Renal impairment related to antibiotic dosing and dosing errors in different care settings, a systematic review

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Abstract

Background: Optimal dose of antibiotics is crucial for the effective treatment of an infection. Though appropriate dosing in renal patients is usually difficult and is subject to dosing errors for different factors. Nevertheless, these types of dosing errors and considerations in renal patients are controversial. **Objective:** This study aims at evaluating the renal impairment of different levels (including at-risk) in relation to antibiotic dosing and dosing errors. **Method:** the literature was examined through Medline, PubMed, Embase, and Ovid database in 2010 and 2020. Searching terms included were a combination of "renal" OR "kidney" AND "impairment" OR "injury" AND "Antibiotic" AND "dos*" AND "errors." Following this, results were refined to include only original research articles investigating antibiotic dosing considerations or errors in patients with varying renal impairment levels in different care settings. Selected trials mentioned the types of antibiotics and the degree of renal impairment**.** **Result:** A total of 1902 articles were returned. After the exclusion of articles on animals and including only studies on humans, 32 studies were found. A total of nine articles were identified as eligible, covering 5591 patients who had prescribed antibiotics in different care settings and with variable levels of renal impairment. Two of the included studies were pharmacokinetic models, while the other two were prospective observational studies and the remaining five studies were retrospective. **Conclusion:** Dosing of antibiotics in renal impairment patients or those at risk of renal impairment needs to be individualized and depend on appropriate choice of equations to calculate creatinine clearance based on the level of renal impairment.

Key-words: Renal impairment, antibiotics, dosing errors, optimal dosing

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Introduction and Background

Antibiotic levels are critical in treating infection, particularly severe infections or infections with multidrug-resistant strains [1]. Consequently, maintaining therapeutic levels can guarantee that the antibiotics are effective when it is not sub-therapeutic and safe when not at a supra-therapeutic level [2].

Over the past three decades, pharmaceutical companies were obliged to undergo pharmacokinetic studies to get approval for an antibiotic; this includes studies in renal impairment. However, the dosing of antibiotics in renal patients is challenging [3, 4].

Due to the considerable variability in renal impairment from patients at risk to patients with end-stage renal disease, the dosing of antibiotics might not reach optimal levels when manufacturers' recommendations are followed for dosing antibiotics in all patients with renal impairment [5]. Additionally, relying mainly on Cockcroft and gault equation to calculate creatinine clearance for renal dosing might not be appropriate for all renal impairment [6].

This variability in dosing can reflect on inaccurate levels of antibiotics in the blood, which can lead to increased renal toxicity or worsening an existing renal impairment, in addition to being ineffective in the case of subtherapeutic levels [7, 8]. Accordingly, clinical pharmacy plays a significant role in adjusting antibiotic doses in patients with renal impairment. Clinical pharmacists have shown a significant reduction in the incidence of antibiotic dosing errors when treating renally impaired patients with infections [9].

Despite the presence of data evaluating the renal dosing of different antibiotics. The data on the optimal dosing consideration and dosing errors of antibiotics in different renal impairment levels is still unclear. Therefore, this systematic review aims to examine the literature to consider the renal dosing of antibiotics and dosing errors in this particular population.

