JPHSR Journal of Pharmaceutical Health Services Research

ROYAL PHARMACEUTICAL SOCIETY

Research Paper

JPHS 2020, 11; 269–274

Received April 1, 2020
Accepted April 21, 2020
DOI 10.1111/jphs.12358
ISSN 1759-8885

# Trimethoprim–Sulfamethoxazole: new lessons on an old antimicrobial; a retrospective analysis

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## Abstract

**Objective** This study aimed to evaluate the appropriateness of TMP-SMX prescriptions as part of drug utilization review.

**Method** Charts of all patients (adults and paediatrics) admitted to Hamad General Hospital who received TMP-SMX from December 2016 till May 2017 were reviewed and assessed for prescribing/administering appropriateness.

**Key findings** Total of 149 patients was included (55 paediatrics, 94 adults). None of the adults were tested for G6PD before initiating TMP-SMX, while most of the paediatrics (85.5%) had a record of G6PD status. Dosing of TMP-SMX was considered appropriate in 65% of the paediatrics, whereas only in 49% of adults. Bone infections and *S. maltophilia* were the uppermost indications associated with inappropriate dosing (85.7 and 74.3%, respectively). Errors in dosing were observed to be higher with intravenous formulations (51.2%) compared to orals (35.2%). With regard to pharmacy verification/dispensing, 135 out of 149 orders (90.6%) were correctly verified/dispensed. Appropriateness of the prescribed dosing was only significantly affected by the indication for TMP-SMX use ($P$-value $< 0.001$), while the route of administration was the only variable that correlated significantly with pharmacy verification/dispensing errors ($P$-value 0.032).

**Conclusion** TMP-SMX prescribing patterns were not always optimum. The results of this study should promote healthcare facilities to review/ensure optimal utilization of TMP-SMX which can consequently help in diminishing burden of antimicrobial resistance.

**Keywords** anti-infective agents; co-trimoxazole; drug resistance; drug utilization review; inappropriate prescribing

## Introduction

Healthcare providers and administrators are usually faced by the dilemma of ensuring a rational use of drug therapy. According to the World Health Organization (WHO), statement issued in 1985, they stated that 'The rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community'.[1]Despite the benefits gained by having uniformed medication formularies and/or treatment protocols, such does not always concur with precise medication prescribing patterns.[2]

Drug use evaluation (DUE) is a method of performance enhancement that focuses on assessing and improving the use process of drugs and thus helps in optimizing patients' outcomes.[3] It aids in identifying, preventing and/or resolving any actual or potential problems related to drug therapy.[2–5]

Antimicrobial resistance is a well-recognized threat that has been associated with deleterious consequences on human health worldwide. Resistance to penicillin, the first antimicrobial agent used clinically, was identified in 1948 and ever since, almost every known pathogen has been linked to different resistance patterns against one or more of the antimicrobial agents being used in clinical practice.[6] Previous international studies have estimated that the total economic burden caused by antibiotic-resistant infections to be as high as $20 billion a year in healthcare costs.[7] On a national scale, according to Hamad General Hospital local antibiogram of 2017,[5] TMP-SMX resistance patterns were approaching 50% for both gram-positive and gram-negative bacteriacea that are commonly sensitive to TMP-SMX. For example, of all tested *Escherichia coli* samples

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within inpatient setting, 55% were reported to be resistant to TMP-SMX. The emergence of antimicrobial resistance can be attributed to different causes; however, one of the well-known risks associated with increased incidence is the inappropriate use of the drug therapy. This can happen with failure to commence the right antimicrobial, for the right indication, at the right dose and frequency and for the appropriate duration.[5,7–9] With these alerting percentages, DUEs of antimicrobials are highly warranted to assess prescribing appropriateness and provide feedbacks for improvement purposes.

