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ORIGINAL RESEARCH ARTICLE

Comparing Acute Kidney Injury Reports Among Antibiotics: A Pharmacovigilance Study of the FDA Adverse Event Reporting System (FAERS)

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Abstract

Background A study using the US FDA Adverse Event Reporting System (FAERS) found significant acute kidney injury (AKI) reporting associations with vancomycin, fluoroquinolones, penicillin combinations, and trimethoprim–sulfamethoxazole. Other antibiotics may also lead to AKI, but no study has systemically compared AKI reporting associations for many available antibiotics.

Objective The objective of this study was to evaluate the reporting associations between AKI and many available antibiotics using FAERS.

Methods FAERS reports from 1 January 2015 to 31 December 2017 were included in the study. The Medical Dictionary for Regulatory Activities (MedDRA) was used to identify AKI cases. Reporting odds ratios (RORs) and corresponding 95% confidence intervals (CIs) for the reporting associations between antibiotics and AKI were calculated. A reporting association was considered statistically significant when the lower limit of the 95% CI was > 1.0.

Results A total of 2,042,801 reports (including 20,138 AKI reports) were considered. Colistin had the greatest proportion of AKI reports, representing 25% of all colistin reports. AKI RORs (95% CI) for antibiotics were, in descending order: colistin 33.10 (21.24–51.56), aminoglycosides 17.41 (14.49–20.90), vancomycin 15.28 (13.82–16.90), trimethoprim–sulfamethoxazole 13.72 (11.94–15.76), penicillin combinations 7.95 (7.09–8.91), clindamycin 6.46 (5.18–8.04), cephalosporins 6.07 (5.23–7.05), daptomycin 6.07 (4.61–7.99), macrolides 3.60 (3.04–4.26), linezolid 3.48 (2.54–4.77), carbapenems 3.31 (2.58–4.25), metronidazole 2.55 (1.94–3.36), tetracyclines 1.73 (1.26–2.36), and fluoroquinolones 1.71 (1.49–1.97).

Conclusion This study found 14 classes of antibiotics having significant reporting associations with AKI. Among the antibiotics evaluated in this study, colistin had the highest AKI ROR and moxifloxacin had the lowest.

Key Points

1. This study found 14 classes of antibiotics with statistically significant acute kidney injury (AKI) reporting odds ratios (RORs).
2. Among the antibiotics evaluated in this study, colistin had the highest AKI RORs and moxifloxacin had the lowest.

1 Introduction

Acute kidney injury (AKI) is defined as the rapid decrease in the kidney's excretory function, with the retention of nitrogenous (urea and creatinine) and non-nitrogenous waste products [1]. AKI occurs in about 20% of hospitalized patients and more than half of critically ill patients [2, 3]. Following

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AKI, patients face a greater risk of chronic kidney disease, dialysis dependence, and higher mortality [4, 5].

Medications are one of the leading contributors to AKI among hospitalized patients [6]. Among these medications, antibiotics are known to be associated with AKI. Common antibiotic classes associated with AKI include colistin, aminoglycosides, β-lactams, and vancomycin [7].

Drug–drug interactions leading to AKI are a great concern with antibiotic therapy [8]. A meta-analysis demonstrated that vancomycin plus piperacillin–tazobactam combination therapy had higher odds of AKI than vancomycin monotherapy, piperacillin–tazobactam monotherapy, and vancomycin plus cefepime or carbapenem combination therapy [8].

A previous study using the FDA Adverse Event Reporting System (FAERS) demonstrated that vancomycin, trimethoprim–sulfamethoxazole, piperacillin–tazobactam, and ciprofloxacin had significant reporting associations with AKI [9]; however, the study did not mention less commonly used colistin or aminoglycosides as being associated with AKI. Due to the rise in infections caused by multidrug resistance (MDR) bacteria, prescribing of these nephrotoxic antibiotics have increased [10]. A retrospective study conducted in Spain reported on the increased use of colistin in the treatment of MDR gram-negative bacteria infections, specifically *Acinetobacter baumannii* [11]. Currently, colistin is being used to treat pediatric and adult cystic fibrosis caused by resistant *Pseudomonas aeruginosa*, along with MDR gram-negative bacteria contributing to ventilator-associated pneumonia and bacteremia [12]. This poses a concern for clinicians when deciding the most appropriate and safe medication regimen for a patient who has not responded to other antibiotic therapy and is at risk for developing AKI.

