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ORIGINAL RESEARCH

Aminoglycoside or Polymyxin Monotherapy for Treating Complicated Urinary Tract Infections Caused by Extensively Drug-Resistant *Pseudomonas aeruginosa*: A Propensity Score-Adjusted and Matched Cohort Study

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ABSTRACT

Introduction: Extensively drug-resistant (XDR) *Pseudomonas aeruginosa* (PA) infections are difficult to treat. We aimed to compare aminoglycosides or polymyxin monotherapy versus other antibiotic regimens (carbapenems, aztreonam, ceftazidime, cefepime, ceftolozane-tazobactam, or ceftazidime-avibactam) in complicated urinary tract infections (cUTI) caused by XDR-PA.

Methods: Study performed at a tertiary-care hospital from 2010 to 2019. All consecutive

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adult patients with XDR-PA urine cultures and diagnosed with cUTI were retrospectively reviewed. XDR phenotype was defined according to Magiorakos et al. A propensity score was used as a covariate in multivariate analyses and for matching. Primary outcome was early clinical failure and at end of treatment (EOT). Main secondary outcomes were 30- and 90-day mortality, microbiological clearance, and antibiotic-related side effects.

Results: Of the 465 episodes screened, 101 were included, 48% were treated with aminoglycoside or colistin monotherapy. Most XDR-PA were susceptible to colistin (100%) and amikacin (43%). Patients treated with antibiotic regimens other than aminoglycosides or polymyxin monotherapy were more likely to have hematologic malignancy ($p < 0.001$), higher SOFA score ($p = 0.048$), and bacteremia ($p = 0.003$). In multivariate models adjusted by propensity score, aminoglycoside or colistin monotherapy was not associated with worse outcomes. After propensity score matching, 28 episodes in each treatment group were matched. Adjusted ORs (95% CI) for early clinical failure and at EOT with aminoglycosides or polymyxin monotherapy were 0.53 (0.18–1.58) and 1.29 (0.34–4.83), respectively. Aminoglycoside or colistin monotherapy was not associated with higher 30-day (HR 0.93, 95% CI 0.17–5.08) or 90-day mortality (HR 0.68, 95% CI 0.20–2.31), nor with absence of microbiological clearance (OR 0.72, 95% CI 0.33–1.58). No statistically significant differences were found in terms of nephrotoxicity. *Clostridioides difficile* infection was observed only in the "other antibiotic regimens" group ($n = 6$, 11.3%).

Conclusions: Aminoglycosides or polymyxin monotherapy showed good efficacy and safety profile in treating cUTI caused by XDR-PA. These results may be useful for antibiotic stewardship activities.

Keywords: Extensively drug-resistant *Pseudomonas aeruginosa*; Urinary tract infections; Amikacin; Colistin; Antimicrobial stewardship

Key Summary Points

Aminoglycosides or polymyxin monotherapy might be an alternative for urinary tract infections (UTIs) caused by extensively drug-resistant (XDR) *P. aeruginosa*.

Aminoglycosides or polymyxin monotherapy was not associated with poor outcomes compared to other antibiotic regimens.

Patients treated with antibiotic regimens other than aminoglycosides or polymyxin monotherapy were more likely to have *Clostridioides difficile* infection

These results may be useful for antimicrobial stewardship activities.

INTRODUCTION

The increasing incidence of multidrug-resistant gram-negative bacteria (GNB) is a worldwide problem. *Pseudomonas aeruginosa* is particularly worrisome because of its extraordinary capacity to develop resistance [1]. The emergence of extensively drug-resistant (XDR) strains in recent years has increased the concern [2]. *P. aeruginosa* is frequently isolated in complicated urinary tract infection (UTI), mainly those of nosocomial or healthcare-related acquisition [3]. Aminoglycosides and colistin are usually active against GNB, including many XDR *P. aeruginosa* isolates [4]. Both agents have favorable pharmacokinetics characteristics, which theoretically makes them suitable molecules for the treatment of complicated UTIs. Aminoglycosides are excreted in high concentrations in the urine, exceeding plasma concentrations by up to 100-fold, and remain above therapeutic levels for 72 h or longer [5]. Approximately 60–70% of colistimethate sodium (CMS) is eliminated in the urine. Furthermore, the conversion of CMS into colistin

can occur in the renal tubular cells and in the bladder, suggesting that concentrations of formed colistin may be higher than those in plasma [6, 7]. However, as a result of concern about their nephrotoxicity [8, 9], clinical effectiveness [10, 11], and the risk of emergence of resistance in vivo [11, 12], combined antimicrobial therapy or broad-spectrum antibiotics such as carbapenems, ceftolozane-tazobactam, or ceftazidime-avibactam are frequently used to treat complicated UTIs caused by XDR *P. aeruginosa*.

