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Original Article

The Effect of Aminoglycoside Use on the Hearing of Children with Cystic Fibrosis

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ABSTRACT

Aim: This study aimed to examine the effects of aminoglycoside (AG) antibiotics on hearing in children with cystic fibrosis (CF), to determine the risk factors for ototoxicity and the most appropriate audiological tests.

Materials and Methods: This was a retrospective observational study. Hearing tests of CF patients who were regularly followed up in our pediatric chest disease clinic and who had undergone hearing tests between January 2017 and December 2021 were evaluated. All patients underwent standard pure tone audiometry (PTA), extended high-frequency (EHF) PTA, and distortion product otoacoustic emission tests.

Results: This study included 65 patients, aged 5-18 years, who were diagnosed with CF in two groups, one being a study group treated with AG (n=40) and the other being a control group not exposed to AG (n=25). Ototoxicity was determined in 30% of the patients treated with intravenous AG and in 4% of the control group. There was seen to be a high risk of ototoxicity in those patients who received ≥8 cycles of AG. The hearing thresholds at high frequencies, such as 16,000 hertz, were determined to be higher in the right and left ears of the AG treated group in comparison to the control group (p=0.025, p=0.001). Ototoxicity was determined in 2 more patients at high frequency which could not be determined in PTA.

Conclusion: Patients with CF for whom AG antibiotics are frequently used should be followed up at certain intervals with EHF PTA, which is more sensitive, even when there are no complaints.

Keywords: Cystic fibrosis, aminoglycoside, hearing loss

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Introduction

Cystic fibrosis (CF) is a chronic disease with autosomal recessive transmission and usually has respiratory tract involvement. The frequency of *Pseudomonas aeruginosa (P. aeruginosa)* infection has been reported to be approximately 29% between the ages of 0 and 10 years, and 43% in the 11-17 years age group. Aminoglycoside (AG) group antibiotics are administered intravenously (IV) and in nebulized form in *P. aeruginosa* infections. One of the most common causes of ototoxicity is AG use, and when it is considered that these drugs are widely used in CF patients, it has been reported that these patients constitute a high-risk group with respect to ototoxicity.

AG antibiotics are often used in patients with CF (1). They are administered in systemic and nebulized form, especially in *P. aeruginosa* infections (1). The inhalation form of tobramycin is used for the eradication of chronic *P. aeruginosa* colonization in patients aged >6 years (2). IV forms are used in flare-ups of acute infection and the inhalation form of tobramycin is used for long-term eradication in children age ≥6 years. Hearing loss caused by AG depends on the cumulative dose (3,4). Hearing loss may emerge after a single dose, can be bilateral and irreversible, and may require cochlear implantation (5-7).

Ototoxic drugs generally cause hearing and/or vestibular problems (8,9). The prevalence of ototoxicity shows variability (10-12). Our aim in this study was to examine the effects of AG group antibiotics on hearing in children with CF and to determine the most suitable hearing test.

Materials and Methods

Our study was a retrospective cohort study at a pediatric pulmonology department between January 2017 and December 2021. Approval for this study was granted by the Ege University Medical Research Ethics Committee (decision no.: 23-3.IT/38, dated: 23.03.2023). The inclusion criteria of the patients were as follows; I) patients whose ages ranged from 5 to 18, and who were regularly followed up with a diagnosis of CF [This diagnosis was based on the European Cystic Fibrosis Society Patient Registry inclusion criteria and included patients who fulfilled the diagnostic criteria: (a) two sweat tests greater than 60 mmol/L chloride, and (b) one sweat test greater than 60 mmol/L chloride and DNA analysis with two identified disease causing CF mutations]. II) Hearing test given due to AG use. Those patients who received IV AG were determined as the study group and a control group of those who did not receive any AG was also formed. The exclusion criteria of patients were as follows; I) being between the ages of 0-5, II) patients who did not comply with the hearing tests or whose tests could not be evaluated [the standard pure tone audiometry (PTA), expanded high-frequency (EHF) PTA, and distortion product otoacoustic emission (DPOAE) tests were applied]. III) patients who were diagnosed with hearing problems due to another cause or had a family history of hearing loss were also excluded. There is no consensus in the literature on when to perform a hearing test after AG use. The hearing tests of all patients were evaluated retrospectively by an otolaryngologist. The patients were separated into 2 groups as follows: 40 patients who received IV AG antibiotic treatment and a control group of 25 patients who had never received IV AG. The American Speech-Language-Hearing-Association classification was used for hearing loss evaluation (13-15).

