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BRIEF REPORT

Early Multicenter Experience With Imipenem-Cilastatin-Relebactam for Multidrug-Resistant Gram-Negative Infections

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A multicenter case series of 21 patients were treated with imipenem-cilastatin-relebactam. There were mixed infection sources, with pulmonary infections (11/21,52%) composing the majority. The primary pathogen was *Pseudomonas aeruginosa* (16/21, 76%), and 15/16 (94%) isolates were multidrug-resistant. Thirty-day survival occurred in 14/21 (67%) patients. Two patients experienced adverse effects.

Keywords. carbapenem-resistant *Enterobacterales*; imipenem-cilastatin-relebactam; multidrug-resistant; *Pseudomonas aeruginosa*.

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The increasing prevalence and spread of resistant gram-negative bacteria, such as multidrug-resistant (MDR) *Pseudomonas aeruginosa* and carbapenem-resistant *Enterobacterales* (CRE), are of high concern [1, 2]. Encouragingly, agents displaying in vitro and clinical activity against MDR gram-negative bacteria have recently been introduced to overcome several mechanisms of resistance and are now recommended in the Infectious Diseases Society of America CRE and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR *P. aeruginosa*) guidelines as preferred antibiotics [3–10].

Imipenem-cilastatin-relebactam (I-R; Recarbrio) is the combination of a carbapenem (imipenem), a renal dehydropeptidase-I inhibitor (cilastatin), and a dual-class A/C β-lactamase inhibitor (relebactam) that was Food and Drug Administration (FDA)–approved on July 17, 2019, for patients with complicated urinary tract infections and complicated intra-abdominal infections (IAIs). More recently, it was FDA-approved for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) [11–13]. This is the first antimicrobial that incorporates relebactam, a novel β-lactamase inhibitor that can restore the activity of imipenem in imipenem-resistant strains of Enterobacterales [14, 15]. Specifically, relebactam can inhibit class A β-lactamases including *K. pneumoniae* carbapenemase (KPC) and several extended-spectrum β-lactamases, as well as class C β-lactamases including several AmpC enzymes, and is unaffected by porin channel-mediated resistance due to OprD loss or efflux pump-mediated resistance (eg, MexAB, MexCD, MexXY) in *P. aeruginosa* [9, 16, 17]. Relebactam is based on a diazabicyclooctane core just like avibactam; however, relebactam has a piperidine ring for its R1 side chain and has been suggested to be more stable than avibactam when comparing active sites among KPC-2 complexes [18].

Although randomized controlled trials are considered to be the highest quality of scientific evidence, they often do not represent how agents are actually used in clinical practice [19]. The objective of this case series is to provide preliminary real-world evidence regarding the safety and efficacy of I-R in patients with drug-resistant gram-negative infections.

METHODS

This was a multicenter, retrospective, observational case series of hospitalized patients at 8 medical centers in 6 states treated with I-R between January 2020 and August 2021. Patients were included if they were ≥18 years old and received I-R for ≥48 hours. Patients were excluded if they were pregnant, a prisoner, or if they had received a prior I-R course within 60 days. Case sampling among collaborating centers was based on readiness and convenience sampling.

The primary outcome of all-cause 30-day mortality was assessed 30 days from the index culture collection date. The index culture was defined as the culture that necessitated I-R treatment. Secondary outcomes included clinical cure, defined as a resolution of signs and symptoms of infection within 7 days of antibiotic initiation, microbiological recurrence, defined as subsequent microbiological failure (growth of similar microbial species to index infection in a sterile site) with concomitant signs and symptoms of infection within 30 days after the end of antibiotic treatment and after initial microbiologic eradication, and adverse effects possibly attributable to I-R. Development of I-R nonsusceptibility during treatment was defined by an increase to minimum inhibitory concentration (MIC) ≥4/4 mg/L or ≥2/4 mg/L and a disk diffusion (DD) zone diameter of <23 mm or <24 mm (the Clinical and Laboratory Standards Institute [CLSI] intermediate to resistant break point ranges) for *P. aeruginosa* or *Enterobacterales*, respectively, up to 14 days after the end of I-R treatment [20, 21].

Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault equation and serum creatinine (SCr), and acute kidney injury (AKI) was staged using the KDIGO 2012 guideline [22, 23]. MDR risk factors were defined using classical criteria in pneumonia: antimicrobials ≥24 hours within 90 days before index culture, hospitalization ≥48 hours within 90 days before index culture, admission from a nursing home or extended care facility, home infusion, chronic dialysis, home wound care, surgery within 30 days before index culture, and colonization and/or prior infection with resistant organisms [24]. Study data were collected and managed using the Research Electronic Data Capture (REDCap) tool hosted at Wayne State University [25]. Descriptive statistics were calculated using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Twenty-one patients were included, as noted in Table 1, with a median age (interquartile range [IQR]) of 65 (48–75) years and a median BMI (IQR) of 29.2 (24.8–33.2) kg/m^2. Fifty-seven percent of patients were male, 48% were Caucasian, and 38% were African American. The most common comorbidities included heart failure (11/21, 52%) and diabetes (11/21, 52%). A majority of patients (14/21, 67%) had AKI on admission (at least 0.5 increase in SCr or 50% increase from baseline SCr), and most patients (14/21, 67%) received a renally adjusted dose of I-R. Sixty-seven percent of patients were admitted from home, followed by 3 patients from nursing homes and 2 patients each from long-term care facilities and transfers from outside hospitals. Patients had a median (IQR) of 3 (2–4) MDR risk factors [24]. Most patients (16/21, 76%) received antimicrobials for ≥24 hours in the 90 days before their index culture, and 67% had a hospitalization for ≥48 hours in the 90 days before their index admission. The median Charlson Comorbidity Index (CCI) score (IQR) was 4.0 (2.5–6.0), and the median APACHE II score (IQR) was 21.5 (13.0–28.0; n = 16). Most patients (16/21, 76%) were admitted to the intensive care unit at a median (IQR) of 0 (0–5.3) hospital-days from admission. Infectious diseases consultation was obtained in 95% of patients, surgery was consulted in 29% of patients, and 33% of patients received a source control procedure.

The most common infections were respiratory tract infections, including HAP and VAP (PNA; 11/21, 52%), urinary tract infections (UTIs; 3/21, 14%), and invasive prosthetic device (IPD) infections (3/21, 14%). Bacteremia occurred in 29% of patients. I-R was utilized for the following bacteria: *Pseudomonas aeruginosa* (16/21, 76%), *Klebsiella pneumoniae* (3/21, 14%), and *Proteus mirabilis* (3/21, 14%), among other gram-negative pathogens. Resistance was common, with 3/8 patients with *Enterobacterales* having a CRE infection, and nearly all (15/16, 94%) *P. aeruginosa* cases were MDR (drug nonsusceptibility present in at least 3 antimicrobial classes), as shown in Table 2 [26, 27]. I-R was used for polymicrobial bacterial infection 29% of the time. Only 52% of cases had I-R MICs performed, which were done primarily by Etest, with an MIC range of 0.125/4 to ≥32/4, where 8/11 or 73% were susceptible.

I-R was used as combination therapy 29% (6/21) of the time, with tobramycin as the most common concomitant antibiotic (4/6,67%). The median duration of I-R therapy (IQR) was 8 (4.5–14) days. Clinical reasoning for I-R was primarily due to "no other active agent for infection" (14/21, 67%), followed by "double coverage for suspected CRE/carbapenem-resistant *P. aeruginosa*" (5/21, 24%). Inhaled antibiotics were used in 14% (3/21) of patients. I-R was switched in only 3/21 patients to a different agent; 2 patients were switched to meropenem-vaborbactam (MEV) and 1 patient to ceftazidime-avibactam (CZA).

Mortality occurred in 7/21 (33%) patients. Clinical cure occurred in 13/21 (62%) patients treated with I-R. Nonsusceptibility to I-R developed on treatment in only 1 case (1/21, 5%) or in only 11% (1/9) of those isolates with subsequent MIC testing post–index culture. Microbiological recurrence occurred in 5/21 (24%) patients. Subsequent cultures were obtained in 5/21 patients within 90 days post–I-R initiation. Two of the cultures grew isolates that demonstrated increased I-R MICs relative to the index culture from 1.5/4 mg/L and 2/4 mg/L (susceptible) to 12/4 mg/L and 8/4 mg/L (resistant), respectively. Two adverse events occurred, 1 gastrointestinal (nausea, vomiting, diarrhea) and 1 encephalopathic (altered mental status, somnolence, new-onset seizures). Neither of the adverse events led to drug discontinuation.

