


## The Role of Trimethoprim/ Sulfamethoxazole in the Treatment of Infections Caused by Carbapenem- Resistant *Enterobacteriaceae*

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In the Consortium on Resistance Against Carbapenems in *Klebsiella* and other *Enterobacteriaceae* (CRACKLE), trimethoprim-sulfamethoxazole (TMP-SMX) had a limited role in the treatment of less severe carbapenem-resistant *Enterobacteriaceae* (CRE) infections, especially urinary tract infections. Of tested CRE, only 29% were susceptible to TMP-SMX. Development of resistance further limits the use of TMP-SMX in CRE infections.

**Keywords.** antimicrobial resistance; carbapenem-resistant *Enterobacteriaceae*; *Klebsiella pneumoniae*; trimethoprim-sulfamethoxazole; urinary tract infection.

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The increase in carbapenem-resistant *Enterobacteriaceae* (CRE) infections is of great concern. CRE cause a broad range of infections in humans, including urinary tract, bloodstream, wound, and respiratory infections. Patients in hospitals, nursing homes, and other health care settings are at an increased risk of developing CRE infections due to weakened immune defenses, dysbiosis, and increased levels of exposure to antimicrobials and other patients harboring multidrug-resistant Gram-negative organisms [1]. In the first years of the CRE epidemic, treatment options were severely limited and included polymyxins, tigecycline, and aminoglycosides. Recently, ceftazidime-avibactam, meropenem-vaborbactam, and plazomicin have been added as possible treatment choices with superior outcomes and improved tolerability [2, 3]. Other agents are in the development pipeline [2]. However, limited ability of laboratories to provide susceptibility testing, high costs, and reports of treatment-emergent resistance have hindered widespread use of new antibiotics [4].

Therefore, resistance rates and use of trimethoprim-sulfamethoxazole (TMP-SMX) as a low-cost alternative treatment were evaluated in the Consortium on Resistance Against Carbapenems in *Klebsiella* and other *Enterobacteriaceae* (CRACKLE) [5].

### METHODS

The CRACKLE-1 study has been previously described [5]. Briefly, it is a multicenter, prospective observational study of hospitalized patients with CRE involving 18 hospitals located in the Great Lakes region and North Carolina. The 2012 criteria from the Centers for Disease Control and Prevention (CDC) were used to define CRE [5]. A nested cohort was created to include unique patients at the time of their first infection caused by CRE and tested for susceptibility to TMP-SMX during the study period from December 24, 2011, until June 30, 2016. For available strains, detection of carbapenemase genes and repetitive extragenic palindromic (rep)-polymerase chain reaction (PCR) strain typing was performed as previously described [5]. TMP-SMX in vitro resistance was determined in participating clinical microbiology laboratories and defined per Clinical and Laboratory Standards Institute guidelines as a minimum inhibitory concentration  $\geq 4/76$   $\mu\text{g/mL}$ . Pitt Bacteremia score (PBS) and Charlson comorbidity score (CMS) were calculated as previously described [5]. Antibiotics given within 7 days of the first positive CRE culture were evaluated. Antibiotics of interest were TMP-SMX, polymyxins, aminoglycosides, tigecycline, carbapenems, fosfomycin, and ceftazidime-avibactam. Statistical analyses were performed using R, version 3.5.0 (R Foundation for Statistical Computing) [6].

## RESULTS

During the study period, 476 unique patients were infected with a CRE tested for susceptibility to TMP-SMX. Of these CRE, 138 (29%) were susceptible to TMP-SMX (Table 1). The baseline characteristics of patients with CRE infection caused by a TMP-SMX-susceptible isolate were similar to those of patients with TMP-SMX-resistant CRE. Similarly, no differences were seen between the 2 groups in chronic comorbidities, acute illness, or infection types. Common infection types included urinary tract infection (UTI; 32%), bacteremia (24%), and pneumonia (22%). TMP-SMX-susceptible isolates were more likely to be non-*Klebsiella pneumoniae* CRE species. Overall, 255/276 (92%) of tested CRE were positive for at least 1 carbapenemase gene, which predominantly were *bla*<sub>KPC-2</sub> (45%) and *bla*<sub>KPC-3</sub> (45%).

