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Trimethoprim-sulfamethoxazole vs. colistin or ampicillin–sulbactam for the treatment of carbapenem-resistant *Acinetobacter baumannii*: A retrospective matched cohort study

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ABSTRACT

Objectives: This study aimed to assess the effectiveness of trimethoprim–sulfamethoxazole (TMP/SMX) as monotherapy for the treatment of carbapenem-resistant *Acinobacter baumannii* (*A. baumannii*) (CRAB) infections.

Methods: This retrospective cohort study included patients receiving TMP/SMX as the main treatment for severe infections caused by CRAB, who were matched with patients treated with colistin or ampicillin–sulbactam (AMP/SUL) by age, Charlson score, department, and source of infection. Outcomes were compared among all patients and in a subgroup of propensity-score (PS) matched patients. The PS matching was performed using a match tolerance of 0.15 with replacement.

Results: Fifty-three patients treated with TMP/SMX and 83 matched patients treated with colistin or AMP/SUL were included. Variables that were independently significantly associated with TMP/SMX treatment included admission for infection and septic shock, while abnormal cognition on admission and intensive care unit admission were associated with colistin or AMP/SUL treatment. All-cause 30-day mortality was lower with TMP/SMX compared with the comparator antibiotics among all patients (24.5%, 13 of 53 vs. 38.6%, 32 of 83, $P = 0.09$) and in the PS-matched subgroup (29%, 9 of 31 vs. 55.2% 16 of 29, $P = 0.04$). Treatment failure rates were not significantly different overall (34%, 18 of 53 vs. 42.4%, 35 of 83, $P = 0.339$) and in the PS-matched subgroup (35.5%, 11 of 31 vs. 44.8%, 13 of 29, $P = 0.46$). Time to clinical stability and hospitalization duration were significantly shorter with TMP/SMX. Patients treated with TMP/SMX probably had less severe infections than those treated with other antibiotics, even after matching.

Conclusions: TMP/SMX might be a valuable treatment option for TMP/SMX-susceptible CRAB infections. Given the very limited available treatment options, further studies assessing its effectiveness and safety are necessary.

1. Introduction

Carbapenem-resistant *Acinetobacter baumannii* (*A. baumannii*) (CRAB) has been recently classified as the top of three critical priority bacteria in the World Health Organization's list of priority bacteria for discovery, research, and development of new antibiotics [1]. Indeed, *A. baumannii* has emerged as one of the most problematic nosocomial pathogens, and its occurrence has particularly increased among patients admitted to intensive care units (ICU). The reasons for this emergence in nosocomial settings include its tendency to colonize multiple body sites, ability to survive for long periods on inanimate surfaces, intrinsic resistance to numerous antibiotics, and tendency to rapidly acquire new resistance determinants [2–6]. A rise in the susceptible population, with advancements in medical support of critically ill and frail

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patients, further contributes to the spread of *A. baumannii* in hospitals.

A. baumannii infections have become increasingly difficult to treat because of the emergence of strains resistant to almost all drugs [7]. Of the critical priority pathogens, it is the pathogen with the highest rate of carbapenem resistance. These strains are frequently susceptible to polymyxins alone, with variable susceptibility to sulbactam and trimethoprim-sulfamethoxazole (TMP/SMX) [8]. Furthermore, very few of the new antibiotics or those in the pipeline are active against CRAB. Only cefiderocol, two new tetracyclines and ETX2514/sulbactam, all still in development, possess activity. Of them, only cefiderocol is also active against carbapenem-resistant Enterobactericeae, allowing broad-spectrum empirical treatment against carbapenem-resistant Gram-negative bacteria.

