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Effectiveness and Toxicity of High-Dose Colistin Treatment in Patients with Multidrug-Resistant Gram-Negative Bacterial Infections

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Eficacia y toxicidad del tratamiento con colistina a dosis altas en pacientes con infecciones bacterianas gramnegativas multirresistentes

ABSTRACT

Hospital-acquired infections by multidrug-resistant Gram-negative bacteria (MDRGN) have become a global public health problem. Colistin is considered one of the last therapeutic options due to its limited clinical effectiveness and high rate of adverse effects. Unfortunately, its use has increase in recent years given the increase of MDRGN-associated infections and narrow therapeutic alternatives. With the aim of improving effectiveness using pharmacokinetic/pharmacodynamic knowledge, higher doses of colistin have been used in recent years but with few reported outcomes. ***Methods:*** *A retrospective cohort analysis was performed in patients with MDRGN infections treated with high-dose colistin with the aim of evaluating clinical improvement as primary outcome and the incidence of acute kidney injury (AKI) and other adverse events as secondary outcomes.* ***Results:*** *Fifty-five courses of colistin treatment were identified in 50 patients, with 45% applied on intensive care unit. Clinical improvement was achieved in 35 (63.6%) treatments, while extrapulmonary infections were significantly associated with a higher clinical failure rate (OR 10; 95%CI: 1.18-84.5). By multivariate analysis, only the failure to control the infection source influenced significantly for mortality of patients (aOR= 19.6; IC95 3.0-126, p= 0.002). AKI was observed in 30 treatments (54.5%) and was only significantly associated with the use of a loading doses (OR= 6.0, 95%CI: 1.61-22.3). Eosinophilia was frequent (35.7%) and, besides, two respiratory depression events were observed.* ***Conclusion:*** *High doses of colistin could be associated with a favorable clinical*

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improvement in patients with MDRGN infections but has a limited effectiveness in extra-pulmonary infections, especially when a source-control procedure is not performed. AKI is frequently observed and limits its use, while eosinophilia and respiratory depression should be considered also as part of safety monitoring. Prescription of this drug should be judiciously analyzed weighing benefits-to-risk ratio.
Keywords: *Antibiotic Resistance; Clinical efficacy; Colistin; Drug Resistance, Microbial; Safety.*

RESUMEN
Las infecciones hospitalarias por bacterias gram negativas multirresistentes (MDRGN) se han convertido en un problema de salud pública mundial. Colistin se considera una de las últimas opciones terapéuticas dada su limitada eficacia clínica y su alta tasa de efectos adversos. Desafortunadamente, su uso ha aumentado en los últimos años dado el aumento de infecciones asociadas a MDRGN y las escasas alternativas terapéuticas. Con el objetivo de mejorar la eficacia, utilizando el conocimiento farmacocinético/farmacodinámico, se han utilizado dosis más altas de colistin en los últimos años, con resultados poco conocidos. ***Metodología:*** *Se realizó un análisis de cohorte retrospectivo en pacientes con infecciones por MDRGN tratados con colistin en dosis altas, con el objetivo de evaluar la respuesta clínica como resultado primario y la incidencia de falla renal aguda (IRA) y otros eventos adversos como resultados secundarios.* ***Resultados:*** *Se identificaron 55 ciclos de tratamiento con colistin en 50 pacientes, de los cuales el 45% se aplicó en la unidad de cuidados intensivos. Se logró respuesta clínica en 35 (63,6%) tratamientos, mientras que las infecciones extrapulmonares se asociaron significativamente con una mayor tasa de fracaso clínico (OR 10; IC del 95%: 1,18-84,5). Por análisis multivariado, solo el fracaso en el control del foco infeccioso influyó significativamente en la mortalidad de los pacientes (ORa= 19,6; IC95 3,0-126, p= 0,002). La IRA se observó en 30 tratamientos (54,5%) y solo se asoció significativamente con el uso de dosis de carga (OR= 6,0, IC del 95%: 1,61-22,3). La eosinofilia fue frecuente (35,7%) y, además, se observaron dos eventos de depresión respiratoria.* ***Conclusiones:*** *dosis altas de colistin podrían ser beneficiosas en pacientes con infecciones por MDRGN, pero tiene una efectividad limitada en infecciones extrapulmonares, especialmente cuando no se realiza un procedimiento que permita el control del foco. La IRA se observa con frecuencia y limita su uso, mientras que la eosinofilia y la depresión respiratoria también deben considerarse como parte del control de seguridad. La prescripción de este fármaco debe analizarse criteriosamente, sopesando el riesgo y beneficio.*
Palabras clave: *Colistina; Farmacorresistencia Microbiana; Resultado del Tratamiento; Seguridad.*

