



# Prevalence and risk factors of trimethoprim/sulfamethoxazole-related acute kidney injury in pediatric patients: an observational study from a public database

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**Background:** Trimethoprim/sulfamethoxazole (TMP/SMZ) is widely used in various clinical settings. Studies have revealed that it may cause acute kidney injury (AKI) in adults. However, the correlation between the use of TMP/SMZ and renal injury in pediatric patients is still unclear. This study aimed to identify the impact of TMP/SMZ on the occurrence of AKI in children.

**Methods:** A retrospective observational study was conducted using data of patients treated with TMP/SMZ from the Paediatric Intensive Care clinical database. A newly developed criterion was used for the diagnosis of AKI, and univariate and multiple logistic regression analyses were performed to identify the risk factors of TMP/SMZ-related renal injury.

**Results:** A total of 113 patients were included. The prevalence of AKI was 21.2% (24/113). Univariate analysis indicated that the AKI group showed significantly higher baseline serum creatinine level (46.00 *vs.* 37.00  $\mu\text{mol/L}$ ;  $P=0.034$ ) and in-hospital mortality rate [29.2% (7/24) *vs.* 9.0% (8/89);  $P=0.01$ ] than that of the non-AKI group. Multivariate analysis revealed that the occurrence of AKI was significantly associated with increased baseline serum creatinine level [odds ratio (OR) =1.029; 95% CI: 1.006–1.053;  $P=0.014$ ] and concurrent use of vancomycin (OR =5.349; 95% CI: 1.381–20.714;  $P=0.015$ ). A proportion of 79.2% of patients (19/24) developed AKI within the first 10 days of TMP/SMZ use.

**Conclusions:** Elevated baseline serum creatinine level ( $\geq 40.25 \mu\text{mol/L}$ ) and concurrent use of vancomycin were associated with the development of AKI in young patients. Further large multi-center prospective studies are necessary to confirm these relationships and validate their clinical significance.

**Keywords:** Trimethoprim/sulfamethoxazole (TMP/SMZ); acute kidney injury (AKI); pediatric population; risk factors

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## Introduction

Sulfonamides are a group of antimicrobial drugs with great clinical importance. They are active against gram-positive and gram-negative aerobic bacteria and certain species of fungi and protozoa. They have been widely used in various clinical settings because they are affordable, convenient to use, and have a broad antimicrobial spectrum. Notably, sulfonamides have exhibited their antimicrobial functions in the treatment of infections of multi-drug resistant organisms, such as methicillin-resistant *Staphylococcus aureus* and carbapenem-resistant organisms (1,2). In China, Trimethoprim/sulfamethoxazole (TMP/SMZ) is the most used sulfonamide. Though well-tolerated, TMP/SMZ can induce adverse events such as hypersensitivity reactions, gastrointestinal upset, and headache (3). Furthermore, its renal toxicity has been reported over years (4-15). A few studies have explored the association between TMP/SMZ use and acute kidney injury (AKI) (12-17). However, most of the existing research focused on adult populations, and the impact of TMP/SMZ use on the development of AKI in pediatric patients is still unclear. In the present study, we investigated the relationship between TMP/SMZ and AKI and identified the potential risk factors of TMP/SMZ-related AKI. We present the following article in accordance with the STROBE reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-21-600/rc>).

## Methods

### Data collection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study is a retrospective observational study, using data from a large clinical database named the Paediatric Intensive Care (PIC, version 1.1). PIC is a publicly accessible clinical database with information of more than 12,000 patients admitted to the Children's Hospital of Zhejiang University (Hangzhou, Zhejiang, China) from 2010 to 2018 (18). Data was extracted using MySQL (version 8.0.16, Oracle Corporation) and Python (version 3.9.1, Python Software Foundation) by 2 independent researchers. The following data of each patient were extracted according to the manager's guide: demographic characteristics, diagnosis on admission/discharge, dates and results of laboratory tests and prescriptions, and other related data. Baseline laboratory tests were defined as the latest test taken within a week before the treatment started. Concomitant

drugs were defined as medications administered for an overlapping duration of more than 48 h with TMP/SMZ treatment, especially angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid, and other potentially nephrotoxic antimicrobials (e.g., vancomycin).

