U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Dean L, Kane M. Gentamicin Therapy and *MT-RNR1* Genotype. 2015 Apr 29 [Updated 2022 Sep 22]. In: Pratt VM, Scott SA, Pirmohamed M, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Gentamicin Therapy and *MT-RNR1* Genotype

Laura Dean, MD[1] and Megan Kane, PhD[2]

Created: April 29, 2015; Updated: September 22, 2022.

Introduction

Gentamicin (brand names Garamycin, Cidomycin, and Septopal) is an aminoglycoside antibiotic that is used to treat sepsis. Gentamicin is administered by injection to treat serious infections caused by gram-negative bacteria (for example, *Pseudomonas aeruginosa*, *Proteus* species, *Escherichia coli*, *Klebsiella-Enterobacter-Serratia* species, and *Citrobacter* species). Additionally, gentamicin is used as an adjuvant treatment for infections caused by gram-positive bacteria (such as *Staphylococcus* species) (1). Gentamicin may also be used topically to treat ophthalmic and dermatological infections.

In most individuals, prolonged exposure to high gentamicin levels will cause ototoxicity (damage to the inner ear). However, among individuals who have specific variants in the mitochondrial gene *MT-RNR1*, a single dose of gentamicin can result in hearing loss (cochleotoxicity). This toxicity occurs in genetically susceptible individuals, despite serum drug concentrations within the normal therapeutic range (2). This hearing loss can be triggered not only by gentamicin, but by other aminoglycoside antibiotics and is referred to as aminoglycoside-induced hearing loss (AIHL).

Substantial literature has reported that a high proportion of individuals with the *MT-RNR1* m.1555A>G variant (NC_012920.1:m.1555A>G) develop hearing loss after receiving aminoglycoside therapy. The onset of hearing loss among these individuals varies, but once it occurs, it is usually moderate to profound, bilateral, and irreversible (3). Additional *MT-RNR1* genotypes associated with increased risk of AIHL include m.1095T>C and m.1494C>T (4).

The FDA-approved drug label for gentamicin does not include a statement regarding *MT-RNR1* (5); however, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines for administration of aminoglycosides, including gentamicin, with respect to variants in the *MT-RNR1* gene (4). These guidelines (Table 1) recommend avoiding the use of aminoglycoside antibiotics, such as gentamicin unless there are no satisfactory alternatives, by individuals who have a *MT-RNR1* genotype that puts them at high risk for AIHL. The CPIC guideline further advises that individuals with normal-risk alleles or uncertain-risk alleles at the *MT-RNR1* locus should all use aminoglycosides at standard doses for the shortest feasible course, with regular evaluation for hearing loss. This extends the 2014 American College of Medical Genetics and Genomics guideline with the following recommendation: "Single-gene testing may be warranted in cases in which the medical or family history, or presentation of the hearing loss, suggests a specific etiology. For example, testing for

Author Affiliations: 1 NCBI; Email: mgs@ncbi.nlm.nih.gov. 2 NCBI; Email: mgs@ncbi.nlm.nih.gov.

Corresponding author.

mitochondrial DNA variants associated with aminoglycoside ototoxicity may be considered for individuals with a history of use of aminoglycoside antibiotics" (6, 7).

Table 1: The CPIC Recommendations for Aminoglycoside Use and *MT-RNR1* Phenotype

Phenotype	Example genotype(s)*	Recommendation (strength)	Implications	Considerations
MT-RNR1 increased risk of aminoglycoside-induced hearing loss	m.1095T>C m.1494C>T m.1555A>G	Avoid aminoglycoside antibiotics unless the high risk of permanent hearing loss is outweighed by the severity of infection and lack of safe or effective alternative therapies. (Strong)	Very high risk of developing hearing loss if administered an aminoglycoside antibiotic	If no effective alternative to an aminoglycoside antibiotic is available, evaluate for hearing loss frequently during therapy and ensure that all appropriate precautions are utilized (namely, lowest possible dose and duration, utilization of therapeutic drug monitoring, hydration, renal function monitoring).
MT-RNR1 normal risk of aminoglycoside-induced hearing loss	m.827A>G	Use aminoglycoside antibiotics at standard doses for the shortest feasible course with therapeutic dose monitoring. Evaluate regularly for hearing loss in line with local guidance. (Strong)	Normal risk of developing hearing loss if administered an aminoglycoside antibiotic.	Individuals without *MT-RNR1* aminoglycoside-induced hearing loss increased risk variants are still at risk of aminoglycoside-associated hearing loss, especially with high drug levels or prolonged courses.
MT-RNR1 uncertain risk of aminoglycoside-induced hearing loss	m.663A>G m.961T>G m.961T>del+Cn m.1189T>C m.1243T>C m.1520T>C	Use aminoglycoside antibiotics at standard doses for the shortest feasible course with therapeutic drug monitoring. Evaluate regularly for hearing loss in line with local guidance. (Optional)	Weak or no evidence for an increased risk of *MT-RNR1*-associated hearing loss if administered an aminoglycoside antibiotic.	Individuals without *MT-RNR1* aminoglycoside-induced hearing loss increased risk variants are still at risk of aminoglycoside-associated hearing loss, especially with high drug levels or prolonged courses.

This table is adapted from (4). *Example genotypes are based on mitochondrial reference sequence NC_012920.1.

Drug: Gentamicin

Aminoglycosides such as gentamicin are among the earliest formulations of antibiotics (8). They are effective against most aerobic bacteria, both gram positive and gram negative. However, because they are inactive against anaerobes, they are often used with another antibiotic, such as a beta-lactam antibiotic or a cephalosporin, to increase coverage (9).

