316th KATRD Symposium
2026-06-15

Amikacin-Induced Hearing Disturbance

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김형준

Table of Contents

75/M

- Chief complaint: hemoptysis, 2YA

- Present illness
  - Intermittent hemoptysis with cough and sputum; prior bronchial artery embolization
  - Diagnosed as bronchiectasis with NTM-PD
  - Prior azithromycin / ethambutol / rifampicin, self-discontinued (GI intolerance)

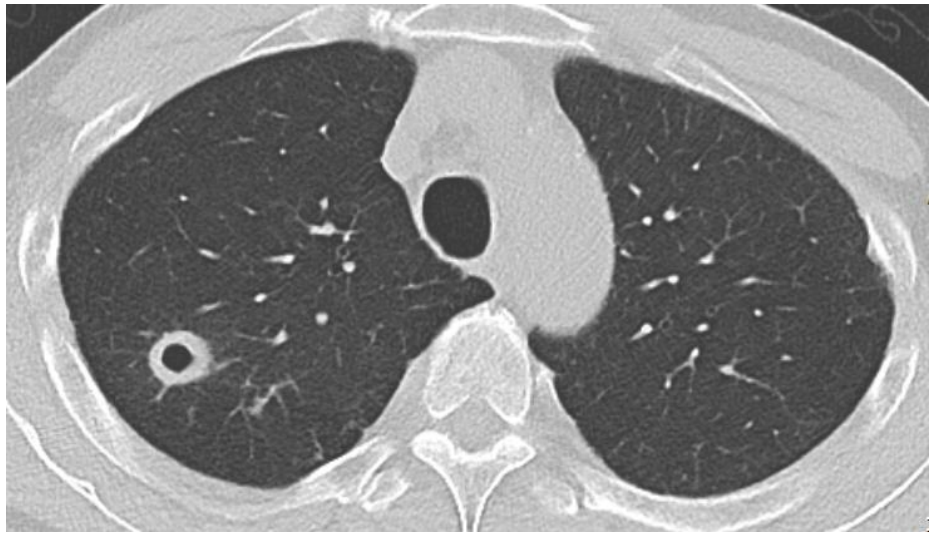
- Comorbidities
  - Coronary artery disease (prior PCI), on clopidogrel
  - Lifelong non-smoker
  - No history of tuberculosis or allergy

Lab & Microbiology

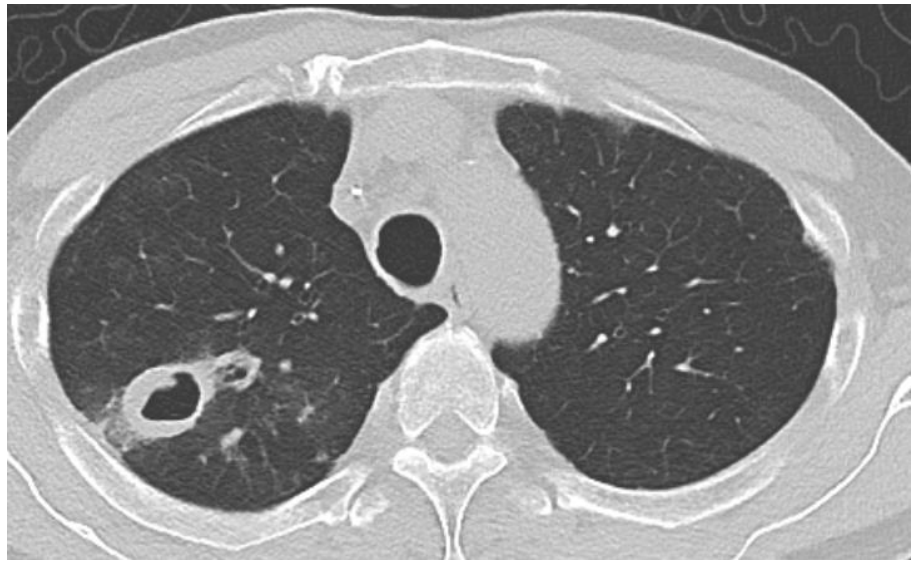
- Labs
  - WBC 10,810/mm³, Hb 14.0 g/dL, Platelets 237,000/mm³
  - BUN 16 mg/dL, Creatinine 0.89mg/dL, Albumin 4.2 g/dL
  - CRP 0.43 mg/dL, ESR 36 mm/hr

- AFB smear/culture
  - 2020-01 BW -/NTM
  - 2021-06 BW -/NTM
  - 2024-06 -/NTM (massiliense)
  - 2024-11-27 -/Contam
  - 2025-02-26 -/NTM (intracellulare, Clari S AMK I)
  - 2025-06-26 2+/NTM (intracellulare + massiliense)
  - 2025-07-22 2+/NTM (intracellulare)

CT Findings



2025-02-26



2025-07-23

Decided to treat

- 1st treatment d/t aggravation of CT and hemoptysis (massiliense + intracellulare)

  - Azm Emb Cfz Amk (IV 10mg/kg qd) (2025-07-12 ~)

Amikacin TDM: Dose Titrated to Target

Date	Dose	Target Peak / Trough (µg/mL)	Measured Peak / Trough (µg/mL)	Action
2025-07-12	IV 10 mg/kg daily (700 mg)	25–35 / <5 (daily)	NA	Treatment started
2025-07-17	600 mg daily (8.5 mg/kg)	25–35 / <5 (daily)	35.0 / 1.7	High peak → reduce dose
2025-07-21	500 mg daily (7.1 mg/kg)	25–35 / <5 (daily)	23.7 / 1.1	Subtherapeutic for NTM → Change to tiw
2025-07-24	1100 mg 3×/wk (16 mg/kg)	65–80 / <5 (tiw)	59.4 / <0.8	SCr ↑ → hold dose
2025-09-11	1100 mg 3×/wk (16 mg/kg)	65–80 / <5 (tiw)	68.8 / <0.8	Therapeutic → maintain

Treatment Course

- 1st treatment d/t aggravation of CT and hemoptysis (massiliense + intracellulare)

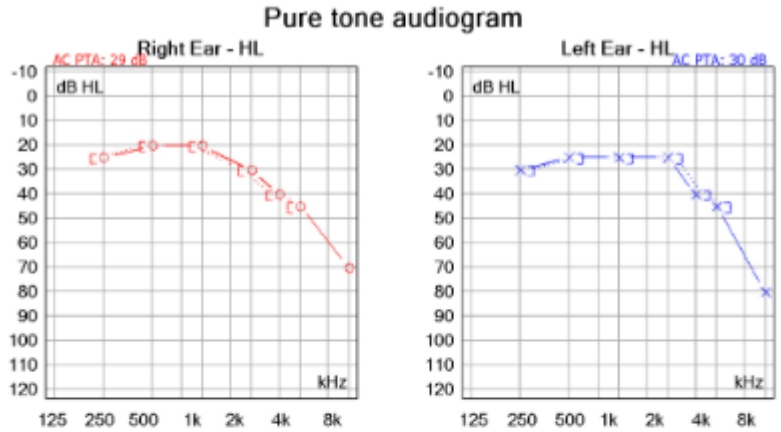
  - Azm Emb Cfz Amk (2025-07-12 ~ 2025-09-11)

  > Amk IV to nebul d/t decreased audio (subjective)

  - Azm Emb Cfz Amk(nebul) (2025-09-12 ~)

Audiometry

Azm Emb Cfz Amk 사용하면서 청력 저하



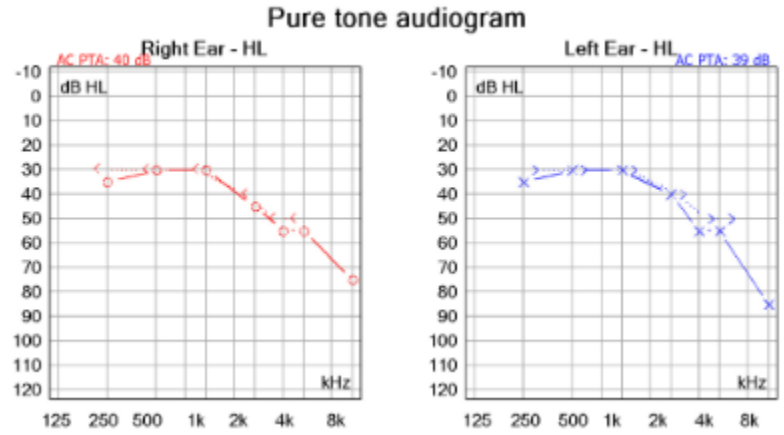
Speech Audiometry

Speech Recognition Test (SRT)					
Transducer	Test type	Intensity	Masking		Aided/ Binaural
Right	HL	22 dB	--	dB	
Left	HL	24 dB	--	dB	

Word Recognition Score (WRS)					
Transducer	WR	Intensity	Masking	Score	Aided/ Binaural
Right	WR1	62 dB	dB	100 %	
Left	WR1	64 dB	dB	100 %	

2025-07-14

IV Amikacin start 2025-07-12



Speech Audiometry

Speech Recognition Test (SRT)					
Transducer	Test type	Intensity	Masking		Aided/ Binaural
Right	HL	30 dB	--	dB	
Left	HL	28 dB	--	dB	

Word Recognition Score (WRS)					
Transducer	WR	Intensity	Masking	Score	Aided/ Binaural
Right	WR1	70 dB	dB	100 %	
Left	WR1	68 dB	dB	96 %	

2025-10-16

Amikacin IV to Nebulized form 2025-09-12

Treatment Course

- 1st treatment d/t aggravation of CT and hemoptysis (massiliense + intracellulare)

  - Azm Emb Cfz Amk (2025-07-12 ~ 2025-09-11)

  > Amk IV to nebul d/t decreased audio (subjective)

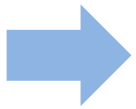
  - Azm Emb Cfz Amk(nebul) (2025-09-12 ~ 2025-10-16)

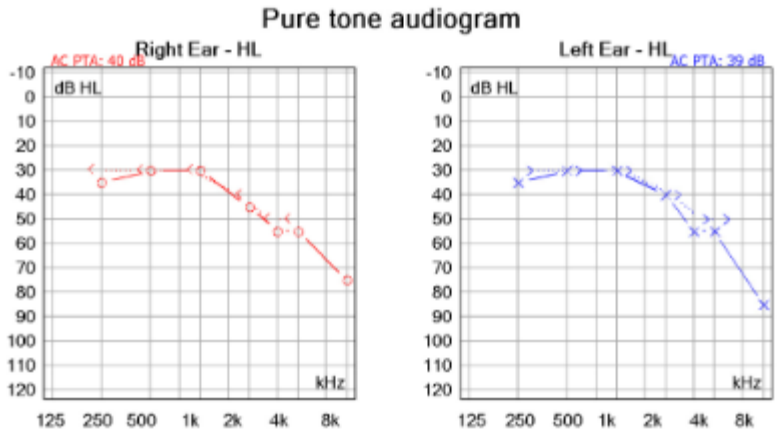
  > Amk hold d/t decreased audio (objective)

  - Azm Emb Cfz (2025-10-17 ~

Audiometry

Azm Emb Cfz Amk 사용하면서 청력 저하





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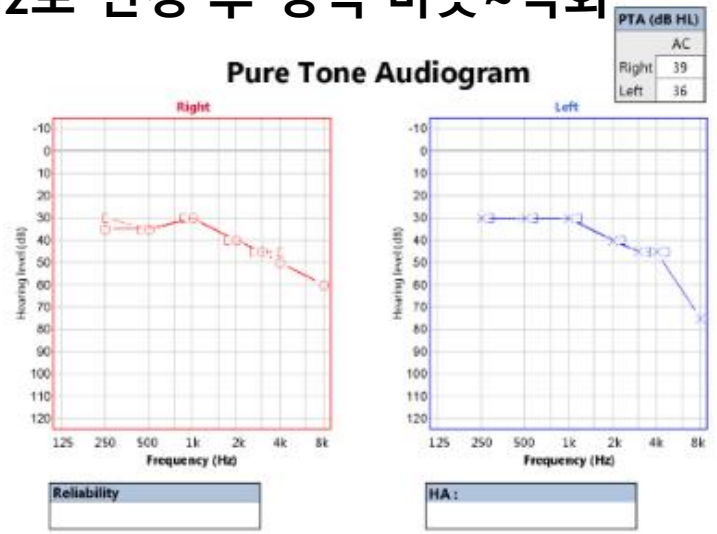
2025-10-16

Amk 중단
Azm Emb Cfz로 변경 후 청력 비슷~악화



Speech Audiometry

#	Ear	Test	dB	Score		
1	R	SRT	34		AC	
2	R	WRS	74	100.0	AC	
3	L	SRT	32		AC	
4	L	WRS	72	100.0	AC	

Tinnitogram

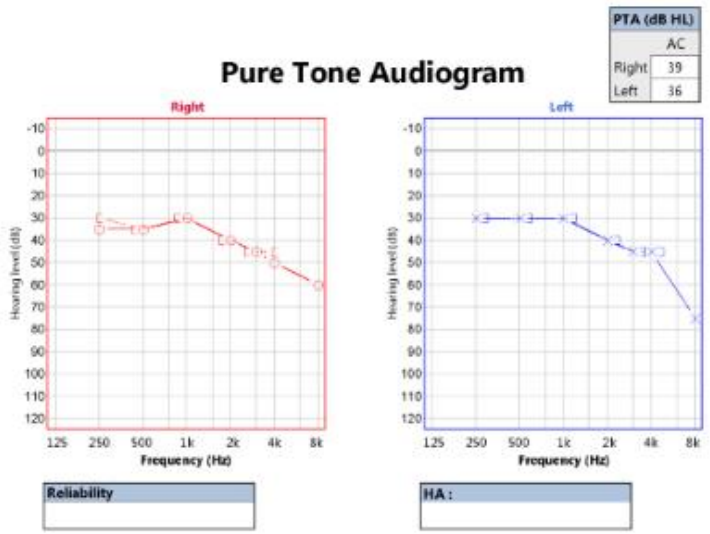
Tinnitus Evaluation			
	Right	Head	Left
Pitch Matching			
Loudness Matching			
Hearing Threshold			
Masking Noise Threshold			

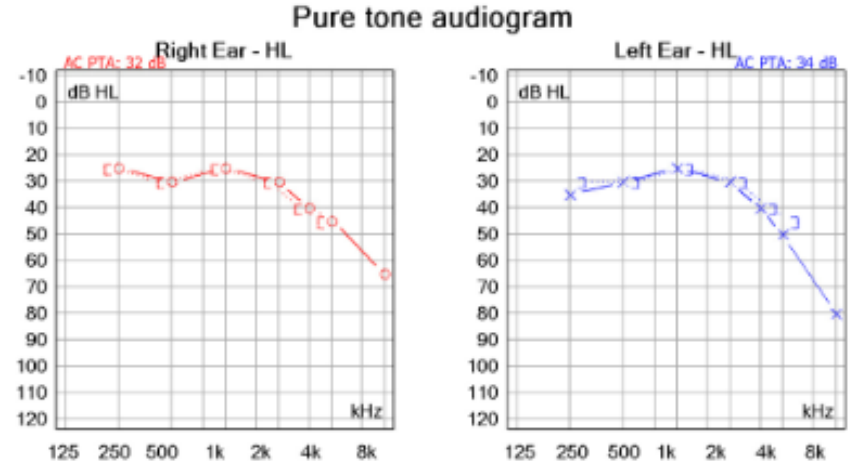
2025-12-24

Amikacin off 2025-10-17

Audiometry

청력 유지~호전





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Tinnitogram

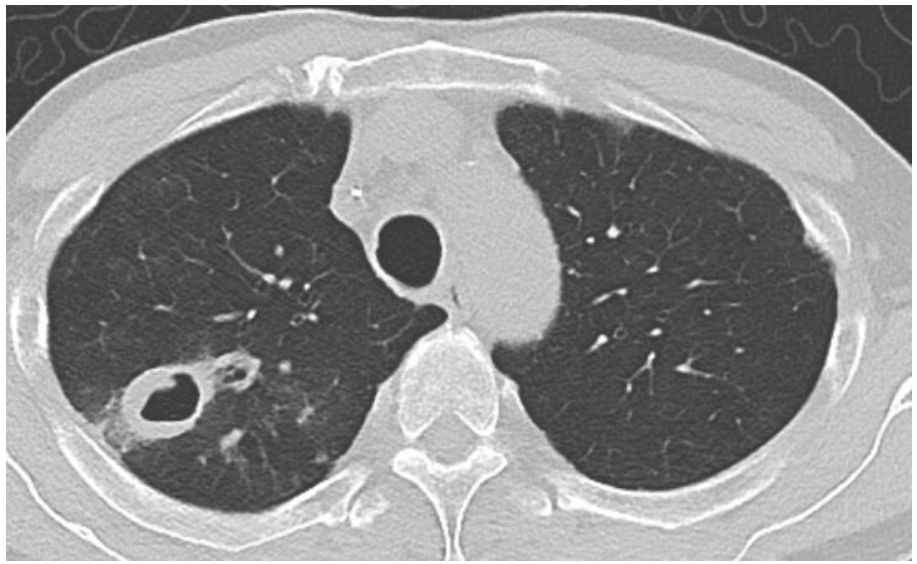
Tinnitus Evaluation	Right	Head	Left
Pitch Matching			
Loudness Matching			
Hearing Threshold			
Masking Noise Threshold			