### Patient selection

We screened data on patients treated with TMP/SMZ for at least 48 h. The exclusion criteria were: (I) serum creatinine level >200  $\mu\text{mol/L}$  on admission; (II) patients less than a month old; and (III) patients without data on serum measurements after TMP/SMZ treatment.

### Diagnosis of AKI

The pediatric reference change values optimized for AKI in children (pROCK) criterion, which defines AKI as an increase in creatinine levels ( $\geq 20 \mu\text{mol/L}$ ) and increase by  $\geq 30\%$  within 7 days, was used for diagnosis (16). TMP/SMZ-associated AKI was defined as AKI which developed between 48 h and 30 days after the start of TMP/SMZ treatment.

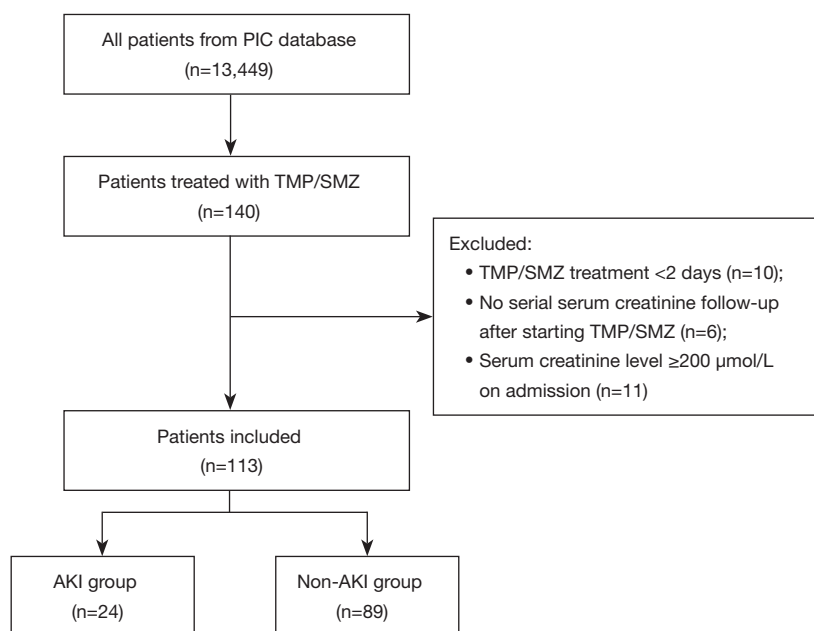
### Statistical analysis

Data were processed with SPSS for Windows (Version 22.0; SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using the Student's *t*-test or Mann-Whitney U test, whereas categorical variables were analyzed using the chi-squared test or Fisher's exact test. Variables with *P* value <0.1 in univariate analysis were analyzed using logistic regression. Statistical significance was set at *P*<0.05. Missing data were omitted in the analysis.

## Results

### Patient cohort

Among all the patients in the PIC database, 140 patients received at least one dose of TMP/SMZ. Among them, 27 patients were excluded; 10 were treated with TMP/SMZ for <48 h, 6 did not have serum creatinine measurements after the start of the TMP/SMZ therapy, and 11 had serum creatinine level  $\geq 200 \mu\text{mol/L}$  on admission. Finally, a total of 113 patients were included for further analysis (Figure 1).



**Figure 1** Flow chart of patient selection. PIC, Paediatric Intensive Care; TMP/SMZ, trimethoprim/sulfamethoxazole; AKI, acute kidney injury.

### *TMP/SMZ use and the development of AKI*

In the enrolled cohort, 24 patients (21.2%) met pROCK criteria, while the other 89 constituted the non-AKI group. The baseline characteristics of both groups are described in *Table 1*. Ninety-two percent (104/113) of the patients were between 3–18 years old and 38.9% (44/113) of the patients were female. Hematological malignancy was the most common underlying systemic condition and were found in 47.8% (54/113) of the patients. Vancomycin was the most used concomitant drug, and a total of 36 patients (31.9%) received TMP/SMZ plus vancomycin treatment.

