

Evaluation of Colistin Sensitivity in Panresistant Enterobacterales, Acinetobacter, and Pseudomonas Species by Broth Microdilution Method

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Abstract

Background: Colistin, discovered in the 1940s, was initially used as a broad-spectrum antibiotic against gram-negative bacteria. Due to its significant nephrotoxic and neurotoxic effects, its systemic use declined in the 1970s. However, colistin has re-emerged as a critical therapeutic option with the increasing prevalence of multidrug-resistant pathogens, particularly those producing carbapenemases and extended-spectrum beta-lactamases.

Objective: This study aimed to evaluate colistin susceptibility in panresistant Enterobacterales, Acinetobacter, and Pseudomonas species using the broth microdilution method.

Methods: A total of 124 non-duplicate clinical isolates were collected from March 2021 to April 2023, including Klebsiella pneumoniae (52%), Acinetobacter baumannii (35%), Escherichia coli (6%), Pseudomonas aeruginosa (6%), Acinetobacter jejunii (2%), and Klebsiella oxytoca (1%). Patient samples were obtained from various hospital units. Colistin susceptibility testing was performed using the CLSI-EUCAST 2016 guidelines, following the broth microdilution method. MIC values ≤ 2 $\mu\text{g/ml}$ were considered susceptible, and ≥ 4 $\mu\text{g/ml}$ resistant.

Results: Out of 124 isolates, 77 (62.1%) were colistin-susceptible, and 47 (37.9%) were resistant. Resistance rates among key species were: K. pneumoniae (39.1%), A. baumannii (30.2%), E. coli (28.6%), and P. aeruginosa (85.7%). Resistant isolates were identified in urine (8.1%), blood (14.5%), and respiratory samples (4.8%).

Conclusion: Colistin remains a valuable therapeutic agent against multidrug-resistant gram-negative bacteria. Routine susceptibility testing is essential to guide appropriate use and prevent the emergence of further resistance.

Keywords: Colistin; Enterobacterales; Acinetobacter; Pseudomonas; Drug Resistance

1. Introduction

Polymyxins were first produced in 1947 from the bacterium Paenibacillus polymyxa and represent a unique class of antibiotics characterized by their polypeptide structure (1). Among the polymyxin family, colistin, a mixture of polymyxin E1 and E2, has garnered significant attention, especially in the context of infections caused by Gram-negative bacteria. Its mechanism of action is primarily directed towards the bacterial outer membrane. Colistin interacts with the lipopolysaccharides (LPS) that decorate the outer membrane of these bacteria, binding to the negatively charged sites and displacing the stabilizing divalent cations, specifically Ca^{2+} and Mg^{2+} (2, 3). This displacement compromises the integrity of the bacterial outer membrane, resulting in increased permeability, leakage of cellular contents, and ultimately bacterial cell death.

Historically, colistin was one of the frontline antibiotics used during its initial introduction. However, its clinical use diminished in the 1970s due to the recognition of significant nephrotoxic and neurotoxic side effects associated with systemic administration (4). Despite these concerns, colistin has re-emerged as a critical therapeutic option in recent years. This resurgence is primarily due to the escalating challenge posed by multidrug-resistant (MDR) bacterial infections. In particular, the limited treatment options available for diseases caused by carbapenem-resistant pathogens have forced clinicians to reconsider the utility of colistin (5).

The current global scenario is marked by a rapid increase in multidrug resistance, particularly among notorious pathogens such as Acinetobacter baumannii, Pseudomonas aeruginosa, and various members of the Enterobacterales family (6). These organisms are adept

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Received: 27-Aug-2025

Revised: 13-Sep-2025

Accepted: 21-Oct-2025



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at developing resistance to multiple antibiotic classes and frequently harbor additional resistance mechanisms, such as extended-spectrum beta-lactamases (ESBLs) and carbapenemases, which further complicate the treatment landscape. Consequently, colistin has become the last resort antibiotic for managing infections caused by these formidable pathogens (7).