To our knowledge, no studies using FAERS have specifically looked at antibiotics and compared their reporting associations with AKI. The objective of this study was to evaluate the reporting associations between AKI and many available antibiotics using FAERS.

2 Methods

2.1 Data Source

FAERS is a publicly available database, which is composed of adverse event reports submitted to the US FDA by healthcare professionals, consumers, and manufacturers [13]. FAERS data contain drug information (drug name, active ingredient, route of administration, the drug's reported role in the event) and reaction information. Each report has a primary suspected drug with one or more adverse drug reactions (ADR) and may include other drugs taken by the patient. The Institutional Review Board (IRB) of The University of Texas Health Science Center at San Antonio determined that this study did not require IRB approval because FAERS is a publicly available database (IRB number: HSC20190309N).

2.2 Study Design

FAERS data from 1 January 2015 to 31 December 2017 were included in this study. We chose more recent data because AKI epidemiology is constantly changing. Some reports were submitted to the FDA multiple times with updated information. Therefore, duplicate reports were removed by case number, with only the most recently submitted version included in the study. Reports containing drugs that were administered in oral, intramuscular, subcutaneous, intravenous, and parenteral routes were included in this study, while other routes of administration were excluded.

2.3 Drug Exposure Definition

The antibiotic list was derived from the Drugs@FDA Database [14–17]. Each antibiotic was identified in FAERS by generic and brand names listed in the Drugs@FDA Database [14–17]. Drugs with a reported role coded as 'PS' (Primary Suspect Drug) or 'SS' (Secondary Suspect Drug) were evaluated for inclusion [18]. Antibiotics with less than three AKI ADR reports were excluded from the data analysis [19].

2.4 Adverse Drug Reaction Definition

FAERS defines ADRs using Preferred Terms (PT) from the Medical Dictionary for Regulatory Activities (MedDRA) [20]. We only used the MedDRA Preferred Term 'Acute kidney injury" to identify AKI cases. Other terms, such as 'Kidney dysfunction', were not used because these terms do not guarantee AKI (a patient with kidney dysfunction may have chronic kidney disease but no AKI).

2.5 Statistical Analysis

A disproportionality analysis was conducted by computing reporting odds ratios (ROR) and corresponding 95% confidence intervals (CIs) for the reporting association between AKI and each antibiotic class or individual antibiotic [21]. The ROR was calculated as the odds that a report listed AKI versus did not list AKI for a given drug compared with the same odds for all reports not mentioning the given drug [21]. The remaining antibiotics were in the denominator for

each ROR calculation. A reporting association was considered to be statistically significant if the lower limit of the 95% CI was above 1.0 [21]. A higher ROR suggested a stronger reporting association between the antibiotic and AKI. Data analysis was performed using Microsoft Access 2016, Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA), and JMP Pro 13.2.1 (SAS Institute, Cary, NC, USA).

3 Results

A total of 2,042,801 reports (including 20,138 AKI reports) were considered, after the inclusion criteria were applied. Colistin had the greatest proportion of AKI reports, representing 25% of all colistin reports. AKI RORs (95% CI) for antibiotics were, in descending order: colistin 33.10 (21.24–51.56), aminoglycosides 17.41 (14.49–20.90), vancomycin 15.28 (13.82–16.90), trimethoprim–sulfamethoxazole 13.72 (11.94–15.76), penicillin combinations 7.95 (7.09–8.91), clindamycin 6.46 (5.18–8.04), cephalosporins 6.07 (5.23–7.05), daptomycin 6.07 (4.61–7.99), macrolides 3.60 (3.04–4.26), linezolid 3.48 (2.54–4.77), carbapenems 3.31 (2.58–4.25), metronidazole 2.55 (1.94–3.36), tetracyclines 1.73 (1.26–2.36), and fluoroquinolones 1.71 (1.49–1.97) (Fig. 1). AKI RORs (95% CI) for vancomycin combinations were, in descending order: vancomycin plus cefepime 24.31 (15.26–38.73), vancomycin plus piperacillin–tazobactam 22.20 (17.25–28.56), and vancomycin plus carbapenem 2.04 (0.91–4.59) (Fig. 2).