Univariate analysis of patient characteristics for the AKI and non-AKI groups are detailed in *Table 1*. Baseline serum creatinine level of the AKI group was significantly higher than that of the non-AKI group (46.00 *vs.* 37.00  $\mu\text{mol/L}$ ;  $P=0.034$ ). A higher in-hospital mortality rate [29.2% (7/24) *vs.* 9.0% (8/89);  $P=0.010$ ] was observed in the AKI group than in the non-AKI group. There were no significant differences observed for baseline measurements for white blood cell count, platelet count, and lactate levels between the two groups. Multivariate logistic regression analysis showed that elevated baseline serum creatinine level (OR =1.029; 95% CI: 1.006–1.053;  $P=0.014$ ) and concomitant use of vancomycin (OR =5.349; 95% CI: 1.381–20.714;  $P=0.015$ ) are risk factors of developing TMP/SMZ-

associated AKI (*Table 2*).

Survival curves describing baseline serum creatinine and AKI occurrence after TMP/SMZ treatment were drawn (*Figure 2*). Kaplan-Meier analysis demonstrated significant differences in time of onset of AKI for the patients with different baseline serum creatinine before the use of TMP/SMZ. Baseline serum creatinine  $\geq 40.25 \mu\text{mol/L}$  was associated with an increased probability of developing AKI (hazard ratio =2.90;  $P=0.037$ ).

### *Time of onset of AKI*

*Figure 3* details the timelines of the 24 patients who developed AKI; 19 patients (79.2%) developed AKI within the first 10 days of TMP/SMZ use. The median time of onset of AKI was 4.5 days (interquartile range =3.9).

## **Discussion**

To the best of our knowledge, this is the first study exploring the relationship between the use of TMP/SMZ and the development of AKI in a pediatric population. Our results indicated that 21.2% of the patients that received TMP/SMZ developed AKI, which is higher than the results from previous studies (19,20). Retrospective analysis of