With the reintroduction of colistin into clinical practice, ensuring its judicious and effective use has become paramount. One critical aspect of this is accurately determining bacterial susceptibility to colistin (8). Traditional testing methods, such as disc diffusion and gradient tests, have proven unreliable regarding colistin. Their inability to consistently produce reproducible and interpretable results has led to discrepancies that can adversely impact clinical decisions (9). Given these challenges, the broth microdilution (BMD) method has been endorsed as the reference standard for colistin susceptibility testing. Both the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) recognize BMD as the only acceptable method for this purpose (10, 11).

Although the BMD method provides reliable and accurate results, it has challenges. It is demanding, time-consuming, and requires high expertise, which limits its routine use in some laboratory settings (12). Accurate preparation of bacterial suspensions, careful serial dilutions, and strict adherence to incubation times and temperatures are all critical factors that determine the quality of the susceptibility testing. Furthermore, the interpretation of minimum inhibitory concentrations (MICs) demands meticulous attention, as even slight deviations in procedural protocol can lead to significant variations in results (5).

The clinical implications of colistin susceptibility testing extend far beyond the laboratory. In the era of multidrug resistance, where therapeutic options are limited, the ability to accurately determine bacterial sensitivity to colistin can directly influence patient outcomes (13). By ensuring that clinicians have precise information regarding the susceptibility of pathogens to colistin, the BMD method plays a crucial role in guiding appropriate antibiotic therapy and mitigating the risk of further resistance development. This is particularly important in intensive care units and other high-risk clinical environments where infections with MDR bacteria are most prevalent (14).

Given these considerations, this study used the broth microdilution method to evaluate colistin sensitivity

in panresistant Enterobacterales, Acinetobacter, and Pseudomonas species. The aim was to provide robust and reliable susceptibility data that can help inform clinical decision-making and ultimately contribute to improved patient management in the face of growing antimicrobial resistance.

2. Materials and Methods

2.1. Sample Collection and Bacterial Isolates

This cross-sectional laboratory-based study was conducted between March 1, 2021, and April 30, 2023. Total 124 non-duplicate, panresistant clinical bacterial isolates were collected from a tertiary care hospital's inpatient and outpatient departments. The isolates included 64 (52%) *Klebsiella pneumoniae*, 43 (35%) *Acinetobacter baumannii*, 2 (2%) *Acinetobacter jejunii*, 7 (6%) *Escherichia coli*, 1 (1%) *Klebsiella oxytoca*, and 7 (6%) *Pseudomonas aeruginosa*.

All isolates were obtained from individual patients; no patient was included more than once in the study. Of the 124 patients, 69 (55.6%) were male and 55 (44.4%) were female.

The clinical samples originated from diverse hospital units, including the adult emergency department (2 samples; 1.6%), pediatric emergency department (4 samples; 3.2%), anesthesia intensive care unit (21 samples; 16.9%), neonatal intensive care unit (29 samples; 23.4%), neurosurgery ward (2 samples; 1.6%), surgical ward (1 sample; 0.8%), pediatric ward (26 samples; 21%), pediatric intensive care unit (26 samples; 21%), internal medicine ward (3 samples; 2.4%), infectious diseases service (3 samples; 2.4%), orthopedic service (3 samples; 2.4%), urology ward (1 sample; 0.8%), and pediatric outpatient clinic (3 samples; 2.4%).

The types of clinical specimens from which the bacterial isolates were recovered were as follows: abscess (2 samples; 1.6%), sputum (3 samples; 2.4%), unspecified samples (8 samples; 6.5%), tissue samples (6 samples; 4.8%), urine (22 samples; 17.7%), blood (50 samples; 40.3%), respiratory tract samples (22 samples; 17.7%), and wound cultures (11 samples; 8.9%).

2.2. Colistin Susceptibility Testing via Broth Microdilution Method

The susceptibility of all isolates to colistin was evaluated using the broth microdilution (BMD) method, which is currently the gold standard as per the guidelines jointly issued by the Clinical and Laboratory Standards

Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in 2016. To prepare for the test, stock solutions of colistin sulfate (Sigma Aldrich, St. Louis, MO, USA) were made at a concentration of 128 µg/ml, following the manufacturer's instructions. These stock solutions were then serially diluted in cation-adjusted Mueller-Hinton broth to obtain final concentration ranges from 0.06 µg/ml to 64 µg/ml in sterile 96-well microdilution plates.