Review

Methodology

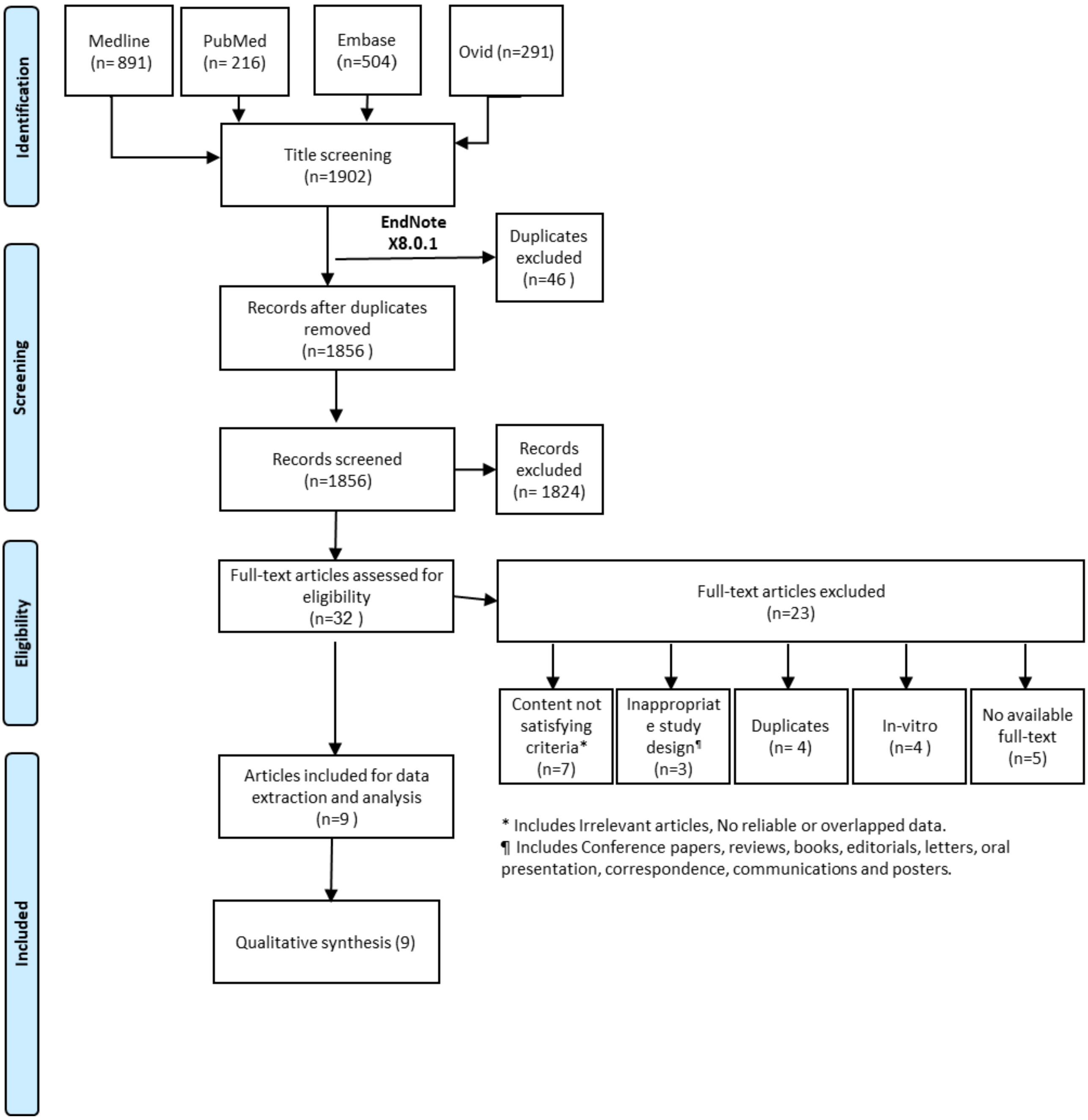
This systematic review is compliant with the PRISMA checklist recommendations for systematic review and meta-analysis [10]. This systematic review was performed through searching electronic databases to include eligible trials from January 2010 till September 2020 in four databases, including Medline, Pubmed, Ovid, and Embase.

Search Strategy

Searching terms included “renal” OR “kidney” AND “impairment” OR “injury” AND “Antibiotic" AND "dos*" AND "errors." All the titles and abstracts that appeared from this search were reviewed thoroughly to prevent missing any eligible articles. The results were then refined to include only original research articles investigating antibiotic dosing considerations or errors in patients with varying renal impairment levels in different care settings. Moreover, the selected trials mentioned the types of antibiotics and the degree of renal impairment. Additionally, all study designs from different countries were included. Only trials that are published in the English language were classified as related articles, which can be further evaluated in the second step.

Eligibility Criteria

After this stage, the inclusion criteria to select the studies considered in the systematic review were determined. Abstracts were examined manually to choose the appropriate abstracts to be considered. The inclusion criteria were mentioning enough data on the dosing consideration of antibiotics and renal impairment levels. Moreover, only trials recruiting adult participants were included. Furthermore, references of selected trials were evaluated to identify any related articles. Finally, the required data sets were gathered from the final record of eligible articles and summarized. Articles were excluded in case of in vitro or animal involvement, overlapped or incomplete data, and unavailability of full-text articles or inappropriate study design. Full details on the search strategy are shown in figure 1.



