Egyptian Journal of Medical Microbiology Volume 34 / No.4 / October 2025 221-227 Online ISSN: 2537-0979

ORIGINAL ARTICLE

Occurrence and Diagnostic Evaluation of Colistin Resistance among Pediatric patients

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Key words:
Pediatrics, superbugs, Colistin, mcr-1

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ABSTRACT

Background: *The world is now facing a formidable from the emergence of bacteria that are resistant to almost all available antibiotics. There won't be any new antibiotics to combat these "superbugs", there is now renewed interest in reviving older antibiotics that were for clinical use, especially the polymyxins (colistin and polymyxin B), to be used as "last resort" antimicrobials.* ***Objectives:*** *This work aims to detect colistin resistance in Gram negative bacteria using broth microdilution, colistin broth disc elution, and PCR for mcr-1 colistin resistance gene.* ***Methodology:*** *Samples were collected from 50 hospitalized pediatric patients. Antibiotic susceptibility was assessed by disk diffusion and VITEK-2. Colistin susceptibility tests by disk elution and broth microdilution and* ***mcr-1*** *gene PCR.* ***Results:*** *Mean age of our patients was (65.9±54.9) days. Most common isolates were Klebsiella spp. (86%). All isolates were resistant to b-lactams, Colistin resistance was 40%. The mcr-1 were revealed in 12 isolates. No impact of mcr-1 on antibiotic sensitivity. Higher percentage of cases with positive mcr-1 were resistant by colistin Broth micro dilution. Sensitivity and specificity of Colistin broth disc elution were 100%. No statistical significance difference in age, Colistin previous administration, or mechanical ventilation as regards result of broth Micro dilution.* ***Conclusion:*** *Our study underlines critical need of improved infection control strategies, antimicrobial stewardship, to fight multidrug-resistant infections in pediatrics. Patient outcomes are seriously threatened by the great resistance rates to several antibiotics, especially last-resort treatments as colistin. Future studies are needed to clarify the genetic factors of colistin resistance.*

INTRODUCTION

A significant and growing threat to the world is the emergence of bacteria that are resistant to almost every antibiotic currently in use. For many years, polymyxins—colistin and polymyxin B—have been employed as bactericidal agents to combat uncontrollable Gram-negative bacteria. Because of their dangerous side effects, their use has been reduced. They have, however, been reintroduced into clinical practice as a last resort against multidrug resistant Gram negative bacteria (MDR GNB) due to their rapid bactericidal activity[1].

The five distinct chemical compounds that make up polymyxins are A, B, C, D, and E. The only two that are currently on the market and have been used in clinical practice are colistin A (polymyxin E1) and colistin B (polymyxin E2); their only difference is in their fatty acid tails.[2].

Colistin's main target is the outer membrane's (OM) lipopolysaccharide (LPS), where it interacts directly with the lipid A component of the LPS to produce its antibacterial effects. The lipid A component of LPS is then attached to colistin, which causes the OM to become deranged and cellular contents to leak. Colistin then inserts its hydrophobic regions (fatty acyl tail and amino acids at positions 6 and 7) through these cracks, which causes inner membrane lysis, periplasmic and cytoplasmic contents to leak, and cell death [1, 3].

Colistin may be useful in treating infections in critically ill children brought on by Gram-negative bacteria that are resistant to multiple drugs.It was successful to create a population pharmacokinetic model for intravenous colistin in pediatric patients [4].

Inevitably, colistin-resistant pathogens have emerged globally as a result of the overuse and abuse of colistin in both human and animal medicine. However, the emergence of colistin-resistant bacteria can also happen without any prior colistin exposure [5].

Likewise to bacteria that have intrinsic resistance to polymyxins, colonistin resistance is primarily caused by changes to the lipid A moiety of LPS. These changes prevent colistin binding and action by protecting phosphate and carboxyl groups, which lowers the LPS/membrane negative net charge. Other mechanisms, such as efflux pumps, lipid A loss, OM remodeling events, and capsule formation, have been proposed for Enterobacteriaceae.Both chromosome-mediated and plasmid-mediated resistance to colistin are possible [6,7].

