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ORIGINAL RESEARCH

Clinical Outcomes of Omadacycline in Critically Ill Patients Treated for Carbapenem-Resistant Organism Infections: A Retrospective Study

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Objective: This study aimed to evaluate the efficacy and safety of omadacycline (OMA) for the treatment of carbapenem-resistant organisms (CROs) infections, which are associated with substantial morbidity and mortality and limited therapeutic options.

Methods: The patients included were ≥18 years old, had CRO-positive cultures, and had been treated with OMA-based combination therapy for ≥72 hours. Common clinical comorbidities and markers of disease progression were collected. The primary outcome was 30-day all-cause mortality. The secondary outcomes included 30-day recurrence, resolution of signs and symptoms of infection, 90-day readmission, and OMA-possible adverse events.

Results: This study included 132 patients treated with OMA for CRO infections, with a median age of 67 years and a majority of male patients. Of the 132 patients analyzed, 78.8% were admitted to the intensive care unit, with hypertension, diabetes, and chronic pulmonary disease being the most frequent comorbidities. The median Charlson Comorbidity Index (CCI) score for the entire cohort was 5 (interquartile range [IQR], 4–7), indicating a moderate to high comorbidity burden. Pneumonia represented the predominant infection (84.8%). The overall 30-day mortality rate was 27.3%. In the Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) cohort (n=89), OMA therapy was initiated promptly following culture confirmation, with a median treatment duration of 8 days. The 30-day mortality rate in this subgroup was 29.2% (26/89). Adverse events included elevated aspartate transaminase (21.3%, 19/89), alanine aminotransferase (18.0%, 16/89), alkaline phosphatase (23.6%, 21/89), blood urea nitrogen (25.8%, 23/89) and decreased fibrinogen levels (18.0%, 16/89). In the Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) cohort (n=57), the 30-day mortality rate was 29.8% (17/57), with a safety profile comparable to the CRAB group.

Conclusion: The results demonstrated that OMA has promising clinical efficacy against CRAB or CRKP infections in critically ill patients.

Keywords: omadacycline, Carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Klebsiella pneumoniae*, tetracycline

Introduction

In 2019, antimicrobial-resistant bacterial pathogens were estimated to cause approximately 1.3 million deaths worldwide.[1] Among these, carbapenem-resistant organisms (CROs), including carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), pose a significant threat. International multicenter studies have reported 30-day all-cause mortality rates of 18–20% for infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP), CRAB, and CRPA.[2,3] These pathogens represent a major challenge in healthcare settings.[4–6]

The Infectious Diseases Society of America (IDSA) 2024 guidelines for treating resistant gram-negative infections recommend combination therapy with at least two agents for moderate to severe CRAB infections, preferably those with in vitro activity.[7] For tetracycline derivatives, high-dose minocycline[8] or high-dose tigecycline[9] are suggested as

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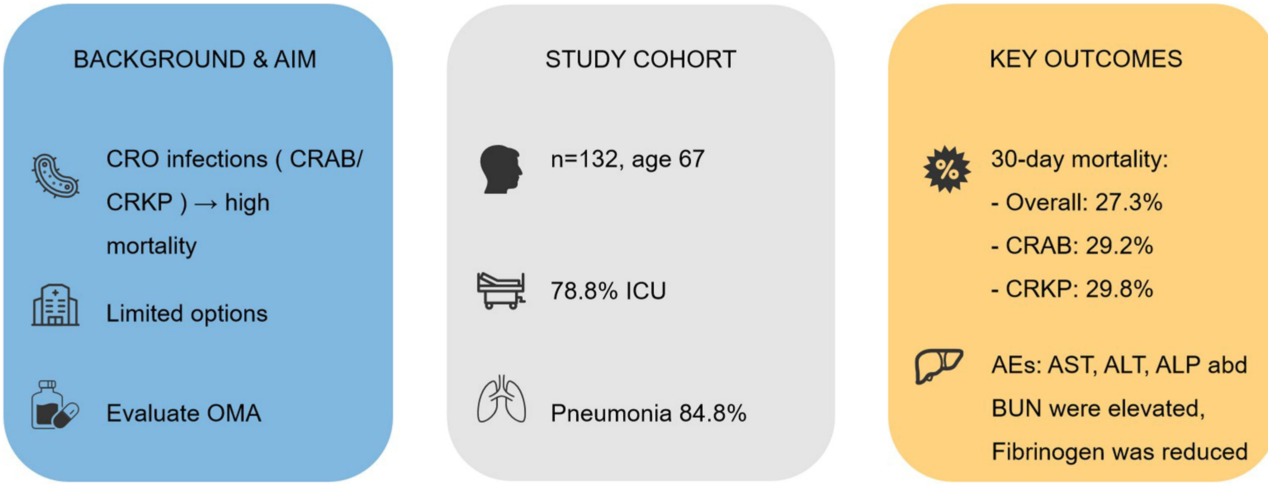
Graphical Abstract