Trimethoprim–Sulfamethoxazole (TMP-SMX) is a combination of two antimicrobial agents that act synergistically to treat a variety of bacterial infections. It covers a wide range of aerobic gram-positive/negative bacteria, fungi and protozoa.[10] Based on the WHO recommendation, TMP-SMX has been listed as one of the essential treatments required in a basic health system.[11] The drug is manufactured as a fixed-ratio combination of trimethoprim and sulfamethoxazole (1:5). Although the recommended dose varies based on the intended indication, nevertheless, numerous indications are dosed merely based on trimethoprim component of the combination.[10,11] Medication errors can arise if the prescriber did not account for the ratio of the combined therapy while prescribing the dose required, or did not accommodate for the different dosing required based on the intended indication.

The aim of this study was to evaluate the appropriateness of the prescribed doses of TMP-SMX in form of drug use evaluation. The study was conducted to analyse if the TMP-SMX dose was appropriate/correct for the following: age, indication, TMP-component based dosing and adjustment for comorbidity (i.e. renal failure, obesity). The study was also aimed to evaluate whether contraindications of drug usage were considered before prescribing. Those include the following: pregnancy, sulfa-allergy, known glucose-6-phosphate dehydrogenase (G6PD) deficiency or age less than two months.

## Methods

### Study design and setting

This was a retrospective chart review study evaluating the appropriateness of Trimethoprim–Sulfamethoxazole prescriptions across the main tertiary hospital in Qatar. The study was approved by the hospital Medical Research Center in Qatar (MRC# 17268/17). Informed consent was approved to be waived by Institutional Review Board since this was a retrospective chart review and involved no more than minimal risk to the subjects included.

### Population

All patients (adults and paediatrics) who were admitted to Hamad General Hospital as an inpatient admission from December 2016 till May 2017 (6 months) and have received TMP-SMX were included in the study. Restriction to inpatient setting was chosen to allow better assessment of the exact verified, dispensed and administered dose to the patients and would thus aid in ensuring accurate assessment of the whole process. Hence, patients with unavailable medical records were excluded.

### Procedure

Pharmacy computer system was used to identify patients who met the inclusion criteria above and had TMP-SMX dispensed to them. Electronic medical records of the identified patients were then solely examined. This involved reviewing physicians' and nurses' notes, medications' prescriptions, medication administration charts, laboratory results, and any other documentation that helped completing the data collection sheet designed specifically for the purpose of this study. Required information included: (1) Patient-related information: age, weight, BMI and baseline creatinine clearance, presence of any contraindications of drug use (i.e. pregnancy, sulfa-allergy, known G6PD deficiency, or age < 2 months), and (2) TMP-SMX prescription-related information: indication, dose, frequency, TMP-component weight-based dose (if indicated), route of administration/ formulation and dispensed amount/quantity. After collecting the required data, TMP-SMX-related information was evaluated for appropriateness based on the following parameters:

1 Appropriate dose for age and specified indication.
2 Dosing calculation based on weight-based trimethoprim (TMP) component (if indicated).
3 Correct verified/dispensed quantity based on prescribed dose.
4 Dose adjustment in special comorbidities (i.e. renal impairment, obesity).
5 Consideration of different contraindications (i.e. pregnancy, sulfa-allergy, G6PD deficiency, age < 2 months) before prescribing TMP-SMX.

To unify the assessment, dosing appropriateness was assessed in accordance with recommendations of Lexi-Comp,[12] Sanford guide for dosing antimicrobials 2017[13] and BNF-paediatrics 2017.[14] In cases where the recommended dosing based on the documented indication was not available, international clinical practice guidelines were reviewed to assess dose appropriateness.

### Sample size calculation

This study was the first study evaluating the appropriateness of Trimethoprim–Sulfamethoxazole prescriptions for all different indications either nationally or internationally. Thus, the required sample size was difficult to calculate using previous available literature. For that reason, we included all patients over a period of 6 months to allow better reflection of the whole population.

### Statistical analyses

Qualitative and quantitative data values were expressed as frequencies along with percentages, mean ± SD, median, and range. Descriptive statistics were used to summarize

demographic (age, gender, pregnancy status) as well as other characteristics of the participants (kidney function, G6PD deficiency status, indication for commencing therapy and others). Associations between two or more qualitative or categorical variables (e.g. Indication of treatment, age group, route of administration and baseline creatinine clearance versus appropriateness of dose or pharmacy verification) will be assessed using chi-square test or Fisher's exact test as indicated. Pictorial presentations of the key results were made using appropriate statistical graphs. *P*-value $< 0.05$ was considered to be statistically significant. All statistical analyses were done using statistical packages SPSS 22.0 (SPSS Inc. Chicago, IL, USA).