It has been reported that colistin resistance is conferred by plasmid-mediated colistin resistance gene *mcr*, the, the small protein gene *ecr*, and the efflux pump [3,8].

Horizontally acquired colistin resistance is caused by the *mcr* genes. By adding PEtN to either the 1′ or 4′-phosphate of lipid A, the cytoplasmic transmembrane protein encoded by *mcr-1* functions as a phosphoethanolamine transferase enzyme, reducing the negative net charge of LPS and preventing colistin from binding and entering bacterial cells. According to studies, the mcr-1 gene causes the MICs of colistin to increase by 4–8 times [9,10].

While *mcr-2* and *mcr-9* were primarily discovered within the last decade, *mcr-1*; the most prevalent *mcr* gene, has been revealed over time [7].

Our study aimed to detect colistin resistance in Gram negative bacteria using broth microdilution, colistin broth disc elution test, and conventional PCR for mcr-1 colistin resistance gene.

METHODOLOGY

This observational cross-sectional study was conducted in the Department of Clinical and Chemical Pathology at Beni-Suef University Hospital (Inpatient) on pediatric patients infected with carbapenem-resistant Gram-negative bacteria, starting in April 2022. Ethical approval was obtained from the Beni-Suef University Ethical Committee Board under approval number [FMBSUREC/10042022/Fathy].

Sample Collection

Samples were collected from pediatric patients who had been hospitalized for more than 48 hours and exhibited clinical signs of infection, all had history of empirical b-lactam administration (cephalosporin or b-lactamase inhibitors combinations, few sever cases received aztereonam), only 6 cases had history of receiving colistin antibiotic. Our samples included urine, blood, and sputum, all of which were promptly transported to the microbiology laboratory for culture and sensitivity testing.

Identification of Isolates

Colony morphology, Gram stain characteristics (negative), and biochemical testing, including a positive catalase and oxidase test, and VITEK-2 compact system GN-ID cards (bioMérieux, France) were used to identify the bacterial isolates.

Antibiotic Susceptibility Testing

The antibiotic susceptibility of the isolates was assessed using the disk diffusion method and further confirmed using VITEK-2 AST-GN73 cards (bioMérieux, France), following the manufacturer's instructions. The antibiotics tested included:

Piperacillin (PPL, 100 µg). Piperacillin/tazobactam (TZP, 100/10 µg), Ceftazidime (CAZ, 30 µg). Cefepime (FEP, 30 µg), Aztreonam (ATM, 30 µg), Imipenem (IPM, 10 µg), Meropenem (MEM, 10 µg), Gentamicin (CN, 10 µg), Tobramycin (TOB, 10 µg), Amikacin (AK, 30 µg), Ciprofloxacin (CIP, 5 µg), Levofloxacin (LEV, 5 µg), Ofloxacin(OFX,5µg), (All antibiotic disks were obtained from Oxoid, UK.). Interpretation was done according to CLSI[11].

Colistin Disk Elution Test

Colistin susceptibility screening was performed using the disk elution method as described by CLSI [12]. Briefly, bacteria in exponential growth phase were adjusted to a turbidity of 0.08–0.1, then diluted 100-fold into four tubes containing Mueller-Hinton broth (Oxoid, UK). Each tube was supplemented with either 0, 1, 2, or 4 colistin discs (10 µg/disc) (Oxoid, UK) and incubated for 18–20 hours before assessing bacterial growth.

Determination of Colistin MIC via Broth Microdilution

A conventional broth microdilution assay [13] was used to measure the minimum inhibitory concentration (MIC) of colistin against 50 strains of Gram-negative bacteria that were resistant to carbapenem. After adjusting the bacterial cultures to an OD of 0.6, they were further diluted to meet the McFarland turbidity standard of 0.5. 96-well microtiter plate wells with colistin concentrations ranging from 2 to 16 µg/mL were filled with a 100-fold dilution. MIC values were calculated using the lowest concentration that showed no discernible turbidity after the plates were incubated for 18 hours at 37°C.