Hospital-acquired infections by multidrug-resistant Gram-negative bacteria (MDRGN), such as Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae, have become a global public health problem[1]. Colistin (also known as polymyxin E) is an antibiotic of the polymyxin group that despite having an excellent in vitro activity against MDRGN[2], is considered one of the last therapeutic option given its limited clinical effectiveness and high rate of adverse effects, including renal failure[3,4]. Unfortunately, due to the increase in MDRGN infections and the absence of therapeutic alternatives, in-hospital use of colistin has become frequent in recent years[5].

To optimize the use of colistin, their pharmacokinetics (PK) and pharmacodynamics (PD) has been extensively studied in recent years[6] specially among critically ill patients[7]. Some studies have proposed a new dosing regimen incorporating both a loading and maintenance dose of approximately 9 million international units (MUI) per day[8], with the potential to improve their effectiveness without increasing renal failure[9]. Unfortunately, the current information available at the local level is scarce and the impact of the new dosing strategies on patient outcomes, as well as those covariates that could have conditioned them, is unknown. The objective of this study is to evaluate the effectiveness and toxicity of high-dose colistin guidelines and the risk factors associated with each of these outcomes in a regional reference center in a developing country.

Methods

Study description and patients included

A retrospective observational study was conducted at the Hospital Base Valdivia (HBV) in Valdivia, Chile, from January 2013 to December 2019. Patients were included in the study if they were adults (≥18 years) treated with colistin using doses greater than 3 MUI/day for more than 48 hours due to a suspected or documented infection by MDRGN. Patients prescribed colistin as surgical prophylaxis or did not meet the inclusion criteria were excluded from the study.

Variables included

All included patients received intravenous colistin in the methanesulfonate form. The following clinical variables were collected: age, body weight, comorbidities, Charlson Index, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assesment Index (SOFA), infection site, loading dose, daily dose and duration of colistin therapy, treatment opportunity, infectious source control, concomitant antibiotics, concomitant nephrotoxics, serum creatinine, blood eosinophils and need for kidney replacement. Furthermore, clinical and microbiological outcomes were evaluated by an infectious disease specialist through the analysis of clinical records, while renal failure was assessed based on the Acute Kidney Injury Network (AKIN) criteria[10]. A causal analysis was performed for renal failure and all other suspected adverse effects developed during colistin therapy by the Naranjo Algorithm[11]. Clinical improvement was defined as the absence of all signs or symptoms of infection or a return to the pre-infection state at the end of antimicrobial treatment. The microbiological response was defined as the achievement of bacterial eradication in cultures taken at least 48 hours after the end of treatment.

Microbiological aspects

The strains were isolate from clinical specimens, including sputum, alveolar lavage fluid, peritoneal fluid, blood, bone, urine and soft tissue. Microbial identification was performed using the VITEK®2 automated system. In vitro colistin susceptibility and minimum inhibitory concentrations (MIC) were determined using the VITEK®2 automated system in most of the strains studied(30). Broth microdilution was used in some patients (n= 9). In only one very old case (2013) was the diffusion method used. Regarding the identification and susceptibility to carbapenems, the VITEK®2 automated system was used. All susceptibility interpretation was performed according to the Clinical and Laboratory Standards Institute guidelines (CLSI, M100). If available, *in vitro* rapid diagnostic test

for the detection of OXA-48, KPC and NDM carbapenemases was examined using a rapid chromogenic biochemical assay (Kit Rapid Carba NP®, BioMerieux) and a immunochromagraphic test – lateral flow (Coris BioConcept®).

Statistical Analysis

Continuous variables were presented as central trend measures, including the average and standard deviation for variables with normal distribution, and the median values and interquartile range (IQR) for other variables. Dispersion (ranges) and categorical variables were summarized as proportions. The univariate analysis of potential factors associated with the development of nephrotoxicity and clinical success was performed by calculating Odds Ratios (ORs) with 95% confidence intervals and p-values (<0.05 as significant). A multivariate analysis was performed using logistic regression when two or more variables associated with the outcomes under study were found. The statistical analysis was performed using SPSS software® version 22. The Scientific Ethics Committee of the Valdivia Health Service approved this work.

