Original Article

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Aminoglycoside Resistance in Common Pathogens

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Abstract

Objective: This study investigated the resistance patterns to aminoglycosides among 137 bacterial isolates derived from various clinical specimens submitted to the Microbiology Laboratory at XXX Training and Research Hospital in the year 2005.

Materials and Methods: The bacterial isolates were Escherichia coli (n=34), Klebsiella pneumoniae (n=30), Pseudomonas aeruginosa (n=30), Acinetobacter baumannii (n=23), and Staphylococcus aureus (n=20). Staphylococcus aureus was further classified into methicillin-susceptible strains (MSSA, n=13) and methicillin-resistant strains (MRSA, n=7). We examined the susceptibility against eight distinct aminoglycosides.

Results: Isepamicin exhibited the lowest overall resistance rates within Gram-negative bacilli, particularly among isolates of P. aeruginosa and A. baumannii derived from intensive care units (ICUs). Streptomycin presented the highest levels of resistance. Statistically significant differences in resistance rates were observed between ICU and non-ICU isolates for gentamicin ($\chi^2 = 11.19$, $p = 0.0037$), amikacin ($\chi^2 = 8.82$, $p = 0.0121$), and isepamicin ($\chi^2 = 9.67$, $p = 0.0079$). This suggests an increased resistance rate in intensive care units.

Conclusion: MRSA strains were more resistant to various aminoglycosides, including gentamicin, tobramycin, and isepamicin, in comparison to MSSA strains. These observed differences were not statistically significant. These resistance patterns highlight the limitations of older drugs like streptomycin and kanamycin. The sustained efficacy of isepamicin and netilmicin positions them as viable treatment alternatives, particularly for infections caused by multidrug-resistant organisms. The results point to the necessity for routine susceptibility testing, careful antimicrobial stewardship, and judicious antibiotic selection to enhance patient outcomes and address resistance in high-risk environments such as the ICU.

Keywords: Amikacin, Aminoglycoside resistance, Intensive Care Unit, Isepamicin

Introduction

Aminoglycosides have played a significant role in antibacterial treatment since their discovery, following the introduction of streptomycin in 1944. The concentration-dependent bactericidal activity is crucial for the treatment of severe infections, including tuberculosis, and remains influential in modern medicine. Subsequent introductions of other aminoglycosides, which include neomycin, kanamycin, gentamicin, tobramycin, amikacin, and netilmicin, expanded the therapeutic options for bacterial infections, specifically those caused by Gram-negative organisms (1, 2).

Aminoglycosides have a chemical structure characterised by a 6-membered aminocyclitol ring connected to different sugar molecules. This configuration contributes to their high solubility and limited lipophilicity, which are necessary for their ability to kill bacteria (3). Their mechanism of action entails an initial electrostatic interaction with the bacterial outer membrane, leading to a disruption of its permeability through the displacement of ions consisting of magnesium and calcium. Upon entering the cell, they irreversibly bind to the 30S ribosomal subunit, obstructing protein synthesis by inducing misreading of mRNA, ultimately leading to bacterial demise (3, 4). Aminoglycosides exhibit enhanced action in alkaline settings and diminished efficacy in acidic situations. This property is particularly significant in clinical settings, as infection sites may exhibit variable pH levels (1, 5).

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Aminoglycosides exhibit optimal efficacy against aerobic Gram-negative bacilli, such as Pseudomonas species, while demonstrating limited effectiveness against Gram-positive bacteria and negligible activity against most anaerobes. Synergy can arise when combined with cell wall-active agents such as beta-lactams; aminoglycosides may exhibit enhanced efficacy. But bacteria often become resistant to them, which makes them less effective. The post-antibiotic effect (PAE) of aminoglycosides keeps bacteria from growing even after the drug level drops below the Minimum Inhibitory Concentration (MIC). This effect depends on the dose (2, 3). Because aminoglycosides don't absorb well in the gut, they need to be given parenterally. They show good tissue distribution, but they have trouble getting through certain biological barriers, like the blood-brain barrier. The main way that aminoglycosides leave the body is through the kidneys. When they build up in kidney and auditory cells, they can cause nephrotoxicity and ototoxicity, which are serious side effects (1, 2, 3). In the clinic, it is used to treat serious infections like blood infections that are hospital-acquired, urinary tract infections, endocarditis, and infections that are linked to cystic fibrosis (1).