Aminoglycoside drugs approved for use by the FDA include amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, and tobramycin. The ending of these drug names, -mycin or -micin, reflects from which genus of bacteria the aminoglycoside was derived, either *Streptomyces* or *Micromonospora* (10).

Aminoglycosides exert antibacterial effects by binding to bacterial ribosomes and inhibiting bacterial protein synthesis. They bind to the 30S ribosomal subunit, which interferes with the decoding site, which is where the ribosome facilitates the accurate match of the tRNA in accordance with the appropriate mRNA codon. Errors here lead to inappropriate translation of the mRNA codons, so that incorrect amino acids are inserted into the polypeptide chain, which can disrupt elongation of the peptide chain (11, 12).

Like all aminoglycosides, gentamicin is poorly absorbed from the gut, so it is not taken orally. It is either given by intravenous (IV) or, less commonly, intramuscular (IM) injection with regular blood tests to monitor drug

levels, or given topically in the form of drops, cream, or ointment to treat infections of the eye or skin. Gentamicin is also used for prevention and treatment of recurrent urinary tract infections (UTIs) via intravesical delivery, also called bladder irrigation (13, 14). Systemic exposure following topical gentamicin cream has been reported to be low, though this may be higher among individuals being treated for burns (15, 16). The FDA-approved labels for topical gentamicin formulations do not discuss absorption kinetics, nor a need for therapeutic drug monitoring (17, 18).

The scope of this document is limited to gentamicin therapy, though much of the guidance and literature related to therapy-induced ototoxicity is inclusive of multiple aminoglycoside antibiotics. Readers are encouraged to review regulatory labeling and the CPIC guideline for aminoglycosides regarding those related medications (4).

The toxicity of aminoglycosides, along with the discovery of equally potent but less toxic antibiotics, has meant that the use of aminoglycoside injections is reserved for serious infections that are proven, or strongly suspected to be, caused by susceptible bacteria. Aminoglycosides are most commonly used in the treatment of neonatal septicemia, especially in premature or low-birth-weight babies, with estimates of 61–90% receiving some kind of aminoglycoside therapy during the first weeks of life (19, 20, 21). Aminoglycosides are also used with other antibiotics as surgical prophylaxis among individuals who are allergic to penicillin, and for febrile neutropenia, septic shock, and drug-resistant tuberculosis (8). Individuals with cystic fibrosis frequently require aminoglycoside antibiotic therapy to manage recurrent lung infections, though tobramycin and amikacin are the recommended medications (22, 23). Aminoglycoside antibiotics are also recommended for management of peritoneal dialysis-associated peritonitis with gram-negative bacterial infection, and empiric antibiotic selection that covers both gram-positive and -negative bacterial species administered promptly is associated with better outcomes (24).

Neonatal sepsis is often treated with aminoglycosides such as gentamicin with ampicillin. The World Health Organization (WHO) recommends one of 2 treatment courses for children in the first 60 days of life who present with clinical severe infection in a setting without access to hospitalization. The first course is IM gentamicin injection (when hospitalization and IV administration are not feasible) (5–7.5 mg/kg or 3–4 mg/kg for low-birth-weight infants) once daily for 7 days with twice daily oral amoxicillin (50 mg/kg per dose) for 7 days. The second option for managing a neonate with clinical severe infection is IM injection of gentamicin (5–7.5 mg/kg or 3–4 mg/kg for low-birth-weight infants) once daily for 2 days and twice daily oral amoxicillin (50 mg/kg per dose) for 7 days. If the second option is selected, a close evaluation of the child must be made on day 4 to verify improvement. (25) Recently, simplified dosing regimens for neonates have been proposed (26). The American Academy of Pediatrics recommends empirical use of use of either ceftazidime or gentamicin (IM or IV, 4 mg/kg per dose) along with ampicillin for the treatment of well-appearing febrile infants (aged 8–21 days old) with either an unknown source of infection or known UTI (27).

The main toxicities associated with aminoglycoside therapy are kidney damage (nephrotoxicity) and damage to the inner ear (ototoxicity) (28). Nephrotoxicity primarily involves the proximal tubules and is often, but not always, reversible (29). A Fanconi-like syndrome, with aminoaciduria and metabolic acidosis, has occurred in some adults and infants receiving gentamicin injection (5). Studies for medications that can be co-administered to reduce gentamicin nephrotoxicity have shown promising results (30, 31). In contrast, aminoglycoside-induced ototoxicity is typically irreversible. Ototoxicity from gentamicin may damage the cochlea (cochleotoxicity)—resulting in sensorineural hearing loss—or the vestibular system (vestibulotoxicity)—causing problems with balance, vertigo, ataxia, nausea, and vomiting. Increased risk of vestibulotoxicity has not been reported to be associated with *MT-RNR1* variation. Gentamicin is more toxic to the vestibular system so is used for vestibular ablation to treat Ménière's disease via intratympanic dosing (32). However, the risk of hearing loss is greater with gentamicin therapy as compared with other pharmacologic methods, despite improved outcomes with respect to vertigo (32). Amikacin and neomycin are examples of aminoglycosides that are more toxic to the cochlea (28, 33). Monitoring for signs of ototoxicity or co-administration of aminoglycosides with N-acetylcysteine have

been recommended for individuals with an elevated infection risk that require aminoglycoside therapy, such as those with cystic fibrosis or individuals undergoing peritoneal dialysis (23, 24). The proposed mechanism underlying the otoprotective effects of N-acetylcysteine is its ability to act as an antioxidant, thereby reducing levels of reactive oxygen species that may be damaging the inner ear (34). The frequency of hearing loss or other ototoxicity in the pediatric population following aminoglycoside use has been reported to range from 0–57% (35), and among adults the incidence of hearing loss following aminoglycoside therapy ranges from 20–63% (36).