2025-12-24

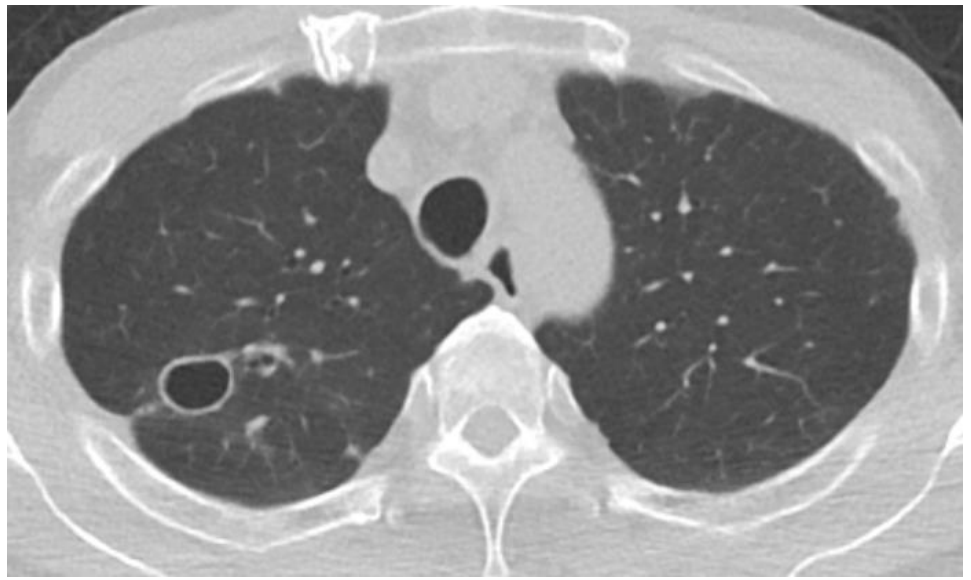
2026-02-25

Amikacin off 2025-10-17

CT Findings



2025-07-23



2025-12-14

Treatment start 2025-07-12

Sputum Studies

- AFB s/c
  - 2020-01 BW -/NTM
  - 2021-06 BW -/NTM
  - 2024-06 massiliense

  - 2024-11-27 -/Contam
  - 2025-02-26 -/NTM (intracellulare, Clari S AMK I)
  - 2025-06-26 2+/NTM (intracellulare + massiliense)
  - 2025-07-22 2+/NTM (intracellulare)
  - **2025-08-14 -/-**
  - 2025-09-11 -/-
  - 2025-09-11 -/-
  - 2025-10-16 -/-
  - 2025-12-24 -/-

← Treatment start 2025-07-12

➔ **Culture conversion(+) on treatment**

Role of Amikacin in TB/NTM-PD

Amikacin for TB

Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

- For longer MDR-TB regimen
- Amikacin included in Group C
- Less utilized, with recent focus on shorter oral regimens

WHO consolidated guidelines on tuberculosis. 2020

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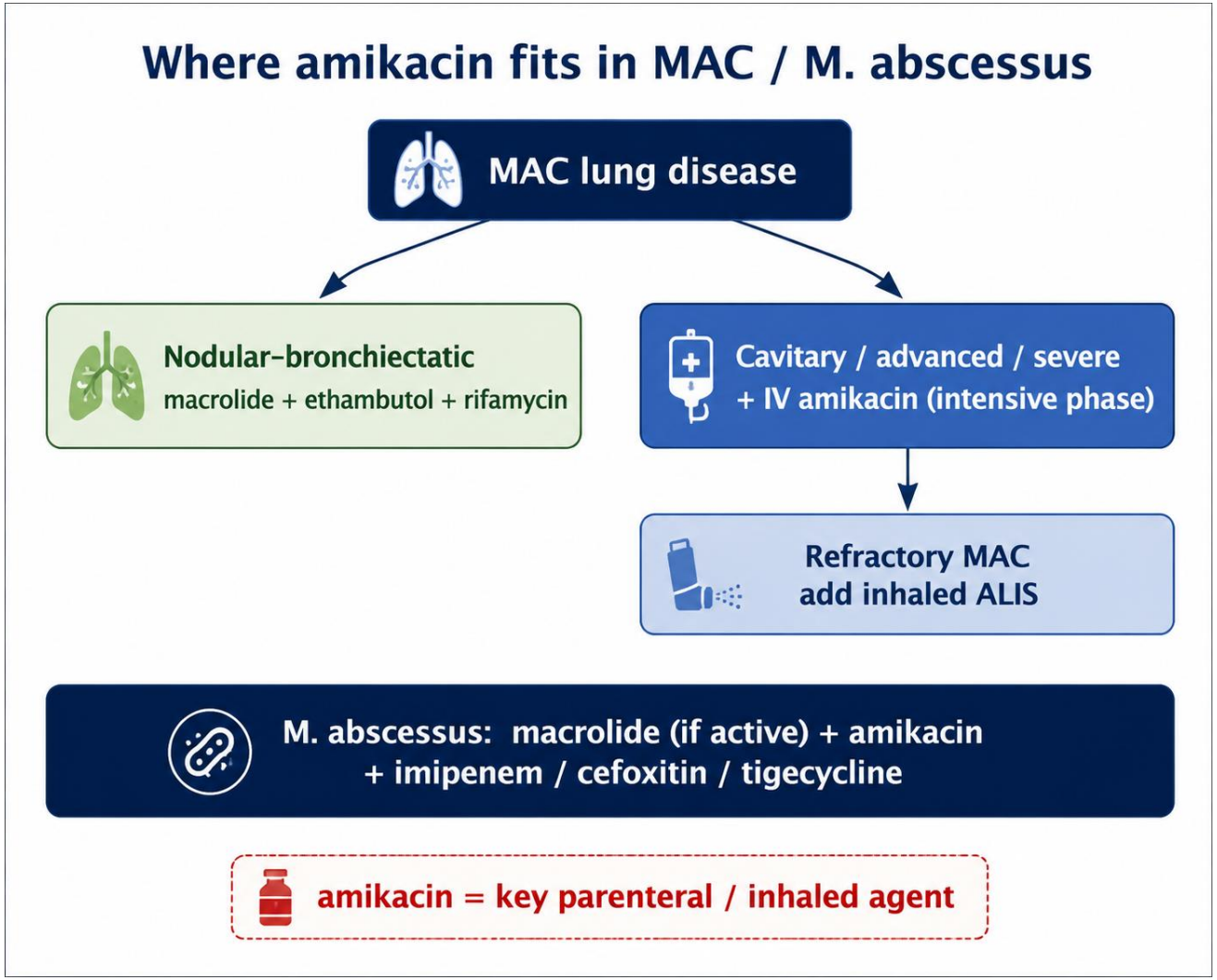
Amikacin for NTM-PD

- *M. avium* complex
  - Cavitary / advanced / macrolide-resistant
  - Nebulized form also used
- *M. abscessus*
  - susceptibility-based macrolide + amikacin



Daley CL et al. Clin Infect Dis. 2020

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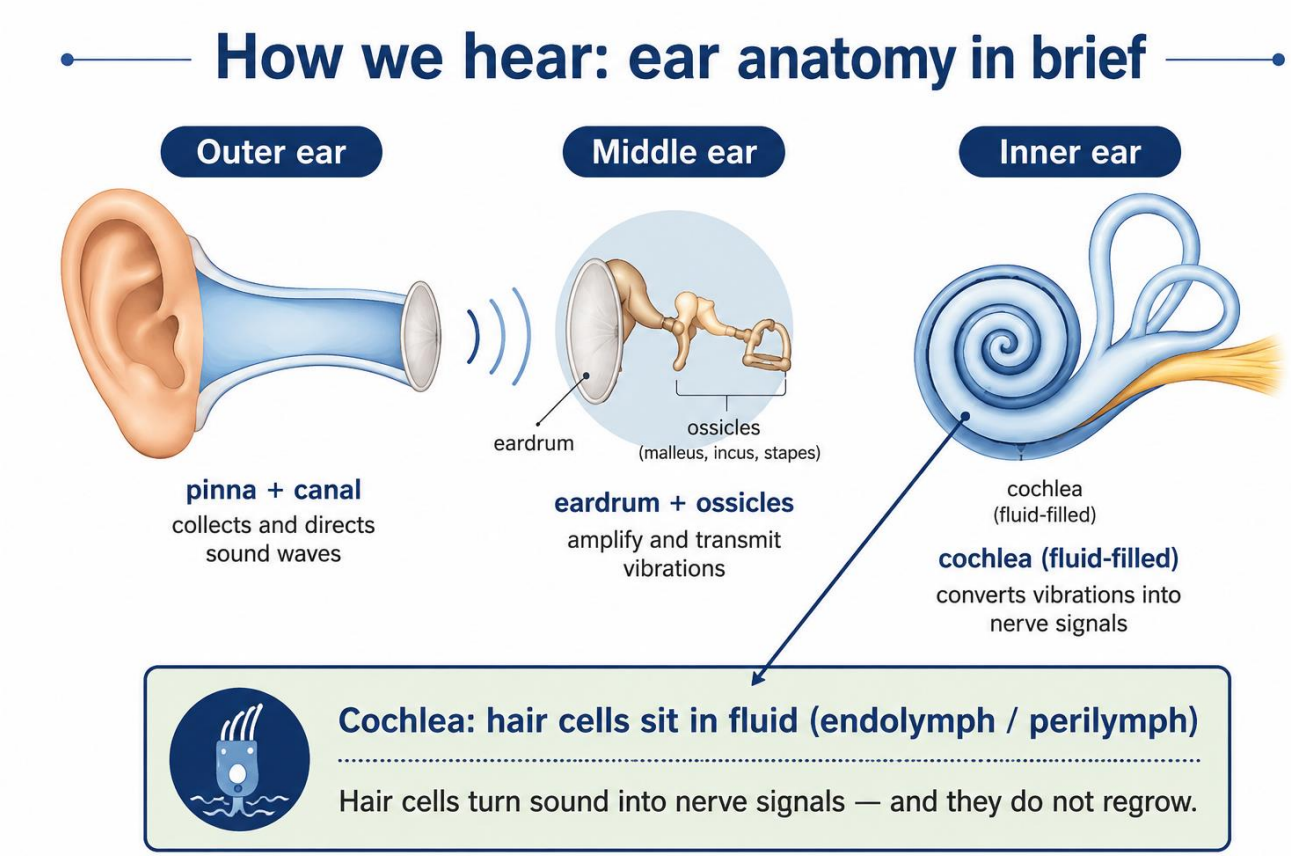
How We Hear: Ear Anatomy in Brief

- The ear has three parts: outer, middle, and inner.
- Sound is carried to the cochlea in the inner ear.
- The cochlea is filled with fluid (endolymph and perilymph).
- Hair cells in the cochlea turn sound into nerve signals.
  - They do not regrow, so damage here is mostly permanent



Cunningham LL et al. N Engl J Med. 2017

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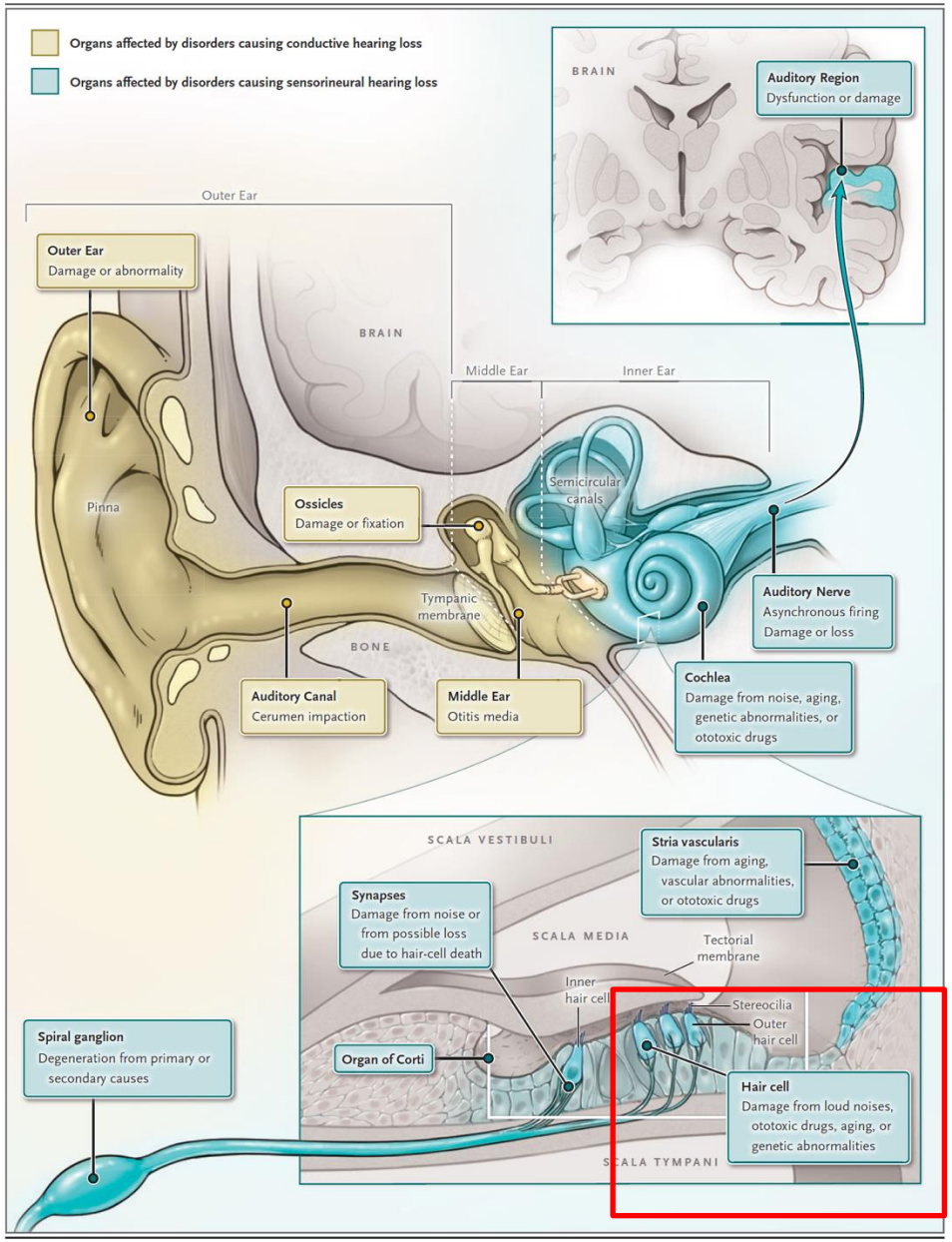
Ototoxicity with Amikacin



- Hair cells are damaged by ototoxic drugs.
- Hair cells do not regenerate, so hearing loss is mostly irreversible.
- Hearing loss may be asymptomatic in its early phase.
  - The audiogram detects it before the patient notices.

