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Sensibilité au triméthoprim dans les infections urinaires à *E. coli* communautaires en France
Trimethoprim susceptibility in *E. coli* community-acquired urinary tract infections in France

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Contributions of authors

C. Duployez gathered the results, analyzed the data, and wrote the article.

J. Robert and A. Vachée wrote the study protocol and sent the questionnaires, collected results from the 35 laboratories, performed statistical analysis, and contributed to reviewing and approving the article.

RÉSUMÉ

Objectifs. - Le triméthoprimé a été récemment introduit dans les recommandations françaises pour le traitement des infections urinaires. Devant l'absence de données épidémiologiques, notre objectif était de déterminer le taux de sensibilité des souches de *E. coli* responsables d'infections urinaires communautaires chez les femmes jeunes.

Matériels et méthodes. - Enquête nationale prospective sur 350 souches de *E. coli* isolées d'urines incluses par 35 laboratoires et antibiogrammes réalisés par chacun des laboratoires participants.

Résultats. - Le taux de sensibilité au triméthoprimé était de 78 %. Les catégorisations cliniques au triméthoprimé et au cotrimoxazole étaient équivalentes pour 97,4 % des isolats. Il existait une association entre la résistance au triméthoprimé et à d'autres familles d'antibiotiques.

Conclusion. - Nos résultats appuient les nouvelles recommandations proposant le triméthoprimé comme traitement de seconde ligne sur la base des résultats de l'antibiogramme. Les taux de sensibilité au triméthoprimé et au cotrimoxazole restent très similaires en France.

ABSTRACT

Objectives. - Trimethoprim has been recently included in the French guidelines for the treatment of urinary tract infections, but no epidemiological data supports its use. We aimed to determine the trimethoprim susceptibility of *E. coli* isolates responsible for community-acquired urinary tract infections in women of childbearing age.

Materials and methods. - We conducted a national prospective survey. A total of 350 strains of *E. coli* isolated from urines in 35 laboratories were included. Antibiotic susceptibility testing was performed in each laboratory.

Results. - We reported a susceptibility rate of 78%, and a similar clinical categorization between trimethoprim and cotrimoxazole for 97.4% of isolates. We pointed out an association between resistance to trimethoprim and other antibiotic classes.

Conclusion. - The results support trimethoprim as a second-line therapy based on antibiotic susceptibility testing. We confirm that trimethoprim and cotrimoxazole susceptibility rates are very close.

Introduction

Urinary tract infections (UTIs) are one of the most common causes of medical consultation and antibiotic use in women in community settings. *Escherichia coli* is responsible for most of these infections and the constant increase in antibiotic resistance among this species is worrisome. Trimethoprim (TMP) is a former antimicrobial agent that is active against *Enterobacteriaceae*. It acts by competitive inhibition of dihydrofolate reductase (DHFR), and mutations in the *dhfr* genes are the most common mechanisms of TMP resistance [1]. In France, TMP is usually combined with sulfamethoxazole in a single pill but it was recently launched as a single drug for treating cystitis [2]. Indeed, TMP alone has been shown to be as effective as fosfomycin-trometamol, fluoroquinolones, or trimethoprim-sulfamethoxazole (SXT) for treating cystitis [3]. In addition, a recent European study reported equivalent resistant rates for TMP and SXT [4]. Recent French guidelines for UTIs management in women recommend TMP alone as an alternative drug for treating all types of cystitis including cystitis in pregnant women and recurrent cystitis [3]. However, recent data on the susceptibility to TMP alone of *E. coli* isolated from urines is lacking in France, and guidelines are usually based on SXT susceptibility test results. Thus, we sought to determine the TMP susceptibility of *E. coli* isolates responsible for community-acquired UTIs in women of childbearing age.

