Evidence-Based Systematic Review: Drug-Induced Hearing Loss—Gentamicin

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Introduction

Introduced in 1963, gentamicin is commonly used for the treatment of infections caused by gram-negative and some gram-positive bacteria (Singhal, Sharma, & Singhal, 1992). It has been studied in the treatment of peritonitis (Gendeh et al., 1993), early-onset sepsis in neonates (Agarwal, Rastogi, Pyati, Wilks, & Pildes, 2002), urinary tract infection (Chong et al., 2003), febrile episodes in neutropenic patients (El Bakri, Pallett, Smith, & Duncombe, 2000), osteomyelitis (Haydon, Blaha, Mancinelli, & Koike, 1993), and otitis media (Indudharan, Valuyeetham, & Raju, 2005). Gentamicin is often used in combination with penicillin, vancomycin, or rifampin (Edson & Terrell, 1987). Like other aminoglycosides, gentamicin use is associated with nephrotoxicity, cochleotoxicity, and vestibulotoxicity. Reported hearing loss from gentamicin-induced cochleotoxicity ranges from 0% to 27%; however, these findings should be considered with caution because of difficulties with defining the criteria for ototoxicity and variability in audiological measurement across studies.

The purpose of this systematic review is to evaluate the incidence and persistence of gentamicin-induced hearing loss and to determine the effects of dosage, route of administration, schedule of administration, and concomitant ototoxic drug use on the incidence of hearing loss. The intent is that audiologists will use information from this review to better understand the effects of gentamicin regimens on hearing and to advise physicians on the potential ototoxic

effects of gentamicin. Audiologists also should consider this information when determining an appropriate audiological monitoring schedule and treatment options as necessary.

This systematic review is one of a series of three systematic reviews, each addressing a separate aminoglycoside drug (gentamicin, tobramycin, and amikacin). Additional information pertaining to the objectives of these systematic reviews and procedures for searching, sifting, and appraising the evidence is included in the introductory paper titled Evidence-Based Systematic Review (EBSR): Drug-Induced Hearing Loss—Aminoglycosides.

The following six clinical questions were targeted for this review:

1. What is the likelihood of persons treated with gentamicin developing hearing loss?
2. What is the persistence of hearing loss in persons treated with gentamicin?
3. Is the likelihood of gentamicin-induced hearing loss affected by dosage?
4. Is the likelihood of gentamicin-induced hearing loss affected by route of administration?
5. Is the likelihood of gentamicin-induced hearing loss affected by schedule of administration?
6. Is there evidence of a synergistic effect on hearing loss if multiple ototoxic drugs (i.e., aminoglycosides, antineoplastics) are taken concomitantly with gentamicin?

Results

Twenty studies were identified for inclusion in this review. Table 1 highlights the clinical questions addressed by these studies.

Table 1. Included studies and corresponding clinical questions.

Study	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
Agarwal et al., 2002	X		X	X	X	
Bailey et al., 1996	X		X	X		
Chayasirisobhon et al., 1996	X	X	X			
Cheung et al., 1990	X					X
Chong et al., 2003	X		X	X	X	
El Bakri et al., 2000	X					
Elhanan et al., 1995	X	X	X	X	X	
Fausti et al., 1999	X					
Gendeh et al., 1993	X			X	X	
Gendeh et al., 1991	X			X		
Haydon et al., 1993	X	X		X		
Indudharan et al., 2005	X		X	X	X	
Kharkheli et al., 2007	X		X	X	X	
Kos et al., 2003	X	X		X		
Nordström et al., 1990			X		X	
Prins et al., 1994	X		X	X	X	
Raz et al., 1995	X		X	X	X	
Singhal et al., 1992			X	X	X	
Stavroulaki et al., 2002	X		X	X	X	
Whatley et al., 2006	X		X	X	X	

Study Quality and Participant Characteristics

Ten controlled trials were included in the review, along with nine case series and one case control. Of these studies, 11 investigated the effects of gentamicin on the hearing of adults, and six explored the effects on children. Two studies examined both children and adults, and one study failed to report participants' ages. Study participants received gentamicin for infection or fever. Medical diagnoses of participants included infection of the kidneys, urinary tract, lung, and nose/throat, peritonitis, osteomyelitis, otitis media, rhinosinusitis, leukemia, and cystic fibrosis (see Table 2).