Rarely, neuromuscular blockade can occur after aminoglycoside therapy. The boxed warning on the FDA-approved drug label recommends that aminoglycosides "be used with caution in individuals with neuromuscular disorders, such as myasthenia gravis or parkinsonism, because they may aggravate muscle weakness (9)"; whereas in 2014, the British National Formulary stated that aminoglycosides should not be given to individuals with myasthenia gravis (37). The European Medicines Agency cautions that acute renal failure and Fanconi-like syndrome are 2 very rare adverse reactions to gentamicin medication and notes that irreversible hearing loss or deafness is also a risk of unknown frequency (38).

Elderly individuals who may have reduced renal function may experience elevated exposure to aminoglycoside antibiotics, increasing the risk of toxicity. The FDA-approved drug label for injectable gentamicin recommends that creatinine clearance is a more useful indication of renal function as compared with other tests.

The use of gentamicin or other aminoglycoside antibiotics during pregnancy can result in fetal exposure to the medication, as these compounds can cross the placenta. There are documented reports of total irreversible congenital deafness in children whose mothers were administered streptomycin during pregnancy, though serious effects on either the mother, fetus, or newborn have not been observed for other aminoglycosides. The FDA states that pregnant individuals should be advised of the risk to the fetus if gentamicin is used during pregnancy (5). Gentamicin is poorly excreted into breastmilk following systemic administration and maternal use of ear or eye drop medications that include gentamicin present little to no risk for a nursing infant (39). While infant gastrointestinal absorption of gentamicin from breastmilk can occur, the resulting serum concentrations in newborns and older infants were well below the therapeutic levels and are reportedly unlikely to have systematic effects (39).

Gene: *MT-RNR1*

Mitochondria are the main source of energy in most cells, as they use oxygen, sugars, and fats to create energy in the form of adenosine triphosphate. This process is known as oxidative phosphorylation. Any genetic variation that disrupts normal mitochondrial function can have severe effects on health.

Mitochondria have their own genome, which is small, circular, and resembles the bacterial prokaryotes from which they evolved. The mitochondrial genome (mtDNA) is passed down from mother to child (maternal inheritance) and has 37 genes, one of which is the *MT-RNR1* gene ("mitochondrially encoded 12S RNA"). The ribosomal RNA (rRNA) encoded by *MT-RNR1* is essential in the synthesis of the proteins that perform oxidative phosphorylation. (3) Each mitochondrion holds multiple copies of its genome, and the number of mitochondria can vary between cells and tissues. It is possible for these multiple copies of mtDNA to vary in genotype at specific loci within an individual. This is called heteroplasmy and the relative frequencies of genotypes can differ from cell to cell and tissue to tissue. Homoplasmy is the term for all mitochondria having the same genotype at the locus of interest.

Consistent with their bacterial origin, mitochondrial rRNA more closely resembles bacterial rRNA than human rRNA. However, at a highly conserved decoding region in the *MT-RNR1* gene, the sequence in humans is distinct from the sequence in bacteria. This difference means that aminoglycosides, which target the decoding region in bacteria, normally do not bind to this region in humans (11).

However, genetic variation in the ribosomal decoding region can result in mitochondrial rRNA appearing more like bacterial rRNA, thereby facilitating the binding of aminoglycosides. This results in inhibition of protein synthesis, as in the bacterial ribosome, leading to cellular toxicities. The mechanism of cellular toxicity is unclear, but aminoglycosides preferentially damage the sensory hair cells in the cochlea that mediate hearing (40, 41, 42). Hearing loss is a common symptom in many mitochondrial disorders, pointing to a critical role for mitochondria in the auditory system.

The most common *MT-RNR1* variant is a single nucleotide substitution of a guanine nucleotide at position 1555 in place of an adenine nucleotide (m.1555A>G). Individuals with this variant are exquisitely sensitive to AIHL, which is moderate to profound, bilateral, irreversible, and may have a rapid onset. Even a single dose of aminoglycoside can be sufficient to cause ototoxicity (2, 43).

Genetically susceptible individuals who are not exposed to aminoglycosides may nonetheless develop hearing loss, referred to as "non-syndromic mitochondrial hearing loss," though more data are needed to understand this relationship. The course of hearing loss may be affected by the presence of additional genetic factors as well as environmental factors, such as exposure to loud noise. However, preliminary findings suggest that normal hearing may be preserved until at least 44 years of age (2).

The prevalence of the m.1555A>G variant varies among different populations. In the US, the UK, and Finland, the prevalence is estimated to be 0.2% (7, 21, 44, 45). Data summarized from CPIC reports the overall frequency of the m.1555A>G variant to be 0.11% for both central/south Asia and Europe, 1.81% for East Asian ancestry, 0.14% for near Eastern populations, and 0.3% for sub-Saharan Africa (46). Individuals with either m.1555A>G or m.1494C>T (described below) were observed at a frequency of 0.227% in one study from Beijing, China (47). Among hearing-impaired populations, the prevalence is much greater; however, the estimates vary widely based on study differences, such as the age of onset of hearing loss and whether there has been exposure to aminoglycosides. Estimates include a prevalence of 3.5% among the hearing-impaired population in Japan (48), 5% among deaf individuals in Indonesia (49), and 6% of individuals with postlingual hearing loss from the UK and Southern Italy (50). Additionally, a prevalence of 15% has been reported in "ethnically diverse patients in the United States with hearing loss after aminoglycoside exposure" (51), and in 15-–20% of individuals from Spain with hearing loss (52).