Amikacin was administered as the IV AG antibiotic and usage for 10 days was accepted as 1 cycle. Demographic and clinical characteristics were compared between the groups with and without ototoxicity. Chronic bacterial colonization of the respiratory tract was examined (16). The patients' sweat tests, genetic mutations, cumulative AG doses, and hearing test results were recorded.

Statistical Analysis

All data were analysed using Statistical Package for the Social Sciences (SPSS) software (version 25.0) (SPSS Inc., Chicago, USA). Descriptive analyses, including plots of mean and standard deviation or median (interquartile range-IQR), and minimum-maximum (min.-max.) of the audiological assessments, were performed. For the comparison of groups, the chi-square test was used for categorical data with or Fisher's exact test being used where appropriate, and the Mann-Whitney U test was used for continuous but non-normally distributed data. Further analysis of the risk factors of each of the audiological tests was performed using multivariable linear regression analysis in order to confirm which factors were significantly associated with ototoxicity. Spearman's rho correlation test was performed in order to test the correlation between the average lung function forced expiratory volume (FEV) 1% predicted and several IV AG courses received and between the type of AG used and the occurrence of HF hearing loss. The receiver operating characteristic (ROC) curve was used to determine the cumulative AG dose in those patients with ototoxicity. The cumulative AG area under the curve (AUC) was calculated from the ROC. All tests of significance were two-tailed, and p-values of <0.05 were considered statistically significant.

Results

PTA, EHF PTA, and DPOAE tests were performed on 65 (52.4%) of the 124 CF patients followed up in our clinic. Of

all of the patients, 54.3% were female and their median age was 110 (min.: 60-max.: 216) months. There were 40 Patients who used IV AG. Ototoxicity in PTA was determined in 12 (30%) patients who used IV AG. Hearing loss in PTA was determined in 8 (20%) of 40 patients using IV AG. The hearing losses were in the range of 6,000-8,000 hertz (Hz). Hearing loss was bilateral in 7 (87.5%) patients and unilateral in 1 (12.5%). The numbers of patients in both groups who were determined to have impairments in the audiological tests are shown in Figure 1.

In the comparisons of the DPOAE thresholds of both groups, the hearing thresholds at 1,000 and 4,000 Hz in both ears were determined to be significantly higher in those patients who used IV AG. Comparisons of DPOAE test hearing thresholds of those patients either receiving or not receiving AG are shown in Table I.

At 16,000 kilo-Hz, the median hearing threshold value was 15 (min.: 10-max.: 50) decibel (dB) in the right ear for those who used IV AG, 5 (min.: 0-max.: 20) dB in those who did not use IV AG (p=0.025), and a median of 20 dB in the left ear of those who used IV AG and 5.5 dB in those who did not use IV AG (p=0.001). Comparisons of the hearing thresholds in the standard PTA and EHF PTA tests are shown in Table II.

