Plazomicin: A promising novel antimicrobial in the era of bacterial resistance (Review)

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Received July 2, 2025; Accepted October 31, 2025

DOI: 10.3892/etm.2025.13037

Abstract. Gram-negative bacterial infections that are multidrug-resistant are on the rise and present a severe risk to patients and the general population. These infections can be challenging to treat and cause severe morbidities and multiple mortalities. A semisynthetic antimicrobial called plazomicin received approval from the US Food and Drug Administration for the treatment of adults with severe complicated urinary tract infections (cUTIs) caused by bacterial pathogens, in cases where the patients have no or limited other therapeutic options. In treating cUTIs, plazomicin has demonstrated that it is comparable to meropenem, and is a practical treatment option for outpatient antibiotic treatment settings (given intravenously, once daily, with a brief 30 min administration duration). In addition, plazomicin shows low frequency side effects including nephrotoxicity and ototoxicity. Except for the approved use of plazomicin to treat cUTIs, there is a gap in the literature regarding the role of plazomicin in therapy for patients with aggressive and life-threatening bacterial infections including Enterobacterales. Plazomicin is a reasonably expensive drug that should be used sparingly. In the present review, the molecular characteristics, chemical properties, mechanism of action, antibacterial spectrum, pharmacokinetics, clinical therapeutic indications, side effects, role in therapy and special considerations of plazomicin are discussed.

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Abbreviations: AACs, aminoglycoside acetyltransferases; AGs, aminoglycosides; AMEs, aminoglycoside-modifying enzymes; AMR, antimicrobial resistant; AP, acute pyelonephritis; APHs, aminoglycoside phosphotransferases; BSI, blood stream infection; CARE, Combating Antibiotic-Resistant Enterobacteriaceae; CFU, colony-forming unit; CLSI, Clinical and Laboratory Standards Institute; CRE, carbapenem-resistant Enterobacterales; cUTI, complicated urinary tract infection; EPIC, Evaluating Plazomicin In cUTI; ESBLs, extended spectrum β-lactamases; GNB, Gram-negative bacteria; HAP, healthcare-associated pneumonia; IV, intravenous; MDR, multidrug resistant; MIC, minimum inhibitory concentration; 16RMT, 16S rRNA methyltransferases; SSTI, skin and soft tissue infection; TDM, therapeutic drug monitoring; TOC, test-of-cure; USCAST, United States Committee on Antimicrobial Susceptibility Testing; US FDA, United States Food and Drug Administration; VAP, ventilator-associated pneumonia

Key words: aminoglycoside modifying enzymes, antibacterial drugs, gram-negative enterobacterales, pharmacokinetics, toxicity, urinary tract infection

Contents

1. Introduction

Since their initial discovery in the mid-1940s, aminoglycoside (AG) antimicrobials have been used extensively to treat severe infections. The first AG was streptomycin, which was initially created to treat tuberculosis (1); gentamicin (1963), tobramycin (1967) and amikacin (1972) are three of the other AGs that have been discovered and are still widely used in modern medicine (2-4). Due to the ability of AGs to specifically bind to the 30S ribosomal subunit, which effectively prevents bacterial intracellular protein synthesis, they demonstrate potent

bactericidal activity (5). Due to their narrow therapeutic index (a small range between the minimum effective dose and the minimum toxic dose) and potential for ototoxicity and nephrotoxicity, AGs must only be prescribed under strict guidelines and in accordance with meticulous therapeutic drug monitoring (TDM) (6). Currently, patients with sepsis or septic shock who are at high risk of multidrug-resistant (MDR) Gram-negative bacilli infections are frequently treated empirically with AGs in combination with another antimicrobial drug (mostly a β-lactam) (6).

Antimicrobial resistance has emerged as a significant global threat to healthcare. By 2050, it is predicted that 10 million individuals per year could die from infections that are antimicrobial resistant (AMR), according to the World Health Organization (7). The different resistance mechanisms produced by MDR bacteria against new-generation and broad-spectrum antibiotics are quickly growing, limiting the treatment options for infections (8). Particularly relevant to carbapenem resistance mechanisms is the identification of five carbapenemase genes (*oxa*-48, *imp*, *ndm*, *vim* and *kpc*) in Gram-negative bacteria (GNB). These genes are all carried by plasmids, which allows for a high rate of horizontal transmission. Extended spectrum β-lactamases (ESBLs)-producing Enterobacterales and carbapenemase-producing *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacterales were among the bacterial pathogens that indicated a strong ability to be AMR. These infections are becoming more difficult to treat empirically after being microbiologically confirmed (9).

The ESKAPE healthcare-associated infections are caused by a group of GNB and Gram-positive bacterial pathogens including *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter*. These healthcare-associated infections are extremely resistant to antibiotics, including AGs (10). The two main mechanisms of Enterobacterales resistance to AGs are enzymatic drug modification or target site modification (11,12). The most common mechanism is enzymatic drug modification by aminoglycoside-modifying enzymes (AMEs): N-acetyltransferases (AACs), o-adenyl transferases (nucleotidyltransferases) and o-phosphotransferases (APHs), are three major classes of AMEs, each with several variants, and certain AGs are impacted by each specific enzyme but not others. Gram-negative bacilli, especially *Klebsiella pneumoniae* and *Escherichia coli*, usually have the *aac(60)* gene encoding the acetyltransferase enzyme. This modification reduces the antibacterial activity of AGs by preventing it from attaching to the bacterial ribosome. Notably, the microbe may create several enzymes from the same or distinct classes, resulting in high-level resistance (6).

ArmA and RmtB are the most expressed 16S rRNA methyltransferases (16RMT) that modify (by methylation) the target site of AGs (12). Nevertheless, they are rarely encountered in clinical settings, with only 1.28, 0.14 and 0.05% isolates reported from Europe and parts of Asia (13), the US (14) and Canada (15), respectively, that have been recorded expressing ArmA and RmtB. Additionally, drug impermeability with porin channel down-regulation or active drug elimination by efflux pumps (*AcrD*) might lead to resistance against AGs, especially with *Acinetobacter baumannii* and *Pseudomonas aeruginosa,* explaining the higher minimum inhibitory concentrations (MICs) frequently exhibited by these bacterial pathogens (16,17).

The use of traditional AGs has been limited by AME generation and the toxicity/benefit ratio experienced in patients with infected with AME-producing bacteria (18). These factors highlight the need for a next-generation AG antibiotics with unquestionable efficacy and little toxicity. Plazomicin has exhibited notable bactericidal action (observed in 2010) against most AG-resistant organisms with lower toxicity (9,19-21). The United States Food and Drug Administration (US FDA) approved the plazomicin antibiotic (formerly known as ACHN-490) in June 2018 (22). Plazomicin is a semisynthetic antimicrobial that has been created to target MDR Enterobacterales including carbapenemases, ESBLs and AME-producing bacteria (23,24). These resistant bacteria have the potential to cause dangerous bacterial infections that are a problem all over the world, including ventilator-associated pneumonia (VAP), healthcare-associated pneumonia (HAP) and blood stream infection (BSI). Since the emergence of carbapenem-resistant Enterobacterales (CRE), clinicians have had few alternatives for treating MDR bacterial pathogens. Traditional AGs, such as gentamicin, tobramycin and amikacin, have little effectiveness against bacterial strains that can produce AMEs (22).

In the present review, the molecular characteristics, chemical properties, mechanism of action, antibacterial spectrum, pharmacokinetics, clinical therapeutic indications, side effects, role in therapy and special considerations of plazomicin are addressed.