**Table 1** Baseline characteristics

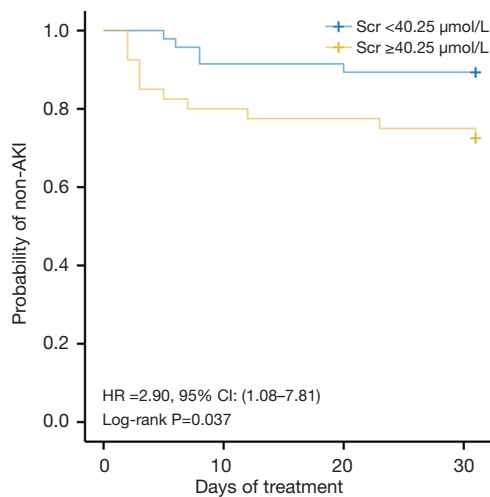
Characteristics	AKI group (n=24)		Non-AKI group (n=89)		P value
	N	Result	N	Result	
Age, n (%)					
<3 years	24	0 (0)	89	9 (10.1)	0.104
3–18 years	24	24 (100.0)	89	80 (89.9)	0.104
Male, n (%)	24	14 (58.3)	89	55 (61.8)	0.757
White blood cell count, $\times 10^9/L$ , median (IQR)	19	4.87 (1.49–18.48)	75	3.33 (0.70–8.99)	0.150
Platelet count, $\times 10^9/L$ , median (IQR)	19	44.0 (15.5–74.0)	75	94.0 (28.0–248.0)	0.068
Alanine transaminase, U/L, median (IQR)	17	18.0 (10.0–31.0)	68	33.0 (19.8–53.5)	0.035
Serum lactate, mmol/L, median (IQR)	19	1.50 (1.25–1.75)	78	1.85 (1.40–2.90)	0.088
ICU admission, n (%)	24	14 (58.3)	89	50 (56.2)	0.85
In-hospital mortality, n (%)	24	7 (29.2)	89	8 (9.0)	0.010
Baseline serum creatinine, $\mu\text{mol/L}$ , median (IQR)	16	46.00 (37.00–58.75)	71	37.00 (30.00–47.50)	0.034
Duration of TMP/SMZ treatment, days, median (IQR)	24	10.5 (6.0–19.4)	89	7.0 (4.0–12.0)	0.053
Concomitant drugs, n (%)					
ARB/ACEI	24	2 (8.3)	89	4 (4.5)	0.457
NSAIDs	24	7 (29.2)	89	26 (29.2)	0.996
Spirolactone	24	2 (8.3)	89	14 (15.7)	0.356
Glucocorticoid	24	8 (33.3)	89	15 (16.9)	0.075
Vancomycin	24	11 (45.8)	89	25 (28.1)	0.098
Piperacillin/tazobactam	24	2 (8.3)	89	10 (11.2)	0.682
Meropenem	24	14 (58.3)	89	45 (50.9)	0.499
Imipenem/cilastatin	24	7 (29.2)	89	17 (19.1)	0.285
Azithromycin	24	3 (12.5)	89	13 (14.6)	0.793
Voriconazole	24	11 (45.8)	89	54 (60.7)	0.192
Fluconazole	24	0 (0)	89	6 (6.7)	0.191
Caspofungin	24	13 (54.2)	89	39 (43.8)	0.367
Methotrexate	24	2 (8.3)	89	9 (10.1)	0.794
Comorbidities, n (%)					
Respiratory tract diseases	24	5 (20.8)	89	18 (20.2)	0.948
Heart diseases	24	0 (0)	89	3 (3.4)	0.362
Central nervous system diseases	24	0 (0)	89	7 (7.9)	0.156
Autoimmune diseases	24	1 (4.2)	89	4 (4.5)	0.945
Hematological diseases	24	2 (8.3)	89	9 (10.1)	0.794
Digestive system disease	24	0 (0)	89	6 (6.7)	0.191
Urinary system disease	24	3 (12.5)	89	5 (5.6)	0.243
Hematological malignancy	24	12 (50.0)	89	42 (47.2)	0.807
Solid organ malignancy	24	1 (4.2)	89	4 (4.5)	0.945

AKI, acute kidney injury; IQR, interquartile range; ICU, intensive care unit; TMP/SMZ, trimethoprim/sulfamethoxazole; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs.

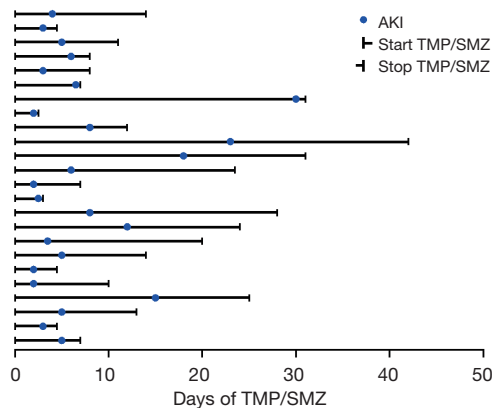
**Table 2** Multivariate logistics analysis of risk factors for AKI in pediatric patients treated with TMP/SMZ

Parameter	OR	95% CI	P value
Baseline serum creatinine level	1.029	1.006–1.053	0.014
Platelet count	0.996	0.990–1.002	0.243
Serum lactate	0.825	0.525–1.295	0.403
Concomitant with vancomycin	5.349	1.381–20.714	0.015
Concomitant with corticosteroid	3.049	0.709–13.121	0.134

AKI, acute kidney injury; TMP/SMZ, trimethoprim/sulfamethoxazole; OR, odds ratio; CI, confidence interval.



**Figure 2** An increased baseline serum creatinine is associated with higher probability of developing AKI. AKI, acute kidney injury; HR, hazard ratio; Scr, serum creatinine.



**Figure 3** Timeline of the 24 patients with TMP/SMZ induced AKI. AKI, acute kidney injury; TMP/SMZ, trimethoprim/sulfamethoxazole.