The 40 patients who received IV AG antibiotics were separated into two subgroups, namely those determined with ototoxicity and those without ototoxicity. The demographic and clinical characteristics were compared

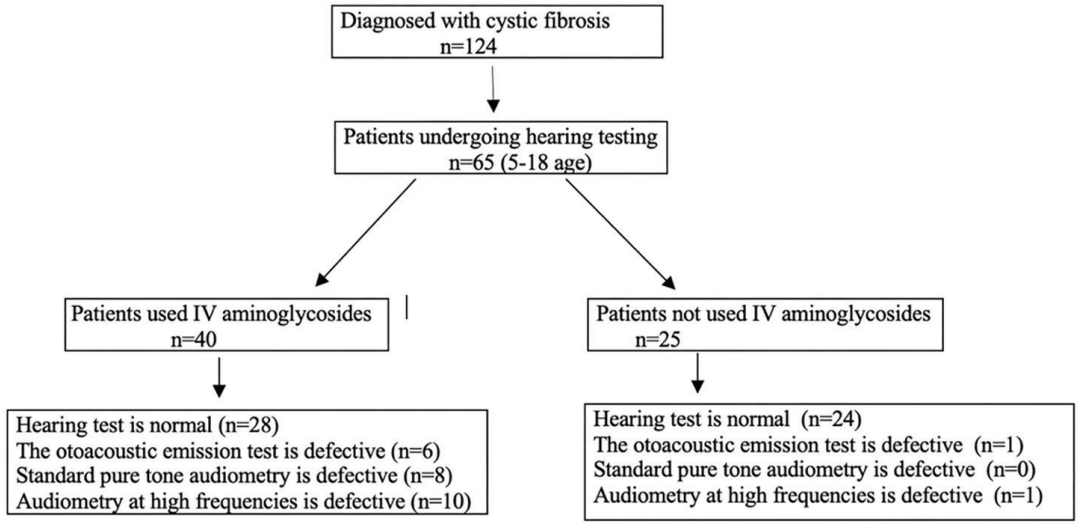

Figure 1. Hearing test results of patients
IV: Intravenously

Table I. Comparison of otoacoustic emission test hearing thresholds of patients receiving and those not receiving IV AG

Frequency (Hz)	Ear (median) (min.-max.)	Patients who used AG (n=40) (dB)	Patients who did not use AG (n=25) (dB)	p-value
1,000	Right Left	12.3 (5.2-15.9) 11.4 (6.1-14.3)	9.6 (5.6-12.8) 9.9 (7.9-10.3)	0.041 0.028
1,400	Right Left	8.1 (4.5-12.3) 8.7 (7.9-16.5)	10.2 (6.1-14.2) 9.2 (6.1-13.7)	0.312 0.224
2,000	Right Left	19.9 (3.2-14.3) 8.7 (3.4-15.1)	12.1 (6.9-13.7) 3.2 (9.2-17.1)	0.412 0.540
2,800	Right Left	10.9 (5.7-14.8) 7.8 (4.3-11.3)	12.1 (5.2-13.8) 6.5 (4.2-9.6)	0.379 0.265
4,000	Right Left	10.1 (2.5-16.1) 12.3 (6.8-14.9)	8.2 (6.1-13.6) 11.6 (9.4-13.5)	0.004 0.047
6,000	Right Left	11.2 (5.1-13.4) 10.7 (5.2-14.3)	8.7 (4.5-14.4) 9.5 (3.4-13.9)	0.103 0.329

dB: Decibel, Hz: Hertz, AG: Aminoglycoside, IV: Intravenous, min.-max.: Minimum-maximum

between these two groups, and no difference was determined with respect to their age or gender. The delta f508 mutation was seen more frequently in the group with ototoxicity, but this difference was not statistically significant (p=0.321). The m1555a> g mutation, which is associated with the development of ototoxicity in the literature, was examined in 5 (12.5%) patients in the group receiving IV AG and was not detected in any. *P. aeruginosa* colonization was determined at higher rates in the group with ototoxicity (p=0.004). In the examination of exposure to AG, the median cumulative AG dose was 354 mg/kg in the group with ototoxicity and 213 mg/kg in the group without ototoxicity (p=0.001). The number of AG cycles had a median of 6 (min.: 3-max.: 20) in the group with ototoxicity and in the group without ototoxicity (p=0.012).