2. Molecular characteristics, chemical properties and mechanism of action

Being a semisynthetic antimicrobial, plazomicin [6'-(hydroxylethyl)-1-(haba)-sisomicin] has a unique molecular structure (Fig. 1) that makes it resistant to being inactivated by a variety of enzymes produced by MDR bacteria. Sisomicin (dehydro analog of gentamicin C1a) is the source of plazomicin; sisomicin, similar to gentamicin, is susceptible to several AMEs that GNB may produce (11). The majority of AMEs are inhibited by sisomicin modifications when an N1 2(S)-hydroxy aminobutyryl and a hydroxethyl group are added at the 6' position (25). The activity of plazomicin can be improved against isolates producing AMEs due to these molecular modifications, but not against 16RMT, which cause AGs (including plazomicin) to have less affinity for the ribosomal target (12). When compared with sisomicin, the antibacterial effectiveness of plazomicin is only slightly reduced by these molecular modifications; however, action is restored in the presence of AMEs (26). Comparing plazomicin with traditional AGs, the deleted or added domains (Table I) explain the resistance of plazomicin to enzymatic inactivation by AMEs (9,27). With this design, plazomicin can be prescribed not only to treat infections caused by traditional AG-resistant Enterobacterales, but also to treat infections caused by Enterobacterales that resist colistin (polymyxin B) and carbapenems (carbapenemases producers), including the bacteria that produce ESBLs (23).

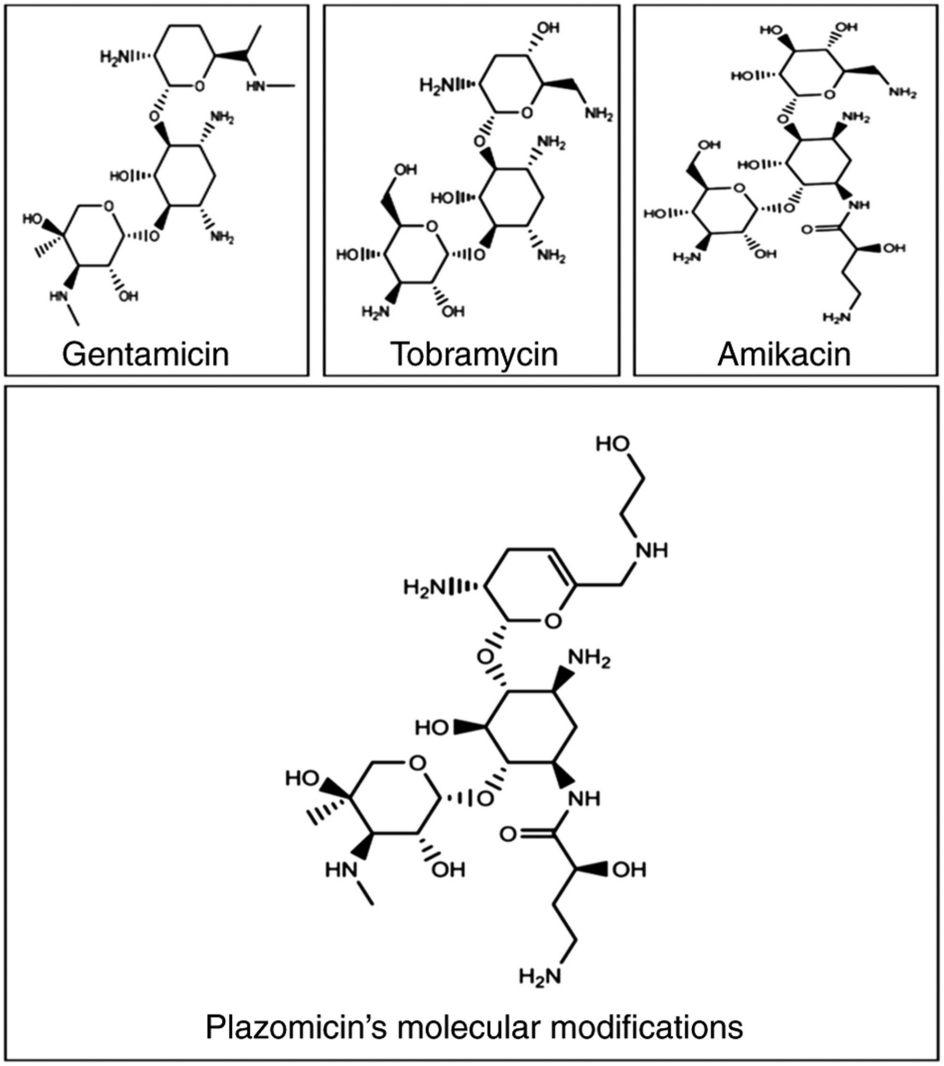

Figure 1. Plazomicin structure. The structural modifications of plazomicin compared with some traditional aminoglycosides. Modifications include no -OH groups at the C-3' and 4' sites, addition of a hydroxyethyl group to the amine at location C-6' and a hydroxy-aminobutyric acid at the C-1' position.

Due to the fact AGs are hydrophilic cationic compounds, they are hypothesised to enter GNB via porin channels or breakdown of the lipopolysaccharide outer membrane (28). AGs must be transported across the cytoplasmic membrane, and the transport of plazomicin inside bacterial cell cytoplasm is an aerobic energy-dependent process that can be slowed down by a drop in pH and/or anaerobic condition. AGs are not very effective in an anaerobic and/or acidic environment due to the drop in their antibacterial action. The effect of AGs relies on the proton motive force, which consists of $\Delta\psi$ (electrical potential across membrane) and ΔpH (transmembrane difference in hydrogen ion concentration) (29). The aminoacyl-transfer RNA recognition site (A-site) of the 16S rRNA of the 30S ribosomal subunit is the main intracellular target of action for AGs, including plazomicin, where they interfere with bacterial protein synthesis. Following their binding to the target site, several intracellular steps (including severe translocation inhibition, miscoding and complete collapse of the proteome) occur that prevent translation, elongation of the nascent protein sequence and enhance the bactericidal activity of AGs (30).

3. Antibacterial spectrum of plazomicin

Overall, the Gram-negative *in vitro* activity of plazomicin is comparable with or superior to that of other AGs (20,23). In nearly half of the cases (46.97%), the bacterial pathogens tested for plazomicin activity belong to the order Enterobacterales (9). The Enterobacterales-susceptible/-resistant breakpoints for plazomicin are ≤2/≥8, ≤2/≥8 and ≤4/≥8 μg/ml according to the Clinical and Laboratory Standards Institute (CLSI 2023) (31), US FDA 2019 (32) and United States Committee on Antimicrobial Susceptibility Testing (USCAST 2019) (33), respectively. The discrepancies between CLSI, US FDA and USCAST breakpoints were based on the most recent pharmacokinetic/pharmacodynamic data (34).

Between 2017 and 2021, 9,809 Enterobacterales isolates (1/patient) were obtained in 37 medical centers in USA, and the antimicrobial susceptibility was assessed using the broth microdilution method, and CLSI 2023 and US FDA 2019 criteria were used to calculate susceptibility rates. Plazomicin had strong activity against isolates that produced ESBLs (98.9%), MDR (94.8%) and CRE (94.0%), and it was active

Table I. Relationship between plazomicin molecular structure and its resistance to inactivation by AMEs when compared with traditional aminoglycosides (9).

