DO AMINOGLYCOSIDES ENHANCE THE POTENTIAL NEPHROTOXICITY OF COLISTIN IN CARBAPENEM RESISTANT GRAM-NEGATIVE BACTERIA?

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ABSTRACT

Aim: This study aimed to investigate the safety and efficacy potentials of adding aminoglycosides to colistin for synergism in treating of multidrug-resistant gram-negative bacteria in critically ill patients.

Methods; This retrospective study was conducted at King Hussein Medical Centre in Jordan examining the safety issues among four antibiotic groups (ABs Group I-IV) based on patients' estimated creatine clearance (CrCl). We used the Shock Index (SI) as a covariate during the analysis of covariance (ANCOVA) to compare the safety issues among these groups. The study also used the Age-Adjusted Charlson Comorbidity Index (AACCI) to assess patients' comorbidity burden. In addition, we compared categorical variables, such as age, BMI, CrCl, VFDs, and AACCI, and explored the adopted thresholds of CrCl and VFDs by conducting ROC and sensitivity analysis against the binary mortality status (non-survivors vs. survivors).

Results: We found that the distribution of creatinine (CrCl) in critically ill patients was insignificant across the four adipose tissue (ABs) groups. The overall rate for CrCl<39.07 ml/min versus CrCl≥39.07 ml/min was 969 (41.3%) vs. 1377 (58.7%). There were no significant differences between critically ill patients who were given nephrotoxic ABs (colistin, amikacin, or both colistin and amikacin) and those given β-lactam ABs (Group I). Patients' comorbidity burden was not found to be statistically significant across the four ABs groups. The mean values for CrCl and VFDs were also insignificant for the ABs categories I-III for the dependent variable CrCl but significant for the dependent variable VFDs. On the other hand there were statistically significant differences in the efficacy concern in improving VFDs while accounting for SI.

Conclusion: We demonstrated that adding aminoglycosides, particularly amikacin, to colistin therapy to combat infection did not significantly worsen patients' CrCl and extend their VFDs. However, emerging evidence suggests that adding amikacin to colistin may delay the emergence of colistin resistance.

Keywords: Colistin, aminoglycosides, nephrotoxicity, critically ill patients.

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INTRODUCTION

In vitro interactions of colistin and antibiotics, such as β-lactams and aminoglycosides, can lead to killing of multi-drug-resistant gram-negative bacteria like acinetobacter, pseudomonas,and enterobacteriaceae. However, kidney damage caused by colistin and aminoglycosides is not yet known. (1) The risk of kidney damage deters the use of colistin

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and aminoglycosides,especially when multiple antibiogramsshow resistance to all antibiotics except these two. (2) Due to the rapid spread of multi-drug-resistant (MDR) bacteria, two or more antibiotics are often used together in order to boost their efficacy and to produce greater effect. (3) Polymyxins, especially colistin (polymyxin E) as colistimethate sodium sulfonate prodrug, are being studied as treatment of hospital-acquired infections caused by carbapenem-resistant gram-negative bacteria. (4)The ability of aminoglycoside therapy to rapidly kill bacteria, low propensity for developing resistance in vivo when used with other antibiotics, synergistic or additive effects with other antibiotics, and post-antibiotic effects remain appealing. (5) In serious sepsis, where the patient's bacteria are unknown, aminoglycosides are justified in the treatment. (6) Aminoglycosides, derived from microorganisms, can kill gram-negative bacteria like Enterobacteriaceae, Pseudomonas, Acinetobacter, and Mycobacterium tuberculosis. (7) They can also kill gram-positive bacteria, especially staphylococcus strains. Moreover, the pathogen spectrum includes MRSA. (8) Although they have limited therapeutic range, low oral absorption, and significant toxicity, especially kidney and auditory system damage, they have significant bactericidal activity. (9)Colistin, discovered in 1947, is a key antimicrobial for MDR Gram-negative bacterial infections. Polypeptides polymyxin B and polymyxin E (colistin) are produced from Bacillus polymyxa. (10) Colistin was widely used in clinical settings before the 1980s, but kidney toxicity and poor clinical application reduced its use. (11) Due to their increased prevalence, colistin has been used to treat multi-drug-resistant Gram-negative bacteria infections again. Many antibiotics, especially aminoglycosides, cause nephrotoxicity either immediate or long-term e effects. (12) Cells take up aminoglycosides via organic cation transporter type 2, sodium phosphate transporter type 2a, and polyamines. (13) Colistin can induce apoptosis by altering caspase-17 gene expression and caspase-3 composition. In renal cells, aminoglycosides damage DNA, disrupt organelles, and generatreactive oxygen species. (14) As well as activating inflammation and fibrosis genes. Colistin's complex nephrotoxicity is linked to excessive reactive oxygen species production. (15)One-third of patients who used colistin experience nephrotoxicity, with single-center and investigator reports showing high rates. (16) Colistin nephrotoxicity is often underestimated due to patients’ heterogeneity, polypharmacy, and acute/chronic kidney disease. (17) Excess reactive oxygen species can activate matrix metalloproteinases, deplete anti-inflammatory cells and increase proinflammatory, proapoptotic, and profibrotic signaling pathways. (18) After few days of aminoglycoside therapy, nephrotoxicity is usually reversible and rarely causes tubular necrosis. (19) However, this adverse effect should not be underestimated due to its association with worse clinical outcomes and potential long-term effects on survivors. Long-term aminoglycoside exposure is common risk factor for AKI. (20)

In this study we primarily aimed to investigate the safety and efficacy potentials when aminoglycosides are added to colistin for synergism in combating multidrug-resistant gram-negative bacteria in critically ill patients.