Each bacterial isolate was prepared to match a turbidity equivalent to a 0.5 McFarland standard. The bacterial suspension was further diluted to achieve a final inoculum concentration of approximately 5×10^5 colony-forming units per milliliter (cfu/ml). This standardized bacterial suspension was added to each well of the microdilution plate.

The inoculated plates were incubated at 35°C for 16–20 hours in ambient air. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of colistin at which no visible bacterial growth was observed. For quality assurance, all tests yielding inconsistent or borderline results were repeated in duplicate to confirm MIC accuracy.

EUCAST breakpoints interpreted colistin MICs. For Enterobacteriales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, isolates were classified as Susceptible if MIC ≤ 2 µg/ml and Resistant if MIC > 2 µg/ml (11). This standardized classification allowed for a consistent and clinically relevant evaluation of colistin resistance.

2.3. Statistical Analysis

All collected data were entered and statistically analyzed using SPSS (Statistical Package for the Social Sciences) version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize bacterial species distributions, sample sources, and susceptibility patterns. Where necessary, categorical data were expressed as frequencies and percentages to facilitate colistin sensitivity interpretation and comparison across different pathogens and sample types.

3. Results

Colistin susceptibility testing by broth microdilution of the 124 clinical isolates in this study revealed that 77 isolates (62.1%) were susceptible to colistin (MIC ≤ 2 µg/ml), while 47 isolates (37.9%) were resistant (MIC ≥ 4 µg/ml). Among the resistant isolates,

10 (8.1%) originated from urine samples, 18 (14.5%) from blood cultures, and 6 (4.8%) from respiratory specimens. Species-specific resistance rates showed that 25 (39.1%) of the *Klebsiella pneumoniae* isolates were colistin-resistant, while 39 (60.9%) remained susceptible. In *Acinetobacter baumannii*, 13 isolates (30.2%) were resistant and 30 (69.8%) susceptible. For *Escherichia coli*, 2 isolates (28.6%) exhibited resistance and 5 (71.4%) were susceptible. Notably, a high resistance rate was observed in *Pseudomonas aeruginosa*, with 6 isolates (85.7%) resistant and only 1 isolate (14.3%) susceptible to colistin.

Table 1 presents the distribution of bacterial isolates, their colistin minimum inhibitory concentration (MIC) values as determined by broth microdilution (BMD), and the corresponding clinical sample sources. Among the 64 *Klebsiella pneumoniae* isolates, the majority exhibited MICs ranging from 0.125 to 64 µg/ml, with the highest frequency at MIC 2 µg/ml (23 isolates), primarily derived from blood, urine, wound, and respiratory samples. Notably, higher MICs of 8, 16, 32, and 64 µg/ml were associated with isolates from blood, urine, tissue, sputum, abscesses, and wounds, indicating increasing resistance. For *Escherichia coli* (7 isolates), most had MICs of 1 or 2 µg/ml, while two isolates showed resistance with MICs of 4 and 8 µg/ml from blood and urine samples, respectively. *Pseudomonas aeruginosa* (7 isolates) also displayed elevated MICs, with four isolates resistant (MIC 8 µg/ml), mainly from blood, urine, and respiratory sources. *Acinetobacter baumannii* (43 isolates) demonstrated a broader MIC distribution, with the majority showing MICs of 1 and 2 µg/ml. However, several isolates exhibited resistance at MICs of 4 and 8 µg/ml, primarily from blood, respiratory, wound, and tissue samples. Both *Acinetobacter jejunii* isolates had MICs of 1 µg/ml from blood and sputum, while the single *Klebsiella oxytoca* isolate had an MIC of 2 µg/ml from a blood sample. Overall, the table highlights significant variability in colistin susceptibility among species and sample types, with higher MICs generally linked to invasive infections such as bloodstream and respiratory tract infections.