In Israel, about 30% of *A. baumannii* isolates are susceptible to TMP/SMX. In other locations, variable susceptibility rates have been reported, with <20% in most reports on CRAB [9] but perhaps higher in the East Mediterranean region [10,11]. Given the poor efficacy of polymyxins in the treatment of severe CRAB infections [12] and rising resistance to colistin [13], when active in-vitro, TMP/SMX represents an interesting option for the treatment of *A.*

Table 1
Baseline characteristics of patients treat with TMP/SMX vs. colistin/AMP/SUL.[a]

	TMP/SMX	Colistin/AMP/SUL	*P*
Demographics and background conditions			
Age (years)	71.5 (52.6, 78.1) n = 53	63 (50, 76) n = 83	0.092
Male	29/53 (54.7%)	62/83 (74.7%)	0.016
Normal cognition on admission	38/53 (71.7%)	73/83 (88%)	0.017
Independent functional capacity	33/53 (62.3%)	56/83 (67.5%)	0.534
Charlson score	2 (0, 4) n = 53	4 (1, 5) n = 83	0.005
Congestive heart failure	6/53 (11.3%)	10/83 (12%)	0.898
Chronic renal failure	7/53 (13.2%)	9/83 (10.8%)	0.676
Diabetes	15/53 (28.3%)	33/83 (39.8%)	0.173
Chronic lung disease	10/53 (18.9%)	10/83 (12%)	0.273
Cancer	9/53 (17%)	9/83 (10.8%)	0.303
Immunocompromised	10/53 (18.9%)	38/83 (45.8%)	0.001
Permanent nasogastric tube	3/53 (5.7%)	4/83 (4.8%)	1 (Fisher)
Indwelling urine catheter	4/53 (7.5%)	12/83 (14.5%)	0.223
Days in hospital to infection	13 (8, 25) n = 53	13 (8, 20) n = 83	0.727
Infection presentation			
Nasogastric tube	35/53 (66%)	68/83 (81.9%)	0.035
Urine catheter	42/53 (79.2%)	77/83 (92.8%)	0.02
Mechanical ventilation	38/53 (71.7%)	70/83 (84.3%)	0.075
Central venous catheter	22/53 (41.5%)	59/83 (71.1%)	0.001
Decubitus ulcers	13/53 (24.5%)	19/83 (22.9%)	0.838
Admission for infection	24/53 (45.3%)	17/83 (20.5%)	0.002
Highest temperature (°C)	38.6 (38, 39.4) n = 53	39 (38.5, 39.5) n = 83	0.031
Lowest systolic blood pressure (mmHg)	80 (72, 94) n = 53	87 (70, 96) n = 83	0.47
Highest white blood cell count (X 10^9 cells per liter)	20.74 (17.57, 28.32) n = 53	23.5 (17.78, 32.3) n = 82	0.164
Highest creatinine (mg/dL)	1.6 (1.315, 2.73) n = 53	2.065 (1.23, 3.3) n = 82	0.466
Lowest albumin (g/liter)	1.6 (1.3, 1.9) n = 51	1.5 (1.2, 1.8) n = 82	0.321
Pitt score	4 (2, 6) n = 53	6 (3, 7) n = 83	0.151
Normal cognition at onset of infection	22/53 (41.5%)	16/83 (19.3%)	0.005
Septic shock	27/53 (50.9%)	22/83 (26.5%)	0.004
Respiratory source of infection	36/53 (67.9%)	61/83 (73.5%)	0.484
ICU department	9/53 (17%)	39/83 (47%)	<0.001
Infection and treatment characteristics			
MIC_{50}/MIC_{90} of *A. baumannii*[b]	20/320 (n = 52)	Colistin 1/1 n = 59) AMP/SUL 4/16 (n = 16)	Not relevant
Appropriate empirical antibiotic, first 24 h	11/53 (20.8%) n = 53	8/83 (9.6%) n = 83	0.068
Concomitant antibiotics[c]			0.278
None	25 (47.2%)	40 (48.2%)	
Meropenem	4 (7.5%)	15 (18.1%)	
Vancomycin	3 (5.7%)	4 (4.8%)	
Amikacin	2 (3.8%)	0	
Quinolone	7 (13.2%)	8 (9.6%)	
Other (single or combination)	12 (22.6%)	16 (19.3%)	