Results

Fifty-five courses of colistin treatment were identified in 50 patients treated in HBV. Five patients received 2 treatments separated by more than 1 month (independent events). Median age was 56 years (IQR 41-65 years) and about 30% of patients were over 65 years. A predominance of male patients was observed (ratio 2:1). All patients had comorbidities, predominantly hypertension, neoplasms, diabetes mellitus and obesity (Table 1).

Table 1. General characteristics of colistin treated in-hospital patients. Hospital Base de Valdivia. Chile, 2012-2019.

Variable	Results
Age (median, range)	55 (41-65years)
Age ≥ 65	15 (30%)
Male n (%)	32(64%)
Comorbidities*	
High blood pressure	25 (50%)
Neoplasia	18 (36%)
Diabetes Mellitus	14 (28%)
Obesity	8 (16%)
Chronic Kidney Disease	4 (8%)
Cardiopathy	3 (6%)
Chronic liver damage	3 (6%)
Asthma	3 (6%)
Chronic Lung Disease	1 (2%)

*: Conditions not mutually exclusive.

Characterization of use of colistin

Most infection sites were related to lung, intra-abdominal or skin and soft tissue infections (SSTIs) (Table 2). Almost half of the patients were treated in critical units (ICU; n= 24, 43.6%). Median treatment duration was 7 days (IQR 5-12 days). The median daily dose used was 9 MUI (IQR 6,6-9) and the median total cumulative dose per patient was 79,5 MIU (IQR 60,7-118,9). 39 patients of 55 patients received loading doses of 6 to 9 MUI, of which the majority was 9 MUI (37 of 39; 95%).

Toxicity associated with colistin use

Twenty four of 55 patients (44%) presented acute kidney injury during the month prior to receiving colistin, however only 6 of them had creatinemia >1.5 mg/dL at the time of initiation of treatment, receiving doses adjusted according to glomerular filtration rate. A high frequency of acute renal injury was observed (30 events, 54.5%) during 55 colistin treatment courses. Renal injury presented within a median of 6 days (range 4-7 days). According to the application of the Naranjo Algorithm for the development of AKI, 28 patients were categorized as "possible", 1 patient as "probable" and 1 patient as "definite".

No association was found between this complication and patient´s age, gender, comorbidities, weight, Charlson comorbidity Index, APACHE II and SOFA severity scores, or other variables associated with patient management, such as ICU admission, vasoactive drug use or mechanical ventilation. Further, no association was found with laboratory variables, such as hypoalbuminemia, leukocytosis, eosinophilia, thrombocytopenia, prior renal injury or use of other potentially nephrotoxic compounds, or daily dose or daily dose per kg of estimated weight. Only the use of a loading doses was identified as a risk factor associated with the development of acute renal injury (OR= 6.0, 95%CI: 1.61-22.3). Duration of treatment with colistin was significantly lower in patients developing renal injury because of discontinuation due to the adverse effect (6 versus 10 days). In 7 patients (12.7%), treatment was discontinued due to the development of renal injury, and in 2 of the 30 treatment courses associated with renal injury, hemodialysis was needed (3.6% of total; 6.7% of subgroup with renal failure).

Table 2. Infectious site distribution among 55 colistin therapy courses. Hospital Base de Valdivia. Chile, 2012-2019.

Infectious focus	Results
Non-MV-associated nosocomial pneumonia*	14 (25.5%)
Pneumonia associated with MV*	2 (3.6%)
Abdominal focus	15 (27.3%)
Skin and soft tissue infections	11 (20.0%)
Urinary tract infection	6 (10.9%)
Bone tissue	5 (9.1%)
Bacteremia without focus	1 (1.8%)
Catheter-related bloodstream infection	1 (1.8%)
Total	55 (100%)

*MV: mechanical ventilation.

Four treatment courses (7.3%) were associated with respiratory toxicity (transient respiratory depression). In addition, eosinophilia (count >500/L) was observed in 20 (36.4%) treatment courses and no clinical factors were linked to this phenomenon (data not shown). Treatment was discontinued in one patient due to respiratory toxicity, in one patient due to a combination of respiratory and renal toxicity, and in one patient due to intense eosinophilia (3,700/L).

