Farmacia Hospitalaria xxx (xxxx) xxx–xxx

Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria
www.elsevier.es/farmaciahospitalaria

Brief report

[Translated article] Evaluation of trimethoprim-sulfamethoxazole prescribing and dosage optimisation in a tertiary care hospital

Maialen Inclán-Conde[a,*], Clara Vila-Gallego[a], Maite Vara-Urruchua[a], Ana Victoria Aguirrezabal-Arredondo[a], Óscar Luis Ferreiro-Benéitez[b], Matxalen Vidal-García[c], Pamela Ruiz-Rodríguez[d] and José Antonio Domínguez-Menéndez[a]

[a] *Servicio de Farmacia, Hospital Universitario de Basurto, Bilbao, Spain*
[b] *Servicio de Enfermedades Infecciosas, Hospital Universitario de Basurto, Bilbao, Spain*
[c] *Servicio de Microbiología Clínica, Hospital Universitario de Basurto, Bilbao, Spain*
[d] *Departamento de Zoología y Biología Celular, Facultad de Ciencia y Tecnología, Universidad del País Vasco (UPV/EHU), Leioa, Spain*

ARTICLE INFO

Article history:
Received 9 December 2024
Accepted 8 March 2025
Available online xxxx

Keywords:
Posological optimization
Trimethoprim-sulfamethoxazole
Pharmaceutical interventions
Stenotrophomonas maltophilia

ABSTRACT

Objective: Evaluate the impact on improving the appropriateness of prescribing following a pharmaceutical intervention based on the review and optimisation of sulfamethoxazole-trimethoprim prescriptions.
Methods: A before-after intervention study was conducted in a tertiary hospital. The first period, or intervention period, was prospective and ran from September 2021 to January 2022. The second or post-intervention period was retrospective and covered the period March-December 2022.

In case of discrepancy between indication and prescribed and recommended dosage, the physician was notified and the degree of acceptance was recorded. In the post-intervention period, we retrospectively analysed the adequacy of the dosage, checking whether any intervention had been carried out by the Pharmacy Department. Statistical analysis was performed using the chi-square test.
Results: During the intervention period, 69 prescriptions were analysed, and 18 were found to be inappropriate (26%), 12 related to *Stenotrophomonas maltophilia* infection. In the post-intervention period, 129 prescriptions were reviewed, and 12 were considered inadequate (9%). Statistical analysis of the results obtained in both periods (18/69 and 12/129) showed statistically significant differences ($p = 0.0082$).
Conclusions: Pharmaceutical intervention in the review and optimisation of prescriptions improves the use of sulfamethoxazole-trimethoprim. The results obtained provide evidence of the importance of pharmaceutical review of such prescriptions.
© 2025 The Author(s). Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Farmacia Hospitalaria (S.E.F.H). This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Evaluación de la prescripción de sulfametoxazol-trimetoprima y optimización posológica en un hospital de tercer nivel

Palabras clave:
Optimización posológica
Sulfametoxazol-trimetoprima
Intervenciones farmacéuticas
Stenotrophomonas maltophilia

RESUMEN

Objetivo: evaluar el impacto en la mejora de la adecuación de la prescripción tras una intervención farmacéutica basada en la revisión y optimización posológica de las prescripciones de sulfametoxazol-trimetoprima.
Métodos: se realizó un estudio de intervención de tipo antes-después en un hospital de tercer nivel. El primer periodo (intervención) fue prospectivo y abarcó desde septiembre de 2021 hasta enero de 2022. El segundo periodo (posintervención) fue retrospectivo y comprendió desde marzo hasta diciembre de 2022.

En caso de discrepancia entre la indicación y la posología pautada y recomendada, se notificó al facultativo y se registró el grado de aceptación. En el periodo posintervención, se analizó de forma retrospectiva la adecuación posológica, comprobando si se había intervenido desde el servicio de farmacia. Se realizó análisis estadístico mediante la prueba de chi-cuadrado.

