Risk Assessment for Anti-Infectives-Related Acute Kidney Injury Using the Japanese Adverse Drug Event Report Database

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Abstract

**Background:** Acute kidney injury (AKI) is associated with significant increases in short- and long-term morbidity and mortality. Drug-induced AKI is a major concern in the present healthcare system. Our spontaneous reporting system (SRS) analysis assessed links between AKIs, along with patients’ age, as healthcare-associated risks and administered anti-infectives. We also generated anti-infectives-related AKI-onset profiles.

**Method:** We calculated adjusted reporting odds ratios (RORs) for reports of anti-infectives-related AKIs (per Medical Dictionary for Regulatory Activities) in the Japanese Adverse Drug Event Report database and evaluated associations between anti-infectives and age by association rule mining. We evaluated time-to-onset data and hazard types using the Weibull parameter.

**Results:** Among 534,688 reports (submission period: April 2004–June 2018), there were 21,727 AKI events. Anti-infective treatments including glycopeptide antibacterials, fluoroquinolones, third-generation cephalosporins, triazole derivatives, and carbapenems were associated with 596, 494, 341, 315, and 313 AKI incidences, respectively. Adjusted RORs of anti-infectives-related AKIs increased among older patients and were higher in anti-infective combination therapies [anti-infectives, ≥ 2; ROR, 2.75 (2.56–2.95)] than in monotherapies [ROR, 1.52 (1.45–1.61)]. In association rule mining, the number of anti-infectives and age were associated with anti-infectives-related AKI lift values (as consequent). Moreover, 48.1% of AKIs occurred within 5 days (median, 5.0 days) of anti-infective therapy initiation.

**Conclusion:** Thus, adjusted RORs derived from our new SRS analysis indicate potential AKI risks linked to age and number of administered anti-infectives.

Background

Acute kidney injury (AKI) is associated with significant increases in short- and long-term morbidity and mortality [1] and occurs in approximately 1 – 5% of all patients treated at the hospital [2]. AKI is a sudden episode of kidney failure or kidney damage that happens within a few hours or a few days [1, 3]. Drug-induced AKI has been implicated in 8–60% of all cases of in-hospital AKI and as such is a recognized source of significant morbidity and mortality [4]. Thus, drug-induced AKI is a major concern in the present healthcare system. AKIs are pre-renal caused by cardiovascular disorders and hypovolemia, intra-renal caused by acute tubular necrosis and other parenchymal disorders, or post-renal caused by bladder obstruction and ureteral obstruction [2, 4, 5]. Several antibiotics including penicillin analogs, cephalosporins, and ciprofloxacin are known to increase the risk of intra-renal AKI [5], and other antibiotics such as aminoglycosides, amphotericin B, and vancomycin have been identified as the cause of adverse events (AEs) in AKI [4].

Spontaneous reporting systems (SRSs), such as the US Food and Drug Administration (FDA) adverse event reporting system (FAERS) and the Japanese Adverse Drug Event Report (JADER) database, have been used in pharmacovigilance assessments [6–9]. The reporting odds ratio (ROR) has been used to
derive an index for detecting drug-associated adverse events (AEs) [7, 8]. We previously analyzed an SRS database and found that the combination of medications might increase the risk of AEs according to the index derived from the RORs [10–12]. In this study, we evaluated the anti-infectives-related AKI profiles using ROR.

Older patients often suffer from multiple diseases and receive several drugs, which is referred to as polypharmacy [13–15]. Polypharmacy is a well-known risk factor for AEs. Altered liver and kidney functions are considered a cause for changes in the pharmacokinetics in elderly patients [16]. Polypharmacy and the incidence of AEs increase with advancing age. By evaluating the adjusted RORs using a multivariate logistic regression analysis technique, Abe et al. showed that polypharmacy and age might be more closely linked to an increased risk of kidney disorder than liver disorder [10]. Association rule mining in large databases is a new analytical approach for evaluating association rules between variables [11, 17]. Hatahira et al. applied this algorithm to assess the association rules among fall-related AEs, the number of administered drugs, and age in the JADER database [11]. Our study was focused on the association rules among anti-infectives-related AKI, the number of administered anti-infectives, and age. To our knowledge, time-to-onset profiles of anti-infectives-related AKI derived from SRS databases have been rarely reported. We evaluated the time-to-onset data of AKI relative to the anti-infective therapy initiation.

**Methods**

Ethical approval was not sought for this study because the study was an observational study without any research subjects. The JADER dataset can be downloaded from the website of the Pharmaceuticals and Medical Devices Agency (PMDA) (www.pmda.go.jp). The JADER database is publicly available. All data from the JADER database were fully anonymized by the PMDA before we used them. This study used a dataset containing information recorded between April 2004 and June 2018. The JADER database consists of four tables: 1) DEMO (patients’ demographic information); 2) DRUG (drug information); 3) REAC (AE information); and 4) HIST (primary disease information). We built a relational database system that integrates the four data tables using the FileMaker Pro 14 software (FileMaker, Santa Clara, CA, USA). In the DRUG table, the causality of each drug was assigned a code depending on its association with adverse drug reactions, such as “suspected drug,” “concomitant drug,” or “interacting drug.” All drugs in the “suspected drug,” “concomitant drug,” and “interacting drug” association classes were used for the analyses.

We used the terminology preferred by the Medical Dictionary for Regulatory Activities ver. 19.0/Japanese (MedDRA/J, www.pmrj.jp/jmo/php/indexj.php) to extract case reports of AKI-related AEs. The following preferred terms (PTs) were used: “acute kidney injury” (PT code: 10069339), “azotaemia” (PT code: 10003885), “renal failure” (PT code: 10038435), “renal impairment” (PT code: 10062237), “albuminuria” (PT code: 10001580), “blood creatinine abnormal” (PT code: 10005481), “blood creatinine increased” (PT code: 10005483), “blood urea abnormal” (PT code: 10005846), “blood urea increased” (PT code: 10005851), “creatinine renal clearance abnormal” (PT code: 10068447), “creatinine renal clearance
decreased” (PT code: 10011372), “glomerular filtration rate decreased” (PT code: 10018358), “hypercreatininaemia” (PT code: 10062747), “oedema due to renal disease” (PT code: 10049630), “protein urine present” (PT code: 10053123), “proteinuria” (PT code: 10037032), “renal function test abnormal” (PT code: 10061480), “renal tubular disorder” (PT code: 10038537), and “renal disorder” (PT code: 10038428).