Treated microorganisms and antibiotic resistance

Most treatments were associated with non-fermenting Gram-negative bacilli (P. aeruginosa in 56.4% and *A. baumannii* in 18.2%. In eight patients, treatments were applied on an empirical basis (14.5%). The prevalence of antibiotic resistance in the bacterial species studied was 88.4% (38 of 43) for meropenem, 88.6% (39 of 44) for imipenem and 31.7% (13 of 41) for amikacin.

All strains studied (n= 38) were "susceptible" to colistin according to the cutoff points established at that time, however, only 9 were studied by broth microdilution. The prevalence of carbapenem resistance was higher in *P. aeruginosa* and *A. baumannii* and lower for *K. pneumoniae* (Table 3).

Clinical effectiveness and microbiological response

No association was observed between microbiological eradication and clinical cure (data not shown), however, this could only be evaluated in 22 treatments due to absence of follow up cultures in most patients.

The clinical improvement/cure was reached in about two-thirds of treatments especially among pulmonary infections (Table 4). When empirical treatments were excluded, the estimated clinical cure was slightly higher (65,9% versus 64%). Extrapulmonary infections were significantly associated with a higher clinical failure rate (OR 10; 95%CI: 1.18-84.5), but the association was not significant when empirical treatments were excluded (p= 0.67).

Higher clinical improvement rates were observed in infections caused by *Pseudomonas aeruginosa* (70,9%) and Enterobacterales (66.7%) compared to those caused by *Acinetobacter baumannii* (50%), although these differences were not statistically significant (p= 0,7) (Table 3).

No association between clinical improvement rate and age, gender, comorbidities, development of renal injury, admission to ICU or laboratory variables was found.

Others factors associated with therapeutic failure

Twelve patients had another concomitant microorganism in the same infectious focus (mainly abdominal infections and necrotizing skin infections), with a variable resistance profile, and all had adequate antimicrobial coverage (Table 3). No association was observed between the presence of other microorganisms and clinical failure (p= 0.6).

A sub-analysis of the 16 treatments without clinical success indicated that 11 treatment failures (68.8%) were due to an uncontrolled infection source, 4 (25%) were due to problems associated with antibiotic medical management, and one (6.3%) was due to suspension because of an adverse drug reaction. Failure to control the infection focus was distributed in different types of infections: abdominal infections (n= 5), SSTIs (n= 2), bone tissue (n= 2), pneumonia (n=1) and urinary tract infection (n= 1).

Survival of patients

Of the 50 patients, 14 died during hospitalization (28%). Analysis of potential risk factors associated with mortality found no association with gender, older age, comorbidities, development of acute renal injury, leukocytosis, thrombocytopenia, hypoalbuminemia, need for hemodialysis or site of infection, SOFA score and Charlson comorbidity index; however, a significant association was observed between mortality and lack of infection source control (OR 23; IC95 3.8-148, <0.001) and APACHE II score (OR 5.5; IC95 1.3-23.2, p<0.05). Risk of death was approximately 5 times higher in patients with APACHE II scores ≥22 (OR= 5.5, 95%CI: 1.3-23.2). By multivariate analysis, only the failure to control the infection source remained significant (aOR= 19.6; IC95 3.0-126, p= 0.002).

Table 3. Distribution of microorganisms identified and clinical response among 55 colistin therapy courses. Hospital Base de Valdivia, Chile, 2012-2019.

Microorganism or empirical use	**Frequency n/N (%)**	**Coinfection (n)**	**Clinical Improvement**
Pseudomonas aeruginosa	31/55 (56,4%)	*K. pneumoniae* (2), *E. faecalis* (1), *A. baumanii* (1), *E. coli* (1), *P. mirabilis* (1), *K. oxytoca (1).*	22/31 (70,9%)
Meropenem resistant*	26/29 (89,7%)		
Imipenem resistant*	27/30 (90%)		
Amikacin resistant*	9/30 (30%)		
CPN positive	4 /17 (23,5%)**		
Acinetobacter baumannii	10 (18,2%)	*K. pneumoniae* (2)	5/10 (50%)
Meropenem resistant*	8/8 (100%)		
Imipenem resistant*	8/8 (100%)		
Amikacin resistant*	3/5 (60%)		
CPN positive	1/1 (100%)***		
Enterobacterales	6 (10,9%)	*K. pneumoniae* (2), *E. coli* / *E. faecalis* (1)	4/6 (66,7%)
Klebsiella pneumoniae	5 (9,1%)		
Meropenem resistant*	3/5 (60%)		
Imipenem resistant*	3/5 (60%)		
Amikacin resistant*	1/5 (20%)		
CPN positive	1/3 (33,3%)		
Enterobacter cloacae	1 (1,8%)		
Empirical use	8 (14,5%)		4/8 (50%)
Total *	55 (100%)		35/55 (63,6%)