Abbreviations: TMP/SMX, trimethoprim-sulfamethoxazole; AMP/SUL, ampicillin–sulbactam; *A. baumannii*, *Acinobacter baumannii*.
[a] Continuous variables presented as medians (minimum, maximum), number of patients with data available.
[b] Minimal inhibitory concentrations (μg/mL) of *A. baumannii* isolates to the antibiotics with which the patients were treated.
[c] Concomitant antibiotics given for ≥2 days, inactive in-vitro against CRAB.

baumannii. Clinical data on the effectiveness of TMP/SMX for *A. baumannii* are lacking. The aim of this study was to compare the outcomes of patients treated with TMP/SMX vs. those treated with colistin or ampicillin–sulbactam (AMP/SUL) for CRAB infections.

2. Methods

This was a retrospective matched-cohort study conducted at the Rambam Health Care Campus, which is a 950 bed, tertiary care, university-affiliated hospital serving over 1 000 000 citizens of northern Israel. At the time of the study, the hospital operated a combined medical and surgical ICU of 18 beds, a large bone marrow transplant department, chest and cardiac surgery and neurosurgery. The hospital serves as the referral center for trauma and burns in northern Israel. The study was approved by the hospital's ethics committee. No informed consent was required given the non-interventional design of the study and anonymous data analysis.

Patients with documented CRAB infections were included. Patients treated with TMP/SMX alone for TMP/SMX-susceptible CRAB were matched with patients treated with colistin or AMP/SUL for *A. baumannii* susceptible to these antibiotics. Treatment was defined when the patient was treated for at least 5 days within the first week after the culture taken date with the respective antibiotic, TMP/SMX, colistin or AMP/SUL, and these were single covering antibiotics. Matching was based on age (±5 years), Charlson score (±4), hospital department when the culture was obtained, and source of the culture (blood, sputum, urine, etc.). Inclusion criteria and matching were applied to all patients with an isolate of *A. baumannii*, allowing one-to-many matching. Infections were defined using the CDC/NHSH criteria for specific healthcare-associated infections [14]. Colistin was dosed 4.5 million units (MIU) twice daily following a loading dose of 9 MIU, AMP/SUL 2000/1000 mg four times daily, and TMP/SMX 800/160 mg twice daily, for patients with normal renal function; all were administered intravenously as bolus injections and adjusted as necessary to renal failure.

The primary outcome was 30-day all-cause mortality calculated from the day the target antibiotic (TMP/SMX, colistin or AMP/SUL) was started. Secondary outcomes included: treatment failure, defined as persistent temperature >38 °C on day 7 from antibiotic start; the time to clinical stability, defined as the number of days from start of antibiotics until temperature normalization (<38 °C) reaching hemodynamic stability and normal mental status (12); and length of hospital stay for patients who survived the hospitalization episode. TMP/SMX patients were identified by linking those in whom *A. baumannii* was isolated with those starting treatment with one of the exposure antibiotics in the week following the culture taken date. The data required for matching were also automatically extracted from the microbiology and hospital databases. Final inclusion — based on clinical criteria, group assignment and matching – was applied following review of electronic patient files. Data were manually collected from patients' electronic charts on demographics, medical background, reason for admission (infectious/noninfectious), infection presentation including septic shock [15,16] and the Pitt score. Whether the empirical antibiotic treatment given in the first 24 h after culture taking was appropriate (covering) was also identified. Identification of *A. baumannii* and susceptibility testing to the combination of TMP/SMX were performed by the VITEK-2 automated system.

Patients treated with TMP/SMX vs. other antibiotics (colistin or AMP/SUL) were compared. Despite the baseline matching of groups, significant between-group differences were observed. Variables significantly differentiating between the treatment groups were used in a logistic regression analysis to compute a propensity score (PS) for TMP/SMX treatment. Outcomes were compared between the treatment groups overall and in a PS-matched analysis, using a match tolerance of 0.15 and allowing replacement in patient sampling. Risk factors for mortality were also assessed. Variables significant on the univariate analysis together with the exposure variable (the treatment group) were entered into a multivariate logistic regression analysis to compute the independent association between antibiotic treatment and mortality. Categorical variables were compared using a χ^2 or the Fisher's exact test. Continuous variables were compared using *t*-test or the Mann–Whitney *U* test. Binary logistic regression was performed with mortality as the dependent variable. Analyses were conducted using SPSS 24.

