



## Does amikacin treatment cause subclinical hearing loss in patients with cystic fibrosis?



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### ABSTRACT

**Introduction:** Aminoglycosides (AGs) have been widely used for potential life-threatening bacterial infections. Although AGs are well known for their ototoxic side effects, some AGs such as amikacin are considered less harmful to auditory functions; thus, auditory monitoring is mostly neglected during treatment with these drugs.

**Objective:** To reflect the potential auditory hazards of repeated amikacin use on the patients with cystic fibrosis (CF).

**Method:** 32CF patients with prior exposure to at least 3 courses of amikacin (the CF group) and 35 non-CF patients visiting the outpatient clinic with any complaint other than hearing loss and no history of treatment with any AG(the control, or C group) were compared with pure-tone audiometry(PTA). The diagnosis of CF was made by Nanoduck sweat test.

**Results:** The average age of the participants were  $8.25 \pm 2.76$  years in the CF group and  $8.58 \pm 2.00$  years in the C group (ranging from 5 to 13 years). 29 (43.28%) of the cases were female and 38 (56.71%) were male. Clinical SNHL(sensorineural hearing loss) was detected in 4 of the 32 subjects in the CF group. None of the subjects in the C group exhibited clinical SNHL. There was no statistically significant difference between the groups with regard to presence or absence of clinical SNHL ( $p > 0.05$ ). However, hearing levels of the CF group were around 20 dB(decibel) HL(hearing loss), whereas hearing levels of the C group were around 5 dB. This difference was statistically significant for the pure tone averages of both all frequencies and speech frequencies ( $p < 0.05$ ).

**Conclusion:** Repetitive exposure to AGs can cause permanent, although mild, sensorineural hearing loss. For prevention, hearing status of the patient should be closely monitored and treatment of choice should be precisely tailored according to the audiological evaluation. This is especially important in patients with CF who frequently experience medical conditions necessitating AGs use.

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### 1. Introduction

Aminoglycosides (AGs) are bactericidal antibiotics which have been widely used for potentially life-threatening bacterial infections since their invention in 1944 [1]. They are especially important in certain medical conditions such as cystic fibrosis (CF), mainly due to the high bactericidal activity against *Pseudomonas aeruginosa*, the ability to reach high concentrations in respiratory secretions, and the synergistic effect with beta-lactam antibiotics

[2,3]. They are also readily available worldwide, since they are cost-effective and easy to produce in large amounts. These advantages, however, are limited by the ototoxicity of this class of drugs, which is aggravated by their repeated use in these patients. Clinical studies report a rate of sensorineural hearing loss through a range of 0–17% in CF patients [4,5]. Newer AGs such as amikacin and netilmicin are considered less harmful to auditory functions; thus, in most instances auditory monitoring is neglected by physicians responsible for treating these patients. This study presents auditory evaluation of pediatric CF patients who had been repeatedly treated with amikacin and compares it to that of healthy children of the same age group.

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**Table 1**  
Comparison of the hearing results between groups.

Variables	L(left), R(right)	CF(Cystic Fibrosis)	C(Control)	P value
Audiometry mean(500, 1000, 2000,4000Hz > 25 dB)	L	4/32	0/35	>0.05
	R	4/32	0/35	>0.05
Audiometry mean(500, 1000, 2000, 4000Hz > 15 dB)	L	21/32	0/35	<0.05
	R	30/32	0/35	<0.05

**Table 2**  
Comparison of the mean hearing levels.

Variables	L(left), R(right)	CF(Cystic Fibrosis) (Mean ± SD)	C(Control) (Mean ± SD)	P value
Audiometric mean of all frequencies	L (dB)	17.96 ± 5.27	5.86 ± 2.58	0.00004
	R(dB)	21.39 ± 4.20	5.43 ± 2.78	0.01018
Audiometric mean of 500, 1000, 2000, 4000 Hz frequencies	L(dB)	16.25 ± 4.91	5.32 ± 2.71	0.00048
	R(dB)	20.52 ± 4.52	5.15 ± 2.80	0.00366