Methods

The adult critical care unit at King Hussein Medical Centre in Royal Medical Services, Amman, conducted a retrospective, single-centre, observational study on critically ill patients who were admitted between 2018 and 2022. This study received ethical approval from our Institutional Review Board committee on July 21, 2024, of a registration number 62_8/2024.Patients who were critically ill, aged over 18, have been admitted for at least two days, and have undergone an antibiotic regimen that includes either colistin monotherapy (Group II), aminoglycoside monotherapy (Group III), dual colistin and aminoglycoside combination (Group IV), or -lactam antibiotics (Group I). Experiencing colistin and/or aminoglycosides was primarily for targeted therapy, as revealed by antibiograms that showed in vitro resistance to β-lactam antibiotics. Aminoglycosides that were adopted in our critically ill department and in our study were almost amikacin. The β-lactam antibiotics that were used in this study were mostly included higher dose with extended infusion of either piperacillin/tazobactam or carbapenems piperacillin/tazobactam. Of importance, all antibiograms revealed resistant to most included tested antibiotics except colistin and amikacin.

This study hospital stays included patients' gender, age, body mass index BMI), administered antibiotics, length of hospital stays baseline comorbidity burden, ventilation duration or ventilation free days (VFDs), hemodynamics, and serum creatinine as primary data. We compared the categorical data across the four ABs groups to express their distribution rates and p-values using a chi square test.Clinical practice frequently uses the Shock Index (SI), and valid hemodynamic index, to assess the shock status of patients in emergency and critically ill departments. In this study, we selected SI as a covariate during the analysis of covariance (ANCOVA) to investigate the significant differences in safety issues among the four antibiotic groups (ABs Group I-IV) when tested to the patients' estimated creatine clearance (CrCl).We assessed the estimated CrCl in this study using the Jelliffe equation for unstable patients,and mathematically calculated SI by dividing the average heart rate in bpm by the systolic blood pressure in mmHg. Age adjusted charlson comorbidity index (AACCI) was adopted in this study for assessing the patients' comorbidity burden. Additionally, we conducted ANCOVA test against the patients' VFDs to investigate the significant differences in efficacy issues of the four ABs groups, and adopted SI as a covariate.

Categorical variables were identified in this study and compared their distribution rates across the 4 ABs groups. We dichotomized each patient's age, BMI, CrCl, VFDs, and AACCI based on predetermined thresholds of 60 years, 30 kg/m2, 39.07 ml/min, 4.5 days, and 8, respectively. In this study, we reviewed thresholds of CrCl and VFDs by conducting ROC and sensitivity analysis of each against the binary mortality status (non-survivors vs. survivors).Data was collected and filtered using Microsoft Excel version 20, then analysed data and revealed the results using SPSS version 23. This study adopted a significance level of 0.05.

Results

Total of 2346 critically ill patients were investigated in this retrospective study. Approximately, 24.34% (571 patients) were experienced higher dose and extended infusion of broad-spectrum β-lactam antibiotics, 25.62% (601 patients) were experienced colistin monotherapy, 25.45% (597 patients) were experienced amikacin monotherapy, and approximately 24.59% (577 patients) were experienced dual therapies of colistin and amikacin. This study included approximately 30.7% (720 females) and 69.3% (1626 males). There were statistically insignificant distribution rates across the 4 compared ABs groups (p-value = 0.953). Furthermore, there were statistically insignificant distribution differences in patients' obesity status (non-obese versus obese) among the

4 ABs groups (p-value = 0.777). However, we revealed statistically significant differences in distribution rates among overall patients aged <60 years and patients aged 60 years [1642 (70.0%) vs. 704 (30.0%), respectively, p-value = 0.026].

There were insignificant distributions in mortality rates for tested critically ill patients across the 4 ABs groups (p-value = 0.221). In contrast, there were significant distribution rates in patients' VFDs across Group I-IV (p-value = 0.000). We revealed that the highest distribution rates for VFDs 4.5 days (shorter ventilation-free days or longer ventilation days) were in non-colistin-based groups, Group I (310 (54.3%) and Group III (328 (54.9%). The colistin monotherapy group (Group II) and the dual colistin amikacin group (Group IV) had the highest distribution rates for VFDs 4.5 days (longer ventilation-free days or shorter ventilation days), with rates of 388 (64.6%) and 375 (65.0%), respectively, while β-lactam group (Group I) and amikacin monotherapy group (Group III) had rates of 261 (45.7%) and 269 (45.1%), respectively.

