DOI: https://doi.org/10.53555/nnmhs.v9i5.1680 Publication URL: https://nnpub.org/index.php/MHS/article/view/1680

EFFICACY AND SAFETY OF USING COLISTIN IN NEONATES : A SYSTEMATIC REVIEW

Dea Nabila Ratu Alicia*

**Faculty of Medicine, University of Malahayati, Indonesia*

Corresponding Author:
deanabilaratu@gmail.com

Abstract

Colistin is a cationic polypeptide antibiotic that belongs to the family of polymyxins and kills bacteria by interfering with the functioning of the bacterial cell. When given intravenously, colistin has the potential to cause a number of potentially harmful side effects, the most prevalent of which is nephrotoxicity. Recent studies have shown that patients who receive therapy with intravenous colistin run a risk of developing decreased kidney function ranging from 7.5% to 18.6% of the time. This risk is higher in patients who are older. However, it is essential to keep in mind that treatment with intravenous colistin, in the same way as treatment with other nephrotoxic drugs can result in conditions such as infection, septic shock, and the failure of several organs, it is vital to keep in mind that treatment with intravenous colistin. The bactericidal actions of colistin are demonstrated to be effective against a significant proportion of Gram-negative aerobic bacilli. It wasn't until the 1950s that it was first used in the United States, but by the 1980s, intravenous versions of the drug had been phased out due to the nephrotoxicity they caused. However, due to a rise in the incidence of illnesses caused by carbapenem-resistant Gram-negative (CRGN) bacteria and a dearth of newly developed antimicrobial drugs that are active against multidrug-resistant Gram-negative germs, the effectiveness of colistin has been called into question once again. The effectiveness of colistin in newborns might range anywhere from 50 to 98 percent. In this particular research endeavor, hyponatremia was identified as a potential adverse impact.

Katakunci: *Carbapenem-resistant Gram-negative; Colistin; Neonates; Hyponatremia*

INTRODUCTION

The UN Millennium Development Goal number 4, to reduce newborn infection by two thirds by 2015, was not met by the neonatal community. Since aetiology and preventative methods differ, the historical split into early onset sepsis (EOS) (up to 48–72 h) and late onset (LOS) remains useful.[1,2] Infection-related mortality after the millennium are regrettably high and vary by nation, NICU, gestation, and postnatal age. Infection-related mortality in preterm infants in high income countries has a changing etiology. Infection causes one in ten preterm fatalities in the UK and USA.[3]

Although our understanding of the mechanisms underlying adverse neurodevelopmental outcomes following infection has improved, our capacity to prevent long-term damage to survivors has not. UK data from a large randomized feeding trial of neonates (2013–2015).[4] Rates, changes, related features, causative organisms, and antibiotic use must all be understood precisely if we are to reduce the prevalence of newborn infection. The methods we use now, such as observational studies, surveillance mechanisms, and interventional research, are difficult and not standardized.[4,5]

Colistin belongs to the class of polypeptide antibiotics. This drug can be divided into 2 types, namely colistimethate sodium and colistin sulphate. Colistin sulphate is available as oral or inhaled tablets and colistemethate sodium is available as injections or inhaled.[6] Intravenous (IV) colistin has been studied for its safety and effectiveness in burn units, intensive care units, and cancer centers, as well as on people who don't have cystic fibrosis. A few new studies have shown that giving IV colistin to children and babies works and is safe.[7,8]

Due to the use of other drugs along with colistin and the presence of other health conditions, we still don't know much about how safe and effective colistin is. We give some current and research-stage methods to clarify this topic.[7–10] This article proved the efficacy and safety of using colistin in neonates.

METHODS

The methodology of this systematic review was based on the criteria established by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist. The purpose of this systematic review was to assess the efficacy and safety of using colistin in neonates. The subject matter being examined is the focus of the studies under evaluation. To effectively evaluate existing studies, it is important that these studies meet certain criteria, including: 1) It is important that articles are available online for easy accessibility; 2) It is preferred that articles are written in English; and 3) The systematic review will only consider articles published between 2015 and the present time.