Traditional aminoglycosides inactivated by AMEs	Molecular of plazomicin modifications	Plazomicin's protection against AMEs granted from the molecular modifications
Amikacin	Hydroxyl (-OH) groups deletion	O-phosphotransferase [APH (3')]
Amikacin and tobramycin	in the C-3' and 4' positions	O-adenyltransferases [ANT (4')]
Amikacin, gentamicin, and tobramycin	Unsaturated hydroxyethyl group addition at the C-6' position	N-acetyltransferase [AAC (6')]
Gentamicin and tobramycin	Addition of 4-amino-2-hydroxybutanoic	N-acetyltransferase [AAC (3')]
Gentamicin and tobramycin	acid (hydroxy-aminobutyric acid; HABA)	O-adenyltransferases [ANT (2')]
Amikacin, gentamicin, and tobramycin	at the C-1' position.	O-phosphotransferase [APH (2')]

Plazomicin has molecular structural alterations that protect it from all clinically relevant AMEs. As there are no-OH groups at the C-3' and 4' sites, APH (3') and ANT (4') cannot act. The addition of a hydroxyethyl group to the amine at position C-6' protects plazomicin against AAC (6'). Additionally, a HABA at the C-1' location makes plazomicin resistant to AAC (3'), ANT (2') and APH (2'). AMEs, aminoglycoside-modifying enzymes; APH, aminoglycoside phosphotransferase; ANT, aminoglycoside nucleotide transferase; AAC, aminoglycoside acetyltransferases.

against 96.4% of the total isolates. Plazomicin was markedly more effective against AMR Enterobacterales compared with gentamicin, tobramycin or amikacin. AMEs-encoding genes were detected in 801 (8.2%) isolates, whereas 11 (0.1%) isolates included 16RMT-encoding genes; plazomicin inhibited 97.3% of the AMEs and none (0.0%) of the 16RMT producers (Table II) (34,35).

Plazomicin use can be an effective method for treating carbapenems-resistant bacterial infections, particularly in countries where the prevalence of AMR is rising, including countries in Europe and Asia (9). Plazomicin was found to be more effective compared with the other tested AGs and comparable with ceftazidime/avibactam and merpenem/vaborbactam when tested against ESBLs-producing *Klebsiella pneumoniae*, ESBL-producing *Escherichia coli*, CRE and colistin-resistant Enterobacterales (Table III) (22). Alternatively, it was reported that plazomicin displayed low activity against *Acinetobacter* species (mostly *A. baumannii*) (17,23), *Pseudomonas aeruginosa* (24) and *Stenotrophomonas maltophilia* (22) with an MIC to inhibit 90% of tested strains (MIC_{90}) of ≥16, ≥16 and >64 μg/ml, respectively. Moreover, plazomicin has been tested by Castanheira *et al* (13) against 99 *Acinetobacter* species isolated from European nations (13), and the results showed that it had a MIC_{90} of >128 μg/ml and a susceptibility of 40.0%. This low activity was not superior to those of other comparator drugs, including gentamicin, amikacin, levofloxacin and meropenem, which displayed susceptibilities ranging from 34-41%. A total of 90% of these *Acinetobacter* species strains were susceptible to colonistin. Furthermore, the authors tested plazomicin against 60 Enterobacterales isolates that are producers of 16RMT, but it displayed no activity with MIC_{50}/MIC_{90} of >128/>128 μg/ml (13).

Plazomicin had comparable anti-Gram-positive isolate activity to other AGs (22,24) (Table IV); methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* are both susceptible with an MIC_{90} of 1 μg/ml and a MIC_{90} ≤0.5 μg/ml, respectively. Plazomicin also demonstrated strong efficacy against *Staphylococcus epidermidis*. Plazomicin are not effective against streptococci; its MIC_{90} values for *Streptococcus agalactiae*, *Streptococcus pneumoniae* and *Streptococcus pyogenes* are 64, 32 and 32 μg/ml, respectively. Plazomicin is similarly ineffective against *Enterococcus faecalis* and *Enterococcus faecium* strains with MIC_{90} >64 and 16 μg/ml, respectively (22). No notable activity of plazomicin has been demonstrated against the *Clostridium* species, other Gram-positive anaerobes and Gram-negative anaerobes (specifically *Bacteroides* and *Prevotella* species) (18).

Recently, it was reported that plazomicin was effective in monotherapy (9). Plazomicin in combination with numerous antibiotics appears to inhibit the development of AMR without posing any hazards (36). The synergy of plazomicin with other antibiotics (such as carbapenems, ceftazidime and piperacillin/tazobactam) used to treat complicated infections is notable; it can be utilized in combination to treat severe Gram-negative infections caused by MDR Enterobacterales, including isolates that are resistant to β-lactams and AGs. Carbapenems in combination with plazomicin showed synergism against *Acinetobacter baumannii* (22).

Plazomicin has also been shown to have *in vitro* synergistic activity against *Pseudomonas aeruginosa* when combined with cefepime, imipenem, doripenem or piperacillin-tazobactam, as well as against methicillin-resistant *Staphylococcus aureus*, heteroresistant vancomycin-intermediate *Staphylococcus aureus* (hVISA), VISA and vancomycin-resistant *Staphylococcus aureus* when combined with ceftobiprole or daptomycin (37).

4. Bacterial resistance to plazomicin

Fig. 2 shows a schematic representation of the resistance determinants of plazomicin. Clark and Burgess (38) reported that the identification of plazomicin-resistant bacteria was uncommon, and the expression of 16RMT was confirmed among the plazomicin-resistant isolates. High-level resistance to classical AGs (gentamicin, tobramycin and amikacin) as well as plazomicin is caused by acquired 16RMT such as ArmA and RmtC (18). Plazomicin is ineffective against bacteria that express 16RMT isolated mainly in East

Table II. Plazomicin and comparator antimicrobial activity against Enterobacterales (34).

A, Enterobacterales (n=9,809)[a]

Plazomicin and comparator antimicrobials	MIC_{50}, μg/ml	MIC_{90}, μg/ml	US FDA[b]		CLSI (2023)[c]	
			Resistant, %	Susceptible, %	Resistant, %	Susceptible, %
Plazomicin	0.50	1.00	0.8	96.4	0.8	96.4
Amikacin	2.00	4.00	0.2	99.4[d]	1.4	94.6
Tobramycin	0.50	4.00	6.1	90.6[d]	9.4	88.0
Gentamicin	0.50	2.00	7.7	91.5[d]	8.5	90.6
Meropenem	0.03	0.06	1.0	98.7[d]	1.0	98.7
Levofloxacin	0.06	8.00	16.4	80.3[d]	16.4	80.3
Colistin	0.25	>8.00	-	-	15.3	84.7[e]

B, Extended-spectrum β-lactamases producer-Enterobacterales (n=1,011)[f]

Plazomicin and comparator antimicrobials	MIC_{50}, μg/ml	MIC_{90}, μg/ml	US FDA[b]		CLSI (2023)[c]	
			Resistant, %	Susceptible, %	Resistant, %	Susceptible, %
Plazomicin	0.50	1.00	0.9	98.9	0.9	98.9
Amikacin	4.00	8.00	1.3	96.9[d]	8.4	79.7
Tobramycin	8.00	>16.00	41.7	43.9[d]	56.1	40.4
Gentamicin	1.00	>16.00	42.2	55.7[d]	44.3	54.5
Meropenem	0.03	0.12	5.5	93.5[d]	5.5	93.5
Levofloxacin	8.00	>16.00	67.2	23.2[d]	67.2	23.2
Colistin	0.25	0.25	-	-	1.8	98.2

C, Carbapenem-resistant Enterobacterales (n=117)[g]

Plazomicin and comparator antimicrobials	MIC_{50}, μg/ml	MIC_{90}, μg/ml	US FDA[b]		CLSI (2023)[c]	
			Resistant, %	Susceptible, %	Resistant, %	Susceptible, %
Plazomicin	0.25	1.00	5.1	94.0	5.1	94.0
Amikacin	4.00	32.00	8.5	75.2[d]	31.6	59.0
Tobramycin	16.00	>16.00	61.5	29.9[d]	70.1	27.4
Gentamicin	4.00	>16.00	35.9	56.4[d]	43.6	47.0
Meropenem	-	-	100.0	0.0	100	0.0
Levofloxacin	16.00	>16.00	78.6	14.5[d]	78.6	14.5
Colistin	0.25	0.50	-	-	8.6	91.4[e]

D, Aminoglycoside-modifying enzymes producer-Enterobacterales (n=801)[h]

Plazomicin and comparator antimicrobials	MIC_{50}, μg/ml	MIC_{90}, μg/ml	US FDA[b]		CLSI (2023)[c]	
			Resistant, %	Susceptible, %	Resistant, %	Susceptible, %
Plazomicin	0.50	1.00	1.4	97.3	1.4	97.3
Amikacin	4.00	16.00	2.0	94.3[d]	13.1	68.4
Tobramycin	16.00	>16.00	68.0	12.0[d]	88.0	2.0
Gentamicin	>16.00	>16.00	83.3	15.2[d]	84.8	14.0
Meropenem	0.03	0.25	7.7	91.4[d]	7.7	91.4
Levofloxacin	8.00	>16.00	63.4	29.0[d]	63.4	29.0
Colistin	0.25	0.25	-	-	4.3	95.7[e]

Table II. Continued.