Mechanisms of resistance are complicated and multifactorial and include changing the ribosomal target, making the drugs less permeable, and modifying the drugs with aminoglycoside-modifying enzymes (AMEs) (1, 7). This study shows how important it is to keep doing surveillance on resistance rates so that clinicians can make precise decisions about when to use aminoglycosides. Researchers often believe that certain bacterial strains, like Escherichia coli and Pseudomonas aeruginosa, are resistant because they have certain resistance genes (2). Aminoglycosides are still an important part of antibiotherapy, even though they are hard to use because of resistance. This is why researchers are still looking into how they work and what new derivatives might be able to get around existing resistance pathways (1, 2, 3).

Materials and Methods

This study included a total of 137 bacterial strains isolated from biological specimens submitted to the Microbiology Laboratory of the University of Health Sciences, XXX Training and Research Hospital, throughout the year 2005. The isolates were 20 strains of *Staphylococcus aureus*, 34 strains of *Escherichia coli*, 30 strains of *Klebsiella pneumoniae*, 30 strains of *Pseudomonas aeruginosa*, and 23 strains of *Acinetobacter baumannii*. This study was conducted following the Principles of the Declaration of Helsinki. The isolates were used with institutional permission. The susceptibility of these isolates to the following aminoglycoside antibiotics was assessed: streptomycin, neomycin, kanamycin, gentamicin, amikacin, netilmicin, tobramycin, and isepamicin. We applied Gram staining to all bacterial isolates. We used the catalase test on Gram-positive cocci. The tube coagulase test was done to examine isolates that tested positive for catalase. Those with positive results were identified as *Staphylococcus aureus*. We divided gram-negative bacilli into two groups: fermentative and non-fermentative. Then, we applied standard biochemical methods to identify the species. On MacConkey agar, *E. coli* isolates were lactose-positive, citrate-negative, acid-producing on Triple Sugar Iron Agar (TSI), fermentative in oxidation-fermentation (OF) medium, motile, indole-positive, and methyl red (MR)-positive. *K. pneumoniae* isolates were lactose-positive on MacConkey agar, citrate-positive, acid or acid/alkaline on TSI, non-motile, indole-negative, fermentative, MR-negative, Voges-Proskauer (VP)-positive, and urease-positive. *P. aeruginosa* was found to be oxidase-positive, citrate-positive, alkaline on TSI, motile, and capable of producing pyocyanin pigment in the chloroform test. It could also grow at +42°C. *A. baumannii* was oxidase-negative, citrate-positive, non-motile, alkaline on TSI, and able to grow at +44°C. We followed the Clinical and Laboratory Standards Institute (CLSI) guidelines for antimicrobial susceptibility testing. The Kirby-Bauer disk diffusion method was used to determine the susceptibility of isolates to aminoglycoside antibiotics such as streptomycin, neomycin, kanamycin, gentamicin, amikacin, netilmicin, tobramycin, and isepamicin.

Statistical Analysis: Descriptive statistics were used to characterise the distribution of bacterial isolates across clinical departments, specimen types, and patient demofigureics. Categorical variables, including species identification, isolation sources, and aminoglycoside resistance profiles, were summarised using frequencies and proportions. Antimicrobial resistance rates were calculated and reported as percentages for each pathogen-antibiotic pairing. Inferential statistical analysis employed the chi-square (χ^2) test of independence to assess differences in antimicrobial susceptibility profiles (resistant, intermediate, and susceptible categories) between isolates from intensive care units (ICU) versus the broader clinical population. Two-by-three contingency tables were constructed for each aminoglycoside agent tested. Statistical significance was defined as $p < 0.05$. All statistical computations were performed using IBM SPSS Statistics version 28. Comparative analyses were conducted to elucidate resistance patterns across bacterial taxa and hospital departments, with a focused examination of ICU-derived isolates. Resistance data were stratified by Gram staining characteristics (Gram-positive versus Gram-negative organisms). Data visualisation techniques were employed to illustrate temporal trends in isolate recovery and resis-

Table 1. Distribution of isolates among the clinics where they have originated

Clinics	*E. coli*	*K. pneumoniae*	*P. aeruginosa*	*A. baumannii*	*S. aureus*	Total
Intensive Care Unit	3	7	23	19	6	**58**
Internal Medicine	8	3	4	2	2	**19**
Pediatrics	5	9	-	-	1	**15**
Surgery	6	3	-	-	3	**12**
Infectious Diseases	3	2	1	1	2	**9**
Orthopedics	-	1	2	-	5	**8**
Others	9	5	-	1	1	**16**
Total	**34**	**30**	**30**	**23**	**20**	**137**

tance prevalence. Raw data management and preliminary statistical tabulations were performed using Microsoft Excel, with subsequent figureical representations generated to facilitate interpretation of resistance patterns and epidemiological trends.