Materials and methods

We conducted a national prospective survey with 35 laboratories participating to the French National Observatory for Epidemiology of Bacterial Resistance to Antibiotics (French acronym ONERBA). All *E. coli* isolates from urine samples with a significant bacteriuria ($>10^3$ CFU/mL) drawn from ambulatory women aged 15-45 years were included between June 1 and 30, 2016. Patients with an indwelling urinary catheter or recent hospitalization >48 hours were excluded. Duplicates were excluded. Species identification and antimicrobial susceptibility testing (AST) were performed in each participating laboratory. TMP susceptibility was determined by the disk diffusion method for 24 laboratories and by automated liquid methods for 11 laboratories. Susceptibility to other antibiotics was determined by the disk diffusion method for 13 laboratories and by automated methods for the 22 other laboratories. AST results were interpreted in accordance with the Antibiogram Committee of the French Society for Microbiology (French acronym CA-SFM) guidelines, which are very similar to European guidelines [5]. The ATCC 25922 *E. coli* strain was used as a quality control in each laboratory.

Results

A total of 350 isolates were included by 16 private practices (n=159, 45.4%) and 19 hospital laboratories (n=191, 54.6%). AST results are presented in Table I. Only three (1%) *E. coli* isolates produced extended-spectrum beta-lactamase (ESBL). Overall, 273 (78.0%) isolates were susceptible to TMP including two of the ESBL-producing isolates. None of the isolates were in the intermediate clinical category. A total of 49 of the 77 resistant isolates were tested by the disk diffusion method and had no inhibition zone around the TMP disk. Isolates from hospital laboratories were less frequently susceptible to TMP (74.4%) than those from private laboratories (82.4%), but the difference was not statistically significant ($P=0.09$). However, isolates from hospital laboratories were less frequently susceptible to SXT (75.4%) than those from private laboratories (85.4%, $P=0.02$). There were no other differences in antibiotic susceptibility of isolates according to the type of laboratory. Among the 296 isolates with information on the pregnant status of the patient, TMP susceptibility of isolates from pregnant women was 70.3%, not significantly different than that of non-pregnant women (78.8%, $P=0.15$). The frequency of susceptibility to other antibiotics was not statistically different among pregnant and non-pregnant women. There was a good correlation between TMP and SXT susceptibility: only two (2.9%) of the 70 SXT-resistant isolates were TMP-susceptible and seven (2.5%) of the 278 SXT-susceptible isolates were TMP-resistant. As previously described [2,6], TMP resistance was associated with other resistance determinants (Table I). Compared with the 273 TMP-susceptible isolates, the 77 TMP-resistant isolates were significantly less likely to be susceptible to gentamicin (93.5% versus 99.3%), ciprofloxacin (88.3% versus 97.0%), and of course SXT (9.3% versus 99.3%). Overall, TMP-resistant isolates were less likely to be susceptible to other antibiotics, but differences were not statistically significant.

Discussion

We report a resistance rate to TMP of 22.0% (29.7% for pregnant women) among 350 isolates of *E. coli* isolated from urinary samples of women of childbearing age. This rate is rather high and prevents any use of TMP as an empirical drug for UTI in this population before AST [3]. However, experiences of other European countries suggest the benefit of using TMP alone for treating UTI, and TMP may therefore remain of interest as a second-line therapy.

Our study brings two information of interest for clinicians. First, we confirm that TMP and SXT susceptibility rates are very close. Hence, SXT susceptibility result could be used as a surrogate for TMP susceptibility, and TMP could be an alternative to SXT to avoid the adverse effects of sulfamethoxazole. However, TMP advantages over SXT for treating UTI in pregnant women remain debatable [7]. Second, resistance to TMP is often associated with resistance to other antibiotics. Hence, although TMP is a theoretical alternative for treating UTI infections due to resistant bacteria because of a lack of cross-resistance, the frequency of associated resistance may decrease its benefit. In addition, a review of the literature points out an increase in TMP resistance after its wide use as a single drug [8] and in other antibiotics [2]. Moreover, the decreased use of TMP does not reduce TMP resistance rate caused by the low fitness cost of this resistance, combined with co-selection due to high levels of other resistance determinants [2,6].

Conclusion

The use of TMP as a first-line agent in women presenting with UTI is not warranted by its susceptibility rate. This result supports the recent French guidelines, recommending the use of TMP as a second-line agent based on AST. The results support TMP use instead of SXT for such infections. However, the association with other resistance determinant may preclude its use for the treatment of multidrug-resistant bacterial infections.