## Results

A total of 257 patients who received TMP-SMX were initially identified using pharmacy computer system. After duplicates removal, a total of 149 patients were included (55 paediatrics, 94 adults). TMP-SMX was utilized similarly across males and females (56.4%, 43.6%, respectively). The median age for paediatrics was 4.5 years versus 50.5 years in adults (whole cohort ranged from 37 days to 99 years). Most of the included patients had baseline of normal kidney function (creatinine clearance > 50 ml/min). Only 11.7% of adults and 1.8% of paediatrics were classified as end-stage renal disease requiring haemodialysis (Table 1). The vast majority of the patient had no known drug allergy, and of those with documented drug allergy, none were sulfa or TMP-SMX related.

With regard to the general TMP-SMX precaution and contraindication, we found that none of the adults were ever tested for G6PD before initiating TMP-SMX. On the other hand, most of the paediatrics (85.5%) had a record for G6PD status before starting TMP-SMX. Only one paediatric patient was documented to have G6PD deficiency and prescribed TMP-SMX. Nonetheless, only one dose was administered before the medication was changed. Although pregnancy testing was deemed not required for most of the included population (i.e. males, age > 50 or < 12 years), yet none of the females at childbearing age were tested for pregnancy before commencing therapy. Finally, out of the paediatrics population, two were found to have received TMP-SMX during the studied period despite being less than two months old (aged 36 and 41 days, respectively). However, in both cases, the indication for TMP-SMX was considered part of first-line treatment regimen with no other safer alternatives being available (*Stenotrophomonas maltophilia* pneumonia and PCP treatment, respectively).

Oral administration was the most commonly utilized route for TMP-SMX (72.5%), with 59.6% tablet formulation utilization in adults and 65.5% oral suspension utilization in paediatrics. The main indications for TMP-SMX prescription were PCP prophylaxis (38.9%) and treatment of *Stenotrophomonas maltophilia* species (23.5%).

Dosing of TMP-SMX was considered appropriate in 65% of the paediatrics, and only in less than half of the adults (49%).