Results

A total of 137 bacterial isolates were included in the study, consisting of 34 *E. coli*, 30 *Klebsiella pneumoniae*, 30 *Pseudomonas aeruginosa*, 23 *Acinetobacter baumannii*, and 20 *Staphylococcus aureus* strains. These were isolated from various clinical specimens submitted in 2005 to the Microbiology Laboratory of XXX Training and Research Hospital. Sample Origins: Most isolates were obtained from urine (33%), followed by sputum (24%), blood (23%), swab (12%), and abscess (9%) samples. Clinical Distribution: The Intensive Care Unit (ICU) accounted for the highest proportion of isolates (42%), with *P. aeruginosa* and *A. baumannii* being the most prevalent organisms in that setting. (Table 1). Age Distribution: 86% of isolates were from adult patients, while 14% were from paediatric cases. Antimicrobial Resistance: Among Gram-negative isolates, isepamicin demonstrated the highest overall efficacy, showing the lowest resistance rate (16%), followed by amikacin (28%) and netilmicin (32%) (Figure 1). Streptomycin exhibited the highest resistance rate (45%) among Gram-negative isolates. In the ICU subgroup, isepamicin remained the most effective agent, especially against *P. aeruginosa* and *A. baumannii*. (Figure 2) (Table 2). Among the eight aminoglycosides evaluated, statistically significant differences were observed for gentamicin ($\chi^2 = 11.19$, $p = 0.0037$), amikacin ($\chi^2 = 8.82$, $p = 0.0121$), and isepamicin ($\chi^2 = 9.67$, $p = 0.0079$), indicating a higher resistance rate among ICU isolates. Other antibiotics, including streptomycin, neomycin, kanamycin, tobramycin, and netilmicin, did not show statistically significant differences, although kana-

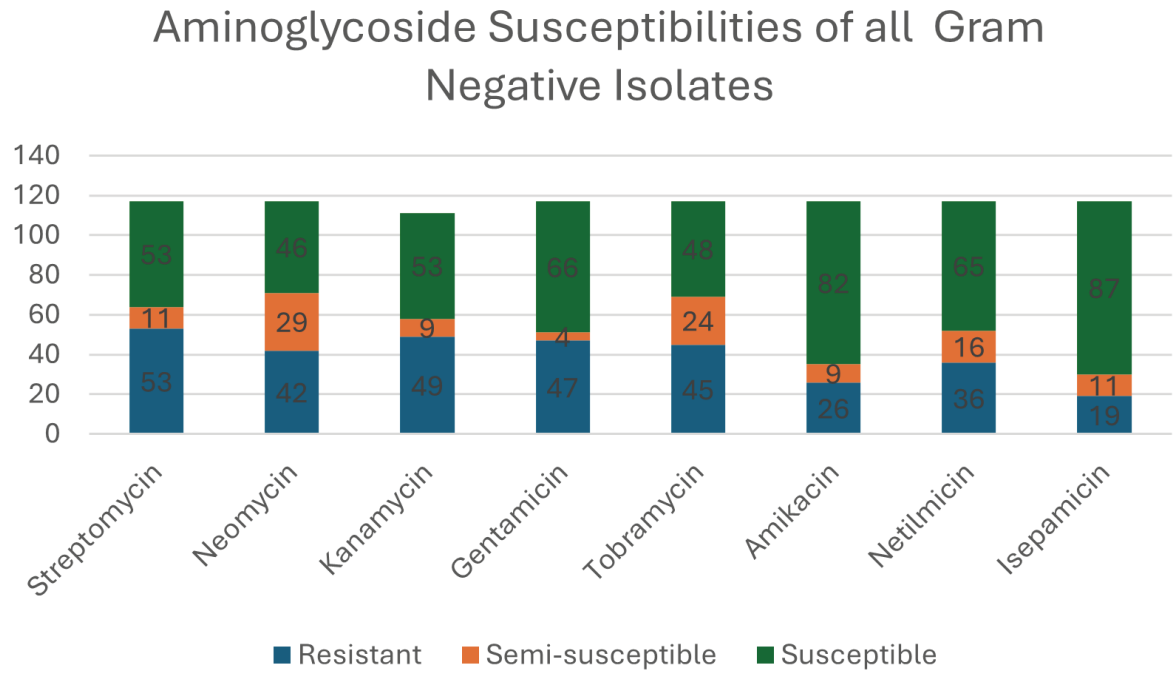

Figure 1. Aminoglycoside Efficacies of all Gram-Negative Isolates.

