Tropical Journal of Pharmaceutical Research January 2020; 19 (1): 201-208
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v19i1.29

Original Research Article

A clinical study of drugs associated with acute kidney injury in the Chinese population

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Sent for review: 25 May 2019 *Revised accepted: 29 December 2019*

Abstract

Purpose: *To carry out a study aimed at comprehensive identificat6ion of classes of drugs which cause acute kidney injury (AKI).*
Methods: *A total of 110,508 patients enrolled in Weihai Central Hospital, Weihai, Shandong, China between March 2014 to April 2018 were asked to provide information on comprehensive prescription drug coverage including antivirals, antibiotics, NSAIDs, diuretics and anti-cancer drugs. Only the active users of these classes of drugs were included in the study. Daily prescription dose, duration, date and time of each drug were recorded. Furthermore, the characteristics and other conditions of the patients such as hypertension, congestive heart failure, diabetes, liver disease, angiotensin receptor blockers (ARBs), alpha-receptor blockers, beta-receptor blockers, and calcium channel-blockers were included.*
Results: *A total of 1230 patients presented with AKI during the first 60 days of follow-up, while 1546 (58 %) patients were diagnosed with AKI in the secondary endpoint. Indomethacin, valacyclovir, fluorouracil, levofloxacin, ibuprofen and rofecoxib produced higher frequencies of AKI than the control drug, celecoxib. Indomethacin (OR = 2.97 ; 95 % CI= 1.94 - 3.89) and valacyclovir (OR = 2.85 ; 95 % CI = 1.56 - 3.42) were mostly responsible for AKI, followed by rofecoxib (OR = 2.48 ; 95 % CI = 2.32 - 2.71), fluorouracil (OR = 2.58 ; 95 % CI = 1.94 - 3.11), ibuprofen (OR = 1.68 ; 95 % CI = 1.28 - 2.21) and levofloxacin (OR = 1.58 ; 95 % CI = 1.48 - 2.73), in that order*
Conclusion: *This study has identified various classes of drugs which frequently induced AKI. Therefore, physicians should exercise caution in prescribing these drugs, and should consider other medicines to minimize the risk of AKI.*

Keywords: *Acute kidney injury, Antiviral, NSAID, Toxicity*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Acute kidney injury (AKI) is defined as a sudden loss of renal function [1]. It is associated with high morbidity and mortality, especially in critically-ill patients [2]. The kidney performs various essential functions such as clearing of endogenous waste products, acid-base balance, electrolyte balance, and endocrine function. Thus, kidney injury may lead to complications such as metabolic acidosis, uremia, high potassium levels, imbalance in body fluids, multiple organ failure and ultimately death [3]. The causes of AKI vary from patient to patient, with a majority of cases due to damage to kidney

tissue. Decreased blood flow to the kidney may be due to several factors such as inflammatory response, urinary tract infection, low blood pressure, and exposure to toxic substances which are injurious to the kidney [4]. The symptoms of AKI which arise due to urea accumulation, cause headache, loss of appetite, nausea, vomiting, and fatigue. Apart from urea, other nitrogenous substances also get accumulated in the bloodstream, and may cause disorientation [5]. In some cases, potassium also gets accumulated and causes an irregular heart rhythm which is a serious threat to patient's survival. There is also an increased risk of chronic kidney injury in future [6].

Acute kidney injury (AQKI) is diagnosed based on laboratory results for blood urea and nitrogen contents, level of serum creatinine, and abnormalities in urination [7]. The disease was considered a reversible syndrome, but results from animal model experiments and human studies have demonstrated that majority of AKI result in permanent kidney damage [8]. Anti-inflammatory drugs and antibiotics are amongst the most widely prescribed medications in China. However, these drugs tend to have lots of side effects which include stomach ulcer, gastrointestinal bleeding and kidney injury. In some cases, antiviral and anti-cancer drugs cause various harmful side effects. There are also reports which suggest that NSAIDS are associated with an increased risk for chronic kidney disease [9]. Therefore, the objective of this study was to identify on a comprehensive basis, various classes of drugs which cause AKI.