The CrCl distribution rates across the four ABs groups were insignificant (p-value=0.499). The overall rate for CrCl<39.07 ml/min versus CrCl≥39.07 ml/min in the studied patients was 969 (41.3%) vs. 1377 (58.7%). We found that there were no statistically significant differences between patients who were given nephrotoxic ABs like colistin (Group II), amikacin (Group III),

), or both colistin and amikacin (Group IV) and those who were given β-lactam ABs (Group I) in terms of their declining kidney function, as shown by <CrCl 39.07 ml/min [235 (39.1%), 248 (41.5%), or 251 (43.5%) vs 235 (41.2%), respectively]. Regarding patients' comorbidity burden as manifested by AACCI, we also didn't reveal statistically significant differences in distribution rates across the 4 ABs groups (p-value = 0.319). Table 1 below expresses the statistical results related to the chi square. The Means±SDs in CrCl for the tested patients across the 4 ABs groups (Group I-IV) were determined at 46.36±18.95 ml/min, 45.84±19.25 ml/min, 45.09±17.84 ml/min, and 44.24±17.55 ml/min, respectively. While the Means±SDs in VFDs for the tested critically ill patients were determined at 4.70±3.069 days, 6.51±4.078 days, 4.66±3.109 days, and 6.37±4.041 days, respectively. The ABs categories had statistically insignificant (F (3, 513.5) =2.1, p-value=0.098, ηp2=0.003) when the ANCOVA related tests of between subjects' effects for dependent variables CrCl was evaluated. While the ABs categories had statistically significant (F (3, 650.1) =54.992, p-value=0.000, ηp2=0.066). When expressing the parameter estimates for the dependent variables CrCl and VFDs, we revealed statistically insignificant for ABs categories I-III for the dependent variable CrCl but we found statistically significant in ABs categories I and III for the dependent variable VFDs (both p-Value=0.000) with B±SE (95% CI; LB-UB) of -1.706±0.203(95% CI; -2.104-(-)1.308) and -1.801±0.201(95% CI; -2.195-(-)1.408), respectively. When we conducted the bonferroni adjustment approaches for multiple comparisons between the ABs categories regarding safety concern in declining CrCl while accounting for SI, we didn't find any statistically significant. differences. While we conducted the bonferroni adjustment approaches for multiple comparisons between the ABs categories regarding efficacy concern in improving VFDs while accounting for SI, we revealed statistically significant Mean differences ± SEMs (95% CI; LB-UB) in dual colistin and amikacin group (Group IV) vs β-lactam group (Group I) and amikacin monotherapy group (Group III) [1.706±0.203 (95% CI; 1.170-2.242) and 1.801±0.201 (95% CI; 1.271-2.332), respectively].

The ANCOVs related statistically results are expressed in Table 2-6 below.

Discussion

Aminoglycosides cause renal injury through various mechanisms, including endocytosis and accumulation within proximal tubular cells. These drugs produce oxygen-derived free radicals, leading to oxidative stress and lipid peroxidation, resulting in cell necrosis. (21) Despite their therapeutic efficacy, aminoglycosides are associated with significant risk of developing nephrotoxicity, with the prevalence of acute kidney injury (AKI) reported to be around 20%. The concomitant use of tobramycin and colistin has been found to enhance serum creatinine, pathological scores, and proximal tubular apoptosis in rats. Inhibition of the Akt signal may be a potential nephroprotective strategy to reduce colistin-induced nephrotoxicity. (22) Aminoglycosides are commonly used in combination treatment against Pseudomonas infections, but their combined use raises concerns about clinically significant drug interactions. (23) Colistin, an older antibiotic used to treat resistant bacteria to most antibiotics, is limited by its nephrotoxicity. Aminoglycosides are commonly used for the treatment of serious infections caused by Gram-negative bacilli, especially when originating from the urinary tract or bloodstream. (24)Currently, data about the interaction between different aminoglycosides and colistin are still scarce. It is reported that co-administration of colistin with gentamicin in patients with chronic renal insufficiency resulted in potentially fatal intoxication. (25) The possible linking mechanisms of enhanced colistin-induced nephrotoxicity and co-administration of aminoglycosides, particularly the features of pharmacokinetic and pharmacodynamic interactions, have not been clearly illustrated. Further researches are urgently needed to establish the clear pharmacokinetic and mechanistic properties to provide solid foundation for guidance on dosing and use of colistin with aminoglycosides. (26) Several emerging studies summarize in vitro and in vivo data that address the impact of aminoglycosides on colistin-induced nephrotoxicity to better understand clinical problems associated with such a combination. Recent animal studies have reported the interaction between colistin and aminoglycosides concerning colistin-induced nephrotoxicity, but the results of these experiments are conflicting and inconsistent. Some studies revealed that the association increases the nephrotoxicity of colistin, while others showed that the combination of two drugs has no additional toxicity. (27) Recent phase 3 prospective clinical trials examined how the treatment regimens of pulmonary (nebulized) / patients with pneumonia (IV) responded to colistin treatment and were also administered in combination therapy. (28) However, none of these studies detected significant nephrotoxicity, proving the safety of these treatment in reducing multidrug-resistant bacterial pneumonia and ventilator-associated pneumonia (VAP) sepsis. Although elderly patients are often not enrolled in phase III clinical trials of novel antimicrobials, colistin is mainly utilized for managing multiresistant pathogens in this patient subpopulation. (29) One of the major drawbacks in colistin usage is the development of superinfections, which led to increased length of stay and overall expenses, complicating enrollment in clinical trials. (30)A study conducted by Sorlí L et al investigated the relationship between colistin plasma concentrations and clinical outcomes in patients with hospital-acquired pneumonia (HAP) caused by extended spectrum pseudomonas aeruginosa (XDR-PA) which was a prospective observational cohort study

Table 1. Chi square results for the patients' variables across 4 ABs groups.