The number of days of receiving AG was greater in the group with ototoxicity but this difference between the groups was not statistically significant (p=0.060). The use of nebulized tobramycin was determined to be 78.9% in the group with ototoxicity and 38.1% in the other group (p=0.030). The use of vancomycin was determined at a higher rate in the group with ototoxicity but this difference between the groups was not statistically significant (p=0.217). Spirometry values were compared between the groups, and the mean FEV1%, forced vital capacity %, and mid expiratory flow 25-75% values were lower in the group with ototoxicity but not to a level of statistical significance.

The risk factors for ototoxicity of the 40 patients using AG are shown in Table III. The use of nebulized tobramycin was found to be higher in the ototoxicity group (p=0.003). *P. aeruginosa* colonization, the number of AG cycles, and the cumulative AG dose were determined to be high. As a result of univariate and multivariate logistic regression analyses of these potential risk factors, only the cumulative AG dose and the number of cycles were determined to be risk factors for ototoxicity. For a cumulative AG dose of ≥390 mg/kg,

Table II. Comparison of standard pure tone audiometry and expanded high-frequency audiometry hearing thresholds of patients who received and those who did not receive IV AG

Frequency (Hz)	Ear (median) (min.-max.)	Patients who used AG (n=40) (dB)	Patients who did not use AG (n=25) (dB)	p-value
250	Right Left	5 (5-15) 5 (5-10)	6 (4-10) 4 (5-15)	0.063 0.208
500	Right Left	10 (5-30) 10 (5-20)	4 (5-15) 8 (5-25)	0.008 0.118
1,000	Right Left	12.5 (5-25) 12.5 (7.5-20)	10 (5-20) 15 (5-20)	0.430 0.567
2,000	Right Left	15 (10-40) 10 (15-30)	10 (7.5-30) 10 (5-20)	0.930 0.230
3,000	Right Left	7.5 (5-20) 10 (5-20)	12.5 (5-30) 12.5 (2.5-20)	0.268 0.531
4,000	Right Left	5 (2.5-10) 2.5 (0-7.5)	5 (2.5-7.5) 5 (2.5-10)	0.578 0.251
6,000	Right Left	15 (0-30) 10 (5-25)	10 (5-40) 7.5 (5-20)	0.411 0.620
8,000	Right Left	15 (5-40) 10 (5-35)	10 (5-20) 5 (0-20)	0.278 0.322
9,000	Right Left	10 (7.5-30) 7.5 (5-30)	10 (5-25) 5 (2.5-15)	0.211 0.256
10,000	Right Left	10 (0-40) 10 (5-45)	10 (5-25) 5 (2.5-12.5)	0.080 0.094
12,000	Right Left	12.5 (10-55) 10 (5-60)	10 (5-20) 7.5 (0-15)	0.112 0.233
14,000	Right Left	15 (10-55) 12.5 (5-40)	5(0-20) 5.5 (5-30)	0.003 0.008
16,000	Right Left	15 (10-50) 20 (5-70)	5 (0-15) 5.5 (0-25)	0.025 0.001

dB: Decibel, Hz: Hertz, AG: Aminoglycoside, IV: Intravenous, min.-max.: Minimum-maximum

the OR (95%) was determined to be 5.140 (min.: 4.801-max.: 10.388) (p=0.003). For the number of AG cycles ≥8, the OR (95%) was determined to be 8.333 (min.: 5.556-max.: 11.334) (p<0.001). Table IV shows the risk factors for hearing loss.

The cut-off value for the cumulative AG dose causing ototoxicity was calculated from the ROC curve as 390 mg/kg (AUC: 0.798, sensitivity 57%, specificity 82%). The cut-off value for the number of AG cycles causing ototoxicity was calculated from the ROC curve as 8 (AUC: 0.822, sensitivity 59%, specificity 81%), and the cut-off value for the number of days of AG was determined to be 45 (AUC: 0.792, sensitivity 48%, specificity 85%). The ROC curve of the AG dose, the number of cycles, and the days causing ototoxicity is shown in Figure 2.