METHODS

Ethical approval and standards

All procedures in this study were carried out in accordance with the Declaration of Helsinki of 1964 and its later amendments [10]. Informed consent was obtained from all the patients and participants. Informed consent was also obtained from the parents, guardians or authorized representative of the participants. All the protocols and procedures were approved by the Hospital Ethical Research Committee (approval number: ERC/DICU/3546-R35A).

Study population and data source

The study started in March 2014 and was completed in April 2018. In this program, a total of 110508 patients who were enrolled in the Weihai Central Hospital, Weihai, Shandong, China provided information on comprehensive prescription drug coverage which included antiviral, antibacterial, NSAIDs, diuretic and anti-cancer drugs. The study selected only patients who had been active users of these drugs for more than one year, and were in the age range of 60 – 75 years.

Main exposures

From the point of index prescription, the patients were categorized as users of antivirals (acyclovir and valacyclovir), NSAIDs (loxoprofen, ibuprofen and indomethacin), COX-2 inhibitors (celecoxib, diclofenac and rofecoxib); antibiotics (clarithromycin, levofloxacin and vancomycin), anti-cancer drug (fluorouracil) and diuretics (furosemide and spironolactone). The use of NSAIDs was defined as regular daily use of celecoxib, rofecoxib, ibuprofen, indomethacin and loxoprofen. Antibiotic use was defined as the use of drugs such as clarithromycin, levofloxacin, and vancomycin, whereas anticancer users were defined as those who used fluorouracil daily. Diuretic users were defined as patients on daily use of furosemide and spironolactone.

Daily prescription dose, duration, date and time for each drug were recorded. Patients who were prescribed more than one drug were not included during the study period. Track records on drug usage of all the patients were recorded until the patients were prescribed with different drugs, or until the completion of the follow-up period. There was more than 92% follow-up for the patients. Based on the enrollment files, the patients were characterized based on age-group and gender. Furthermore, the characteristics and other conditions of the patients such as hypertension, congestive heart failure, diabetes, liver disease, angiotensin receptor blockers (ARBs), alpha-receptor blockers, beta-receptor blockers, and calcium channel-blockers were recorded.

Assessment of health effects and LD_{50}

The health effects and lethal dose (LD_{50}) of the drugs were measured using iLab 2.0. (ACD Lab Inc, Toronto, Canada), to understand the toxic behavior of the investigated drugs.

Statistical analysis

Statistical analyses were carried out using SPSS Statistical Software 22.0 (SPSS Inc, USA). Frequencies for the different variables were calculated based on the category of drug usage. Characteristics of the patients were accessed for all the categories of drug exposure. Mean values for continuous variables such as age and BMI

were calculated for each category and frequency of drugs used, and were compared using Student's *t*-test. Multivariable logistic regression was used to estimate the odds ratios (OR), and 95 % confidence intervals (CI) for the association between drug use, and AKI, adjusting for age (in years), sex, hypertension, diabetes, congestive heart failure, myocardial infarction and gout. The relative risk for AKI was estimated based on the adjusted and unadjusted drug proportional hazard model. Celecoxib was used as the reference or the control since it was widely used among the investigated subjects.

RESULTS

In this study, 15348 out of a total of 110508 patients between the ages of 60 - 75 were identified as having been under prescription for NSAIDs, antivirals, antibiotics and other drugs for at least six months. The median age was 71 years for males, and 68 years for females. Non-steroidal anti-inflammatory drugs (NSAIDs) were the most commonly prescribed medicines among the patients (73.18%). Other prescribed drugs were antivirals (7.4 %), antibiotics (7.17 %), anticancer drugs (6.37 %) and diuretics (5.88 %). Details of information on the characteristics and drug usage are presented in Table 1. During the first 60 days of the follow-up period, a total of 1230 patients experiencing AKI were identified, whereas a total of 1546 (58 %) patients were claimed to be diagnosed with AKI in the secondary endpoint. Overall, there were 2776 cases of AKI at the end of the study. The incidence of AKI varied from 5.78 % (for aciclovir) to 32.43 % (for rofecoxib) for the primary outcome, whereas the incidence of AKI for the control (celecoxib) was 9.8 % (Table 2).