Methodological quality of the included studies was assessed on the basis of criteria reported elsewhere in the introductory paper (Evidence-Based Systematic Review: Drug-Induced Hearing Loss—Aminoglycosides) of the series. Two authors, blinded to one another's results, evaluated each study on six quality criteria (see Table 2), with 83% reliability between reviewers. Quality scores of all included studies ranged from 2 to 6 out of a possible score of 6. Two studies (Gendeh, Said, Gibb, Aziz, & Zahir, 1991; Kharkheli, Kevanishvili, Maglakelidze, Davitashvili, & Schacht, 2007) received the highest quality rating (6/6). The majority of studies (85%) received a score of 4 or 5 out of 6. Only three studies (Singhal et al., 1992; Fausti et al., 1999; Nördstrom, Ringberg, Cronberg, Tjernström, & Walder, 1990) received a score of 3 or below. Studies commonly failed to report assessor blinding, stratify results by administration regimen, or assess/report participants' pre-treatment hearing status.

Table 2. Methodological quality and patient characteristics of the 21 included studies.

Study	Study design	Medical diagnosis	Mean age yrs (range)	Sample clearly defined	Pre-hearing status reported	> 80% follow up	Outcome measure(s) clearly defined	Assessors blinded	Same treatment regimen or stratified	Quality score
Agarwal et al., 2002	Trial	Infection	Neonates	Y	N	Y	Y	N	Y	4/6
Bailey et al., 1996	Trial	Infection	32 (18–68)	Y	N	N	Y	Y	Y	4/6
Chayasirisobhon et al., 1996	Case series	Infection	Neonates	Y	N	Y	Y	N	Y	4/6
Cheung et al., 1990	Case series	Infection	78 (67–88)	Y	Y	Y	Y	N	N	4/6
Chong et al., 2003	Trial	Infection	Infants	Y	Y	Y	Y	N	N	4/6
El Bakri et al., 2000	Case control	Cancer	(19–75)	Y	N	Y	Y	N	Y	4/6
Elhanan et al., 1995	Trial	Infection	6 (< 1–16)	Y	Y	Y	Y	N	Y	5/6
Fausti et al., 1999	Case series	NR	NR	N	Y	Y	Y	N	N	3/6
Gendeh et al., 1993	Case series	Infection	49 (36–58)	Y	Y	Y	Y	N	Y	5/6
Gendeh et al., 1991	Case series	Infection	49	Y	Y	Y	Y	Y	Y	6/6
Haydon et al., 1993	Case series	Infection	48 (18–79)	Y	N	N	Y	Y	Y	4/6

(continued)

Table 2 (continued)

Study	Study design	Medical diagnosis	Mean age yrs (range)	Sample clearly defined	Pre-hearing status reported	> 80% follow up	Outcome measure(s) clearly defined	Assessors blinded	Same treatment regimen or stratified	Quality score
Indudharan et al., 2005	Trial	Infection	(2–84)	Y	Y	Y	Y	N	Y	5/6
Kharkheli et al., 2007	Trial	Infection	29 (18–65)	Y	Y	Y	Y	Y	Y	6/6
Kos et al., 2003	Case series	Infection	Infants	Y	Y	Y	Y	N	N	4/6
Nordström et al., 1990	Trial	Infection	58 (adults)	Y	N	N	Y	Y	N	3/6
Prins et al., 1994	Trial	Infection	54 (adults)	Y	Y	N	Y	Y	N	4/6
Raz et al., 1995	Trial	Infection	53 (16–82)	Y	Y	Y	Y	N	N	4/6
Singhal et al., 1992	Trial	Infection	(25–46)	Y	N	Y	N	N	N	2/6
Stavroulaki et al., 2002	Case series	Cystic fibrosis/ infection	8 (5–14)	Y	Y	Y	Y	Y	N	5/6
Whatley et al.,2006	Case series	Infection	42 (4–74)	Y	Y	Y	Y	N	Y	5/6

Note. NR = not reported.