CPN: *Carbapenemase detection*
* strains studied
* includes non-evaluable cases in the denominator
** of the strains studied (2 VIM, 2 KPC)
*** detected only by CarbaNP.

Table 4. Microbiological and clinical response by type of infection in 55 colistin treatments. Hospital Base de Valdivia, Chile, 2012-2019.

Type of infection	Microbiological cure*		Clinical improvement*	
Pulmonary	3/16	(18.8%)	14/16	(87.5%)
Bacteremia	0/2	(0%)	0/2	(0%)
Abdominal	3/15	(20%)	9/15	(60%)
Urinary Infection	2/6	(33.3%)	4/6	(66.7%)
SSTIs	3/11	(27.3)	6/11	(54.5%
Bone tissue	0/5	(0%)	2/5	(40%)
Total	11/55	(20%)	35/55	(63.6%)

* includes non-evaluable cases in the denominator, SSTIs: skin and soft tissue infections.

Discussion

In our study colistin treatment was associated with a favorable clinical improvement in 64% of patients, higher than the 50% reported in the single national series previously reported[12]. The use of a loading and maintenance dose regimen of 9 MUI/day (2-3 times higher than conventional doses), could have facilitated achieving optimal concentrations of colistin at the infection site. This high-dose regimen was proposed by Garonzik et al, which recommended an average dose of 9 MUI of colistin to achieve a PK/PD target of AUC0-24h of 60 g/mL*h, that is associated with a maximum bactericidal activity[8]. Clinical cure rates as high as 82% have been demonstrated using this new dosing regimens[9]. Additionally, Falagas and colleagues in a retrospective study with 258 patients affected by microbiologically documented MDRGN infections, observed a lower in-hospital mortality with increasing colistin daily dose up to 8.1 MUI per day[13]. Additionaly, multivariate analysis of survival data showed that higher daily colistin dose was independently associated with increased probability of survival [aOR= 1.22, 95% CI 1.05–1.42; P= 0.009][13].

In a retrospective study published by Cheng et al, 51% of patients treated with high-dose colistin achieved a successful response, lower than described in our study, however, they included a higher population of ICU patients (63%)[14]. Markedly, multivariate analysis showed that a higher APACHE II score was independently associated with poor clinical response (OR= 1.14, 95%CI: 1.02-1.28)[14]. Our study had a lower percentage of patients admitted to ICU (45%) and lower disease severity after the first 24 hours, with only 24% of patients with APACHE II scores >20 points, which potentially explain clinical response differences. On the other hand, in our study lung infections were more prevalent and were related to a more favorable clinical cure (n= 14, 87.5%), when compared with extra-pulmonary sites. In our study, when colistin was used in non-pulmonary infections (versus pneumonia), the clinical failure rate was 10 times higher. These findings are in contrast to that described by a previous Chilean report, where pulmonary infections treated with colistin were associated with therapeutic failure (p= 0.04)[12]. Part of the explanation may be related to the near 3 times lower doses used in that study, perhaps conditioning a suboptimal concentration of colistin into the infectious site. Finally, many patients with extra-pulmonary infections did not have control of the source of infection.

In our study, colistin failure was mainly associated when used for abdominal, SSTIs or bone

infections. These infections commonly require surgical intervention, such as deep tissue cleaning, debridement, necrosectomy and drainage, which are complex procedures that are not often timely available at our center. These findings are in line with previous report in literature, where inadequate or late source control in patients with sepsis or septic shock has proven to be an independent mortality factor regardless of the antimicrobial therapy used[15].