In the univariate analyses, indomethacin, valacyclovir, fluorouracil, levofloxacin, ibuprofen, and rofecoxib were associated with a higher risk of AKI than the control drug celecoxib. It was also observed that indomethacin and valacyclovir were associated with more than 60 % of the increased risk of AKI, when compared to celecoxib (95 % CI, 23 - 81 %). As shown in Table 3, the relative risks of AKI for valacyclovir, fluorouracil, levofloxacin, ibuprofen and rofecoxib were 2.23 (95 % CI = 1.63 - 2.83), 2.58 (95 % CI = 1.94-3.11), 1.58 (95 % CI = 1.48 - 2.73), 1.68 (95 % CI =.28 - 2.21), and 48 (95 % CI = 2.32 - 2.71), respectively. Even after adjusting for multivariate comparisons, the association with AKI remained statistically significant. The results remained unchanged among the outpatient and inpatient subjects, based on the analysis of incidence of AKI (Table 3). The risk for AKI did not vary much among users of indomethacin (OR = 2.97; 95 % CI= 1.94 - 3.89) and valacyclovir (OR = 2.85; 95 % CI = 1.56 - 3.42). Users of rofecoxib tended to have a higher risk of developing AKI than those who used other drugs. On the other hand, the reference drug celecoxib did not produce any dose-dependent association with AKI.

Besides, results from the assessment of health effects and LD_{50} revealed that most of these drugs resulted in negative effects on the blood, cardiovascular system, gastrointestinal tract, kidney, liver or lungs (Table 4). As shown in Table 5, majority of the drugs appeared to have low LD_{50} values which is an indication of their potential toxic effects.

DISCUSSION

In the present study, a comprehensive investigation was carried out on drugs which cause acute kidney injury. A total of 110508 patients were investigated during the study period, 15348 (13.89 %) of whom were diagnosed with kidney injury. Among the AKI cases, 1230 patients experienced AKI during the first 60 days of follow-up. In this study, elderly patients aged 60 - 75 years were investigated for risk of AKI among users of anti-inflammatory, antibiotics, antivirals, diuretics and anticancer drugs. It was observed that 3 in every 500 patients were diagnosed with AKI during the 60 days of initial hospital admission. The study also observed that the risk of AKI varied among drug users. Rofecoxib, ibuprofen and indomethacin (NSAIDs), fluorouracil (anticancer), levofloxacin (antibiotic), and valacyclovir (antiviral) were associated with high risk for AKI. The results also revealed that the period from drug exposure to occurrence of AKI was between 45 - 60 days. Furthermore, it was observed that the AKI patients were mostly above 70 years of age, especially the male population. This may be due to the fact that kidney function parameters were already elevated prior to exposure to these drugs. It was also observed that most of the AKI survivors recovered after the AKI episode.

A similar observation has also been reported in a study by Tonelli *et al* [11] which revealed that elderly male patients were more susceptible to AKI than other groups investigated. Studies have also shown that the incidence of AKI is rising among the elderly patients due to combinations of multiple diseases which include diabetes, vascular diseases and chronic kidney diseases [12,13].