**Table 1** Patients' demographics

| | Adult ($n$ = 94) | Paediatrics ($n$ = 55) | All patients ($n$ = 149) |
|---|---|---|---|
| Age (years) | | | |
| Mean ± SD | 52.4 ± 20.6 | 4.6 ± 3.4 | 34.7 ± 28.4 |
| Range | 18–99 | 0.1–12 | 0.1–99 |
| Gender, *n* (%) | | | |
| Female | 37 (39.4) | 28 (50.9) | 65 (43.6) |
| Male | 57 (60.6) | 27 (49.1) | 84 (56.4) |
| Baseline creatinine clearance, *n* (%) | | | |
| Normal (≥50 ml/min) | 69 (73.4) | 52 (94.6) | 121 (81.2) |
| 49–30 ml/min | 7 (7.4) | 1 (1.8) | 8 (5.4) |
| 29–10 ml/min | 3 (3.2) | 1 (1.8) | 4 (2.7) |
| <10 ml/min | 1 (1.1) | 0 (0) | 1 (0.7) |
| Haemodialysis | 11 (11.7) | 1 (1.8) | 12 (8.0) |
| Peritoneal dialysis | 1 (1.1) | 0 (0) | 1 (0.7) |
| No laboratory[1] | 2 (2.2) | 0 (0) | 2 (1.3) |
| Allergy, *n* (%) | | | |
| No known allergy | 78 (83) | 47 (85.5) | 125 (83.9) |
| Others | 16 (17) | 8 (14.5) | 24 (16.1) |
| G6PD status, *n* (%) | | | |
| Normal | 0 (0) | 47 (85.5) | 47 (31.5) |
| Deficient | 0 (0) | 1 (1.8) | 1 (0.7) |
| Not checked | 94 (100) | 7 (12.7) | 101 (67.8) |
| Pregnancy test, *n* (%) | | | |
| Checked before commencing TMP-SMX | 0 (0) | 0 (0) | 0 (0) |
| Not checked | 14 (14.9) | 0 (0) | 14 (9.4) |
| Not applicable | 80 (85.1) | 55 (100) | 135 (90.6) |
| Male | 57 (71.2) | 27 (49.1) | 84 (62.2) |
| Age < 12 years | 0 (0) | 28 (50.9) | 28 (20.8) |
| Age> 50 years | 23 (28.8) | 0 (0) | 23 (17) |
| Route of TMP-SMX administration, *n* (%) | | | |
| Intravenous | 27 (28.7) | 14 (25.5) | 41 (27.5) |
| Oral | 67 (71.3) | 41 (74.5) | 108 (72.5) |
| Formulation utilized, *n* (%) | | | |
| Solution for injection | 27 (28.7) | 14 (25.5) | 41 (27.5) |
| Oral suspension | 11 (11.7) | 36 (65.5) | 47 (31.5) |
| Tablet | 56 (59.6) | 5 (9) | 61 (41) |
| Indication for TMP-SMX use, *n* (%) | | | |
| Bone infection[2] | 7 (7.5) | 0 (0) | 7 (4.7) |
| Stenotrophomonas | 28 (29.8) | 7 (12.7) | 35 (23.5) |
| SSTI | 6 (6.4) | 0 (0) | 6 (4.1) |
| PCP prophylaxis | 24 (25.5) | 34 (61.8) | 58 (38.9) |
| PCP treatment | 5 (5.3) | 5 (9.1) | 10 (6.7) |
| UTI treatment | 5 (5.3) | 4 (7.3) | 9 (6) |
| Not documented | 3 (3.2) | 0 (0) | 3 (2.01) |
| Others | 16 (17) | 5 (9.1) | 21 (14.09) |

G6PD, Glucose-6-phosphate dehydrogenase; PCP, Pneumocystis pneumonia; STI, soft and skin tissue infection; UTI, urinary tract infection.
[1]No laboratory was done within 4 weeks of start TMP-SMX.
[2]Bone infection includes both osteomyelitis or prosthetic joint infection.

The most common reason for dosing inappropriateness in adults was with indications that required weight-based dose (mg/kg) of the trimethoprim component rather than fixed dosing recommendation. For instance, bone infections

**Table 2** Dose appropriateness across different indications

| Indication | Dose | | | Total |
|---|---|---|---|---|
| | Appropriate | Inappropriate | Could not be assessed | |
| Bone infection | 1 (14.3%) | 6 (85.7%) | 0 (0.0%) | 7 |
| Stenotrophomonas | 9 (25.7%) | 26 (74.3%) | 0 (0.0%) | 35 |
| SSTI | 6 (100.0%) | 0 (0.0%) | 0 (0.0%) | 6 |
| UTI | 5 (55.6%) | 4 (44.4%) | 0 (0.0%) | 9 |
| PCP treatment | 7 (70.0%) | 3 (30.0%) | 0 (0.0%) | 10 |
| PCP prophylaxis | 44 (75.9%) | 14 (24.1%) | 0 (0.0%) | 58 |
| Others | 10 (47.6%) | 6 (28.6%) | 5 (23.8%) | 21 |

and *S. maltophilia* were the uppermost indications associated with inappropriate dosing (85.7 and 74.3%, respectively) compared with SSTI and PCP prophylaxis (0 and 24.1%, respectively) (Table 2). Errors in dosing were observed to be higher with intravenous formulations (51.2%) compared to orals (35.2%). Inappropriate dosing was observed to happen similarly regardless of whether the patients had conditions requiring dosing modifications (i.e. renal failure, obesity) or not.

With regard to pharmacy verification and dispensing, 135 out of 149 orders (90.6%) were correctly dispensed. Errors pertaining to dispensed quantity/amount of oral formulations occurred less frequent (4.9% with oral tablets and 4.3% with oral suspension). Conversely, confusions were more commonly encountered with the intravenous formulation verification and dispensing (17.1%, *P*-value 0.032). This took place at a similar rate across both adults and paediatrics (9.6 and 5.5%, respectively, *P*-value: 0.12).