Cunningham LL et al. N Engl J Med. 2017
Black RE et al. Antimicrob Agents Chemother. 1976
Sagwa EL et al. BMC Pharmacol Toxicol. 2015

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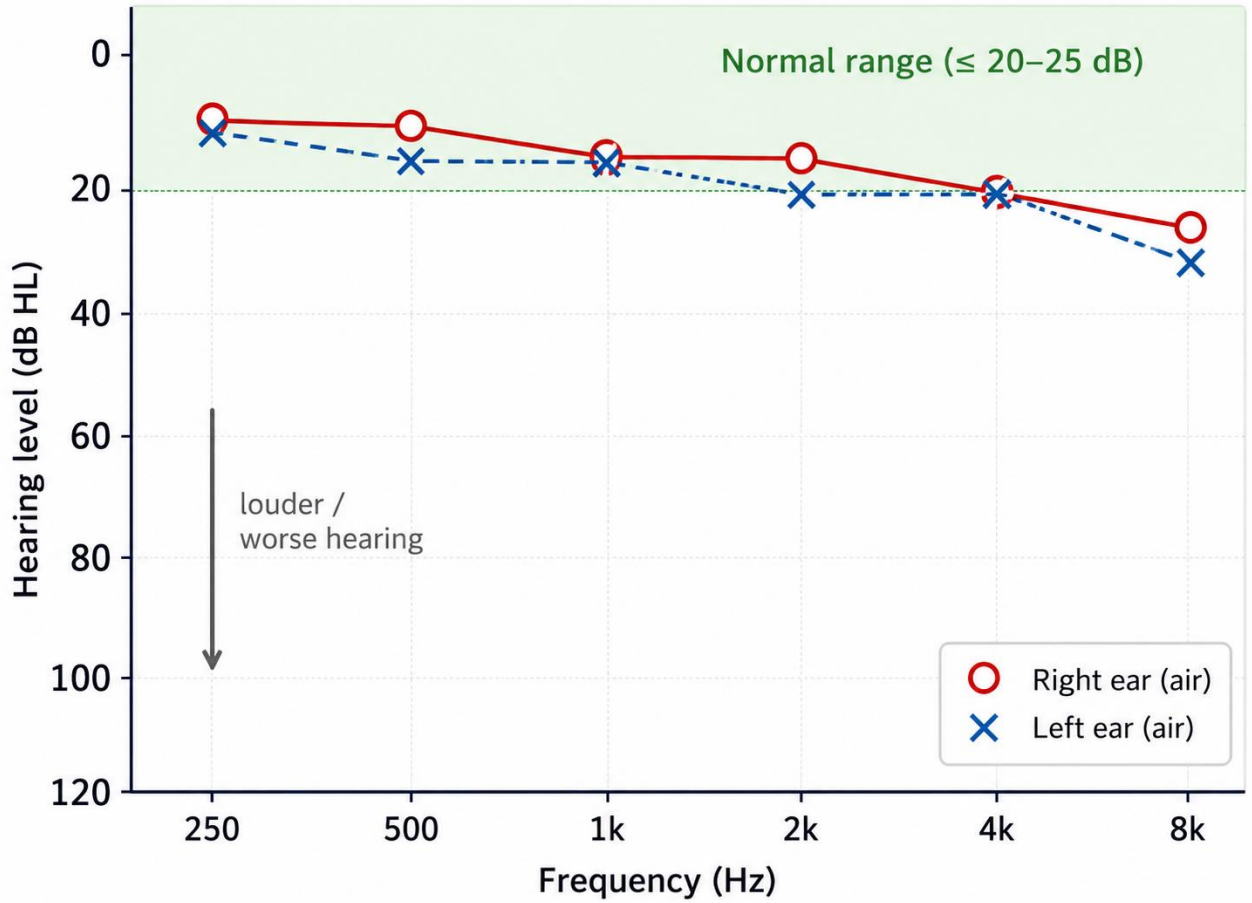
How to Read the Audiogram

How to Read an Audiogram (1): Axes & Symbols

- X-axis = frequency (Hz)
- Y-axis = intensity, decibels hearing level (dB HL)
- Lower on the graph = worse hearing
- Right = red O, Left = blue X



Sehgal M et al. Am Fam Physician. 2024

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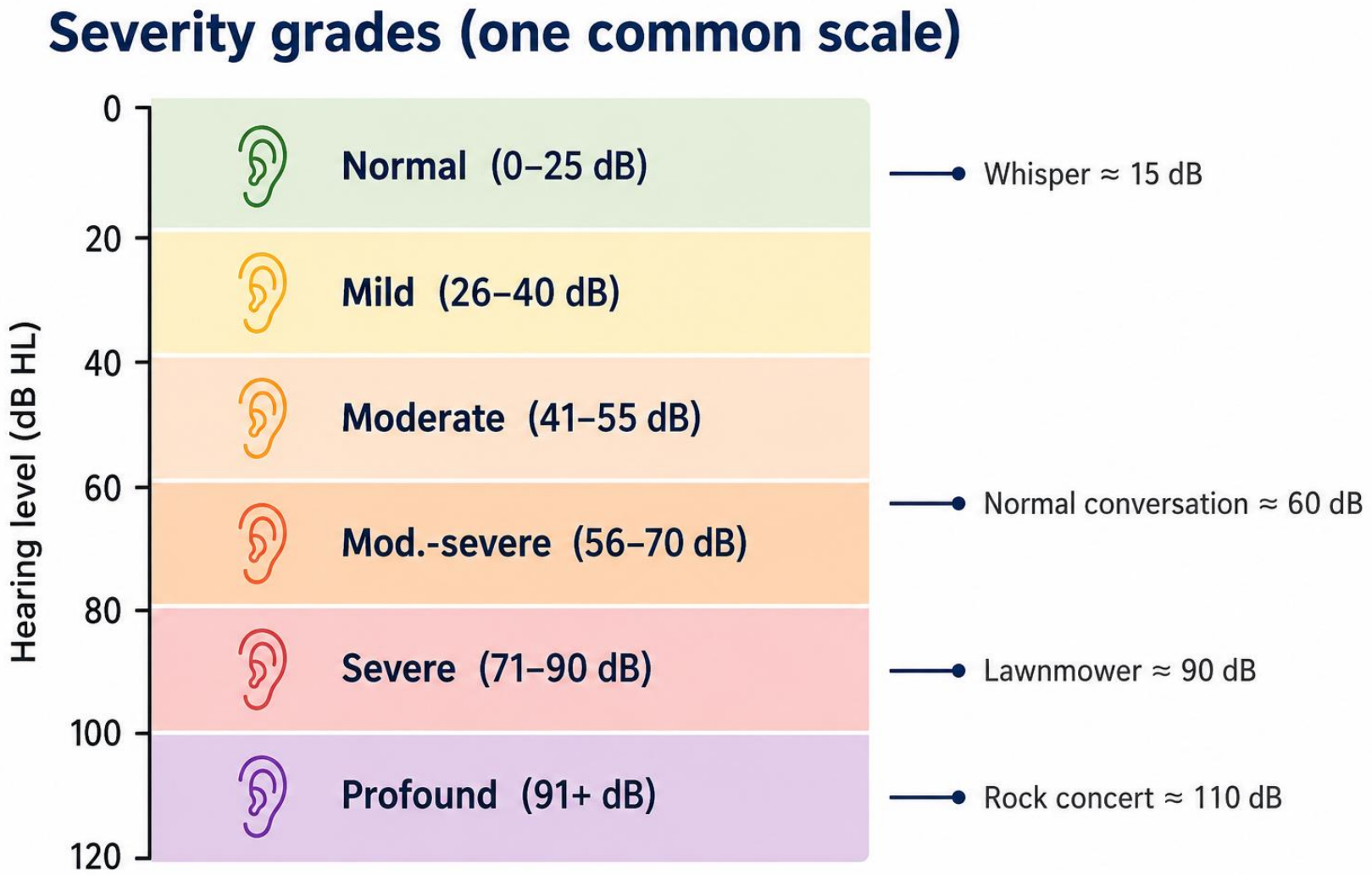
How to Read an Audiogram (2): Severity



Sehgal M et al. Am Fam Physician. 2024
https://iowaprotocols.medicine.uiowa.edu/protocols/how-read-audiogram

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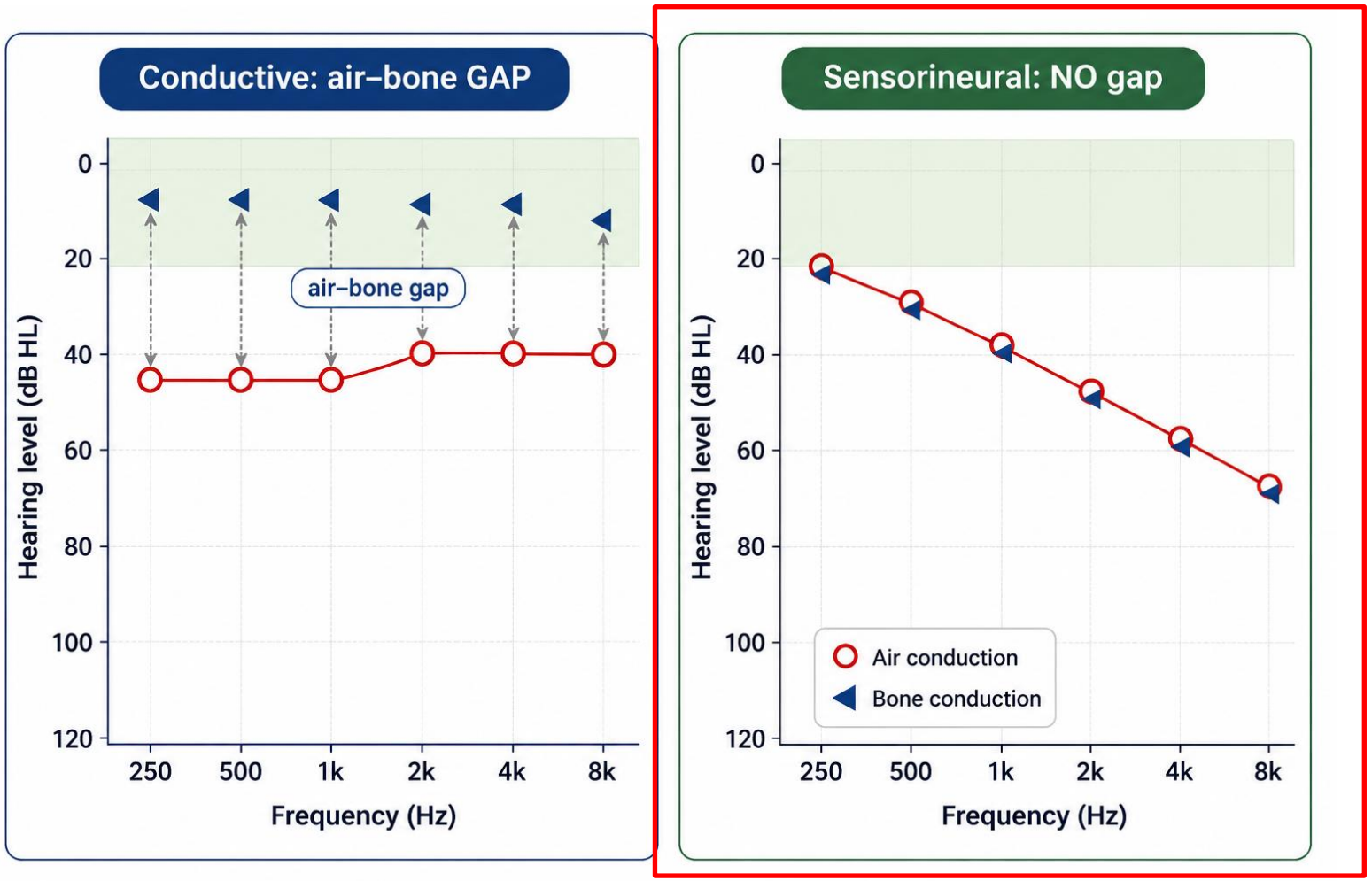
Conductive *vs.* Sensorineural Loss

- Hearing is tested two ways: through air, through bone



Amikacin injury is sensorineural: no gap

Sehgal M et al. Am Fam Physician. 2024
Cunningham LL et al. N Engl J Med. 2017

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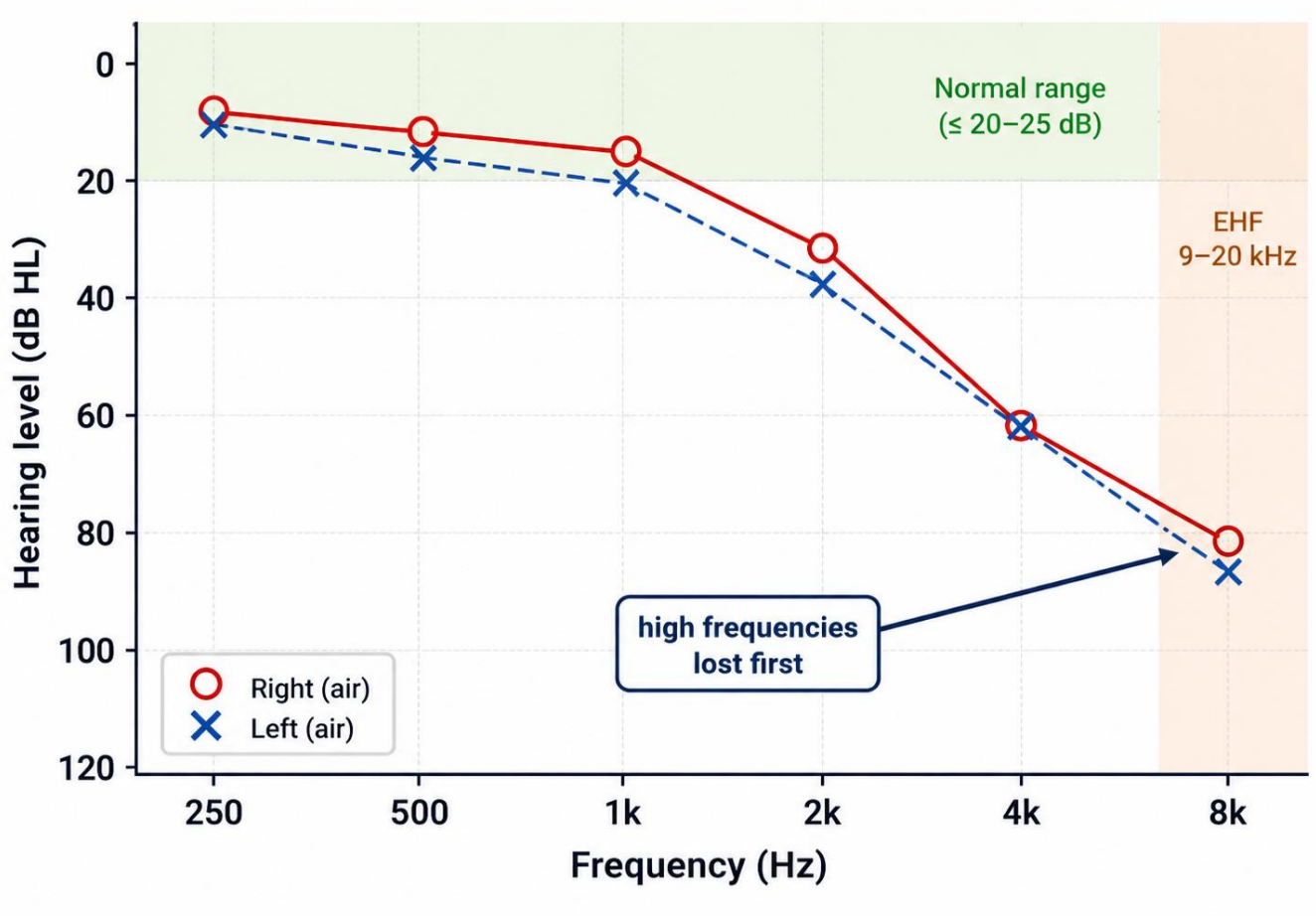
The Pattern for Amikacin Ototoxicity



- Bilateral, symmetric, sensorineural
- High frequencies affected first
  - Makes it hard to hear consonants (자음)
  - Makes hard to talk in noisy places

Salmon MK et al. Audiogram interpretation. 2023
Cunningham LL et al. N Engl J Med. 2017

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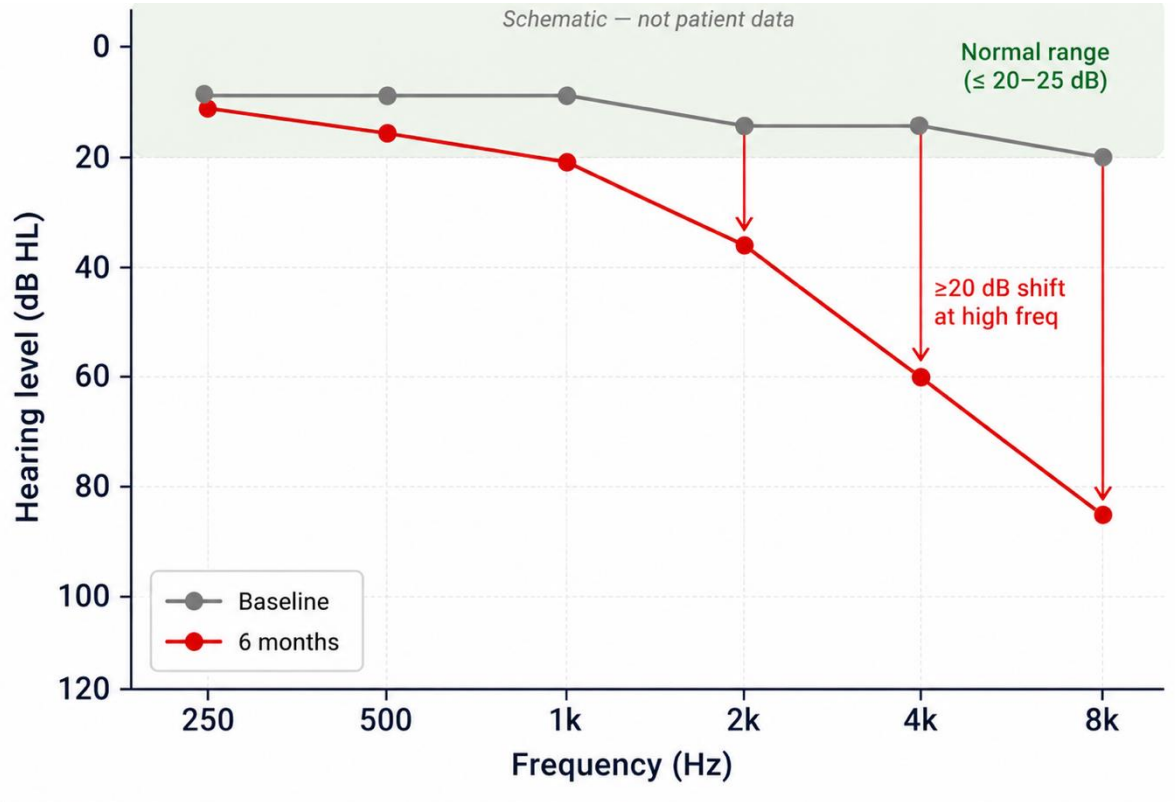
Reading a Real Shift: Baseline vs Follow-up

- Compare the follow-up audiogram with baseline.
- Look for a downward shift at the high frequencies.
- A ≥ 20 dB drop at one frequency is a significant shift.