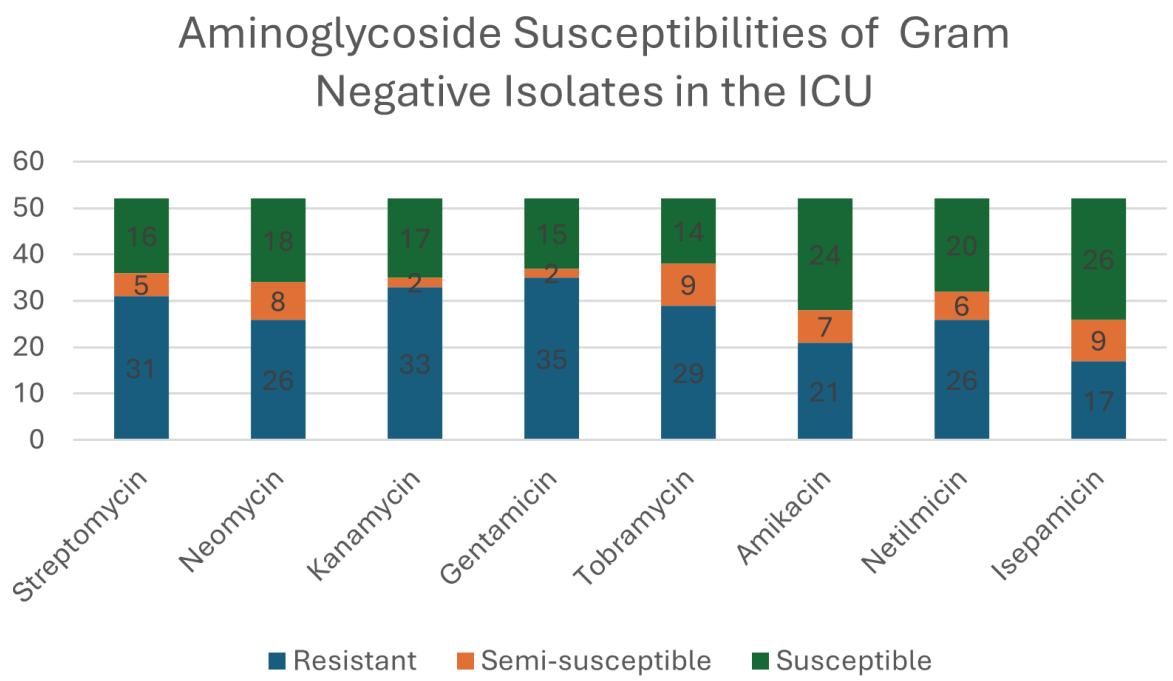

Figure 2. Aminoglycoside Efficacies of Gram-Negative Isolates in the Intensive Care Unit (ICU).

mycin and netilmicin approached significance ($p = 0.065$ and $p = 0.054$, respectively). (Table 3)

Among *E. coli* isolates, resistance to isepamicin was as low as 3%, while streptomycin resistance reached 47%. *K. pneumoniae* isolates showed 0% resistance to isepamicin, making it the most effective option against this pathogen. *A. baumannii* isolates demonstrated high levels of resistance across all aminoglycosides, although isepamicin remained more effective. The total resistance rates for all the isolates from all the clinics are summarised in Table 4. There were 20 S. aureus isolates. 35% of *S. aureus* isolates were identified as methicillin-resistant S. aureus (MRSA). The total resistance rates of *S. aureus*, MSSA, and MRSA aresummarised in Table 5. The resistance rates are also displayed in Figure 3. While some antibiotics showed trends toward higher resistance in MRSA isolates, particularly gentamicin, tobramycin, and isepamicin ($p \approx 0.062$) (Fisher Exact test), the overall resistance distribution did not differ significantly between MRSA and MSSA groups. ($p > 0.05$)