A total of 1,973,885 reports listed reporters' occupations, i.e. consumers (927,743 reports, 47%), physicians (466,932 reports, 24%), pharmacists (176,138 reports, 9%), other health professionals (388,719, 20%), and lawyers (14,353 reports, 1%), and a total of 19,420 AKI reports listed reporters' occupations, i.e. consumers (4767 reports, 25%), physicians (6244 reports, 32%), pharmacists (2274 reports, 12%), other health professionals (5927 reports, 31%), and lawyers (208 reports, 1%).

4 Discussion

This study identified 14 antibiotic classes having significant reporting associations with AKI in FAERS (Fig. 1). Of the macrolides and fluoroquinolones, only azithromycin and moxifloxacin did not have significant reporting associations with AKI. Levofloxacin was found to have an ROR and its 95% CI of < 1, indicating that the odds of reporting levofloxacin with AKI in FAERS was significantly less than that of other drugs.

The mechanisms to explain how certain antibiotics can cause AKI are not fully established. Colistin-induced kidney injury is thought to be primarily caused by damage to proximal tubule cells, which ultimately lead to apoptosis in the nephron [22]. High doses of vancomycin that result in an increased plasma trough concentration and extended duration are risk factors for causing nephrotoxicity. Experimental studies describe the mechanism of vancomycin-induced kidney injury as increased production of free oxygen radicals, which leads to mitochondrial dysfunction and, eventually, cellular apoptosis [23]. Aminoglycosides are preferentially taken up by proximal tubular epithelial cells, and alter phospholipid metabolism, which leads to necrosis. Aminoglycosides also cause renal vasoconstriction, which can contribute to AKI [24]. The rank order of AKI reporting association is consistent with the clinical pharmacology of these agents.

This study indicated that colistin had the highest ROR among antibiotics associated with AKI, followed by aminoglycosides, vancomycin, and trimethoprim–sulfamethoxazole. Consistent with a recently published article that analyzed AKI reports and associated medications in FAERS, vancomycin, piperacillin–tazobactam, aminoglycosides, and trimethoprim–sulfamethoxazole had some of the highest AKI RORs among the antibiotics evaluated in this study [9]. However, there are differences identified in this study that are significant to address. In contrast to the study by Welch et al., this study compared the ROR for each drug's reports of AKI, while the previous article compared the total number of AKI reports [9]. According to the previous article's methodology, only the antibiotics with the highest number of AKI reports were considered, and rarely utilized antibiotics would not be considered, such as colistin. Colistin was excluded from the previously published study, which may project a harmful message that it is not commonly reported with AKI [9].

A retrospective analysis of 50 patients and a case report demonstrated clindamycin-induced AKI [25, 26]. A case–control study found an increased risk of AKI associated with the use of fluoroquinolones [27]. Our study was able to confirm these findings, as well as rank the antibiotics by their ROR for AKI reports in FAERS.

This study also looked at the significance of drug–drug interactions reported with AKI. Consistent with previous literature, this study found that higher odds of AKI were reported when vancomycin plus piperacillin–tazobactam combination therapy was administered compared with vancomycin monotherapy and piperacillin–tazobactam monotherapy [8]. Luther et al. assessed vancomycin plus cefepime or carbapenem combination therapy as a whole, but did not assess vancomycin plus cefepime combination therapy and vancomycin plus carbapenem combination therapy individually [8]. In our study, vancomycin plus cefepime combination therapy and vancomycin plus carbapenem combination therapy were assessed individually. AKI RORs for the vancomycin plus cefepime

