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ORIGINAL RESEARCH ARTICLE

Medicine-Induced Acute Kidney Injury Findings from Spontaneous Reporting Systems, Sequence Symmetry Analysis and a Case–Control Study with a Focus on Medicines Used in Primary Care

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Abstract

Introduction Primary care provides an opportunity to prevent community acquired, medicine or drug-induced acute kidney injury. One of the barriers to proactive prevention of medicine-induced kidney injury in primary care is the lack of a list of nephrotoxic medicines that are most problematic in primary care, particularly one that provides a comparison of risks across medicines.

Objective The aim of this study was to consolidate evidence on the risks associated with medicines and acute kidney injury, with a focus on medicines used in primary care.

Method We searched the MEDLINE and EMBASE databases to identify published studies of all medicines associated with acute kidney injury identified from spontaneous report data. For each medicine positively associated with acute kidney injury, as identified from spontaneous reports, we implemented a sequence symmetry analysis (SSA) and a case–control design to determine the association between the medicine and hospital admission with a primary diagnosis of acute kidney injury (representing community-acquired acute kidney injury). Administrative claims data held by the Australian Government Department of Veterans' Affairs for the study period 2005–2019 were used.

Results We identified 89 medicines suspected of causing acute kidney injury based on spontaneous report data and a reporting odds ratio above 2, from Japan, France and the US. Spironolactone had risk estimates of 3 or more based on spontaneous reports, SSA and case–control methods, while furosemide and trimethoprim with sulfamethoxazole had risk estimates of 1.5 or more. Positive association with SSA and spontaneous reports, but not case control, showed zoledronic acid had risk estimates above 2, while candesartan telmisartan, simvastatin, naproxen and ibuprofen all had risk estimates in SSA between 1.5 and 2. Positive associations with case–control and spontaneous reports, but not SSA, were found for amphotericin B, omeprazole, metformin, amlodipine, ramipril, olmesartan, ciprofloxacin, valaciclovir, mycophenolate and diclofenac. All with the exception of metformin and omeprazole had risk estimates above 2.

Conclusion This research highlights a number of medicines that may contribute to acute injury; however, we had an insufficient sample to confirm associations of some medicines. Spironolactone, furosemide, and trimethoprim with sulfamethoxazole are medicines that, in particular, need to be used carefully and monitored closely in patients in the community at risk of acute kidney injury.

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Key Points

One of the barriers to proactive prevention of medicine-induced kidney injury in primary care is the lack of a definitive list of nephrotoxic medicines, particularly one that provides a comparison of risks across medicines.

We identified 89 medicines suspected of causing acute kidney injury based on spontaneous report data with a reporting odds ratio above 2, from three different countries, with 21 associations confirmed by SSA or case–control studies using administrative health claims data.

Spironolactone, furosemide, and trimethoprim/sulfamethoxazole had the highest risk of acute kidney injury. They need to be monitored closely in patients in the community at risk of acute kidney injury.

1 Introduction

Acute kidney injury is a clinical syndrome associated with up to 15% of hospital admissions [1, 2], and occurs in up to 50% of persons in intensive care [3]. The development of acute kidney injury, even mild forms, is associated with poorer health outcomes in the longer term [4, 5], thus prevention of acute kidney injury is the first aim of care [4].

A number of factors have been associated with acute kidney injury, including patient characteristics, sepsis and shock, as well as medications [6]. Medications are thought to account for as much as 20% of all cases of community-acquired acute kidney injury [4]. Many of the factors associated with acute kidney injury are not modifiable, however medications represent one of the most easily modifiable risk factors; thus, being alert to the medicines that can contribute to acute kidney injury represents one opportunity for prevention [4].

Primary care provides an opportunity to prevent community-acquired acute kidney injury due to medicines. Studies suggest use of contraindicated medicines in persons with renal failure is frequent in primary care. A US study examined use of nephrotoxic medicines in persons with predialysis chronic kidney disease and found 72% were exposed to a potentially nephrotoxic medicine, with half prescribed two nephrotoxic medicines. [7] Furthermore, nephrotoxic medicine use in this population was associated with increased health service use and costs [7]. A systematic review involving 18 studies reported up to 37% of persons with renal impairment in primary care had inappropriate medicine use [8], Inappropriate medicine use leads to significant harm. A Dutch study showed that 10% of medicine-related hospital admissions were due to renal impairment [9]. Renal failure has been found to be a significant predictor of readmissions due to adverse medicine reactions [10].