Table 1: Characteristics of drug usage of the patients

N =15348	Celecoxib	Rofecoxib	Acicl ovir	Diclof enac	Ibupr ofen	Indome thacin	Loxop rofen	Clarithr omycin	Vanco mycin	Furos emide	Fluoro uracil	Levofl oxacin	Valacyc lovir	Spirono lactone
Percentage	31.13	18.06	6.31	4.76	9.84	3.86	5.53	2.81	1.38	4.01	6.37	2.98	1.09	1.87
Age (years)	69.21	67.43	69.32	70.23	64.67	67.84	68.43	69.23	70.34	69.45	70.23	67.45	68.53	69.42
Population (n)	4778	2769	969	731	1511	593	848	432	212	615	978	457	168	287
Diabetes	14.8	15.34	14.12	13.45	15.32	13.12	14.6	16.1	13.24	14.32	15.21	13.56	15.1	13.45
Hypertension	60.21	57.13	61.23	57.45	55.35	59.89	60.87	60.12	57.45	58.23	56.45	60.13	57.45	56.42
Gout	3.82	4.2	4.3	3.76	7.21	8.43	4.21	4.32	2.56	5.43	6.21	7.23	5.43	6.73
COPD	3.31	6.21	3.43	5.34	4.76	5.32	4.56	4.21	5.38	2.15	4.67	3.45	6.23	4.37
Renal disease	2.3	1.98	3.21	2.13	3.12	3.86	4.51	3.45	2.36	2.78	3.51	6.12	3.24	4.12
Myocardial infarction	5.12	4.43	3.78	4.12	3.89	5.83	5.62	4.13	4.52	4.12	5.38	4.93	4.12	4.73
Congestive heart failure	5.04	5.13	2.98	3.2	4.12	7.34	4.23	3.21	2.98	3.56	3.86	3.78	3.12	3.75
Pulmonary vascular disease	8.76	8.63	9.24	6.89	8.32	9.34	8.43	8.79	8.23	6.76	7.22	8.34	6.23	7.43
Liver disease	0.71	0.67	0.63	0.43	0.72	0.63	0.58	0.35	0.51	0.53	0.35	0.64	0.45	0.42
Malignancy	2.14	2.32	1.93	2.43	3.12	2.78	2.32	2.13	2.64	3.43	2.87	3.12	3.54	2.86
ACE Inhibitors	26.54	26.87	27.22	26.76	28.65	34.86	32.65	33.76	28.92	31.42	29.23	31.65	27.23	28.23
Angiotensin receptor blockers	14.23	13.54	21.65	11.43	9.23	14.21	15.65	21.65	11.43	12.32	8.63	12.32	10.43	10.43
Beta-blockers	29.43	29.23	32.43	27.34	28.23	35.32	32.65	33.76	28.23	28.79	26.23	30.11	27.32	28.25
Calcium blockers	34.65	33.65	32.65	33.67	31.34	32.56	32.54	33.54	34.23	30.23	33.42	33.45	31.34	30.54
Vasodilators	0.72	0.74	0.63	0.73	0.83	1.63	0.94	0.75	0.73	0.84	0.43	1.32	0.89	0.75
Diuretics	27.43	27.23	29.54	26.43	24.79	32.43	28.34	29.43	27.32	26.33	26.23	29.43	25.65	26.34

Table 2: Incidence of AKI due to various classes of drugs

Variable	Celecoxib	Rofecoxib	Aciclovir	Diclofenac	Ibuprofen	Indomethacin	Loxoprofen	Clarithromycin	Vancomycin	Furosemide	Fluorouracil	Levofloxacin	Valacyclovir	Spironolactone
Population	4778	2769	969	731	1511	593	848	432	212	615	978	457	168	287
Events	471	898	56	43	436	153	108	63	34	72	268	108	29	37
Percent	9.8	32.43	5.78	5.88	28.86	25.8	12.74	14.58	16.04	11.71	27.4	23.63	17.26	12.89

