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Editorial

Exploring New Predictors of Colistin-Associated Nephrotoxicity

Eun Jung Kim [1] **and Eu Suk Kim** [2,3]

[1]Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, Korea
[2]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

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Corresponding Author:
Eu Suk Kim, MD
Division of Infectious Diseases, Department of Internal Medicine, Seoul National University Bungdang Hospital, 82 Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam 13620, Gyeonggi-do, Korea.
Tel: +82-31-787-7062
Fax: +82-31-787-4052
E-mail: eskim@snubh.org

ORCID iDs
Eun Jung Kim
https://orcid.org/0000-0003-3302-7827
Eu Suk Kim
https://orcid.org/0000-0001-7132-0157

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Colistin is a polymyxin-class antimicrobial agent. Polymyxins were first produced in 1947 but were replaced with different therapeutic agents because of the emergence of nephrotoxic side effects. Extensively drug-resistant Gram-negative bacteria (XDR-GNB) are now a major public health crisis worldwide. Colistin is a re-emerging agent of last resort to treat infections caused by XDR-GNB. However, colistin-associated nephrotoxicity is the main safety concern. Previous studies have estimated the cumulative incidence of acute kidney injury (AKI) among patients receiving colistin to be between 12 and 48% [1].

Colistin-associated nephrotoxicity occasionally develops rapidly. AKI was reported within the first 5 days of treatment [2], and the majority of toxicity also developed within the first week of treatment [3]. AKI was reported in 54.6% of patients receiving colistin, with approximately 70% incidence within 7 days of treatment and the rest after 7 days. Patients with AKI within 7 days had a higher mortality rate than those with AKI after 7 days [4]. In a prospective study in patients receiving 3–9 million units/day colistin methanesulfonate, the prevalence of AKI was 25.5% and 49% at day 7 and the end of treatment (EOT) day, respectively. At day 7, the only independent predictor of AKI was the minimum concentration (C_{min}) of drug with a breakpoint of 3.33 mg/L. At EOT day, independent risk factors for AKI were the Charlson score, C_{min} at the breakpoint of 2.42 mg/L, and co-administration of ≥2 nephrotoxic drugs [5]. In a case–control study, after adjustment for age, sex, hypoalbuminemia, site of infection, concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and cumulative dose of aminoglycosides, hypoalbuminemia, and concomitant use of NSAIDs were independent risk factors for nephrotoxicity [6]. Consequently, risk factors for colistin-associated nephrotoxicity can be categorized by dose and duration of colistin therapy, coadministration of other nephrotoxic drugs, and patient-related factors such as age, sex, hypoalbuminemia, hyperbilirubinemia, underlying diseases, and severity of the disease [7].

Clinical assessment of nephrotoxicity is variable, and there is no gold standard in classifying AKI severity. There is insufficient data on the biomarker for detection of colistin-associated nephrotoxicity. In studies on colistin-associated nephrotoxicity, serum creatinine and risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria have been commonly used for detection of nephrotoxicity. However, using serum creatinine level for estimation of glomerular filtration rate has some limitations, such as its dependence on

sex, age, nutrition, and body mass. Neutrophil gelatinase-associated lipocalin (NGAL) is a protein of the lipocalin family, and its expression is detected predominantly in proliferating cell nuclear antigen-positive proximal tubule cells. Urine NGAL was used in a recent study for early detection of AKI during colistin treatment of urinary tract infection (UTI) [8]. There was no significant increase in urinary NGAL in either acute tubular necrosis (ATN) or non-ATN groups of patients. The limitation of the findings with regard to the predictive value of urinary NGAL is probably due to the strong influence of UTI itself on NGAL levels in patients with or without kidney diseases. In contrast, Park et al. suggested a possible role of plasma NGAL in predicting nephrotoxicity in patients receiving intravenous colistin. The study showed that nephrotoxicity in patients receiving colistin can be predicted earlier with plasma NGAL level than with serum creatinine level and reported the operating characteristics for the NGAL cutoff [9]. These findings were considered a basis for the investigation of biomarkers for nephrotoxicity even though further studies are required to establish the optimal cutoff to be used in clinical practice. Moreover, cystatin C and kidney injury molecule 1 (Kim-1) are possible biomarkers for prediction of AKI. Cystatin C is a cysteine protease inhibitor that is synthesized by all nucleated cells and freely filtered by the glomerulus, reabsorbed completely in the proximal tubules, and not secreted. Kim-1 is a phosphatidylserine receptor that is expressed in normal proximal tubular epithelial cells, and urinary Kim-1 has been reported to be specific to proximal tubular damage. Keirstead et al. evaluated the changes in plasma cystatin C and Kim-1 as biomarkers for prediction of nephrotoxicity in the animal model of colistin-associated nephrotoxicity [10]. Further trials for comparison of new generations of biomarkers to detect colistin-associated nephrotoxicity are needed.

Therefore, colistin has re-emerged as a preferred treatment option with the increasing number of XDR-GNB recently. Nephrotoxicity is the main adverse effect of this drug, especially with the newly recommended high-dose regimen. New generations of biomarkers to detect colistin-associated nephrotoxicity should be explored for effective colistin therapy without nephrotoxicity.

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