Table III. Comparison of clinical features of patients with and without ototoxicity

n=40	**Ototoxicity (n=12)**	**Non-ototoxicity (n=28)**	**p-value**
Age (months) (median) (IQR) (min.-max.)	120 (60-216)	109 (36-214)	0.596
Sex (M/F)	7/5	15/13	0.809
Mutation, n (%) p.F508del	 7 (58.3)	 13 (46.4)	 0.321
Colonization, n (%) *P. aeruginosa* *S. aureus*	 9 (75.0) 3 (25.0)	 7 (25.0) 3 (10.7)	 0.004 0.074
IV AG exposure (median) (IQR) (min.-max.) Total dose AG (mg/kg) Total AG days Total AG cycles	 354 (44.6-2150) 40.0 (10.0-200.0) 6.0 (3.0-20.0)	 213 (18.1-1023) 20.0 (10.0-80.0) 2.0 (1.0-6.0)	 0.023 0.060 0.012
Nebulized tobramycin, n (%)	11 (91.6)	8 (38.1)	0.003
IV vancomycin, n (%)	10 (83.3)	13 (61.9)	0.217
Oral azithromycin, n (%)	5 (41.6)	6 (21.4)	0.425
Spirometry values (median) (IQR) (min.-max.) FEV1% FVC% FEV1/FVC%	 62.1 (20.2-82.1) 65.3 (38.4-86.2) 68.7 (29.1-87.0)	 64.4 (25.3-86.5) 68.2 (37.5-84.2) 69.4 (32.6-85.9)	 0.241 0.467 0.352

IQR: Interquartile range, min.-max.: Minimum-maximum, AG: Aminoglycoside, IV: Intravenous, FEV1: Forced expiratory volume in 1, FVC: Forced vital capacity, *S. aureus: Staphylococcus aureus, P. aeruginosa: Pseudomonas aeruginosa*

Table IV. Univariate and multivariable logistic regression analyses for ototoxicity

Variable	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age	0.013 (0.001, 0.029)	0.253		
Sex	0.019 (0.002, 0.054)	0.123		
P. aeruginosa colonization	0.823 (0.356, 0.788)	0.680		
Mutation (Delta f508)	0.549 (0.356, 1.223)	0.267		
Nebulized tobramycin	0.119 (0.056, 2.373)	0.061		
AG cycles >8 cycle	7.544 (0.229, 0.948)	0.001	8.333 (5.556, 11.334)	<0.001
Cumulative AG dose >390 mg/kg	7.272 (6.354, 8.343)	0.006	5.140 (4.801, 10.388)	0.003
IV vancomycin	0.378 (0.234, 1.755)	0.192		
Oral azithromycin use	0.017 (0.072, 0.924)	0.083		