	Group I	**Group II**	**Group III**	**Group IV**	**Total**	**p-Value**
	571 (24.34%)	**601 (25.62%)**	**597 (25.45%)**	**577 (24.59%)**	**2346**	
Mortality						
Survivors	347 (60.8%)	365 (60.7%)	341 (57.1%)	323 (56.0%)	1376 (58.7%)	0.221
Non-survivors	224 (39.2%)	236 (39.3%)	256 (42.9%)	254 (44.0%)	970 (41.3%)	
VFDs (Days)						
<4.5	310 (54.3%)	213 (35.4%)	328 (54.9%)	202 (35.0%)	1053 (44.9%)	0
≥4.5	261 (45.7%)	388 (64.6%)	269 (45.1%)	375 (65.0%)	1293 (55.1%)	
CrCl (ml/min)						
<39.07	235 (41.2%)	235 (39.1%)	248 (41.5%)	251 (43.5%)	969 (41.3%)	0.499
≥39.07	336 (58.8%)	366 (60.9%)	349 (58.5%)	326 (56.5%)	1377 (58.7%)	
COL dose (MIU/day)						
<4	0	221 (36.8%)	0	248 (42.9%)	469 (39.8%)	0
≥4	0	380 (63.23%)	0	329 (57.0%)	709 (60.2%)	
AMK dose (mg/day)						
<1000	0	0	242 (40.5%)	244 (42.3%)	486 (41.1%)	0
≥1000	0	0	355 (59.5%)	333 (57.7%)	688 (58.6%)	
AACCI						
<8	485 (84.9%)	505 (84.0%)	523 (87.6%)	489 (84.7%)	2002 (85.3%)	0.319
≥8	86 (15.1%)	96 (16.0%)	74 (12.4%)	88 (15.3%)	344 (14.7%)	
Gender						
Female	170 (29.8%)	188 (31.3%)	184 (30.8%)	178 (30.8%)399	720 (30.7%)	0.953
Male	401 (70.2%)	413 (68.7%)	413 (69.2%)	(69.2%)	1626 (69.3%)	
Age (Years)						
<60	419 (73.4%)	425 (70.7%)	421 (70.5%)	377 (65.3%)	1642 (70.0%)	0.026
≥60	152 (26.6%)	176 (29.3%)	176 (29.5%)	200 (34.7%)	704 (30.0%)	
BMI (Kg/m2)						
<30	515 (90.2%)	552 (91.8%)	546 (91.5%)	527 (91.3%)	2140 (91.2%)	0.777
≥30	56 (9.8%)	49 (8.2%)	51 (8.5%)	50 (8.7%)	206 (8.8%)	

ABs: Antibiotics.
Group I: Neither Colomycin nor amikacin.
Group II: Colomycin.
Group III: Amikacin.
Group IV: Colomycin+Amikacin

VFDs: Ventilation free days.
CrCl: Creatinine clearance.
AACCI: Age adjusted charlson comorbidity index.
BMI: Body mass index.
COL: Colistin
AMK: Amikacin
MIU: Million international units

Table 2. CrCl and VFDs means with SDs and SEMs.

ABs Category 1-4	ABs Category	N, %	Mean±SD	Mean±SEM (95% CI; LB-UB) *
CrCl (ml/min)				
Neither COL nor AMG	**Category I**	**571, 24.34%**	**46.36±18.95**	46.35±0.65 (95% CI; 45.063-47.629)
COL	**Category II**	**601, 25.62%**	**45.84±19.25**	46.03±0.64 (95% CI; 44.782-47.284)
AMG	**Category III**	**597, 25.45%**	**45.09±17.84**	44.62±0.64 (95% CI; 43.362-45.873)
COL+AMG	**Category IV**	**577, 24.59%**	**44.24±17.55**	44.54±0.65 (95% CI; 43.266-45.819)
	Category I-IV	**2346**	**45.38±18.42**	
VFDs (Days)				
Neither COL nor AMG	**Category I**	**571, 24.34%**	4.70±3.069	4.697±0.144 (95% CI; 4.415-4.980)
COL	**Category II**	**601, 25.62%**	6.51±4.078	6.533±0.140 (95% CI; 6.258-6.808)
AMG	**Category III**	**597, 25.45%**	4.66±3.109	4.602±0.141 (95% CI; 4.326-4.879)
COL+AMG	**Category IV**	**577, 24.59%**	6.37±4.041	6.404±0.143 (95% CI; 6.123-6.684)
	Category I-IV	**2346**	**5.56±3.714**	

CrCl: Creatinine clearance.
VFDs: Ventilation free days.
ABs: Antibiotics.
COL: Colomycin.
AMG: Aminoglycosides.

SD: Standard deviation.
SEM: Standard error of mean.
N: Number.
CI: Confidence interval.
LB: Lower band.
UB: Ubber band.

Table 3. Tests of Between-Subjects Effects for dependent variables CrCl and VFDs.