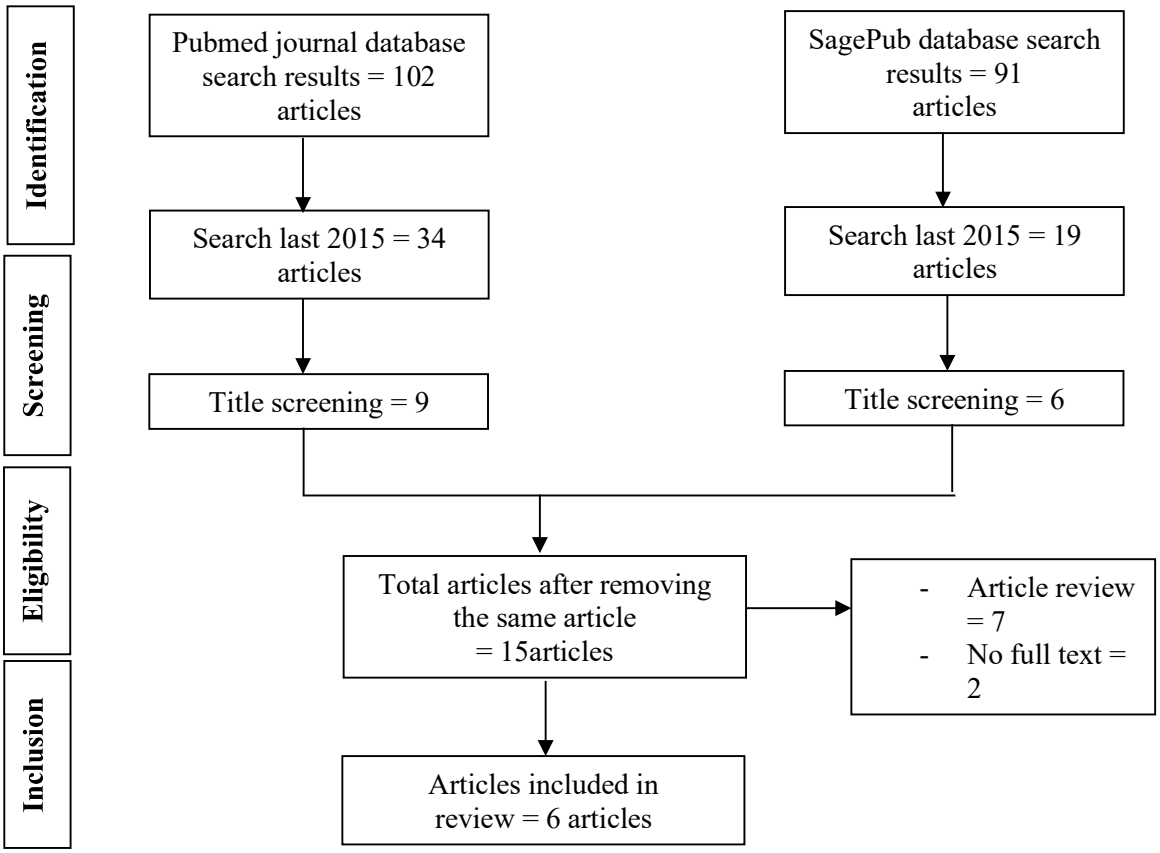

Figure 1. Article search flowchart

The search for studies to be included in the systematic review was carried out from May 4th, 2023 using the PubMed and SagePub databases by inputting the words: “efficacy”, “safety”, “colistin” and “neonates”. Where *("efficacies"[All Fields] OR "efficacious"[All Fields] OR "efficaciously"[All Fields] OR "efficaciousness"[All Fields] OR "efficacy"[All Fields]) AND ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields]) AND ("colistin"[MeSH Terms] OR "colistin"[All Fields] OR "colistine"[All Fields] OR "colistins"[All Fields]) AND ("infant, newborn"[MeSH Terms] OR*

("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields] OR "neonate"[All Fields] OR "neonates"[All Fields] OR "neonatality"[All Fields] OR "neonatals"[All Fields] OR "neonate s"[All Fields]) is used as search keywords.

The study's inclusion and exclusion criteria were revised following a thorough review of the literature based on an inspection of the titles and abstracts of previously published research. Only research projects that met all of the requirements were included in the systematic review. The title, author, publication date, country of origin, research design, and variables being researched are just a few of the crucial factors to consider when comparing one research study to another.