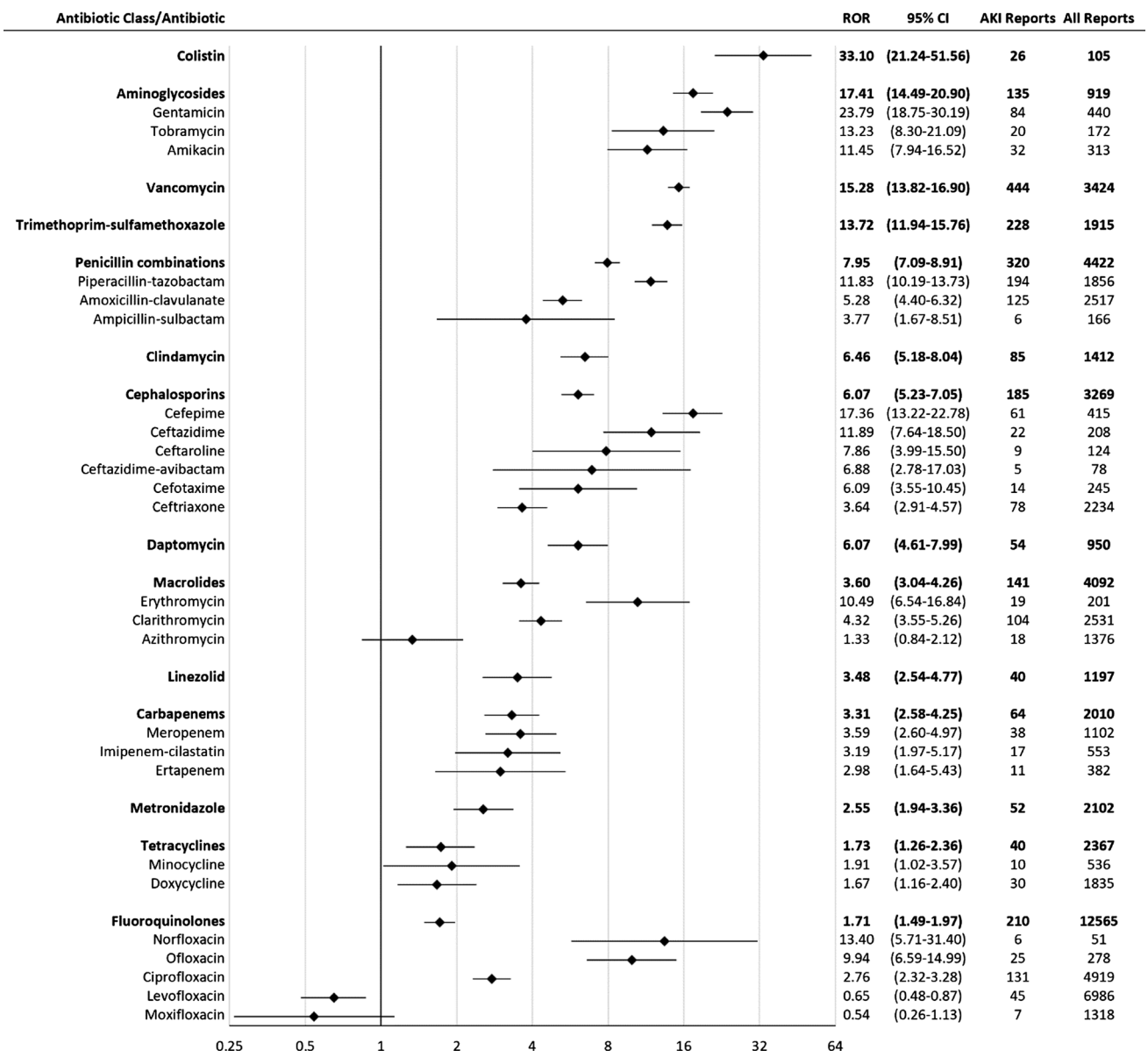

Fig. 1 RORs for AKI with antibiotics. A total of 2,042,801 reports (including 20,138 AKI reports) were included in the study. This is an example demonstrating how to calculate RORs: AKI RORs for colistin = [26/(105 − 26)/((20,138 − 26)/(2,042,801 − 20,138 − (105 − 26)))] = 33.10. *ROR* reporting odds ratio, *AKI* acute kidney injury, *CI* confidence interval