American Speech-Language-Hearing Association. 1994

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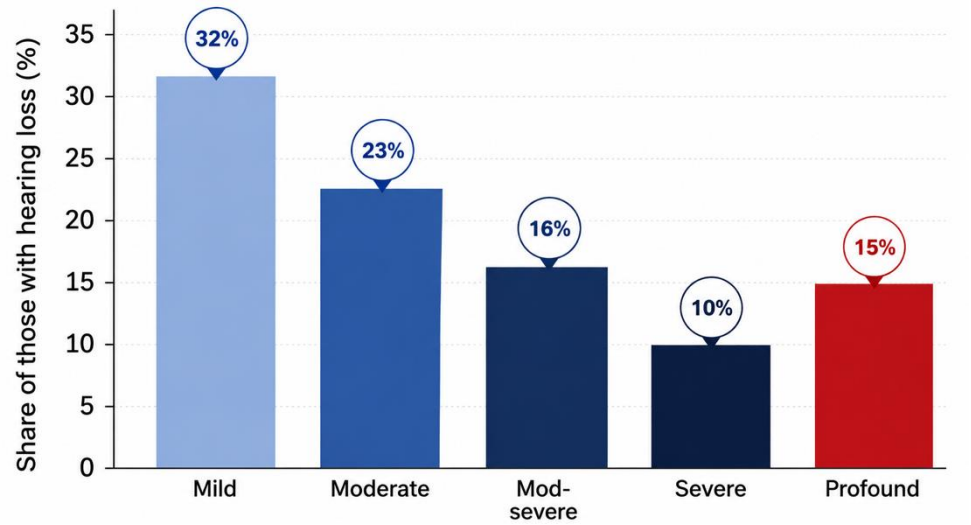
Mechanism of Ototoxicity by Amikacin

How AG-induced Hearing Loss Looks Like

- Retrospective cohort study (N = 353)
  - MDR-TB, Namibia
  - Long term regimen (intensive phase 6~8m)
  - Aminoglycoside 15mg/kg qd
- Main findings
  - Incidence of ototoxicity 58% (75% with AMK)
  - Bilateral, sensorineural, high-frequency first



Example of profound hearing loss

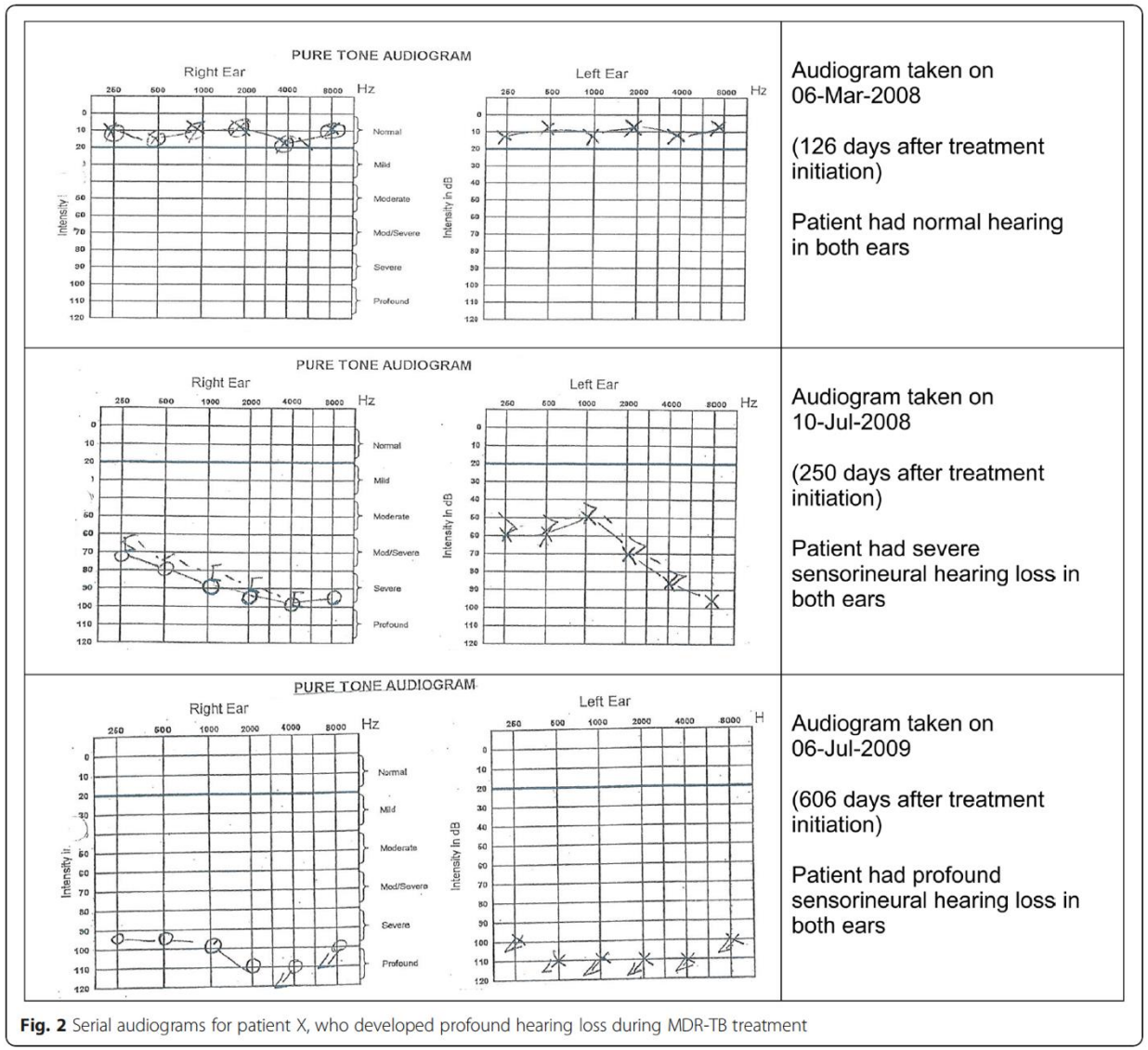


Fig. 2 Serial audiograms for patient X, who developed profound hearing loss during MDR-TB treatment

Sagwa EL et al. BMC Pharmacol Toxicol. 2015

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Tinnitus with Amikacin

- Tinnitus is a cochlear symptom:
  - Often the first thing patients notice
  - Sometimes before measurable threshold loss

Profile	Aminoglycosides
Cochleotoxic (hearing, tinnitus)	***Amikacin*** · Kanamycin · Neomycin
Vestibulotoxic (balance)	Streptomycin · Gentamicin

Selimoglu E. Curr Pharm Des. 2007

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Progression of Hearing Loss After Cessation

- Prospective audiometric surveillance, London MDR-TB unit (N=12)
- **3 of 4** gradable-loss cases **progressed after stopping**.

➔ ***Loss can begin or worsen after the drug stops.***

TABLE 1 Amikacin use, ototoxicity detected during treatment and rationale for discontinuation of treatment

Hearing loss	Age years	Tinnitus	Maximal hearing loss# dB	Frequencies¶ n (NCI CTCAE grade)	Stopped amikacin early (reason)	Progression of hearing loss after amikacin cessation?	Total treatment period days	Total dose g
Gradable hearing loss	29	Yes	50	2 (2)	Yes (hearing loss)	Yes	139	104.3
	26	Yes	75	6 (3)	Yes (hearing loss)	Yes	160	160
	37	No	55	1 (2)	Yes (hearing loss)	No	91	81.9
	23	No	75	4 (3)	Yes (hearing loss)	Yes	125	87.5
Early non-gradable hearing loss	31	No	15	1 (-)	Yes (hearing loss)	Unknown	75	75
	26	No	15	1 (-)	Yes (hearing loss)	No	123	115
	42	No	25	1 (-)	Yes (hearing loss)	No	178	109.9
No hearing loss	28	Yes	20	1 (-)	Yes (tinnitus)	No	119	107
	20	No	10	0 (-)	Yes (eczematous drug reaction+)	No	121	77.5
	19	No	5	0 (-)	Yes (morning fatigue§)	Unknown	78	54.6
	50	No	0	0 (-)	No	Unknown	92	92
	24	No	10	0 (-)	No	No	180	119.4

Melchionda V et al. Eur Respir J. 2013

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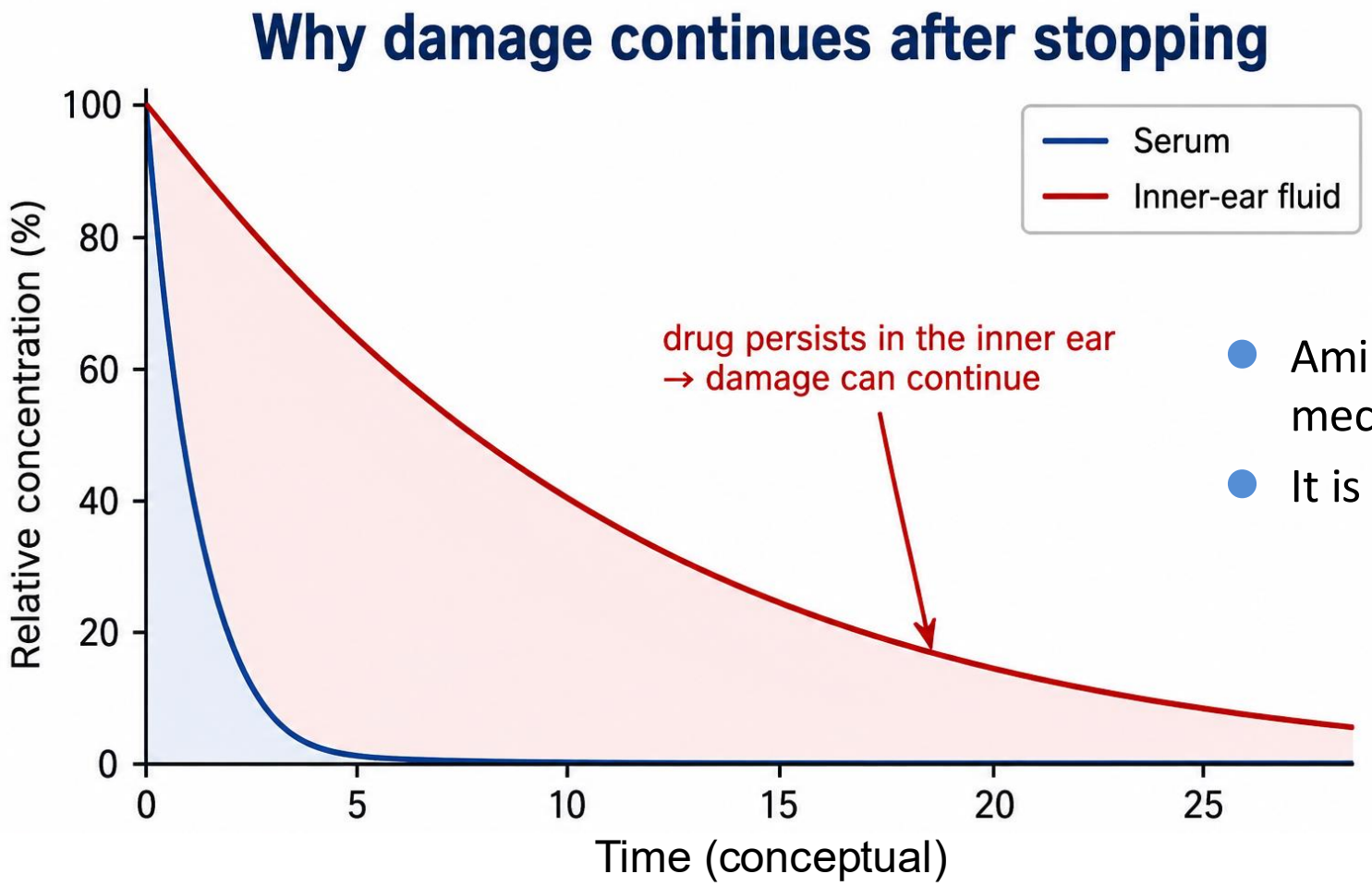
Drug Entry & Inner-ear Retention

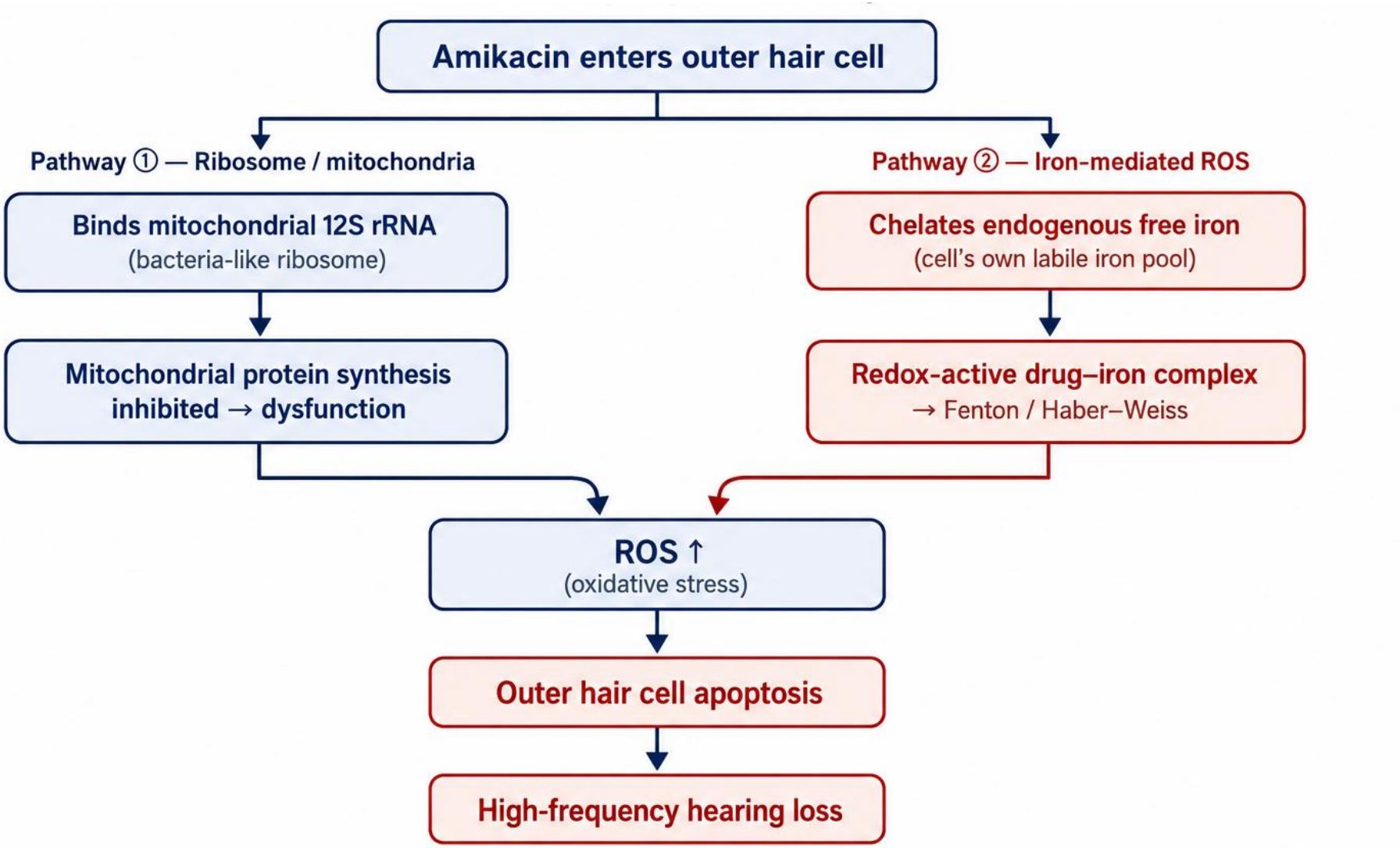


- Amikacin enters hair cells via the mechanotransduction channel.
- It is cleared slowly from inner-ear fluids.