Our study shows a high rate of nephrotoxicity (55.4%), close to described in the studies by Ceylan[16] and Temocin[17], with similar rates (58.9% and 48%, respectively). To date, nephrotoxicity is one of the main limitations of colistin use in clinical practice, depending on various factors, such as cumulative dose, patient age, and use of concomitant vasoactive or nephrotoxic drugs[3]. In our study, only the use of colistin loading doses was associated with an increased risk of acute renal failure ($p<0.05$), while admission to ICU, hypoalbuminemia, prior acute renal failure or use of nephrotoxic drugs conditioned a non-significant increased trend. Notably, the loading dose, received in 71.4% of our patients, was proposed by the PK/PD study of Garonzik[8], which was validated and recommended for critical patients, who represented only 44.6% of our patients. Loading doses may have generated toxic concentrations of colistin in patients without the clinical and pharmacokinetic characteristics of a critical condition, thus increasing the likelihood of acute renal failure development[18].

In the single previous study of the use of colistin in Chile no patient developed nephrotoxicity[12], while in an international retrospective series of 125 patients, nephrotoxicity occurred in 12.8% of patients[19]. In both studies, lower colistin doses were used and more stringent criterion for recognizing renal failure was applied, possibly underestimating this adverse effect.

Another important finding of our study was the high rate of eosinophilia during therapy (> 500 cel/µL; 35.7%). This hematological alteration has previously been described in treatment with inhaled colistin, where patients have developed an allergic reaction with rash, cough, sore throat and bronchoconstriction[20]. Another study reported hypersensitivity pneumonitis with colistin[21], as well as eosinophilia in adult[22], pediatric and neonatal patients receiving colistin[23].The high incidence of eosinophilia in our study (35.7%) could be related to an early warning sign of acute interstitial nephritis (AIN), but we were unable to associate this adverse event with the appearance of kidney injury. In drug-induced AIN disease, early discontinuation of the suspicious drug is the cornerstone of treatment. In our research, colistin therapy was discontinued in one case due to intense eosinophilia (3,700 cel/µL).

This study has some limitations. First, due to retrospective methodology, some cases of colonization may have been treated as clinical infections. We believe this limitation was mitigated through an exhaustive review of medical records, nursing records, vital signs, laboratory and radiological examinations by infectious disease specialists. Second, the small sample size limits the power of our conclusions and could have impact to detect difference in outcomes, especially the logistic regression analysis (multivariate) could have been affected. Another important limitation is that most colistin susceptibility tests were performed at that time using Vitek®2. Suboptimal determinations have been reported with automated methods, with broth microdilution being the gold standard[24]. The above, added to the recent elimination of the "susceptible" category by the CLSI, prevents establishing a correlation between susceptibility tests and clinical results in our study.

Colistin remains a useful alternative for MDGRBN infections in selected patients with comprehensive clinical follow up, mainly of kidney function, to ensure that it remains as a safe and effective therapy. In addition, the high direct cost of new therapeutic alternatives, such as ceftazidime/avibactam or meropenem/vaborbactam, limits their widespread use and favors the perpetuation of alternatives such as colistin with a more unfavorable benefit/risk profile.

Conclusion

Our findings suggest that the use of higher doses of colistin could be associated with a better

clinical response in patients with MDRGN infections, especially in those affected with a pulmonary focus. For extra-pulmonary infections controlling the infection source is as relevant as the antibiotic treatment for patient´s survival. Finally, the risks and benefits must be carefully balanced when prescribing colistin especially for the high risk of developing acute renal failure which could affect more than half of the patients.