AG: Aminoglycoside, IV: Intravenous, *P. aeruginosa: Pseudomonas aeruginosa*

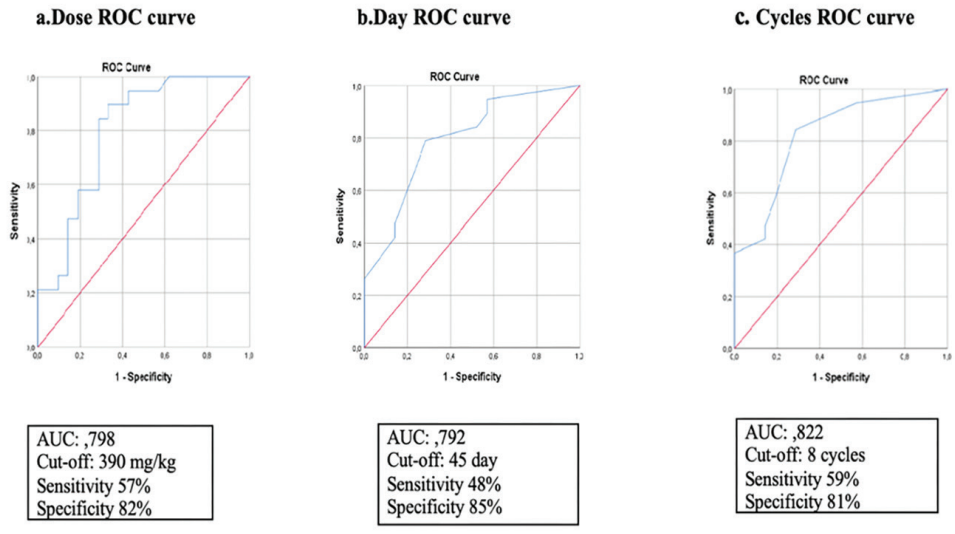

Figure 2. (a, b, c) ROC curve and AUC ROC of total aminoglycoside causing ototoxicity cumulative dose, number of days and cycles
ROC: Receiver operating characteristic, AUC: Area under the curve

Discussion

In the current study, ototoxicity was determined at a rate of 30% in the group receiving AG antibiotics. This rate has been reported in the literature as being 43% by Cheng et al. (17), 24% by Al-Malky et al. (18) and 17% by Martins et al. (19). In a report on the patient records of the Cystic Fibrosis Foundation, the prevalence of hearing loss was reported to be 1.3% in all children (<18 years) with CF (20). In a systematic review which examined studies of AG ototoxicity in children with CF between 1970 and 2014, sensorineural hearing loss was reported to vary between 0% and 29% in 44% of patients receiving 0-10 cycles of AG (21). In a screening of 9,939 children aged 0-6 years in France, the frequency of hearing loss was found to be 10.9% (22).

In the group receiving AG, a difference was found at 500 Hz compared to the control group, and at high frequencies, the difference was determined to be at 14,000 and 16,000 Hz. In a study by Weigert et al. (23), a difference was determined at 10,000 and 16,000 Hz. These differences at high frequencies suggest that there could be subclinical hearing loss even when the patients have no complaints.

There was no difference determined between the current study patients with or without ototoxicity with respect to their age, gender, or CF genetic mutations. *P. aeruginosa* colonization was determined at a significantly higher rate in the group with ototoxicity, which can be attributed to the frequent use of AG antibiotics in acute flare-ups of *P. aeruginosa* infections and the use of nebulized tobramycin in chronic *P. aeruginosa* colonization. The total AG dose, AG dose per kilo, and the number of AG cycles were determined to be significantly higher in the group with ototoxicity. The m1555a>g mutation, which has been associated with the development of ototoxicity in the literature, even at low-dose AG exposure, was not detected in any of the current study patients. Since our study was planned retrospectively, we could not examine the m1555a>g mutation in all patients. The use of nebulized tobramycin was higher in the group with ototoxicity. However, the difficulty in statistically determining the time and amount of usage by the patients is among the limitations of our study. The cumulative AG dose and the number of cycles were found to be risk factors for ototoxicity in the current study. This suggests that care should be taken in the repeated use of AG in patients with CF. Previous studies have also shown that AG ototoxicity is proportional to the number of cycles and the cumulative dose (24,25). In the current study, the use of IV AG for 8 cycles or more was found to increase the risk of ototoxicity. The results of the logistic regression analysis showed that the cumulative AG dose (7.5-fold) and number of cycles (8.7-fold) were risk factors for ototoxicity. Therefore, care should be taken in the repeated use of AG in CF patients. This rate was reported to be 10 cycles in a study by Geyer et al. (25). The minimum number of cycles was 3 AG cycles in the ototoxicity group. In another study of children receiving at least 3 cycles of AG, hearing loss was determined at a rate of 12.5% (26). In a study by Elson et al. (27), audiogram abnormalities were determined in 63% of patients exposed to IV AG, and in 53% of patients exposed to nebulized AG, and a strong correlation was reported between IV AG usage and hearing loss.