  ➔ Progression after the drug stops.

Cunningham LL et al. N Engl J Med. 2017

Outer Hair Cell Apoptosis by Amikacin



Selimoglu E. Curr Pharm Des. 2007

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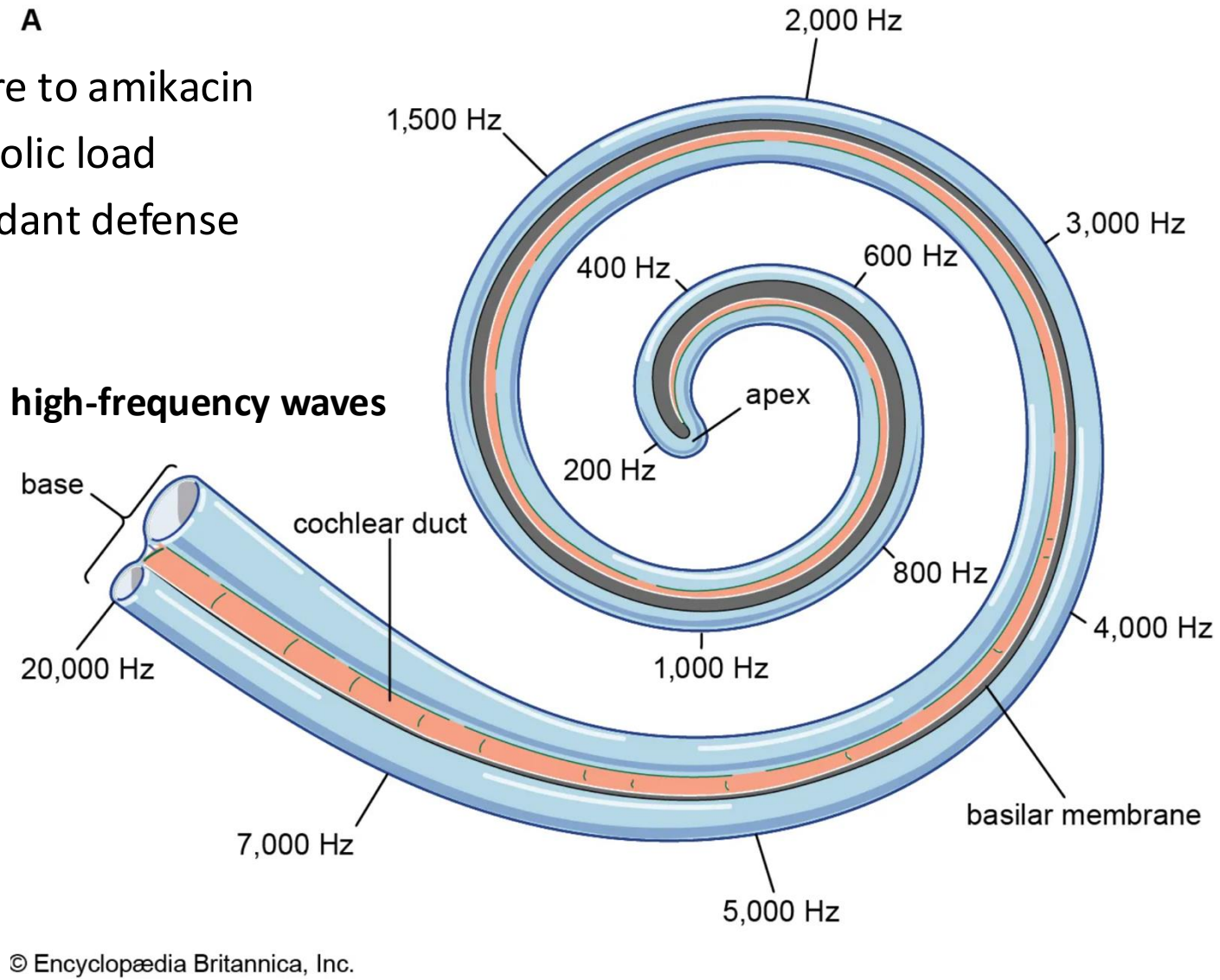
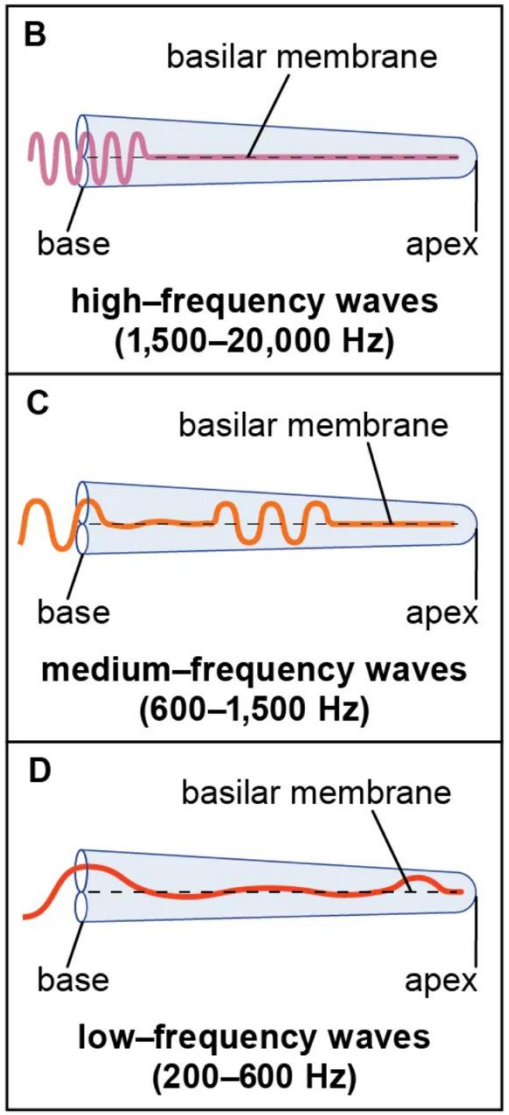
Why High Frequencies First

- More exposure to amikacin
- Higher metabolic load
- Lower antioxidant defense

Base of cochlea
- Associated with high-frequency waves





Selimoglu E. Curr Pharm Des. 2007

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Summary: Ototoxicity by amikacin

- Amikacin is a key drug for NTM-PD and still used for MDR-TB.
- Its ototoxicity is common and largely irreversible: cochlear outer hair cells are killed by ROS and do not regenerate.
- The loss is bilateral, symmetric, and sensorineural, and starts in the high frequencies (basal outer hair cells first).
- It is often asymptomatic at onset, so it is caught by audiometry, not symptoms (tinnitus may be the first clue).
- Because drug is retained in inner-ear fluid, hearing loss can begin or progress even after amikacin is stopped.

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Ototoxicity by Amikacin: Who is at Risk?

Incidence of Amikacin-Induced Hearing Loss

Study	Country	Disease	Design	N	Amikacin dose	Duration	Target Cmax (peak)	Incidence
Black 1976	US	non-TB/NTM	Prospective	55	>7.5 mg/kg q8h	**Median 9 days**	None preset; peak >32 µg/mL flagged toxic	**24%**
Javadi 2011	Iran	MDR-TB	Cross-sectional	41	500 mg/d	**6 months**	None	**70%**
Modongo 2014	Botswana	MDR-TB	Retrospective	437	15–25 mg/kg IM (max 1000 mg/d); daily→tiw	**Intensive phase; variable**	None	**62%**
Sagwa 2015	Namibia	MDR-TB	Retrospective	353	15 mg/kg/d (adjustable), IM	**6–8 months**	None	**75%**
Lee 2017	Korea	*M. abscessus* -PD	Retrospective	24	15 mg/kg/d once-daily Cmax-adjusted	**~4 weeks**	55–65 µg/mL	**25%**
Aznar 2019	Canada	NTM-PD	Retrospective	77	median 9.9 mg/kg/d 2–7×/wk	**7 months**	20–25 µg/mL	**39%**

- Range from 24% to 75%
- Higher rate with higher cumulative dose

Black RE et al. Antimicrob Agents Chemother. 1976
Javadi MR et al. Iran J Pharm Res. 2011
Modongo C et al. BMC Infect Dis. 2014
Sagwa EL et al. BMC Pharmacol Toxicol. 2015
Lee H et al. Int J Tuberc Lung Dis. 2017
Aznar ML et al. BMC Pharmacol Toxicol. 2019

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What is Associated with Ototoxicity?

- Retrospective pharmacokinetic study (N= 28)
  - MDR-TB, Botswana (43% HIV)
- Amikacin dosed per WHO
  - **~15 mg/kg**, IM, once daily
  - Switched to thrice-weekly after culture conversion if hearing loss occurred
  - Median **6 months** of duration
- Main findings
  - Hearing difficulty by symptom: **39%**
  - Audiometry-confirmed hearing loss: **25%**

TABLE 1 Demographic and clinical characteristics on 28 patients enrolled in the study

Clinical variable	Value ($n = 28$)
No. (%) female	12 (43)
No. (%) HIV infected	12 (43)
No. (%) on antiretroviral therapy	12 (43)
No. (%) with hearing loss	11 (39)
Subjective	11 (39)
Tinnitus	9 (32)
Audiometry confirmed	7 (25)
Mean (SD) age (yr)	44 (18)
Mean (SD) initial wt (kg)	50.57 (10.34)
No. (%) with prior aminoglycoside exposure	10 (36)
Median (range) amikacin dose (mg)	875 (400–1,000)
Median (range) therapy duration (days)	183.5 (28–866)
Median (range) cumulative dose (mg)	94,914 (17,864–601,394)

Modongo C et al. Antimicrob Agents Chemother. 2015

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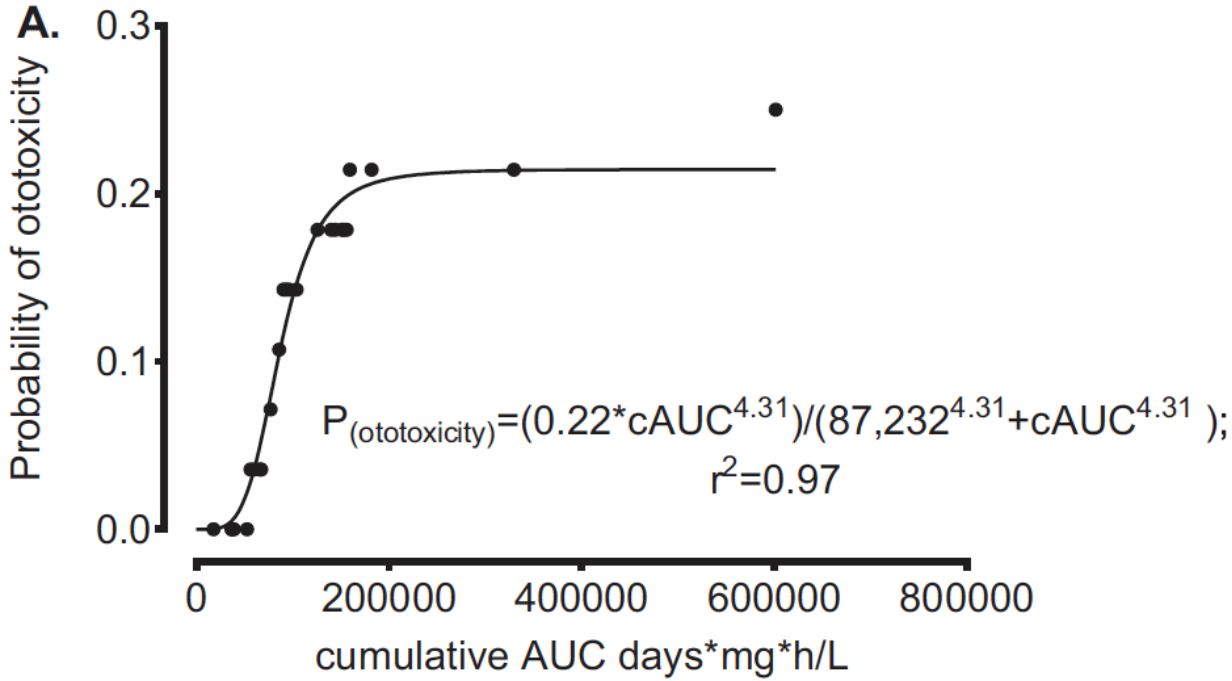
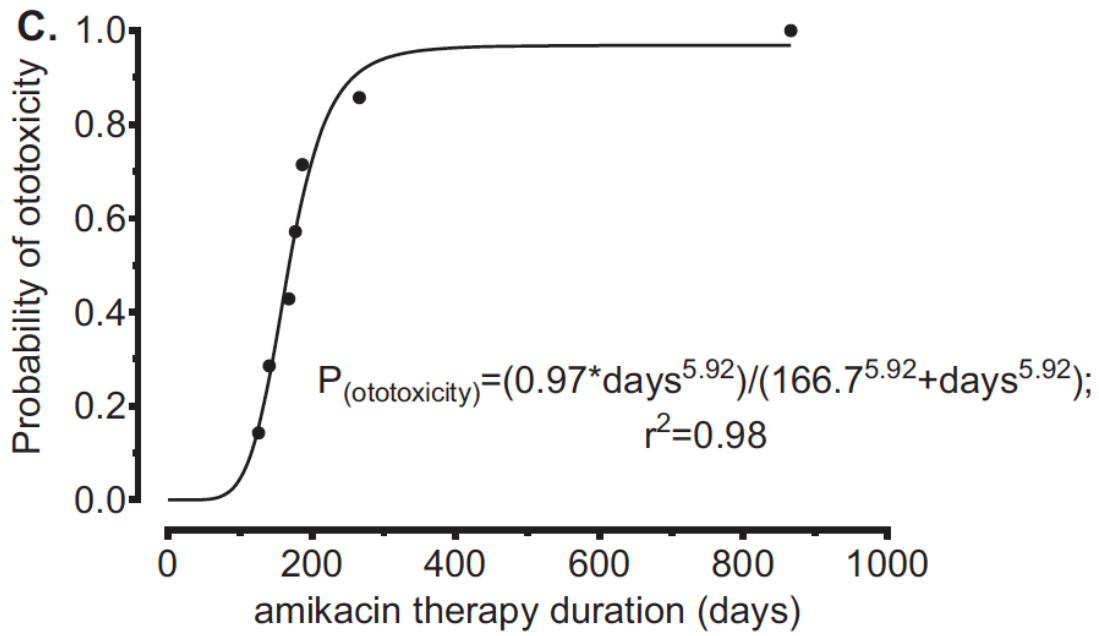
What is Associated with Ototoxicity? (cont'd)

Cumulative AUC days



Amikacin therapy duration



- **Cumulative AUC days & duration** were associated with higher risk of ototoxicity.
- **Peak levels** of amikacin was **not** associated with higher risk of ototoxicity.

