



Renal Impairment Associated with Sulfamethoxazole/Trimethoprim Use in the Pediatric Population

Loma Linda University School of Pharmacy | Loma Linda, CA

Yen Tran, PharmD Candidate, Lacey Oana, PharmD Candidate, Caroline Sierra, PharmD, BCPPS

Correspondence to:
Caroline Sierra, PharmD,
BCPPS
Phone: 909-558-7535
Email: csierra@llu.edu

BACKGROUND

- Sulfamethoxazole/trimethoprim (SMX/TMP) has several effects on renal function, including serum creatinine (SCr) elevation and crystal nephropathy, which can lead to acute kidney injury (AKI) [1,2].
- Adult studies have shown that the trimethoprim component in SMX/TMP may obstruct the kidney, resulting in AKI [3].
- There are limited studies on AKI in children related to SMX/TMP use.

OBJECTIVES

- Primary objective: determine the association of AKI with SMX/TMP use in pediatric patients.
- Secondary objectives: determine the time to development of AKI; incidence of hyperkalemia, anemia, thrombocytopenia and leukopenia associated with SMX/TMP use in pediatric patients.

METHODS

- Retrospective, IRB-approved study
- Complete electronic medical records were reviewed for patients admitted to Loma Linda University Children's Hospital (2/1/2013 to 10/31/2019)
- Inclusion criteria: < 18 years of age who received SMX/TMP for bacterial infection
- Exclusion criteria: unavailable baseline SCr, previous AKI, on hemodialysis, duration of therapy < 5 days, and admission to oncology unit

RESULTS

- Eighty-three pediatric patients received 98 antibiotic treatments with SMX/TMP (Table 1).

Table 1. Baseline characteristics

Characteristic	Results
Age - years (mean ± STD) (n=98)	8.4 ± 6.2
Gender: Male – no.(%) (n=83)	43 (51.8)
Ethnicity – no.(%) (n=83)	
Caucasian	18 (21.7)
African American	7 (8.4)
Hispanic	56 (67.5)
Asian	2 (2.4)
Comorbidities – no.(%) (n=98)	
Lung disease	34 (34.7)
Chronic respiratory failure	27 (27.6)
Asthma	26 (26.5)
Gastroesophageal reflux disease	24 (24.5)
Cystic fibrosis (CF)	19 (19.4)
Concurrent nephrotoxic drugs – no.(%) (n=98)	87 (88.8)
≥ 2 other nephrotoxic drugs (n=87)	60 (69)
≥ 3 consecutive days of nephrotoxic drugs (n=87)	78 (90)
Duration of therapy – days (median, IQR) (n=98)	8.6 (6.6-11.8)
Daily dose of TMP – mg/kg (median, IQR) (n=98)	10.0 (9.9-15.0)
Indications by disease – no.(%) (n=98)	
Pneumonia	48 (49.0)
CF exacerbation	15 (15.3)
Urinary tract infection	9 (9.2)
Meningitis	4 (4.2)
Indication by organism – no.(%) (n=98)	
<i>Stenotrophomonas maltophilia</i>	39 (40.0)
<i>Staphylococcus aureus</i> (including MRSA)	19 (19.4)
<i>Escherichia coli</i>	9 (9.2)
<i>Enterobacter</i> spp.	6 (6.1)

Primary Outcome

- Of all 98 antibiotic treatments with SMX/TMP, 29 (29.6%) and 9 (9.2%) treatments belonged to patients who developed AKI stage 1 and stage 2, respectively (Table 2 and Figure 1).

Table 2. Incidence of AKI

Incidence of AKI	Results (n=98)
No AKI – no.(%)	60 (61.2)
AKI stage 1 – no.(%)	29 (29.6)
Change in SCr – mg/dL (median, IQR)	0.2 (0.1-0.3)
AKI stage 2 – no.(%)	9 (9.2)
Change in SCr – mg/dL (median, IQR)	0.4 (0.2-0.6)
AKI stage 3 – no. (%)	0 (0)