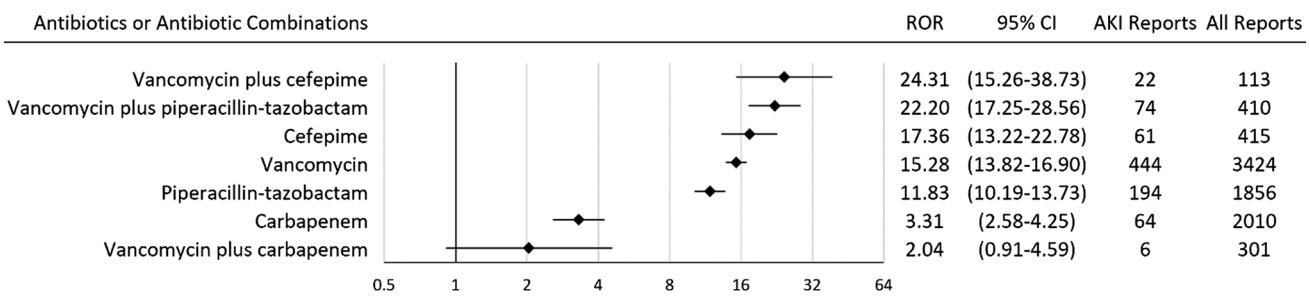

Fig. 2 RORs for AKI with vancomycin combinations. A total of 2,042,801 reports (including 20,138 AKI reports) were included in the study. This is an example demonstrating how to calculate RORs: AKI RORs for vancomycin plus cefepime = [22/(113 − 22)/(20,138 − 22)/((2,042,801 − 20,138 − (113 − 22)))] = 24.31. *RORs* reporting odds ratios, *AKI* acute kidney injury, *CI* confidence interval

combination was slightly higher than that for the vancomycin plus piperacillin–tazobactam combination. AKI RORs for the vancomycin plus carbapenem combination was the lowest. This finding is important because vancomycin plus piperacillin–tazobactam and vancomycin plus cefepime are common empiric antibiotic combinations used in hospitals to help treat severe infections. The mechanism of high AKI RORs of the vancomycin plus cefepime combination is unknown. The lower AKI ROR of the vancomycin plus carbapenem combination might be due to the nephroprotective effects of cilastatin, which is an inhibitor of dehydropeptidase and is included in the imipenem formulation [28]. Antimicrobial stewards should pay attention to the AKI reporting association differences among different vancomycin combinations.

This study was able to compare classes of antibiotics, rank individual antibiotics by their ROR, and confirm that combination antibiotic therapy increased the odds of a patient experiencing AKI. These findings have important implications for antimicrobial stewardship. Therapeutic interchanges could be identified, especially for those patients who have a high baseline risk for AKI (e.g. elderly and patients with chronic kidney disease). For example, to treat non-severe purulent skin and skin structure infections in patients with a high risk of AKI, clindamycin could be preferred to trimethoprim–sulfamethoxazole, considering the much lower AKI ROR of clindamycin.

4.1 Limitations

A causal relationship between a drug and an ADR cannot be established by FAERS. Significant bias may occur because of the spontaneous and voluntary reporting of ADRs. Media attention and recent publication of an ADR in the literature might affect reporting behaviors. The reporting association between a drug and an ADR is confounded by comorbid conditions and concomitant drugs. The definition of AKI is not provided in FAERS, and AKI, acute kidney disease, and chronic kidney disease might not be differentiated by the reporter. Only the primary and secondary suspect drugs were included in the data analysis. FAERS has missing information, such as the route of administration; if the route of administration was not reported, the report was not included in the data analysis. In spite of these limitations, FAERS has a large sample size and is suitable for discovering new and rare drug–ADR reporting associations and drug–drug interactions.

5 Conclusions

This study found 14 classes of antibiotics having significant reporting associations with AKI. Among the antibiotics evaluated in this study, colistin had the highest AKI ROR and moxifloxacin had the lowest. While this study confirmed previous literature of certain antibiotics associated with AKI, it also compared antibiotic classes and analyzed RORs for drug–drug interactions. Results obtained from FAERS should be interpreted with caution in the context of data limitations. Antibiotic stewardship is needed to prevent AKI and to improve health outcomes.

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Compliance with Ethical Standards

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Conflict of interest Taylor M. Patek, Chengwen Teng, Kaitlin E. Kennedy, Carlos A. Alvarez, and Christopher R. Frei have no conflicts of interest that are directly relevant to the content of this study.

Data Sharing Statement The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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