Genotypic Identification of the *mcr-1* Gene

The presence of the ***mcr-1*** gene in Gram-negative isolates was identified using conventional PCR with primers as outlined by [14]:

- ***mcr1*_320bp_fw:** AGTCCGTTTGTTCTTGTGGC
- ***mcr1*_320bp_rev:** AGATCCTTGGTCTCGGCTTG

DNA Extraction and Purification

Genomic DNA was extracted and purified using the Thermo Scientific GeneJET™ Genomic DNA Purification Kit, following the manufacturer's protocol.

DNA Amplification

PCR amplification was performed using primers from Thermo Fisher Scientific (USA). The PCR mixture included: 2x DreamTaq Green PCR Master Mix, 10 µL of DNA extract, 0.25 µL of forward primer and 0.25 µL

of reverse primer.The thermal cycling conditions were as follows: Initial denaturation at 94°C for 3 minutes, 40 cycles of denaturation at 94°C for 40 seconds, Annealing at 55°C for 45 seconds, Extension at 72°C for 1 minute and final extension at 72°C for 10 minutes.

Detection of PCR Amplified Products

A 2% agarose gel electrophoresis stained with ethidium bromide (Sigma, USA) was used to visualize the PCR products. The ***mcr-1*** gene (320 bp) was identified by comparing the bands to a DNA ladder (500–3000 bp) (Fermentas, Germany). Bands were examined using a UV trans-illuminator and documented with a digital camera.

Statistical Analysis

Version 22 of the Statistical Package of Social Science (SPSS) software for Windows 7 was used to analyze the data (SPSS Inc., Chicago, IL, USA). Standard deviations are a measure of the dispersion of quantitative parametric data, arithmetic means are a way to measure central tendency, and simple descriptive analysis is expressed as numbers and percentages of qualitative data. Range and median for quantitative non-parametric data. Two non-parametric quantitative variables are subjected to the Man Whitent test. When comparing two or more qualitative groups, the chi square test is utilized. A new test using the "Receiver Operating Characteristic" ROC curve is tested for sensitivity and specificity. A P-value of less than 0.05 was deemed statistically significant.

RESULTS

Our study included 50 pediatric patients with a mean age of (65.9±54.9) days ranged between (3 and 240) days. Our 50 isolates included 43(86%) *Klebsiella spp.*, 3(6%) *Pseudomonas spp.*, 2(4%) *E. coli*, and 2(4%) *Actinobacter spp.* All isolates were resistant to (Meropenem, and Cephalosporins), 94% were resistant to each of (Gentamycin, Amikacin, Ciprofloxacin, and levofloxacin), 88% of cases were resistant to Sulfamethoxazole- trimethoprim.

The *mcr-1* gene were revealed in 12 isolates as shown in (figure 1,2)