Modongo C et al. Antimicrob Agents Chemother. 2015

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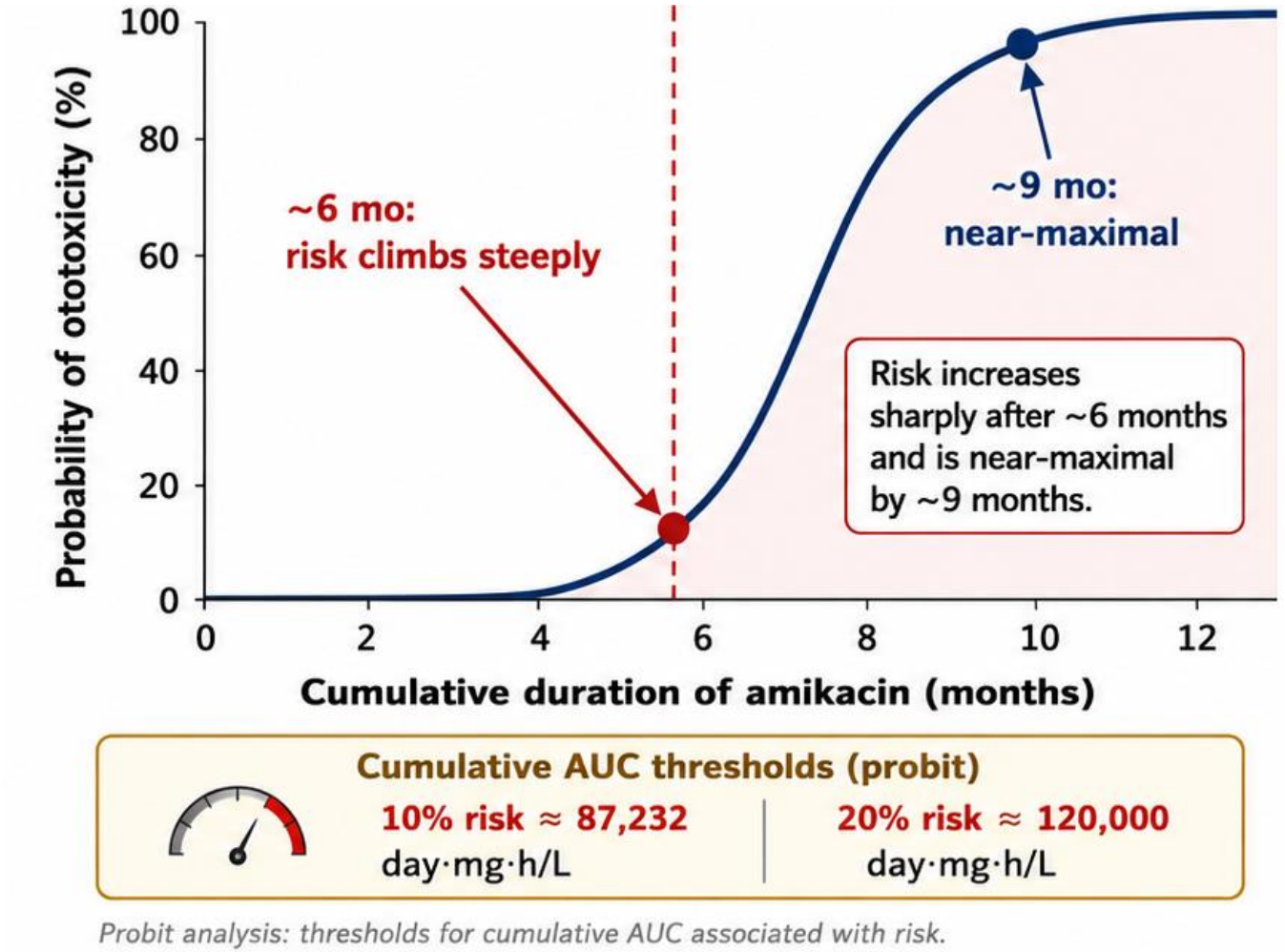
The 6-Month Cliff

- Risk climbs **steeply after about 6 months** and is **near-maximal by about 9 months**.



Probit analysis: thresholds for cumulative AUC associated with risk.

Modongo C et al. Antimicrob Agents Chemother. 2015

Daily *vs.* Thrice-weekly Dosing

- Prospective randomized trial (n = 87)
  - Single-center, USA
  - TB or NTM-PD
- Patients grouped by:
  - Three drugs: Streptomycin, Kanamycin, Amikacin
  - Schedule (**<u>total 75mg/kg/wk</u>**)
    - 5/wk 15 mg/kg
    - 3/wk 25 mg/kg

Table 1. Patient characteristics, by drug and frequency of administration.

Characteristic	Streptomycin		Kanamycin		Amikacin	
	Administered daily (n = 16)	Administered 3 times per week (n = 16)	Administered daily (n = 16)	Administered 3 times per week (n = 17)	Administered daily (n = 11)	Administered 3 times per week (n = 11)
Age, median years (range)	54 (26–73)	58 (25–76)	42 (19–68)	55 (32–79)	51 (27–75)	48 (35–70)
No. of male subjects/no. of female subjects	7/9	5/11	9/7	10/7	4/7	5/6
MTB	6	3	10	6	2	2
MAC	10	13	4	9	5	7
Other NTM	0	0	2	2	4	2
History of renal disease	0	0	0	0	1	0
History of hearing loss	1	0	1	1	1	1
Previous receipt of aminoglycosides	4	4	5	7	1	4
Duration of therapy, median weeks (range)	9 (2–38)	14 (2–107)	16 (1–139)	12 (2–38)	16 (1–22)	23 (2–43)
Underwent surgery	1	1	5	5	1	3
Dose, median mg (range)	800 (500–1150)	1225 (800–1900)	1075 (550–1200)	1600 (1200–2600)	800 (600–1400)	1300 (1100–1900)
Total dose, median mg/kg (range)	564 (130–2446)	828 (127–6538)	1095 (76–10,895)	787 (93–2604)	1168 (30–1472)	1689 (126–2985)
C_{max}, median μg/mL (range)	44 (33–58)	71 (44–100)	44 (32–65)	72 (33–113)	46 (26–54)	79 (54–98)
$t_{1/2}$, median h (range)	3.5 (2.4–5.8)	3.3 (2.0–6.7)	2.2 (1.5–3.6)	2.5 (1.6–4.0)	2.5 (1.7–3.0)	2.1 (1.4–3.3)

NOTE. Data are no. of patients with the specified characteristic, unless otherwise indicated. C_{max}, maximum serum concentration back-calculated to the end of infusion; MAC, disease due to *Mycobacterium avium* complex; MTB, *Mycobacterium tuberculosis;* NTM, disease due to nontuberculous mycobacteria; $t_{1/2}$, half-life.

Peloquin CA et al. Clin Infect Dis. 2004

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Daily *vs.* Thrice-weekly Dosing (cont'd)

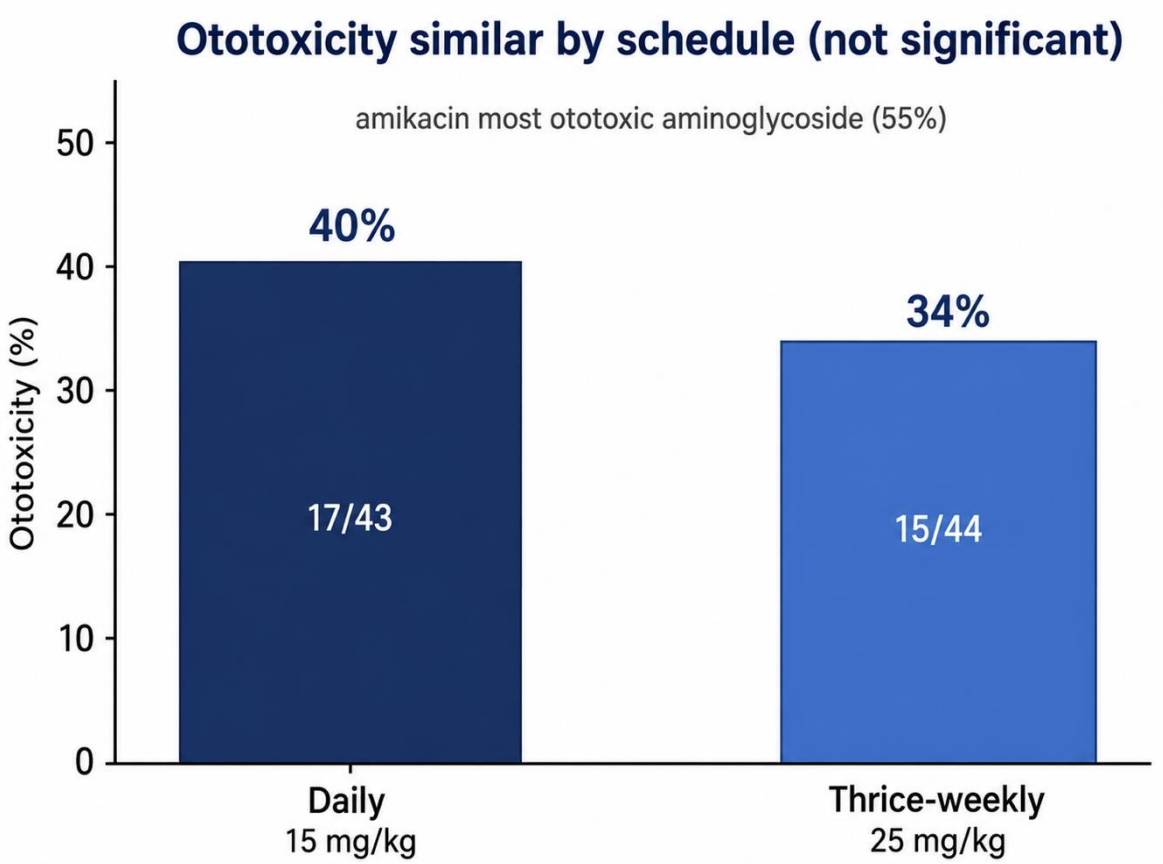

Table 4. Patients with adverse events, by number of weeks of treatment received when adverse event occurred, regardless of total duration of treatment.

Adverse event	No. (%) of patients		
	≤4 weeks (n = 87)	5–8 weeks (n = 82)	>8 weeks (n = 77)
Nephrotoxicity	3 (3)	2 (2)	8 (10)
Ototoxicity	7 (8)	8 (10)	17 (22)
Positive nystagmus test result	3 (3)	0 (0)	0 (0)
Positive Romberg test result	2 (2)	0 (0)	0 (0)
Positive heel-to-toe test result	4 (5)	0 (0)	0 (0)

- Ototoxicity: **daily 40% (17/43) vs thrice-weekly 34% (15/44)**; **NOT** significantly different
  - Overall 37%; amikacin was the most ototoxic aminoglycoside (55%)
- **Older age and longer duration** was associated with higher risk of ototoxicity.

Peloquin CA et al. Clin Infect Dis. 2004

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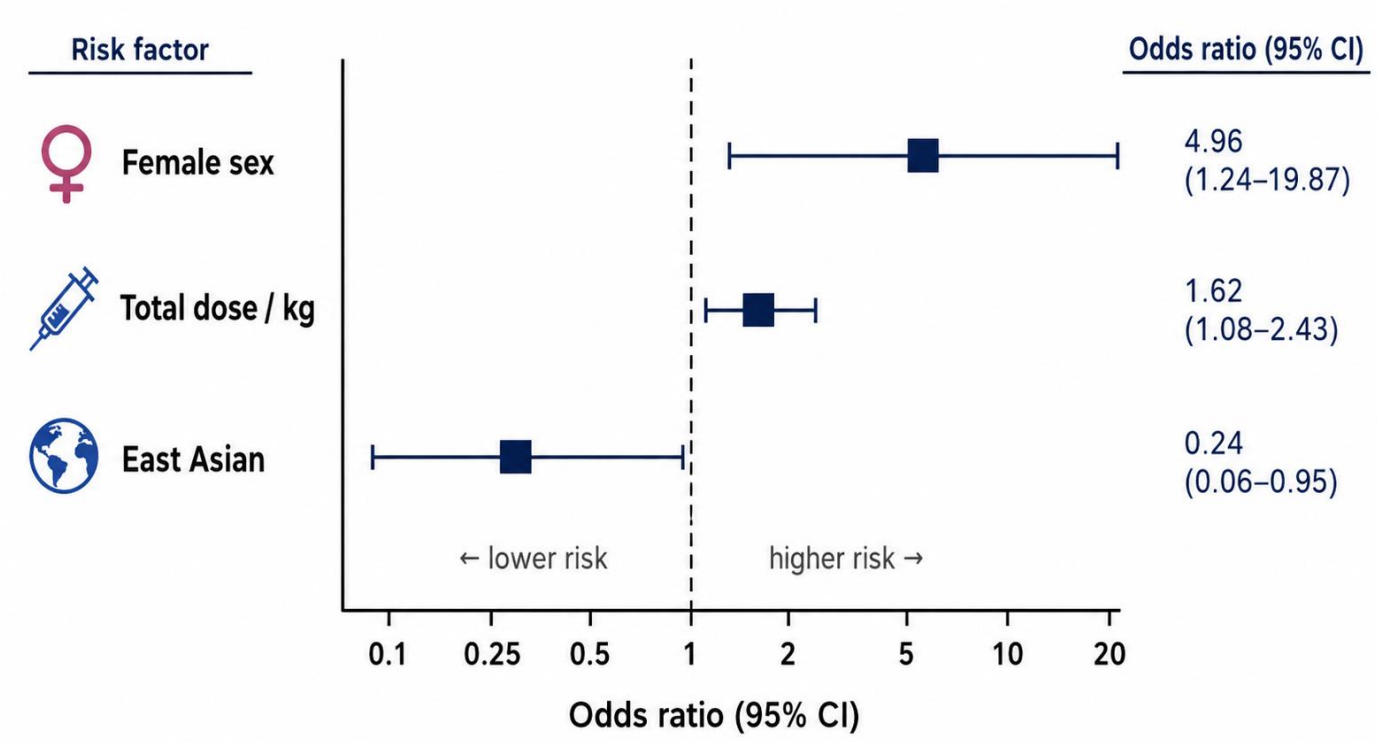
Low-dose Amikacin?

- Retrospective NTM cohort (N = 107)
  - Single-center, Canada
- Details regarding amikacin
  - Starting dose **median 9.9mg**/kg
    - **3/wk 72%**
    - 5/wk 18.7%
    - 7/wk 4.7%
  - Target peak evel 20-25ug/ml
  - **Median duration 7 months**
- Main findings
  - **Subjective hearing discomfort: 40.2%**
  - **Hearing impairment in audiogram: 39.0%**
  - At-risk: female sex, higher total dose, non-Asians



Aznar ML et al. BMC Pharmacol Toxicol. 2019

Use of TDM?

- Retrospective cohort study (N=80)
  - MDR/XDR-TB, Netherlands
  - Longer regimen
- Dosing of aminoglycoside
  - Initial dosing 15mg/kg
  - Dosing was guided by TDM, leading **6.5mg/kg**
    - Target Cmax/MIC > 20
- Outcomes
  - Treatment success rate: 35/52 (67.3)
  - **Ototoxicity: 9.1% with amikacin**

TABLE 3 Treatment details and side effects

Parameter or side effect	No. (%) of patients or median (IQR)	
	Amikacin	Kanamycin[a]
Common parameters		
Duration (days) of hospital stay	92.5 (67.3–162.3)	110.0 (90.5–186.5)
Duration (days) of treatment with aminoglycosides	138.0 (69.8–187.0)	104.0 (82.0–179.8)
Creatinine level (μmol/liter) after 90 days of treatment	80.0 (66.0–93.0)	77.0 (62.0–100.5)
Creatinine level (μmol/liter) after 180 days of treatment	82.0 (70.0–95.0)	83.5 (67.8–101.5)
Observed side effects[a]		
Nephrotoxicity	11 (22.9)	9 (34.6)
Ototoxicity	4 (9.1)	5 (21.7)

van Altena R et al. Antimicrob Agents Chemother. 2017

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Amikacin TDM Targets in NTM-PD

- Targets differ by regimen: peak is higher with less-frequent, higher doses.
- For Asians (???)

Regimen	Target peak	Trough
Daily	**35–45 µg/mL**	< 5 µg/mL
Intermittent (3×/week)	**65–80 µg/mL**	< 5 µg/mL

Daley CL et al. Clin Infect Dis. 2020

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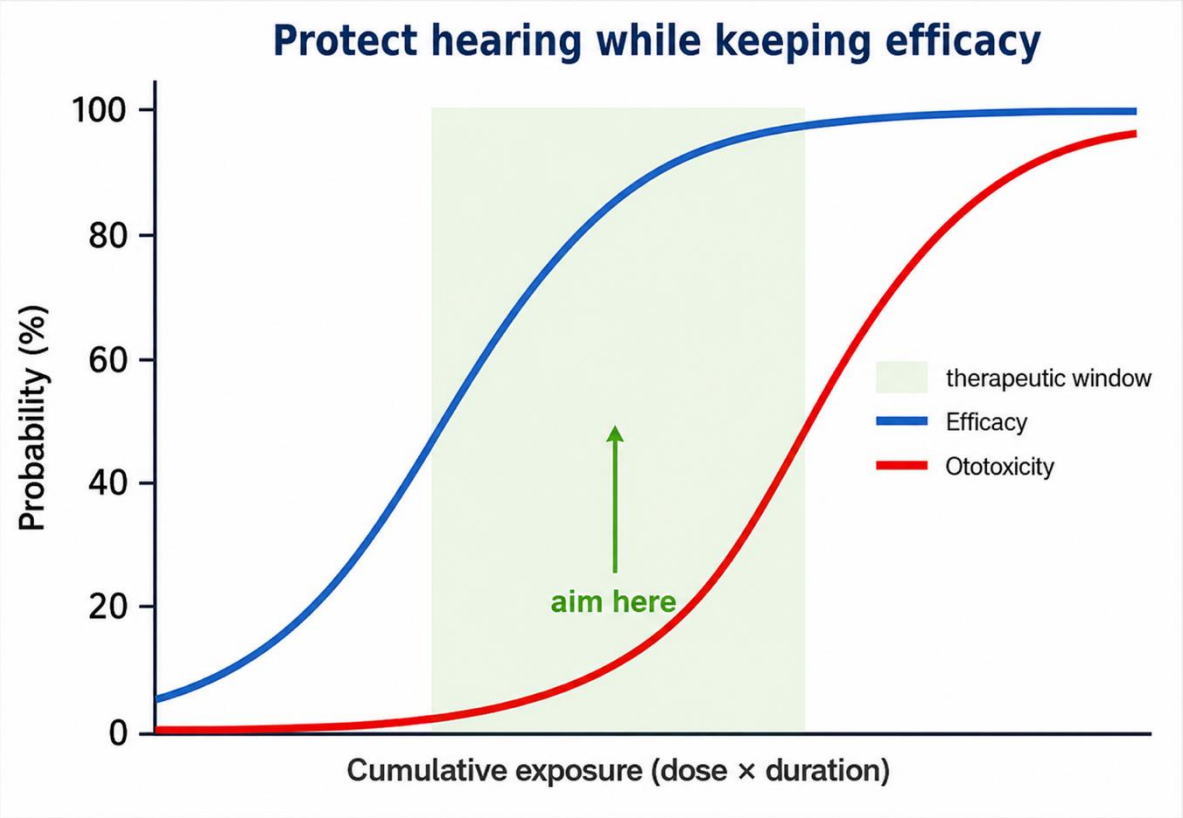
Toxicity *vs.* Efficacy: The Core Trade-off

- Toxicity rises with cumulative exposure.
- Efficacy needs adequate drug exposure.