On the other hand, previous studies [13, 14] have shown that in *P. aeruginosa* infections, UTI is associated with lower mortality rates and is therefore considered a low-risk source of infection. Thus, antibiotic monotherapy with aminoglycosides or colistin could be explored as an alternative therapeutic strategy, even in complicated UTIs. Furthermore, the prescription of broad-spectrum or combined antimicrobial therapy can also have deleterious effects, such us development and persistence of antimicrobial resistance [15], higher risk of *Clostridioides difficile* infection [16], and higher pharmacy costs [17].

We hypothesized that aminoglycosides or polymyxin monotherapy could be an alternative effective option for the treatment of complicated UTIs caused by XDR *P. aeruginosa*.

The aim of the present study was to evaluate the efficacy and safety of aminoglycosides or polymyxin monotherapy in comparison to other antibiotic regimens, including combined antimicrobial therapy, in complicated UTIs due to XDR *P. aeruginosa*.

METHODS

Hospital Setting, Study Design, and Participants

This study was conducted from January 2010 to June 2019 at the Hospital del Mar, a tertiary-care university hospital in Barcelona (Spain), within the framework of an antimicrobial stewardship (AMS) program.

All consecutive positive urinary cultures for XDR *P. aeruginosa* during the study period were retrospectively reviewed. XDR *P. aeruginosa* was defined as non-susceptible to one or more agent in all but no more than two antipseudomonal antimicrobial categories, according to Magiorakos et al. [18].

The inclusion criteria were patients aged at least 18 years old, diagnosed with acute pyelonephritis or complicated UTI and with a monomicrobial urine culture positive for XDR *P. aeruginosa*. Non-complicated UTIs and asymptomatic bacteriuria were excluded. All episodes were retrospectively reviewed by two authors (I.L.M. and S.G.-Z.). Patients treated with aminoglycosides or colistin in the form of CMS monotherapy were compared to those treated with other antibiotic regimens including carbapenems, aztreonam, ceftazidime, cefepime, ceftolozane-tazobactam, or ceftazidime-avibactam, alone or in combination (including also combinations with aminoglycosides or CMS). Dose selection was at the discretion of the responsible clinicians and was adjusted according to glomerular filtration rate (GFR).

Patients were followed for up to 90 days from the date of the urine culture. In cases of more than one episode of *P. aeruginosa* UTI, the second and following episodes were assessed if they occurred at least 90 days after the prior one. Patients who died within the first 48 h or did not complete follow-up were not included in the analysis.

Ethics

The study was approved by the Clinical Research Ethics Committee of the Parc de Salut Mar (register no. 2020/9321). The need for written informed consent was waived because of the observational nature of the study and retrospective analysis. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guideline and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Clinical Variables, Data Source, and Definitions

The main outcome variable was clinical failure assessed early (day 7) and at end of treatment (EOT). Secondary outcomes were crude 30- and 90-day mortality; recurrence, reinfection, microbiological clearance, and readmission rates within 90 days. The incidence of acute kidney injury (AKI), *C. difficile* infection, rash, hematological toxicity, hepatotoxicity, and neurological symptoms were also evaluated as secondary outcomes to study antibiotic-related side effects.

Demographic, clinical, and microbiological data were collected from hospital medical charts. Recorded data included the following: age and sex; comorbidities and severity of underlying diseases, assessed using the Charlson comorbidity index [19], and immunosuppression state, defined as neutropenia (absolute neutrophil count of 500 cells/mm^3 or less), chemotherapy or other immunosuppressant drugs, HIV infection, and/or congenital immunosuppression. Prior history of benign prostatic hypertrophy, urologic malignancy, obstructive nephropathy, recurrent UTI, and urological devices in the last 14 days were also recorded.

Severity of illness was calculated using the Sequential Organ Failure Assessment (SOFA) score [20], the need for intense care unit (ICU) admission, and the presence of septic shock [21]. The Pitt score [22] was applied in the case of bacteremia.

Acute pyelonephritis was considered if the patient had at least two of the following criteria: temperature above 37.7 °C, UTI symptoms (dysuria, urgency, suprapubic pain, and/or pollakiuria), local pain (lumbar back pain, costovertebral angle tenderness, and/or pelvic or perineal pain in men), and/or altered mental status in people up to 70 years. Those with the same criteria and a prior history of benign prostatic hyperplasia, intermittent or permanent indwelling urinary catheter (or withdrawal within 48–72 h before infection onset), or underlying urologic abnormalities such us nephrolithiasis, strictures, stents, history of renal transplant or urinary diversions or neurogenic bladder were classified as complicated UTI. The site of infection acquisition was defined according to Friedman et al. [23].

Appropriate empiric antibiotic therapy was considered when at least one antipseudomonal antibiotic with in vitro activity was administered during the first 24 h after urine cultures were taken. Appropriate definite antibiotic therapy was treatment based on the results of antibiotic susceptibility testing. Combination therapy was defined as two or more antipseudomonal drugs used for at least 48 h.

Adequate source control was defined as removal or insertion of indwelling urinary catheters, percutaneous drainage of the urinary tract (double-J stent, nephrostomy), or surgical intervention, as appropriate.