Study Limitations

The limitations of this study were its retrospective, cross-sectional design, and that there were no basal hearing tests of the patients before they received AG. However, a significant difference was determined between the results of those patients with CF who did not receive AG.

Conclusion

In conclusion, CF is a disease in which AG group antibiotics, known to have nephrotoxic and ototoxic side effects, are often used. Even when there are no clinical findings suggesting ototoxicity, such as hearing loss, the evaluation of CF patients by means of different hearing tests, especially HF audiometry, at regular intervals after the first use of AG, especially for those using high-dose (cumulative 390 mg/kg) AG antibiotics for more than 8 cycles, is important for the early detection of ototoxicity. When it is considered that the life expectancy of CF patients is being extended with newly developed treatment methods, hearing loss in these patients is extremely important and care must be taken in the use of AG antibiotics. As AG group antibiotics are frequently used in children with CF, these patients must be followed up in collaboration with the ear, nose, and throat clinic even when there are no complaints such as hearing loss or balance problems, and audiological tests should be performed via annual otoscopic examinations.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Medical Research Ethics Committee (approval no.: 23-3.IT/38, dated: 23.03.2023).

Informed Consent: This study was designed retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.M.Ö., G.T., M.F.Ö., H.D.Ş., M.B., F.Ç., G.K.Ö., B.G.D., F.G., E.D., Concept: M.M.Ö., H.D.Ş., F.G., E.D., Design: M.M.Ö., G.T., M.F.Ö. H.D.Ş., F.Ç., F.G., E.D., Data Collection and/or Processing: M.M.Ö., G.T., M.F.Ö., Analysis and/or Interpretation: M.M.Ö., G.T., B.G.D., Literature Search: M.M.Ö., M.B., G.K.Ö., Writing: M.M.Ö., M.F.Ö., G.K.Ö., F.G., E.D.

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References

1. Hewer SCL, Smyth AR, Brown M, et al. TORPEDO-CF study group. Intravenous versus oral antibiotics for eradication of Pseudomonas aeruginosa in cystic fibrosis (TORPEDO-CF): a randomised controlled trial. Lancet Respir Med. 2020; 8:975-86.
2. Ratjen F, Moeller A, McKinney ML, et al. Eradication of early *P. aeruginosa* infection in children <7 years of age with cystic fibrosis: The early study. J Cyst Fibros. 2019; 18:78-85.
3. Garinis AC, Cross CP, Srikanth P, et al. The cumulative effects of intravenous antibiotic treatments on hearing in patients with cystic fibrosis. J Cyst Fibros. 2017; 16:401-9.
4. Hirose K, Li SZ, Ohlemiller KK, Ransohoff RM. Systemic lipopolysaccharide induces cochlear inflammation and exacerbates the synergistic ototoxicity of kanamycin and furosemide. J Assoc Res Otolaryngol. 2014; 15:555-70.
5. Smyth AR, Bhatt J, Nevitt SJ. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. Cochrane Database Syst Rev. 2017; 3:CD002009.
6. Yelverton JC, Arnos K, Xia XJ, Nance WE, Pandya A, Dodson KM. The clinical and audiologic features of hearing loss due to mitochondrial mutations. Otolaryngol Head Neck Surg. 2013; 148:1017-22.
7. Zhu Y, Huang S, Kang D, et al. Analysis of the heteroplasmy level and transmitted features in hearing-loss pedigrees with mitochondrial 12S rRNA A1555G mutation. BMC Genet. 2014; 15:26.
8. Durrant JD, Campbell K, Fausti S, et al. American Academy of Audiology Position Statement and Clinical Practice Guidelines: ototoxicity monitoring. Am Acad Audiol. 2009.
9. Mulheran M, Degg C, Burr S, Morgan DW, Stableforth DE. Occurrence and risk of cochleotoxicity in cystic fibrosis patients receiving repeated high-dose aminoglycoside therapy. Antimicrob Agents Chemother. 2001; 45:2502-9.
10. Mishra SK, Saxena U, Rodrigo H. Hearing impairment in the extended high frequencies in children despite clinically normal hearing. Ear Hear. 2022; 43:1653-60.
11. McDermott JH, Mahaveer A, James RA, et al. Rapid point-of-care genotyping to avoid aminoglycoside-induced ototoxicity in neonatal intensive care. JAMA Pediatr. 2022; 176:486-92.
12. Musiek FE, Shinn J, Chermak GD, Bamiou DE. Perspectives on the pure-tone audiogram. J Am Acad Audiol. 2017; 28:655-71.
13. Beahan N, Kei J, Driscoll C, Charles B, Khan A. High-frequency pure-tone audiometry in children: a test-retest reliability study relative to ototoxic criteria. Ear Hear. 2012; 33:104-11.
14. Jedrzejczak WW, Pilka E, Skarzynski PH, Olszewski L, Skarzynski H. Tone burst evoked otoacoustic emissions in different age-groups of schoolchildren. Int J Pediatr Otorhinolaryngol. 2015; 79:1310-5.
15. American Speech-Language-Hearing Association. Audiologic Management of individuals receiving cochleotoxic drug therapy. ASHA. 1994:11-9.
16. Salsgiver EL, Fink AK, Knapp EA, et al. Changing epidemiology of the respiratory bacteriology of patients with cystic fibrosis. Chest. 2016; 149:390-400.
17. Cheng AG, Johnston PR, Luz J, et al. Sensorineural hearing loss in patients with cystic fibrosis. Otolaryngol Head Neck Surg. 2009; 141:86-90.