alternative therapies. Ceftazidime/avibactam, meropenem/vaborbactam, and imipenem/cilastatin/relebactam are the preferred agents for CRKP infection.[7] However, there has been a delay in the launch of novel antimicrobial agents in China, and rapidly developing resistance to ceftazidime/avibactam further limits the activity of antimicrobial treatment. There is an urgent need for innovative therapeutic strategies against KPC-producing *Klebsiella pneumoniae*, such as the use of adjuvant, non-traditional agents that significantly enhance the antimicrobial activity against highly resistant CRKP.[10] Therefore, tetracyclines, including tigecycline[11] and eravacycline,[12] serve as alternative options when β-lactam agents are either inactive or not tolerated.

Omadacycline (OMA), a first-in-class aminomethylcycline antibiotic and the latest generation of tetracycline-class agents, features structural modifications at the C7 and C9 positions. These modifications enable OMA to effectively overcome the most common mechanisms of tetracycline resistance, including TetK and TetB efflux pumps and TetM and TetO-based ribosome protection.[13–15] OMA exhibits in vitro activity against a broad spectrum of pathogens, including gram-positive aerobes, gram-negative aerobes, some anaerobes and atypical bacteria, including *Legionella* spp. and *Chlamydia* spp.[16] Additionally, OMA has high oral bioavailability, facilitating oral administration. In a small case series, oral OMA demonstrated a relatively high success rate with minimal adverse effects in treating multidrug-resistant (MDR) and extensive drug-resistant (XDR) gram-negative infections.[17] With a large volume of distribution, low plasma protein binding, and no need for dose adjustment in specific populations, OMA is an ideal tetracycline derivative for treating CRAB and CRKP infections.

The Spanish National *Acinetobacter* spp. 2020 Study Group and the GEMARA-SEIMC/REIPI Enterobacterales Study Group evaluated the activity of third-generation tetracyclines—tigecycline, eravacycline, and omadacycline—against carbapenemase-producing Enterobacterales (n=399) and *A. baumannii* (n=118) isolated nationwide in Spain. Tigecycline and eravacycline demonstrated the highest activity against both Enterobacterales (MIC_{50}/MIC_{90}: 0.5/1 mg/L and 1/2 mg/L, respectively) and *A. baumannii* (MIC_{50}/MIC_{90}: 1/2 mg/L and ≤0.25/1 mg/L, respectively). In contrast, omadacycline showed no improvement over classic tetracyclines, with MIC_{50}/MIC_{90} values of 8/32 mg/L for Enterobacterales and 8/16 mg/L for *A. baumannii*.[18] Despite its lower in vitro antimicrobial activity compared to tigecycline, omadacycline has the advantage of higher and sustained concentrations in the plasma, epithelial lining fluid, and alveolar cells.[19] Therefore, the use of omadacycline (OMA), is growing in the treatment of CRAB and CRE infections.

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The objective of this study was to describe real-world clinical experience with OMA for CROs infections and to evaluate its effectiveness and adverse events.

Materials and Methods

Patients

This was a real-world, retrospective observational study conducted at the First Affiliated Hospital, Zhejiang University School of Medicine, between January 2023 to December 2023. We included patients who were (i) ≥18 years of age, (ii) had CRO-positive cultures, and (iii) had been treated with OMA-base combination therapy for ≥72 h. The exclusion criteria were as follows: (i) patients who had undergone hematopoietic stem cell transplantation or solid organ transplantation and (ii) pregnant or lactating individuals.