4. Discussion

Colistin, a member of the polymyxin class of antibiotics, was first introduced in the 1940s and quickly gained prominence. It has potent bactericidal activity against Gram-negative organisms. Despite its broad-spectrum efficacy, its clinical application declined in the 1970s due to a high incidence of nephrotoxic and neurotoxic

Bacterium	NUMBER OF ISOLATES	COLISTIN BMD MIC	MATERIEL
K.pneumoniae (64)	1	0.125	1 blood
	3	0.25	2 urine-1 CSF
	4	0.50	1 blood-1 respiratory
1 urine-1 wound			
	8	1	3 blood-2 urine
1 respiratory-1 CSF			
1 abscess			
	23	2	3 wound-4 urine
10 blood-2 CSF			
2 respiratory-1 sputum			
1 tissue			
	8	4	3 urine-3 blood
1 respiratory-1 abscess			
	5	8	3 urine -2 respiratory
	5	16	1 respiratory-4 blood
	5	32	1 blood-1 urine
1 tissue-1 sputum			
1 wound			
	2	64	1 urine-1 abscess
E.coli (7)	3	1	2 urine-1 blood
	2	2	1 urine-1 respiratory
	1	4	1 blood
	1	8	1 urine
PSA(7)	1	1	1 respiratory
	2	4	2 blood
	4	8	2 blood-1 respiratory
1 urine			
A.baumannii(43)	1	0.25	1 wound
	1	0.50	1 blood
	10	1	5 blood-4 respiratory
1 CSF			
	18	2	8 blood-6 respiratory
3CSF-1 wound			
	7	4	3 blood-1 respiratory
1 wound-2 tissue			
	5	8	2 blood
3 wound			
A.jejuni (2)	2	1	1 blood
1 sputum			
K.oxytoca (1)	1	2	1 blood

side effects associated with systemic use (15). However, in the current era of escalating antimicrobial resistance, colistin has re-emerged as a vital therapeutic option, particularly in treating infections caused by multidrug-resistant (MDR) and carbapenem-resistant Gram-negative bacilli (16). This resurgence is driven by the global rise in the production of carbapenemases and extended-spectrum beta-lactamases (ESBLs), which render many conventional antibiotics ineffective against pathogens such as *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* (17).

Studies indicate that between 2006 and 2012, colistin usage increased approximately threefold, underscoring its growing importance in clinical practice (18). Its concentration-dependent bactericidal activity and ability to achieve therapeutic serum levels make colistin one of the few remaining effective treatments for bloodstream infections caused by carbapenem-resistant *K. pneumoniae* (19). However, its clinical utility is complicated by challenges in laboratory testing. Due to its large molecular size and cationic nature, colistin demonstrates poor diffusion in agar media, compromising susceptibility testing accuracy using traditional disc diffusion or gradient methods (20).

To overcome these limitations, the broth microdilution (BMD) method has been endorsed by both the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) as the sole reference method for colistin susceptibility testing (10, 11). The BMD method is particularly advantageous because it accurately determines colistin's minimum inhibitory concentration (MIC), although it requires skilled personnel, strict procedural adherence, and specialized laboratory resources. Nevertheless, BMD remains the most reliable approach given the critical need for reliable susceptibility data, especially for last-resort antibiotics (21).

The present study evaluated 124 panresistant Gram-negative isolates using the BMD method. Among these, 77 isolates (62.1%) were susceptible to colistin (MIC \leq 2 μ g/ml), while 47 (37.9%) demonstrated resistance (MIC \geq 4 μ g/ml). These findings are consistent with those of Yiş, who examined colistin susceptibility in carbapenem-resistant Enterobacterales using various methods and found that 66 isolates (55%) were susceptible and 54 (45%) resistant based on BMD results (22). This agreement supports the robustness of our findings and reaffirms the prevalence of colistin resistance among clinically significant Gram-

negative pathogens.

Further comparison with the literature reveals similar trends. Sarıkaya et al. conducted a study involving 157 Gram-negative bacterial isolates and reported that, using BMD, 54 of the *K. pneumoniae* isolates were resistant, while 20 were susceptible. Among *A. baumannii*, 24 were resistant and 9 susceptible; for *E. coli*, 2 were resistant and 24 susceptible; and for *P. aeruginosa*, only one isolate showed resistance, while 23 were sensitive (23). Our results are aligned with these findings, particularly in *K. pneumoniae*, where 25 isolates (39.1%) were resistant and 39 (60.9%) susceptible. Similarly, among *A. baumannii*, 13 isolates (30.2%) were resistant and 30 (69.8%) susceptible. Although our resistance rates for *E. coli* (28.6%) and *P. aeruginosa* (85.7%) appear higher than those of Sarıkaya et al., this variation could be attributed to differences in sample size, geographical distribution, and prior antibiotic exposure (23).