DOI of original article: https://doi.org/10.1016/j.farma.2025.03.008.
* Corresponding author.
E-mail address: maialeninclan26@gmail.com (M. Inclán-Conde).

https://doi.org/10.1016/j.farma.2025.04.006
1130-6343/© 2025 The Author(s). Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Farmacia Hospitalaria (S.E.F.H). This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Please cite this article as: Inclán-Conde M, et al.. [Translated article] Evaluation of trimethoprim-sulfamethoxazole prescribing and dosage optimisation in a tertiary care hospital. Farmacia Hospitalaria. 2025. https://doi.org/10.1016/j.farma.2025.04.006

Resultados: en el periodo intervención se analizaron 69 prescripciones y se detectaron 18 inadecuadas (26%), 12 relacionadas con infección por *Stenotrophomonas maltophilia.* En el periodo posintervención se revisaron 129 prescripciones y 12 fueron consideradas inadecuadas (9%). En el análisis estadístico de los resultados obtenidos (18/69 y 12/129) se observaron diferencias estadísticamente significativas ($p = 0{,}0082$).
Conclusiones: la intervención farmacéutica en la revisión y optimización posológica mejora el uso de sulfametoxazol-trimetoprima. Los resultados obtenidos aportan evidencia sobre la importancia de la revisión farmacéutica de dichas prescripciones.
© 2025 Los Autores. Publicado por Elsevier España, S.L.U. en nombre de Sociedad Española de Farmacia Hospitalaria (S.E.F.H). Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Following the COVID-19 pandemic, our hospital found an increase in *Stenotrophomonas maltophilia* isolates. The risk factors identified as contributing to the emergence of this opportunistic pathogen include immunosuppression, prolonged hospital stay—especially in specialised units—and the use of broad-spectrum antibiotics, intravascular devices, or mechanical ventilation.[1,2]

During the pandemic period, our pharmacy service occasionally detected subtherapeutic doses of sulfamethoxazole-trimethoprim (SMX-TMP) (less than 9 mg/kg/day of trimethoprim) for the treatment of conditions associated with *S. maltophilia*.[3–6]

Given the association between SMX-TMP (also known as cotrimoxazole) and prescribing errors, a prospective study was proposed to review patients receiving active treatment in the hospital. Such errors are often caused by the variability in dosing across different indications and potential confusion about the correct dose for each active pharmaceutical ingredient.[7,8]

The objective of this study was to evaluate the impact of a pharmaceutical intervention on improving prescribing appropriateness based on the review and optimisation of SMX-TMP prescriptions.

Materials and methods

A before-and-after intervention study was conducted at a tertiary hospital. The intervention period followed a prospective design and took place from September 2021 to January 2022. The post-intervention period was retrospective and ran from March to December 2022.

All patients over the age of 18 years who had received SMX-TMP treatment during the specified dates were included in both periods.

To establish the criteria for the appropriate dosage, recommended SMX-TMP doses were reviewed across several treatment guidelines[3,4] and drug information databases.[5,6] We also reviewed the Summary of Product Characteristics (SPC) of the drug.[9] For the treatment of *S. maltophilia* infection, a trimethoprim dose of at least 9 mg/kg/day[6] was considered appropriate, although the majority of the sources reviewed recommended 15 mg/kg/day (Table 1).

Patients were identified using the hospital prescription software system, and their data were obtained by reviewing each patient's electronic medical record.

The following variables were collected: patient characteristics (age, sex, and weight), prescribing service, treatment indication, and the causative microorganism when microbiological confirmation was available.

During the intervention period, if a discrepancy was identified between the indication and the prescribed dosage and the recommended dosage, a dosage recommendation was communicated by telephone to the responsible physician and the hospital's Antimicrobial Stewardship Programme (ASP) team. Finally, the level of implementation of these interventions was recorded.

During the post-intervention period, all patients treated with SMX-TMP were retrospectively reviewed to assess the appropriateness of the dosage. It was also checked whether any pharmaceutical intervention had been recorded in the electronic prescribing system. The data obtained were collected in an Excel spreadsheet.

A descriptive statistical analysis was performed. Categorical variables are expressed as frequencies and percentages, and quantitative variables are expressed as medians and interquartile ranges (IQRs).

The Chi-squared test was used to compare the populations and the results obtained in each period, using the SPSS V.24 software package. A P-value of ≤0.05 was used as a cutoff for statistical significance.