One of the barriers to proactive prevention of medicine-induced kidney injury in primary care is the lack of a definitive list of nephrotoxic medicines, particularly one that provides a comparison of risks across medicines. Lists have been generated based on literature review, expert opinion and pathological processes [11–18]. In the last few years, a number of authors have also reported lists of potentially nephrotoxic medicines based on associations generated from spontaneous reports of adverse medicine events [19–21]. These analyses provide opportunity to compare results across databases and create lists of nephrotoxic medicines with differential risk estimates because the studies used a consistent method and consistent data source. Spontaneous reports are effective in identifying new signals of adverse medication events but are limited by underreporting of events. Confirmation bias possibly restricts new medicines being identified, as to make a spontaneous report the reporter is required to first be suspicious that the event is an adverse event of the medicine and have sufficient motivation to report. Electronic health records offer a mechanism to confirm suspected associations between medicines and acute kidney injury, with electronic databases providing complete capture of both medicine use and the adverse event.

This study aimed to consolidate the evidence from the studies that used spontaneous report data to identify the range of medicines associated with acute kidney injury, with a particular focus on medicines used in primary care, and confirm the associations using administrative claims data.

Combinations of methods are recommended for confirming safety associations [22], with self-controlled methods considered to have higher predictive accuracy [23, 24]. Consistent with this, we used two different pharmacoepidemiological methods to determine the associations: sequence symmetry analysis (SSA), which mimics a within-person design and thus inherently adjusts for patient-specific confounders, and a traditional pharmacoepidemiological design, the case–control study that has the advantage of overcoming small sample sizes.

2 Method

2.1 Spontaneous Report Studies

We searched the MEDLINE and EMBASE databases to identify all studies that had investigated all medicines associated with acute kidney injury from spontaneous adverse event reporting databases. Search terms included drug-related side effects or adverse reactions or drug-induced;

acute kidney injury or acute kidney failure; adverse drug reaction reporting systems or pharmacovigilance or drug surveillance programme or spontaneous report. The full search is included in electronic supplementary Tables 1 and 2.

We included studies that had identified the range of possible medicines that were associated with acute kidney injury, but excluded studies that had examined a single medicine class, single medicine or medicine interaction.

For each result, we extracted the medicine name or class, disproportionality measure and 95% confidence interval (CI). The list of medicines associated with acute kidney injury was generated where at least one study had found a reporting odds ratio (ROR) above 2 and the CIs did not contain 1 [25].

2.2 Observational Studies

We used a self-controlled design, SSA, and a case–control design to confirm the associations identified from spontaneous reports.

Setting We used the Australian Government Department of Veterans' Affairs administrative health claims database, which contains details of all prescription medicines, medical and allied health services, and hospitalisations provided to Department of Veterans' Affairs clients for which the Department of Veterans' Affairs pays a subsidy. The data cover a treatment population of approximately 250,000 clients.

The Study Period This study was conducted between 1 July 2005 and 30 June 2019.

The Primary Outcome Hospitalisations for acute kidney injury (primary diagnosis; International Classification of Diseases, Tenth Revision [ICD-10] code N17). We used the primary diagnosis code only, which indicates the cause of admission, and thus the primary outcome represents community-acquired acute kidney injury. Secondary diagnoses, which may include acute kidney injury that occurred during hospital stay, were not assessed because we did not have complete capture of medicines administered during hospital stay. The ICD-10 code N17 has been validated and shown to have high specificity but low-to-moderate sensitivity for acute kidney injury [26, 27].

The exposure Medicines identified as potentially nephrotoxic using data from the spontaneous reporting systems, i.e. medicines with an ROR above 2 and the CIs did not contain 1. Medicines used in the hospital setting only, such as parenteral antibiotics, were excluded from the analysis, as were medicines not available in Australia.