The offered content has been presented in a specific format for your attention and critical evaluation. The writers conducted independent appraisals of a selection of research endeavors stated in the titles and abstracts of the publications to determine whether the investigations were eligible for inclusion. The full texts of the studies that meet the criteria for inclusion in the systematic review will then be assessed to determine which publications are eligible for categorical inclusion in the review.

RESULT

Serafettin, et al (2015)[11] showed clinical and microbiological response of patients to the drug and its adverse effects were evaluated. Included were twelve newborn neonates with a mean gestational age of 31.8 3.5 weeks and a mean birth weight of 1482 (810-3200) grams. 11 of 12 (91.7%) patients who received intravenous colistin demonstrated microbiological clearance. One patient with recurring cerebrospinal fluid culture positivity was administered intraventricular colistin. Hyponatremia and hypokalemia were the main adverse effects observed in 2 (16.6%) patients; all infants required magnesium supplementation.

All of Ilhan, et al (2018)[12] patients received standard colistin treatment of 5 mg/kg per day in three doses and the median duration of colistin treatment was 14 days. Regarding the efficacy of colistin (defined as microbiological clearance in control cultures and the absence of mortality during treatment), there were no significant differences between groups (89.3 vs 86.8%, p >0.99). Serum magnesium and potassium levels were significantly lower in the VLBW group than in the non-VLBW group during colistin therapy (magnesium, 1.30 vs 1.70 mg/dL, $p < 0.001$; potassium, 3.6 vs 4.6 mEq/L, $p < 0.001$). Acute kidney injury was observed in four infants in the VLBW group and one in the non-VLBW group, without significant differences ($p = 0.15$).

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Serafettin, 2015[11]	Turkey	Retrospective study	12 patients	There is evidence that administering colistin intravenously to neonates, particularly preterm infants, for the treatment of multidrug-resistant gram-negative infections is both safe and effective. However, we are of the opinion that extensive prospective controlled studies on neonates are required in order to verify both its efficacy and its safety.
Ilhan, 2018[12]	Turkey	Retrospective study	1,260 patients	Colistin administration appears to be successful in VLBW newborns; nevertheless, renal function tests and blood electrolytes should be monitored more closely in these infants during treatment.
Mountasser, 2021[13]	Kingdom of Saudi Arabia	Retrospective study	42 patients	It was discovered that newborns treated with fluoroquinolone had a greater microbiological clearance than those infants treated with colistin. During the course of treatment, kidney and liver function tests, in addition to electrolyte levels, demonstrated a discernible rise in both of the groups' median values. Only in circumstances in which there are no other options available that are both safe and effective should colistin and fluoroquinolones be prescribed to patients.
Zumrut, 2018	Turkey	Retrospective study	104 patients	In children who are severely ill, the antibiotic colistin may be useful in the treatment of infections caused by Gram-negative bacteria that are resistant to many drugs. However, patients need to be monitored for any signs of adverse effects throughout the entirety of their colistin treatment, not only during the initial phase. In addition, medical professionals need to be aware of the rise in the incidence of nephrotoxicity in patients who are being treated with many nephrotoxic medications at the same time.
Cagan, 2017[14]	Turkey	Retrospective study	65 patients	Colistin was discovered to be an efficient and safe treatment for MDR-GNB infections in preterm newborns and infants whose birth weight was very low. The adverse effects of the colistin were manageable at the levels that were observed given the severity of the infection.
Jasani, 2016	India	Retrospective study	62 patients	The treatment of neonatal sepsis with intravenous colistin was shown to be both safe and efficacious in this retrospective study including neonates who were suffering from sepsis. To validate these findings, additional prospective clinical tests that are carefully controlled are need to be carried out.

Colistin- and fluoroquinolone-treated infants had 17 and 34 positive cultures for GN organisms, respectively. The cultures of thirty-four patients who received fluoroquinolone were positive. The majority of patients presented with sepsis as VAP, and six infants had positive cultures from multiple sites. In the colistin group, however, the organisms were predominantly isolated from blood, with two infants having positive cultures from multiple sites. The change between the beginning and end of treatment for creatinine and urea in both groups was insignificant; however, the change between the beginning and end of treatment for ALT and AST in the colistin group was statistically significant.[13]

Zumrut, et al (2018)[15] showed 11 (10.5%) patients experienced nephrotoxicity. 63% of colistin-induced nephrotoxicity occurred during days 3-7. In the subgroup analysis of patients who developed nephrotoxicity during colistin treatment versus those who did not, P values were 0.615, 0.762, 0.621, and 0.803, respectively. All patients received concomitant nephrotoxic agents (P = 0,355). The majority of treatment failure patients (52%) had main or secondary immunological insufficiency, and sepsis was the most common reason of intensive care admission (P = 0.007 and 0.045). Colistin failure caused 14.4% and crude mortality 29.8%.