Results

During the intervention period, we analysed 69 prescriptions from 65 patients (men 55%; median age, 66 years; range, 55–79 years). The admission units were as follows: infectious diseases (15), resuscitation (11), respiratory (10), cardiology (4), general surgery (4), gastroenterology (3), haematology (3), internal medicine (3), urology (3), otolaryngology (3), and other (10). The indications for treatment were as follows: 23 prophylactic treatments, 5 empirical treatments, and 41 targeted treatments. The microorganisms detected were as follows: 14 *S. maltophilia*, 6 *Pneumocystis jirovecii*, 6 *methicillin-resistant Staphylococcus aureus* (MRSA), 6 *Escherichia coli*, 3 *Klebsiella pneumoniae*, 2 *Acinetobacter baumannii*, 1 *Toxoplasma gondii*, and 3 others.

We identified 18 inappropriate prescriptions (26%). Of these, 12 prescriptions were subtherapeutic doses related to the microbiological diagnosis (10 corresponded to patients with *S. maltophilia* infection, 1 with *K. pneumoniae*, and 1 with MRSA); 1 prescription was related to empirical treatment; 2 were adjustments based on renal function for treatments targeting *S. maltophilia*, and 3 were reconciliation errors for prophylactic home treatment. In total, 17 interventions were accepted and implemented (94%).

Table 1
Recommended dosages for microorganisms requiring high doses (expressed as trimethoprim mg/kg/day), according to several sources (accessed August 30, 2021).

	SPC	Antimicrobial therapy guide (mg)	UpToDate (mg)	Micromedex (mg)	Sanford Guide to Antimicrobial therapy (mg)
Pneumocystis jirovecii	15–20 mg	20	15–20	15–20	15
Nocardia spp.	15 mg	15	15	15	15
Stenotrophomonas maltophilia[a]	No data	15	15	9–15	15–20

[a] Following the 2023 update of the 2023 Infectious Diseases Society of America (IDSA) Guidelines for the treatment of resistant Gram-negative bacteria, the recommended trimethoprim doses were modified throughout 2024 to the following ranges: 8–12 mg/kg/day;[6,10] 8–15 mg/kg/day;[5] or 10–15 mg/kg/day).[11] The IDSA also recommended combination therapy in this setting.[12] In the most recent revision of the 2024 IDSA Guidelines, the recommended dose was further increased to 10–15 mg/kg/day.[13]

During the retrospective analysis period, 129 prescriptions from 127 patients were reviewed (men 61%; median age 66 years; range 54–77). The admission units were as follows: resuscitation (28), infectious diseases (17), respiratory (16), internal medicine (10), emergency (9), nephrology (8), cardiology (8), haematology (6), otolaryngology (6), vascular surgery (5), medical oncology (3), urology (3), and other (10). The indications for treatment were as follows: 43 prophylactic treatments, 12 empirical treatments, 3 suppressive treatments, and 71 targeted treatments. Of the targeted treatments, the microorganisms were as follows: 14 *S. maltophilia*, 12 *E. coli*, 8 *Klebsiella oxytoca*, 6 *Enterobacter cloacae*, 5 *P. jirovecii*, 4 *A. baumannii*, 4 MRSA, 3 *K. pneumoniae*, 3 *Nocardia spp.*, 2 *methicillin-sensitive Staphylococcus aureus* (MSSA), 2 *T. gondii*, and 8 others.

Of the 129 prescriptions retrospectively analysed, 12 were considered inappropriate (9%). Pharmaceutical interventions were recorded for 7 prescriptions (5%), and 6 of them (86%) were accepted.

The reasons for the prescriptions being considered inappropriate were as follows: 10 used subtherapeutic doses (5 related to *S. maltophilia*, 2 to *Nocardia spp.*, 1 to *P. jirovecii*, 1 to *E. cloacae*, and 1 was an empirical treatment); 1 used a dosage higher than the recommended dose for prophylaxis; and 1 was an adjustment based on renal function for treatment targeting *S. maltophilia*. Table 2 shows the results obtained.

The results of the Chi-squared test were significantly different ($p = 0.0082$) for the periods analysed (18/69 and 12/129).