E, Multidrug-resistant Enterobacterales (n=844)[i]

Plazomicin and comparator antimicrobials	MIC_{50}, μg/ml	MIC_{90}, μg/ml	US FDA[b]		CLSI (2023)[c]	
			Resistant, %	Susceptible, %	Resistant, %	Susceptible, %
Plazomicin	0.25	1.00	2.5	94.8	2.5	94.8
Amikacin	4.00	16.00	2.0	94.0[d]	13.3	71.0
Tobramycin	16.00	>16.00	59.1	20.1[d]	79.9	15.2
Gentamicin	>16.00	>16.00	59.0	36.4[d]	63.6	33.8
Meropenem	0.03	4.00	12.0	85.5[d]	12.0	85.5
Levofloxacin	8.00	>16.00	72.8	16.5[d]	72.8	16.5
Colistin	0.25	0.50	-	-	8.6	91.4[e]

F, Extensively drug resistant Enterobacterales (n=84)[j]

Plazomicin and comparator antimicrobials	MIC_{50}, μg/ml	MIC_{90}, μg/ml	US FDA[b]		CLSI (2023)[c]	
			Resistant, %	Susceptible, %	Resistant, %	Susceptible, %
Plazomicin	0.25	1.00	6.0	94.0	6.0	94.0
Amikacin	8.00	>32.00	11.9	65.5[d]	44.0	41.7
Tobramycin	>16.00	>16.00	86.9	0.0[d]	100.0	0.0
Gentamicin	8.00	>16.00	48.8	40.5[d]	59.5	29.8
Meropenem	16.00	>32.00	88.1	2.4[d]	88.1	2.4
Levofloxacin	>16.00	>16.00	95.2	0.0[d]	95.2	0.0
Colistin	0.25	0.50	-	-	7.1	92.9[e]

G, Amikacin-non-susceptible Enterobacterales based on 2023 CLSI criteria (n=528)

Plazomicin and comparator antimicrobials	MIC_{50}, μg/ml	MIC_{90}, μg/ml	US FDA[b]		CLSI (2023)[c]	
			Resistant, %	Susceptible, %	Resistant, %	Susceptible, %
Plazomicin	1.00	4.00	6.4	86.4	6.4	86.4
Amikacin	8.00	32.00	3.6	89.4[d]	26.5	0.0
Tobramycin	8.00	>16.00	49.4	46.0[d]	54.0	42.2
Gentamicin	2.00	>16.00	31.8	66.9[d]	31.1	66.9
Meropenem	0.03	0.50	8.7	90.7[d]	8.7	90.7
Levofloxacin	4.00	>16.00	54.4	42.6[d]	54.4	42.6
Colistin	0.25	>8.00	-	-	16.5	83.5[e]

n=number of tested isolates. [a]Organisms include *Escherichia coli* (3,271), *Klebsiella pneumoniae* (3,185), *Klebsiella oxytoca* (715), *Citrobacter freundii* species complex (367), *Proteus mirabilis* (334), *Klebsiella aerogenes* (305), *Serratia marcescens* (302), *Morganella morganii* (289), *Citrobacter koseri* (283), *Enterobacter cloacae* species complex (208), *Providencia stuartii* (139), *Providencia rettgeri* (134), *Proteus vulgaris* group (99), *Enterobacter cloacae* (89), *Proteus vulgaris* (76), *Citrobacter freundii* (4), unspeciated Providencia (4), *Klebsiella variicola* (1), *Proteus penneri* (2), *Providencia alcalifaciens* (1) and unspeciated Klebsiella (1). [b]Criteria as published by US FDA (32). [c]Criteria as published by CLSI (31). [d]The CLSI M100 (2022) standard (35) that is recognized by the US FDA. [e]The percentage intermediate; CLSI does not release a susceptible breakpoint for colistin (31). [f]Organisms include *Escherichia coli* (509), *Klebsiella pneumoniae* (471), *Klebsiella oxytoca* (24), *Citrobacter freundii* species complex (3), *Enterobacter cloacae* species complex (1), *Proteus vulgaris* (1), *Serratia marcescens* (1) and unspeciated Klebsiella (1). [g]Organisms include *Klebsiella pneumoniae* (82), *Escherichia coli* (9), *Citrobacter freundii* species complex (7), *Serratia marcescens* (5), *Klebsiella aerogenes* (4), *Klebsiella oxytoca* (4), *Enterobacter cloacae* species complex (3), *Providencia rettgeri* (2) and *Citrobacter koseri* (1). [h]Organisms include *Escherichia coli* (409), *Klebsiella pneumoniae* (328), *Klebsiella oxytoca* (31), *Proteus mirabilis* (16), *Enterobacter cloacae* species complex (13), *Proteus vulgaris* (2), *Klebsiella aerogenes* (1), and unspeciated Klebsiella (1). [i]Organisms include *Klebsiella pneumoniae* (413), *Escherichia coli* (267), *Klebsiella oxytoca* (35), *Citrobacter freundii* species complex (29), *Enterobacter cloacae* species complex (21), *Morganella morganii* (19), *Klebsiella aerogenes* (15), *Serratia marcescens* (15), *Providencia stuartii* (13), *Proteus mirabilis* (6), *Citrobacter koseri* (5), *Providencia rettgeri* (4), *Proteus vulgaris* (1) and unspeciated Klebsiella (1). Multi drug resistant Enterobacterales was defined as non-susceptible to ≥1 drug from ≥3 antimicrobial classes. [j]Organisms include *Klebsiella pneumoniae* (68), *Escherichia coli* (5), *Citrobacter freundii* species complex (4), *Serratia marcescens* (3), *Klebsiella oxytoca* (2), *Enterobacter cloacae* species complex (1) and *Klebsiella aerogenes* (1). Enterobacterales were defined as susceptible to only one or two antimicrobial classes. CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inhibitory concentration; US FDA, United States Food and Drug Administration.

Table III. Plazomicin and comparator antimicrobial *in vitro* MIC_{90} against some resistant Gram-negative bacterial isolates (22).