Out of the tested correlations, appropriateness of the prescribed dosing was only significantly affected by the indication for TMP-SMX use. On the other hand, the route of administration was the only variable that correlated significantly with pharmacy verification and dispensing errors (Table 3).

## Discussion

Drug utilization studies are frequently conducted to help in understanding the local clinical practice of medication consumption.[1–5] With the emerging evidence of increased antibiotics' resistance, DUE is more emphasized to ensure that antimicrobials are appropriately prescribed.[8] This observational retrospective study was conducted with a goal of determining the appropriateness of TMP-SMX use at Hamad General Hospital. To the best of our knowledge, this is the first DUE published studying the appropriateness of TMP-SMX across different age categories without any indications' restrictions.

**Table 3** Significance of different variables correlated to affect the dosing appropriateness or pharmacy verification/dispensing (*P*-value)

| Variable | Appropriateness of prescribed dose | Pharmacy Verification/ Dispensing |
|---|---|---|
| Indication | <0.001* | 0.907 |
| Baseline creatinine clearance | 0.152 | 0.990 |
| Route of administration | 0.121 | 0.032* |
| Formulation | 0.087 | 0.100 |
| Age group | 0.031 | 0.126 |

*Indicate statistically significant (*P*-value < 0.05).

Emerging evidence suggests that inappropriate antimicrobial dosing can contribute to the cumulative rate of pathogen resistance.[15–17] In our study, we found that prescription errors due to inappropriate dosing happened at relatively high rates across both adult (42.6%) and paediatric populations (34.5%). Confusions happened at different prescribing aspects. Those include select appropriate dose per specified indication, dosing calculation based on the trimethoprim component especially with the intravenous formulation, weight-based dosing calculation in obese patients, dosage adjustments in renal disease, along with others. To elaborate, TMP-SMX was used for the treatment of *Stenotrophomonas maltophilia* in almost quarter of the study population. Although the optimum dose of TMP-SMX for such indication has been debated,[18,19] the dose for patients treated for S.*maltophilia* was deemed to be inappropriate in 75% of the cases, with 56% being under-dosed. Most of the under-dosed cases were with the oral formulations, where TMP-SMX was dosed empirically as with other oral general dosing recommendation (i.e. 1 double strength tablet twice daily) rather than utilizing the recommendation of TMP-component weight-based dosing. Similar findings were observed with treatment of osteomyelitis. All the seven cases treated as osteomyelitis were due to MRSA osteomyelitis. None had native vertebral osteomyelitis (NVO). Yet, the dose utilized in all the cases was based on the recommendation of the NVO[20] (i.e. 1 double strength tablet twice daily) instead of non-vertebral dosing recommendation (i.e. 4 mg/kg/dose every 12 h, TMP weight-based dosing).[21]

Medication errors usually rise not only during prescribing, but also at dispensing or administration stages. According to Aldhwaihi *et al.*,[22] although dispensing errors can vary by incidence across different countries, yet the most common reported dispending errors include dispensing wrong strength, or wrong quantity of a medication. In contrast to many combination products available on the market, TMP-SMX is one of the few combined therapy where its dosing is usually referred to a single component of the whole product (i.e. trimethoprim). This heterogeneity may result in confusion not only during prescribing but also at the dispensing stages. We found that pharmacy verification and dispensing errors happened in 8.1% of the entire studied cohort and were more common across adults rather than paediatrics. Most of those errors were due to mistakenly verifying and/or calculating the prescribed dose as a total combined quantity rather than based on TMP component only and that led to lower than intended dose being administered to the patient.