Cagan, et al (2017)[14] conducted a study with 65 patients, 18 of whom were full-term and 47 of whom were preterm. Klebsiella pneumoniae and Acinetobacter baumannii were the most frequently isolated pathogens, followed by Pseudomonas aeruginosa and Enterobacter cloacae. The mean duration of colistin treatment was 153.5 days. All colistin-treated patients were also receiving at least one other antibiotic. While 51 (72.3%) patients attained a complete clinical response, 14 (21.5%) patients died during treatment. Four (7.7%) patients perished due to an additional infection. Three patients developed renal toxicity, three patients experienced seizures, and three patients exhibited apnea.

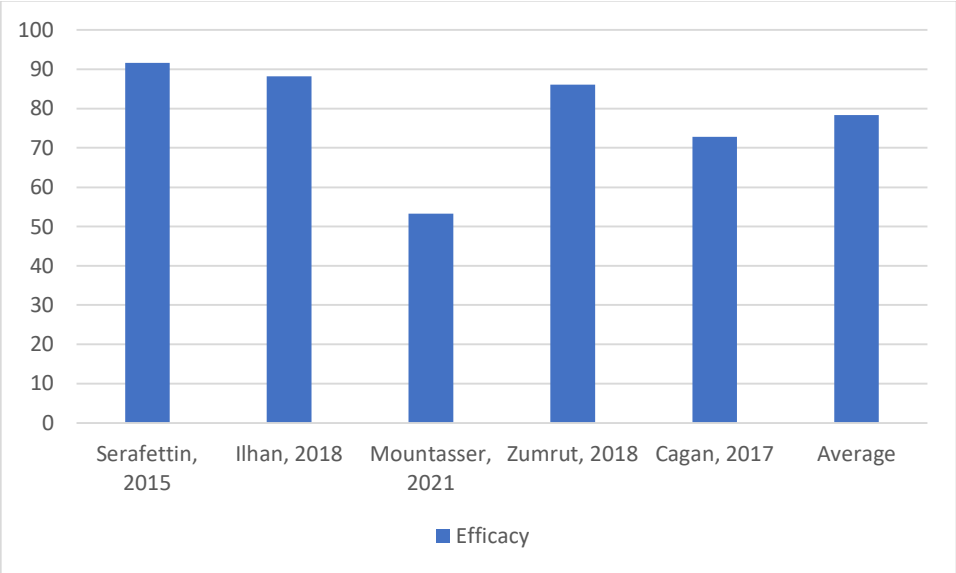

Figure 2. Overview of drug efficacy

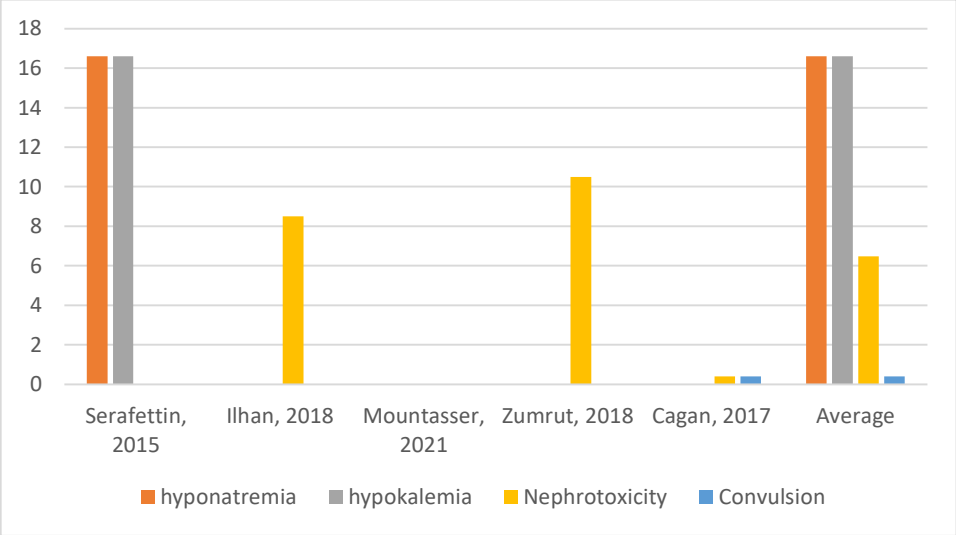

Figure 3. Overview of drug side effect

Jasani, et al (2016)[16] conducted a study with sixty two neonates. The isolated pathogens in decreasing order of frequency were *Acinetobacter baumannii*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*. Of the total 62 neonates, 41 (66.12%) survived and 21 (33.87%) died. Significantly higher mortality was observed in neonates with lower body weights

(P < 0.05). A significant association of mortality was found in those with sepsis due to *Klebsiella species*. Only one of seven with this infection survived as against 15 of the 23 who grew other organisms [P = 0.03; crude odds ratio = 11.25 (1.2, 110.5)]. None of the neonates developed neurotoxicity or nephrotoxicity.

DISCUSSION

Colistin is a cationic polypeptide antibiotic belonging to the polymyxin family, that kills bacteria by disrupting cellular functions.[17] The majority of Gram-negative aerobic bacilli are susceptible to the bactericidal effects of colistin. It wasn't until the 1950s that it was initially used in the United States, but by the 1980s intravenous versions had been discontinued because of their nephrotoxicity. However, due to an increase in the number of infections caused by carbapenem-resistant Gram-negative (CRGN) and a lack of newly developed antimicrobial medicines that are active against multidrug-resistant Gram-negative germs, colistin has been brought back into question.[18]