Table 3: Association between AKI and various classes of drugs

Drug	Classification	End Point Diagnosis with 1230 outcomes		Secondary Diagnosis with 1546 outcomes	
		Unadjusted	Adjusted	Unadjusted	Adjusted
Celecoxib	COX-2 Inhibitor	1.0	1.0	1.0 (Reference)	1.0 (Reference)
Rofecoxib	COX-2 Inhibitor	2.45 (2.17-2.78)	2.48 (2.32-2.71)	2.32 (2.13-2.66)	2.51 (2.34-2.63)
Aciclovir	Antiviral	1.14 (0.68-1.38)	1.12 (0.83-1.47)	1.14 (0.69-1.41)	1.18 (0.89-1.52)
Diclofenac	COX-2 Inhibitor	0.92 (0.61-1.42)	1.12 (0.72-1.68)	0.97 (0.55-1.38)	1.12 (0.83-1.57)
Ibuprofen	NSAID	1.59 (1.21-1.76)	1.68 (1.28-2.21)	1.63 (1.32-1.85)	1.71 (1.28-2.32)
Indomethacin	NSAID	2.97 (1.94-3.89)	2.12 (1.84-2.65)	2.74 (2.12-3.53)	2.23 (1.73-2.83)
Loxoprofen	NSAID	0.93 (0.71-1.23)	0.85 (0.63-1.23)	0.92 (0.71-1.23)	0.92 (0.59-1.25)
Clarithromycin	Antibiotic	0.94 (0.74-1.28)	0.95 (0.66-1.54)	0.94 (0.67-1.62)	1.17 (0.67-1.74)
Vancomycin	Antibiotic	0.83 (0.56-1.23)	0.91 (0.68-1.52)	0.78 (0.56-1.23)	0.83 (0.53-1.37)
Furosemide	Diuretics	1.16 (0.78-1.39)	1.41 (1.13-1.72)	1.21 (0.92-1.54)	1.27 (1.14-1.74)
Fluorouracil	Anticancer	2.18 (1.72-3.16)	2.58 (1.94-3.11)	2.39 (1.16-2.53)	2.69 (2.05-3.07)
Levofloxacin	Antibiotic	1.53 (1.43-3.14)	1.58 (1.48-2.73)	2.15 (1.19-3.65)	2.76 (2.12-3.11)
Valacyclovir	Antiviral	2.85 (1.56-3.42)	2.23 (1.63-2.83)	1.79 (1.51-2.38)	1.91 (2.67-2.54)
Spironolactone	Diuretics	0.97 (0.78-1.31)	0.96 (0.63-1.48)	0.74 (0.54-1.27)	0.86 (0.61-1.43)

Table 4: Health effects of the investigated drugs

Health Effect on	Aciclovir	Celecoxib	Ciclosporin	Clarithromycin	Diclofenac	Edaravone	Fluorouracil	Furosemide	Ibuprofen	Indomethacin	Ketorolac	Levofloxacin	Loxoprofen	Meloxicam	Nabumetone	Naproxen	Oxaprozin	Rofecoxib C	Spironolactone	Sulindac	Valacyclovir	Vancomycin
Blood	0.51	0.26	0.95	0.56	0.22	0.21	0.26	0.39	0.19	0.17	0.19	0.38	0.21	0.16	0.13	0.2	0.39	0.42	0.97	0.27	0.84	0.03
Cardiovascular System	0.16	0.83	0	1	0.36	0.09	0.76	0.24	0.24	0.2	0.29	0.28	0.18	0.03	0.94	0.44	0.38	0.82	1	0.3	0.66	0.52
Gastro-intestinal tract	0.08	0.62	0.4	0.81	0.53	0.43	0.78	0.25	0.07	0.83	0.42	0.93	0.13	0.28	0.62	0.65	0.32	0.81	1	0.33	0.59	1
Kidney	0.05	0.17	0.82	0.88	0.33	0.16	0.06	0.21	0.08	0.27	0.18	0.58	0.29	0.13	0.81	0.32	0.56	0.73	0.96	0.58	0.15	0.62
Liver	0.13	0.14	1	0.91	0.18	0.06	0.19	0.27	0.17	0.17	0.32	0.5	0.24	0.02	0.07	0.18	0.27	0.1	0.83	0.34	0.24	0.96
Lungs	0.16	0.43	0.17	0.75	0.63	0.09	0.97	0.34	0.24	0.44	0.31	0.47	0.15	0.14	0.21	0.13	0.34	0.3	0.99	0.35	0.64	0.04