To identify an AE signal, we calculated the crude RORs by comparing one of the index groups with the reference group. Each ROR was calculated from a two-by-two contingency table; it is the ratio of the odds of reporting AEs versus all other events associated with the drug of interest compared with the reporting odds for all other drugs present in the database. RORs were expressed as point estimates with 95% confidence intervals (CIs). A ROR estimate of less than 1 indicated the absence of a potential exposure-event relationship, but if it was more than 1, it indicated a potential exposure-event safety signal. The signal of a drug-event combination was positively identified when the lower limit of the 95% CI of the ROR exceeded 1. The positive identification of a signal required two or more cases [7, 18].

Using RORs allowed adjustments by multivariate logistic regression analysis and offered the advantage of controlling for covariates [6, 19–22]. We calculated the adjusted RORs according to previous reports [21, 22]. To calculate adjusted RORs, only reports containing reporting year, sex, age, and the number of administered anti-infectives were used. The following multivariate logistic model was used for analysis:

$$\text{Log (odds)} = \beta_0 + \beta_1 Y + \beta_2 S + \beta_3 A + \beta_4 N$$

where Y is the reporting year, S is the sex, A is the age-stratified group (≤ 19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, 80–89 years, and ≥ 90 years), and N is the number of administered anti-infectives. The adjusted RORs were calculated using two reference groups, the female, 20–29-year-old group and the zero anti-infective group. A Wald test can be used to evaluate the effect of adding a specific term. Because the difference in the −2 log-likelihoods follows a chi-square distribution with one degree of freedom, adding an interaction term was statistically significant (p < 0.05).

To comparatively evaluate the effect of variables, we selected explanatory variables using a stepwise method [23] at a significance level of 0.05 (forward and backward, Table 2). The contributions of selected variables in the final model were evaluated using the likelihood ratio test. A p ≤ 0.05 indicated statistical significance of the difference in the −2 log-likelihoods following a chi-square distribution with 1 degree of freedom. Chi-Square is the likelihood-ratio chi-square test of the hypothesis that all regression parameters are zero.

Association rule mining is focused on finding frequent co-occurring associations among a collection of items. Given a set of transactions T (each transaction is a set of items), an association rule can be expressed as X [the antecedent of the rule (left-hand-side, lhs)] → Y [the consequent of the rule (right-hand-side, rhs)], where X and Y are mutually exclusive sets of items [24]. The association rule was evaluated by measures of support, confidence, and lift. The support of the rule is defined as the
percentage of transactions in T that contain both X and Y [24, 25]. The support was calculated as follows:

\[
\text{Support} = P(X \cap Y) = \frac{\{X \cap Y\}}{D}
\]

where D is the total number of transactions in the database.

The confidence of the association rule is the ratio of the support of the itemset \( X \cap Y \) to the support of the itemset \( X \), which roughly corresponds to the conditional probability \( P(Y|X) \) [23]. Because confidence is an indicator of the accuracy of related rules, an association rule with high confidence is critical. The formula for calculating confidence is as follows:

\[
\text{Confidence} = \frac{P(X \cap Y)}{P(X)}
\]

The lift value is the ratio of the confidence of the rule and the expected confidence of the rule. It is defined as follows:

\[
\text{Lift} = \frac{P(X \cap Y)}{P(X) \cdot P(Y)}
\]

Lift evaluates the independence of X and Y, suggesting that the greater the lift value, the stronger the relationship. If X and Y are independent, the lift is 1. If X and Y are positively or negatively correlated, the lift is > 1 or < 1, respectively.

The Chi-squared value to evaluate the association rules is defined using the values of confidence, support, and lift according to of the single rule [26, 27]:

\[
\text{Chi-squared} = D(Lift-1)^2 \cdot \frac{\text{Support} \cdot \text{Confidence}}{(\text{Confidence} - \text{Support}) \cdot (\text{Lift} - \text{Confidence})}
\]

The association rule mining was performed using the apriori function of the arules library in the arules package of the R software (version 3.5.1) [28]. In the first step, the apriori algorithm searched for itemsets that had more than minimum support as predetermined by the user [29, 30]. In the second step, the rules were generated by selecting the itemsets that were based on a threshold of confidence from those found in the first step. Because all possible rules were enumerated from a large database, the first step was a narrow path. Therefore, to extract association rules efficiently, the thresholds of the minimum support and confidence were defined depending on factors such as the size of data and the number of items. In this study, we defined the minimum support and confidence thresholds as 0.0001 and 0.01, respectively. Furthermore, the maximum size of mined frequent itemsets (maxlen; maximum length of itemset/rule: a parameter in the arules package) was restricted to 3.

To assess the time-to-onset profile, the median time from the first prescription of each report to the onset of AKI was used in conjunction with the interquartile range and Weibull shape parameter (WSP). We selected an analysis period of 90 days after therapy initiation. We used the WSP test for the statistical
analysis of time-to-onset data to describe a non-constant incidence rate of AEs. The WSP represents the failure rate distribution against time and was used to evaluate hazard functions for detecting AEs. The scale parameter $\alpha$ of the Weibull distribution determines the scale of the distribution function. A larger scale value ($\alpha$) stretches the distribution whereas a smaller scale value shrinks the data distribution. The shape parameter $\beta$ of the Weibull distribution determines the shape of the distribution function. The WSP $\beta$ value indicates the hazard without a reference population; when $\beta$ is equal to 1, the hazard is estimated to be constant over time. If $\beta > 1$, the hazard is considered to increase over time [31, 32]. The information obtained from the WSP could be of complementary value for the pharmacovigilance analysis using ROR.

All data analyses were performed using JMP 12.0 (SAS Institute, Cary, NC, USA).