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	ηp2
CrCl (ml/min)						
Corrected Model	223204.9	4	55801.2	228.232	0	0.281
Intercept	385682.8	1	385682.8	1577.48	0	0.403
SI (bpm/mmHg)	221729.5	1	221729.5	906.895	0	0.279
ABs Categories	1540.6	3	513.5	2.1	0.098	0.003
Error	572358.1	2341	244.5			
Total	5627269.6	2346				
Corrected Total	795563	2345				
VFDs (Days)						
Corrected Model	4677.3	4	1169.3	98.916	0	0.145
Intercept	5147.4	1	5147.4	435.431	0	0.157
SI (bpm/mmHg)	2845.5	1	2845.5	240.707	0	0.093
ABs Categories	1950.2	3	650.1	54.992	0	0.066
Error	27673.9	2341	11.821			
Total	104955	2346				
Corrected Total	32351.2	2345				

CrCl: Creatinine clearance.
VFDs: Ventilation free days.
SI: Shock index.
ABs: Antibiotics.
ηp2: partial eta-squared
Sig: Significance level.

Table 4. Parameter estimates for dependent variables CrCl and VFDs.

Parameter	B±SE (95% CI; LB-UB)	t	Sig.	Noncent. Parameter	Observed Power
CrCl (ml/min)					
Intercept	185.476±4.735 (95% CI; 176.191-194.761)	39.171	0	39.171	1
SI (bpm/mmHg)	-133.087±4.419 (95% CI; -141.754-(-)124.421)	-30.115	0	30.115	1
ABs Category=1	1.803±0.923 (95% CI; -0.007-3.613)	1.953	0.051	1.953	0.497
ABs Category=2	1.490±0.911 (95% CI; -0.297-3.277)	1.635	0.102	1.635	0.373
ABs Category=3	0.075±0.913 (95% CI; -1.716-1.865)	0.082	0.935	0.082	0.051
ABs Category=4	0	.	.	.	.
VFDs (Days)					
Intercept	22.369±1.041(95% CI; 20.327-24.411)	21.485	0	21.485	1
SI (bpm/mmHg)	-15.077±0.972(95% CI; -16.982-(-)13.171)	-15.515	0	15.515	1
ABs Category=1	-1.706±0.203(95% CI; -2.104-(-)1.308)	-8.407	0	8.407	1
ABs Category=2	0.129±0.200(95% CI; -0.264-0.522)	0.643	0.52	0.643	0.099
ABs Category=3	-1.801±0.201(95% CI; -2.195-(-)1.408)	-8.971	0	8.971	1
ABs Category=4	0				

CrCl: Creatinine clearance.
VFDs: Ventilation free days.
SI: Shock index.
ABs: Antibiotics.

Table 5. Bonferroni adjustment approaches for multiple comparisons between the ABs categories regarding safety concern in declining CrCl while accounting for SI.

ABs Category	ABs Category	Mean Difference ± SEM	95% Confidence CI (LB-UB)	Sig
Neither COL nor AMG (Category I)	**COL (Category II)**	0.313±0.914	(95% CI; -2.100-2.726)	1
	AMG (Category III)	1.728±0.915	(95% CI; -0.689-4.146)	0.355
	COL+AMG (Category IV)	1.803±0.923	(95% CI; -0.634-4.240)	0.305
COL (Category II)	**Neither COL nor AMG (Category I)**	-0.313±0.914	(95% CI; -2.726-2.100)	1
	AMG (Category III)	1.416±0.904	(95% CI; -0.971-3.802)	0.704
	COL+AMG (Category IV)	1.490±0.911	(95% CI; -0.916-3.897)	0.613
AMG (Category III)	**Neither COL nor AMG (Category I)**	-1.728±0.915	(955 CI; -4.146-0.689)	0.355
	COL (Category II)	-1.416±0.904	(95% CI; -3.802-0.971)	0.704
	COL+AMG (Category IV)	0.075±0.913	(95% CI; -2.337-2.486)	1
COL+AMG (Category IV)	**Neither COL nor AMG (Category I)**	-1.803±0.923	(95% CI; -4.240-0.634)	0.305
	COL (Category II)	-1.490±0.911	(95% CI; -3.897-0.916)	0.613
	AMG (Category III)	-0.075±0.913	(95% CI; -2.486-2.337)	1

ABs: Antibiotics.
SI: Shock index.
CrCl: Creatinine clearance in ml per minute.
SEM: Standard error of means.
CI: Confidence interval.
LB: Lower band.
UB: Upper band.

Sig: Significance (p-value<0.05)
COL: Colistin methanesulfonate (CMS).
AMG: Aminoglycosides (mostly amikacin).
Category I: Neither COL or AMG.
Category II: COL monotherapy.
Category III: AMG monotherapy.
Category IV: COL+AMG.

Table 6. Bonferroni adjustment approaches for multiple comparisons between the ABs categories regarding efficacy concern in improving VFDs while accounting for SI.