The safe intravenous colistin dose in newborns and preterm infants is unknown. However, recent multicenter studies show that doses of 2.5 - 5 mg/kg/day and 5.4 ± 0.6 mg/kg/day are safe in the juvenile age group.[19,20] In newborns and premature infants, Jajoo et al.[8] used 50,000-75,000 IU/kg/day (1 mg colistimethate sodium = 12,500 IU), while Alan et al.[9] used 2.5-5 mg/kg/day. All patients in the current study received intravenous colistin at a dose of 5 mg/kg/day. According to the 2004 guidelines of the Infectious Diseases Society of America, intraventricular colistin was delivered in a single dose of 10 mg/day.[21]

Nephrotoxicity is the most common adverse effect that can be caused by receiving colistin intravenously. Recent research indicates that the risk of developing impaired kidney function as a result of receiving intravenous colistin treatment ranges anywhere from 7.5-18.6% of the time. However, it is important to keep in mind that treatment with intravenous colistin, just like treatment with other nephrotoxic medications, can result in situations such as infection, septic shock, and the failure of numerous organs.[8,18]

As a result, it is challenging to estimate the rates of nephrotoxicity that are caused by the intravenous administration of colistin alone.[8,18] Through receiving supportive care, these individuals saw an improvement in their electrolyte imbalance. Every patient who had intravenous colistin had at least one magnesium ion replacement procedure performed on them.[11] Cakir et al. reported that a preterm newborn had hypokalemia, hypocalcemia, hypomagnesemia, and metabolic alkalosis after receiving intravenous colistin treatment; this clinical condition was similar to Bartter-like syndrome.[22]

CONCLUSION

The efficacy of colistin in neonates ranges from 50-98%. The side effect that was found in this study was hyponatremia.