Results

The JADER database contains 534,688 reports submitted between April 2004 and June 2018, and we identified 21,727 AKI events. According to the Anatomical Therapeutic Chemical (ATC) Classification System (www.whocca/ntc_ddd_index/), 145 anti-infectives were selected and categorized into 36 ATC-drug classes (Table 1).

In the top five anti-infective therapies, glycopeptide antibacterials (ATC code: J01XA), fluoroquinolones (ATC code: J01MA), third-generation cephalosporins (ATC code: J01DD), triazole derivatives (ATC code: J02AC), and carbapenems (ATC code: J01DH), we identified 596, 494, 341, 315, and 313 reported AKI-associated AEs, respectively (Table 2). The lower limit of the 95% CI (confidence interval) of ROR was > 1 for the following drug groups: combinations of penicillins, incl. beta-lactamase inhibitors (ATC code: J01CR), second-generation cephalosporins (ATC code: J01DC), third-generation cephalosporins (ATC code: J01DD), fourth-generation cephalosporins (ATC code: J01DE), monobactams (ATC code: J01DF), carbapenems (ATC code: J01DH), intermediate-acting sulfonamides (ATC code: J01EC), combinations of sulfonamides and trimethoprim, incl. derivatives (ATC code: J01EE), lincosamides (ATC code: J01FF), other aminoglycosides (ATC code: J01GB), fluoroquinolones (ATC code: J01MA), other quinolones (ATC code: J01MA), glycopeptide antibacterials (ATC code: J01XA), polymyxins (ATC code: J01XB), other antibacterials (ATC code: J01XX), antibiotics (ATC code: J02AA), triazole derivatives (ATC code: J02AC), and other antimycotics for systemic use (ATC code: J02AX).

The adjusted RORs and 95% CIs are summarized in Table 3. The results of the model indicated significant contributions by the reporting year ($p < 0.0001$), sex (male, $p < 0.0001$), age (40–49, 50–59, 60–69, 70–79, 80–89, and $\geq 90$ years, $p < 0.0001$), and the number of administered anti-infectives (1 and $\geq 2$, $p < 0.0001$). The adjusted RORs of the age groups 40–49, 50–59, 60–69, 70–79, 80–89, and $\geq 90$ years were 1.26 (1.13 – 1.41), 1.38 (1.25 – 1.54), 1.57 (1.42 – 1.74), 1.75 (1.59 – 1.93), 2.33 (2.11 – 2.58), and 3.07 (2.70 – 3.48), respectively. The adjusted RORs of anti-infective monotherapy and combination therapy ($\geq 2$ anti-infectives) were 1.52 (1.45 – 1.61) and 2.75 (2.56 – 2.95), respectively.

The association rule mining technique was applied to AKI using demographic data, such as the age group, sex, and the number of anti-infectives administered (Table 4). We efficiently extracted the
association rules by setting the optimized support thresholds and confidence thresholds to 0.0001 and 0.01, respectively, and limiting maxlen (parameter in the arules package) to 3. The result of the mining algorithm was a set of 36 rules: it is presented as the heat map of the lift and support derived from the stratified age group, sex, and the number of administered anti-infectives (Table 4, Fig. 1). For AKI AEs caused by anti-infectives, combination therapies tended to have higher lift values than monotherapies; the lift values were 2.36 for combination therapies (≥ 2 anti-infectives) and 1.38 for anti-infective monotherapies (Table 4, id. [6, 15], Fig. 1). The lift values increased relative to the interaction between age and the number of administered anti-infectives (Table 4, id. [1–4], Fig. 1).

Combinations containing the complete information on the treatment start date and AE onset date were extracted for the time-to-onset analysis. We evaluated 14 anti-infectives categories for which the number of cases was more than 100 and the lower limit of the 95% CI exceeded 1 according to Table 2 (Table 5, Fig. 2). Figure 2 shows a histogram of the number of AKI onsets in relation to the number of days after anti-infective treatment initiation (from day 0 to day 90). The median period (interquartile range) until AKI onset caused by anti-infectives was 5.0 (2.0–11.0) days for orally (per os, po) administered anti-infectives and 5.0 (2.0–9.0) days for administration by intravenous (iv) injection. The upper limits of the 95% CI of the β value were less than 1 for po administered anti-infectives.

Discussion

AKI is a complication in clinical care that can be linked to a variety of anti-infectives. Signals indicating an association with AKI were detected in many categories of anti-infectives (Table 2). Polymyxins (ATC code: J01XB) had the highest crude ROR among 36 ATC-drug classes of anti-infectives (Table 2). The detailed mechanism of AKI by polymyxin remains unclear [33]. In our study, 106 out of 107 reports on polymyxin-related AKI indicated colistin (ATC code: J01XB01) administration, which was associated with an AKI incidence rate of approximately 10–55% [34]. ROR signals were also associated with other anti-infectives. Aminoglycosides cause tubular cell toxicity, and vancomycin is linked to acute interstitial nephritis [34]. The incidence rate of nephrotoxicity is reportedly up to 58% in patients treated with aminoglycosides, but most recent reviews suggest rates of 5–15% [4]. All AKI reports in antimycotics were from amphotericin B. Amphotericin B causes AKI when used as monotherapy or combination therapy [4] and raises blood urea nitrogen (BUN) and serum creatinine in 80% of patients receiving a complete course of amphotericin B therapy [35].

The crude ROR values indicated the occurrence of AKI in anti-infectives-treated patients in the age ranges of 70–79 years, 80–89 years, and ≥ 90 years and in patients receiving anti-infective monotherapy or combination treatment (≥ 2 anti-infectives) (Table 3). However, the crude ROR is insufficient for assessing the relative strength of causality between drugs and AEs and only provides an approximation of the signal strength [7, 19]. The crude RORs were used to make adjustments by multivariate logistic regression analyses, which mitigated the effects of covariates. The adjusted RORs of anti-infectives-related AKI increased with the age group (Table 3). Furthermore, the adjusted RORs tended to be higher in anti-infective combination therapy than in monotherapy; the adjusted ROR was 2.75 (2.56–2.95) for ≥ 2
anti-infectives and 1.52 (1.45–1.61) for one anti-infectives. These results suggested that the patient age and the number of administered anti-infectives are related to the occurrence of AKI. Accordingly, our study further demonstrated that the number of administered anti-infectives and age were both associated with the lift value of anti-infectives-related AKI (as the consequent) (Table 4, Fig. 1). Aging is known to decrease renal drug elimination [36], which is associated with an increased risk of AKI by high drug exposure in the elderly. Rybak et al. reported AKI incidence rates of 5%, 11%, and 22% in patients treated with vancomycin monotherapy, aminoglycoside monotherapy, and combination therapy consisting of vancomycin and one aminoglycoside, respectively [37]. Thus, anti-infective combination therapy may increase the risk of AKI in older patients, which should be considered more carefully in clinical practice.