Table 5: LD_{50} values of the investigated drugs

LD_{50} (mg/kg)	**Aciclovir**	**Celecoxib**	**Ciclosporin**	**Clarithromycin**	**Diclofenac**	**Edaravone**	**Fluorouracil**	**Furosemide**	**Ibuprofen**	**Indomethacin**	**Ketorolac**	**Levofloxacin**	**Loxoprofen**	**Meloxicam**	**Nabumetone**	**Naproxen**	**Oxaprozin**	**Rofecoxib**	**Spironolactone**	**Sulindac**	**Valacyclovir**	**Vancomycin**
Mouse (intraperitoneal)	430	630	13	440	540	1200	500	4600	800	120	400	450	510	760	850	350	470	730	370	890	740	22
Mouse (oral)	44	810	85	2900	410	1100	860	3400	1100	220	570	800	2300	440	3600	590	1200	650	320	850	18	260
Mouse (intravenous)	470	150	40	170	130	230	120	470	270	120	280	170	370	170	130	330	190	93	13	260	230	330
Mouse (subcutaneous)	730	360	2.4	1500	410	430	400	700	690	160	590	820	1000	830	490	580	920	190	13	520	280	750
Rat (intraperitoneal)	780	1300	160	190	130	570	290	1200	600	120	330	98	360	320	650	250	840	240	440	740	1300	460
Rat (oral)	340	500	330	2300	220	2100	2200	3700	1500	88	330	1200	220	61	2800	560	2700	680	31	550	180	32

These patients also have a higher degree of exposure to several nephrotoxic agents during the diagnostic procedures and drug administration [14]. The results of the present study indicate that the drug classes most frequently associated with AKI were NSAIDs, followed by antivirals and antibiotics. Among the NSAIDs, indomethacin, rofecoxib, and ibuprofen were associated with the highest incidents of AKI.

Valacyclovir (antiviral), fluorouracil (anticancer) and levofloxacin (antibiotic) were also associated with a high frequency of AKI. A similar report of acute renal failure among elderly patients due to valacyclovir has been made by Carlon *et al,* based on data from long-term use of valacyclovir [15]. Levofloxacin (antibiotic) was more associated with AKI than clarithromycin and vancomycin. Bird *et al* also reported risk of AKI associated with the use of levofloxacin, a fluoroquinolone [16]. Zhang *et al* reported the various effects of COX-2 inhibitors and their renal outcomes, including renal dysfunction, peripheral edema, and hypertension [17]. Their report revealed an increased risk of renal disease among rofecoxib users, when compared to celecoxib users. This is consistent with the results of the present study. Griffin *et al* [18] also reported elevated risk of AKI among elderly patients who used indomethacin and ibuprofen, when compared to other NSAIDs. This is also in agreement with the findings in this study. Moreover, Huerta *et al* [19] reported an association between NSAIDs and acute renal failure (ARF) among users of ibuprofen and diclofenac, especially among patients with hypertension, heart failure and diabetes [20].

Overall in this study, it is confirmed that a higher incidence of acute kidney injury is associated with the users of indomethacin, valacyclovir, rofecoxib, fluorouracil, ibuprofen, and levofloxacin. However, the other drugs such as celecoxib, aciclovir, diclofenac, loxoprofen, clarithromycin, vancomycin, furosemide, spironolactone produced high rates of remission and recovery.

CONCLUSION

The results obtained in this study indicate that NSAIDs viz, indomethacin, rofecoxib, and ibuprofen, and levofloxacin, fluorouracil and valacyclovir are associated with risk of AKI. These findings strongly suggest the need for caution by medical practitioners when prescribing these drugs to avoid risk of developing acute kidney injury.