ABs Category	ABs Category	Mean Difference ± SEM	95% Confidence CI (LB-UB)	Sig
Neither COL nor AMG (Category I)	**COL (Category II)**	-1.835±0.201	(95% CI; -2.366-(-)1.305)	0
	AMG (Category III)	0.095±0.201	(95% CI; -0.437-0.626)	1
	COL+AMG (Category IV)	-1.706±0.203	(95% CI; -2.242-(-)1.170)	0
COL (Category II)	**Neither COL nor AMG (Category I)**	1.835±0.201	(95% CI; 1.305-2.366)	0
	AMG (Category III)	1.930±0.199	(95% CI; 1.405-2.455)	0
	COL+AMG (Category IV)	0.129±0.200	(95% CI; -0.400-0.658)	1
AMG (Category III)	**Neither COL nor AMG (Category I)**	-0.095±0.201	(95% CI; -0.626-0.437)	1
	COL (Category II)	-1.930±0.199	(95% CI; -2.455-(-)1.405)	0
	COL+AMG (Category IV)	-1.801±0.201	(95% CI; -2.332-(-)1.271)	0
COL+AMG (Category IV)	**Neither COL nor AMG (Category I)**	1.706±0.203	(95% CI; 1.170-2.242)	0
	COL (Category II)	-0.129±0.200	(95% CI; -0.658-0.400)	1
	AMG (Category III)	1.801±0.201	(95% CI; 1.271-2.332)	0

ABs: Antibiotics.
VFDs: Ventilation free days.
SI: Shock index.
SEM: Standard error of means.
CI: Confidence interval.
LB: Lower band.
UB: Upper band.
Sig: Significance (p-value<0.05)

COL: Colistin methanesulfonate (CMS).
AMG: Aminoglycosides (mostly amikacin).
Category I: Neither COL or AMG.
Category II: COL monotherapy.
Category III: AMG monotherapy.
Category IV: COL+AMG.

and included 75 patients between 2010 and 2018. The median plasma concentration was 1.1 mg/L, with 30.7% of patients achieving AUC/MIC24h of 30-60 mg/L. High colistin exposure was not associated with improved clinical outcomes, suggesting caution in intravenous colistin treatment for HAP caused by XDR-PA. Nephrotoxicity at the end of treatment was 38.7%. (31) Another study conducted by Wang SH et al investigated the prevalence of colistin susceptible-only Acinetobacter baumannii (CSO AB) pneumonia and compared its presentation and outcome with carbapenem resistant acinetobacter baumannii (CRAB)-associated pneumonia in critically ill patients. The study recruited 955 patients with CR-GNB pneumonia and 575 with CRAB nosocomial pneumonia. The CSO AB group had a prevalence of 13.74% among all cases of CRAB pneumonia, with similar demographic characteristics and disease severity. The CSO AB group had better clinical outcomes at day 7 but longer ICU stay compared to the CRAB group. (32) post-hoc analysis between the groups, we found that the differences between dual colistin and amikacin group (Group IV) and beta-lactam antibiotics group (Group I) and amikacin monotherapy group (Group III) were statistically significant, but not the colistin monotherapy group (Group II).

CONCLUSION

In this study, we concluded that adding aminoglycosides, especially amikacin, to colistin therapy to combat infection guided by an antibiogram revealed multi-drug resistance, including carbapenems, had a statistically insignificant effect on worsening patients CrCl, and this adjunctive therapy didn't also add statistically significant potential for extending the patients VFDs. However, according to some emerging evidence, the addition of amikacin to colistin may delay the emerging of colistin resistance. The retrospective, single-centre, and non-adopting biochemical tests, which strongly correlate with efficacy or safety issues, limited the scope of this study. Our recommendations for the next research work to focus on conducting multicenter, controlled, randomised, and prospective studies to provide more confident answers to our study's debated question, "Does aminoglycosides increase the nephrotoxicity of colistin or enhance its efficacy?".

REFERENCES

1.Arrayasillapatorn N, Promsen P, Kritmetapak K, Anunnatsiri S, Chotmongkol W, Anutrakulchai S. Colistin-induced acute kidney injury and the effect on survival in patients with multidrug-resistant gram-negative infections: significance of drug doses adjusted to ideal body weight. International Journal of Nephrology. 2021 Dec 20;2021.

2.Sisay M, Hagos B, Edessa D, Tadiwos Y, Mekuria AN. Polymyxin-induced nephrotoxicity and its predictors: a systematic review and meta-analysis of studies conducted using RIFLE criteria of acute kidney injury. Pharmacological Research. 2021 Jan 1; 163:105328.

3.Elsayed E, Elarabi MA, Sherif DA, Elmorshedi M, El-Mashad N. Extensive drug resistant Acinetobacter baumannii: a comparative study between non-colistin based combinations. International Journal of Clinical Pharmacy. 2020 Feb;42:80-8.

4.Ni W, Yang D, Guan J, Xi W, Zhou D, Zhao L, Cui J, Xu Y, Gao Z, Liu Y. In vitro and in vivo synergistic effects of tigecycline combined with aminoglycosides on carbapenem-resistant Klebsiella pneumoniae. Journal of Antimicrobial Chemotherapy. 2021 Aug 1;76(8):2097-105.

5.Kong J, Wu ZX, Wei L, Chen ZS, Yoganathan S. Exploration of antibiotic activity of aminoglycosides, in particular ribostamycin alone and in combination with ethylenediaminetetraacetic acid against pathogenic bacteria. Frontiers in Microbiology. 2020 Jul 29; 11:1718.

6.Prasannan BK, Mukthar FC, Unni VN, Mohan S, Vinodkumar K. Colistin nephrotoxicity-age and baseline kidney functions hold the key. Indian Journal of Nephrology. 2021 Sep 1;31(5):449-53.