The time-to-onset analysis derived the daily numbers of onset events. We found that 48.1% of anti-infectives-related AKI occurred within 5 days of treatment initiation, and the median for anti-infectives-related AKI onset was 5.0 days post-initiation (Table 5, Fig. 2). We did not detect statistically significant differences of time-to-onset profiles among the different types of anti-infectives (14 ATC-drug classes) or the route of administration (iv versus po).

There are inherent limitations in using SRS data. For example, the length of the post-launch period of the drug, the notification of AEs, over-reporting, and under-reporting affect SRS analysis. There was no suitable comparison group, and data on patient characteristics were incomplete. Multivariate logistic regression analysis was used to adjust potential data bias. The results of this study were partially refined using the multivariate logistic regression analysis technique. Therefore, covariates-corrected adjusted RORs are likely to have improved odds accuracy compared to that of regular RORs. It has been reported that angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, calcineurine inhibitor (cyclosporine, tacrolimus), sulfonamides, acyclovir, rifampin, phenytoin, interferon, and proton pump inhibitors are involved in AKI [5]. In this study, we did not evaluate the effect of concomitant drugs other than anti-infectives. More reliable epidemiological studies will be needed to derive the causal constraints from this analysis.

**Conclusions**

The JADER database, which includes clinicians’ reports of potential AE concerns related to drugs, is a useful tool for pharmacovigilance because it is based on real-world data derived from clinical practice. To our knowledge, this is the first study to report the association between anti-infectives and AKI using SRS. We used adjusted RORs to identify the risk of anti-infectives-related AKI linked to older patients and the number of administered anti-infectives. Based on association rule mining technique, the number of administered anti-infectives and patient age were both associated with the lift value of anti-infectives-related AKI. The median period until anti-infectives-related AKI onset was 5 days after therapy initiation. We believe that our data will provide guidance for reducing the incidence of AEs in elderly patients receiving polypharmacy.

**Abbreviations**
AKI: Acute kidney injury; SRS: Spontaneous reporting systems; JADER: Japanese Adverse Drug Event Report; PMDA: Pharmaceuticals and Medical Devices Agency; MedDRA: Medical Dictionary for Regulatory Activities; WSP: Weibull shape parameter

Declarations

Ethics approval and consent to participate

Ethical approval was not sought for this study because the study was an observational study without any research subjects. All results were obtained from data openly available online from the PMDA website. All data from the JADER database were fully anonymized by the regulatory authority before we accessed them.

Consent for publication

Not applicable.

Competing interests

Ryogo Umetsu is an employee of Micron Inc. The rest of authors have no conflict of interest.

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Authors’ contributions

All authors have contributed to this scientific work and approved the final version of the manuscript. SN, SH, and MN designed this study, performed the data analyses, and wrote the manuscript. RU, and YN involved in methodology and software. KS, RM, MT, KM, YY, MI, and RS assisted the data curation and validation. JL supervised the drafting of the manuscript. All authors took responsibility for the integrity of the data and accuracy of the data analysis.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables
Table 1. Suspected drugs classified by the Anatomical Therapeutic Chemical classification system and the Defined Daily Dose (ATC/DDD)