Clinical failure was considered if there was persistence or worsening signs and/or symptoms of UTI, the need to modify antibiotic therapy because of antibiotic side effects, the emergence of resistance to the study drug, and/or death.

Recurrence was defined as recurrent signs or symptoms of UTI and a urinary isolate of XDR *P. aeruginosa* with the same susceptibility profile as the index infection. Reinfection was defined as recurrent signs or symptoms of UTI with isolation of a *P. aeruginosa* strain with a different phenotypic profile from the prior one and/or a urinary isolate different from *P. aeruginosa*. Microbiological clearance was considered if there was no growth of *P. aeruginosa* in the final urine culture, if available. Episodes with missing urine samples during follow-up were classified as indeterminate. All microbiological assessments referred to up to 90 days following onset of the index UTI.

Antibiotic side effects (i.e., nephrotoxicity, *C. difficile* infection, rash) were also recorded. GFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), was registered at baseline and at EOT. In case of AKI, the RIFLE score [24] was applied.

Microbiological Studies

Bacterial isolates were identified as *P. aeruginosa* following standard procedures. Antibiotic

susceptibility testing of isolates was performed by broth microdilution using MicroScan® panels [Beckman-Coulter] in the automated MicroScan® WalkAway system [Beckman-Coulter]. The following antimicrobials were tested: ciprofloxacin, piperacillin-tazobactam, ceftazidime, cefepime, imipenem, meropenem, aztreonam, gentamicin, tobramycin, amikacin, and colistin. Ceftolozane-tazobactam was not in routine use for a large part of the study; it was tested by Etest® gradient diffusion (bioMérieux, Marcy-l'Etoile, France) from 2017 onwards. Antibiotic susceptibility testing results were categorized according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria [25] in force at the time of urine culture.

Statistical Analysis

The required sample size (100 patients) was determined from the results of a previous study [26] to detect a 20% difference in early clinical failure between an aminoglycoside-based or colistin group vs. "other regimens" group for infections caused by drug-resistant *P. aeruginosa*; statistical power was set at 80%, alpha error at 0.05, and 0.2 estimated losses to follow-up.

Categorical variables were compared by the χ^2 test or Fisher exact test and continuous variables by Student's *t* test or Mann–Whitney *U* test, as appropriate. A logistic regression model examined associations between exposures and clinical failure and microbiological clearance whereas Cox proportional hazards regression was applied to assess mortality until day 30 and 90. Variables with a *p* value of at most 0.1 in univariate analysis and those clinically relevant were included in the multivariate models and selected manually using backward stepwise regression.

A propensity score for receiving monotherapy with aminoglycosides or colistin was calculated. Variables used for calculating propensity score were age, sex, Charlson comorbidity index, hematologic malignancy, positive blood cultures, SOFA score, and presentation with sepsis/septic shock. Its predictive ability was estimated by calculating the area under the receiver operating characteristic curve (AUC) with 95% confidence interval (CI). The variance inflation factor value was calculated for every variable included to control for the potential occurrence of collinearity between the propensity score and other potential confounders. We selected the best model according to the likelihood ratio test. The final model showed a *p* value of 0.71 for the Hosmer–Lemeshow goodness-of-fit test and an AUC of 0.8 (95% CI 0.71–0.88). The propensity score was used in two different ways, as a covariate of control for residual confounding in multivariate models, and to perform a matched cohort analysis in which patients receiving amikacin or CSM were matched 1:1 according to their propensity score with those receiving other antibiotic regimens. The caliper was set to a width equal to 0.2 of the standard deviation of the logit of the propensity score [27]. Clinical failure in the matched pairs was compared by conditional logistic regression whereas Cox regression was used to compared mortality. Sensitivity analyses for all the studied outcomes were performed excluding patients receiving amikacin or CMS as part of a combination therapy from the control group. All *p* values were two-tailed and those less than 0.05 indicated statistical significance. The STROBE recommendations were used to ensure the reporting of the study (Supplementary Material). Statistical analyses were performed using STATA 15.1.

RESULTS

Of the 465 cases with urine cultures positive for XDR *P. aeruginosa* screened, 101 episodes met the inclusion criteria and were included in the final analysis (Fig. 1). Only four patients had two episodes of UTI, the rest had a single episode. Most XDR *P. aeruginosa* were susceptible to colistin (100%) and amikacin (42.6%, *n* = 43/101). Complete antimicrobial susceptibility phenotypes are shown in the Supplementary Material.