Discussion

In our study of 137 bacterial isolates collected in 2005, isepamicin demonstrated exceptional efficacy against Gram-negative organisms, corroborating findings from both Turkey and Greece that highlight its stability against prevalent aminoglycoside-modifying enzymes, such as AAC (6')-I, and its improved efficacy over older agents like gentamicin and tobramycin (8, 9, 10). This is especially important because rates of resistance are rising in clinical settings. Notably, isepamicin's ability to work against multidrug-resistant strains makes it an even better candidate for being the mainstay of antimicrobial therapy, especially in severe infections where traditional aminoglycosides have stopped working (11, 12). On the other hand, streptomycin had very high resistance rates—almost 60% among isolates of Pseudomonas aeruginosa and Acinetobacter baumannii—showing that it is less useful in the clinic (13). This trend shows how streptomycin has been used too much in the past, which has led

Table 2. Resistance Rates of the different Aminoglycosides of the ICU Gram-negative isolates

Aminoglycosides	*E. coli (n=3) %*	*K. pneumoniae (n=7) %*	*P. aeruginosa (n=23) %*	*A. baumannii (n=19)%*
Isepamicin	0	0	30	53
Neomycin	0	43	57	53
Gentamicin	33	57	74	68
Tobramycin	33	43	52	68
Amikacin	33	14	26	68
Netilmicin	33	14	52	63
Streptomycin	67	29	70	58
Kanamycin	100	57	61	63

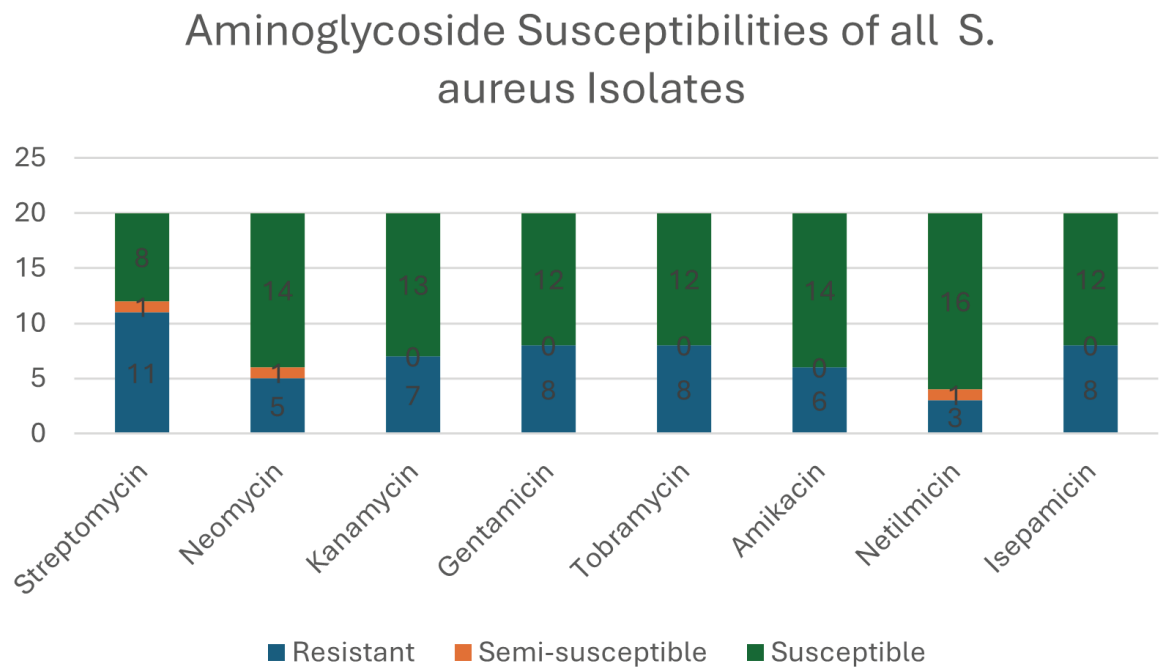

Figure 3. The total resistance rates of all *S. aureus* isolates

Table 3. The statistical difference between all isolates and ICU isolates

Aminoglycosides	Chi²	p-value	Significant (p < 0.05)
Streptomycin	3.35	0.188	No
Neomycin	3.44	0.179	No
Kanamycin	5.45	0.066	No
Gentamicin	11.19	0.0037	Yes
Tobramycin	4.60	0.100	No
Amikacin	8.82	0.0121	Yes
Netilmicin	5.85	0.054	No (but close)
Isepamicin	9.67	0.0079	Yes