| Classification (ATC code) | Anti-infectives (Code No.) |
|--------------------------|---------------------------|
| **Antibacterials**       |                           |
| Tetracyclines (J01AA)    | demeclocycline (J01AA01), doxycycline (J01AA02), oxytetracycline (J01AA06), tetracycline (J01AA07), minocycline (J01AA08), tigecycline (J01AA12), combinations of tetracyclines (J01AA20) |
| Amphenicols (J01BA)      | chloramphenicol (J01BA01), thiamphenicol (J01BA02) |
| Penicillins with extended spectrum (J01CA) | ampicillin (J01CA01), carbenicillin (J01CA03), amoxicillin (J01CA04), bacampicillin (J01CA06), piperacillin (J01CA12), talampicillin (J01CA15), sulbenicillin (J01CA16), aspoxicillin (J01CA19), ampicillin combinations (J01CA51) |
| Beta-lactamase sensitive penicillins (J01CE) | benzylpenicillin (J01CE01), phenoxymethylpenicillin (J01CE02), pheneticillin (J01CE05) |
| Beta-lactamase resistant penicillins (J01CF) | cloxacillin (J01CF02) |
| Beta-lactamase inhibitors (J01CG) | sulbactam (J01CG01), tazobactam (J01CG02) |
| Combinations of penicillins, incl. beta-lactamase inhibitors (J01CR) | ampicillin and beta-lactamase inhibitor (J01CR01), sultamicillin (J01CR04), piperacillin and beta-lactamase inhibitor (J01CR05), combinations of penicillins (J01CR50) |
| First-generation cephalosporins (J01DB) | cefalexin (J01DB01), cefaloridine (J01DB02), cefalotin (J01DB03), cefazolin (J01DB04), cefadroxil (J01DB05), cefatrizine (J01DB06), cefapirin (J01DB08), cef cetaxime (J01DB10), cefroxadine (J01DB11) |
| Second-generation cephalosporins (J01DC) | cefoxitin (J01DC01), cefuroxime (J01DC02), cefaclor (J01DC03), cefotetan (J01DC05), cefotiam (J01DC07), cefmetazole (J01DC09), cefminox (J01DC12), cefbuperazone (J01DC13), flomoxef (J01DC14) |
| Third-generation cephalosporins (J01DD) | cefotaxime (J01DD01), ceftazidime (J01DD02), cefsulodin (J01DD03), ceftriaxone (J01DD04), cefmenoxime (J01DD05), latamoxef (J01DD06), ceftizoxime (J01DD07), cefixime (J01DD08), cefodizime (J01DD09), ceftiramide (J01DD11), ceftoperazone (J01DD12), cefpodoxime (J01DD13), cefditoren (J01DD15), cefditoren (J01DD16), cefcapene (J01DD17), cefoperazone and beta-lactamase inhibitor (J01DD62) |
| Fourth-generation cephalosporins (J01DE) | cefepime (J01DE01), cepirome (J01DE02), ceftazopran (J01DE03) |
| Antimicrobial Class                      | Examples                                      |
|----------------------------------------|-----------------------------------------------|
| Cephalosporins (J01DE)                 | aztreonam (J01DF01), carumonam (J01DF02)     |
| Monobactams (J01DF)                    | meropenem (J01DH02), doripenem (J01DH04), biapenem (J01DH05), imipenem and cilastatin (J01DH51), panipenem and betamipron (J01DH55) |
| Carbapenems (J01DH)                    | faropenem (J01DI03)                           |
| Other cephalosporins and penems (J01DI)| trimethoprim (J01EA01)                        |
| Trimethoprim and derivatives (J01EA)   | sulfamethoxazole (J01EC01), sulfadiazine (J01EC02) |
| Intermediate-acting sulfonamides (J01EC)| sulfaadimethoxine (J01ED01), sulfaadimethoxine (J01ED08) |
| Long-acting sulfonamides (J01ED)       | sulfamethoxazole and trimethoprim (J01EE01)  |
| Other cephalosporins and penems (J01DI) | sulfamethoxazole and trimethoprim (J01EE01)  |
| Macrolides (J01FA)                     | erythromycin (J01FA01), spiramycin (J01FA02), midecamycin (J01FA03), roxithromycin (J01FA06), josamycin (J01FA07), clarithromycin (J01FA09), azithromycin (J01FA10), rokitamycin (J01FA12), telithromycin (J01FA15) |
| Lincosamides (J01FF)                   | clindamycin (J01FF01), lincomycin (J01FF02)  |
| Streptogramins (J01FG)                 | quinupristin/dalfopristin (J01FG02)           |
| Streptomycins (J01GA)                  | streptomycin (J01GA01)                        |
| Other aminoglycosides (J01GB)          | tobramycin (J01GB01), gentamicin (J01GB03), kanamycin (J01GB04), neomycin (J01GB05), amikacin (J01GB06), netilmicin (J01GB07), sisomicin (J01GB08), dibekacin (J01GB09), isepamicin (J01GB11), arbekacin (J01GB12), bekamycin (J01GB13) |
| Fluoroquinolones (J01MA)               | ofloxacin (J01MA01), ciprofloxacin (J01MA02), enoxacin (J01MA04), norfloxacin (J01MA06), lomefloxacin (J01MA07), fleroxacin (J01MA08), sparflaxin (J01MA09), levofloxacin (J01MA12), moxifloxacin (J01MA14), gatifloxacin (J01MA16), prulifloxacin (J01MA17), pazufloxacin (J01MA18), garenoflaxin (J01MA19), sitafloxacin (J01MA21) |
| Other quinolones                       | nalidixic acid (J01MB02), piromidic acid (J01MB03), pipemidic acid (J01MB04) |
| **Category** | **Substances** |
|--------------|---------------|
| **J01MB**    | Penicillins combinations with other antibacterials (J01RA01) |
| **J01RA**    | Glycopeptide antibacterials (J01XA) |
| **J01XA**    | Vancomycin (J01XA01), teicoplanin (J01XA02) |
| **J01XB**    | Polymyxins (J01XB) |
| **J01XB01**  | Colistin (J01XB01), polymyxin B (J01XB02) |
| **J01XC**    | Steroid antibacterials (J01XC) |
| **J01XC01**  | Fusidic acid (J01XC01) |
| **J01XD**    | Imidazole derivatives (J01XD) |
| **J01XD01**  | Metronidazole (J01XD01), tinidazole (J01XD02) |
| **J01XE**    | Nitrofuran derivatives (J01XE) |
| **J01XE01**  | Nitrofurantoin (J01XE01) |
| **J01XX**    | Other antibacterials (J01XX) |
| **J01XX01**  | Fosfomycin (J01XX01), spectinomycin (J01XX04), mandelic acid (J01XX06), linezolid (J01XX08), daptomycin (J01XX09), bacitracin (J01XX10) |
| **J02AA**    | Antimycotics, Antibiotics (J02AA) |
| **J02AA01**  | Amphotericin B (J02AA01) |
| **J02AB**    | Imidazole derivatives (J02AB) |
| **J02AB01**  | Miconazole (J02AB01), ketoconazole (J02AB02) |
| **J02AC**    | Triazole derivatives (J02AC) |
| **J02AC01**  | Fluconazole (J02AC01), itraconazole (J02AC02), voriconazole (J02AC03) |
| **J02AX**    | Other antimycotics for systemic use (J02AX) |
| **J02AX01**  | Flucytosine (J02AX01), caspofungin (J02AX02), micafungin (J02AX03) |
Table 2. Number of reports and crude reporting odds ratio of acute kidney injury associated with anti-infectives