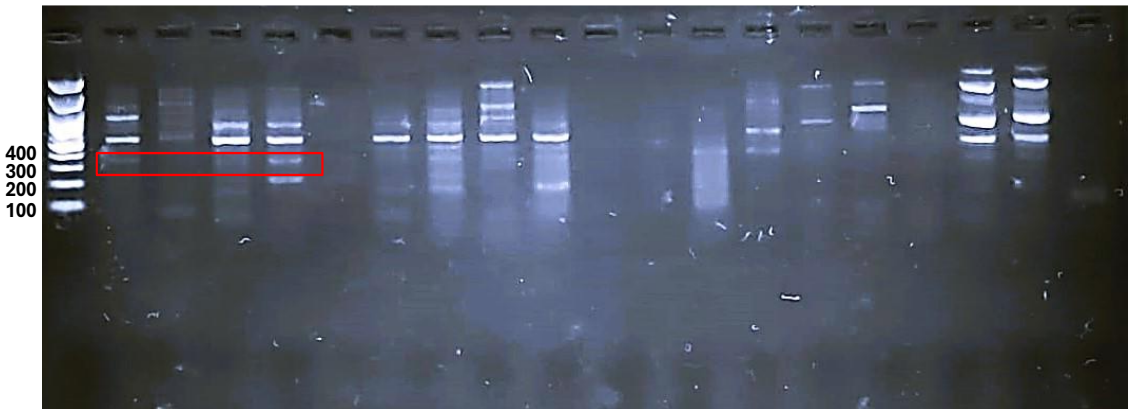

Fig. 1: Lanes 1,3,4 are positive for *mcr-1* gene

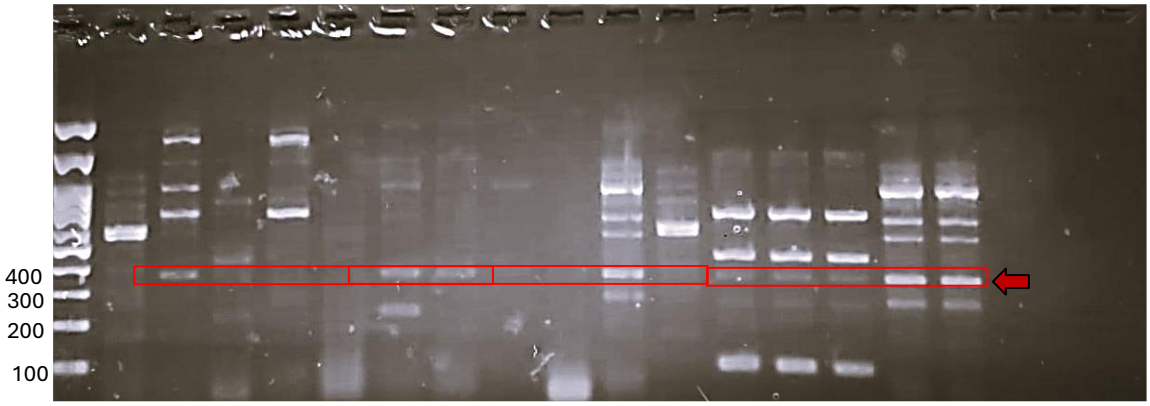

Fig. 2: Lanes 36, 40,41 44, 46-50 are positive for *mcr-1* gene

Frequency sensitivity and resistance by *mcr-1* gene PCR, Disc elution, and micro dilution among study group. As shown in table 1 colistin resistance were as high as 40% by both broth microdilution and disc elution tests. While by PCR for *mcr-1* gene, frequency sensitivity and resistance were 24% and 76% respectively. (table1)

Table 1: Frequency sensitivity and resistance by *mcr-1* PCR, Disc elution, and micro dilution among study group:

Variables (n=50)	Frequency	
	No	**%**
mcr-1 gene by PCR		
Negative	38	76%
Positive	12	24%
Colistin broth disc elution test		
Resistant	40	80%
Sensitive	10	20%
Broth Micro dilution		
Resistant	40	80%
Sensitive	10	20%

There was no statistical significance difference in antibiotic sensitivity of tested antibiotics as regards Broth Micro dilution results with p-value >0.05. Also there were no association or impact to *mcr-1* gene on antibiotic sensitivity to all tested antibiotics (Meropenem, Cephalosporins, Gentamycin, Amikacin, Ciprofloxacin, and levofloxacin, and Sulfamethoxazole-trimethoprim).

There was a statistical significance difference in antibiotic sensitivity by Broth Micro dilution, and *mcr-1* gene by PCR with p-value <0.001, as higher percentage of cases with positive *mcr-1* gene were resistant by Broth micro dilution test. On the other hands, there was no statistical significance difference in antibiotic sensitivity by Broth Micro dilution, and Colistin broth disc elution test with p-value >0.05. (Table 2)

Considering Broth micro dilution as a gold standard; sensitivity and specificity test illustrated no significant diagnostic effect to *mcr-1* gene in detection of Broth micro dilution sensitivity with p-value 0.15. However, for Colistin broth disc elution results it showed a significant sensitivity and specificity results 100% with p-value <0.001.