Microbiological Data

Clinical samples (eg, blood, sputum, urine) were collected from patients during hospitalization and processed in accordance with standard microbiological protocols. Microbial identification was performed using the VITEK MS, a matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) system. Antimicrobial susceptibility testing was conducted using the VITEK 2 Compact System, a fully automated microbial identification and antimicrobial susceptibility analysis system. Both procedures adhered to Clinical and Laboratory Standards Institute (CLSI) guidelines. MIC values were determined for a range of antimicrobial agents, including carbapenems, tigecycline, colistin, and others. Susceptibility was interpreted based on CLSI breakpoints.

Data Collection and Outcomes

We collected data on common clinical comorbidities and disease progression markers, and calculated the Charlson Comorbidity Index (CCI) scores for all enrolled patients. The primary outcome was 30-day all-cause mortality. The secondary outcomes included 30-day infection recurrence, resolution of signs and symptoms of infections, and 90-day all-cause mortality. Adverse events possibly related to OMA were assessed.

Thirty-day infection recurrence was defined as a positive culture for the same pathogen isolated in the index culture within 30 days after the end of OMA treatment. Resolution of infection-related signs and symptoms was defined as the resolution or improvement of infection-associated abnormalities in white blood cells count, body temperature, C-reactive protein level or procalcitonin level, or as documented by the physician in clinical records. Combination therapy was defined as any therapy used in tandem with omadacycline for ≥48 h targeted for CRO.

For *Achinetobacter baumannii* and *Klebsiella pneumoniae*, susceptibility was interpreted via the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints. When CLSI information was not available, the FDA antibacterial susceptibility interpretive criteria were used if available. Descriptive statistics were utilized for data analysis via IBM SPSS software version 27.0 (SPSS, Inc., Chicago, IL, USA).

Ethical Considerations

This study was approved by the First Affiliated Hospital of Zhejiang University School of Medicine (Approval no. IIT20241492A). Informed consent was waived due to the retrospective nature of this study. Patient data were anonymized to ensure confidentiality and this research complies with the requirements of the Declaration of Helsinki.

Results

A total of 132 patients treated with OMA for CROs infections were included (Table 1). The median (interquartile range [IQR]) age was 67 years (58–75), and 76.5% (101/132) were male. At the time of index culture, 78.8% (104/132) of patients were in the intensive care unit (ICU), with a median (IQR) APACHE-II score of 21 (15–27) and a SOFA score of 8.5 (4.7–11.2). Additionally, 21.2% (28/132) of patients were receiving continuous renal replacement therapy (CRRT). The most common comorbidities were hypertension (59/132, 44.7%), diabetes (35/132, 26.5%), chronic pulmonary disease (23/132, 17.4%), and chronic kidney disease (23/132, 17.4%). The median CCI score for the entire cohort was 5

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Table 1 Demographic and Clinical Characteristics of Patients

Criteria	Population (n=132)	CRAB (n=89)	CRKP (n=57)
Demographics			
Age, y, median (IQR)	67 (58–75)	67 (56–76)	66 (59–74)
Age of ≥65 y, n (%)	68, 51.5%	46, 51.7%	29, 50.9%
Sex, male, n (%)	101, 76.5%	67, 75.3%	46, 80.7%
Weight, kg, median (IQR)	66.0 (55.0–75.0)	67.2 (56.0–75.0)	65.0 (55.0–72.5)
BMI, kg/m^2, median (IQR)	23.5 (21.3–25.8)	24.2 (21.3–26.0)	23.2 (20.7–24.5)
BMI of ≥30	15, 11.4%	12, 13.5%	4, 7.0%
Baseline serum creatinine, μmol/L, median (IQR)	77.0 (53.0–155.5)	83.5 (54.7–160.7)	70.0 (49.0–155.2)
CL_{CR}, mL/min, median (IQR)	77.2 (38.2–105.8)	71.8 (36.8–106.0)	80.6 (414.2–107.0)
Residence prior to admission, n (%)			
Home	32, 24.2%	18, 20.2%	19, 33.3%
Transfer from outside hospital	97, 73.5%	68, 76.4%	38, 66.7%
Nursing home, skilled nursing facility, long term care facility	1, 0.8%	1, 1.1%	0, 0%
Other	2, 1.5%	2, 2.2%	0, 0%
Comorbid conditions			
Charlson Comorbidity Index (CCI) score	5 (4–7)	5 (4–7)	6 (4–7)
Cerebrovascular disease, n (%)	14, 10.6%	8, 9.0%	7, 12.3%
Chronic pulmonary disease, n (%)	23, 17.4%	18, 20.2%	7, 12.3%
Moderate to severe kidney disease or on chronic dialysis, n (%)	23, 17.4%	15, 16.8%	8, 14.0%
Dementia, n (%)	4, 3.0%	2, 2.2%	2, 3.5%
Diabetes, n (%)	35, 26.5%	24, 27.0%	19, 33.3%
Heart failure, n (%)	4, 3.0%	2, 2.2%	3, 5.3%
Tumor, n (%)	14, 10.6%	6, 6.7%	12, 21.0%
Liver disease, n (%)	11, 8.3%	8, 9.0%	6, 10.5%
Hypertension, n (%)	59, 44.7%	39, 43.8%	27, 47.4%
Other	2, 1.5%	1, 1.1%	1, 1.8%
In the general ward, n (%)	28, 21.2%	12, 13.5%	16, 28.1%
In intensive care unit, n (%)	104. 78.8%	77, 86.5%	41, 71.9%
Under CRRT, %	28, 21.2%	20, 22.5%	10, 17.5%
APACHE II, median (IQR)	21 (15–27)	19 (14–28)	24 (15–26)
SOFA, median (IQR)	8.5 (4.7–11.2)	8.0 (5.0–12.0)	8.0 (4.0–11.0)