DECLARATIONS

Acknowledgement

The authors acknowledged the support (including grants) received from the Weihai Central Hospital, Weihai, Shandong, China (Project no. WCH2014/0223-R).

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

REFERENCES

1. *Konstantinos M, Loukia S. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. Clin Biochem Rev 2016, 37(2): 85–98.*
2. *Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care.2007; 11: R31*
3. *Sawhney S, Mitchell M, Marks A, Fluck N, Black C. Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. BMJ Open 2015; 5: e006497.*
4. *Venkatachalam MA, Weinberg JM, Kriz W, Bidani AK. Failed Tubule Recovery, AKI-CKD Transition, and Kidney Disease Progression. J Am Soc Nephrol 2015; 26(8): 1765-1776.*
5. *Levey AS, James MT. Acute Kidney Injury. Ann Intern Med 2017; 167(9): ITC66-ITC80.*
6. *Barnett LMA, Cummings BS. Cellular and molecular mechanisms of kidney toxicity. Semin Nephrol 2019; 39(2): 141-151.*
7. *Cruz DN, Ricci Z, Bagshaw SM, Piccinni P, Gibney N, Ronco C. Renal replacement therapy in adult critically ill*

patients: when to begin and when to stop. Contrib Nephrol 2010; 165: 263-273.

8. *Gonsalez SR, Cortês AL, Silva RCD, Lowe J, Prieto MC, Silva Lara LD. Acute kidney injury overview: From basic findings to new prevention and therapy strategies. Pharmacol Ther 2019; 200: 1-12.*
9. *Dalili N, Kashani K. Acute kidney injury risk recognition in resource-sufficient versus resource-limited regions. Iran J Kidney Dis 2018; 12(5): 261-267*
10. *Carlson RV, Boyd KM, Webb DJ. The revision of the Declaration of Helsinki: past, present and future. Br J Clin Pharmacol 2004; 57: 695-713*
11. *Tonelli M, Lloyd AM, Bello AK, James MT, Klarenbach SW, McAlister FA, Manns BJ, Tsuyuki RT, Hemmelgarn BR; Alberta Kidney Disease Network. Statin use and the risk of acute kidney injury in older adults. BMC Nephrol 2019; 20(1): 103.*
12. *Clemens KK, O'Regan N, Rhee JJ. Diabetes management in older adults with chronic kidney disease. Curr Diab Rep 2019; 19(3): 11.*
13. *Dieter BP, Daratha KB, McPherson SM, Short R, Alicic RZ, Tuttle KR. Association of acute kidney injury with cardiovascular events and death in systolic blood pressure intervention trial. Am J Nephrol 2019; 49(5): 359-367.*
14. *Oyama S, Hosohata K, Inada A, Niinomi I, Mori Y, Yamaguchi Y, Uchida M, Iwanaga K. Drug-induced tubulointerstitial nephritis in a retrospective study using spontaneous reporting system database. Ther Clin Risk Manag 2018; 14: 1599-1604.*
15. *Carlon R, Possamai C, Corbanese U. Acute renal failure and severe neurotoxicity following valacyclovir. Intensive Care Med 2005; 31(11): 1593-1598*
16. *Bird ST, Etminan M, Brophy JM, Hartzema AG, Delaney JA. Risk of acute kidney injury associated with the use of fluoroquinolones. CMAJ 2013; 185(10): E475-E482.*
17. *Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. JAMA 2006; 296(13): 1619-32*
18. *Griffin MR, Yared A, Ray WA. Nonsteroidal anti-inflammatory drugs and acute renal failure in elderly persons. Am J Epidemiol 2000; 151(5): 488-496.*
19. *Huerta C, Castellsague J, Varas-Lorenzo C, García Rodríguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. Am J Kidney Dis 2005; 45(3): 531-539.*
20. *Winkelmayer WC1, Waikar SS, Mogun H, Solomon DH. Nonselective and cyclooxygenase-2-selective NSAIDs and acute kidney injury. Am J Med. 2008; 121(12): 1092-1098.*