Forty six percent of our patients needed mechanical ventilation; however there was no statistical significance difference in age, Colistin previous administration , or mechanical ventilation as regards result of broth Micro dilution with p-value >0.05 as shown in table 3.

Table (2): Comparison of *mcr-1* gene by PCR, and Colistin broth disc elution test results in different Broth Micro dilution sensitivity among study group.

Variables (n=50)		Broth Micro dilution				p-value
		Resistant (n=10)		Sensitive (n=40)		
		No.	(%)	No.	(%)	
mcr-1 gene by PCR	-Ve	10	100%	28	70%	**<0.001***
	+Ve	0	0%	12	30%	
Colistin broth disc elution test	R	10	100%	0	0%	0.99
	S	0	0%	40	100%	

Table 3: Comparison of Colistine, and mechanical ventilation in different Broth Micro dilution sensitivity among study group.

Variables (n=50)		Broth Micro dilution				p-value
		Sensitive (n=10)		Resistant (n=40)		
		Median	Range	Median	Range	
Age (days)		56.5	25-240	57.5	3-210	0.56
		No.	(%)	No.	(%)	
Colistine	No	10	100%	34	85%	0.32
	Yes	0	0%	6	15%	
Mechanical ventilation (MV)	No	5	50%	22	55%	0.99
	Yes	5	50%	18	45%	

DISCUSSION

The analysis of carbapenem-resistant Gram-negative bacterial infections in young patients at Beni-Suef University Hospital reveals various important clinical and epidemiological consequences.

First, the preponderance of *Klebsiella* species (86%) among the isolates corresponds with worldwide trends whereby *Klebsiella pneumoniae* is a main pathogen in healthcare-associated infections, particularly in susceptible pediatric groups [15, 16]. Though less common, the presence of *Pseudomonas aeruginosa*, *E. coli*, and *Acinetobacter baumanii* emphasizes the variety of infections causing multidrug-resistant diseases in this environment [16].

Tests of antibiotic sensitivity exposed a concerning resistance trends and were strong resistance rates also noted for cefoxitin (96%), amikacin, ciprofloxacin, and levofloxacin (each 94%), all isolates were resistant to meropenem and cephalosporins. Sixty percent of isolates showed gentamicin resistance. Especially, only 10% of isolates were responsive to colistin; susceptibility to trimethoprim-sulfamethoxazole (SXT) remained somewhat high (12%). These results show a somewhat restricted therapeutic tool for treating infections caused by these organisms, in line with the worldwide increase of carbapenem-resistant Enterobacteriaceae and the crucial function of colistin as a last-resort antibiotic [15, 17].

In 24% of isolates the *mcr-1* gene, a plasmid-mediated colistin resistance determinant, was found to be molecularly positive. But there was no statistically significant correlation between *mcr-1* presence and antibiotic sensitivity profiles-including colistin resistance ascertained by disc elution and broth microdilution techniques. This implies that other systems outside *mcr-1* could be involved in colistin resistance in this cohort or that *mcr-1* presence by itself does not entirely define phenotypic resistance [15, 17].

Fascinatingly, the colistin broth disc elution test revealed 80% resistance, which matched the broth microdilution findings and displayed 100% sensitivity and specificity over the gold standard broth microdilution assay. This result supports the accuracy and practicality of the colistin disc elution test as a useful screening tool for colistin resistance in clinical microbiology laboratories, therefore supporting timely infection control and therapeutic decisions [12].

The intricacy of colistin resistance mechanisms-which may involve chromosomal mutations or other *mcr* variations not found by the PCR assay used-is highlighted by the lack of appreciable connection between *mcr-1* gene presence and phenotypic resistance. This emphasizes how important thorough molecular surveillance and phenotypic testing are to direct good antimicrobial management [17].