| Classification (ATC code) | Total (n) | Case (n) | Crude ROR† (95% CI ‡) |
|---------------------------|-----------|---------|----------------------|
| **Total**                 | 534,688   | 21,727  |                      |
| **Antibacterials**        |           |         |                      |
| Tetracyclines (J01AA)     | 1,763     | 75      | 1.05 (0.83–1.32)     |
| Amphenicols (J01BA)       | 49        | 0       | –§                   |
| Penicillins with extended spectrum (J01CA) | 3,264 | 121 | 0.91 (0.76–1.09) |
| Beta-lactamase sensitive penicillins (J01CE) | 93 | 6 | 1.63 (0.71–3.72) |
| Beta-lactamase resistant penicillins (J01CF) | 0 | 0 | –§ |
| Beta-lactamase inhibitors (J01CG) | 0 | 0 | –§ |
| Combinations of penicillins, incl. beta-lactamase inhibitors (J01CR) | 2,121 | 292 | 3.81 (3.36–4.31) |||
| First-generation cephalosporins (J01DB) | 1,484 | 46 | 0.75 (0.56–1.01) |
| Second-generation cephalosporins (J01DC) | 1,902 | 101 | 1.33 (1.08–1.62) |||
| Third-generation cephalosporins (J01DD) | 7,551 | 341 | 1.12 (1.002–1.25) |||
| Fourth-generation cephalosporins (J01DE) | 1,318 | 128 | 2.55 (2.12–3.06) |||
| Monobactams (J01DF)       | 21        | 4       | 5.56 (1.87–16.51)   |
| Carbapenems (J01DH)       | 3,551     | 313     | 2.30 (2.05–2.59)    |
| Other cephalosporins and penems (J01DI) | 132 | 9 | 1.73 (0.88–3.40) |
| Trimethoprim and derivatives (J01EA) | 0 | 0 | –§ |
| Intermediate-acting sulfonamides (J01EC) | 36 | 7 | 5.70 (2.50–13.01) |||
| Drug Class                                      | Count | Error | CI     |
|-----------------------------------------------|-------|-------|--------|
| Long-acting sulfonamides (J01ED)              | 4     | 0     | -§     |
| Combinations of sulfonamides and trimethoprim, incl. derivatives (J01EE) | 2,738 | 261   | 2.51 (2.20–2.85)‡ |
| Macrolides (J01FA)                            | 5,283 | 200   | 0.93 (0.81–1.07)   |
| Lincosamides (J01FF)                          | 757   | 55    | 1.85 (1.41–2.44)‡ |
| Streptogramins (J01FG)                        | 2     | 0     | -§     |
| Streptomycins (J01GA)                         | 153   | 9     | 1.48 (0.75–2.89)   |
| Other aminoglycosides (J01GB)                 | 932   | 258   | 9.13 (7.91–10.55)‡ |
| Fluoroquinolones (J01MA)                      | 8,571 | 494   | 1.45 (1.33–1.59)‡ |
| Other quinolones (J01MB)                      | 24    | 3     | 3.37 (1.01–11.31)‡ |
| Combinations of antibacterials (J01RA)        | 638   | 11    | 0.41 (0.23–0.75)   |
| Glycopeptide antibacterials (J01XA)           | 2,752 | 596   | 6.68 (6.10–7.32)‡ |
| Polymyxins (J01XB)                            | 137   | 107   | 84.62 (56.43–126.89)‡ |
| Steroid antibacterials (J01XC)                | 2     | 0     | -§     |
| Imidazole derivatives (J01XD)                 | 667   | 12    | 0.43 (0.24–0.77)   |
| Nitrofuran derivatives (J01XE)                | 0     | 0     | -§     |
| Other antibacterials (J01XX)                  | 2,119 | 107   | 1.26 (1.03–1.53)‡ |
| Antimycotics                                  |       |       |        |
| Antibiotics (J02AA)                           | 1,337 | 299   | 6.88 (6.05–7.83)‡ |
| Imidazole derivatives (J02AB)                 | 100   | 1     | -§     |
| Triazole derivatives (J02AC)                  | 3,130 | 315   | 2.67 (2.37–3.00)‡ |
| Other antimycotics for systemic use (J02AX) | 1,148 | 161 | 3.87 |
|-------------------------------------------|-------|-----|------|
|                                           |       |     | (3.28–4.58) |

† Reporting Odds Ratio, ‡ Confidence Interval, § Number of cases < 2, ‖ Lower limit of 95% CI > 1
Table 3. Crude reporting odds ratio and adjusted reporting odds ratio of acute kidney injury

|                      | Total   | Case| Crude ROR‡ (95% CI§) | Estimated beta | Adjusted ROR‡ (95% CI§) | P-value* |
|----------------------|---------|-----|-----------------------|----------------|-------------------------|----------|
| Total                | 534,688 | 21,727 |                       | 0.014         | 1.21 (1.15−1.27)     |  < 0.0001* |
| Reporting year       |         |      |                       | 0.283         | 1.33 (1.29−1.37)     |  < 0.0001* |
| Male                 | 260,713 | 11,988 | 1.31 (1.27−1.34)      | 0.283         | 1.33 (1.29−1.37)     |  < 0.0001* |
| Age                  |         |      |                       | 0.006         | 0.99 (0.89−1.12)     |  0.9244 |
| ≤ 19 years           | 37,941  | 992  | 0.62 (0.58−0.66)      | -0.006        | 0.99 (0.89−1.12)     |  0.9244 |
| 20–29 years          | 17,049  | 440  | 0.62 (0.56−0.68)      | 1.00          | 1.00 (as reference)  |          |
| 30–39 years          | 29,004  | 704  | 0.57 (0.53−0.62)      | -0.061        | 0.94 (0.83−1.06)     |  0.3242 |
| 40–49 years          | 38,486  | 1,247 | 0.78 (0.73−0.82)      | 0.235         | 1.26 (1.13−1.41)     |  < 0.0001* |
| 50–59 years          | 63,734  | 2,266 | 0.86 (0.82−0.89)      | 0.326         | 1.38 (1.25−1.54)     |  < 0.0001* |
| 60–69 years          | 113,007 | 4,603 | 1.00 (0.97−1.04)      | 0.451         | 1.57 (1.42−1.74)     |  < 0.0001* |
| 70–79 years          | 122,114 | 5,527 | 1.16 (1.12−1.20)      | 0.559         | 1.75 (1.59−1.93)     |  < 0.0001* |
| 80–89 years          | 61,022  | 3,606 | 1.58 (1.52−1.64)      | 0.845         | 2.33 (2.11−2.58)     |  < 0.0001* |
| ≥ 90 years           | 8,202   | 602  | 1.89 (1.74−2.06)      | 1.121         | 3.07 (2.70−3.48)     |  < 0.0001* |
| Anti-infectives (Antibacterials+Antimycotics) | | | | | | |
| 0 drug               | 495,039 | 19,472 | 0.68 (0.65−0.71)      | 1.00          | 1.00 (as reference)  |          |
| 1 drug               | 29,938  | 1,529 | 1.29 (1.22−1.36)      | 0.421         | 1.52 (1.45−1.61)     |  < 0.0001* |
| ≥ 2 drugs            | 9,711   | 726  | 1.94 (1.80−2.09)      | 1.010         | 2.75 (2.56−2.95)     |  < 0.0001* |