7.Ali EM, Albarraq AA, Makeen HA, Ezzi A, Mashragi YA. Intravenous colistin in the treatment of multidrug-resistant gram-negative organism in tertiary hospital, Jazan, KSA. Journal of Family Medicine and Primary Care. 2021 Jan 1;10(1):333-8.

8. Mahi-Birjand M, Yaghoubi S, Abdollahpour-Alitappeh M, Keshtkaran Z, Bagheri N, Pirouzi A, Khatami M, Sineh Sepehr K, Peymani P, Karimzadeh I. Protective effects of pharmacological agents against aminoglycoside-induced nephrotoxicity: A systematic review. Expert Opinion on Drug Safety. 2020 Feb 1;19(2):167-86.

9. Igwebuike C, Yaglom J, Huiting L, Feng H, Campbell JD, Wang Z, Havasi A, Pimentel D, Sherman MY, Borkan SC. Cross organelle stress response disruption promotes gentamicin-induced proteotoxicity. Cell Death & Disease. 2020 Apr 3;11(4):217.

10. Aitullina A, Purviņa S, Krūmiņa A. Colistin co-administration with other nephrotoxins: experience of teaching hospital of Latvia. International Journal of Clinical Pharmacy. 2021 Jun;43(3):509-17.

11. Sies H, Belousov VV, Chandel NS, Davies MJ, Jones DP, Mann GE, Murphy MP, Yamamoto M, Winterbourn C. Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. Nature Reviews Molecular Cell Biology. 2022 Jul;23(7):499-515.

12. Le TA, Hiba T, Chaudhari D, Preston AN, Palowsky ZR, Ahmadzadeh S, Shekoohi S, Cornett EM, Kaye AD. Aminoglycoside-related nephrotoxicity and ototoxicity in clinical practice: a review of pathophysiological mechanism and treatment options. Advances in therapy. 2023 Apr;40(4):1357-65.

13. Baltogianni M, Dermitzaki N, Kosmeri C, Serbis A, Balomenou F, Giapros V. Reintroduction of Legacy Antibiotics in Neonatal Sepsis: The Special Role of Fosfomycin and Colistin. Antibiotics. 2024 Apr 5;13(4):333.

14. Shafik MS, El-Tanbouly DM, Bishr A, Attia AS. Insights into the role of PHLPP2/Akt/GSK3β/Fyn kinase/Nrf2 trajectory in the reno-protective effect of rosuvastatin against colistin-induced acute kidney injury in rats. Journal of Pharmacy and Pharmacology. 2023 Aug 1;75(8):1076-85.

15. Chen T, Xu W, Yu K, Zeng W, Xu C, Cao J, Zhou T. In vitro activity of ceftazidime-avibactam alone and in combination with amikacin against colistin-resistant Gram-negative pathogens. Microbial Drug Resistance. 2021 Mar 1;27(3):401-9.

16.Papazachariou A, Tziolos RN, Karakonstantis S, Ioannou P, Samonis G, Kofteridis DP. Treatment Strategies of Colistin Resistance Acinetobacter baumannii Infections. Antibiotics. 2024 May 6;13(5):423.

17. Moussa M, Abou Chakra M, Dellis A, Moussa Y, Papatsoris A. Pharmacotherapeutic advances for recurrent urinary tract infections in women. Expert Opinion on Pharmacotherapy. 2020 Nov 1;21(16):2011-26.

18. Chiu S, Hancock AM, Schofner BW, Sniezek KJ, Soto-Echevarria N, Leon G, Sivaloganathan DM, Wan X, Brynildsen MP. Causes of polymyxin treatment failure and new derivatives to fill the gap. The Journal of Antibiotics. 2022 Nov;75(11):593-609.

19. Samarkos M, Papanikolaou K, Sourdi A, Paisios N, Mainas E, Paramythiotou E, Antoniadou A, Sambatakou H, Gargalianos-Kakolyris P, Skoutelis A, Daikos GL. The Effect of Different Colistin Dosing Regimens on Nephrotoxicity: A Cohort Study. Antibiotics. 2022 Aug 5;11(8):1066

20. Chien HT, Lin YC, Sheu CC, Hsieh KP, Chang JS. Is colistin-associated acute kidney injury clinically important in adults? A systematic review and meta-analysis. International journal of antimicrobial agents. 2020 Mar 1;55(3):105889.

21. Eronmosele JE, Olurishe TO, Olorukooba AB. Investigation of treatment-time differences in colistin-induced nephrotoxicity in Wistar rats. Chronobiology International. 2021 Feb 1;38(2):224-33.

22. Worakajit N, Thipboonchoo N, Chaturongakul S, Jutabha P, Soontornniyomkij V, Tuchinda P, Soodvilai S. Nephroprotective potential of Panduratin A against colistin-induced renal injury via attenuating mitochondrial dysfunction and cell apoptosis. Biomedicine & Pharmacotherapy. 2022 Apr 1;148:112732.

23. Gergin ÖÖ, Pehlivan SS, Ulger M, Mat OC, Bayram A, Gönen ZB, Gökdemir NS, Biçer C, Yildiz K, Yay AH. Efficacy of stem cell-based therapies for colistin-induced nephrotoxicity. Environmental Toxicology and Pharmacology. 2022 Aug 1;94:103933.