In the group of patients with a TMP-SMX-susceptible isolate, 110/138 (80%) received at least 1 antibiotic of interest within 7 days of first positive culture. TMP-SMX was part of the treatment regimen in 22/110 (20%) patients and was used as monotherapy treatment in 12/110 (11%) patients. Other commonly used antibiotics in this group included carbapenems (45%), tigecycline (41%), aminoglycosides (36%), and colistin (21%). Among patients who received TMP-SMX monotherapy, 7 (58%) had UTIs, 3 (25%) had bacteremia, and 2 (17%) had other CRE infections; 11 (92%) were infected with CRKp, and 1 (8%) had an *Enterobacter* species. As compared with patients who received other therapy (n = 88), those treated with TMP-SMX monotherapy (n = 12) or a TMP-SMX-containing combination regimen (n = 10) had similar comorbid conditions (median Charlson score [interquartile range {IQR}], 3 [1–5] vs 2 [2–5] and 2.5 [1–6]; P = .80) but were substantially less acutely ill (median Pitt bacteremia

score [IQR], 4 [2–4] vs 2 [0–3] and 2 [2–3]; P = .01). For TMP-SMX-susceptible CRE infections, all-cause 30-day in-hospital mortality in patients treated with TMP-SMX monotherapy or a TMP-SMX-containing combination regimen was similar to patients who did not receive TMP-SMX: 1/12 (8%), 0/10 (0%), and 17/88 (19%; P = .214).

We evaluated subsequent resistance development in those patients who presented with initially susceptible TMP-SMX CRE and who later presented with another positive CRE culture. Resistance was observed in 3/4 patients (75%) treated with TMP-SMX who had a subsequent CRE culture at a later date. These 4 patients all received TMP-SMX monotherapy. None of the 10 patients who received TMP-SMX as part of combination therapy had subsequent CRE cultures. In 1 of 3 of these patients, the TMP-SMX-resistant isolate represented a different strain. In the other 2 patients, strain type by rep-PCR and carbapenemase type were identical in the TMP-SMX-susceptible index strain and the subsequent TMP-SMX-resistant strain. In comparison, subsequent TMP-SMX resistance was observed in 13/29 patients (45%) who were treated with other antibiotics (P = .335). Paired strains were available for 3/13 (23%) in this group, of which all were identical by rep-PCR and carbapenemase type.

## DISCUSSION

In this study, we investigated the use of TMP-SMX in the treatment of CRE infections in hospitalized patients. TMP-SMX has demonstrated activity against multiple *Enterobacteriaceae* species and in some cases may be one of the few remaining treatment options for bacteria resistant to other antibiotic classes. However, increasing global levels of antibiotic resistance to

**Table 1. Characteristics of Patients Infected With Carbapenem-Resistant *Enterobacteriaceae* Compared by Susceptibility to Trimethoprim-Sulfamethoxazole**

	All	TMP-SMX Resistant	TMP-SMX Susceptible	P <sup>a</sup>
No.	476	338 (71)	138 (29)	
Female sex	244 (51)	173 (51)	71 (51)	1.0
Age, median (IQR), y	65 (53–76)	65 (54–75)	64 (50–76)	.840
Charlson score, median (IQR)	3 (1–5)	3 (2–5)	3 (1–5)	.273
Pitt bacteremia score, median (IQR)	3 (1–4)	3 (1–4)	3 (2–4)	.605
Length of stay, median (IQR), d	13 (7–28)	13 (7–30)	13 (6–24)	.759
30-d hospital mortality	81 (17)	62 (18)	19 (14)	.282
<i>Klebsiella pneumoniae</i>	464 (97)	335 (99)	129 (93)	<.01
Carbapenemase present/tested <sup>b</sup>	255/276 (92)	176/193 (91)	79/83 (95)	.326
Infection type				.695
Bacteremia	116 (24)	84 (25)	32 (23)	
Pneumonia	105 (22)	76 (22)	29 (21)	
Urinary tract	152 (32)	105 (31)	47 (34)	
Wound	65 (14)	49 (15)	16 (12)	
Other	38 (8)	24 (7)	14 (10)	

Abbreviations: IQR, interquartile range; TMX-SMP, trimethoprim-sulfamethoxazole.

<sup>a</sup>Compared by Fisher exact test for proportions, Pearson's chi-squared test for distributions, and median test for medians.