The m.1555A>G variant is the best studied *MT-RNR1* variant with regards to aminoglycoside ototoxicity, but other mitochondrial variants are also associated with hearing loss. In 10 small studies, all individuals with the m.1494C>T (NC_012920.1:m.1494C>T, rs267606619) variant developed hearing loss after receiving an aminoglycoside antibiotic. The CPIC guidelines state that both the m.1555A>G and m.1494C>T variants are risk alleles for AIHL, with high levels of evidence. Another variant, m.1095T>C (NC_012920.1:m.1095T>C, rs267606618), is similarly associated with a risk of AIHL by CPIC, with a moderate level of evidence (3, 4). In addition, the m.827A>G (NC_012920.1:m.827A>G) variant, and variants at position 961, have also been associated with nonsyndromic hearing loss, both with and without the use of aminoglycosides (3); however, due to the high frequency of m.827A>G in certain populations, CPIC determined that this allele is associated with normal risk of AIHL. (4)

Several studies have highlighted the complex issues raised by screening for pathogenic *MT-RNR1* variants. The aim of screening is to prevent avoidable hearing loss in genetically susceptible individuals by administering an alternative antibiotic whenever possible. Issues include the costs of universal screening, for example, as part of the newborn screening program—given that the prevalence of m.1555A>G is thought to be one in 385 Caucasians (2, 53, 54) —versus limiting genetic testing to a case-by-case basis (that is, individuals with tuberculosis, children with leukemia, individuals with cystic fibrosis, and individuals requiring surgery who are allergic to beta-lactam antibiotics) (7, 55). A family history of hearing loss may be useful in identifying candidates for genetic testing, but not necessarily indicative of AIHL risk due to *MT-RNR1* variation, as multiple genes can contribute to inherited hearing loss in syndromic or nonsyndromic forms (6). A report from the

WHO's Essential Medicines and Pharmaceutical Policies comments that "pre-treatment screening is an important consideration to prevent aminoglycoside related hearing loss but given cost and access issues, asking about a maternal family history of deafness may be more practical" (56).

In the US, aminoglycosides are most commonly used in the neonatal intensive care unit, where acute, life-threatening sepsis means that aminoglycoside therapy cannot be delayed to wait for the results of genetic testing (57). However, recent advances in screening have allowed for rapid, accurate, and inexpensive testing (58, 59, 60). A recent study from the UK described the development and implementation of a rapid point-of-care test for septic infants requiring intensive care, which was successfully integrated into routine care and returned results in less than 30 minutes (61).

Linking Genetic Variation to Treatment Response

Individuals who have one of the *MT-RNR1* at-risk alleles will not always develop hearing loss upon exposure to aminoglycosides. The highest risk allele, based on a review of over 40 studies, is the m.1555A>G variant. As reviewed by Barbarino and colleagues, over 96% of individuals with this genotype developed some degree of AIHL (466 individuals with hearing loss as compared with 16 without hearing loss out of 482 individuals in the reviewed articles) (3). One study of a Spanish family with heteroplasmy for this variant reported that individuals with <20% variant burden at the m.1555 locus did not develop hearing loss, or the loss was mild (62). Other recent studies that show a lack of AIHL among individuals with m.1555A>G were primarily performed in the neonatal setting, following use of gentamicin in septic newborns. The proportion of infants with m.1555A>G who failed the newborn screening test after aminoglycoside treatment was 4 out of 15, leading one group to conclude that this genotype is a risk factor for a failed newborn hearing test (63, 64, 65). However, the degree and timing of the onset of AIHL attributed to at-risk genotypes is still unclear. While some reports suggest the degree of mitochondrial heteroplasmy may affect the penetrance of the hearing-loss phenotype (62, 66), CPIC's recommendations to avoid aminoglycosides (including gentamicin) apply to individuals who are heteroplasmic or homoplasmic for the at-risk genotype(s) (4).

The variants at m.1555 and m.1494 have been shown to affect the structure of the eukaryotic rRNA, increasing the relative affinity of aminoglycosides for the ribosome (3). The m.1095T>C variant is associated with increased cellular apoptosis in the presence of aminoglycosides, presumably due to a similar increased affinity between the ribosome and medication (67).

Genetic Testing

The NIH's Genetic Testing Registry (GTR) provides examples of the genetic tests that are available for the *MT-RNR1* gene and Gentamicin response. Targeted mutation panels vary among testing laboratories, but most laboratories that interrogate the *MT-RNR1* gene routinely test for m.1555A>G.

The *MT-RNR1* variants are associated with 2 conditions: aminoglycoside hypersensitivity resulting in post-exposure deafness, and nonsyndromic mitochondrial hearing loss that tends to develop gradually over time. While the presence of an *MT-RNR1* variant indicates a high risk of aminoglycoside ototoxicity, the test results do not predict the age of onset or severity of nonsyndromic mitochondrial hearing loss (43).

Mitochondria are exclusively maternally inherited. Therefore, identification of an individual with an *MT-RNR1* risk allele may be relevant to any maternal relatives, or children of a female identified to have the variant, or both (4).

Therapeutic Recommendations based on Genotype

Excerpt from the CPIC guidelines for Aminoglycosides and MT-RNR1 variants.