**Table 3**  
The Mean ± SD of 250, 500, 1000, 2000, 4000 and 8000 Hz frequencies in the CF group.

Case	250 Hz		500 Hz		1000 Hz		2000 Hz		4000 Hz		8000 Hz	
	Left (dB)	Right(dB)	Left (dB)	Right(dB)	Left (dB)	Right(dB)	Left (dB)	Right(dB)	Left (dB)	Right(dB)	Left (dB)	Right(dB)
1	18	22	18	21	15	22	17	24	28	25	30	25
2	20	27	21	24	10	36	16	30	22	32	25	33
3	14	25	10	25	17	22	16	21	18	20	20	23
4	13	25	10	25	15	16	15	17	15	21	21	20
5	22	20	22	24	20	16	16	13	21	22	24	22
6	20	21	27	20	21	23	23	21	29	25	31	24
7	21	20	20	19	14	17	13	18	15	22	16	23
8	16	18	15	15	15	18	11	17	17	21	20	22
9	17	19	15	23	13	17	15	20	16	26	20	24
10	16	14	14	23	16	12	15	15	20	17	22	20
11	22	13	19	25	13	13	11	12	24	16	27	18
12	10	22	10	23	12	18	10	19	16	22	18	21
13	30	19	30	18	27	17	25	19	27	21	29	21
14	15	23	14	25	12	16	12	20	15	22	18	24
15	21	25	21	24	20	15	23	15	22	19	22	23
16	26	25	25	26	26	25	25	25	26	25	30	26
17	15	20	14	15	15	15	18	25	17	18	20	20
18	13	20	11	15	15	15	16	22	20	18	23	20
19	18	21	14	22	15	15	22	20	21	18	25	20
20	15	22	12	24	13	15	16	17	17	18	20	20
21	12	19	11	19	23	16	15	18	17	18	20	19
22	11	20	10	18	13	25	15	21	22	18	23	18
23	12	21	12	21	13	20	13	22	17	18	19	19
24	14	21	15	20	12	21	16	22	16	28	18	25
25	17	19	16	17	14	17	18	18	18	20	22	22
26	17	18	12	18	15	16	13	18	14	22	17	24
27	12	18	10	15	14	17	13	16	15	25	17	23
28	19	20	19	21	20	19	18	18	20	22	20	23
29	21	20	20	18	23	19	21	18	22	20	22	21
30	27	26	25	25	25	25	25	25	26	26	32	27
31	26	26	25	24	25	24	25	25	26	26	26	26
32	20	23	19	22	17	18	18	16	19	19	21	21
Mean ± SD	17.00 ± 4.81	21.56 ± 3.34	16.18 ± 5.77	21.50 ± 3.54	16.06 ± 4.68	19.87 ± 5.86	16.50 ± 4.50	20.18 ± 3.97	19.62 ± 4.44	22.25 ± 4.10	22.43 ± 4.76	23.00 ± 3.66

## 2. Material and methods

### 2.1. Groups

The study design was approved by the ethics committee of the study center. This study was designed prospectively with two groups. A total of 67 subjects were enrolled. The first group (*the CF group, or cystic fibrosis*) was composed of 32CF patients who had history of at least three courses of intravenous treatment with amikacin 10–30 mg/kg daily for at least 10 days per episode, mostly because of pulmonary infections but not for meningitis. The second group (*the control group, or C group*) consisted of 35 children who had visited the pediatric outpatient clinic for any reason other than hearing loss and had no history of exposure to any AGs.

### 2.2. Diagnosis of CF

For the diagnosis of CF, Nanoduck sweat test was performed three times to every patient in the CF group. The test was accepted as positive, suspicious and negative when the result was over 80 mmol/l, between 60 and 80 mmol/l and under 60 mmol/l respectively. Sweat test results ranged between 50 and 122 mmol/l. An informed consent was taken from the patient's parents and a protocol was filled.

### 2.3. Auditory evaluation

All subjects were examined otoscopically (HEINE® K-100 Diagnostic Oscope, HEINE Optotechnic, Herrsching, Germany) to