	MIC_{90}, μg/ml (% susceptible)						
Organism	Plazomicin	Amikacin	Tobramycin	Gentamicin	Meropenem	Meropenem/ vaborbactam	Ceftazidime/ avibactam
ESBLs-producing *Escherichia coli* (n=343)	1.00 (100.0)	8.00 (98.8)	32.00 (55.7)	>32.00 (67.1)	0.06 (99.7)	1.00 (100.0)	0.50 (NA)
ESBLs-producing *Klebsiella pneumoniae* (n=73)	0.50 (98.6)	8.00 (100.0)	32.00 (37.0)	>32.00 (49.3)	0.50 (93.2)	0.50 (99.3)	1.00 (NA)
Carbapenem-resistant Enterobacterales (n=110)	1.00 (98.1)	32.00 (23.6)	64.00 (3.6)	16.00 (81.8)	≥16.00 (2.7)	32.00 (79.6)	2.00 (97.5)
Colistin-resistant Enterobacterales (n=95)	4.00 (93.7)	32.00 (21.0)	32.00 (8.0)	64.00 (12.0)	16.00 (12.0)	NA	2.00 (99.5)

n=number of tested isolates. ESBLs, extended spectrum β-lactamases; MIC_{90}, minimum inhibitory concentration to inhibit 90% of tested strains; NA, non-available microbiology breakpoints.

Table IV. Plazomicin and comparator antimicrobial *in vitro* MIC_{90} against some Gram-positive bacterial isolates (22).

	MIC_{90}, μg/ml (% susceptible)				
Organism	Plazomicin	Amikacin	Tobramycin	Gentamicin	Vancomycin
Methicillin-susceptible *Staphylococcus aureus* (n=3,009)	1.00 (NA)	4.00 (NA)	≤0.50 (NA)	≤0.50 (98.6)	1.00 (100.0)
Methicillin-resistant *Staphylococcus aureus* (n=687)	1.00 (NA)	32.00 (NA)	>64.00 (NA)	≤0.50 (96.2)	1.00 (99.7)
Methicillin-susceptible *Staph. epidermidis* (n=339)	0.25 (NA)	4.00 (NA)	16.00 (NA)	>32.00 (69.3)	2.00 (100.0)
Methicillin-resistant *Staph. epidermidis* (n=25)	0.50 (NA)	16.00 (NA)	>64.00 (NA)	>32.00 (20.0)	2.00 (100.0)

n=number of tested isolates. MIC_{90}, minimum inhibitory concentration to inhibit 90% of tested strains; NA, non-available microbiology breakpoints.

Asia and occasionally co-expressed with the New Delhi metallo-β-lactamase (NDM). Furthermore, the bacterial phenotypes co-expressing 16RMT with NDM have occasionally been observed in the US, other nations in Europe and Asia have reported a more widespread frequency (9). Co-expression of 16RMT with OXA-48-carbapenemases is not uncommon. Thus, plazomicin should be used with caution when treating Enterobacterales that express NDM or OXA-48, and it is advisable to use commercially available rapid detection kits capable of detecting carbapenemases production, particularly NDM, prior to empirical administration of plazomicin (9).

As previously established, structural changes in plazomicin shield it against all clinically notable AMEs. The AAC (2')-I is an AME that is known to have anti-plazomicin activity among GNB, and it is chromosomally expressed in some isolates of *Providencia stuartii* (17). Notably, the AAC (2')-I encoding gene appears not to have transferred to any other bacterial species (17). APH (2')-Iva is another known AME with anti-plazomicin activity; however, this enzyme has only been found in the *Enterococcus* species for which plazomicin would not be considered a recommended therapy option (25).

Bacterial resistance against plazomicin (as in *Pseudomonas aeruginosa* and *Acinetobacter*) can also be generated by additional AG resistance mechanisms, such as efflux pumps or drug impermeability with down-regulation of porin channels. Therefore, traditional AGs can be more effective against *Pseudomonas aeruginosa* or *Acinetobacter baumannii* compared with plazomicin regardless of the absence or presence of AMEs (18).

Salmonella enterica strains with the gentamicin resistance gene (*grdA*) are extremely resistant to plazomicin (MIC >256 μg/ml) according to a study from the USA (39). Compared with the previously identified plazomicin-resistant AMEs *AAC* (2')-*Ia* and *APH* (2')-*Iva*, these results show that *grdA* confers markedly greater resistance to plazomicin (39). Healthcare professionals should continue to use plazomicin susceptibility testing because tests for identifying the genetic type of bacterial resistance are not always easily available (22).

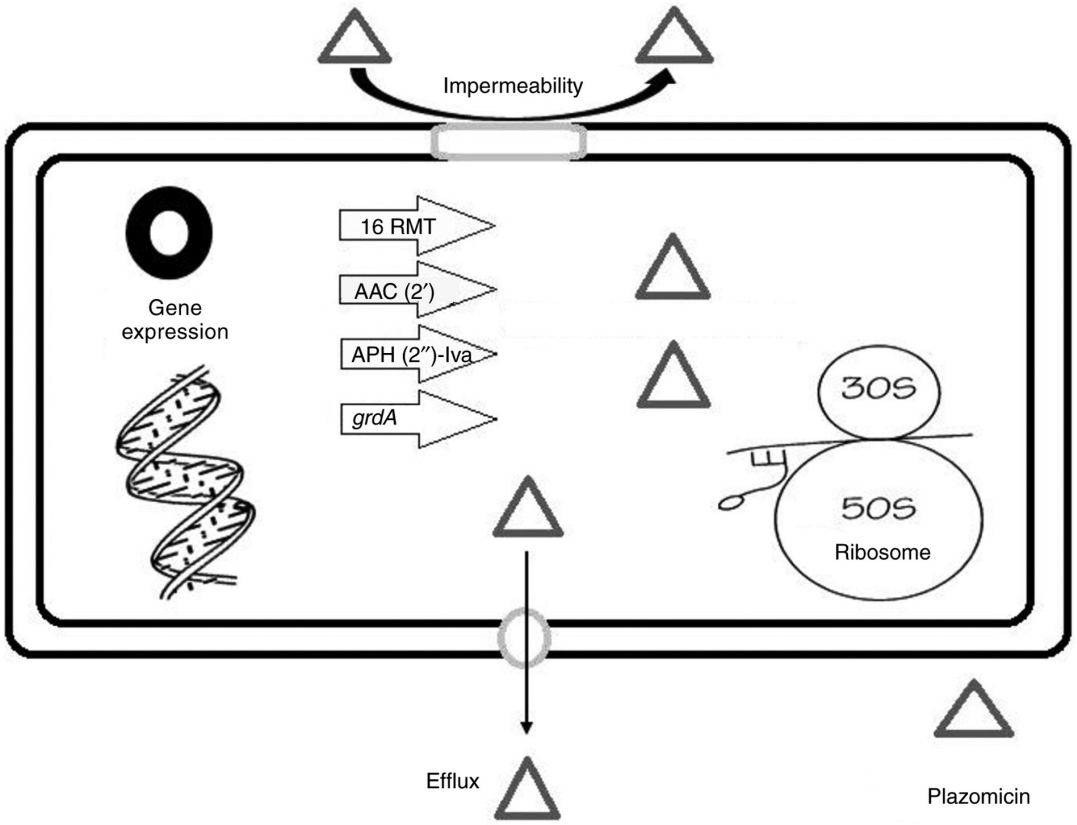

Figure 2. Schematic representation of resistance determinants of plazomicin. The resistance mechanisms include the expression of 16S rRNA methyltransferases (16RMT), aminoglycoside acetyltransferase AAC-(2')-I, aminoglycoside phosphotransferase APH (2')-Iva, *grdA* gene, efflux pumps or drug impermeability.

5. Pharmacokinetics and dosing

As with other AGs, plazomicin has modest plasma protein binding (~20%) and first-order linear elimination and is mainly excreted by the kidneys (glomerular filtration) without undergoing plasma or hepatic metabolism (9). Plazomicin must be taken parenterally because, similar to other AGs, it is poorly absorbed. The volume of distribution (Vd) of the AGs is ~25% of body weight, which is comparable with the volume of extracellular fluid, and they do not penetrate most cells. Adults with cUTIs and healthy adults both had mean Vd values of 18 and 31 liters, respectively, for plazomicin. In patients with cUTI, the mean maximum serum concentration was 51 mg/l and the area under the concentration time curve was 226 mg h/l after receiving a single intravenous (IV) dosage of plazomicin (15 mg/kg). Plazomicin neither induces nor inhibits the cytochrome P450 drug-metabolizing enzymes, it is not metabolized to any considerable level and in patients with normal renal function, the typical serum elimination half-life of plazomicin is ~3.5 h (22).