Data Review and Analysis

The first step included a preliminary review, a specially designed excel sheet was used for data extraction. Selected data from eligible studies were then revised through the excel sheet. Any articles published by one research group investigating similar variables were reviewed for any possible duplication. Cochrane, a quality assessment tool, was also used to evaluate the quality of the included clinical studies [11].

Results and Discussion

After searching the abstracts and checking for the eligibility criteria in identified potential abstracts, a total of nine articles [12-20] were considered as eligible to be included in the present systematic review that was published between 2010 and 2020, a total of 5591 patients who had prescribed antibiotics in different care settings and with variable levels of renal impairment.

Out of the nine studies, two studies [12, 20] were pharmacokinetic studies, while another two studies [17, 19] were prospective observational studies, while the other five studies were retrospective [13-16, 18]. As for the examined antibiotics, almost all antibiotic classes were included, except for three studies, one of them examined tigecycline [12], another two studies examined vancomycin [15, 17], and daptomycin was examined in one study [20].

Turning to the level of renal impairment, patients at risk of renal impairment were included in three studies [14, 16, 17]. At the same time, patients with varying levels of exciting renal impairment were included in four studies [12, 13, 18, 20]. Drug-induced renal impairment was also evaluated in two studies [15, 19].

According to extracted results, all the trials considered the evaluation of antibiotic dosing and errors in patients with different renal impairment levels in different care settings. The included trials are discussed in detail in table 1.

Table 1. Shows included trials

Author(s)	Year	Study design	Sample size	Antibiotic examined	Type of renal impairment	Objective	Result
Li et al. [12]	2020	Pharmacokinetic study (Monte Carlo simulations)	22	Tigecycline	Severe and End-stage renal impairment and hemodialysis	to evaluate the cumulative fraction of response (CFR) of different tigecycline dosing schedules in renal impairment.	The regular tigecycline dose (50mg twice daily) was effective against Gram-positive bacteria and Escherichia coli in renal impairment patients. In severe renal impairment and Klebsiella pneumonia, and Enterobacter cloacae, patients with severe renal failure can use the same dose, while other patients require higher doses.
Jarab et al. [13]	2020	Retrospective study	80	All antibiotic classes (110 antibiotic prescriptions)	38.75% had a moderate decline in kidney function (CrCl<60ml/min), 5% had kidney failure without dialysis with (CrCl < 15 mL/min).	to investigate the compliance with guidelines in the adjustment of antibiotics doses in renal impairment.	36.25% of patients administered antibiotics without renal dose adjustments based on their CrCl. 62% of Imipenem/cilastatin doses were not adjusted, while 3.45% of vancomycin doses were not renally adjusted. There is a general non-adherence to recent guidelines of renal dose adjustment for renally excreted antibiotics.
Silva et al. [14]	2020	Retro-spective cohort	589	Different antibiotics	At-risk (Hospitalized patients ≥ 80 years)	To evaluate the correlation between estimated CrCl and the estimated GFR, and to audit antibiotic dosing errors	Based on the Cockcroft-Gault equation, there were errors in the daily defined dose in 52% of the measured serum creatinine day. There was a strong correlation between Cockcroft-Gault with the estimated GFR. Regardless of the assessment method for renal impairment, the incidence of antibiotic dosing errors is high in elderly patients.
Burger et al [15]	2018	retrospective study	1871	cefazolin with single-dose vancomycin	Renal toxicity (Drug-induced)	to evaluate prosthetic joint infection (PJI) and renal toxicity rates after total joint arthroplasty (TJA).	The addition of one vancomycin dose did not significantly reduce PJI rates compared to cefazolin alone (P value=0.32). However, the PJI rate was significantly lower following primary TJA when vancomycin was initiated at least 45 minutes before incision compared to other TJA procedures using cefazolin and vancomycin (P <0.01) or cefazolin alone (P < 0.01). There was a non-significant difference in renal toxicity between treatment groups.