Regional fluctuation in *mcr-1* frequency: Mostly in *Pseudomonas aeruginosa* (61.5%), a study from a rural tertiary care hospital in Western Maharashtra found *mcr-1* in 13.97% of colistin-resistant isolates. *Klebsiella pneumoniae* (23.1%) was the other finding. This runs counter to the greater *mcr-1* detection rate of 24% in the present investigation, which points to geographical variations in resistance gene distribution most likely related to agricultural colistin use or regional antibiotic use [18].

In our work *mcr-1*-positive bacteria demonstrating MICs of 4 mg/L, research on *E. coli* isolates revealed a clear increase in colistin MIC values (≥1 mg/L) from 17–20% (2015–2017) to 74% . This emphasizes the growing concern of plasmid-mediated resistance and corresponds with the noted 80% phenotypic colistin resistance in the present population [15].

In our study 24% of isolates the *mcr-1* gene, a plasmid-mediated colistin resistance determinant, was found to be molecularly positive. But there was no statistically significant correlation between *mcr-1* presence and antibiotic sensitivity profiles-including colistin resistance ascertained by disc elution and broth microdilution techniques

This clarifies the lack of association between *mcr-1* existence and phenotypic resistance in the present work, therefore stressing the importance of thorough genetic profiling [17]. Mechanistic Complexity of Colistin Resistance: Beyond *mcr-1*: Chromosomal mutations Colistin resistance, according to genomic research, usually results from mutations in genes controlling lipid A modification (e.g., *pmrA/B*, *phoP/Q*, and *mgrB*), not detectable by *mcr-1*-specific PCR assays[17].

Unique *mcr-1* variations: *E. coli* revealed a Met2Ile mutation in *mcr-1*, therefore illustrating the evolutionary flexibility of the gene. Such variations may avoid identification by conventional PCR primers, so revised molecular monitoring techniques are needed [15].

Children's use of colistin and its toxicity: In 22% of children receiving colistin, a multicenter U.S. trial found nephrotoxicity; teenagers are more likely to be affected. These results emphasize the need of therapeutic medication monitoring and renal function tests in pediatric environments, especially in cases when colistin stays a last-resort choice [18].

Plasmid-mediated distribution: The combination of the *mcr-1* gene with mobile genetic elements (e.g., IncI2, IncHI2, and IncX4 plasmids) promotes fast horizontal transfer between bacterial species, hence aggravating resistance spread in hospitals. This emphasizes how urgently infection control strategies must limit plasmid spread [17].

Expanded genetic screening: Along with phenotypic testing, use whole-genome sequencing to find chromosomal mutations and new *mcr* variations (e.g., *mcr-2* to *mcr-10*) [17].

One Health surveillance: Examine, as advised by rural hospital data, relationships between colistin usage in agriculture and clinical resistance [18].

Combining therapy trials: Using synergistic effects seen in vitro, assess colistin coupled with β-lactams or carbapenems to combat resistance [19].

Contextualizing these results with worldwide data helps the conversation highlight the multifaceted character of colistin resistance and the vital need of multidisciplinary approaches to stop its dissemination.

The study underlines generally the critical need of improved infection control strategies, antimicrobial stewardship, and creation of new therapeutic choices to fight multidrug-resistant Gram-negative infections in pediatric environments. Patient outcomes and public health are seriously threatened by the great resistance rates to several antibiotics, especially last-resort treatments such as colistin.

CONCLUSIONS

Future studies should concentrate on clarifying the genetic factors of colistin resistance, assessing combination treatments, and using fast diagnostic methods to enhance care of these difficult infections. The results also support routine *mcr* gene screening in conjunction with phenotypic susceptibility testing to better grasp resistance epidemiology and guide therapy plans.

Declarations:

Consent for publication: Not applicable

Availability of data and material: Data are available upon request.

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

This manuscript has not been previously published and is not under consideration in another journal.

Funding: Authors did not receive any grants from funding agencies.

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