Assessing the effectiveness of plazomicin against respiratory infections, particularly in patients with resistant bacteria, requires an understanding of its distribution in lung tissue. Plazomicin can infiltrate the lungs to a comparable extent to amikacin even without lung inflammation (40). Plazomicin showed little to no affinity for melanin; therefore, it is unlikely that it will be retained in pigmented skin tissues (18). Plazomicin is supplied as a single use, fliptop, 10-ml vial containing 500 mg plazomicin (50 mg/ml), and sterilely compounded products are stable for 24 h at room temperature (41). The US FDA has approved a single daily IV infusion dose of 15 mg/kg, given over 30 min in 0.9% sodium chloride or lactated Ringers. After the initial dose, TDM should be used to adjust the dosing interval by 1.5 folds to keep the plasma trough concentration (the concentration of drug in the blood immediately before the next dose is given) <3 μg/ml (38). Plazomicin's renal clearance is comparable with its overall body clearance; following a single 15 mg/kg IV injection, 56 and 97.5% of the unmodified plazomicin is excreted in urine within the first 4 h and a week, respectively, with <0.2% recovered in stool (42).

To reduce toxicity, a reduction in the dose of plazomicin is recommended in patients suffering from moderate (creatinine clearance <60 ml/min) and severe (creatinine clearance <30 ml/min) renal impairment to 10 mg/kg every 24 h and 10 mg/kg every 48 h, respectively (22). The following formula should be used to determine the adjusted body weight (ABW): For patients whose total body weight (TBW) is >25% greater than IBW, ABW=ideal body weight (IBW) + 0.4 (TBW-IBW) (41).

6. Clinical therapeutic indications

The US FDA has approved plazomicin for cUTIs and acute pyelonephritis (AP) treatment in patients aged 18 years and older when these infections are caused by susceptible bacteria with few or no other therapeutic options (41,43). A general review of plazomicin data has clearly highlighted two clinical indications (38) as presented in Table V: cUTI

(approved by the US FDA after passing the phase 2 clinical trial NCT01096849 (44) and the Evaluating Plazomicin In cUTI (EPIC) trial (45) and serious CRE infections including BSI, VAP and HAP (up to date, it is not approved by the US FDA after premature termination of the Combating Antibiotic-Resistant Enterobacteriaceae (CARE) trial (46).

Connolly *et al* (44) performed the phase 2 clinical trial (trial no. NCT01096849) for comparing the efficacy and safety of plazomicin (15 mg/kg/day) with levofloxacin (750 mg/day) by IV for the treatment of cUTI and AP. In this multicenter, randomized, double-blind research, 145 patients participated. In comparison with the levofloxacin treatment group, the plazomicin treatment group experienced a lower rate of microbiological recurrence (6.5 vs. 23.5%) 1 month following the final dose of the study drug. Furthermore, 3.4% of the plazomicin therapy group experienced an increase in serum creatinine of ≥0.5 mg/dl, although none of the levofloxacin treatment groups did.

The EPIC study group (45) reported that plazomicin was non-inferior when compared with meropenem for the treatment of cUTI and AP. This study was a multicenter, international, randomized, double-blind phase 3 trial. Plazomicin was demonstrated to be non-inferior to meropenem regarding composite (microbiological and clinical) cure on day 5 of therapy and at the test-of-cure (TOC) visit, which occurred 15 to 19 days after the start of IV therapy. In brief, after at least 4 days, the trial assessed the effectiveness of IV plazomicin (15 mg/kg once daily) and IV meropenem (1 g/8 h) for 7-10 days, followed by optional oral levofloxacin 500 mg once a day, and there was no TDM performed. The main goals were to show that plazomicin was non-inferior to meropenem based on the variance in the clinical cure rates and microbiological cure rates on days 5 and 15-19 after the start of therapy. A 15% non-inferiority margin was applied during the trials. *Escherichia coli* was the most prevalent uropathogen, followed by *Klebsiella pneumoniae*. On day 5 of therapy, plazomicin had a composite (microbiological and clinical) rate of 168 out of 191 cases (88%), whereas meropenem had a cure rate of 180 out of 197 cases (91.4%). Plazomicin and meropenem had composite cure rates of 156 of 191 (81.7%) and 138 of 197 (70.1%), respectively at the TOC visit. Furthermore, a rise in serum creatinine of ≥0.5 mg/dl occurred in 3.7 and 3.0% of plazomicin and meropenem treatment groups, respectively. Moreover, 100 and 81.8% of patients taking meropenem and plazomicin, respectively, experienced complete renal recovery.

In the CARE trial, plazomicin (15 mg/kg/day)-based combinations were compared with colistin (5 mg/kg/day)-based combinations with adjunctive meropenem or tigecycline in patients with CRE-related BSI, HAP and VAP. Although preliminary findings suggested that the plazomicin group had lower all-cause mortality (at 28 days) and fewer major adverse events including nephrotoxicity, the study was discontinued early due to the limited number of the enrolled patients (a total of 39 individuals were enrolled as the following; 29 patients having proven CRE-related BSI, 8 patients having proven CRE-related HAP or VAP and CRE-related infection was not proven in 2 patients) (46). Thus, the US FDA has not approved plazomicin's use in case of bacterial infections causing BSI, HAP and VAP as the findings lacked the strength required for accurate hypothesis testing (22). Data from the USA has demonstrated notable bactericidal activity against a wide range of bacteria that are resistant to AGs, β-lactams, fluoroquinolones and carbapenems, including the MDR isolates (resistant to ≥1 agent in ≥3 different antibiotic classes) (34). The data presented by Alfieri *et al* (9) is encouraging for the use of plazomicin monotherapy or in combination with another antibiotic in three key scenarios (cUTI, BSI and VAP); however, the research team recommended that data meta-analysis is required to characterize the benefits.

7. Side effects and safety profile

The safety profile of traditional AGs reveals that they have always had a wide range of adverse effects, particularly when compared with the β-lactam antibiotics (9). Nephrotoxicity, ototoxicity and neuromuscular inhibition are the three most reported toxicities of AGs. Nephrotoxicity affects 3-11% of individuals, whereas vestibular and cochlear toxicity affect 10 and 26% of patients, respectively (Table VI) (6). The nephrotoxicity caused by AGs is caused by drug accumulation in the cortical portion of the kidney. It is a reversible process that relies on the capacity of tubular epithelial cells to regenerate. As a result, in cases of patients with poor kidney functions, a dose reduction must be considered (9). Ototoxicity, on the other hand, is the result of direct oxidative damage to the vestibular organ, cochlea and its hairy cells and related cranial nerves. The resulted harm is permanent; thus, it must be avoided. When used in combination with AGs, aspirin, N-acetylcysteine, dexamethasone and antioxidant compounds as N-methyl-D-aspartate receptor antagonists have been shown to effectively reduce ototoxicity (9).