The critical pharmacogenetics recommendation for a person with an *MT-RNR1* variant which predisposes to AIHL is that aminoglycoside antibiotics are relatively contraindicated, meaning that aminoglycosides should be avoided unless the increased risk of hearing loss is outweighed by the severity of infection and lack of safe or effective alternative therapies. There is insufficient evidence to suggest that the adverse drug reaction may be more profound with some members of the aminoglycoside class than others. As such, this guidance covers all aminoglycoside antibiotics irrespective of class. We provide a strong recommendation that carriers of *MT-RNR1* variants that predispose to AIHL should avoid aminoglycosides unless the increased risk of permanent hearing loss is outweighed by the risk of infection without safe or effective alternative therapies… If no effective alternative to an aminoglycoside is thought to be available, we advise use for the shortest possible time, consultation with an infectious disease expert for alternative approaches, therapeutic drug monitoring and frequent assessment for hearing loss, both during and after therapy, in consultation with an audiovestibular physician.

An individual with no detectable *MT-RNR1* variant or carrying *MT-RNR1* variants not considered to be predisposing to AIHL (normal risk), including the m.827A>G variant, should still be considered at risk of AIHL. In addition to *MT-RNR1*, AIHL is often associated with other risk factors such as prematurity, renal impairment, severe inflammatory response syndrome, prolonged therapy regimens, and supratherapeutic plasma concentrations. As such, irrespective of the presence of an *MT-RNR1* variant which predisposes to AIHL, precautions such as renal monitoring, therapeutic drug monitoring, and utilizing the lowest effective dose should be applied. Finally, if an individual with an actionable *MT-RNR1* variant has previously received aminoglycosides and not developed AIHL, this does not preclude them from developing AIHL with subsequent doses.

Considerations for aminoglycoside use in patients at increased risk of AIHL. For the purposes of this guideline, appropriateness for use of aminoglycoside antibiotics can be considered for three scenarios: First, an equally or more effective agent is available for the condition; second, there is reason to believe that an aminoglycoside might lead to superior outcomes, but evidence is poor, the effect-size is small, or the outcome is not clinically meaningful; and third, there is good evidence for significantly superior efficacy of an aminoglycoside-containing treatment regimen for a clinically meaningful outcome.

[….]

In all cases, an aminoglycoside used in patients at increased risk of AIHL due to the presence of an *MT-RNR1* variant should be administered for the shortest possible period, under expert supervision, with therapeutic drug and ototoxicity monitoring, and with clinical audiovestibular assessment performed during and after treatment. Irrespective of whether an individual carries a pathogenic *MT-RNR1* variant, all patients who receive aminoglycoside antibiotics, especially those prescribed prolonged courses, should be monitored for ototoxicity in line with existing local and international guidelines.

[….]

Based on the available literature, at present there is not sufficient evidence to define a level of heteroplasmy where aminoglycoside administration becomes safe, especially as the mutational load may differ from tissue to tissue and be dependent upon the genotyping technique utilized. As such, we have not tailored this guideline based on the level of heteroplasmy. Rather, we recommend that if a relevant *MT-RNR1* variant is detected, the guidance should be followed as set out for a homoplasmic variant.

Please review the complete CPIC therapeutic recommendations that are located here: (4).

Excerpt from the American College of Medical Genetics and Genomics (ACMG) Guideline for the Clinical Evaluation and Etiologic Diagnosis of Hearing Loss:

For individuals lacking physical findings suggestive of a known syndrome and having medical and birth histories that do not suggest an environmental cause of hearing loss, a tiered diagnostic approach should be implemented.

Pretest genetic counseling should be provided, and, with patient's informed consent, genetic testing should be ordered.

Single-gene testing may be warranted in cases in which the medical or family history, or presentation of the hearing loss, suggests a specific etiology. For example, testing for mitochondrial DNA mutations associated with aminoglycoside ototoxicity may be considered for individuals with a history of use of aminoglycoside antibiotics.

Please review the complete ACMG therapeutic recommendations that are located here: (6).

Nomenclature

Common allele name	Alternative names	HGVS reference sequence			dbSNP reference identifier for allele location
		Genomic	Coding*	Protein#	
m.1555A>G	A1555G	NC_012920.1:m.1555A>G	N/A	N/A	rs267606617
m.1494C>T	C1494T	NC_012920.1:m.1494C>T	N/A	N/A	rs267606619
m.1095T>C	T1095C	NC_012920.1:m.1095T>C	N/A	N/A	rs267606618
m. 827A>G	A827G	NC_012920.1:m.827A>G	N/A	N/A	rs28358569
m.663A>G	A663G	NC_012920.1:m.663A>G	N/A	N/A	rs56489998
m.961T>G	T961G	NC_012920.1:m.961T>G	N/A	N/A	rs3888511
m.961T>del+Cn	T961del+Cn	NC_012920.1:m.961delTinsC(2_7)	N/A	N/A	rs1556422499
m.1189T>C	T1189C	NC_012920.1:m.1189T>C	N/A	N/A	rs28358571
m.1243T>C	T1243C	NC_012920.1:m.1243T>C	N/A	N/A	rs28358572

* RNA coordinates not available.
# MT-RNR1 encodes an RNA gene product, there is no translated protein.

Acknowledgments

Current version:

The authors would like to acknowledge William Newman, MA, FRCP, PhD, Professor of Translational Genomic Medicine, The Manchester Centre for Genomic Medicine at the University of Manchester, Honorary Consultant at Manchester University NHS Foundation Trust, Manchester, UK; John McDermott, MRes, BSc, MBChB, NIHR Doctoral Research Fellow, University of Manchester, Clinical Genetics Registrar, Manchester University NHS Foundation Trust, Manchester, UK; and Hyun Kim, PharmD, Clinical Pharmacist, Boston Children's Hospital Clinical Pharmacogenomics Service, Boston, MA, USA for their expert review of this summary.