DeWitt et al. [16]	2016	retrospective cohort study	210	cefazolin, cefepime, ciprofloxacin, piperacillin-tazobactam, or vancomycin	Risk of renal impairment (critically ill patients)	to examine the effect of emergency medicine pharmacist(EMP) availability in the ED on antibiotic dosing appropriateness.	Overall, (95%) of the antibiotic orders were appropriate when an EMP was present compared to 74% when an EMP was absent. Antibiotic appropriateness was independently correlated to the presence of the EMP and CrCl. Antibiotics that require renal dosing adjustment are 6.5 folds to be appropriately dosed in the ED if an EMP is available. The incidence of antibiotic dosing error is correlated to the availability of EMPs and the level of renal impairment.
Tafelski et al. [17]	2015	observational	675	vancomycin	Risk of renal impairment (critically ill patients)	to evaluate the safety and effectiveness of vancomycin in two different regimens.	39% of patients received intermittent dosing, and 61% received continuous infusion. Patients on continuous infusion achieved target serum levels significantly earlier ($p = 0.022$). During the ICU, acute renal failure occurred in 35% of patients with intermittent infusion versus 26% in continuous infusion ($p=0.324$). Severe infections or higher fluctuation in renal function could benefit from this method of administration.
Farag et al. [18]	2014	Population-based retrospective time series analysis	1464	Different prescribed antibiotics	Chronic kidney disease	to identify the antibiotic dosing errors in chronic kidney disease (CKD).	There was a non-significant difference in antibiotic prescribing errors (64% versus 68%) before and after eGFR reporting (p value=0.9). Nitrofurantoin, which is contraindicated in CKD, yet prescribed 169 times. Ambulatory antibiotic dosing errors are exceedingly common in CKD care.
Bailey et al. [19]	2014	observational cohort comparison	238	Cefuroxime, flucloxacillin, gentamicin.	Acute kidney injury (drug-induced)	To evaluate the risk of acute kidney injury with changing antibiotic prophylaxis.	1.69% of cefuroxime developed renal impairment. All patients returned to normal by th e third postoperative day. New-onset renal impairment incidence was significantly higher in the flucloxacillin-and-gentamicin group at 9.45% ($p < 0.001$).
Chaves et al. [20]	2014	population pharmacokinetic model	442	daptomycin	Severe renal impairment	To identify the optimum dose of daptomycin in Staphylococcus aureus bacteremia (SAB) and severe renal impairment.	More patients with SAB and severe renal impairment were underexposed at 4 mg/kg every 48 h compared to 6 mg/kg. 6 mg/kg every 48 hours is more effective than 4 mg/kg every 48 h. For patients with SAB and Crcl<,30 mL/min, or receiving HD or CAPD, the dose recommendation of 6 mg/kg every 48 h provides appropriate daptomycin exposure for this indication, which is more effective compared to 4 mg/kg every 48 h.

Renal impairment is a significant challenge for clinicians when deciding the dose and antibiotic type, especially in critically ill patients and those with multidrug-resistant infections. Tigecycline, a glycil cycle used for multidrug-resistant and life-threatening infections, has been evaluated by Li et al. [12] to evaluate the appropriate dosing in patients with renal impairment in order not to be subtherapeutic or supratherapeutic.

Li et al. [12] demonstrated that Tigecycline's standard dose would be used in patients with severe renal impairment. The use of reduced-dose would be effective enough for resistant strains, such as *Escherichia coli,* while other strains might even require a higher dose, even though in patients with severe renal impairment, to achieve therapeutic levels.

Similarly, another pharmacokinetic study, Chaves et al. [20], evaluated the use of daptomycin in bacteremia in patients with severe renal impairment (with CrCl<30ml/min). Chaves et al. [20] evaluated different dosing and their corresponding levels and demonstrated that a higher dose would be recommended (6 mg/kg every other day) to achieve appropriate therapeutic levels.

These pharmacokinetic studies reflect on the increased chances of dosing errors in patients with renal impairment due to the high variability of drug levels in the blood, which could be attributed to drug clearance variation. This was described by Silva et al. [14], which showed that there were 51% of dosing errors of antibiotics in patients at risk f renal impairment despite calculating CrCl for patients. It should be noted that patients included in Silva et al. [14] were above 80 years old.