3. Results

A total of 990 patients with *A. baumannii* infection treated with the study drugs were identified between January 2013 and December 2015. Of these, 53 patients treated with TMP/SMX for CRAB infection fulfilled the clinical criteria for infection and treatment, and were matched with 83 patients treated with colistin (n = 59) or AMP/SUL (n = 24) for CRAB, comprising the full matched cohort. Most patients had pneumonia (97 of 136, 71.3%); other sources of infection included skin/soft tissue (18, 13.2%), urinary (11, 8.1%) and central line-associated bacteremia (10, 7.4%).

Demographic, background and infection characteristics of patients treated with TMP/SMX compared with colistin or AMP/SUL are shown in Table 1. Patients treated with TMP/SMX were non-significantly older, and more of them were female and admitted for infection (not necessarily *A. baumannii* infection). Despite matching, the median Charlson score in the TMP/SMX group was lower than in the control group, driven mostly by fewer conditions causing immune suppression in this group. The patients given colistin or AMP/SUL were sicker or with more severe infections, as reflected by more abnormal cognition on admission or at infection onset, more catheters and mechanical ventilation, higher temperature, and were more frequently in the ICU. The patients treated with TMP/SMX were twice as likely to have septic shock at presentation (27 of 53, 50.9%) than those treated with colistin or AMP/SUL (22 of 83, 26.5%). Appropriate empirical antibiotic treatment in the first 24 h was given to 19 of 136 (14%) patients and concomitant antibiotics (inactive in-vitro against CRAB) were given to 71 of 136 (52.2%), with no statistically significant between-group differences. Isolates' susceptibilities to the study antibiotics are shown in Table 1.

This comparison was used to generate the PS for TMP/SMX treatment (Table 2). Variables remaining independently significantly associated with TMP/SMX treatment included admission for infection and septic shock, while abnormal cognition on admission and ICU admission were associated with colistin or AMP/SUL treatment. Using the PS, 31 patients treated with TMP/SMX could

Table 2
Factors associated with TMP/SMX treatment for *A. baumannii* infections.

	OR (95% CI)	*P*
Female	2.42 (0.956, 6.122)	0.062
Admission for infection	3.119 (1.191, 8.168)	0.021
Immunocompromised	0.338 (0.0115, 0.999)	0.05
Central venous catheter	0.573 (0.208, 1.58)	0.282
Normal cognition at onset of infection	3.376 (1.174, 9.706)	0.024
ICU department	0.349 (0.123, 0.987)	0.047
Septic shock	3.543 (1.357, 9.254)	0.01
Charlson score	0.858 (0.688, 1.069)	0.173

Abbreviations: TMP/SMX, trimethoprim-sulfamethoxazole; ICU, intensive care unit; *A. baumannii*, *Acinobacter baumannii*.

Table 3
Outcomes for TMP/SMX vs. colistin/AMP/SUL treatment for *A. baumannii* infections.

	TMP/SMX	Colistin/AMP/SUL	*P*
All patients in matched cohort study			
30-day mortality	13/53 (24.5%) n = 53	32/83 (38.6%) n = 83	0.09
Treatment failure at day 7	18/53 (34%)	35/83 (42.4%)	0.339
Days to clinical stability (among patients achieving stability)	0 (0–30) n = 40	4 (0–32) n = 51	<0.001
Days from treatment start to discharge (among patients discharged alive)	25 (4, 319) n = 32	38 (2, 413) n = 49	0.03
Propensity-matched cohort subgroup			
30-day mortality	9/31 (29%)	16/29 (55.2%)	0.04
Treatment failure at day 7	11/31 (35.5%)	13/29 (44.8%)	0.46
Days to clinical stability (among patients achieving stability)	0 (0, 17) n = 22	1 (0, 10) n = 13	0.038
Days from treatment start to discharge (among patients discharged alive)	14 (4, 319) n = 17	30 (2, 223) n = 12	0.107

Abbreviations: TMP/SMX, trimethoprim-sulfamethoxazole; AMP/SUL, ampicillin–sulbactam; *A. baumannii*, *Acinobacter baumannii*.

be matched to 28 comparator patients. Among them the between-group differences were not apparent (Supplementary Table 1).