(*Continued*)

Table 1 (Continued).

Criteria	Population (n=132)	CRAB (n=89)	CRKP (n=57)
MDR risk factors, n (%)			
Chronic dialysis in 30 days before index culture	10, 7.6%	6, 6.7%	4, 7.0%
Colonization with resistant organisms	1, 0.8%	1, 1.1%	0, 0%
Prior antimicrobials for >24 h in 90 days prior to index culture	123, 93.2%	84, 94.4%	53, 93.0%
Prior hospitalization for at least 48 h in 90 days prior to index culture	113, 85.6%	80, 89.9%	46, 80.7%
Prior infection with resistant organisms at any time	40, 30.3%	30, 33.7%	17, 29.8%
Prior surgery in 30 days preceding index culture	14, 10.6%	11, 12.4%	5, 8.8%
Sources of infection, n (%)			
Bone and joint	7, 5.3%	4, 4.5%	4, 7.0%
Intra-abdominal	11, 8.3%	5, 5.6%	6,10.5%
Intracranial	5, 3.8%	2, 2.2%	3, 5.3%
Primary bacteremia	5, 3.8%	4, 4.5%	1, 1.8%
Pneumonia	112, 84.8%	80, 89.9%	46, 80.7%
Mechanically ventilated for 48 h prior to pneumonia	4, 3.0%	2, 2.2%	2, 3.5%
Skin and soft tissue	4, 3.0%	3, 3.4%	3, 5.3%
Urinary	6, 4.5%	3, 3.4%	4, 7.0%
Unknown	1, 0.8%	0	1, 1.8%
Pathogens isolated beyond CRAB and CRKP, n (%)			
Pseudomonas aeruginosa	18, 13.6%	13, 14.6%	5, 8.8%
Acinetobacter nosocomialis	1, 0.8%	1, 1.1%	0, 0%
Enterobacter cloacae	2, 1.5%	1, 1.1%	0, 0%
Serratia marcescens	1, 0.8%	1, 1.1%	1, 1.8%
Klebsiella oxytoca	2, 1.5%	2, 2.2%	0, 0%
Enterobacter aerogenes	1, 0.8%	1, 1.1%	0, 0%
Escherichia coli	5, 3.8%	2, 2.2%	3, 5.3%
Burkholderia multivorans	3, 2.3%	1, 1.1%	2, 3.5%
Burkholderia cepacia	6, 4.5%	6, 6.7%	1, 1.8%
Burkholderia cenocepacia	3, 2.3%	2, 2.2%	1, 1.8%
Stenotrophomonas maltophilia	10, 7.6%	5, 5.6%	5, 8.8%
Staphylococcus epidermidis	2, 1.5%	1, 1.1%	1, 1.8%
Staphylococcus aureus	4, 3.0%	4, 4.5%	1, 1.8%
Staphylococcus haemolyticus	1, 0.8%	1, 1.1%	0, 0%
Enterococcus faecalis	6, 4.5%	4, 4.5%	2, 3.5%

(*Continued*)

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Table 1 (Continued).