Clinical Question 1: What Is the Likelihood of Persons Treated With Gentamicin Developing Hearing Loss?

Eighteen studies reported the incidence of hearing loss following gentamicin treatment (see Table 3). The incidence ranged from 0% to 58%. One study (Fausti et al., 1999) calculated incidence of hearing loss by percentage of ears instead of by individual and reported an incidence rate of 34%. Fourteen of the studies assessed hearing using pure-tone audiometry, five studies used brainstem auditory-evoked potentials (BAEP), and three used otoacoustic emissions (OAE). Four of the studies used more than one type of instrument (see Table 3). The criteria used by each investigator to characterize the presence or absence of hearing loss varied across studies, with 17 different definitions used.

Three studies (Bailey et al., 1996; Fausti et al., 1999; Kharkheli et al., 2007) assessed participants with high-frequency audiometry (> 8 kHz). Of these, only one (Bailey et al., 1996) analyzed data to determine the incidence of hearing loss at high frequency levels and noted that 24% (10/41) of the participants demonstrated hearing loss in two or more adjacent frequencies based on serial audiometry at 10–18 kHz.

The heterogeneity of the included studies, particularly the variability in hearing loss criteria, did not allow for a reliable calculation of the pooled incidence of hearing loss for the purposes of a meta-analysis. Additional factors such as medical diagnosis, age, and study design also contributed to the differences among the included studies. Although these differences did not allow for combining of the findings from the studies, the results can be further stratified along these factors in order to note trends in the data. Because Fausti et al. (1999) reported the incidence of hearing loss by number of ears and not by number of participants, it was not included in these additional analyses. Furthermore, for the two studies that examined the incidence of ototoxicity based on various definitions (Kharkheli et al., 2007; Whatley, Chandra, & MacDonald, 2006), the incidence calculated from the mid-level criteria (i.e., Whatley et al., ≥ 10 dB in one frequency in one ear; Kharkheli et al., ≥ 15 dB in two frequencies) was used for these additional analyses.

Hearing loss criteria

The criteria used to define hearing loss in the studies ranged from a 5-dB to a 30-dB loss. In addition, some criteria required hearing loss in only one ear or at only one frequency, whereas others required hearing loss in both ears or at two or more adjacent frequencies. Studies using criteria with a relatively high specificity of hearing loss of at least a 20-dB loss at a single frequency or at least a 15-dB loss at multiple frequencies (Elhanan, Siplovich, & Raz, 1995; Gendeh et al., 1991, 1993; Prins, Buller, Kuijper, Tange, & Speelman,1994; Raz, Adawi, & Romano, 1995) reported incidences ranging from 0% to 20%. Studies using more sensitive criteria of hearing loss of 5 or 10 dB at a single frequency (Cheung et al., 1990; Haydon et al., 1993; Indudharan et al., 2005) reported incidence ranging from 22% to 29%.

Two studies (Kharkheli et al., 2007; Whatley, Chandra, & MacDonald, 2006) analyzed the incidence of hearing loss in a single group of subjects using several different definitions (Table 3). Incidence in Kharkheli et al. (2007) ranged from 3% to 14% as the various criteria for hearing loss were examined, and in Whatley et al. (2006), the incidence rates ranged from 8% to 58%, depending on which criterion was applied.

Medical diagnosis

Of the 18 included studies, 16 involved patients with infection with a reported incidence of hearing loss ranging from 0% to 42%. One included patients with cystic fibrosis and infection with no reported incidence of hearing loss, and one examined patients with cancer with an 8% rate of hearing loss post-treatment.

Age

Six studies were limited to children and reported incidence ranging from 0% to 11%. The nine adult studies reported incidences ranging from 0% to 22%. Two studies contained both adult and pediatric subjects but did not present the results separately by age group. The reported incidence from these two studies ranged from 29% (Indudharan et al., 2005) to 42% (Whatley et al., 2006).