Also, Jarab et al. [13] included patients with different levels of renal impairment, with more than a third, the included sample with moderate renal impairment (CrCl<60 ml/min). Jarab et al. [13] showed that 36.25% of antibiotic doses were prescribed without calculating CrCl and that 62% of imipenem/cilastatin prescriptions had were not renally adjusted.

These findings from Jarab et al. [13] highlights the importance of interventions to improve renal dosing calculation to reduce dosing errors in patients at risk or with a pre-existing renal impairment. These findings were also confirmed in patients with chronic kidney disease by Farag et al. [18]. One of the proposed solutions was the pharmacist's availability to adjust renal doses, which was raised by DeWitt et al. [16].

DeWitt et al. [16] examined the impact of an emergency medicine pharmacist's availability in the emergency room to calculate renal doses of antibiotics. Dosing appropriateness increased from 74% to 95% with the availability of pharmacists. Additionally, DeWitt et al. [16] estimated that the likelihood of appropriate dosing of antibiotics in patients at risk of renal impairment is six and a half folds in a pharmacist [16].

The renal toxicity of antibiotics was also evaluated. Burger et al. [15] evaluated the renal toxicity accompanying the addition of a vancomycin dose to the pre-existing prophylactic cefazoline dose for the prevention of prosthetic surgery infections. Burger et al. [15] showed that there was a significant reduction in the incidence of infection after total joint arthroplasty (p-value<0.01), with a non-significant difference in the renal toxicity [15].

Additionally, Tafelski et al. [17] evaluated the safety and effectiveness of different administration methods of vancomycin in patients at risk of renal impairment because of critical illness. Despite of the high rate of renal impairment, Tafelski et al. [17] showed that there was a non-significant difference in renal impairment rates between intermittent and continuous infusion of vancomycin (p value=0.324) [17].

However, all the included studies were performed in one center, which may decrease the external validity of outcomes. Also, some studies did not identify the precise levels of renal impairment using CrCl levels, which could affect the reliability of these studies' outcomes. These limitations should be considered in future studies.

Finally, to our knowledge, this is considered the first systematic review to evaluate the consideration of antibiotic dosing and dosing errors in patients who are at risk or with a pre-existing renal impairment in different care settings.

Conclusion

Dosing of antibiotics in patients with renal impairment is conflicting and is subjected to a high dosing error incidence. It can affect both the safety and efficacy of antibiotics, especially in critically ill patients. Accordingly, the use of adequate renal clearance equations is crucial in the process of dosing calculation. A pharmacist's availability for adjusting renal dosing of antibiotics could play a significant role in reducing the incidence of dosing errors, particularly in high-risk patients such as elderly patients and critically ill patients.