DISCUSSION

We report early, real-world observations of I-R use among patients at 8 medical centers. Our findings suggest that I-R is used for MDR *P. aeruginosa*, in some cases for CRE, and that I-R seems to lead to clinical cure in the majority of cases. In

Table 1. Clinical Characteristics of Patients and Infections Treated With Imipenem-Cilastatin-Relebactam

ID #	Age/ Sex	CrCl at I-R Start, mL/min	APACHE/ CCI	Infection	Index Organism(s)	Antibiotic(s) for Index Infection (Days used)[a]	I-R Dose	I-R Selection Reason(S)	Clinical Cure	30-Day Mortality	I-R Nonsusceptibility on Tx?	Microbiologic Recurrence
1	79/M	81	13/10	SSTI	• *Proteus mirabilis* • *Pseudomonas aeruginosa* • *Staphylococcus aureus* (MRSA)	I-R (days 0–4) VAN (days 0–9) CZA (days 4–10) MZ (days 5–9)	1000 mg q6 hours	•Double coverage for CRE/C-R *Pseudomonas*	Yes	No	No repeat MIC testing	No
2	73/F	128	10/6	UTI	• *Proteus mirabilis* • *Pseudomonas aeruginosa* • *Enterococcus faecalis*	I-R (days 4–18)	1000 mg q6 hours	• Consolidation of regimen • No other active agent for infection • Antibiotic shortage	Yes	No	No repeat MIC testing	No
3	70/F	17	22/5	IPD	• *Achromobacter* spp. • *Pseudomonas aeruginosa*	I-R (days 6–10) MEV (days 10–103)	500 mg q6 hours	• No other active agent for infection	No	No	No repeat MIC testing	Yes
4	34/M	149	NA/0	PNA	• *Pseudomonas aeruginosa*	I-R (days 5–12)	1250 mg q6 hours	• No other active agent for infection	Yes	No	No	No
5	64/M	72	NA/4	Bone/joint	• *Pseudomonas aeruginosa*	I-R (days 13–48)	1250 mg q6 hours	• Antibiotic shortage	Yes	No	No	No
6	77/F	49	NA/4	PNA	• *Pseudomonas aeruginosa*	I-R (days 2–9)	750 mg q6 hours	• No other active agent for infection	Yes	No	No	No
7	42/F	116	21/1	PNA	• *Pseudomonas aeruginosa*	Inhaled CST + Inh TOB (days 0–9) I-R (days 7–10)	1250 mg q6 hours	• Lack of PO access • No other active agent for infection	No	Yes	No	NA
8	60/M	89	13/3	IPD + BSI	• *Pseudomonas aeruginosa*	C/T (days 1–4) TOB (days 3–20) I-R (days 4–19) FDC (days 13–20) MEV (days 20–23)	1250 mg q6 hours	• Double coverage for CRE/C-R *Pseudomonas*	No	Yes	No repeat MIC testing	NA
9	83/M	15	26/7	UTI + BSI	• *Pseudomonas aeruginosa*	CRO (days 0–1) FEP (day 2) I-R (days 2–8)	500 mg q6 hours	• No other active agent for infection	Yes	No	No repeat MIC testing	No
10	66/M	CRRT: 2 L/h	46/6	PNA	• *Pseudomonas aeruginosa*	FEP (days 0–1) I-R (days 1–9)	500 mg q6 hours	• No other active agent for infection	Yes	No	No repeat MIC testing	Yes
11	65/M	60	35/9	PNA	• *Pseudomonas aeruginosa*	VAN (days 0–1) TZP (days 0–3) C/T (days 3–4) MZ (days 3–4) I-R (days 4–8)	750 mg q6 hours	• No other active agent for infection • Antibiotic shortage	Yes	No	No repeat MIC testing	Yes
12	57/F	82	10/5	IPD	• *Pseudomonas aeruginosa*	CIP (days 0–22) MEM (days 0–1) I-R (days 10–22)	1000 mg q6 hours	• No other active agent for infection	Yes	Yes	No repeat MIC testing	Yes
13	44/M	CVVHD: 1.9 L/h	17/2	PNA	• *Pseudomonas aeruginosa*	TZP (days 123–149) Inhaled CST (days 123–171) SXT (days 150–165) I-R (days 150–186) TOB (days 150–) Inh TOB (days 178–)	500 mg q6 hours	• Double coverage for CRE/C-R *Pseudomonas*	No	No	Yes	Yes