Using the same statistical test, it was determined that there were no statistically significant differences between the populations regarding age, sex, and treatment indication, indicating their similarity.

Only microorganisms requiring high doses were analysed, and no differences were found ($p = 0.0504$).

Discussion

During the first stage of the appropriateness study, the pharmacy service confirmed that a significant percentage of SMX-TMP prescriptions did not comply with the usual recommended dosage, particularly in the case of *S. maltophilia* infection. This high percentage was also found in a previous study assessing dosage appropriateness, where the percentage of inappropriate dosing for *S. maltophilia* was 74.3%.[7] We identified 2 potential causes of underdosing in these treatments. One was related to the information included in the *S. maltophilia* antibiograms, which listed the following EUCAST recommended dose: high dose: 0.24 g trimethoprim + 1.2 g sulfamethoxazole/12 h oral or IV,[14] which was insufficient for patients weighing more than 53 kg. The other was related to the standard reference guide.[3] In the monograph on cotrimoxazole, the dosage section originally listed the standard dose as 160/800 mg/8–12 h. A small note in the comment section mentioned the need for higher doses for some microorganisms, but this could have been easily overlooked. From 2023, this information has been included in the main dosage section, making it easier to consult and reducing the risk of errors.[10]

The pharmacy service recommended changing the information included in the antibiograms. This change, together with the work conducted through individualised interventions by the pharmacy service, may have contributed to the improvement observed in the appropriateness of the doses prescribed in the post-intervention period, especially in the treatment of *S. maltophilia*. Nevertheless, in the post-intervention period, we detected underdosing errors in prescriptions related to *Nocardia spp.* The recommended dosage information provided in the antibiogram was incorrect, and the pharmacy service recommended changing this information.

As observed in previous studies with antibiotics,[15] reviewing and optimising prescriptions through pharmaceutical intervention with SMX-TMP improves antibiotic use.

Given the wide range of potential dosages depending on the indication and the continuous updating of treatment guidelines, we believe it is essential to review SMX-TMP dosing practices to reduce the high rate of inappropriate prescriptions—particularly in cases involving microorganisms that require high-dose regimens.

The results obtained highlight the importance of pharmaceutical review of these prescriptions, supporting its potential implementation in other hospitals and its inclusion as a strategic objective within Antimicrobial Stewardship Programmes.

Table 2
Treatment indications and inappropriate prescriptions identified in both study periods.

Treatment indication	Intervention period Patients (n)	Inappropriate prescriptions n (%)	Post-intervention period Patients (n)	Inappropriate prescriptions (n, %)
Prophylaxis	23	3 (13)	43	1 (2)
Empirical	5	1 (20)	12	1 (8)
Suppressive			3	
Targeted	41	14 (34)	71	10 (14)
S. maltophilia	14	12 (86)	14	6 (43)
P. jirovecii	6		5	1 (20)
MRSA	6	1 (17)	4	
E. coli	6		12	
K. pneumoniae	3	1 (33)	3	
A. baumannii	2		5	
T. gondii	1		2	
K. oxytoca			8	
E. cloacae			6	1 (17)
Nocardia spp.			3	2 (67)
MSSA			2	
Others	3		8	
Total	69	18 (26)	129	12 (9)

Abbreviations: *A. baumannii, Acinetobacter baumannii; E. cloacae, Enterobacter cloacae; E. coli, Escherichia coli; K. oxytoca, Klebsiella oxytoca; K. pneumoniae, Klebsiella pneumoniae; P. jirovecii, Pneumocystis jirovecii; S. maltophilia, Stenotrophomonas maltophilia*; MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-sensitive *Staphylococcus aureus*; T. gondii, *Toxoplasma gondii.*

Presentation at conferences

The first part of the study (initial phase) was presented in poster format at the 67th conference of the Spanish Society of Hospital Pharmacy (Barcelona, November 24–26, 2022).