References

1. Camargo MS, Mistro S, Oliveira MG, Passos LC. Association between increased mortality rate and antibiotic dose adjustment in intensive care unit patients with renal impairment. Eur J Clin Pharmacol. 2019 Jan 18;75(1):119-26. https://doi.org/10.1007/s00228-018-2565-7
2. Eppenga WL, Kramers C, Derijks HJ, Wensing M, Wetzels JF, De Smet PA. Drug therapy management in patients with renal impairment: how to use creatinine-based formulas in clinical practice. Eur J Clin Pharmacol. 2016 Dec 1;72(12):1433-9. https://doi.org/10.1007/s00228-016-2113-2
3. Abdulla A, Ewoldt TM, Hunfeld NG, et al. The effect of therapeutic drug monitoring of beta-lactam and fluoroquinolones on clinical outcome in critically ill patients: the DOLPHIN trial protocol of a multi-centre randomised controlled trial. BMC Infect Dis. 2020 Dec;20(1):1-9. https://doi.org/10.1186/s12879-020-4781-x
4. Khanal A, Peterson GM, Castelino RL, Jose MD. Renal drug dosing recommendations: evaluation of product information for brands of the same drug. Intern Med J. 2014 Jun;44(6):591-6. https://doi.org/10.1111/imj.12446
5. Denny KJ, Cotta MO, Parker SL, Roberts JA, Lipman J. The use and risks of antibiotics in critically ill patients. Expert Opin Drug Saf. 2016 May 3;15(5):667-78. https://doi.org/10.1517/14740338.2016.1164690
6. Delanaye P, Guerber F, Scheen A, et al. Discrepancies between the Cockcroft–gault and chronic kidney disease epidemiology (CKD-EPI) equations: implications for refining drug dosage adjustment strategies. Clin Pharmacokinet. 2017 Feb 1;56(2):193-205. DOI 10.1007/s40262-016-0434-z
7. Kumar BV, Mohan T. Retrospective comparison of estimated GFR using 2006 MDRD, 2009 CKD-EPI and Cockcroft-Gault with 24 hour urine creatinine clearance. Journal of clinical and diagnostic research: JCDR. 2017 May;11(5):BC09. doi: 10.7860/JCDR/2017/25124.9889
8. Bicalho MD, Soares DB, Botoni FA, Reis AM, Martins MA. Drug-induced nephrotoxicity and dose adjustment recommendations: agreement among four drug information sources. International journal of environmental research and public health. 2015 Sep;12(9):11227-40. https://doi.org/10.3390/ijerph120911227
9. Heringa M, Floor-Schreudering A, De Smet PA, Bouvy ML. Clinical decision support and optional point of care testing of renal function for safe use of antibiotics in elderly patients: a retrospective study in community pharmacy practice. Drugs & Aging. 2017 Nov 1;34(11):851-8. https://doi.org/10.1007/s40266-017-0497-z
10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 2009;6(7):e1000100. https://doi.org/10.1016/j.jclinepi.2009.06.006
11. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343 doi: https://doi.org/10.1136/bmj.d5928
12. Li MX, Li N, Zhu LQ, Liu W. Optimization of tigecycline dosage regimen for different infections in the patients with hepatic or renal impairment. J Chemother . 2020 Aug 5:1-9. https://doi.org/10.1080/1120009X.2020.1800318
13. Jarab F, Jarab AS, Mukattash T, Nusairat B, Alshogran O. Antibiotic dosing adjustments in patients with declined kidney function at a tertiary hospital in Jordan. Int J Clin Pract. 2020 Jun 11:e13579. https://doi.org/10.1111/ijcp.13579
14. Silva MA, Dias G, Cardoso T. Correlation of Estimated Creatinine Clearance and Glomerular Filtration Rate in Very Elderly Patients and Antibiotic Prescribing Errors: Cohort Study. Acta Med Port. 2020 Jul

29;33(13). https://doi.org/10.20344/amp.12408

15. Burger JR, Hansen BJ, Leary EV, Aggarwal A, Keeney JA. Dual-agent antibiotic prophylaxis using a single preoperative vancomycin dose effectively reduces prosthetic joint infection rates with minimal renal toxicity risk. J Arthroplasty. 2018 Jul 1;33(7):S213-8. https://doi.org/10.1016/j.arth.2018.03.00
16. Farag A, Garg AX, Li L, Jain AK. Dosing errors in prescribed antibiotics for older persons with CKD: a retrospective time series analysis. Am J Kidney Dis. 2014 Mar 1;63(3):422-8. http://dx.doi.org/10.1053/j.ajkd.2013.09.009
17. DeWitt KM, Weiss SJ, Rankin S, Ernst A, Sarangarm P. Impact of an emergency medicine pharmacist on antibiotic dosing adjustment. The American Journal of Emergency Medicine. 2016 Jun 1;34(6):980-4. http://dx.doi.org/10.1016/j.ajem.2016.02.004
18. Tafelski S, Nachtigall I, Troeger U, et al. Observational clinical study on the effects of different dosing regimens on vancomycin target levels in critically ill patients: continuous versus intermittent application. Journal of Infection and Public Health. 2015 Jul 1;8(4):355-63. http://dx.doi.org/10.1016/j.jiph.2015.01.011
19. Bailey O, Torkington MS, Anthony I, Wells J, Blyth M, Jones B. Antibiotic-related acute kidney injury in patients undergoing elective joint replacement. The bone & joint journal. 2014 Mar;96(3):395-8. doi:10.1302/0301-620X.96B3.
20. Chaves RL, Chakraborty A, Benziger D, Tannenbaum S. Clinical and pharmacokinetic considerations for the use of daptomycin in patients with Staphylococcus aureus bacteraemia and severe renal impairment. J Antimicrob Chemother. 2014 Jan 1;69(1):200-10. doi:10.1093/jac/dkt342