➔ Protect hearing while keeping efficacy!



Optimal Duration of Amikacin for Efficacy?

- Retrospective study, South Korea (N=101)
  - Participants: cavitary MAC-PD receiving IV aminoglycoside
  - Comparison: duration of IV aminoglycoside
  - Outcomes: treatment success rate (culture conversion + 12 months of treatment)
- Main findings
  - Aminoglycoside for **≥ 3 months** gave higher treatment success than < 3 months (69.3% vs 46.2%; adjusted OR 3.6).

Table 4. Association of Duration of Injectable Aminoglycosides Treatment With Treatment Success

		Multivariate Analysis	
Treatment Duration (Months)	n	Adjusted Odds Ratio (95% Confidence Interval)	*P* Value
0–1.4	8	1.0 (reference)	…
1.5–2.9	18	3.793 (0.504–28.546)	.195
3.0–4.4	28	10.560 (1.489–74.867)	.018
4.5–5.9	18	24.534 (2.733–220.261)	.004
6.0–7.4	14	15.481 (1.651–145.186)	.016
7.5–30	15	1.520 (0.180–12.835)	.700

Data are reported as numbers. The "n" means the number of patients in subgroup of interest.

Kim OH et al. Clin Infect Dis. 2019

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Amikacin Liposome Inhalation Suspension (ALIS)

- CONVERT: Phase 3 open-label randomized trial (n = 336)
  - Patients: treatment-refractory MAC-PD
  - Intervention: **ALIS** + GBT
  - Comparator: GBT (no amikacin)
  - Outcome: culture conversion at 6-months

ARIKAYCE®
(amikacin liposome inhalation suspension)
590 mg/8.4 mL

- Main findings (with ALIS vs. GBT alone [no amikacin])
  - Culture conversion: **29%** *vs.* 8.9% (P < 0.0001)
  - Tinnitus: **7.6%** *vs.* 0.9%
  - Hearing loss: **4.5%** *vs.* 6.3%

Griffith DE et al. Am J Respir Crit Care Med. 2018

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Extension of ALIS

- 12-month extension of CONVERT trial (N=163)
  - Refractory MAC-PD
  - Not achieving culture conversion in CONVERT Month 6
  - 590mg once-daily ALIS+GBT for 12 months

- Main findings
  - 26.7~33.3% achieved culture conversion by month 12
  - **Hearing loss: 7.8~9.6%**
  - **Tinnitus: 1.4~6.7%**

Winthrop KL et al. Ann Am Thorac Soc. 2021

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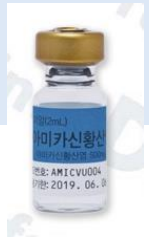
Nebulization of IV Amikacin



Retrospective study, USA (N=20)

- Nebulized amikacin for refractory NTM-PD
- Median **19 months** of nebulized amikacin
- 50% received **250mg daily**
- **Ototoxicity in 10%**

Table 4. Inhaled amikacin dosing

Mo on inhaled amikacin, median (range)	19 (1, 50)
Final inhaled amikacin dose, n (%)	
250 mg daily	10 (50)
250 mg twice daily	4 (20)
250 mg thrice weekly	3 (15)
250 mg every other d	1 (5)
500 mg daily	1 (5)
125 mg twice daily	1 (5)
Reasons for stopping inhaled amikacin	n (%)
Ototoxicity	2 (10)
Hemoptysis	2 (10)
Nephrotoxicity*	1 (5)
Persistent dysphonia	1 (5)
Vertigo	1 (5)

Retrospective study, Korea (N=52)

- Nebulized amikacin with clofazimine for refractory MAC-PD
- Amikacin nebulized **500mg qd ~ tiw**
- Median **12.9 months** of nebulized amikacin
- Audiometry q 3 months
- **Ototoxicity in 33%**

Table 4. Adverse effects associated with inhaled AMK and CFZ therapy in 52 study patients.

	Discontinuation	Dose Change	Total
Amikacin inhalation			
Ototoxicity	12 (23%)	5 (10%)	17 (33%)
Fatigue	2 (4%)	0 (0%)	2 (4%)
Tinnitus	1 (2%)	0 (0%)	1 (2%)
Dizziness	1 (2%)	0 (0%)	1 (2%)
Nausea	1 (2%)	0 (0%)	1 (2%)
Hoarseness	0 (0%)	1 (2%)	1 (2%)
Nephrotoxicity	0 (0%)	1 (2%)	1 (2%)
Total	17 (33%) *	7 (14%) †	24 (46%)

Olivier KN et al. Ann Am Thorac Soc. 2014
Kim BG et al. J Clin Med. 2020

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Summary: Risk factors for ototoxicity by amikacin

- Audiometry-confirmed hearing loss is common (~25–75%), varying by definition, frequencies tested, and exposure.
- Risk is driven by cumulative exposure (dose, duration, cumulative AUC): not a single peak or trough level.
- Risk climbs steeply after about 6 months, and amikacin is the most ototoxic aminoglycoside.
- About 3~6 months balances efficacy and hearing safety; TDM, lower/intermittent dosing, and inhaled formulation reduce systemic exposure.

Monitoring and Prevention

What Does the Guidelines Say?

NTM-PD, BTS guideline 2017

- Audiometry should be considered before starting aminoglycosides and intermittently during treatment (frequency according to perceived risk and symptoms). Patients should be informed to stop aminoglycoside treatment immediately and to inform the prescriber if they develop tinnitus, vestibular disturbance or hearing loss (grade D).

NTM-PD, ATS/ERS/ESCMID/IDSA guideline 2020

Amikacin, Streptomycin, Tobramycin	Vestibular toxicity	Clinical monitoring
	Ototoxicity	Audiograms
	Nephrotoxicity	BUN, creatinine
	Electrolyte disturbances	Calcium, magnesium, potassium
Amikacin liposome inhalation suspension	Dysphonia	Clinical monitoring
	Vestibular toxicity	Clinical monitoring
	Ototoxicity	Audiograms
	Nephrotoxicity	BUN, creatinine
	Cough	Clinical monitoring
	Dyspnea	Clinical monitoring

MDR-TB, MSF guideline 2024

Hearing loss, tinnitus and/or vestibular disorders (vertigo, dizziness, imbalance) are signs of ototoxicity. Ototoxicity is most commonly observed in patients receiving large cumulative doses of aminoglycosides. Concomitant use of loop diuretics (furosemide), particularly in patients with renal insufficiency, may exacerbate ototoxicity.

Baseline and follow-up audiometry is required to detect early hearing loss. Hearing loss in high frequencies (> 4000 Hz) is often the first sign of auditory toxicity due to aminoglycosides and can be unnoticed by the patient.

MDR-TB, WHO guideline 2020

[h] Amikacin and streptomycin are to be considered only if DST results confirm susceptibility, and if high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (i.e. is unavailable or there is documented resistance) and if DST results confirm susceptibility (i.e. resistance to streptomycin is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.

DR-TB, ATS/CDC/ERS/IDSA guideline 2019

Additional considerations. When injectables are used, serum creatinine, electrolyte measurements, clinical assessment for vertigo and tinnitus, high-quality audiometry (including hearing frequency of 6,000–8,000 Hz, as high-frequency hearing loss is seen initially), and clinical examinations should be conducted at least monthly, or more frequently if adverse effects occur. Limited data suggest

➔ ***Audiograms recommended, but details vary.***

Haworth CS et al. BMJ Open Respir Res. 2017
Daley CL et al. Clin Infect Dis. 2020
https://medicalguidelines.msf.org/en/viewport/TUB/english/Ototoxicity
WHO consolidated guidelines on tuberculosis. 2020
Nahid P et al. Am J Respir Crit Care Med. 2019

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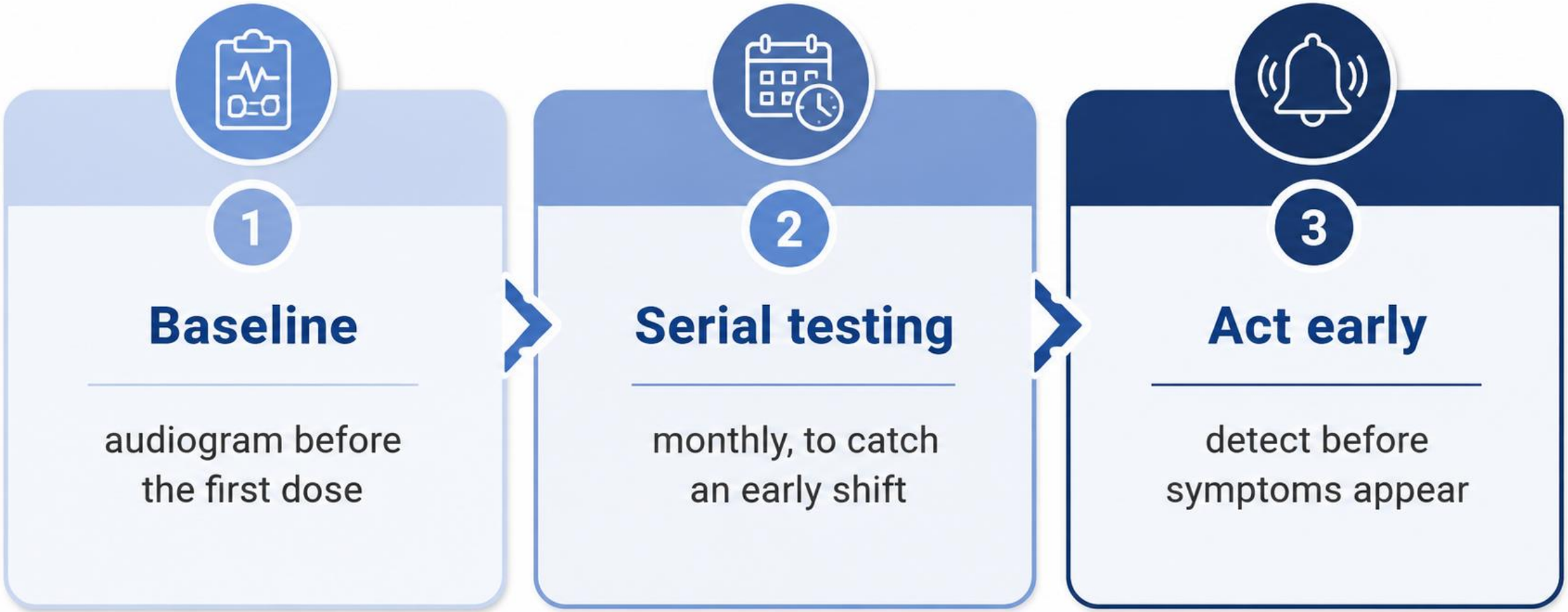
The Monitoring Mindset



American Academy of Audiology. Ototoxicity Monitoring. 2009

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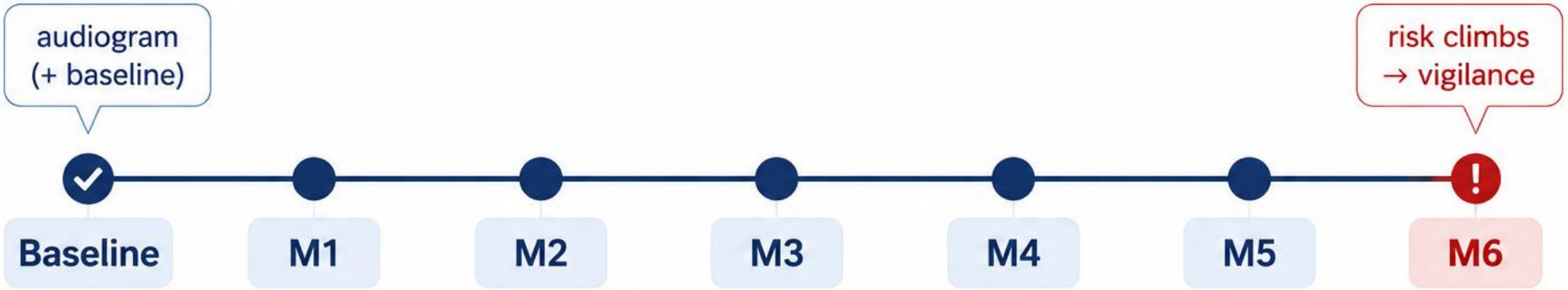
A Practical Monitoring Schedule

Baseline, then monthly
(more often if high-risk)

Heighten vigilance
toward 6 months.

Tell patients to report tinnitus or change at once.

Baseline → monthly audiometry → 6-month alert



The risk of ototoxicity increases over time.
Extra vigilance around 6 months is key.

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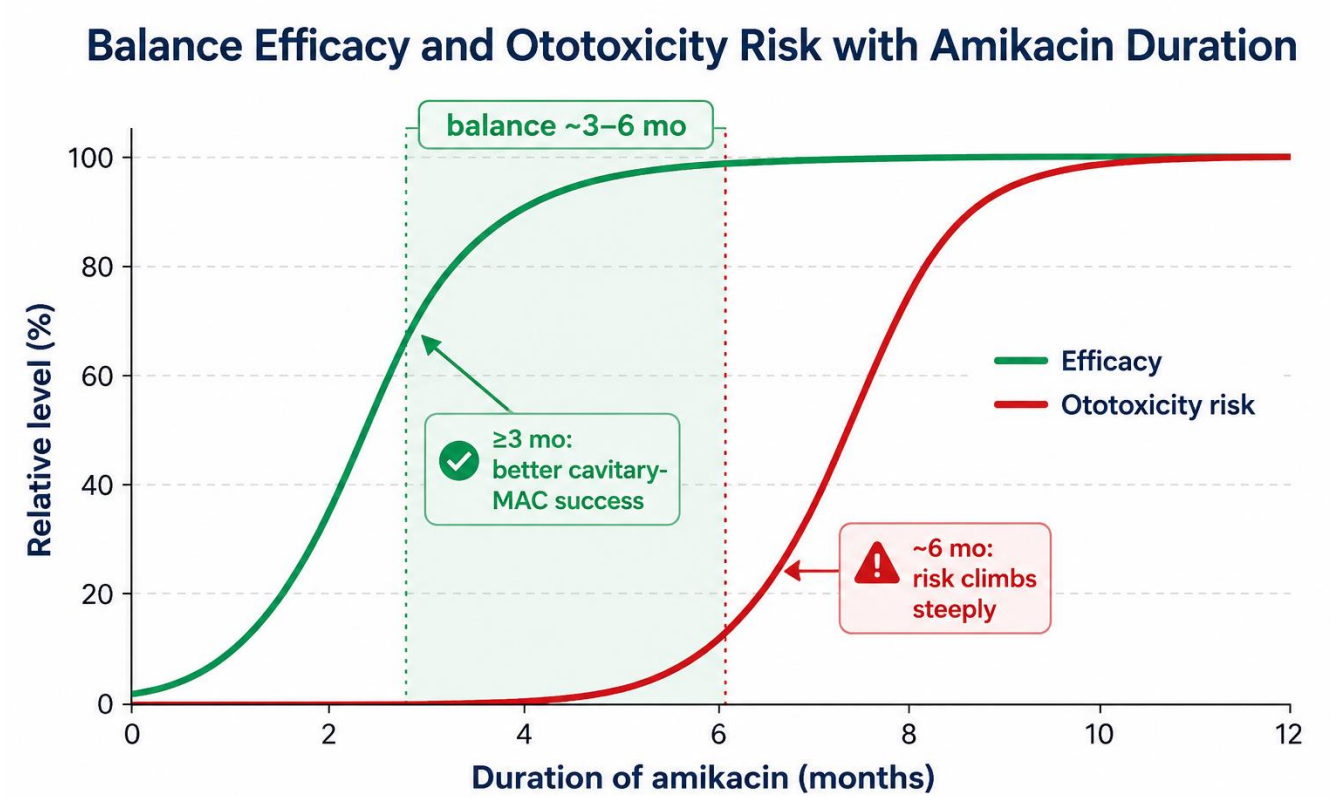
Minimize Cumulative Exposure

- Try TDM to lower cumulative dose.
- Use the shortest effective course.
- Balance efficacy against cumulative exposure.