In the aminoglycoside or CMS monotherapy group (*n* = 48), 27 episodes were treated with

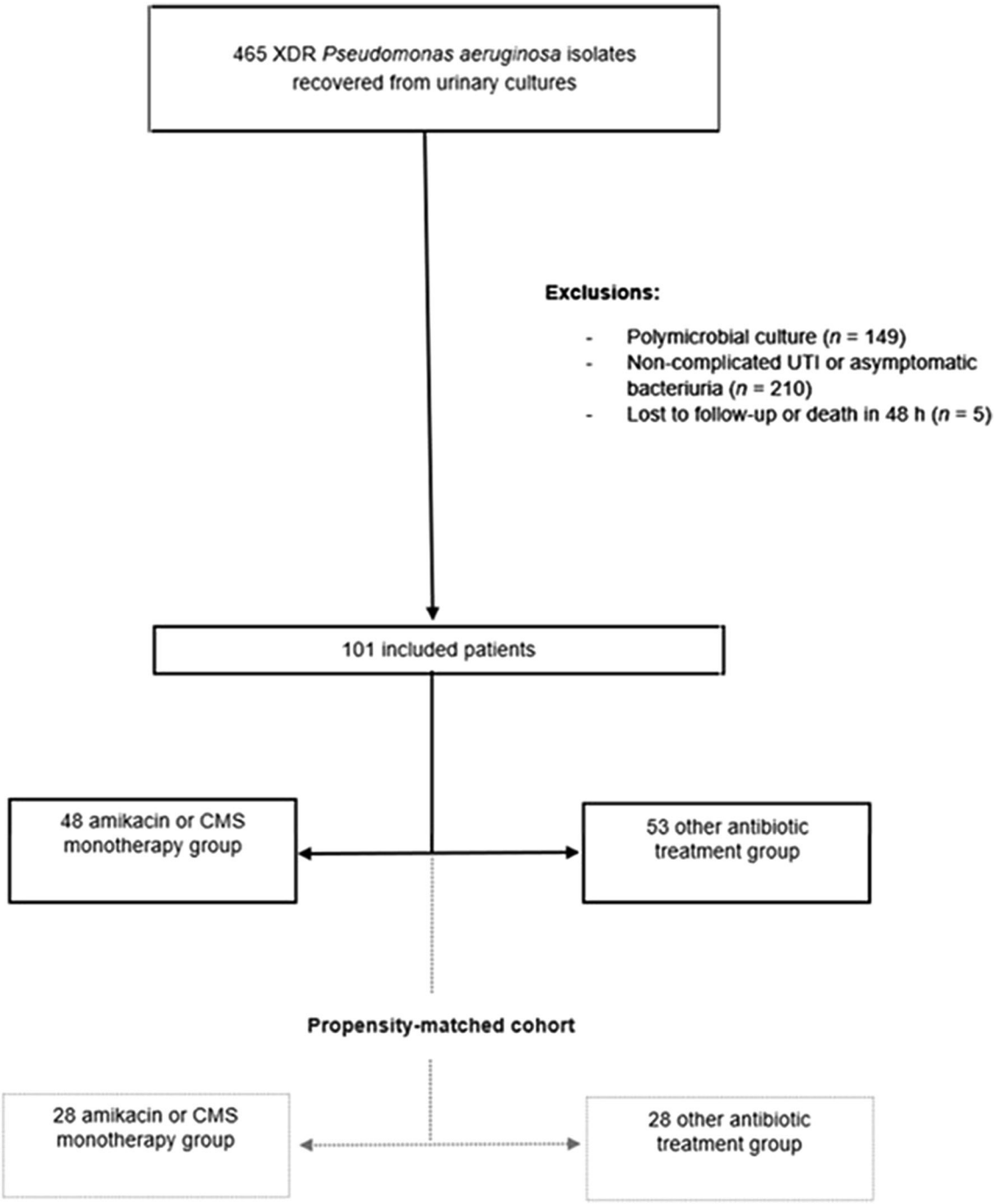

Fig. 1 Flowchart of the patients included in the study. XDR extensively drug-resistant, UTI urinary tract infection, CMS colistimethate sodium

CMS and 21 with aminoglycosides. Among those with other antibiotic therapies (n = 53), the most frequent antibiotic regimens were amikacin and/or CMS plus carbapenem (n = 24), CMS plus ceftazidime or cefepime (n = 7), and amikacin or CMS plus aztreonam

Table.1 Baseline characteristics of patients in overall and propensity-matched cohorts