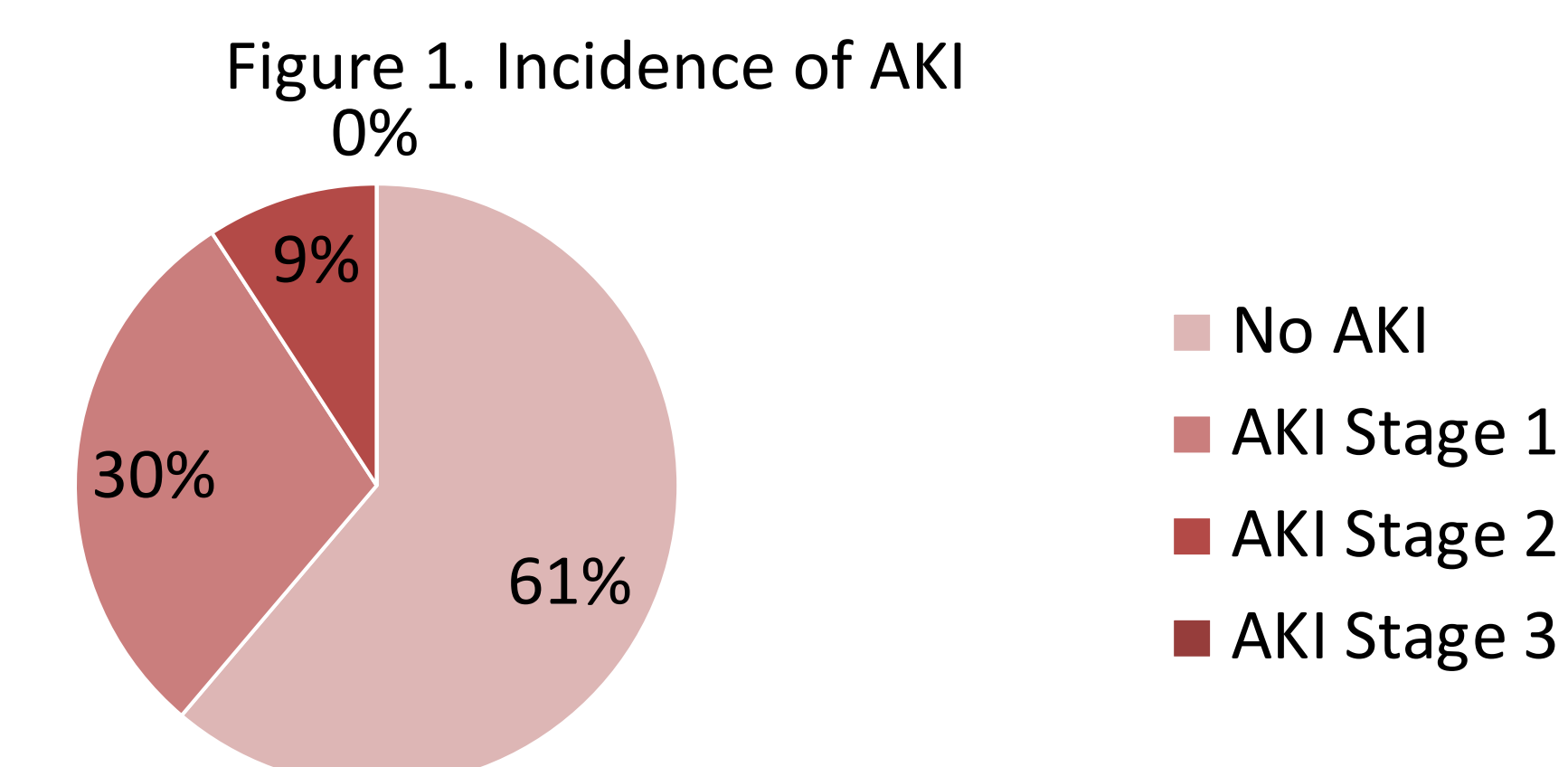


Table 3. Secondary outcomes

	Results
Time to AKI - days (median, IQR)	4 (2-7)
Incidence of hyperkalemia - no.(%) (n=97)	23 (23.7)
Potassium level in hyperkalemia - mEq/L	5.7 (5.3-5.9)*
Incidence of leukopenia - no.(%) (n=84)	9 (10.7)
WBC level in leukopenia - $\times 10^3/\text{mm}^3$	2.76 (2.46-3.44)*
Incidence of thrombocytopenia - no.(%) (n=84)	19 (22.6)
PLTS level in thrombocytopenia - $\times 10^3/\text{mm}^3$	74 (55-106.5)*
Incidence of anemia - no.(%) (n=84)	60 (71.4)
Hgb level in anemia - g/dL	8.7 (7.6-9.6)

*median (IQR)

LIMITATIONS

- Retrospective study design with data limited to patient's electronic medical records
- AKI Stage 1 definition includes SCr increases of 0.1 mg/dL, which may not be clinically relevant
- Concurrent administration of other nephrotoxic drugs
- No collection of vasopressor dependency or hemodynamic instability that could affect SCr

CONCLUSIONS

- Incidence of Stage 2 or greater AKI in pediatric patients receiving SMX/TMP is low.
- Majority of patients developed AKI on day 4 of therapy, which may imply shorter duration of therapy can reduce the risk of AKI.
- Incidence of anemia was high while hyperkalemia, thrombocytopenia and leukopenia was less common.
- Further studies will assess the relationship of developing AKI in pediatric patients and:
 - Daily dose of SMX/TMP
 - Use of other nephrotoxic medications
 - Incidence of hyperkalemia, thrombocytopenia, anemia, and leukopenia

REFERENCES

- Kastrup J, Petersen P, Bartram R, Hansen JM. The effect of trimethoprim on serum creatinine. *Br J Urol.* 1985;57(3):265–268.
- Roy MT, First MR, Myre SA, Cacini W. Effect of cotrimoxazole and sulfamethoxazole on serum creatinine in normal subjects. *Ther Drug Monit.* 1982;4(1):77–79.
- Delanaye P, Mariat C, Cavalier E, et al. Trimethoprim, Creatinine and Creatinine-Based Equations. *Nephron Clin Pract.* 2011;119:c187-c194.
- Khawaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract.* 2012;120(4):c179-c184.