2.2.1 Study Design: Sequence Symmetry Analysis

The SSA is a self-controlled design that has been validated for adverse medicine event detection, showing moderate sensitivity, high specificity and robust performance [28, 29]. We examined the incident events of medicine exposure and hospitalisation for acute kidney injury, and included persons for whom both events occurred within a 12-month period.

SSA statistical methods For each medicine of interest, we calculated the sequence ratio [SR] by dividing the number of people who had acute kidney injury in the 12 months after initiation of the medicine by the number of people who had acute kidney injury in the 12 months before initiation of the medicine. To adjust for temporal changes in prescribing and hospitalisation trends over time, an adjusted SR [ASR] was calculated by dividing the crude SR by a null-effect SR [30]. The 95% CI was derived from bootstrapping with 10,000 samples of the ASR [31].

2.2.2 Study Design: Case–Control Study

We defined cases as persons who had their first hospitalisation for acute renal failure (ICD-10 code N17) in the study period, while controls were persons hospitalised for medical conditions other than acute renal failure in the same calendar year as the case. All cases and controls had at least one full year of claims history prior to the index admission.

Each case was matched to five controls by sex, age at date of admission (± 2 years) and year of admission (± 1 year). Cases could be controls prior to becoming a case, and controls were sampled with replacement. Medicine exposure was assessed in the year prior to the index date. We estimated medicine exposure based on the number of days supplied at the time of dispensings. The estimated days of supply was defined by the time period in which 75% of people returned for a repeat dispensing [19, 20]. For the majority of medicines in Australia, 1 month supply is provided under the national Pharmaceutical Benefits Scheme, and the time period within which 75% of people return is 35 days (the exposure period), allowing a 5-day grace period of non-adherence.

People were categorised into four groups: (1) *new users* were defined as people exposed at the time of admission (i.e. the supply period crossed the date of admission) and this was their first supply in that year; (2) *current users* were defined as persons who were on the medicine at the time of hospital admission but had previously had supplies during the year; (3) *past users* were defined as those who had had supplies previously in the year but did not have sufficient days supplied to cover the period, including the hospital admission; and (4) *n*ever users, i.e. persons with no dispensing of the medicine within the year prior to hospitalisation (see Fig. 1 in the electronic supplementary Appendix).

Case–Control Design Statistical Methods Descriptive statistics were used to report patient characteristics assessed at the time of hospital admission, including age, sex, residential status (living in the community or an aged care facility).

Conditional logistic regression was used to determine the association between exposure and acute kidney injury using non-exposure as the reference. The model was implemented once as a full model adjusting for other nephrotoxic medicines and number of dispensings of medicines in the year prior to the hospitalisation. ORs and 95% CIs were calculated for the medicines at a group and individual medicine level.

We used SAS version 9.4 (SAS Institute, Cary, NC, USA) to analyse the data.

3 Results

We located three studies that had all used RORs to identify potentially nephrotoxic medicines. The studies analysed data from the US FDA Adverse Event Reporting database [21], the Japanese Adverse Drug Event Report Database [19] and the French National Pharmacovigilance Database [20]. Across the three databases, there were 89 medicines that had an ROR above 2 in at least one database (Table 1).

Of the 89 medicines identified, 53 were able to be assessed in the Australian dataset.

For the SSA, populations were available over the entire study period. The number of people with both a medicine exposure and a hospital record for acute kidney injury ranged from 2 to 1798 (see electronic supplementary Table 3).

For the case–control study, a total of 7735 cases who were hospitalised with acute renal failure were matched by sex, age (± 2 years) and year of admission (± 1 year), with 38,675 controls (17,589 unique patients) without this condition at hospital admission. The median number of prescription dispensings in the year prior to admission was 84 for cases and 75 for controls. More cases than controls were living in a residential aged care facility prior to admission (22.5% vs. 16.9%). The full case–control results are available in electronic supplementary Table 4.

Spironolactone, furosemide, and trimethoprim with sulfamethoxazole were the three medicines with statistically significant associations using all methods. Spironolactone had the highest risk, with risk estimates of 3 or more by all methods, while furosemide and trimethoprim with sulfamethoxazole had risk estimates of 1.5 or more by all methods (Table 1).