Variable	Overall cohort (n = 101)			Propensity score matched cohort (n = 56)		
	Amikacin or CMS treatment (n = 48)	Other treatments (n = 53)	p value	Amikacin or CMS treatment (n = 28)	Other treatments (n = 28)	p value
Demographic information						
Age (years), m (IQR)	74.5 (67–84.5)	77 (67.5–82)	0.796	77 (69.5–87)	77 (66–82)	0.640
Male sex	40 (83.3)	40 (75.5)	0.331	23 (79.3)	21 (77.8)	0.899
Underlying condition						
Charlson comorbidity index, m (IQR)	4 (2–5.75)	4 (2–6)	0.961	3 (2–5)	4 (2–6)	0.337
Diabetes mellitus	13 (27.1)	17 (32.1)	0.583	8 (27.6)	12 (44.4)	0.188
COPD	15 (31.2)	16 (30.2)	0.908	5 (17.2)	8 (29.6)	0.273
Cirrhosis	2 (4.2)	2 (3.8)	1	–	1 (3.7)	0.482
Hematologic malignancy	1 (2.1)	16 (30.2)	< 0.001*	1 (3.4)	2 (7.4)	0.605
Solid tumor malignancy	24 (50)	25 (47.2)	0.776	15 (51.7)	11 (40.7)	0.410
Nephro-urological history						
Baseline GFR (ml/min), m (IQR)	58.1 (35–83)	50 (25.5–83.5)	0.835	43 (27–68.25)	48 (27–82)	0.476
Chronic kidney disease	10 (20.8)	15 (28.3)	0.385	8 (27.6)	9 (33.3)	0.640
Dialysis	1 (2.1)	5 (9.4)	0.208	1 (3.4)	2 (7.4)	0.605
Renal transplant	1 (2.1)	4 (7.6)	0.365	–	1 (3.7)	0.482
Benign prostatic hypertrophy	14 (29.2)	16 (30.2)	0.911	7 (24.1)	10 (37)	0.386
Obstructive urinary disease	6 (12.5)	6 (11.3)	1	3 (10.3)	1 (3.7)	0.612
Recurrent UTI	20 (41.7)	29 (54.7)	0.19	15 (51.7)	14 (51.9)	0.992
Indwelling urinary catheter in last 14 days	36 (75)	33 (62.3)	0.202	23 (79.3)	20 (74.1)	0.643
Other urological devices in last 14 days	6 (12.5)	12 (22.6)	0.205	2 (6.9)	1 (3.7)	1
Acquisition						
Healthcare-related	23 (51)	28 (52.8)	0.622	20 (69)	13 (48.1)	0.114
Nosocomial	25 (52.1)	25 (47.2)	0.622	9 (31)	14 (51.9)	0.114
HCA risk factors						

Table.1 continued

Variable	Overall cohort (n = 101)			Propensity score matched cohort (n = 56)		
	Amikacin or CMS treatment (n = 48)	Other treatments (n = 53)	p value	Amikacin or CMS treatment (n = 28)	Other treatments (n = 28)	p value
Hospital stay in last 3 months	24 (50)	33 (62.3)	0.234	13 (48.1)	17 (58.6)	0.432
Surgery in last 3 months	22 (45.8)	16 (30.2)	0.150	12 (41.4)	8 (29.6)	0.359
ICU admission in last 3 months	13 (27.1)	9 (17)	0.238	7 (24.1)	6 (22.2)	0.865
Residence in long-term care	8 (16.7)	6 (11.3)	0.567	8 (27.6)	1 (3.7)	0.026*
Antibiotic exposure in last 3 months	38 (79.2)	49 (92.4)	0.082	25 (86.2)	24 (88.9)	0.762
Baseline illness severity						
SOFA score, m (IQR)	1 (0–2.7)	2 (1–4)	0.048*	2 (0.5–3)	2 (0–4)	0.973
Sepsis or septic shock	11 (22.9)	21 (39.6)	0.072	10 (34.5)	6 (22.2)	0.310
ICU admission	5 (10.4)	7 (13.2)	0.764	5 (17.2)	2 (7.4)	0.424
Bacteremia	4 (8.3)	17 (32.1)	0.003*	4 (13.8)	4 (14.8)	0.913
Pitt score, m (IQR)	2 (0.5–2.7)	1 (0–1.5)	0.282	2 (0.5–2.7)	0.5 (0–1)	0.134
Management						
Appropriate empirical treatment	8 (16.7)	13 (24.5)	0.331	6 (20.7)	5 (18.5)	0.838
Appropriate definitive treatment	48 (100)	49 (92.5)	0.119	29 (100)	24 (88.4)	0.106
72 h delay to start appropriate antibiotic treatment	24 (50)	30 (56.6)	0.506	15 (51.7)	18 (66.7)	0.256
Adequate source control	44 (91.7)	46 (86.8)	0.432	27 (93.1)	24 (88.9)	0.580

Data are presented as n (%), unless otherwise specified

CMS colistimethate sodium, *COPD* chronic obstructive pulmonary disease, *GFR* glomerular filtration rate, *UTI* urinary tract infection, *HCA* healthcare acquired, *ICU* intensive care unit, *SOFA* Sequential Organ Failure Assessment, *m* median, *IQR* interquartile range

*Statistical significance at $p < 0.05$

(n = 6). Only 14 episodes were treated with amikacin- or colistin-free antibiotic regimens: ceftazidime (n = 5), ceftolozane-tazobactam (n = 5), aztreonam (n = 2), and carbapenems (n = 2). All patients treated with an aminoglycoside (n = 35; 21 in the monotherapy group vs. 14 in the "other therapies" group) received amikacin in a once-daily strategy, with the most frequent regimen being 1 g every 24 h [n = 22, 15/21 (71.4%) in the monotherapy

group vs. 7/14 (50%) in other regimens]. In the case of CMS ($n = 52$; 27 in the monotherapy group vs. 25 in the "other treatments group"), the most frequent doses were 2 million international units (IU) three times a day in 9 (33.3%), 3 million IU twice daily in 8 (29.6%), 1 million IU twice daily in 8 (29.6%), and 1 million IU once a day in 8 (29.6%) episodes.