CRediT authorship contribution statement

Maialen Inclán-Conde: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Clara Vila-Gallego:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maite Vara-Urruchua:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Ana Victoria Aguirrezabal-Arredondo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis. **Oscar Luis Ferreiro-Beneitez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis. **Matxalen Vidal-García:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis. **Pamela Ruiz-Rodríguez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis. **José Antonio Domínguez Menéndez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Authorship

Maialen Inclán-Conde and José Antonio Domínguez-Menéndez participated in the conception and design of the work, data collection, data analysis and interpretation, writing, critical review, and approval of the final version. Clara Vila-Gallego and Maite Vara-Urruchua participated in the design, data collection, analysis, critical review, and approval of the final version. Ana Victoria Aguirrezabal-Arredondo, Oscar Luis Ferreiro-Beneitez, Matxalen Vidal-García, and Pamela Ruiz-Rodríguez participated in data analysis and interpretation, critical review, and approval of the final version for publication.

Funding

None declared.

Conflict of interest

None declared.

References

1. Looney WJ, Narita M, Mühlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. Lancet Infect Dis. 2009;9(5):312–23. https://doi.org/10.1016/S1473-3099(09)70083-0.
2. Said MS, Tirthani E, Lesho E. *Stenotrophomonas maltophilia.* [Updated 2023 Jun 12] StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. [consultado 30 Sep 2024]. Disponible en: https://www.ncbi.nlm.nih.gov/books/NBK572123/.
3. Mensa J, Soriano A, López E, Zboromyrska Y, Llinares P, Barberán J. Guía de Terapéutica Antimicrobiana. 31ª ed. Barcelona: Editorial Antares; 2021.
4. Gilbert DN, Chambers HF, Saag MS, Pavia AT, Boucher HW, Black D, et al. Sanford guide to antimicrobial therapy. 51st ed. Sperryville (VA): Antimicrobial Therapy, Inc.; 2021.
5. UpToDate®. Drugs & drug interaction. [consultado 30 Sep 2024]. Disponible en: https://www.uptodate.com/contents/trimethoprim-sulfamethoxazole-co-trimoxazole-drug-information?search=sulfametoxazol%20trimetoprima&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1.
6. Micromedex®. [consultado 30 Sep 2024]. Disponible en: https://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch?navitem=headerLogout#.
7. Bakdach D, Elajez R. Trimethoprim–sulfamethoxazole: new lessons on an old antimicrobial; a retrospective analysis. J Pharm Health Serv Res. 2020;11(3):269–74. https://doi.org/10.1111/jphs.12358.
8. Bosch Peligero M. Proyecto de seguridad farmacoterapéutica. In: *Prevención de errores de medicación en pacientes pediátricos hospitalizados*, 2016, Facultad de Medicina, Universidad Autónoma de Barceola; Barcelona. [consultado 24 Ene 2025], Disponible en: https://ddd.uab.cat/pub/tesis/2016/hdl_10803_385721/mbp1de1.pdf
9. Ficha Técnica Soltrim®. [consultado 30 Sep 2024]. Disponible en: https://cima.aemps.es/cima/dochtml/ft/54920/FT_54920.html.
10. Mensa J, Soriano A, López E, Poliakova Y, Llinares P, Barberán J. Guía de Terapéutica Antimicrobiana. 34ª ed. Barcelona: Editorial Antares; 2024.
11. Gilbert DN, Chambers HF, Saag MS, Pavia AT, Boucher HW, Black D, et al. Sanford guide to antimicrobial therapy. 54th ed. Sperryville (VA): Antimicrobial Therapy, Inc.; 2024.
12. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. Clin Infect Dis. 2023:ciad428. https://doi.org/10.1093/cid/ciad428.
13. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. Clin Infect Dis. 2024:ciae403. https://doi.org/10.1093/cid/ciae403.
14. EUCAST clinical breakpoint tables v. 11.0 – v. 13.0. [consultado 30 Sep 2024]. Disponible en: https://www.eucast.org/.
15. Arain S, Khalawi F, Parakkal SA, AlHamad HS, Thorakkattil SA, Alghashmari FFJ, et al. Drug utilization evaluation and impact of pharmacist interventions on optimization of piperacillin/tazobactam use: a retrospective analysis and prospective audit. Antibiotics. 2023;12(7):1192. https://doi.org/10.3390/antibiotics12071192.