We found positive associations for digoxin, perindopril, candesartan telmisartan, simvastatin, naproxen, ibuprofen, and zoledronic acid using SSA and spontaneous reports, but not for the case–control study. Zoledronic acid had the highest risk estimates, above 2, while candesartan telmisartan, simvastatin, naproxen and ibuprofen all had risk estimates in the SSA between 1.5 and 2 (Table 1).

We found positive associations for amphotericin B, omeprazole, metformin, amlodipine, ramipril, olmesartan, ciprofloxacin, valaciclovir, mycophenolate and diclofenac using the case–control design and spontaneous reports, but not for the SSA. With the exception of metformin and omeprazole, all had risk estimates in the case–control study above 2.

Results for medicines that were positive in the spontaneous reports but not assessable in our dataset are included in electronic supplementary Table 6.

4 Discussion

Our study focused on medicines that put people at risk of admission to hospital for acute kidney injury and the comparative risks across medicines. Three medicines, spironolactone, furosemide, spironolactone and sulfamethoxazole with trimethoprim, were associated with acute kidney injury across all three methods, with spironolactone having the highest risk.

Risk estimates above 2 by at least two methods were also found for zoledronic acid, amphotericin B, amlodipine, ramipril, olmesartan, ciprofloxacin, valaciclovir, mycophenolate and diclofenac. Other epidemiological studies confirm these associations. A New Zealand study showed a fourfold elevated risk of acute kidney injury where an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker was started in the previous 7 days (adjusted OR 4.07, 95% CI 3.37–4.93), and a sixfold increase in risk for initiation of a diuretic in the previous 7 days (adjusted OR 6.31, 95% CI 5.46–7.29) [32]. This same study found a sevenfold elevated risk for starting non-steroidal anti-inflammatory drugs (NSAIDs) in the previous 7 days (adjusted OR 7.30, 95% CI 6.59–8.10).

One of the challenges in assessing the nephrotoxic nature of medicines is that the medicines implicated, such as medicines affecting the renin angiotensin system, are frequently used to treat morbidities that make people more at risk of acute kidney injury, such as diabetes and heart failure; thus, confounding by indication can be a factor affecting associations. Patient-related precipitating factors, such as infection, dehydration or exacerbation of an illness such as heart failure, may also have confounded the results observed [33, 34]. However, we included SSA as a method to control for patient-specific confounding, which suggests the addition of the medicine was a contributor independent of the disease. These associations are further confirmed by our case–control study, which showed the risk was highest in new users (electronic supplementary Results), as well as the observations from spontaneous reporting systems in three countries.