Overall, 80% were men and the median age was 76 years. Most cases were considered complicated UTI ($n = 93$), whereas acute pyelonephritis was observed in only eight patients. The 20% of episodes were bacteremic UTI. Bloodstream infection was more frequently observed among patients treated with amikacin or CMS monotherapy than those who received other antibiotic regimens (32.1% vs 8.3%, $p = 0.003$).

After propensity score matching, 56 (55.4%) patients were matched, with 28 in each treatment group. Baseline epidemiological and clinical characteristics between treatment groups before and after propensity score analysis are shown in Table 1. No significant differences were observed in the baseline demographic or clinical characteristics after propensity score matching, apart from prior residence in long-term care facility ($p = 0.026$).

Primary Outcome: Clinical Failure

Early clinical failure rate was 28.7% (29/101): 18.7% (9/48) in the amikacin or CMS monotherapy group vs. 37.7% (20/53) in other antibiotic regimens ($p = 0.035$). Reasons for failure were persistence or worsening signs and/or symptom, 26 cases (7/29, 24.1% in amikacin or CMS monotherapy vs. 19/29, 65.5% in other antibiotic regimens); death, two patients (1/29, 3.5% in each group); and need to modify therapy because of antibiotic side effects, one patient (3.5%) in the amikacin or CMS monotherapy group.

The rate of clinical failure at EOT was 19.8% (20/101): 20.8% (10/48) in amikacin or CMS

Table.2 Crude and adjusted associations between different variables and clinical failure at day 7 and at end of treatment in overall and propensity-matched cohorts

	Overall cohort			Propensity-matched cohorts	
	Crude OR (95% CI)	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value
Day 7					
Age (years), m (IQR)	1.01 (1–1.09)	1.05 (1.01–1.1)	0.041	1.01 (0.96–1.06)	0.725
Charlson comorbidity index, m (IQR)	1.06 (0.89–1.25)	1.09 (0.9–1.32)	0.356	1.05 (0.81–1.35)	0.717
SOFA score, m (IQR)	1.12 (0.9–1.38)	1.01 (0.82–1.31)	0.770	1.13 (0.82–1.55)	0.460
Amikacin or CMS treatment	0.38 (0.15–0.95)	0.5 (0.17–1.44)	0.198	0.53 (0.18–1.58)	0.251
Propensity score	0.16 (0.03–0.86)	0.34 (0.04–2.74)	0.311		
End of treatment					
Age (years), m (IQR)	1.03 (0.98–1.08)	1.05 (0.99–1.11)	0.101	1.04 (0.97–1.19)	0.301
Charlson comorbidity index, m (IQR)	1.18 (0.98–1.43)	1.24 (1.01–1.53)	0.047	1.39 (0.97–1.97)	0.071
SOFA score, m (IQR)	1.05 (0.82–1.34)	1 (0.76–1.31)	0.980	0.88 (0.57–1.36)	0.552
Amikacin or CMS treatment	1.13 (0.42–3.01)	1.58 (0.47–5.32)	0.462	1.29 (0.34–4.83)	0.707
Propensity score	0.48 (0.07–3.2)	0.35 (0.31–4)	0.401		

SOFA Sequential Organ Failure Assessment, *ICU* intensive care unit, *CMS* colistimethate sodium, *m* median, *IQR* interquartile range, *OR* odds ratio, *aOR* adjusted odds ratio, *CI* confidence interval

monotherapy vs. 18.9% (10/53) in other antibiotic regimens ($p = 0.805$). Reasons for failure were (amikacin or CMS monotherapy vs. other antibiotic regimens) persistence or worsening signs and/or symptoms, nine patients (4/20, 20% vs. 5/20, 25%); need to modify therapy because of antibiotic side effects, four cases (3/20, 15% vs. 1/20, 5%); death, four patients (1/20, 5% vs. 3/20, 15%); and emergence of resistance, three isolates (2/20, 10% and 1/20, 5%). In all cases, nephrotoxicity was the reason for switching antibiotic treatment because of antibiotic side effects.

Table 2 shows crude and adjusted analyses of variables involved in early clinical failure and at EOT. Monotherapy with amikacin or CMS was not associated with higher rates of clinical failure.

The estimations of the associations of CMS or amikacin in monotherapy with clinical failure at day 7 and at EOT in sensitivity analyses were consistent with the analysis in the whole cohort (Supplementary Material).

Secondary Outcomes: Mortality and Microbiological Clearance

The 30-day mortality rate was 8.3% (4/48 patients) among patients treated with CMS or amikacin in monotherapy and 11.3% (6/53 patients) among those who received other antibiotic regimens ($p = 0.744$). The 90-day mortality was 18.8% (9/48 patients) and 30.2% (16/53 patients), respectively ($p = 0.183$). In multivariate analysis, receipt of amikacin or CMS monotherapy was not associated with either crude 30- or 90-day mortality (Table 3). Sensitivity analyses for mortality did not show different trends (Supplementary Material).