to bacteria developing ways to resist it. The production of aminoglycoside-modifying enzymes, like acetyltransferases and phosphotransferases, which are becoming more common in clinical isolates (14), is what mostly causes resistance to older aminoglycosides. For instance, Strateva et al. found that a large number of P. aeruginosa strains were resistant because of these modifying enzymes. This shows how difficult it is to control bacterial infections around the world (15). Aminoglycosides kill bacteria by stopping protein synthesis by binding to the 30S ribosomal subunit in a way that can't be undone. This causes translation errors and eventually kills the bacterial cell (12). This characteristic enables aminoglycosides to demonstrate notable efficacy in managing multidrug-resistant infections, particularly in the ICU (16). When we looked at isolates obtained from the ICU, we found that gentamicin ($p = 0.0037$), amikacin ($p = 0.0121$), and isepamicin ($p = 0.0079$) had resistance rates that were statistically significantly higher than those of all Gram-negative isolates. These results are in accordance with what we know about how intensive care settings often put selective pressure on microorganisms because they use too many broad-spectrum antibiotics. This makes it easier for strains that are resistant to more than one drug to grow and spread (17, 18). The high level of resistance seen in ICU isolates

Table 4. Resistance Rates of the different Aminoglycosides of all Gram-negative isolates

Aminoglycosides	*E. coli (n=34) %*	*K. pneumoniae (n= 30) %*	*P. aeruginosa (n=30) %*	*A. baumannii (n=23) %*
Isepamicin	3	0	23	48
Neomycin	18	23	57	52
Gentamicin	15	33	60	61
Tobramycin	24	23	50	65
Amikacin	9	7	23	61
Netilmicin	12	20	40	61
Streptomycin	47	23	60	52
Kanamycin	29	33	53	57

Table 5. The total resistance rates of S. aureus, MSSA, and MRSA

Aminoglycosides	*S. Aureus (n=20) %*	*MSSA (n=13) %*	*MRSA (n=7) %*
Isepamicin	40	23	71
Neomycin	25	31	14
Gentamicin	40	23	71
Tobramycin	40	23	71
Amikacin	30	15	57
Netilmicin	15	8	14
Streptomycin	55	46	71
Kanamycin	35	23	57

shows how important it is to carefully prescribe antibiotics in these situations to avoid more problems caused by antibiotic resistance (19). Of the Staphylococcus aureus isolates that were investigated at, 35% were found to be methicillin-resistant S. aureus (MRSA). MRSA strains were less sensitive to gentamicin, tobramycin, and isepamicin than methicillin-sensitive S. aureus (MSSA), but these differences were not statistically significant ($p > 0.05$). For some antibiotics, though, they were almost significant (for example, gentamicin, $p = 0.0623$). The aac(6′)/aph(2″) bifunctional gene makes MRSA isolates more resistant to a number of aminoglycosides. This gene is often found in MRSA isolates that were acquired in hospitals (20, 21). There is a lot of proof that this gene makes bacteria very resistant, especially to gentamicin. This makes us think of other ways to get rid of MRSA infections that work. Even though resistance makes things complicated, agents like netilmicin and amikacin are still suitable alternative therapies because they are less likely to be broken down by enzymes (9, 14). Our results show how important it is to include local resistance data when choosing aminoglycoside treatments. Netilmicin may be a good choice for treating infections that don't respond to other drugs because it has consistently low resistance rates in both Gram-positive and Gram-negative organisms. On the other hand, streptomycin's high resistance rates make it of little use in the medical setting. Amikacin is especially important when it comes to multidrug-resistant infections because it works against a wide range of resistant Gram-negative pathogens and is an important part of combination therapies. Studies have shown that when amikacin is used with cell wall active drugs, it can have synergistic effects that make it easier to eradicate bacteria, especially Pseudomonas aeruginosa and Acinetobacter baumannii (22, 23). This possibility of synergism is especially important when dealing with pathogens that are very resistant and common in ICUs. Researchers are also working on reformulating amikacin and making it more bioavailable, such as through the development of nanoparticle delivery systems, which could lead to better therapeutic outcomes and help overcome current resistance problems (6, 23).

In conclusion, aminoglycosides like isepamicin and netilmicin are still very important treatment options, especially in ICUs and against Gram-negative pathogens that are resistant to multiple drugs. However, our findings show that antimicrobial stewardship, regular susceptibility monitoring, and careful antibiotic prescribing are very important, especially in critical care settings where resistance develops quickly. To keep these important antimicrobial agents working and patients safe, clinicians must constantly adapt to the changing microbial landscape.

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