The US FDA added a black box warning for nephrotoxicity, ototoxicity, neuromuscular blockade and pregnancy risk when approving plazomicin (41,43). Plazomicin is an AG, hence notable renal damage is to be expected; however, the renal toxicity of plazomicin is near that of meropenem, a rise in serum creatinine of ≥0.5 mg/dl from baseline occurred in 3.7 and 3.0% of plazomicin and meropenem treatment group, respectively. It is important to remember that the kidney damage induced by plazomicin is reversible, with most patients (81.8%) having complete renal function at the time of discharge in the EPIC study (45). Both plazomicin and meropenem groups reported the same adverse events in the EPIC study including hypotension (1.0%), headache (1.3%), nausea (1.3%), vomiting (1.3%), diarrhea (2.3%) and hypertension (2.3%). Moreover, in the EPIC trial, there was only one instance of *Clostridoides difficile* in the comparator group and none in the plazomicin group. On the other hand, there was a single mortality in the plazomicin group (a patient passed away on trial day 18 from metastatic uterine cancer that had been discovered 48 h after enrolment) (45).

Cochlear and vestibular function were assessed in a study performed on healthy participants, at baseline and up to 6 months after starting plazomicin treatment, and revealed no signs of ototoxicity, suggesting that plazomicin has a low potential for ototoxicity (40). As the plazomicin reports in the phase 3 trial were not based on cochlear and vestibular examinations, adverse events with possible ototoxicity seemed to be rare. Although there is a documented risk of ototoxicity connected with AGs, the plazomicin phase 3 trials were unable

Table V. Summary of plazomicin clinical trials in phase II and III.

Trial	Phase	Indication	Primary outcome	Results, n (%)		(Refs.)
P2-01 (trial no. NCT01096849)	II	cUTI	Microbiological recurrence at TOC visit (1 month following the final dose of the study drug)	Plazomicin 9 (6.5)	Levofloxacin 34 (23.5)	(44)
			Serum creatinine increases ≥0.5 mg/dl	5 (3.4)	0 (0.0)	
EPIC (trial no. NCT02486627)	III	cUTI	Composite cure[a] on 5th day of therapy	Plazomicin 168 (88.0)	Meropenem 180 (91.4)	(45)
				Statistical difference, 3.4% (95% CI, -10.0-3.1%) in favor of plazomicin		
			Composite cure[a] at TOC visit (after IV therapy initiation by 15-19 days)	156 (81.7)	138 (70.1)	
				Statistical difference, 11.6% (95% CI, 2.7-20.3%) in favor of plazomicin		
CARE (trial no. NCT01970371)	III	Serious CRE infections (including BSI, HAP and VAP)	Disease-related complications or all-cause mortality at 28 days in the microbiologic modified intent-to-treat population (those with a confirmed CRE infection who received at least one dosage of the trial drug)	Plazomicin[b] 4 (24)	Colistin[b] 10 (50)	(46)
				Statistical difference, 26% (95% CI, -55-6%) in favor of plazomicin		

The trial drug doses: IV plazomicin (15 mg/kg/day) with therapeutic drug monitoring for the maintenance doses, IV levofloxacin (750 mg/day), IV meropenem (1 g q 8 h) and IV colistin (loading dose 5 mg/kg) with (maintenance dosing of 5 mg/kg per day divided into 8-12 h dosing intervals). [a]Composite cure includes both clinical cure and microbiological eradication. Clinical cure is the reduction in severity of symptom on 5th day or at the end of infusion, complete resolution of symptom at TOC visit, or the return to patient's baseline before the UTI. Microbiological eradication is the reduction in count of isolated causative bacterial pathogen to $<10^4$ CFUs/ml. [b]Combined with either IV (3 h extended-interval infusion) meropenem (2 g q 8 h) or IV tigecycline (loading dose 100-200 mg) with (maintenance dosing of 50-100 mg q 12 h). BSI, blood stream infection; CARE, Combating Antibiotic-Resistant Enterobacteriaceae; CFU, colony-forming unit; CI, confidence interval; CRE, carbapenem-resistant Enterobacterales; cUTI, complicated urinary tract infection; EPIC, Evaluating Plazomicin In cUTI; HAP, hospital-acquired pneumonia; IV, intravenous; TOC, test-of-cure; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

to identify any possible ototoxicity associated with plazomicin treatment (22). According to previous findings, plazomicin is not ototoxic; thus, it is safe, as well as practical and effective (47). Alfieri *et al* (9) reported that ototoxicity occurred in <2% of patients in numerous trials, on average.

The clinical investigations of plazomicin to date have not revealed any evidence of the AG class danger of neuromuscular blocking leading to respiratory depression. However, care should be taken when prescribing plazomicin to patients who have a neuromuscular condition such as myasthenia gravis or to individuals who are receiving neuromuscular blockers such as succinylcholine because doing so could delay the neuromuscular function recovery (22).

When provided to patients who are pregnant, AGs, including plazomicin, can cross the placenta and cause fetal harm. Streptomycin has been linked to multiple reports of complete, irreversible, bilateral congenital deafness in young children who were exposed *in utero*. Female patients should be informed of the potential risk to the fetus if they use plazomicin while pregnant or become pregnant while using plazomicin. To the best of our knowledge, there is no data available on the presence of plazomicin in human milk, its effects on breastfed infants or its effects on milk production, but minimal levels are anticipated in milk based on the excretion of other AGs; however, plazomicin has been found in rat milk (41,43). The National Institute of Child Health and Human Development expects low plazomicin excretion in human milk (based on the excretion of other AGs). Thus, the institute recommends the inspection of any effects on the gastrointestinal flora of the baby, such as diarrhea, candidiasis (such as thrush or diaper rash) or infrequently, blood in the stool, which could be a sign of antibiotic-associated colitis, when prescribing plazomicin to lactating females (48). The safety and effectiveness of plazomicin in patients <18 years have not been demonstrated (41,43).

Table VI. Main side effects of AGs (6).

Toxicity types	Effects of toxicity	Risk factors of toxicity		Potential treatment of toxicity	Prevention of toxicity
		Clinical	Therapeutic		
Renal	Acute injury of the kidney with preserved diuresis; tubular necrosis	Age; chronic renal disease; dehydration; hyperthermia	Previous treatment with AG; cumulative dose; treatment duration >5 days	Dose adaptation through TDM; stop AG when unnecessary	Avoid co-nephrotoxic drugs; avoid cumulative risk factors; TDM
Cochleovestibular	Cochlear-hearing loss, tinnitus; vestibular-ataxia, vertigo, nystagmus	Past history of hearing loss	Previous treatment with AG; cumulative dose; treatment duration >5 days	Dose adaptation through TDM; stop AG when unnecessary	Avoid co-nephrotoxic drugs; avoid cumulative risk factors; TDM
Neuromuscular	Neuromuscular block	Myasthenia gravis; immediate postoperative period; respiratory acidosis	-	Anti-cholinesterase drugs	Avoid co-nephrotoxic drugs; avoid cumulative risk factors; TDM

AG, aminoglycoside; TDM, therapeutic drug monitoring.

8. Role in therapy and special considerations

Due to the potential for antimicrobials to lose their effectiveness in treating infectious diseases, it is imperative to consider newly developed antimicrobials and put preventive measures in place to stop the emergence of AMR (49). The real-world therapeutic experience will define the role of plazomicin as a monotherapy and/or combination therapy. The therapeutic usage of AGs and polymyxin antibiotics has increased because of the global spread of MDR GNB. The majority of Enterobacterales that are resistant to the traditional AGs can still be killed by plazomicin (20); thus, there are multiple potential roles for plazomicin in therapy depending on its higher potency (lower MICs) against numerous bacterial pathogens.

Plazomicin is effective *in vitro* against a variety of isolates that produce ESBLs and carbapenemase enzymes (19). However, with this class of antibiotics, strong *in vitro* activity does not always indicate clinical efficacy. A poor outcome was noticed while using AGs in treating patients suffering from pneumonia and explained by their low concentrations in alveolar lining fluid and inactivation by the acidic pH within the inflamed lung tissue (50). Therefore, before accepting plazomicin for extended usage, more clinical trials using plazomicin in a variety of diseases, particularly pneumonias, are required. However, due to the lack of therapeutic options for the management of MDR bacterial infections, plazomicin may thus play a special role in antibacterial therapy.