Regarding the microbiological assessment, 51 patients had a follow-up urine culture within 90 days. No statistically significant differences

Table.3 Crude and adjusted associations between different variables and 30- and 90-day mortality in overall and propensity-matched cohorts

	Overall cohort			Propensity-matched cohorts	
	Crude HR (95% CI)	aHR (95% CI)	*p* value	aHR (95% CI)	*p* value
30-day mortality					
Age (years), m (IQR)	1.05 (0.99–1.12)	1.09 (1.01–1.19)	0.033*	1.12 (1.01–1.25)	0.046*
Charlson comorbidity index, m (IQR)	1.21 (0.99–1.49)	1.36 (1.07–1.73)	0.012*	1.73 (1.01–2.99)	0.049*
SOFA score, m (IQR)	1.36 (1.05–1.78)	1.37 (1.02–1.83)	0.036*	1.24 (0.75–2.06)	0.398
Amikacin or CMS treatment	0.73 (0.2–2.57)	1.25 (0.29–5.45)	0.763	0.93 (0.17–5.08)	0.937
Propensity score	0.16 (0.02–1.67)	0.27 (0.01–7)	0.438		
90-day mortality					
Age (years), m (IQR)	1.01 (0.98–1.05)	1.04 (0.99–1.09)	0.113	1.07 (0.99–1.15)	0.065
Charlson comorbidity index, m (IQR)	1.3 (1.14–1.49)	1.37 (1.17–1.59)	< 0.001*	1.59 (1.13–2.22)	0.007*
SOFA score, m (IQR)	1.22 (1.03–1.45)	1.22 (1.01–1.48)	0.037*	1.32 (0.88–1.98)	0.177
Amikacin or CMS treatment	0.59 (0.26–1.34)	0.96 (0.36–2.54)	0.933	0.68 (0.20–2.31)	0.534
Propensity score	0.2 (0.48–0.82)	0.34 (0.06–2.03)	0.236		

SOFA Sequential Organ Failure Assessment, *CMS* colistimethate sodium, *m* median, *IQR* interquartile range, *HR* hazard ratio, *aHR* adjusted hazard ratio, *CI* confidence interval

*Statistical significance at $p < 0.05$

were found between treatment groups after adjusting for confounders (Supplementary Material).

Adverse Events

Antibiotic-related side effects are shown in Supplementary Material. No statistically significant differences were found in terms of nephrotoxicity between groups. *C. difficile* was only observed in patients in the group treated with other antibiotic regimens (11.3%).

DISCUSSION

In the present study, we were unable to demonstrate that amikacin or CMS monotherapy was associated with worse outcomes in terms of mortality, clinical failure, or microbiological clearance than combination or other antibiotic therapies in cases of complicated UTI caused by XDR *P. aeruginosa* isolates, after controlling for confounders. Although these results cannot be interpreted as that amikacin or CMS monotherapy is equally effective as combination or other antibiotic therapies, they reinforce the message that alternative narrow-spectrum antibiotic use should be considered in some scenarios despite that we are facing a difficult-to-treat bacteria.

The challenge of treating XDR *P. aeruginosa* has been thoroughly discussed in the literature. Many clinicians favor combination treatment even though the clinical evidence of the superiority of combination therapy over monotherapy is scarce and of low quality [28, 29]. Although the use of combination therapy may be tempting in this type of infection, combination therapies increase antibiotic pressure in the hospital ecosystem and the selection of multidrug-resistant bacteria [15]. In this setting, the World Health Organization, not surprisingly, has urged the implementation of AMS programs to optimize antibiotic use and control increased multidrug resistance worldwide [30]. Further, although the new antipseudomonal agents ceftolozane-tazobactam and ceftazidime-avibactam have recently become available in daily clinical practice, the emergence of resistant mutants has been already reported [31, 32], suggesting that the "old drugs" still have a place.

The effectiveness of aminoglycosides and/or polymyxins for treating XDR *P. aeruginosa* infections has already been assessed in previous studies. However, most of these included different sources of infection, with few UTI episodes, or had no control group, which makes interpretation difficult. Pogue et al. [26] compared ceftolozane-tazobactam vs. polymyxin or aminoglycoside-based therapy for the treatment of drug-resistant *P. aeruginosa* infections in a multicenter retrospective study. A total of 200 patients were assessed, but only 27 of these had UTI. The authors reported statistical differences in clinical success rate (81% in the ceftolozane-tazobactam group vs. 61% in the comparative group), but not in mortality. Other authors have described their clinical experience of ceftolozane-tazobactam in the treatment of drug-resistant *P. aeruginosa* with large cohorts (more than 100 patients assessed) [33–35], with successful clinical outcome rates ranging from 63% to 83%. However, the limited number of UTIs included ($n < 30$) makes interpretation difficult.