Criteria	Population (n=132)	CRAB (n=89)	CRKP (n=57)
Enterococcus faecium	1, 0.8%	0, 0%	1, 1.8%
Corynebacterium striatum	7, 5.3%	3, 3.4%	4, 7.0%
Flavobacterium meningosepticum	2, 1.5%	1, 1.1%	1, 1.8%
Candida albicans	12, 9.1%	8, 9.0%	5, 8.8%
Candida parapsilosis	1, 0.8%	0, 0%	1, 1.8%
Candida tropicalis	1, 0.8%	1, 1.1%	0, 0%

Abbreviations: BMI, body mass index; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, sequential organ failure assessment; MDR, multidrug resistant; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRKP, carbapenem-resistant *Klebsiella pneumonia*;

(IQR, 4–7), indicating a moderate to high comorbidity burden. Specifically, in the CRAB cohort (n=89), the median CCI score was 5 (IQR 4–7), and in the CRKP cohort (n=57), the median CCI score was 6 (IQR 4–7). These CCI scores further demonstrate the significant disease burden among the patients included.

The majority of patients (128/132, 97.0%) had at least one risk factor for MDR infections. The most common risk factor was the use of antimicrobials for ≥24 h within 90 days before index culture (123/132, 93.2%), followed by prior hospitalization for at least 48 h 90 days prior to index culture (113/132, 85.6%).

Infection sources were diverse, with pneumonia being the most common frequent (112/132, 84.8%), followed by intra-abdominal infection (11/132, 8.3%) and bone/joint infection (7/132, 5.3%). Among the 132 patients, 89 were in the CRAB subgroup and 57 in the CRKP subgroup. Notably, 14 patients (10.6%) had mixed infections with both CRAB and CRKP. Other pathogens isolated included *Pseudomonas aeruginosa* (18/132, 13.6%), *Stenotrophomonas maltophilia* (10/132, 7.6%), and *Corynebacterium striatum* (7/132, 5.3%). A total of 36 patients died within 30 days of OMA initiation, resulting in an overall 30-day mortality rate of 27.3%.

In the CRAB subgroup (n=89; Tables 1 and 2), 86.5% (77/89) of patients were treated in the ICU, and 89.9% (80/89) had pulmonary infections. Most patients received combination therapy, with cefoperazone/sulbactam as the most common adjunct agent (22/89, 24.7%), followed by intravenous colistin sulfate (20/89, 22.5%); 18.0% (16/89) of

Table 2 Clinical Characteristics and Health Outcomes of Patients

Criteria	CRAB (n=89)	CRKP (n=57)
OMA		
Duration, days, median (IQR)	8, (6–11)	7, (4.5–10.5)
Start from index culture, days, median (IQR)	0, (0–2)	0, (0–2)
Load dosing, n (%)	70, 78.6%	44, 77.2%
Susceptible to tetracycline[a]	54, 60.7%	42/47 [b], 89.4%
Intermediate	33, 37.1%	0, 0%
Resistance	2, 2.2%	5/47,10.6%
Treatment-related factors		
Inhaled antibiotics, any, n (%)	16, 18.0%	6, 10.5%
i.v. combination therapy for ≥48 h, n (%)		
Amikacin	3, 3.4%	1, 1.8%

(*Continued*)

Table 2 (Continued).

Criteria	CRAB (n=89)	CRKP (n=57)
Colistimethate Sodium	9, 10.1%	8, 14.0%
Colistin sulfate	20, 22.5%	8, 14.0%
Meropenem	8, 9.0%	8, 14.0%
Imipenem/Cilastatin	——	1, 1.8%
Cefoperazone/Sulbactam	22, 24.7%	6, 10.5%
Ceftazidime	——	1, 1.8%
Ceftazidime/Avibactam	4, 4.5%	5, 8.8%
Levofloxacin	1, 1.1%	——
Fosfomycin	——	1, 1.8%
Clinical outcomes		
30-day mortality, n (%)	26, 29.2%	17,29.8%
90-day mortality, n (%)	27, 30.3%	18, 31.6%
30-day recurrence, n (%)	18, 20.2%	7, 12.3%
Remission of signs and symptoms of infection, n (%)	44, 49.4%	32, 56.1%
OMA-possible adverse events, n (%)		
ALT increased, n (%)	16, 18.0%	9, 15.8%
AST increased, n (%)	19, 21.3%	14, 24.6%
ALP increased, n (%)	21, 23.6%	12, 21.0%
TB increased, n (%)	14, 15.7%	12, 21.0%
BUN increased, n (%)	23, 25.8%	17, 29.8%
FIB decreased, n (%)	16, 18.0%	12, 21.0%