2018 version:

The author would like to thank Shannon Manzi, PharmD, BCPPS, Director, Clinical Pharmacogenomics Service, Boston Children's Hospital, and Assistant Professor of Pediatrics, Harvard Medical School, Boston, MA, USA for reviewing this summary.

2015 version:

The author would like to thank Stuart A. Scott, Assistant Professor of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY; Shamima Rahman, FRCP, PhD, Professor of Paediatric Metabolic Medicine at University College London and Honorary Consultant in Paediatric Metabolic Medicine at

Great Ormond Street Hospital, London, UK; and Maria Bitner-Glindzicz, FRCP, PhD, Professor of Clinical Molecular Genetics at University College London and Honorary Consultant in Clinical Genetics at Great Ormond Street Hospital, London, UK.

Version History

To view the 2015 version of this summary (created: April 29, 2015) please click here.
To view the 2018 version of this summary (created: August 1, 2018) please click here.

References

1. GENTAMICIN - gentamicin injection, solution [package insert]. Lake Zurich, IL: Fresenius Kabi USA; 2016. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=be5b414e-d598-4721-80ee-5836156ad210
2. Rahman S., Ecob R., Costello H., Sweeney M.G., et al. Hearing in 44-45 year olds with m.1555A>G, a genetic mutation predisposing to aminoglycoside-induced deafness: a population based cohort study. BMJ open. 2012;2:e000411. p.
3. Barbarino J.M., McGregor T.L., Altman R.B., Klein T.E. PharmGKB summary: very important pharmacogene information for MT-RNR1. Pharmacogenet Genomics. 2016;26(12):558–567. PubMed PMID: 27654872.
4. McDermott J.H., Wolf J., Hoshitsuki K., Huddart R., et al. Clinical Pharmacogenetics Implementation Consortium Guideline for the Use of Aminoglycosides Based on MT-RNR1 Genotype. Clin Pharmacol Ther. 2021.
5. GENTAMICIN - gentamicin sulfate injection, solution. Lake Zurich, IL, USA: LLC, F.K.U.; 2021. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a73a5453-c091-43fd-aae2-d992152363b1
6. Alford R.L., Arnos K.S., Fox M., Lin J.W., et al. American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. Genet Med. 2014;16(4):347–55. PubMed PMID: 24651602.
7. Bitner-Glindzicz M., Pembrey M., Duncan A., Heron J., et al. Prevalence of mitochondrial 1555A-->G mutation in European children. The New England journal of medicine. 2009;360(6):640–2. PubMed PMID: 19196684.
8. Poulikakos P., Falagas M.E. Aminoglycoside therapy in infectious diseases. Expert opinion on pharmacotherapy. 2013;14(12):1585–97. PubMed PMID: 23746121.
9. GENTAMICIN (gentamicin sulfate) injection, solution [package insert]. Schaumburg, IL: AAP Pharmaceuticals; 2012. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a73a5453-c091-43fd-aae2-d992152363b1
10. Procopio, R.E., I.R. Silva, M.K. Martins, J.L. Azevedo, et al., *Antibiotics produced by Streptomyces.* The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases, 2012. **16**(5): p. 466-71.
11. Demeshkina N., Jenner L., Westhof E., Yusupov M., et al. A new understanding of the decoding principle on the ribosome. Nature. 2012;484(7393):256–9. PubMed PMID: 22437501.
12. Tsai A., Uemura S., Johansson M., Puglisi E.V., et al. The impact of aminoglycosides on the dynamics of translation elongation. Cell reports. 2013;3(2):497–508. PubMed PMID: 23416053.
13. Pietropaolo A., Jones P., Moors M., Birch B., et al. Use and Effectiveness of Antimicrobial Intravesical Treatment for Prophylaxis and Treatment of Recurrent Urinary Tract Infections (UTIs): a Systematic Review. Curr Urol Rep. 2018;19(10):78. PubMed PMID: 30094687.
14. Marei, M.M., R. Jackson and D.J.B. Keene, *Intravesical gentamicin instillation for the treatment and prevention of urinary tract infections in complex paediatric urology patients: evidence for safety and efficacy.* J Pediatr Urol, 2021. **17**(1): p. 65 e1-65 e11.