CONFLICTS OF INTEREST: none

REFERENCES

1. Brolund A, Sundqvist M, Kahlmeter G, Grape M (2010) Molecular characterisation of trimethoprim resistance in *Escherichia coli* and *Klebsiella pneumoniae* during a two year intervention on trimethoprim use. *PLoS One*. 16;5(2):e9233. doi: 10.1371/journal.pone.0009233.
2. Société de Pathologie Infectieuse de Langue Française (SPILF). Diagnostic et antibiothérapie des infections urinaires bactériennes communautaires de l'adulte. Recommandations - Argumentaire 2015. <http://www.infectiologie.com/UserFiles/File/spilf/recos/infections-urinaires-spilf-argumentaire.pdf>. Accessed 10 April, 2017
3. Haute Autorité de Santé. Commission de la transparence Triméthoprime. 22 juin 2016. http://www.has-sante.fr/portail/upload/docs/evamed/CT-13148_DELPRIM_PIC_INS_Avis1_CT13148.pdf. Accessed 10 April, 2017
4. Kahlmeter G, Poulsen HO (2012). Antimicrobial susceptibility of *Escherichia coli* from community-acquired urinary tract infections in Europe: the ECO-SENS study revisited. *International Journal of Antimicrobial Agents*. 1;39(1):45–51.
5. Comité de l'Antibiogramme de la Société Française de Microbiologie. CASFMV2_030915. http://www.sfm-microbiologie.org/UserFiles/files/casfm/CASFMV2_030915.pdf. Accessed 10 March 10 2017
6. Sundqvist M1, Geli P, Andersson DI, Sjölund-Karlsson M, Runehagen A, Cars H, Abelson-Storby K, Cars O, Kahlmeter G (2010). Little evidence for reversibility of trimethoprim resistance after a drastic reduction in trimethoprim use. *J Antimicrob Chemother*. 65(2):350-60. doi: 10.1093/jac/dkp387.
7. Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA (2000). Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. 30;343(22):1608-14.
8. Towner KJ, Smith MA, Cowlishaw WA (1983). Isolation of trimethoprim-resistant, sulfonamide-susceptible *Enterobacteriaceae* from urinary tract infections. *Antimicrob Agents Chemother*.23(4):617-8.

Table 1. Antibiotic susceptibility (%) among the 350 isolates from ambulatory female patients**Tableau 1.** Sensibilité aux antibiotiques de 350 souches isolées chez des patientes ambulatoires

Antibiotics	All Isolates (n=350)	Pregnant		Trimethoprim	
		Yes (n=74)	No (n=222)	Susceptible (n=273)	Resistant (n=77)
Trimethoprim	78.0	70.3	78.8	-	-
Co-trimoxazole	79.9 (n=348)	71.6	80.9 (n=220)	99.3	9.3*
Fosfomycin	99.7 (n=321)	100.0 (n=63)	99.5 (n=203)	99.6	100.0
Nitrofurantoin	99.4	100.0	99.1	99.6	98.7
Nalidixic acid	88.8 (n=349)	93.2	87.8 (n=221)	93.8	71.1*
Ciprofloxacin	95.1	97.3	94.1	97.0	88.3*
Co-amoxiclav ^o	93.1	96.0	92.8	94.5	88.3
Mecillinam	95.5 (n=311)	96.3 (n=54)	94.6 (n=203)	96.7	90.9
Cefoxitin	99.1	98.7	99.1	99.6	97.4
Ceftriaxone/cefotaxime	99.1	98.7	99.1	99.3	98.7
Ceftazidime	99.4	98.7	99.6	99.6	98.7
Piperacillin-tazobactam	97.9 (n=341)	98.6 (n=71)	97.7 (n=216)	98.5	96.1
Carbapenem	100.0 (n=341)	100.0 (n=71)	100 (n=216)	100	100
Amikacin	98.3 (n=348)	98.6 (n=73)	97.7 (n=221)	97.8	100.0
Gentamicin	98.0	100.0	100.0	99.3	93.5*

^oUrinary breakpoints [5]

* *P* value <0.05