Notes: [a]Sensitive to doxycycline or minocycline or tigecycline. [b]10 patient of CRKP isolates did not underwent sensitivity testing for tetracycline antibiotics.
Abbreviations: OMA, omadacycline; ALT, Alanine aminostransferase; AST, aspartate transpeptidase; ALP, alkaline phosphatase; TB, total bilirubin; BUN, blood urea nitrogen; FIB, fibrinogen.

patients received inhaled therapies (eg, colistin or amikacin). Ceftazidime/avibactam was used in some cases primarily for the management of mixed infections: 14 patients had mixed CRAB and CRKP infection, and 13 had mixed CRAB and *Pseudomonas aeruginosa* infections. Ceftazidime/avibactam was selected to provide effective coverage for these co-infections, ensuring broad-spectrum activity against both CRAB and the co-pathogens.

OMA was initiated within 0–2 days of culture confirmation, with a median (IQR) duration of 8 days (6–11). A loading dose was administered to 78.6% (70/89) of patients on day 1. Susceptibility testing (Table 3) revealed that 97.8% (87/89) of CRAB isolates were susceptible to at least one of the tetracyclines tested, including minocycline, doxycycline, and tigecycline. The 30-day mortality rate was 29.2% (26/89), increasing to 30.3% (27/89) at 90 days. The 30-day recurrence rate was 20.2% (18/89), and clinical resolution of infection occurred in 49.4% (44/89) of patients. OMA-related adverse events included elevated AST (19/89, 21.3%), ALT (16/89, 18.0%), ALP (21/89, 23.6%), TB (14/89, 15.7%), BUN (23/89, 25.8%), and decreased fibrinogen (16/89, 18.0%).

In the CRKP subgroup (n=57; Tables 1 and 2), 71.9% (41/57) of patients were treated in the ICU, and 80.7% (46/57) had pulmonary infections. Most patients received combination therapy, with intravenous colistin sulfate (8/57, 14.0%),

Table 3 Results of Antibiotic Susceptibility Data Statistics

Antimicrobial Susceptibility	CRAB (n=89)		CRKP (n=57)	
	MIC	Susceptible, n (%)	MIC	Susceptible, n (%)
Imipenem, mg/L, median (range)	≥16	0, 0%	≥16	0, 0%
Meropenem, mg/L, median (range)	≥16	0, 0%	≥16	0, 0%
Cefoperazone/Sulbactam, mg/L, median (range)	64 (16–64)	8, 9.0%	64 (8–64)	4, 7.0%
Doxycycline, mg/L, median (range)	16 (0.5–16)	12, 13.5%	16 (0.5–16)	6, 10.5%
Tigecycline, mg/L, median (range)	2 (0.25–8)	51, 57.3%	1 (0.25–4)	44, 77.2%
Minocycline, mg/L, median (range)	8 (1–16)	37, 41.6%	16 (1–16)	4, 7.0%
Colistin, mg/L, median (range)	0.5 (0.5–4)	85, 95.5%	0.5 (0.125–32)	48, 84.2%
Piperacillin/Tazobactam, mg/L, median (range)	≥128	0, 0%	≥128	0, 0%
Sulfamethoxazole/Trimethoprim, mg/L, median (range)	320 (20–320)	17, 19.1%	20 (20–320)	34, 59.6%
Ciprofloxacin, mg/L, median (range)	≥4	0, 0%	——	——
Levofloxacin, mg/L, median (range)	8 (0.5–8)	1, 1.1%	——	——
Ceftazidime/Avibactam, mg/L, median (range)	——	——	1 (0.25–4) 22 (12–28)	45, 78.9%
Ceftazidime, mg/L, median (range)	——	——	64 (8–64)	0, 0%
Amikacin, mg/L, median (range)	——	——	64 (2–64)	17, 29.8%
Aztreonam, mg/L, median (range)	——	——	64 (16–64)	0, 0%