<sup>b</sup>Most common carbapenemase genes detected were *bla*<sub>KPC-2</sub> (45%) and *bla*<sub>KPC-3</sub> (45%).

TMP-SMX has limited the broad use of this antibiotic. Overall, we found that more than two-thirds of tested CRE isolates were already resistant to TMP-SMX. Carbapenem-resistant *K. pneumoniae* (CRKp) makes up the majority of collected isolates in the CRACKLE-1 data set. In vitro susceptibility rates of CRKp to TMP-SMX reported in the literature are highly variable and dependent on region of the world, varying between 31% and 82% [7–9].

In our cohort, TMP-SMX was infrequently used, even in those patients with TMP-SMX-susceptible isolates. A case series from Rome describes 14 patients with KPC-producing CRKp infections treated with TMP-SMX, of whom 10 received monotherapy [10]. In that report, clinical cure was achieved in 13/14 cases, and 1/14 patients died within 30 days. However, no controls were provided.

In 3 of 4 patients who received TMP-SMX treatment during their initial CRE infection, subsequent CRE isolates were found to be resistant to TMP-SMX. Treatment-emergent resistance is an important issue for all antibiotics used in the treatment of CRE, including ceftazidime-avibactam and tigecycline [4, 11].

This study has a number of limitations. CRACKLE is an observational study; therefore, patients were not randomly assigned to different antibiotic treatments. Given the small sample size, we did not adjust for confounding by indication. We explicitly do not aim to provide comparative hypothesis testing analysis of TMP-SMX vs alternative treatments for CRE infections. However, we aim to provide guidance for clinicians by describing the experience with TMP-SMX as a therapeutic option in difficult-to-treat CRE infections.

In summary, TMP-SMX resistance rates in CRE were high at baseline and increased after treatment. TMP-SMX was an infrequent treatment choice but may be used in highly selected, clinically stable patients with TMP-SMX-susceptible CRE in the urinary tract.

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## References

1. Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *Lancet Infect Dis* **2009**; 9:228–36.
2. Petty LA, Henig O, Patel TS, et al. Overview of meropenem-vaborbactam and newer antimicrobial agents for the treatment of carbapenem-resistant *Enterobacteriaceae*. *Infect Drug Resist* **2018**; 11:1461–72.
3. van Duin D, Lok JJ, Earley M, et al; Antibacterial Resistance Leadership Group. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant *Enterobacteriaceae*. *Clin Infect Dis* **2018**; 66:163–71.
4. Shields RK, Chen L, Cheng S, et al. Emergence of ceftazidime-avibactam resistance due to plasmid-borne blaKPC-3 mutations during treatment of carbapenem-resistant *Klebsiella pneumoniae* infections. *Antimicrob Agents Chemother* **2016**; 61(3).
5. van Duin D, Perez F, Rudin SD, et al. Surveillance of carbapenem-resistant *Klebsiella pneumoniae*: tracking molecular epidemiology and outcomes through a regional network. *Antimicrob Agents Chemother* **2014**; 58:4035–41.
6. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; **2018**.
7. Pouch SM, Kubin CJ, Satlin MJ, et al. Epidemiology and outcomes of carbapenem-resistant *Klebsiella pneumoniae* bacteriuria in kidney transplant recipients. *Transpl Infect Dis* **2015**; 17:800–9.
8. Lombardi F, Gaia P, Valaperta R, et al. Emergence of carbapenem-resistant *Klebsiella pneumoniae*: progressive spread and four-year period of observation in a cardiac surgery division. *Biomed Res Int* **2015**; 2015:871947.
9. Shawky SM, Abdallah A, Khouly M. Antimicrobial activity of colistin and tigecycline against carbapenem-resistant *Klebsiella pneumoniae* clinical isolates in Alexandria, Egypt. *Int J Curr Microbiol Appl Sci* **2015**; 4:731–742.
10. Murri R, Fiori B, Spanu T, et al. Trimethoprim-sulfamethoxazole therapy for patients with carbapenemase-producing *Klebsiella pneumoniae* infections: retrospective single-center case series. *Infection* **2017**; 45:209–13.
11. van Duin D, Cober ED, Richter SS, et al. Tigecycline therapy for carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bacteriuria leads to tigecycline resistance. *Clin Microbiol Infect* **2014**; 20:O1117–20.