**Table 4**  
The Mean ± SD of 250, 500, 1000, 2000, 4000 and 8000 Hz frequencies in the C group.

Case	250 Hz		500 Hz		1000 Hz		2000 Hz		4000 Hz		8000 Hz	
	Left (dB)	Right(dB)	Left (dB)	Right(dB)	Left (dB)	Right(dB)	Left (dB)	Right(dB)	Left (dB)	Right(dB)	Left (dB)	Right(dB)
1	2	3	3	0	3	3	2	3	4	5	6	8
2	2	5	4	2	3	3	5	5	5	5	7	7
3	0	2	5	0	5	2	6	2	4	4	5	5
4	4	5	5	4	5	5	7	6	4	5	5	6
5	0	3	0	3	5	3	4	4	5	5	5	5
6	0	0	3	0	3	0	6	5	5	5	7	5
7	5	4	4	4	5	5	5	5	6	5	8	9
8	4	0	0	0	0	3	0	0	3	3	5	3
9	4	8	5	8	3	10	5	9	10	11	9	12
10	12	13	9	10	10	11	9	11	9	11	11	13
11	8	9	5	8	6	8	5	6	5	8	5	8
12	8	2	5	2	5	6	5	4	7	3	7	4
13	7	3	5	2	5	4	3	3	6	5	7	5
14	6	6	6	5	4	5	5	5	5	5	5	6
15	5	4	4	6	6	5	5	6	7	8	7	9
16	11	10	10	9	10	8	11	9	11	10	14	10
17	6	5	5	5	6	5	5	7	7	6	10	7
18	8	4	8	4	6	3	9	5	9	5	9	5
19	5	5	5	4	5	3	6	3	5	5	8	7
20	4	5	0	5	4	5	0	5	7	5	8	6
21	0	0	0	0	0	2	0	3	0	5	4	6
22	5	5	3	5	6	4	5	4	7	5	9	8
23	6	5	5	6	5	7	5	7	6	5	5	6
24	5	0	5	0	6	5	4	6	5	6	8	6
25	0	0	0	0	5	4	5	3	8	6	7	6
26	8	3	6	3	5	3	6	5	9	6	11	9
27	10	9	8	7	8	8	6	4	5	4	9	8
28	10	8	8	7	5	8	5	6	5	7	9	3
29	4	5	4	5	5	6	5	7	8	6	10	10
30	5	7	5	8	5	6	5	6	5	5	8	11
31	4	6	4	5	5	8	6	8	7	7	8	8
32	8	7	6	6	8	6	8	8	11	8	14	10
33	5	3	0	0	0	0	4	5	2	3	5	4
34	8	3	6	5	6	4	10	5	10	6	12	9
35	6	9	5	9	5	8	8	7	8	9	11	11
Mean ± SD	7.00 ± 2.97	5.00 ± 3.74	5.46 ± 3.01	4.66 ± 3.55	5.26 ± 2.60	5.06 ± 2.56	5.93 ± 3.10	5.58 ± 2.31	6.87 ± 2.60	5.88 ± 2.11	8.76 ± 2.84	7.11 ± 2.86

prove an intact tympanic membrane. All subjects were evaluated by pure-tone audiometry (PTA). PTA tests were performed in standard soundproof cabins. Air-bone conduction thresholds were assessed at frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz.

The pure-tone average hearing levels were calculated both at all frequencies (averages of the full frequency range between 250 and 8000 Hz) and speech frequencies (averages of 500, 1000 and 2000 Hz). Clinical sensorineural hearing loss (SNHL) was defined as pure-tone average of the hearing levels at 500, 1000, 2000 and 4000 Hz over 25 dB HL.

**2.4. Exclusion criteria**

Exclusion criteria for both groups were the history of chronic middle ear disease, prior ear surgery, birth trauma, familial deafness, diseases causing hearing loss such as meningitis, history of noise exposure and concurrent use of other known ototoxic agents. Additional exclusion criteria for the C group were exposure to any AG antibiotic and any diagnosis or suspicion of CF.

**2.5. Data evaluation**

All data were evaluated by using SPSS® version 11.0.1 (SPSS Inc. Chicago, IL, USA). Student’s *t*-test, Fisher’s Exact test and Chi-Square Test were used for statistical analysis. *p* < 0.05 was accepted as significant.

**3. Results**

In this study, a total of 67 cases was evaluated in two groups: the CF (Cystic Fibrosis) group (n:32) and the C (Control) group (n:35). The average age of the participants were 8.25 ± 2.76 years in the CF group and 8.58 ± 2.00 years in the C group (Ranging from 5 to 13 years). 29 (43.28%) of the cases were female and 38 (56.71%) were male. Demographic distribution of the two groups showed no statistical significance (*p* > 0.05).