Abbreviation: MIC, minimal inhibitory concentration.

colistimethate sodium (8/57, 14.0%), and meropenem (8/57, 14.0%) as the most common adjuncts agents; 10.5% (6/57) of patients received inhaled therapies (eg, colistin or amikacin). OMA was initiated within 0–2 days of culture confirmation, with a median (IQR) duration of 7 days (4.5–10.5). A loading dose was administered to 77.2% (44/57) of patients on day 1. Susceptibility testing (Table 3) revealed that 82.4% (47/57) of CRKP isolates were susceptible to at least one tested the tetracyclines (minocycline, doxycycline, or tigecycline), while 8.8% (5/57) were resistant to all tested tetracyclines agents. The 30-day mortality rate was 29.8% (17/57), increasing to 31.6% (18/57) at 90 days. The 30-day infection recurrence rate was 12.3% (7/57), and clinical resolution of infection was achieved in 56.1% (32/57) of patients. OMA-related adverse events included elevated AST (14/57, 24.6%), ALT (9/57, 15.8%), ALP (12/57, 21.0%), TB (12/57, 21.0%), BUN (17/57, 29.8%), and decreased fibrinogen (12/57, 21.0%).

Discussion

The clinical applications of OMA are focused primarily on community-acquired bacterial pneumonia,[20] acute bacterial skin and skin structure infections,[21] and nontuberculous mycobacterial infections.[22] In vitro studies have reported that OMA exhibits good activity against *Acinetobacter baumannii*. In a Chinese study, OMA inhibited all carbapenem-susceptible isolates at 1 mg/L, while the MIC_{90} for CRAB increased to 4 mg/L.[23] According to the SENTRY Antimicrobial Surveillance Program report in the United States, the $MIC_{50/90}$ of OMA against *Acinetobacter baumannii* was 0.5/4 mg/L, with an inhibition rate of 90.8% at ≤4 mg/L.[24] The activity of OMA against *Klebsiella pneumoniae* is not as potent as that against *Acinetobacter baumannii*. Surveillance in China and the United States revealed that the $MIC_{50/90}$ of OMA against *Klebsiella pneumoniae* was 1/4 mg/L, with 93.2% being susceptible, and the MIC_{90} for CRKP was 32 mg/L.[23,24] In a single case study of oral OMA for multidrug-resistant (MDR)/extensively drug-resistant (XDR) gram-negative bacterial infections, four cases were CRAB from bone/joint infections, one case was CRKP from bone/joint infections, and one case each was CRAB and CRKP from ventilator-associated pneumonia, with all six cases achieving clinical treatment success.[17] Unlike previous small-sample case studies that focused on CRAB infections of the bone and joints, our study is the largest real-world observational analysis to date of OMA for the treatment of predominantly pulmonary CRAB and CRKP infections.

The use of tigecycline for the treatment of AB infections remains controversial. A meta-analysis found that tigecycline (loading dose of 100 mg, followed by 50 mg twice daily) for MDR *Acinetobacter* infections was associated with a combined clinical response rate of 58.1% (95% confidence interval [CI] 49.2–66.6) and a failure rate of 40.2% (95% CI 31.1–50.0). The pooled microbiological response rate was 32.1% (95% CI 19.8–47.5), and the pooled all-cause mortality rate was 41.1% (95% CI 34.1–48.4). Common adverse events include cardiotoxicity (25%), abnormal liver function tests (20%), and nausea/vomiting (10.5%).[25] High-dose tigecycline can reduce the mortality rate of CRAB or CRKP pulmonary infections to 22.9%, with common adverse reactions, including liver function damage (37/160, 23.1%), diarrhea (20/162, 12.3%), nausea/vomiting/hematemesis (24/70, 34.3%), and hematopoietic system damage (24/160, 15.0%).[9]

Among tetracycline-class agents, eravacycline has lower $MIC_{50/90}$ values against CRAB and CRKP than tigecycline and OMA;[23,24] however, eravacycline is approved only for intra-abdominal infections, while the lungs are the most common infection site of CRAB and CRKP infections. In a retrospective study with the lung as the primary infection site, the 30-day mortality rate for eravacycline-treated AB patients was 23.9%, and for CRAB patients, it was 21.9%, similar to the outcomes of this study, with only one case (2.2%) of gastrointestinal reactions related to eravacycline.[26] In another case study in which eravacycline was used to treat ventilator-associated pneumonia caused by CRAB, 71% (17/24) of patients achieved clinical resolution of CRAB, and 71% (12/17) achieved microbiological resolution after repeat sputum cultures, with no eravacycline-related adverse reactions observed.[27] This finding is also similar to the clinical outcomes of this study.