References

1. *Hawkey PM. Multidrug-resistant Gram-negative bacteria: A product of globalization. J Hosp Infect. 2015; 89(4): 241-247.*
2. *Walkty A, DeCorby M, Nichol K, Karlowsky JA, Hoban DJ, Zhanel GG. In vitro activity of colistin (polymyxin E) against 3,480 isolates of gram-negative bacilli obtained from patients in Canadian hospitals in the CANWARD study, 2007-2008. Antimicrob Agents Chemother. 2009; 53(11): 4924-4926.*
3. *Falagas ME, Kasiakou SK. Toxicity of polymyxins: A systematic review of the evidence from old and recent studies. Crit Care. 2006; 10(1): R27.*
4. *Kagami K, Ishiguro N, Yamada T, Niinuma Y, Iwasaki S, Taki K, et al. Efficacy and safety of colistin for the treatment of infections caused by multidrug-resistant gram-negative bacilli. J Infect Chemother. 2021; 27(3): 473-479.*
5. *El-Sayed Ahmed MAEG, Zhong LL, Shen C, Yang Y, Doi Y, Tian GB. Colistin and its role in the Era of antibiotic resistance: An extended review (2000–2019). Emerg Microbes Infect. 2020; 9(1): 868-885.*
6. *Phillip J. Bergen JL, Nation RL. Dosing of colistin – back to basic PK/PD. Curr Opin Pharmacol. 2011; 11(5): 464-469.*
7. *Karnik ND, Sridharan K, Jadhav SP, Kadam PP, Naidu RK, Namjoshi RD, et al. Pharmacokinetics of colistin in critically ill patients with multidrug-resistant Gram-negative bacilli infection. Eur J Clin Pharmacol. 2013; 69(7): 1429-1436.*
8. *Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother. 2011; 55(7): 3284-3294.*
9. *Dalfino L, Puntillo F, Mosca A, Monno R, Spada ML, Coppolecchia S, et al. High-dose, extended-interval colistin administration in critically ill patients: Is this the right dosing strategy? A preliminary study. Clin Infect Dis. 2012; 54(12): 1720-1726.*
10. *Mehta RL, Kellum JA, Shah S V., Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007; 11(2): 1-8.*
11. *Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA JE. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981; 30: 239-245.*
12. *Fica C A, Céspedes J I, Gompertz G M, Jalón V M, Sakurada Z A, Sáez L E. Colistín en infecciones nosocomiales por bacilos gramnegativos pan-resistentes TT - Intravenous colistin in the treatment of infections due to pan-resistant Gram negative bacilli. Rev Chil infectología. 2007; 24(5): 360-367.*
13. *Falagas ME, Rafailidis PI, Ioannidou E, Alexiou VG, Matthaiou DK, Karageorgopoulos DE, et al. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: A retrospective cohort study of 258 patients. Int J Antimicrob Agents. 2010; 35(2): 194-199.*
14. *Cheng CY, Sheng WH, Wang JT, Chen YC, Chang SC. Safety and efficacy of intravenous colistin (colistin methanesulphonate) for severe multidrug-resistant Gram-negative bacterial infections. Int J Antimicrob Agents. 2010; 35(3): 297-300.*
15. *Martínez ML, Ferrer R, Torrents E, Guillamat-Prats R, Gomà G, Suárez D, et al. Impact of Source Control in Patients with Severe Sepsis and Septic Shock. Crit Care Med. 2017; 45(1): 11-19.*
16. *Ceylan B, Taniş M, Akkoyunlu ME, Çınar A, Kurt AR, Akkoyunlu Y, et al. Variables determining the development of colistin-associated renal impairment. Wien Klin Wochenschr. 2016; 128: 614-619.*
17. *Temocin F, Erdinc S, Tulek N, Demirelli M, Bulut C, Ertem G. Incidence and risk factors for colistin-associated nephrotoxicity. Jpn J Infect Dis. 2015; 68(4): 318-320.*
18. *Bellos I, Pergialiotis V, Frountzas M, Kontzoglou K, Daskalakis G, Perrea DN. Efficacy and safety of colistin loading dose: A meta-analysis. J Antimicrob Chemother. 2020; 75(7): 1689-1698.*
19. *Zaidi STR, Al Omran S, Al Aithan ASM, Al Sultan M. Efficacy and safety of low-dose colistin in the treatment for infections caused by multidrug-resistant gram-negative bacteria. J Clin Pharm Ther. 2014; 39(3): 272-276.*
20. *Lépine PA, Dumas A, Boulet LP. Pulmonary Eosinophilia From Inhaled Colistin. Chest. 2017; 151(1): e1-e3.*
21. *Leong KW, Ong S, Chee HL, Lee W, Kwa AL. Hypersensitivity pneumonitis due to high-dose colistin aerosol therapy. Int J Infect Dis. 2010; 14(11): e1018-e1019.*
22. *Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. Ann Intern Med. 1970; 72(6): 857-868.*
23. *Al-lawama M, Aljbour H, Tanash A, Badran E. Intravenous Colistin in the treatment of multidrug-resistant Acinetobacter in neonates. Ann Clin Microbiol Antimicrob. 2016; 15(1): 1-4.*
24. *Khurana S, Malhotra R, Mathur P. Evaluation of Vitek®2 performance for colistin susceptibility testing for Gram-negative isolates. JAC Antimicrob Resist. 2020; 2(4): dlaa101.*