18. Al-Malky G, Dawson SJ, Sirimanna T, Bagkeris E, Suri R. High-frequency audiometry reveals high prevalence of aminoglycoside ototoxicity in children with cystic fibrosis. J Cyst Fibros. 2015; 14:248-54.

19. Martins LM, Camargos PA, Becker HM, Becker CG, Guimarães RE. Hearing loss in cystic fibrosis. Int J Pediatr Otorhinolaryngol. 2010; 74:469-73.

20. Cystic Fibrosis Foundation. 2021 annual report. Cystic Fibrosis Foundation; 2021. Available from: https://www.cff.org/about-us/2021-annual-report.

21. Farzal Z, Kou YF, St John R, Shah GB, Mitchell RB. The role of routine hearing screening in children with cystic fibrosis on aminoglycosides: a systematic review. Laryngoscope. 2016; 126:228-35.

22. Milcent K, Gassama M, Dufourg MN, Thierry X, Charles MA, Bois C. Child health screening program in French nursery schools: results and related socioeconomic factors. Front Pediatr. 2023; 11:1167539.

23. Weigert LL, Piltcher OB, Procianoy EFA, Buss CH, Menna Barreto SS. Audiometria em frequências ultra-altas em pacientes submetidos ao uso de ototóxicos. Brasília Med. 2013; 50:6-15.

24. Al-Malky G, Suri R, Sirimanna T, Dawson SJ. Normal hearing in a child with the m.1555A>G mutation despite repeated exposure to aminoglycosides. Has the penetrance of this pharmacogenetic interaction been overestimated? Int J Pediatr Otorhinolaryngol. 2014; 78:969-73.

25. Geyer LB, Menna Barreto SS, Weigert LL, Teixeira AR. High frequency hearing thresholds and product distortion otoacoustic emissions in cystic fibrosis patients. Braz J Otorhinolaryngol. 2015; 81:589-97.

26. Solmaz F, Gündoğdu E, Akduman D, Haksever M, Dikici O, Ünal F. Does amikacin treatment cause subclinical hearing loss in patients with cystic fibrosis? Toxicol Rep. 2016; 3:401-4.

27. Elson EC, Meier E, Oermann CM. The implementation of an aminoglycoside induced ototoxicity algorithm for people with cystic fibrosis. J Cyst Fibros. 2021; 20:284-7.