Another study by Özkaçmaz et al. examined 193 isolates, divided into Enterobacterales (n=97) and non-fermentative Gram-negative bacteria (n=96). They found that 31 Enterobacterales isolates were resistant to colistin, while 66 were susceptible. Among non-fermenters, only 3 isolates were resistant—1 *A. baumannii* and 2 *P. aeruginosa*—whereas 93 were susceptible according to BMD (24). These results suggest a generally lower resistance profile in non-fermentative organisms in their cohort, whereas in our study, *P. aeruginosa* demonstrated an exceptionally high resistance rate (85.7%). This alarming trend may reflect local epidemiology, high antibiotic selection pressure, or limited infection control measures (25).

The resistance observed in *P. aeruginosa* in our study is particularly concerning. Out of the 7 isolates tested, 6 (85.7%) were resistant to colistin, indicating a significant therapeutic challenge in managing infections caused by this organism. This is markedly higher than the findings of Sarıkaya et al. and Özkaçmaz et al., and emphasizes the importance of local surveillance data in guiding empiric therapy (23, 24). Moreover, although not as dramatic, *E. coli* resistance, found in 2 of the 7 isolates (28.6%), is still notable and underscores the need for cautious colistin use even in typically susceptible organisms.

Rojas et al. also reported relevant findings in their comparative study of colistin susceptibility testing using the E-test and BMD. In carbapenem-resistant *K. pneumoniae* isolates, BMD testing revealed a resistance rate of 13%, significantly lower than in our study (26). This discrepancy may be due to differences in patient populations, infection

sources, or local antimicrobial practices. Conversely, Kansak et al. examined 38 multidrug-resistant *K. pneumoniae* isolates and found that 35 (92.1%) were resistant to colistin using BMD, with only 3 (7.9%) being sensitive (27).

These findings collectively reinforce the growing concern over colistin resistance worldwide. The variation in susceptibility rates across different studies underscores the influence of geographic, institutional, and clinical factors on resistance trends. Furthermore, the consistently reported superiority of the BMD method confirms its necessity in obtaining accurate MIC values and informing appropriate antimicrobial therapy (28).

The rise in colistin resistance has significant clinical implications. As one of the last-resort antibiotics for MDR and carbapenem-resistant Gram-negative infections, colistin's efficacy must be preserved through rigorous stewardship practices. Inaccurate susceptibility results can lead to inappropriate therapy, increased morbidity and mortality, and further resistance development. Therefore, reliance on validated methods like BMD is essential for individual patient management, antimicrobial resistance surveillance, and policy-making (29).

Antibiotic resistance remains one of our most critical global health challenges. Colistin's role as a salvage therapy in treating life-threatening infections caused by carbapenem-resistant pathogens makes determining its efficacy vital. Despite its complexity and resource requirements, the broth microdilution method is indispensable in clinical microbiology laboratories for ensuring accurate susceptibility reporting. Routine monitoring of susceptibility patterns and timely clinician communication are vital for guiding empirical and definitive therapy decisions (30).

Our study confirms that while many Gram-negative isolates remain susceptible to colistin, resistance is uncommon and particularly concerning in species such as *P. aeruginosa* and *K. pneumoniae*. The variability observed across species and sample types reinforces the necessity of localized surveillance data. The broth microdilution method remains the gold standard for evaluating colistin susceptibility and should be widely implemented to ensure accurate resistance detection. These findings support the current guidelines and underscore the need for continued vigilance, responsible antibiotic use, and robust laboratory practices to combat the growing threat of antimicrobial resistance.

5. Conclusion

This study concludes that colistin remains an essential last-resort antibiotic against multidrug-resistant Gram-negative infections. However, emerging resistance, particularly in *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, is alarming. Accurate detection using the broth microdilution (BMD) method—endorsed by CLSI and EUCAST—is vital. Routine BMD testing in clinical laboratories can improve treatment outcomes, guide stewardship, and track local resistance trends. Early identification of resistance is key to preventing therapeutic failure and limiting the spread of colistin-resistant pathogens.

Conflict of Interest

The author(s) declare no conflict of interest.

Funding

None.

Acknowledgments

None.

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