Study design

As noted in Table 2, the studies included in this review were roughly equally divided between controlled trials and case series. The controlled trials reported incidence ranging from 0% to 29%, and the case series investigations reported incidences ranging from 0% to 42%.

Study quality

The quality of the studies addressing Question 1 was generally high (i.e., scores of 4 or higher). Incidence of hearing loss among the 11 studies with a quality marker of 4 ranged from 0% to 24%. The four studies with a quality score of 5 reported rates of hearing loss ranging from 0% to 42%. Incidence of hearing loss from the two studies with a quality score of 6 ranged from 0% to 10%.

Table 3. Studies addressing incidence of hearing loss post–gentamicin treatment. (Question 1)

Study	Assessment instrument			HL criteria (dB loss post-treatment)	% HL post-treatment (*N*)
	PTA	BAEP	OAE		
Agarwal et al., 2002		X		Pass/fail	0% (0/41)
Bailey et al., 1996	X			≥ 10 dB in 2 freq. in 2 ears	24% (10/41)
Chayasirisobhon et al., 1996		X		Wave V/I amplitude ratio of < 1	11% (22/200)
Cheung et al., 1990	X			≥ 10 dB in 1 freq.	22% (4/18)
Chong et al., 2003		X	X	≥ 30 dB in 1 freq. on OAE screen, confirmed by abnormal BAER	0% (0/161)
El Bakri et al., 2000	X			> 15 dB in 1 freq.	7% (2/28)
Elhanan et al., 1995	X	X		≥ 15 dB in 2 freq. in 1 ear, or ≥ 10 dB in 2 freq. in 2 ears	8% (4/50)
Fausti et al., 1999	X			≥ 20 dB in 1 freq., > 10 dB in 2 freq., or loss of response at three consecutive freq.	34%[a] (116/339 ears)
Gendeh et al., 1993	X			≥ 15 dB in 2 freq. or ≥ 25 dB in 1 freq.	0% (0/10)
Gendeh et al., 1991	X			≥ 15 dB in 2 freq. or ≥ 25 dB in 1 freq.	0% (0/47)
Haydon et al., 1993	X			≥ 10 dB in 1 freq.	23% (3/13)
Indudharan et al., 2005	X			≥ 5 dB in 1 freq.	29% (28/95)
Kharkheli et al., 2007	X			≥ 10 dB in 2 freq. ≥ 15 dB in 2 freq. ≥ 20 dB in 1 freq.	14% (4/29) 10% (3/29)[b] 3% (1/29)

Table 3 (continued)

Study	Assessment Instruments			HL criteria (dB loss post treatment)	% HL post treatment (N)
	PTA	BAEP	OAE		
Kos et al., 2003		X		Change in wave I latency	7% (1/15)
Prins et al., 1994	X			≥ 15dB in 2 freq. in 1 ear or ≥10 dB in 2 freq. in 2 ears	20% (3/15)
Raz et al., 1995	X			≥ 15 dB in 2 freq. in 1 ear or ≥ 10 dB in 2 freq. in 2 ears	3% (3/100)
Stavroulaki et al., 2002	X		X	≥ 10dB in 2 freq. or ≥ 15dB in 1 freq.	0% (0/12)
Whatley et al., 2006	X		X	≥ 5 dB in 1 freq. in 1 ear ≥ 10 dB in 1 freq. in 1 ear ≥ 30 dB in 1 freq. in 1 ear	58% (7/12) 42% (5/12)[b] 8% (1/12)

Note. HL= hearing loss; dB = decibels; PTA = pure-tone audiometry; BAEP = brainstem auditory-evoked potentials; OAE= otoacoustic emissions; freq. = frequency.

[a]Incidence calculated by percentage of ears.
[b]Incidence rate used in analyses.

Clinical Question 2: What Is the Persistence of Hearing Loss in Persons Treated With Gentamicin?