REFERENCES

[1]. Lawn JE, Blencowe H, Kinney M V, Bianchi F, Graham WJ. Evidence to inform the future for maternal and newborn health. Best Pract Res Clin Obstet Gynaecol. 2016;36:169–83.
[2]. Gomella T, Cuningham M, Eyal F. Neonatology: Management, procedure, On-Call Problems, Disease, and Drug. New York: McGraw-Hill Education; 2020.
[3]. Way C. The Millennium Development Goals Report. New York, United Nations: 2015.
[4]. Oza S, Lawn JE, Hogan DR, Mathers C, Cousens SN. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000–2013. Bull World Health Organ. 2014;93:19–28.
[5]. Samir S; Shams A; Stephanie S; et al. Aetiology of Neonatal Infection in South Asia (ANISA): An Initiative to Identify Appropriate Program Priorities to Save Newborns. Pediatr Infect Dis J. 2016;35-(5):6–8.
[6]. Iosifidis E, Antachopoulos C, Ioannidou M, Mitroudi M, Sdougka M, Drossou-Agakidou V, et al. Colistin administration to pediatric and neonatal patients. Eur J Pediatr. 2010;169:867–74.
[7]. Falagas ME, Vouloumanou EK, Rafailidis PI. Systemic colistin use in children without cystic fibrosis: a systematic review of the literature. Int J Antimicrob Agents. 2009;33(6):503-e1.
[8]. Jajoo M, Kumar V, Jain M, Kumari S, Manchanda V. Intravenous colistin administration in neonates. Pediatr Infect Dis J. 2011;30(3):218–21.
[9]. Alan S, Yildiz D, Erdeve O, Cakir U, Kahvecioglu D, Okulu E, et al. Efficacy and safety of intravenous colistin in preterm infants with nosocomial sepsis caused by Acinetobacter baumannii. Am J Perinatol. 2014;31(12):1079–86.
[10]. 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;15:1–4.
[11]. Serafettin Tekgunduz K, Kara M, Caner I, Demirelli Y. Safety and Efficacy of Intravenous Colistin in Neonates With Culture Proven Sepsis. Iran J Pediatr. 2015 Aug;25(4):e453.
[12]. Ilhan O, Bor M, Ozdemir SA, Akbay S, Ozer EA. Efficacy and Safety of Intravenous Colistin in Very Low Birth Weight Preterm Infants. Pediatr Drugs [Internet]. 2018;20(5):475–81. Available from: https://doi.org/10.1007/s40272-018-0301-5
[13]. Al-Mouqdad M, Eljaaly K, Abdalgader A, Al-Anazi M, Taha M, Alshaibani A, et al. Safety and efficacy of colistin and fluoroquinolone in neonatal persistent late-onset sepsis. Saudi Pharm J [Internet]. 2021;29(9):1013–20. Available from: https://www.sciencedirect.com/science/article/pii/S1319016421001419
[14]. Çağan E, Baş EK, Asker HS. Use of colistin in a neonatal intensive care unit: a cohort study of 65 patients. Med Sci Monit Int Med J Exp Clin Res. 2017;23:548.

[15]. Sahbudak Bal Z, Kamit Can F, Yazici P, Berna Anil A, Duyu M, Yilmaz Ciftdogan D, et al. The evaluation of safety and efficacy of colistin use in pediatric intensive care unit: Results from two reference hospitals and review of literature. J Infect Chemother [Internet]. 2018;24(5):370–5. Available from: https://www.sciencedirect.com/science/article/pii/S1341321X17303185
[16]. Jasani B, Kannan S, Nanavati R, Gogtay NJ, Thatte U. An audit of colistin use in neonatal sepsis from a tertiary care centre of a resource-limited country. Indian J Med Res [Internet]. 2016;144(3). Available from: https://journals.lww.com/ijmr/Fulltext/2016/44030/An_audit_of_colistin_use_in_neonatal_sepsis_from_a.17.aspx
[17]. Karbuz A, Özdemir H, Yaman A, Kocabaş BA, Odek Ç, Güriz H, et al. The use of colistin in critically ill children in a pediatric intensive care unit. Pediatr Infect Dis J. 2014 Jan;33(1):e19-24.
[18]. Nation RL, Li J. Colistin in the 21st century. Curr Opin Infect Dis. 2009 Dec;22(6):535–43.
[19]. Tamma PD, Newland JG, Pannaraj PS, Metjian TA, Banerjee R, Gerber JS, et al. The use of intravenous colistin among children in the United States: results from a multicenter, case series. Pediatr Infect Dis J. 2013 Jan;32(1):17–22.
[20]. Paksu MS, Paksu S, Karadag A, Sensoy G, Asilioglu N, Yildizdas D, et al. Old agent, new experience: colistin use in the paediatric Intensive Care Unit--a multicentre study. Int J Antimicrob Agents. 2012 Aug;40(2):140–4.
[21]. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis an Off Publ Infect Dis Soc Am. 2004 Nov;39(9):1267–84.
[22]. Cakir U, Alan S, Zeybek C, Erdeve O, Atasay B, Yalcinkaya F, et al. Acquired bartter-like syndrome associated with colistin use in a preterm infant. Ren Fail. 2013;35(3):411–3.