The use of TMP-SMP has been commonly linked with some adverse side effects,[23] yet the benefits of its use

usually outweigh the risks. However, two detrimental hazards associated with TMP-SMX use, congenital anomalies with exposure during first trimester of pregnancy and haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. In our studied population, around 15% of the women were at childbearing age, yet none were tested for pregnancy, nor documented that pregnancy was ruled out. In a recent systematic review conducted by Ford *et al*.,[24] it was concluded that the use of TMP-SMX during pregnancy as a life-saving prophylaxis outweighs its risks, nonetheless that was merely among HIV-infected pregnant women with low CD-4 counts. On the contrary, exposing a non-HIV-infected women without an increased probability of opportunistic infection to a drug classified by the Food and Drug Administration (FDA) as category D does not seems appropriate, especially with the availability of other safer alternative. Similar concept applied for G6PD deficiency.[25–27] Out of the 149 patients, only third of them were tested for G6PD and that was carried purely across the paediatric population. None of the 94 adults included in this evaluation were screened for G6PD.

Finally, TMP-SMX is considered contraindicated in infants aged less than two months because of the common belief that sulfamethoxazole would displace bilirubin from protein binding and may potentially lead to hyperbilirubinaemia and kernicterus.[28] In 2013, a literature review of experimental and clinical studies pertaining to TMP-SMX use in neonates was conducted by Thyagarajan *et al*.[29] They stated that the evidence of kernicterus occurrence with the use of TMP-SMX is lacking. Nonetheless, because of heterogeneity, they recommended a need for more large focused human studies on the short and long term use of TMP-SMX to ensure complete safety. Therefore, since solid evidence of safety in this age group is still lacking, many prescribers tend to avoid using TMP-SMX in patients less than 2 months old unless no other alternative was available (i.e. staying in accordance with the drug monograph).[28] In our study, the use of TMP-SMX with the two neonates was considered justifiable since other effective/safe alternatives were not found.

## Limitations

Our study has some limitations. Because of the retrospective nature and sole chart review, the clinical outcomes of utilizing TMP-SMX were difficult to be assessed. Many of the cases lacked documentation of the clinical course of the patient in terms of infection eradication, while others were discharged before the continuation of the medication course and thus no follow-up was documented. Thus, the consequences of inappropriate dosing on clinical patients' outcomes were deemed un-assessable.

Another limitation of this DUE was the assessment of the appropriate dosing per indication. Since our hospital mainly depends on Lexi-Comp© and Sanford guide for dosing antimicrobials©, other places might not utilize similar resources. In order to overcome this limitation, we tried to compare the recommended dose across internationally published clinical practice guidelines when available; however, in many cases, there was no clear dosing recommendation for the specified indication and that might have affected the assessment.

Moreover, this DUE was conducted across a single hospital in Qatar. Although Hamad General Hospital is considered the largest tertiary hospital across Qatar, yet the prescribing/dispensing patterns might not be the same as with other hospitals.

Finally, the results of this research might be considered outdated. Due to some logistical issues, data collection and interpretation got delayed. However, since the main aim of this analysis was to improve utilization and decrease inappropriate use that could lead to detrimental consequences in terms of effectiveness and antimicrobial resistance, we sought to publish our findings so that healthcare providers would pay further attention to TMP-SMX dosing and/or utilization, and ensure the prescribing practices to are appropriately followed.

In spite of these limitations, we believe the findings of TMP-SMX prescribing patterns reported by this study are useful even to other facilities not only nationally, but rather internationally. With the increased rates of antimicrobial resistance, it is the responsibility of every healthcare provider to ensure the antimicrobials are appropriately prescribed and dispensed and thus lessen the burden of resistance expansion resulting from inappropriate utilization.

## Conclusion

Despite Trimethoprim–Sulfamethoxazole is one of the commonly prescribed antimicrobials, prescribing patterns were not always appropriate. Several opportunities to enhance its use exist including medical staff education, development of a simplified dosing chart based on different indications, ensuring a clear diagnosis is mentioned with each prescription to guarantee the prescribed dose is properly verified against the intended indication and consulting infectious disease specialist/clinical pharmacist in cases of doubt.

## Declaration

### Conflict of interest

The authors declares that they have no conflicts of interest to disclose.

### Funding

The authors received no financial support for the research, authorship, or publication of the paper.

### Acknowledgements

We would like to thank Dr Eyad Almadhon for kindly helping in retrieving patients list during studied period.

### Author contributions

D.B. and R.E. conceptualized the research idea, and the study design. Both contributed to the data collection. R.E analyzed the data and D.B. drafted the final manuscript for publication.

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