For the CF group, all of the 32 subjects were evaluated with PTA. Clinical SNHL was detected in 4 of them on both ears; of these 4 patients, 2 had been exposed to more than 8 courses of amikacin, and the other 2 patients had received 7 and 5 courses respectively. Of the control group, PTA was performed in all of the 35 subjects. None of the subjects in the C group exhibited clinical SNHL for neither ear.

There was no statistically significant difference between the groups at the frequencies of 500, 1000, 2000 Hz with regard to presence or absence of clinical SNHL (*p* > 0.05) (Table 1). Pure-tone averages were higher than 15 dB in 30 right and 21 left ears of 32 patients in the CF group, whereas none of the ears in the C group of patients exhibited this phenomenon (*p* < 0.05) (Table 1).

During statistical analysis of hearing levels of the normal ears with PTA, we realized that mean pure-tone average hearing levels of the CF group were around 20 dB, whereas that of the C group were around 5 dB. This difference was statistically significant for the pure tone averages of both all frequencies (250– 8000 Hz) and speech frequencies (500–2000 Hz) (*p* < 0.05) (Table 2).

Audiometric mean of all frequencies and speech frequencies in patients with CF and participants of C group were shown in Tables 3 and 4.

#### 4. Discussion

CF patients are repetitively exposed to AGs throughout their lives due to frequent exacerbations of pulmonary infections which are mainly pseudomonas. Moreover, doses of the antibiotics, even when they are given in combination, should be high in order to be efficacious in these patients [6]. These factors increase the risk of ototoxicity seen with this class of antibiotics.

Although AGs are frequently used drugs, there are few studies which detected hearing loss in these patients. Rates of sensorineural hearing loss were reported in a range between 0% and 62% depending on the AG used, the number of courses given, the amount of cumulative dose, and the method used to detect hearing loss (i.e. PTA vs DPOAE-Distorsion Product Otoacoustic Emission vs ABR-Auditory Brainstem Response) [5,16]. Whereas former studies conducted with PTA had detected SNHL rates of up to 6% [4,5,9], more recent studies conducted with newer, more sensitive techniques such as high frequency PTA, DPOAE and ABR demonstrated higher prevalences, especially if patients had been given AGs repeatedly [14,15].

Studies demonstrate that AG ototoxicity is directly correlated with the number of treatment courses, hence the cumulative dose [10,13,17]. One recent systematic review including twelve studies conducted between 1979 and 2014 reported an overall SNHL prevalence of 0–29% in CF children treated with aminoglycosides; this was increased to 44% if the number of treatment courses was more than 10 [18]. Also in our study 2 of the 4 patients in the CF group with SNHL had been exposed to more than 8 courses of amikacin.

The type of hearing loss due to AG treatment is mostly seen at high frequencies [19], so a high frequency PTA may demonstrate hearing loss at an earlier stage. Also some studies suggest an earlier detection of cochlear damage with DPOAE, which is also useful in young children unsuitable for PTA [7,10]. We were able to perform conventional PTA (250–8000 Hz) to every patient.

An important consideration in the evaluation of these patients by means of hearing thresholds is what should be accepted as “hearing loss”. If 25 dB HL was accepted as SNHL, none of our patients would have SNHL; so, the rate of hearing loss in our amikacin-treated CF patients would be 0%. However, hearing thresholds of these patients were significantly higher than that of the control group consisting of healthy children with no exposure to any AG. Thus, it can be safe to say that at least 3 courses of amikacin treatment causes a subclinical sensorineural hearing loss in CF patients. However, hearing loss may be a result of many variables, even CF itself may be a factor. Especially in a setting that does not include a real control group (which should, in our study, consist of CF patients with no exposure to any AG), this cannot be predicted clearly. But since it would be very difficult to comprise such a control group because it is hard to encounter such patients in real life, our control group consisted of healthy children. This is a major limitation of our study.

#### 5. Conclusion

Repetitive exposure to aminoglycoside antibiotics can cause permanent, although mild, sensorineural hearing loss. For prevention, hearing status of the patient should be closely monitored and

treatment of choice should be precisely tailored according to the audiological evaluation. This is especially important in patients with cystic fibrosis who frequently experience medical conditions necessitating the use of aminoglycosides.

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#### Conflict of interest

None.

#### Transparency document

The Transparency document associated with this article can be found in the online version.

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