† Number of patients with acute kidney injury, ‡ Reporting Odds Ratio, § Confidence Interval
*Probability > Chi-square, * P < 0.05
Table 4. Association parameters of rules based on the number of administered drugs and stratified age group (sort by lift)

| id  | lhs†                     | rhs‡                | case (n) | support | confidence | lift | Chi-squared value |
|-----|--------------------------|---------------------|----------|---------|------------|------|-------------------|
| [1] | {≥ 2 drugs, 80−89 years of age} | {AKI}              | 113      | 0.00021 | 0.11       | 2.66 | 121.94*           |
| [2] | {≥ 2 drugs, 50−59 years of age} | {AKI}              | 129      | 0.00024 | 0.10       | 2.54 | 125.90‡           |
| [3] | {≥ 2 drugs, 60−69 years of age} | {AKI}              | 208      | 0.00039 | 0.10       | 2.46 | 188.06‡           |
| [4] | {≥ 2 drugs, 70−79 years of age} | {AKI}              | 214      | 0.00040 | 0.10       | 2.41 | 184.14‡           |
| [5] | {1 drug, ≥ 90 years of age} | {AKI}              | 65       | 0.00012 | 0.10       | 2.37 | 53.56‡            |
| [6] | {≥ 2 drugs} | {AKI}              | 930      | 0.00174 | 0.10       | 2.36 | 776.49‡           |
| [7] | {≥ 2 drugs, 40−49 years of age} | {AKI}              | 60       | 0.00011 | 0.08       | 2.05 | 33.48‡            |
| [8] | {1 drug, 80−89 years of age} | {AKI}              | 303      | 0.00057 | 0.08       | 1.95 | 147.84‡           |
| [9] | {≥ 90 years of age, female} | {AKI}              | 422      | 0.00079 | 0.08       | 1.90 | 190.76‡           |
| [10] | {1 drug, 70−79 years of age} | {AKI}              | 481      | 0.00090 | 0.07       | 1.72 | 152.02‡           |
| [11] | {≥ 90 years of age, male} | {AKI}              | 165      | 0.00031 | 0.06       | 1.60 | 38.53‡            |
| [12] | {≤ 19 years of age, ≥ 2 drugs} | {AKI}              | 70       | 0.00013 | 0.06       | 1.52 | 13.05‡            |
| [13] | {80−89 years of age, female} | {AKI}              | 1920     | 0.00359 | 0.06       | 1.51 | 360.59‡           |
| [14] | {1 drug, 60−69 years of age} | {AKI}              | 328      | 0.00061 | 0.06       | 1.40 | 39.15‡            |
| [15] | {1 drug} | {AKI}              | 1682     | 0.00315 | 0.06       | 1.38 | 198.51‡           |
| [16] | {80−89 years of age, male} | {AKI}              | 1609     | 0.00301 | 0.06       | 1.38 | 185.14‡           |
| [17] | {1 drug, 50−59 years of age} | {AKI}              | 174      | 0.00033 | 0.05       | 1.23 | 7.60‡             |
| [18] | {70−79 years of age, male} | {AKI}              | 3234     | 0.00605 | 0.05       | 1.19 | 115.46‡           |
|   | Rule                                                                 | AKI | Chi-squared value | p-value | Odds Ratio | 95% CI Low | 95% CI High |
|---|-----------------------------------------------------------------------|-----|-------------------|---------|------------|------------|------------|
| 19| (60–69 years of age, male) → {AKI}                                    | 2992| 0.00560           | 0.05    | 1.19       | 104.08‡    |
| 20| (40–49 years of age, male) → {AKI}                                    | 810 | 0.00151           | 0.05    | 1.12       | 10.48‡     |
| 21| (50–59 years of age, male) → {AKI}                                    | 1451| 0.00271           | 0.04    | 1.10       | 13.77‡     |
| 22| (1 drug, 40–49 years of age) → {AKI}                                  | 96  | 0.00018           | 0.04    | 1.08       | 0.64       |
| 23| (70–79 years of age, female) → {AKI}                                  | 2245| 0.00420           | 0.04    | 1.02       | 1.39       |
| 24| (20–29 years of age, male) → {AKI}                                    | 257 | 0.00048           | 0.04    | 0.95       | 0.82       |
| 25| (30–39 years of age, male) → {AKI}                                    | 435 | 0.00081           | 0.04    | 0.91       | 3.73       |
| 26| (1 drug, 30–39 years of age) → {AKI}                                  | 86  | 0.00016           | 0.04    | 0.90       | 1.11       |
| 27| (60–69 years of age, female) → {AKI}                                  | 1567| 0.00293           | 0.03    | 0.77       | 122.87‡    |
| 28| (≤ 19 years of age, 1 drug) → {AKI}                                   | 85  | 0.00016           | 0.03    | 0.73       | 8.95‡      |
| 29| (≤ 19 years of age, male) → {AKI}                                     | 510 | 0.00095           | 0.03    | 0.69       | 74.09‡     |
| 30| (≤ 19 years of age) → {AKI}                                            | 990 | 0.00185           | 0.03    | 0.64       | 221.09‡    |
| 31| (50–59 years of age, female) → {AKI}                                  | 797 | 0.00149           | 0.03    | 0.64       | 178.32‡    |
| 32| (≤ 19 years of age, female) → {AKI}                                   | 416 | 0.00078           | 0.02    | 0.62       | 107.66‡    |
| 33| (≤ 19 years of age, 0 drug) → {AKI}                                   | 835 | 0.00156           | 0.02    | 0.61       | 238.50‡    |
| 34| (40–49 years of age, female) → {AKI}                                  | 425 | 0.00079           | 0.02    | 0.51       | 211.24‡    |
| 35| (20–29 years of age, female) → {AKI}                                  | 180 | 0.00034           | 0.02    | 0.43       | 142.64‡    |
| 36| (30–39 years of age, female) → {AKI}                                  | 258 | 0.00048           | 0.02    | 0.37       | 296.11‡    |