15. Oesterreicher Z., Lackner E., Jager W., Hoferl M., et al. Lack of dermal penetration of topically applied gentamicin as pharmacokinetic evidence indicating insufficient efficacy. J Antimicrob Chemother. 2018;73(10):2823–2829. PubMed PMID: 30113678.
16. Chaves, B.J. and P. Tadi, *Gentamicin*, in *StatPearls*. 2022: Treasure Island (FL).
17. GENTAMICIN SULFATE solution/ drops. Lake Forest, IL, USA: Inc., A.; 2020. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=32d5af97-70bd-4ee4-81d4-67578dc677a0
18. GENTAMICIN SULFATE- gentamicin sulfate cream. Bronx, NY, USA: Perrigo; 2021. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4cfbe37e-11d6-46fc-b287-0561387b17b7
19. Girardi A., Galletti S., Raschi E., Koci A., et al. Pattern of drug use among preterm neonates: results from an Italian neonatal intensive care unit. Ital J Pediatr. 2017;43(1):37. PubMed PMID: 28412957.
20. Rhone E.T., Carmody J.B., Swanson J.R., Charlton J.R. Nephrotoxic medication exposure in very low birth weight infants. J Matern Fetal Neonatal Med. 2014;27(14):1485–90. PubMed PMID: 24168068.
21. Soini H.K., Karjalainen M.K., Hinttala R., Rautio A., et al. Mitochondrial hearing loss mutations among Finnish preterm and term-born infants. Audiol Res. 2017;7(2):189. PubMed PMID: 29291046.
22. Mogayzel P.J. Jr, Naureckas E.T., Robinson K.A., Brady C., et al. Cystic Fibrosis Foundation pulmonary guideline. pharmacologic approaches to prevention and eradication of initial Pseudomonas aeruginosa infection. Ann Am Thorac Soc. 2014;11(10):1640–50. PubMed PMID: 25549030.
23. Kimple A.J., Senior B.A., Naureckas E.T., Gudis D.A., et al. Cystic Fibrosis Foundation otolaryngology care multidisciplinary consensus recommendations. Int Forum Allergy Rhinol. 2022.
24. Li P.K., Chow K.M., Cho Y., Fan S., et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. Perit Dial Int. 2022;42(2):110–153. PubMed PMID: 35264029.
25. Organization, W.H., *Guideline: managing possible serious bacterial infection in young infants when referral is not feasible.* . 2015, World Health Organization.
26. D'Agate S., Musuamba F.T., Jacqz-Aigrain E., Della Pasqua O. Simplified Dosing Regimens for Gentamicin in Neonatal Sepsis. Front Pharmacol. 2021;12:624662. p. PubMed PMID: 33762945.
27. Pantell R.H., Roberts K.B., Adams W.G., Dreyer B.P., et al. Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old. Pediatrics. 2021;148(2)
28. Forge A., Schacht J. Aminoglycoside antibiotics. Audiology & neuro-otology. 2000;5(1):3–22. PubMed PMID: 10686428.
29. Xie J., Talaska A.E., Schacht J. New developments in aminoglycoside therapy and ototoxicity. Hearing research. 2011;281(1-2):28–37. PubMed PMID: 21640178.
30. Mousavinasab S.R., Akhoundi-Meybodi Z., Mahmoudi L., Karimzadeh I. A randomized double-blinded placebo-controlled clinical trial on protective effects of pentoxifylline on gentamicin nephrotoxicity in infectious patients. Clin Exp Nephrol. 2021;25(8):844–853. PubMed PMID: 33792832.
31. Mahi-Birjand M., Yaghoubi S., Abdollahpour-Alitappeh M., Keshtkaran Z., et al. Protective effects of pharmacological agents against aminoglycoside-induced nephrotoxicity: A systematic review. Expert Opin Drug Saf. 2020;19(2):167–186. PubMed PMID: 31914328.
32. Ahmadzai N., Cheng W., Kilty S., Esmaeilisaraji L., et al. Pharmacologic and surgical therapies for patients with Meniere's disease: A systematic review and network meta-analysis. PLoS One. 2020;15(9):e0237523. p. PubMed PMID: 32870918.
33. Ahmed R.M., Hannigan I.P., MacDougall H.G., Chan R.C., et al. Gentamicin ototoxicity: a 23-year selected case series of 103 patients. The Medical journal of Australia. 2012;196(11):701–4. PubMed PMID: 22554194.
34. Tokgoz B., Ucar C., Kocyigit I., Somdas M., et al. Protective effect of N-acetylcysteine from drug-induced ototoxicity in uraemic patients with CAPD peritonitis. Nephrol Dial Transplant. 2011;26(12):4073–8. PubMed PMID: 21551083.
35. Diepstraten, F.A., A.E. Hoetink, M. van Grotel, A.D.R. Huitema, et al., *Aminoglycoside- and glycopeptide-induced ototoxicity in children: a systematic review.* JAC Antimicrob Resist, 2021. **3**(4): p. dlab184.
36. Steyger P.S. Mechanisms of Aminoglycoside- and Cisplatin-Induced Ototoxicity. Am J Audiol. 2021;30(3S):887–900. PubMed PMID: 34415784.
37. *British National Formulary*. June 2014, BMJ Group and Pharmaceutical Press: London.

