nebulized tobra-

mycin and SNHL in CF patients is concerning (Al-Malky et al.¹⁸). A preliminary study of 10 patients with cystic fibrosis given one dose of nebulized tobramycin showed no change on audiometry. However, more data for a lengthier treatment span are needed.³⁶ Furthermore, aminoglycosides may not be the only antibiotic group in whom exposure in CF patients may lead to SNHL. Cheng et al.²¹ studied macrolide-associated ototoxicity in CF patients and reported SNHL in up to 60% of the cohort with high exposure to the antibiotics. Further studies on macrolide-associated ototoxicity are clearly needed.²¹

Study Limitations

This review has several limitations. First, the heterogeneity of the studies did not allow us to conduct a meta-analysis. Studies had different inclusion and exclusion criteria and were mostly retrospective. The extent of exposure to aminoglycosides was variable or unknown. Two older studies^{25,26} utilized healthy individuals with no aminoglycoside exposure as their control group instead of including CF patients with no aminoglycoside exposure. One study (Martins et al.²⁰) did not exclude patients with predisposing factors for SNHL such as infections during the perinatal period, prematurity, low birth weight, and family history of SNHL. Finally, none of the studies compared ototoxicity for different aminoglycosides administered. Because rates of ototoxicity vary with different aminoglycosides,^{37,38} these data would have provided insight into the overall comparative relationship between various aminoglycosides and ototoxicity in children with CF.

CONCLUSION

Routine hearing screening in patients with cystic fibrosis treated with aminoglycosides has an important role in early detection of SNHL. HFPTA and DPOAEs have an important role in addition to classically employed conventional PTA. The data presented in this review encourage close follow-up of CF patients on aminoglycoside treatment and demonstrates the importance of developing specific screening protocols. Screening is vital for further interventions to minimize linguistic and cognitive developmental delays secondary to SNHL,³⁹ adding to the overall quality of life of CF patients. To reach this goal, further prospective studies that follow patients long term with HFPTA and OAEs in addition to conventional PTA are warranted.

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