Table 1 Medicines and their association with acute kidney injury

ATC code—main systemic	Medication	US FDA adverse drug event reporting system	Japanese adverse drug event reporting system	French adverse drug event reporting system	No. of databases in which the ROR was ≥2 and lower 95% CI >1	SSA result, Australian ASR (95% CI)	Case–control result (new users vs. non-users) [OR (95% CI)]
Positive results in spontaneous reports, sequence symmetry and case–control methods							
C03DA01	Spironolactone	8.97 (8.24–9.77)	7.36 [6.12–8.86]	10.54 [7.39–15.03]	3	2.96 (2.59–3.40)	3.45 (3.01–3.95)
C03CA01	Furosemide	12.61 (11.94–13.32)	4.23 [3.60–4.96]	16.5 [13.63–19.99]	3	1.86 (1.68–2.06)	3.97 (3.54–4.45)
J01EE01	Sulfamethoxazole and trimethoprim	6.96 (6.38–7.59)		4.17 [3.25–5.36]	2	1.56 (1.29–1.89)	17.37 (9.67–31.2)
Positive results by the sequence symmetry and spontaneous reports methods							
C09CA06	Candesartan		4.49 [3.56–5.66]	10.88 [7.28–16.25]	2	1.76 (1.30–2.37)	Not assessable
M01AE02	Naproxen	0.63 (0.59–0.68)		3.68 [1.96–6.9]	1	1.67 (1.05–2.68)	1.99 (0.95–4.19)
M01AE01	Ibuprofen	3.15 (3.01–3.30)		2.03 [1.35–3.05]	2	1.56 (1.07–2.27)	1.49 (0.69–3.22)
M05BA08	Zoledronic acid	2.23 (2.15–2.31)		2.92 [1.52–5.6]	2	2.52 (1.63–3.89)	0.99 (0.8–1.23)
C01AA05	Digoxin	5.77 (5.45–6.10)			1	1.41 (1.19–1.66)	Not assessable
C09AA04	Perindopril			6.95 [5.35–9.03]	1	1.41 (1.20–1.66)	Not assessable
C09CA07	Telmisartan			3.85 [1.51–9.78]	1	1.60 (1.16–2.21)	Not assessable
C10AA01	Simvastatin	4.06 (3.88–4.25)			1	1.53 (1.04–2.23)	1.69 (0.75–3.85)
Positive results by the case–control and spontaneous reports methods							
A01AB04	Amphotericin B	8.08 (7.33–8.91)			1	No pairs	4.41 (1.91–10.21)
A02BC01	Omeprazole	2.35 (2.19–2.53)			1	0.93 (0.77–1.12)	1.57 (1.04–2.37)
A10BA02	Metformin	10.65 (10.31–11.00)		5.17 [3.89–6.86]	2	1.02 (0.71–1.46)	1.72 (1.04–2.83)
C08CA01	Amlodipine	2.32 (2.18–2.48)		3.26 [2.29–4.64]	2	0.64 (0.55–0.75)	2.39 (1.66–3.43)
C09AA02	Enalapril	8.32 (7.57–9.16)		4.21 [2.29–7.72]	2	1.26 (0.65–2.47)[a]	2.02 (0.5–8.18)
C09AA05	Ramipril	7.10 (6.69–7.53)		5.81 [4.26–7.92]	2	1.03 (0.85 - 1.25)	2.02 (1.27–3.21)
C09CA08	Olmesartan	5.08 (4.65–5.56)		7.55 [5.5–10.37]	2	1.59 (0.89–2.82)[a]	4.51 (1.56–13.04)
C09CA03	Valsartan	3.05 (2.88–3.23)	2.15 [1.72–2.69]	6.36 [4.28–9.47]	3	2.77 (0.74–10.4)[a]	1.03 (0.09–11.55)
J01MA02,	Ciprofloxacin	2.4 (2.30–2.63)		1.94 [1.2–3.14]	1	1.08 (0.41–2.79)[a]	3.99 (2.48–6.42)
J05AB11	Valaciclovir	8.49 (8.04–8.96)	24.88 [23.10–26.80]	4.36 [2.48–7.65]	3	1.07 (0.73–1.56)	2.48 (1.34–4.57)
L04AA06	Mycophenolic acid Mycophenolate mofetil	9.53 (8.76–10.38) 3.90 (3.65–4.17)			1	0.96 (0.35–2.64)[a]	30.48 (1.35–690.7)
M01AB05	Diclofenac	4.05 (3.82–4.30)	4.38 [3.78-5.08]	6.27 [4.29–9.16]	3	0.88 (0.27–2.89)[a]	3.05 (1.75–5.32)
Positive results by the spontaneous reports methods							
J05AB01	Aciclovir	8.60 (7.93–9.32)	11.17 [9.55–13.10]	23.25 [15.12–35.77]	3	1.72 (0.92–3.23)[a]	4.91 (0.81–29.71)
C09AA03	Lisinopril	4.24 (3.99–4.50)		7.02 [3.08–16.01]	2	2.00 (0.85–4.73)[a]	1.07 (0.1–12.04)[a]
L04AD02	Tacrolimus	4.40 (4.21–4.60)		2.59 [1.39–4.8]	2	1.91 (0.46–7.99)[a]	Not assessable
L04AX03, L01BA01	Methotrexate	2.59 (2.41–2.78)		2.15 [1.54–2.98]	2	1.85 (0.85–4.05)[a]	0.99 (0.54–1.82)
N05AN01	Lithium	8.86 (8.15–9.64)		2.14 [1.3–3.5]	2	No pairs	0.88 (0.24–3.21)

Table 1 (continued)