38. Gentamicin (systemic use): CMDh Scientific conclusions and grounds for the variation, amendments to the Product Information and timetable for the implementation [Cited Available from: https://www.ema.europa.eu/en/documents/psusa/gentamicin-systemic-use-cmdh-scientific-conclusions-grounds-variation-amendments-product-information/00009159/201703_en.pdf
39. *Gentamicin*, in *Drugs and Lactation Database (LactMed)*. 2006: Bethesda (MD).
40. Guan M.X. Mitochondrial 12S rRNA mutations associated with aminoglycoside ototoxicity. Mitochondrion. 2011;11(2):237–45. PubMed PMID: 21047563.
41. Selimoglu E. Aminoglycoside-induced ototoxicity. Current pharmaceutical design. 2007;13(1):119–26. PubMed PMID: 17266591.
42. Bates D.E. Aminoglycoside ototoxicity. Drugs of today. 2003;39(4):277–85. PubMed PMID: 12743643.
43. Pandya, A., *Nonsyndromic Hearing Loss and Deafness, Mitochondria*, A.M. Pagon RA, Ardinger HH, et al., editors., Editor. 2014, University of Washington: Seattle (WA).
44. Vandebona H., Mitchell P., Manwaring N., Griffiths K., et al. Prevalence of mitochondrial 1555A-->G mutation in adults of European descent. The New England journal of medicine. 2009;360(6):642–4. PubMed PMID: 19196685.
45. Tang, H.Y., E. Hutcheson, S. Neill, M. Drummond-Borg, et al., *Genetic susceptibility to aminoglycoside ototoxicity: how many are at risk?* Genetics in medicine : official journal of the American College of Medical Genetics, 2002. **4**(5): p. 336-45.
46. MT-RNR1 frequency table [Cited 22 Sept 2021]. Available from: https://cpicpgx.org/guidelines/cpic-guideline-for-aminoglycosides-and-mt-rnr1/
47. Dai P., Huang L.H., Wang G.J., Gao X., et al. Concurrent Hearing and Genetic Screening of 180,469 Neonates with Follow-up in Beijing, China. Am J Hum Genet. 2019;105(4):803–812. PubMed PMID: 31564438.
48. Usami S., Abe S., Akita J., Namba A., et al. Prevalence of mitochondrial gene mutations among hearing impaired patients. Journal of medical genetics. 2000;37(1):38–40. PubMed PMID: 10633132.
49. Malik S.G., Pieter N., Sudoyo H., Kadir A., et al. Prevalence of the mitochondrial DNA A1555G mutation in sensorineural deafness patients in island Southeast Asia. Journal of human genetics. 2003;48(9):480–3. PubMed PMID: 12955586.
50. Jacobs H.T., Hutchin T.P., Kappi T., Gillies G., et al. *Mitochondrial DNA mutations in patients with postlingual, nonsyndromic hearing impairment.* European journal of human genetics. EJHG. 2005;13(1):26–33. PubMed PMID: 15292920.
51. Fischel-Ghodsian N., Prezant T.R., Chaltraw W.E., Wendt K.A., et al. Mitochondrial gene mutation is a significant predisposing factor in aminoglycoside ototoxicity. American journal of otolaryngology. 1997;18(3):173–8. PubMed PMID: 9164619.
52. Bravo O., Ballana E., Estivill X. Cochlear alterations in deaf and unaffected subjects carrying the deafness-associated A1555G mutation in the mitochondrial 12S rRNA gene. Biochemical and biophysical research communications. 2006;344(2):511–6. PubMed PMID: 16631122.
53. Linden Phillips L., Bitner-Glindzicz M., Lench N., Steel K.P., et al. The future role of genetic screening to detect newborns at risk of childhood-onset hearing loss. International journal of audiology. 2013;52(2):124–33. PubMed PMID: 23131088.
54. McLeod H.L., Isaacs K.L. Preemptive pharmacogenetic testing: insufficient data equal unsatisfactory guidance. Annals of internal medicine. 2011;154(12):842–4. PubMed PMID: 21690601.
55. Abusamra R., McShane D. Is deafness mutation screening required in cystic fibrosis patients? Paediatr Respir Rev. 2016;20 Suppl:24–6.
56. Matthai, D.E. *Gentamicin - Ototoxicity in children* in *Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicine*. 2008 Geneva, Switzerland: World Health Organisation.
57. Boles R.G., Friedlich P. Should patients be screened for 12S rRNA mutations before treatment with aminoglycosides? Mitochondrion. 2010;10(4):391–2. PubMed PMID: 20302974.

58. Ding Y., Xia B.H., Liu Q., Li M.Y., et al. Allele-specific PCR for detecting the deafness-associated mitochondrial 12S rRNA mutations. Gene. 2016;591(1):148–52. PubMed PMID: 27397648.
59. Yan D., Xiang G., Chai X., Qing J., et al. Screening of deafness-causing DNA variants that are common in patients of European ancestry using a microarray-based approach. PLoS One. 2017;12(3):e0169219. p. PubMed PMID: 28273078.
60. Wang X., Hong Y., Cai P., Tang N., et al. Rapid and Reliable Detection of Nonsyndromic Hearing Loss Mutations by Multicolor Melting Curve Analysis. Sci Rep. 2017;7:42894. PubMed PMID: 28225033.
61. McDermott J.H., Mahaveer A., James R.A., Booth N., et al. Rapid Point-of-Care Genotyping to Avoid Aminoglycoside-Induced Ototoxicity in Neonatal Intensive Care. JAMA Pediatr. 2022;176(5):486–492. PubMed PMID: 35311942.
62. del Castillo F.J., Rodriguez-Ballesteros M., Martin Y., Arellano B., et al. Heteroplasmy for the 1555A>G mutation in the mitochondrial 12S rRNA gene in six Spanish families with non-syndromic hearing loss. J Med Genet. 2003;40(8):632–6. PubMed PMID: 12920080.
63. Ealy M., Lynch K.A., Meyer N.C., Smith R.J. The prevalence of mitochondrial mutations associated with aminoglycoside-induced sensorineural hearing loss in an NICU population. Laryngoscope. 2011;121(6):1184–6. PubMed PMID: 21495045.
64. Johnson R.F., Cohen A.P., Guo Y., Schibler K., et al. Genetic mutations and aminoglycoside-induced ototoxicity in neonates. Otolaryngol Head Neck Surg. 2010;142(5):704–7. PubMed PMID: 20416460.
65. Göpel W., Berkowski S., Preuss M., Ziegler A., et al. Mitochondrial mutation m.1555A>G as a risk factor for failed newborn hearing screening in a large cohort of preterm infants. BMC Pediatr. 2014;14:210. PubMed PMID: 25155176.
66. Ballana E., Govea N., de Cid R., Garcia C., et al. Detection of unrecognized low-level mtDNA heteroplasmy may explain the variable phenotypic expressivity of apparently homoplasmic mtDNA mutations. Hum Mutat. 2008;29(2):248–57. PubMed PMID: 17999439.
67. Muyderman H., Sims N.R., Tanaka M., Fuku N., et al. The mitochondrial T1095C mutation increases gentamicin-mediated apoptosis. Mitochondrion. 2012;12(4):465–71. PubMed PMID: 22735573.

License