Outcomes for all patients and for the PS-matched cohort are presented in Table 3. Among all patients in the matched cohort, the time to clinical stability and discharge was significantly shorter with TMP/SMX compared with colistin or AMP/SUL. Among patients in the PS-matched subgroup, mortality was lower and the time to clinical stability was significantly shorter with TMP/SMX. The trend of all outcomes favored TMP/SMX.

4. Discussion

This matched cohort study showed non-inferior outcomes for patients treated with TMP/SMX for carbapenem-resistant *A. baumannii* infections compared with the standard of care for these infections: ampicillin–sulbactam when susceptible or colistin when resistant to all other antibiotics. Despite an attempt at matching by age, Charlson score, department and source of infection, the patient groups were dissimilar, with patients given TMP/SMX being less immunocompromised and generally with more severe infections than those given the standard antibiotics. Using PS matching, more similar patient groups were obtained, among which outcomes with TMP/SMX were still non-inferior and even superior to colistin or AMP/SUL.

TMP/SMX has a long history of clinical effectiveness for urinary tract infections, respiratory infections, sexually transmitted diseases, Gram-negative sepsis, typhoid fever, and some methicillin-resistant *Staphylococcus aureus* infections caused by susceptible strains [17,18]. Its use for susceptible CRAB infections depends on the validity of current breakpoints for this combination of *A. baumanni* and the automated susceptibility testing, its clinical efficacy, and the potential for rapid resistance development during therapy. Little is known about all these questions. In a systematic review of studies reporting on TMP/SMX for *A. baumannii,* Falagas et al. only identified case reports describing successful therapy [9]. In-vitro studies describe the activity of TMP/SMX against *A. baumannii* and synergistic interactions between colistin and TMP/SMX [19–21]. The current study only evaluated TMP/SMX monotherapy. Increased activity of TMP/SMX and other non-beta-lactam drugs in *A. baumannii* biofilms has been described [22], possibly explaining the effectiveness of TMP/SMX in the current cohort, where most patients had respiratory infections, mainly ventilator-associated pneumonia, as has been shown for TMP/SMX against methicillin-resistant *Staphylococcus aureus* pneumonia [23]. However, penetration of trimethoprim to the lung is better than that of sulphamethoxazole [24]. There is no information on the activity of trimethoprim alone on *A. baumannii* nor on its potential to become more rapidly resistant when exposed to trimethoprim alone.

A limitation of this study was its observational design, which allowed selection bias. Despite a double attempt at matching, it is unlikely that any bias was controlled. The very small sample size remaining after matching decreased the confidence in the results and did not allow further confounding to be addressed. As a retrospective study, there was no control of drug dosing and duration, which might be critical in optimizing the effectiveness of antibiotics against CRAB. This study did not evaluate the development of resistance to TMP/SMX during therapy; but if existent, it did not detect its association with poorer outcomes than comparator antibiotics.

In conclusion, TMP/SMX might be a valuable treatment option against TMP/SMX-susceptible isolates of multidrug-resistant *A. baumannnii.* More data on global susceptibility of CRAB to TMP/SMX are needed. Better and preferable interventional clinical studies are needed to assess its effectiveness for different types of *A. baumannnii* infections. There are currently, and in the foreseeable future, very few treatment options for CRAB. Thus, all available treatment options, including old drugs, must be carefully examined for efficacy.

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Nil.

Conflicts of interests

None declared.

Ethical approval

Ethics approval with waiver of informed consent was obtained from the hospital's ethics committee.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jgar.2018.12.001.

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