† left-hand-sides of rule (antecedents)
‡ right-hand-side of rule (consequents)
* Statistical significance: Chi-squared value ≥ 4
Table 5. The medians and Weibull parameter of each drug

| Classification (ATC code) | Administration route | Case | Median (day) | Scale parameter | Shape parameter |
|---------------------------|----------------------|------|--------------|----------------|----------------|
|                           |                      | (n)  | (25%–75%)    | α (95% CI†)    | β (95% CI†)    |
| (po: per os; iv: intravenous injection) |                        |      |              |                |                |
| **Total**                 | po                   | 756  | 5.0          | 10.60 (9.68–11.59) | 0.87 (0.82–0.92) |
|                           | iv                   | 1800 | 5.0          | 8.28 (7.88–8.71) | 1.03 (0.99–1.06) |
| **Antibacterials**        |                      |      |              |                |                |
| Combinations of penicillins, incl. beta-lactamase inhibitors (J01CR) | po       | 9    | 3.0 (2.5–11.5) | 8.00 (1.94–30.36) | 0.65 (0.34–1.06) |
|                           | iv                   | 180  | 4.0 (2.0–8.0) | 7.43 (6.34–8.69) | 1.04 (0.93–1.15) |
| Second-generation cephalosporins (J01DC) | po       | 8    | 4.5 (1.5–9.0)  | 6.95 (3.85–12.12) | 1.79 (0.83–3.20) |
|                           | iv                   | 56   | 3.0 (1.0–5.8)  | 5.16 (3.86–6.82) | 1.06 (0.85–1.30) |
| Third-generation cephalosporins (J01DD) | po       | 93   | 3.0 (1.0–7.0)  | 7.06 (5.47–9.06) | 0.90 (0.77–1.05) |
|                           | iv                   | 138  | 4.0 (2.0–7.0)  | 7.23 (6.01–8.66) | 1.02 (0.89–1.15) |
| Fourth-generation cephalosporins (J01DE) | po       | 1    | –            | –              | –              |
|                           | iv                   | 83   | 5.0 (2.0–11.0) | 8.24 (6.73–10.02) | 1.19 (0.999–1.40) |
| Carbapenems (J01DH)       | po                   | 0    | –            | –              | –              |
|                           | iv                   | 190  | 5.0 (2.0–9.0)  | 8.63 (7.37–10.08) | 1.03 (0.92–1.14) |
| Combinations of sulfonamides and trimethoprim, incl. derivatives (J01EE) | po       | 112  | 8.5 (4.0–21.0) | 17.57 (13.98–21.94) | 0.89 (0.77–1.01) |
| Antimicrobial Class                        | Route | Dose | CI Low  | CI High | CI Low  | CI High |
|-------------------------------------------|-------|------|---------|---------|---------|---------|
| Other aminoglycosides (J01GB)            | po    | 3    | –       | –       | –       | –       |
|                                           | iv    | 14   | 3.0     | (1.8–4.0) | 3.65    | (2.54–5.15) | 1.75    | (1.12–2.48) |
| Fluoroquinolones (J01MA)                 | po    | 232  | 4.0     | (2.0–8.0) | 7.62    | (6.52–8.89) | 0.92    | (0.83–1.01) |
|                                           | iv    | 95   | 4.0     | (2.0–7.0) | 7.00    | (5.72–8.53) | 1.14    | (0.97–1.33) |
| Glycopeptide antibacterials (J01XA)       | po    | 10   | 7.0     | (2.0–10.3) | 13.15   | (4.90–33.47) | 0.79    | (0.47–1.18) |
|                                           | iv    | 353  | 5.0     | (2.0–10.0) | 8.69    | (7.82–9.63) | 1.10    | (1.01–1.18) |
| Polymyxins (J01XB)                       | po    | 0    | –       | –       | –       | –       |
|                                           | iv    | 83   | 3.0     | (1.0–6.0) | 6.25    | (5.07–7.64) | 1.26    | (1.05–1.49) |
| Other antibacterials (J01XX)             | po    | 9    | 10.0    | (5.5–12.0) | 10.06   | (6.65–14.84) | 2.07    | (1.13–3.27) |
|                                           | iv    | 39   | 3.0     | (1.0–7.0) | 7.75    | (4.92–11.98) | 0.86    | (0.66–1.09) |
| Antimycotics                              |       |      |         |         |         |         |
| Antibiotics (J02AA)                      | po    | 3    | –       | –       | –       | –       |
|                                           | iv    | 154  | 5.0     | (2.0–9.3) | 9.00    | (7.45–10.82) | 0.94    | (0.83–1.05) |
| Triazole derivatives (J02AC)             | po    | 88   | 9.5     | (3.0–23.0) | 19.11   | (14.82–24.44) | 0.94    | (0.79–1.11) |
|                                           | iv    | 59   | 5.0     | (2.0–18.0) | 13.06   | (9.27–18.17) | 0.83    | (0.68–1.01) |
| Other antimycotics for systemic use (J02AX) | po   | 2    | –       | –       | –       | –       |
Association rules for AKIs based on JADER database entries from April 2004 to June 2018. Support and lift are visualized using the R-extension package arulesViz, which implements novel visualization techniques to explore association rules. The plot arguments used in arulesViz were set as follows: method = “graph,” measure = “support,” shading = “lift.” The measures of support are presented as circle areas. The measures of lift are indicated by the color shade of the circle.
Figure 2

Histograms and the corresponding Weibull shape parameters of AKIs associated with 14 anti-infective categories for which the number of cases was more than 100 and the lower limit of the 95% CI exceeded 1 in Table 2. Three different time-to-onset periods of reported cases per anti-infective category were the limit to calculate the Weibull shape parameter. Six anti-infective categories [fourth-generation cephalosporins (po), carbapenems (po), other aminoglycosides (po), polymyxins (po), antibiotics (po), other antimycotics for systemic use (po)] did not meet this limit.