ATC code—main systemic	Medication	US FDA adverse drug event reporting system	Japanese adverse drug event reporting system	French adverse drug event reporting system	No. of databases in which the ROR was ≥2 and lower 95% CI >1	SSA result, Australian ASR (95% CI)	Case–control result (new users vs. non-users) [OR (95% CI)]
A02BA03	Famotidine		2.47 [1.99–3.07]		1	0.65 (0.33–1.26)[a]	Not assessable
A10BB09	Gliclazide			3.16 [1.52–6.57]	1	0.52 (0.38–0.71)	Not assessable
A10BH01	Sitagliptin			2.23 [1.13–4.41]	1	1.47 (0.81–2.68)[a]	Not assessable
B01AE07	Dabigatran	2.18 (2.09–2.27)			1	1.24 (0.53–2.92)[a]	Not assessable
C03AA03	Hydrochlorothiazide			6.39 [5.05–8.09]	1	1.19 (0.94–1.51)	Not assessable
C03BA11	Indapamide			2.36 [1.28–4.38]	1	1.30 (0.89–1.90)	Not assessable
C03DA04	Eplerenone			27.42 [11.62–64.68]	1	0.55 (0.14–2.19)[a]	Not assessable
C09CA01	Losartan			7.35 [3.67–14.71]	1	1.0 (0.06–15.9)[a]	Not assessable
C09CA04	Irbesartan			3.99 [2.55–6.25]	1	1.10 (0.87–1.38)	Not assessable
C10AB05	Fenofibrate			2.5 [1.09–5.76]	1	1.98 (0.93–4.23)[a]	Not assessable
J01DD04	Ceftriaxone	4.66 (4.30–5.06)		1.63 [1.09–2.43]	1	0.65 (0.57–0.74)	Not assessable
J04AB02	Rifampicin, rifampin			2.42 [1.62–3.63]	1	1.18 (0.65–2.16)[a]	Not assessable
L01AA03	Melphalan			4.08 [1.94–8.55]	1	1.07 (0.39–2.95)[a]	Not assessable
L01BA04	Pemetrexed			4.31 [2.4–7.73]	1	2.66 (0.52–13.7)[a]	Not assessable
L01BC05	Gemcitabine			2.99 [1.69–5.3]	1	1.44 (0.61–3.42)[a]	Not assessable
L01CB01	Etoposide			2.06 [1.15–3.71]	1	1.34 (0.46–3.85)[a]	Not assessable
L01XA01	Cisplatin		1.73 [1.52–1.98]	10.46 [7.4–14.79]	1	2.62(0.93–7.34)[a]	Not assessable
L01XA02	Carboplatin	2.19 (2.02–2.38)			1	1.94 (0.96–3.93)[a]	Not assessable
L01XX32	Bortezomib	2.48 (2.34–2.62)			1	0.38 (0.15–0.95)[a]	Not assessable
M04AC01	Colchicine			7.33 [5.1–10.54]	1	1.17 (0.96–1.42)	Not assessable
M05BA03	Pamidronate acid	5.38 (5.06–5.72)			1	0.41 (0.17–1.01)[a]	1.34 (0.2–8.98)
V03AC03	Deferasirox	4.29 (4.11–4.48)			1	1.92 (0.17–21.2)[a]	Not assessable

ATC Anatomical Therapeutic Chemical, *SSA* sequence symmetry analysis, *ASR* adjusted sequence ratio, *OR* odds ratio, *CI* confidence interval, *ROR* reporting odds ratio

[a]Fewer than 50 pairs

The dosage of the medicine used may also have been a factor contributing to the risk of acute kidney disease. An Australian study among persons with renal impairment who were admitted to hospital found that for persons aged 40 years and over with either hypertension or poor renal function (a creatinine clearance of ≤60 mL/min), 32% were receiving a medicine that required renal adjustment or was potentially nephrotoxic at the time of admission; 16% were receiving a contraindicated medicine and 21% were inappropriately dosed [35]. A UK study found similar estimates among persons with a creatinine clearance of ≤60 mL/min in general practice, with 25% requiring a dosage change, discontinuation of the medicine, or change to a safer alternative [36]. Even higher estimates of inappropriate dosage among persons with renal impairment have been identified when specific medicines are studied [37]. We did not have a dataset sufficiently large enough to enable stratification by dose, thus further research identifying the effect of dose on the associations is required.