In a systematic review of polymyxins in monotherapy or in combination for the treatment of carbapenem-resistant GNB, Zusman et al. [36] suggested a less than optimal outcome in patients who received colistin monotherapy, although most studies did not include *P. aeruginosa* infections, and UTI was not a frequent source of infection. Our group has previously assessed the performance of CMS in XDR *P. aeruginosa* infections [7, 37] and detected no differences between monotherapy and combination therapy or in clinical failure or mortality. One of those studies was specifically focused on UTIs [37]. In that prospective cohort of 33 patients, more than half of whom received CMS monotherapy, clinical cure was achieved in 89.5% of patients treated with CMS monotherapy.

Regarding the effectiveness of aminoglycosides, the evidence on monotherapy for treating UTIs caused by drug-resistant *P. aeruginosa* was extrapolated from carbapenem-resistant *Enterobacterales* [38–40], with response rates ranging from 61% to 100%. In a systematic review [11],

Vidal et al. demonstrated that aminoglycosides as single agents were as effective as beta-lactams or quinolones for achieving clinical improvement in patients with UTI, including those caused by *P. aeruginosa*. However, the impact of the new antipseudomonal agents was not assessed as a result of the date of publication.

Our data show that patients treated with other antibiotic regimens had more underlying comorbidities and severe disease compared to those in the amikacin or CMS group. It may be inferred that clinicians were reluctant to administer amikacin or CMS monotherapy in more complicated patients. To overcome this indication bias, a double propensity score analyses was performed and no differences between groups were found for the studied outcomes.

One of the main concerns in treatment with amikacin or CMS is nephrotoxicity. However, since many patients in the "other antibiotic regimens" group were also treated with combination therapies that included amikacin or CMS, this side effect was not properly assessed. In our study the rate of renal toxicity was in fact lower in the amikacin or CMS monotherapy group. There are several possible reasons for this, apart from the antibiotic treatment received: patients in the "other antibiotic regimens" group were more severely ill and some of the cases were probably sepsis-related; second, the kidney infection itself; third, the concomitant use of nephrotoxic drugs; and finally, a cautious attitude to using amikacin or CMS in patients with abnormal GFR baselines.

Another worrisome antibiotic-related side effect is the incidence of *C. difficile* infection. Aminoglycosides and polymyxins are not among the "high-risk" drugs for the development of *C. difficile* infection [16], in accordance with our findings. Reducing the risk of *C. difficile* infection could be another reason for using them in the treatment of XDR *P. aeruginosa* infections.

Perhaps the greatest challenge associated with XDR *P. aeruginosa* is achieving the appropriate balance between efficacy, security, and ecology. Strategies aimed at safeguarding broad-spectrum drugs should be approached with caution, particularly in less severe patients with a low-risk source of infection such us UTI, where the favorable pharmacokinetics characteristics of aminoglycosides and colistin could provide an excellent opportunity to use more ecological agents.

Our study has the inherent limitations of a retrospective design and a single-center study. As a result of imbalances in the baseline characteristics of the treatment groups, a double propensity-based approach was performed to reduce potential biases. Although the initial analysis included 101 patients, the matched cohort resulted in a smaller sample which reduces the statistical power of the study. It could have been of interest to study monotherapy with CMS or amikacin in more severe patients, but groups were too small for specific analyses to be performed. Another limitation is that many patients in the control group used aminoglycosides or colistin combined with other drugs. Although a sensitivity analysis was performed excluding those patients, as a result of the limited number of episodes treated with amikacin- or colistin-free antibiotic regimens (n = 14), results should be cautiously interpreted. In addition, not all patients had a urine control culture to assess microbiological clearance. Another potential limitation is that patient comorbidities were not determined using disease codes. Even though all clinical records were cautiously reviewed for two infectious diseases clinicians, there is a risk of misclassification or measurement error, particularly in a retrospective study. Finally, it would have been interesting to conduct genotypic studies. Prior studies have shown that the major XDR clone involved in our hospital is the less virulent ST-175 clone [4], which is widespread in our country and in Europe [1, 2]. Thus, our results might not be transferable to other settings with a different epidemiology. As strengths, a propensity score approach was used for controlling confounders at baseline. This is one of the recommended strategies to emulate the random assignment of clinical trials [41]. Finally, it explores more ecological agents in a difficult-to-treat bacteria, such as XDR *P. aeruginosa*, in a "real life" situation.

CONCLUSIONS

Our findings might reinforce that amikacin or CMS monotherapy does not have a detrimental impact on outcomes of complicated UTIs caused by XDR *P. aeruginosa* when compared with combination or other antibiotic therapies. These results may be useful for antibiotic stewardship activities given their clinical and ecological impact. However, further studies are needed to confirm these findings, particularly in more severely ill patients.

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Compliance with Ethics Guidelines. The study was approved by the Clinical Research Ethics Committee of the Parc de Salut Mar (register no. 2020/9321). The need for written informed consent was waived because of the observational nature of the study and retrospective analysis. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guideline and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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