Four studies included in this review (Chayasirisobhon, Yu, Griggs, Westmoreland, & Leu, 1996; Elhanan et al., 1995; Haydon et al., 1993; Kos et al., 2003) provided information regarding long-term hearing outcomes (see Table 4). Chayasirisobhon et al. (1996) found that seven out of 22 individuals identified with hearing loss post-treatment demonstrated reversal of the loss. In Elhanan et al. (1995), three of the four children identified with hearing loss were followed up, and all three were found to have normal hearing. Haydon et al. (1993) demonstrated a reversible hearing loss in two of the three individuals found to have hearing loss post-treatment. Six to 11 months post-treatment, Kos et al. (2003) found that hearing loss was reversible in the one participant who had developed hearing loss post-treatment.

Table 4. Persistence of hearing loss.

Study	Hearing loss post-tx (*N*)	Followed-up *N* (%)	Hearing loss at follow-up *N* (%)	Timing of follow-up (months)
Chayasirisobhon et al., 1996	22	22 (100%)	15 (68%)	2
Elhanan et al., 1995	4	3 (75%)	0 (0%)	2
Haydon et al., 1993	3	2 (67%)	0 (0%)	NR
Kos et al., 2003	1	1 (100%)	0 (0%)	6–11

Note. post-tx = post-treatment; N = number; NR = not reported.

Clinical Question 3: Is the Likelihood of Gentamicin-Induced Hearing Loss Affected by Dosage?

Thirteen studies addressed the incidence of hearing loss by gentamicin dosage (see Table 5). Nine of these reported dosage in mg/kg body weight per day. Dosage in these studies ranged from 4 to 12 mg/kg body weight/day. Reported incidence from these studies ranged from 0% to 42% and did not appear to be influenced by dosage.

Table 5. Incidence of hearing loss by dosage.

Study	**Dosage**[a]	***N***	**% HL**
Agarwal et al., 2002	4 5	0/20 0/21	0% 0%
Bailey et al., 1996	10	3/18	17%
Chayasirisobhon et al., 1996	5	22/200	11%
Chong et al., 2003	5 6	0/79 0/82	0% 0%
Elhanan et al., 1995	4.5	4/50	8%
Indudharan et al., 2005	0.3% 0.1%	15/52 13/43	29% 30%
Kharkheli et al., 2007	240 mg/day	3/29	10%[b]
Nordström et al., 1990	4.5	1/20	5%
Prins et al., 1994	4	3/15	20%
Raz et al., 1995	4.5	3/100	3%
Singhal et al., 1992	160 mg/day	5/73	7%
Stavroulaki et al., 2002	12	0/12	0%
Whatley et al., 2006	120 mg solution/day (concentration 80 mg gentamicin/liter saline)	5/12	42%[b]

[a]Dosage is expressed in terms of mg/kg/day unless otherwise specified.
[b]Study reported incidence by several different criteria for hearing loss. This incidence was calculated from the mid-level criterion.

Clinical Question 4: Is the Likelihood of Gentamicin-Induced Hearing Loss Affected by Route of Administration?

Fifteen studies reported sufficient information to address this clinical question (see Table 6). Seven studies administered gentamicin via intravenous injection. Incidence of hearing loss for this route ranged from 0% to 24%. Among the five studies that administered gentamicin topically (eardrops, implant, nasal spray), hearing loss ranged from 7% to 42%. Kharkheli et al. (2007) and Singhal et al. (1992) utilized intramuscular injection of gentamicin, with incidence ranging from 7% to 10%. Two studies (Gendeh et al., 1991, 1993) administered gentamicin via peritoneal catheter. No incidence of hearing loss was noted in either study. One study (Singhal, et al., 1992) undertook a direct comparison by administering gentamicin topically to some subjects and intramuscularly to others. Incidence of hearing loss was significantly higher in the topical group (p = .01), but it was not clear that the groups were comparable at baseline.

Table 6. Incidence of hearing loss by route of administration.