We synthesized findings from three studies that had assessed nephrotoxic medicines from spontaneous reports. While we could assess the majority of medicines that were identified in all three studies or at least two of the studies, there were a number of medicines that were only identified in one of the spontaneous report studies and could not be confirmed by our methods because of lack of availability of the medicines in Australia or lack of events due to small sample sizes. These potential associations need to be confirmed in larger datasets. The US study of spontaneous reports classified their findings into known, possible and possible new nephrotoxins [21]. Known nephrotoxins were those reported in three of four medicine information sources reviewed, while possible nephrotoxins were identified in two sources. Of those identified as possible new nephrotoxins, our sequence symmetry results were positive for two medicines, i.e. digoxin and zoledronic acid, but the case–control results did not confirm the association for zoledronic acid and could not be assessed for digoxin. Both zoledronic acid and digoxin are medicines that require dosage adjustment in persons with renal impairment and it may be that lack of dosage adjustment was a contributing causal factor, highlighting the need for continuous monitoring of renal function and dosage adjustment where necessary in persons on long-term therapy.

A strength of our study results is that the data represent findings from different datasets and across four different countries, increasing the likelihood that our results are generalisable to the larger population. However, a limitation of our study was the sample available. While our database included 250,000 persons and 15 years of history (3.75 million person-years), for many medicines the events were too infrequent for us to obtain reliable estimates. Large or multinational analyses are required to confirm associations between medicines within classes. Our study relied on identification of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as validity studies have demonstrated the code has high specificity but low-to-moderate sensitivity [26, 27]. Misclassification of acute kidney injury will have biased our results to the null, which may account for some known associations not observed in our study. However, the bias to the null also suggests the positive associations found are likely to be true positives. A further limitation was our inability to determine the level of renal dysfunction that resulted from the medicine use because we were reliant on coded medical records and did not have creatinine levels. A validity study undertaken in Canada showed the average change in creatinine was 98 (43–200) μmol/L at hospital admission for persons whose admission included an acute kidney injury code, compared with 6 (−4 to 20) μmol/L in persons without that code [26]. Another limitation of our study was the lack of information on dosage. While we have the strength of the medicine use, the dosage prescribed is unknown and will have influenced the outcomes. We did not find a specific effect for methotrexate, which is frequently reported to be nephrotoxic [38], however this is likely to be due to the fact that the majority of use would be for rheumatoid arthritis with low-dose products used. Our study did not assess the risk of acute kidney injury due to the use of more than one medicine that may be nephrotoxic. In the case–control design, we adjusted for other nephrotoxic medicines, while the sequence symmetry design inherently controls for other medicine use because of its within-person design; we cannot rule out that some of the observed effect may be due to cumulative risk from multiple medicine use.

5 Conclusion

One of the barriers to proactive prevention of medicine-induced kidney injury is the lack of a definitive list of nephrotoxic medicines. This research highlights a number of medicines that may contribute to acute injury; however, we had an insufficient sample to confirm associations of some medicines. Further confirmation is required using larger datasets across multiple countries Spironolactone, furosemide, and trimethoprim with sulfamethoxazole are medicines that, in particular, need to be used carefully and monitored closely in patients in the community at risk of acute kidney injury.

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Declarations

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Conflicts of interest/competing interests Elizabeth E. Roughead, Mhairi Kerr, Anna Moffat, Gizat M. Kassie and Nicole Pratt have no conflicts of interest to declare.

Ethics approval This research was approved by the University of South Australia Human Research Ethics Committee (P203-04) and the Departments of Defence and Veterans' Affairs Human Research Ethics Committee (E016-007).

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The Australian Government Department of Veterans' Affairs are the owners of the data. Requests for data would need to be made directly to the Australian Government Department of Veterans' Affairs

Code availability The code created for this analysis is available on request to the authors.

Author contributions ER conceived and designed the research, interpreted the results, and drafted and finalised the manuscript. NP designed the research, interpreted the results, and critically reviewed the manuscript. MK contributed to the study design, created all study code, undertook all analyses, and assisted with data interpretation and manuscript review. AM contributed to data interpretation and synthesis, as well as manuscript development and review. GK contributed to data interpretation and synthesis, as well as manuscript development and review. All authors read and approved the final version.

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