➔ ***About 3 to 6 months balances efficacy and hearing safety***



Kim OH et al. Clin Infect Dis. 2019
Modongo C et al. Antimicrob Agents Chemother. 2015

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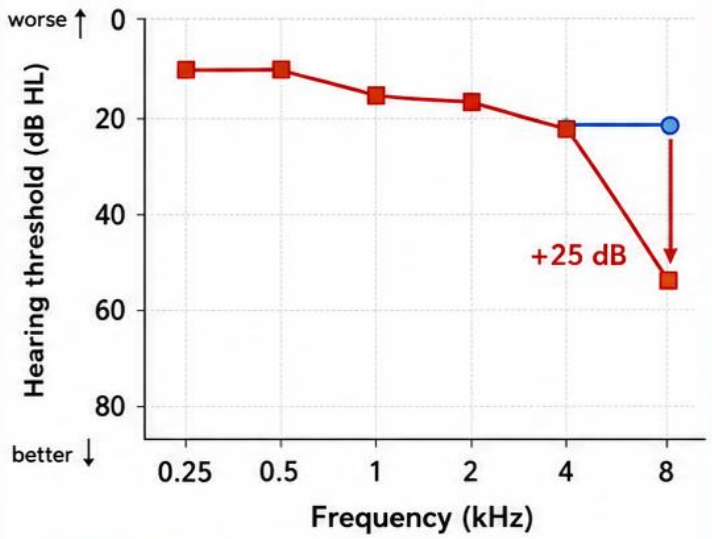
Recognizing Significant Ototoxic Shift

ASHA threshold-shift criteria

Compare follow-up vs baseline; ANY one (confirm on retest) = significant ototoxic shift

1 Single frequency: ≥20 dB

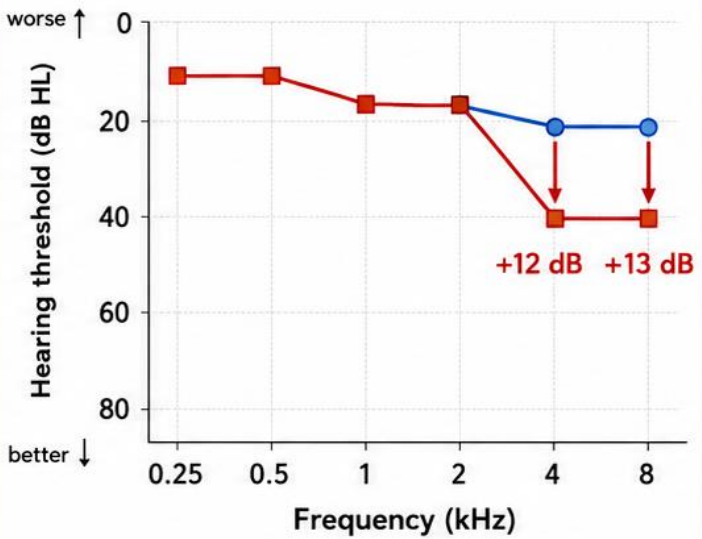
one frequency is enough ✓



A ≥20 dB worsening at any single frequency qualifies.

2 Two adjacent frequencies: ≥10 dB each

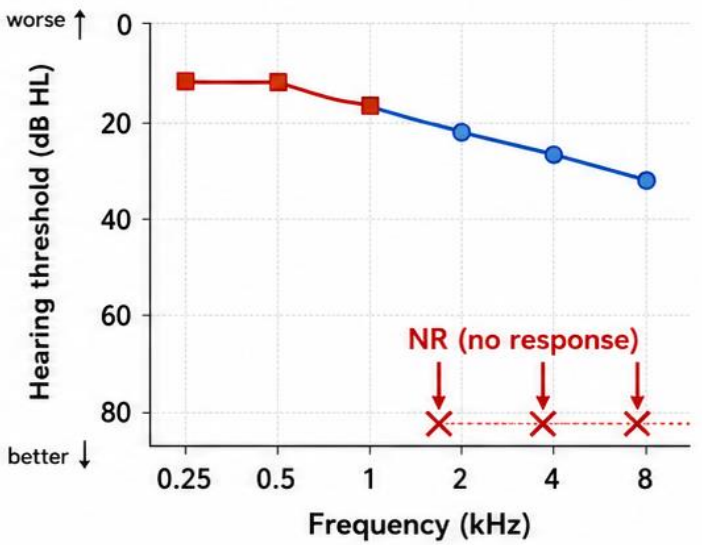
two neighbours, each ≥10 dB ✓



A ≥10 dB worsening at two adjacent frequencies qualifies.

3 Three consecutive: new loss of response

3 consecutive freqs lost ✓



Loss of response (no response) at three consecutive frequencies qualifies.

American Speech-Language-Hearing Association. 1994
American Academy of Audiology. 2009

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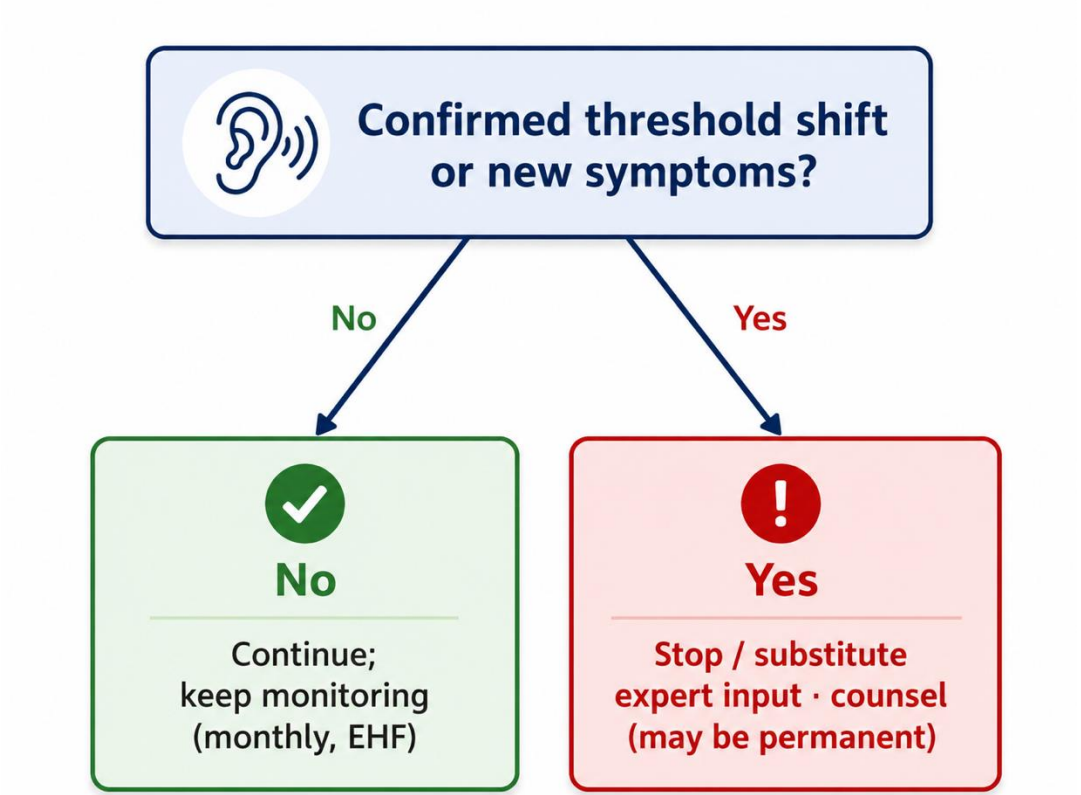
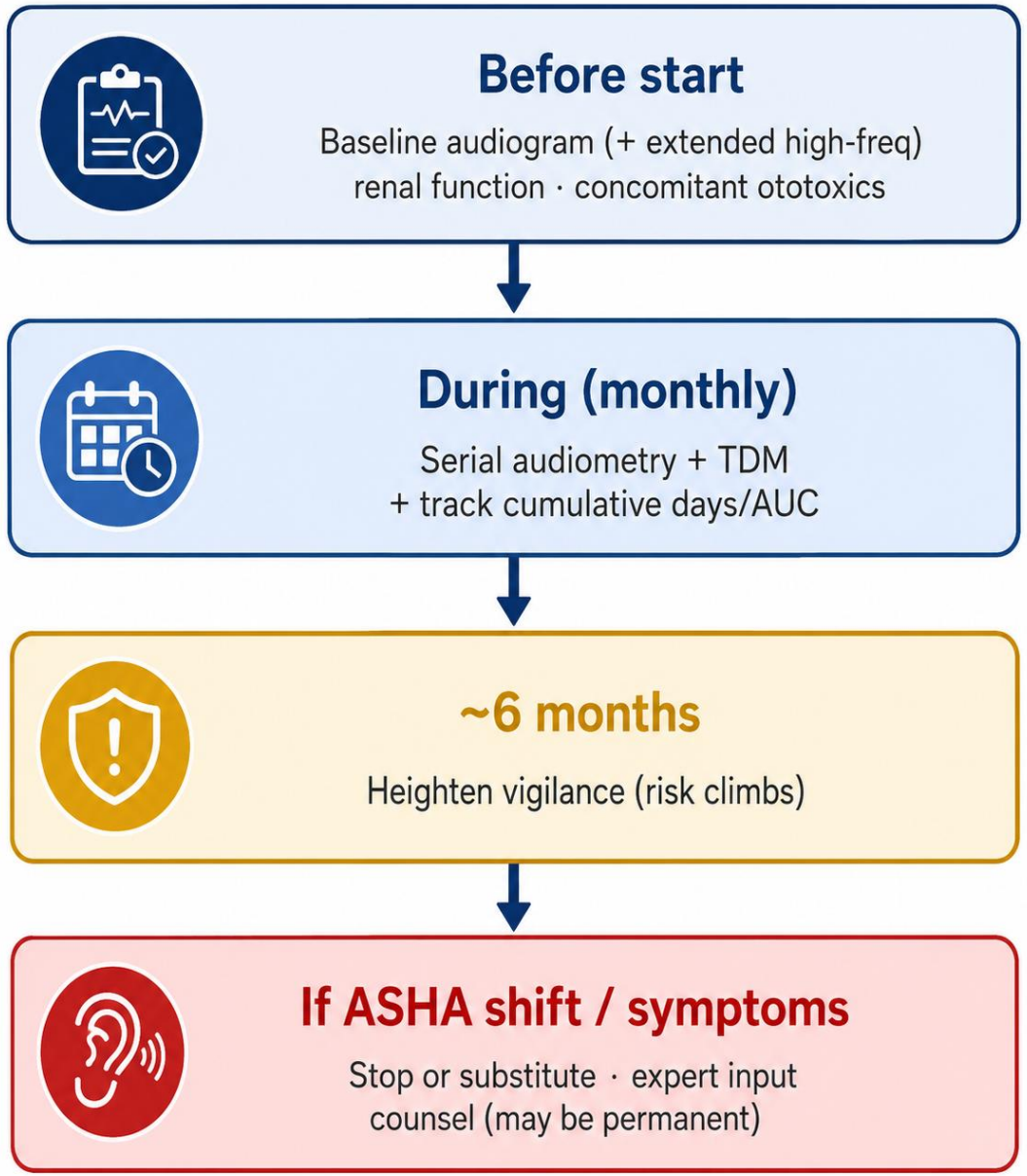
When Criteria Are Met: Stop / Substitute

- On a confirmed ASHA shift or symptoms, stop or substitute.
- Reconfigure the regimen with expert input.
- Counsel that loss may be permanent and may progress.



Putting It Together: Monitoring Algorithm



After the Loss: Stop and Refer

- Stopping the drug does not restore hearing already lost.
- Refer to audiology and ENT to manage the established deficit.
- Hearing aids help mild-to-severe sensorineural loss.
- Cochlear implant evaluation for severe-to-profound loss.
- Address tinnitus; add balance rehabilitation if vestibular symptoms.

Cunningham LL et al. N Engl J Med. 2017
Sehgal M et al. Am Fam Physician. 2024

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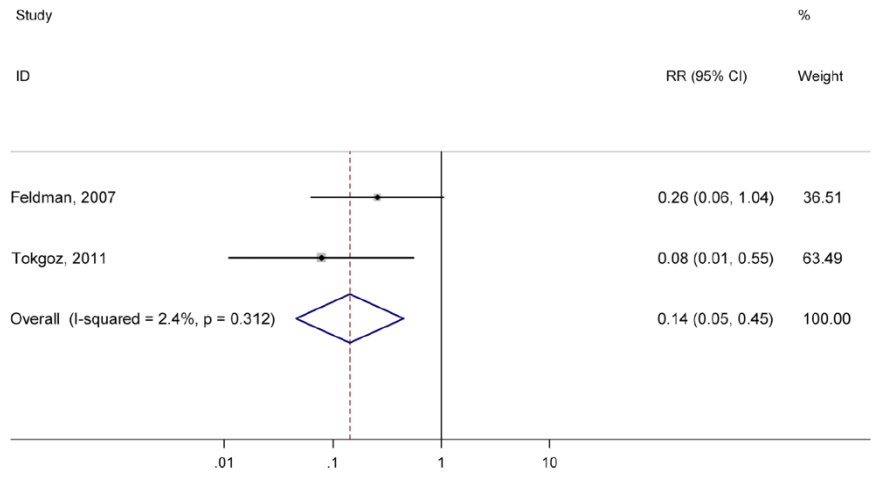
Oto-protection: N-acetylcysteine?

- Systematic review and meta-analysis (two randomized trials, N = 100)
  - P: ESRD on aminoglycosides
  - I: with N-acetylcysteine (thiol-containing anti-oxidant) 600mg bid during AG and 7~14 days after treatment
  - C: without N-acetylcysteine
  - O: Ototoxicity



- Main findings
  - Duration of aminoglycoside was short (maximum 3 weeks)
  - Pooled oto-protection RR was 0.14 (0.05–0.45).
  - Abdominal pain, nausea and vomiting, diarrhea and arthralgia were increased 1.4–2.2 times

Kranzer K et al. Thorax. 2015

Ongoing trial: ORC-13661

- ORC-13661
  - Reversible blocker of the mechanoelectrical transducer channel (entry of AG to cochlea)
  - Protection of hair cells against both ototoxins, the AGs and cisplatin in pre-clinical studies
- Phase 2 RCT, placebo-controlled study
  - NTM patients on IV amikacin
  - Primary outcome: prevent hearing loss
  - Recruiting; results expected 2028, not usable today


Recruiting

Prevention of Ototoxicity in NTM Patients Treated With IV Amikacin

ClinicalTrials.gov ID NCT05730283

Sponsor Kevin Winthrop

Information provided by Kevin Winthrop, Oregon Health and Science University (Responsible Party)

Last Update Posted 2026-05-07

Summary: Monitoring and Prevention

- Get a baseline audiogram and repeat regularly (e.g., monthly during IV use), with extra vigilance toward 6 months.
- Act before symptoms: a confirmed ASHA threshold shift triggers stopping or substituting amikacin.
- Minimize cumulative dose and duration, guide dosing with TDM, and prefer inhaled formulation when appropriate.
- Loss may be permanent and may progress: refer for audiology/ENT and rehabilitation (hearing aids, cochlear implant).
- NAC and ORC-13661 are emerging but not yet standard of care.

Back to Our Patient…

- Serial audiometry detected the shift (subjective, then objective), so amikacin was held early.
- IV amikacin was first switched to nebulized to lower systemic exposure; objective loss still prompted holding it.
- Despite stopping amikacin, the regimen achieved culture conversion and CT improvement.
- Baseline and serial audiometry let us act before disabling, permanent loss.

Take-home Messages

1. Ototoxicity is common
2. Ototoxicity is irreversible
3. Cumulative exposure is the enemy
4. Baseline and serial audiometry is mandatory
5. Stop early on confirmed shift
6. Consider nebulized formation to reduce systemic exposure