Although eravacycline has stronger in vitro activity against CRAB and CRKP than do tigecycline and OMA, its clinical efficacy in pulmonary infections does not appear to show a significant advantage. This may be attributed to difference in the pharmacokinetics of OMA, eravacycline, and tigecycline in the human body. At the therapeutic dosage and frequency specified in the instructions, the plasma AUC and epithelial lining fluid (ELF) concentrations of OMA are slightly higher than those of eravacycline, and the trough concentration within alveolar macrophages is more than seven times that of eravacycline, with all of these concentrations being significantly higher than those of tigecycline.[19,28] This somewhat compensates for the deficiency of the in vitro activity of OMA compared with eravacycline.

This study has several limitations. First, we lack direct OMA susceptibility data for the causative pathogens. All clinical treatment decisions were based on the susceptibility profiles of other tetracycline-class agents, particularly tigecycline MIC values. The correlation between tigecycline MIC and OMA susceptibility remains unclear, and the use of tigecycline MIC to guide OMA therapy may potentially increase the risk of 30-day mortality given the differences in in vitro antimicrobial activity. Nevertheless, this study provides unique real-world evidence on clinical outcomes and safety profiles of OMA in a pragmatic clinical setting where rapid susceptibility testing is not available. This evidence is particularly valuable for guiding empirical therapy in resource-limited clinical scenarios. Meanwhile, we recognize the importance of integrating in vitro susceptibility testing in future research and propose that prospective, multicenter studies integrating clinical endpoints with comprehensive MIC profiling to validate and extend our findings. Second, during the patient inclusion process, we excluded patients with solid organ or bone marrow transplants; it is currently unclear what the clinical benefits and adverse reaction rates might be for this high-risk population when OMA is used to treat hospital-acquired infections. Third, our study did not include a comparison with a control group treated with "best available therapy" or minocycline. Additionally, this study is the widespread use of concomitant antibiotics, which precludes determination of the specific contribution of OMA to clinical outcomes. Our results therefore represent real-world experience with OMA-based combination therapy for CRO infections. Furthermore, our definition of clinical resolution relied on physician documentation rather than standardized quantitative criteria. Future prospective studies with objective clinical endpoints are warranted to evaluate the incremental benefit of OMA in well-defined combination or monotherapy regimens.

Given the limited therapeutic options for CRAB or CRKP infections, OMA may be a reasonable treatment option in specific clinical scenarios. Based on our data, patients with pulmonary CRAB infections appear to derive the greatest

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benefit from OMA-based combination therapy, as reflected by a 30-day mortality rate of 29.2% and clinical resolution rate of 49.4% in this subgroup. Prospective studies are needed to further evaluate the clinical efficacy and safety of OMA in combination with other antibiotics.

Conclusion

This study provides real-world application data for OMA-based combination therapy for CRO infections, particularly pulmonary infections. The results show that the overall 30-day mortality rate of the entire cohort was 27.3% (36/132). OMA has some efficacy in treating CRAB and CRKP infections, with 30-day mortality rates of 29.2% (26/89) and 29.8% (17/57), respectively. Additionally, the study reveal adverse events related to OMA treatment, including elevated transaminases and decreased fibrinogen. Despite limitations such as the lack of direct susceptibility data for OMA and unclear treatment effects and safety for specific high-risk populations (eg, organ transplant patients), OMA may be a viable treatment option in certain situations, especially for patients with pulmonary CRAB infections. Future prospective studies will help further assess the clinical efficacy and safety of OMA when it is used in combination with other antibiotics. A well-designed prospective randomized controlled trial comparing OMA-based combination therapy with standard-of-care regimens in patients with pulmonary CRAB infections is warranted to validate these findings and establish the definitive role of OMA.

Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this work, the authors used OpenAI's DeepSeek-V3 model solely for improvement of language expression and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Disclosure

None of the authors declare any conflict of interest.

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