573 patients (12) indicated a TMP/SMZ -associated AKI prevalence of 11.2%. The lower prevalence could be due to the exclusion criteria used. Patients receiving TMP/SMZ for <6 days were excluded; therefore, early onset of AKI that led to treatment withdrawal could have been missed. Another study involving 214 patients reported a TMP/SMZ-associated AKI prevalence of 19.6%, which is similar to our results (20). However, both studies were based on adult populations, and AKI was diagnosed using the Kidney Disease Improving Global Outcomes classification system, which tests for an increase in serum creatinine and serum urea. In our analysis, AKI was diagnosed using pROCK criterion, a newly developed tool for the identification of renal injury in pediatric populations. The results thus might not be comparable, and this may explain the differences in AKI prevalence rates between our study and others. Given the fact that TMP/SMZ is a commonly used antimicrobial in pediatric settings, more studies concerning TMP/SMZ-related AKI prevalence should be carried out.

To explore the risk factors of TMP/SMZ-related AKI in a pediatric population, univariate and multivariate analysis were performed, the results of which showed that a high baseline serum creatinine measurement significantly increased the risk of AKI. Patients with baseline serum creatinine  $\geq 40.25 \mu\text{mol/L}$  were nearly three times more likely to develop AKI than patients with serum creatinine lower than the cut-off. Similarly, Rajput *et al.* 2020 reported that low baseline renal function served as a significant predictor for TMP/SMZ-related AKI (20). A pre-evaluation of serum creatinine may thus be essential for predicting the risk of AKI in pediatric patients treated with TMP/SMZ, and kids with baseline creatinine  $\geq 40.25 \mu\text{mol/L}$  should be monitored.

Notably, we explored the influence of concomitant drugs use on AKI development, including angiotensin-

converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, NSAIDs, corticosteroid, vancomycin, and aminoglycosides. Concomitant use of vancomycin with TMP/SMZ significantly increased the risk of AKI. This is quite logical because the main adverse reaction of vancomycin is nephrotoxicity. Previous studies found that in pediatric patients, the incidence of vancomycin-associated AKI was about 20% (17). Ninety percent of vancomycin in its original form is reabsorbed by proximal tubules through glomerular filtration, and it can exert renal toxicity mainly through the induction of oxidative stress response in proximal renal tubule epithelial cells leading to the ischemic necrosis of proximal renal tubules (21). On the other hand, TMP/SMZ's metabolite which has a low solubility can precipitate in urine, thus, causing hematuria, and in extreme circumstances, interstitial nephritis and tubular necrosis (7-9). The add-up of both mechanisms may further damage the renal tubule and cause deterioration of renal function, which may explain the synergism of vancomycin and TMP/SMZ.

We also analyzed the time of onset of AKI after TMP/SMZ use. According to previous studies (19,20), most AKI incidence occurred within the first 10 days of TMP/SMZ administration, with a medium onset time of 4 days. However, our results did not indicate a significant difference in duration of treatment between the AKI and non-AKI groups [10.5 (6.0–19.4) vs. 7.0 (4.0–12.0) days;  $P=0.053$ ]. Of note, the relationship between the duration of TMP/SMZ treatment and risk of AKI is unclear. Hence, close monitoring of renal function during the first 10 days of TMP/SMZ use is important.

Notably, this study has several limitations. First, the data on the TMP/SMZ dosage and indication (e.g., prophylaxis or treatment) are not available in PIC database, though other former study suggested that it may be related to the development of AKI (20). Second, the retrospective, single center nature of the study and the relatively small sample size may restrict the reliability of the conclusion. Thus, further prospectively designed studies are required.

## Conclusions

This study was a pilot study based on a publicly available database with limited data accessibility. According to our results, elevated baseline serum creatinine levels and concomitant use of vancomycin with TMP/SMZ are associated with an increased probability of AKI in pediatric patients undergoing TMP/SMZ treatment. However, owing

to the limitations of the study such as small sample size and lack of data, further studies considering patient baseline conditions together with concomitant prescriptions are required. Moreover, the exact mechanisms of nephrotoxicity in patients need to be investigated. To validate the current findings, a larger prospective cohort study is necessary in future.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://tp.amegroups.com/article/view/10.21037/tp-21-600/rc>

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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