24. Gupta S, Portales-Castillo I, Daher A, Kitchlu A. Conventional chemotherapy nephrotoxicity. Advances in Chronic Kidney Disease. 2021 Sep 1;28(5):402-14.

25. Casanova AG, Hernández-Sánchez MT, López-Hernández FJ, Martínez-Salgado C, Prieto M, Vicente-Vicente L, Morales AI. Systematic review and meta-analysis of the efficacy of clinically tested protectants of cisplatin nephrotoxicity. European journal of clinical pharmacology. 2020 Jan;76:23-33.

26. Miyoshi T, Uoi M, Omura F, Tsumagari K, Maesaki S, Yokota C. Risk factors for cisplatin-induced nephrotoxicity: a multicenter retrospective study. Oncology. 2021 Sep 23;99(2):105-13.

27. Sedrak MS, Freedman RA, Cohen HJ, Muss HB, Jatoi A, Klepin HD, Wildes TM, Le-Rademacher JG, Kimmick GG, Tew WP, George K. Older adult participation in cancer clinical trials: a systematic review of barriers and interventions. CA: a cancer journal for clinicians. 2021 Jan;71(1):78-92.

28. Wu D, Nie J, Hu W, Dai L, Zhang J, Chen X, Ma X, Tian G, Han J, Han S, Long J. A phase II study of anlotinib in 45 patients with relapsed small cell lung cancer. International Journal of Cancer. 2020 Dec 15;147(12):3453-60.

29.Dunsmore KP, Winter SS, Devidas M, Wood BL, Esiashvili N, Chen Z, Eisenberg N, Briegel N, Hayashi RJ, Gastier-Foster JM, Carroll AJ. Children's Oncology Group AALL0434: a phase III randomized clinical trial testing nelarabine in newly diagnosed T-cell acute lymphoblastic leukemia. Journal of Clinical Oncology. 2020 Oct 10;38(28):3282.

30. Saelim W, Changpradub D, Thunyaharn S, Juntanawiwat P, Nulsopapon P, Santimaleeworagun W. Colistin plus sulbactam or fosfomycin against carbapenem-resistant Acinetobacter baumannii: improved efficacy or decreased risk of nephrotoxicity?. Infection & Chemotherapy. 2021 Mar;53(1):128.

31.Sorlí L, Luque S, Li J, Benítez-Cano A, Fernández X, Prim N, Vega V, Gómez-Junyent J, López-Montesinos I, Gómez-Zorrilla S, Montero MM. Colistin plasma concentrations are not associated with better clinical outcomes in patients with pneumonia caused by extremely drug-resistant Pseudomonas aeruginosa. Microbiology Spectrum. 2023 Dec 12;11(6):e02967-23.

32. Wang SH, Yang KY, Sheu CC, Lin YC, Chan MC, Feng JY, Chen CM, Chen CY, Zheng ZR, Chou YC, Peng CK. The prevalence, presentation and outcome of colistin susceptible-only Acinetobacter Baumannii-associated pneumonia in intensive care unit: A multicenter observational study. Scientific reports. 2023 Jan 4;13(1):140.

33. Ontong JC, Ozioma NF, Voravuthikunchai SP, Chusri S. Synergistic antibacterial effects of colistin in combination with aminoglycoside, carbapenems, cephalosporins, fluoroquinolones, tetracyclines, fosfomycin, and piperacillin on multidrug resistant Klebsiella pneumoniae isolates. Plos one. 2021 Jan 6;16(1):e0244673.

34. Wang Y, Li C, Wang J, Bai N, Zhang H, Chi Y, Cai Y. The efficacy of Colistin combined with amikacin or levofloxacin against Pseudomonas aeruginosa Biofilm infection. Microbiology Spectrum. 2022 Oct 26;10(5):e01468-22.

35. Almutairi MM. Synergistic activities of colistin combined with other antimicrobial agents against colistin-resistant Acinetobacter baumannii clinical isolates. PLoS One. 2022 Jul 13;17(7):e0270908.

36 Bassetti M, Vena A, Giacobbe DR, Castaldo N. Management of infections caused by multidrug-resistant gram-negative pathogens: recent advances and future directions. Archives of medical research. 2021 Nov 1;52(8):817-27.

37. Almutairy R, Aljrarri W, Noor A, Elsamadisi P, Shamas N, Qureshi M, Ismail S. Impact of colistin dosing on the incidence of nephrotoxicity in a tertiary care hospital in Saudi Arabia. Antibiotics. 2020 Aug 6;9(8):485.

38. Sadyrbaeva-Dolgova S, García-Fumero R, Exposito-Ruiz M, Pasquau-Liaño J, Jiménez-Morales A, Hidalgo-Tenorio C. Incidence of nephrotoxicity associated with intravenous colistimethate sodium administration for the treatment of multidrug-resistant gram-negative bacterial infections. Scientific Reports. 2022 Sep 10;12(1):15261.

39. Ustundag G, Oncel EK, Sahin A, Keles YE, Aksay AK, Ciftdogan DY. Colistin treatment for multidrug-resistant gram-negative infections in children: caution required for nephrotoxicity. Sisli Etfal Hastan Tip Bul. 2022 Sep 22;56(3):427-34.