Study	Route	*N*	% HL
Agarwal et al., 2002	Intravenous	0/41	0
Bailey et al., 1996	Intravenous	10/41	24
Chong et al., 2003	Intravenous	0/161	0
Elhanan et al., 1995	Intravenous	4/50	8
Prins et al., 1994	Intravenous	3/15	20
Raz et al., 1995	Intravenous	3/100	3
Stavroulaki et al., 2002	Intravenous	0/12	0
Haydon et al., 1993	Topical	3/13	23
Indudharan et al., 2005	Topical (eardrops)	28/95	29
Kos et al., 2003	Topical (implant)	1/15	7
Singhal et al., 1992	Topical	4/11	27
Whatley et al., 2006	Topical (nasal spray)	5/12	42[a]
Kharkheli et al., 2007	Intramuscular	3/29	10[a]
Singhal et al., 1992	intramuscular	5/73	7
Gendeh et al., 1993	intraperitoneal	0/10	0
Gendeh et al., 1991	intraperitoneal	0/47	0

[a]Study reported incidence by several different criteria for hearing loss. This incidence was calculated from the mid-level criterion.

Clinical Question 5: Is the Likelihood of Gentamicin-Induced Hearing Loss Affected by Schedule of Administration?

Twelve studies addressed the effect of dosing schedule on hearing loss (see Table 7). Six studies provided gentamicin once daily; three studies provided gentamicin twice daily; seven studies provided gentamicin three times daily; and one study provided gentamicin four times daily. Incidence of hearing loss ranged from 0% to 20% for the once-daily group; 0%–42% for the twice-daily group; and 0%–29% for the three-times-daily group. The one study with four-times-daily administration of gentamicin did not detect any hearing loss in its 10 subjects.

Table 7. Incidence of gentamicin-induced hearing loss by schedule.

Study	Dosage	*N*	% HL post-treatment
Studies with once-daily administration (OD)			
Agarwal et al., 2002	4 mg/kg of body weight	0/20	0
Chong et al., 2003	5 mg/kg of body weight	0/79	0
Elhanan et al., 1995	4.5 mg/kg of body weight	2/26	8
Nordstrom et al., 1990	4.5 mg/kg of body weight	1/12	8
Prins et al., 1994	4 mg/kg of body weight	3/15	20
Raz et al., 1995	4.5 mg/kg of body weight	0/48	0
Studies with twice-daily administration (BD)			
Agarwal et al., 2002	2.5 mg/kg of body weight	0/21	0
Singhal et al., 1992	80 mg	5/73	7
Whatley et al., 2006*	60 mg solution (concentration 80 mg gentamicin /l saline)	5/12	42
Studies with three-times-daily administration (TD)			
Chong et al., 2003	2 mg/kg of body weight	0/82	0
Elhanan et al., 1995	1.5 mg/kg of body weight	2/24	8
Indudharan et al., 2005	0.1%–0.3%	28/95	29
Kharkheli et al., 2007[a]	80 mg	3/29	10
Nordstrom et al., 1990	1.5 mg/kg of body weight	0/8	0
Raz et al., 1995	1.5 mg/kg of body weight	3/52	0
Stavroulaki et al., 2002	4 mg/kg of body weight	0/12	0

(continued)

Table 7 (continued)

Study	Dosage	*N*	% HL post-treatment
Studies with four-times-daily administration			
Gendeh et al., 1993	16 mg	0/10	0%

[a]Study reported incidence by several different criteria for hearing loss. This incidence was calculated from the mid-level criterion.

Five studies (Agarwal et al., 2002; Chong et al., 2003; Elhanan et al., 1995; Nordström et al., 1990; Raz et al., 1995) compared the incidence of two different dosing schedules (see Table 8). None reported a statistically significant difference in rates of hearing loss by dosing schedules.

Table 8. Direct comparisons of dosing schedules.