For patients with cUTI, AGs, including plazomicin, were suggested over tigecycline (9,51). Plazomicin offers certain dosage advantages compared with other antimicrobials, including β-lactam/β-lactamase inhibitors, which are effective against MDR GNB. Plazomicin can be administered intravenously, once daily over a brief period of 30 min, and hospitalized patients may benefit from this administration schedule, but those undergoing outpatient parenteral antibiotic therapy will especially benefit from it (52). However, plazomicin-associated toxicity, especially nephrotoxicity and ototoxicity, is an area of doubt, and it is important to monitor renal function. Notably, when the benefits of plazomicin use as antibacterial therapy are weighed against its side effects, the drug safety in comparison to conventional AGs is notable (9).

In terms of drug-drug interactions, 90% of metformin is eliminated via renal tubular secretion through three transporters (multidrug and toxin extrusion 2-K, multidrug and toxin extrusion 1 and organic cation transporter 2). Although plazomicin selectively inhibits these transporters with variable degrees, there are no noticeable changes in the blood metformin levels when plazomicin was administered concurrently with metformin, according to a study assessing the possibility of interaction (53). Furthermore, another study investigating the effect of plazomicin intake on the heart found no discernible changes in the QT interval length (54). Similar to other AGs, the major drug interaction of concern would likely be additive toxicity when combined with other nephrotoxic drugs (18).

As with other antimicrobials created for the treatment of MDR GNB, plazomicin has a high acquisition cost (55). The actual market entry price of plazomicin per treatment course was $4,955.11 at the time of commercialization in 2018 (56). The price of the recently approved antimicrobials with anti-CRE activity against cUTIs, such as ceftazidime-avibactam (February 2015) and meropenem-vaborbactam (August 2017), was taken into consideration while setting the price of plazomicin. In 2019, the cost of purchasing plazomicin at wholesale was $945.00 a day, based on a dosage of a patient weighing 75 kg, and ceftazidime-avibactam and meropenem-vaborbactam were $1,076 and $990, respectively, whereas colistin ($56.00 per day) and polymixin B ($21.78-45.00) were markedly less expensive (57).

As a result, healthcare professionals may have concerns about the cost of plazomicin therapy. Antimicrobial stewardship will be necessary to avoid this cost and the cost of its TDM. On the other hand, clinicians should also consider that plazomicin monotherapy can improve the prognosis of patients with MDR bacteria, reduce the likelihood of infection progression to septic shock and shorten the hospitalization duration (58). For patients with severe infections, plazomicin therefore may enable the reduction of the overall cost of treatment (59). The additional hospital expenses per patient for antibiotic-resistant healthcare-associated infections among U.S. patients were estimated by Achaogen to be >$15,000 (60).

As mentioned before, cUTIs are the focus of most plazomicin related therapeutic data (9). The scarcity of data from clinical trials other than cUTIs is the main issue with non-extensive therapeutic use of plazomicin (59). Randomized controlled trials were identified by a recent systematic literature review that aimed to evaluate the relative effectiveness of different treatment options for cUTIs and AP. The study concluded that plazomicin demonstrated notably higher relative efficacy vs. carbapenems for both composite outcome and microbiological eradication at TOC (61).

The role of certain AG in therapy should be connected to the susceptibility of the organism producing the infection rather than the infection site (62). A study from Egypt concluded that plazomicin displayed the most potent *in vitro* activity against carbapenem-resistant Gram-negative intensive care unit (ICU) and non-ICU isolates when compared with meropenem-vaborbactam (carbapenem combined with a β-lactamase inhibitor) and omadacycline (a semisynthetic minocycline derivative), with plazomicin inhibiting 82.22% of CRE isolates. The tested samples in the study included non-ICU samples (urine and surgical wound swabs), and ICU samples (urine, blood, sputum, endotracheal aspirates, bronchoalveolar lavage, peritoneal fluid aspirate, pericardial fluid aspirate, pleural fluid aspirates, CSF, infected burn wounds swabs and surgical wound samples) (63).

Most likely, plazomicin will be utilized either alone to treat MDR cUTIs or in combination to treat severe CRE infections, especially those having a variety of AMEs (38). Moreover, plazomicin has been used in the treatment of patients with infections including the UTIs, BSIs and VAPs if caused by plazomicin susceptible organisms. The European Medicines Agency approved the drug because of these encouraging results against the susceptible bacteria, but it is not yet available in the market (6).

Despite their hydrophilicity, AGs effectively penetrate bone and joint tissues (64). Plazomicin was discovered to be active and superior to traditional AGs against CRE isolates from skin and soft tissue infections (SSTIs) (65); however, the relevance of plazomicin in the treatment of SSTIs, bone infections and diabetic foot infections is still understudied (66). In the US, plazomicin showed little or no activity against *Achromobacter* infections (including respiratory, blood, genitourinary and wound infections), with MIC_{50}/MIC_{90} of >4/>4 μg/ml (67).

Plazomicin research has been limited by the fact that it has only been used for conditions that affect the urinary system and by the fact that varied ethnicities and patients who are seriously unwell, such as those who have bacteremia and pneumonia, are underrepresented (22). According to the aforementioned information, plazomicin is a reasonably expensive drug that should be used sparingly, but it can enable patients with serious infections to save money on their entire course of treatment (9).

9. Conclusions and recommendations

Plazomicin is a promising semisynthetic antimicrobial that has been created to target MDR bacterial pathogens, especially GNBs. Except for the approved use of plazomicin to treat cUTIs, there is a gap in the literature regarding its clinical uses for treatment of severe complicated infections such as BSIs, HAPs and VAPs after premature termination of the CARE trial. For the treatment of cUTIs, it is considered the best treatment option against bacterial pathogens with poor sensitivity to carbapenems and other alternatives. It has been demonstrated to be non-inferior to meropenem, it is a convenient treatment choice for outpatient antibiotic therapy settings (given IV, once daily, with a short 30 min administration duration) and it has low frequency side effects. Due to the rising prevalence of highly resistant GNB and the absence or limited alternative treatment options, plazomicin is a valuable non-β-lactam treatment option against MDR bacterial infections such as BSIs, HAPs and VAPs. This costly new antibacterial drug should be properly exploited, prescribed when necessary and sparingly to maintain its effectiveness over time. To help improve understanding of its clinical and therapeutic importance in various bacterial illnesses, a meta-analysis on this trending issue is advised. Clinicians using plazomicin should recognize that the setting of clinical practice is distinct from that of clinical trials. Thus, clinicians are urged, as always, to review their local antibiograms and adhere to the optimal guidelines which include proper plazomicin dosing and administration with TDM, to achieve maximum effectiveness and least toxicity especially for patients with a history of inner ear or kidney diseases who should always be treated with caution. Moreover, healthcare professionals should keep using plazomicin susceptibility testing because tests for identifying the genetic type of bacterial resistance are not always easily available.

Acknowledgements

Not applicable.

Funding

The present review was funded by the Deanship of Graduate Studies and Scientific Research at Jouf University, Saudi Arabia (grant no. DGSSR-2024-01-02130).

Availability of data and materials

Not applicable.

Authors' contributions

The present review was conceptualized by MA and AET; the data was curated by MA, AET, IAT, HMS and GAB; funding was acquired by MA; MA, AET, IAT, HMS and GAB were responsible for resources and project administration; the project was supervised by MA, AET, IAT, HMS and GAB;

validation of references was performed by MA, AET, IAT, HMS and GAB. Writing of the original draft was completed by MA and AET and reviewing and editing of the manuscript was performed by MA, AET, IAT, HMS and GAB. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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