Study	Once-daily administration	Twice-daily administration	Three-times-daily administration	*p*
Agarwal et al., 2002	0% (0/20)	0% (0/21)	Not applicable	1.00
Chong et al., 2003	0% (0/79)	Not applicable	0% (0/82)	1.00
Elhanan et al., 1995	8% (2/26)	Not applicable	8% (2/24)	1.00
Nordström et al., 1990	8% (1/12)	Not applicable	0% (0/ 8)	1.00
Raz et al., 1995	0% (0/48)	Not applicable	6% (3/52)	.24

Clinical Question 6: Is There Evidence of a Synergistic Effect on Hearing Loss if Multiple Ototoxic Drugs (e.g., Aminoglycosides, Antineoplastics, etc.) Are Taken Concomitantly With Gentamicin?

Only one study (Cheung et al., 1990) addressed this question. Of 22 subjects who received gentamicin, four also received furosemide, a loop diuretic also thought to be potentially ototoxic. Two of the four subjects (50%) who received both drugs developed hearing loss. Four of the 18 subjects (22%) who received only gentamicin developed hearing loss. The difference was not statistically significant (p = .29).

Discussion

The aim of this systematic review was to determine the incidence and persistence of gentamicin-induced hearing loss. This review also examined the effects of dosage, dosing schedule, route of administration, and concurrent use of other ototoxic drugs on the likelihood of a person developing hearing loss after gentamicin use. A systematic search of the scientific literature yielded 20 studies with incidence rates ranging from 0% to 58%. The wide range of study-specific incidence rates and heterogeneity of the studies in terms of patient populations, dosing, and diagnostic criteria did not allow for pooling the incidence data from the included studies.

For two of the questions addressed in this review, there was insufficient evidence to draw any conclusions. These were Question 2 (What is the persistence of hearing loss in persons treated with gentamicin?) and Question 6 (Is there evidence of a synergistic effect on hearing loss if multiple ototoxic drugs are taken concomitantly with gentamicin?). Although four studies examined the persistence of hearing loss subsequent to gentamicin treatment (Question 2), only 28 participants across the four studies were followed to determine if their post-treatment hearing loss was transient or permanent. Likewise, the one study that investigated the concomitant use of gentamicin and another potentially ototoixic drug (i.e., furosemide) included only four participants who received both drugs. The small sample sizes and the enormous variability in defining hearing loss do not allow us to interpret the findings with respect to the questions posed.

For the remaining questions, some evidence is available, but few trends were noted. Therefore, the findings fall short of supporting any strong conclusions. The frequency of gentamicin administration did not appear to influence the likelihood of hearing loss. Comparable results and conclusions have been reported in meta-analyses examining the safety and efficacy of various aminoglycoside (including but not limited to gentamicin) dosing schedules (Galloe, Graudal, Christensen, & Kampmann, 1995; Munckhof, Grayson, & Turnidge, 1996). Similarly, dosage amount also did not appear to affect the likelihood of hearing loss. Based on the limited number of studies included in this review addressing the effects of route of administration, topical application of gentamicin may be associated with higher incidence of hearing loss than were other routes. However, because the groups being compared were dissimilar at the outset of the study, further investigations are needed.

The results of this systematic review highlight key areas for future research. First, future investigations exploring the ototoxic effects of drugs should consider a consistent definition of hearing loss or provide sufficient individual participant data to allow for analyses across studies. Furthermore, hearing loss at higher frequencies (i.e., > 8 kHz) also should be assessed to determine if these frequencies are more vulnerable to drug-induced hearing loss or are predictive of future loss in other frequencies. Additional studies should further explore the risks associated with route of gentamicin administration, particularly topical administration.

The findings from these studies do not provide substantial help for clinicians concerned about the potential for hearing loss in patients receiving gentamicin. As of yet, there are no well-documented risk factors that can be used to differentiate higher from lower risk groups. Until more high-quality, experimental studies—using standardized case definitions—are completed, clinical decision making related to initiating, modifying, or terminating gentamicin therapy will be largely or entirely left up to the expertise and judgment of the clinician and the patient's tolerance for risk of hearing loss relative to negative sequelae from the condition being treated.

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References marked with an asterisk indicate studies included in this EBSR.

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