Table 1. Continued

ID #	Age/ Sex	CrCl at I-R Start, mL/min	APACHE/ CCI	Infection	Index Organism(s)	Antibiotic(s) for Index Infection (Days used)[a]	I-R Dose	I-R Selection Reason(S)	Clinical Cure	30-Day Mortality	I-R Nonsusceptibility on Tx?	Microbiologic Recurrence
14	71/F	16	NA/4	PNA	• *Pseudomonas aeruginosa* • *Stenotrophomonas maltophilia*	I-R (days 15–23)	500 mg q6 hours	• No other active agent for infection	No	No	No	No
15	77/M	286	23/4	PNA VP shunt	• *Pseudomonas aeruginosa* • *Serratia marcescens* • *Acinetobacter baumanii*	I-R (days 35–42)	1250 mg q6 hours	• Other: initial VAP *P. aeruginosa* susceptible to I-R 1 month prior	Yes	No	No repeat MIC testing	No
16	63/F	51	10/5	IAI	• *Klebsiella oxytoca* • *Pseudomonas aeruginosa* • *Enterococcus faecalis* • Group B *Streptococcus*	TZP (days 0–3) VAN (day 0) I-R (days 3–13)	1000 mg q6 hours	• Consolidation of regimen • No other active agent for infection	Yes	No	No repeat MIC testing	No
17	23/F	25	28/0	PNA	• *Klebsiella pneumoniae* • *Acinetobacter baumanii* • *Proteus mirabilis* • *Stenotrophomonas maltophilia*	MIN (days 2–6) I-R (days 2–6) Inh TOB (days 3–6)	500 mg q6 hours	• Double coverage for CRE/C-R *Pseudomonas* • No other active agent for infection	Yes	Yes	No repeat MIC testing	NA
18	65/F	97	28/4	IAI	• *Klebsiella pneumoniae* • *Enterococcus avium*	I-R (days 68–80)	1250 mg q6 hours	• No other active agent for infection	Yes	No	No	No
19	39/M	37	30/1	PNA + BSI CDI	• *Enterobacter cloacae* • *Klebsiella pneumoniae*	MEM (days 0–2) CZA (day 2) I-R (days 7–23)	1250 mg q6 hours	• Consolidation of regimen • No other active agent for infection	No	Yes	No repeat MIC testing	NA
20	52/M	69	20/5	PNA + BSI Candidemia MRSA IE	• *Burkholderia cepacia* • *Enterobacter cloacae*	AMK (day 47) FDC (days 47–68) CZA (days 68–73) FDC (days 74–80) I-R (days 74–89)	500 mg q6 hours	• Double-coverage for CRE/C-R *Pseudomonas*	No	Yes	No	NA
21	80/M	67	NA/9	UTI + BSI	• *Escherichia coli*	MEM (days –23 to 14) I-R (days –15 to 2)	1000 mg q6 hours	• Other: worsening on meropenem	No	Yes	No	NA

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation II scoring system; BSI, bloodstream infection (bacteremia); CCI, Charlson Comorbidity Index; CDI, *Clostridiodes difficile* infection; CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; CVVHD, continuous veno-venous hemodiafiltration; I-R, imipenem-cilastatin-relebactam; IAI, intraabdominal infection; IE, infective endocarditis; IPD, invasive prosthetic device; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available; PNA, pneumonia or lower respiratory tract infection; S/SX, signs and symptoms; SCr, serum creatinine; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

Antibacterial agents: AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CIP, ciprofloxacin; CRO, ceftriaxone; CST, colistin; CZA, ceftazidime-avibactam; FDC, cefiderocol; FEP, cefepime; MEM, meropenem; MEV, meropenem-vaborbactam; MIN, minocycline; MZ, metronidazole; SXT, trimethoprim-sulfamethoxazole; TOB, tobramycin; TZP, piperacillin-tazobactam; VAN, vancomycin.

[a]Days starting from index infection culture draw date, or date of empiric antibiotic initiation leading to I-R use.

Table 2. MIC Resistance Profile of Infections Treated With Imipenem-Cilastatin-Relebactam

ID #	Index Organism(S)	MIC Resistance Profile[a]		
1	• *Proteus mirabilis* • *Pseudomonas aeruginosa* • *Staphylococcus aureus* (MRSA)	Pseudomonas: Aztreonam-R Cefepime-I	Ceftazidime-R Ceftaz-Avi-S Cipro/Levo-R	Gent/Tobra-S Meropenem-I Pip-tazo-I(64)
2	• *Proteus mirabilis* • *Pseudomonas aeruginosa* • *Enterococcus faecalis*	Pseudomonas: Cefepime-S Ceftazidime-S Ceftaz-Avi(Etest)-S	Ceftolo-tazo(Etest)-S Cipro/Levo-R Gent/Tobra-S	Imi-Rel-I(3)[b,c] Meropenem-R Pip-tazo-S
3	• *Achromobacter* spp. • *Pseudomonas aeruginosa*	Pseudomonas: Amikacin-S Aztreonam-R Cefepime-R Cefiderocol(DD)-R Ceftazidime-R	Ceftaz-Avi-R Ceftolo-tazo-R Ceftriaxone-R Cipro/Levo-R Colistin-S Gent/Tobra-S	Imipenem-S Imi-Rel(Etest)-S[2,3] Meropenem-R Mero-Vabor-S Pip-tazo-I
4	• *Pseudomonas aeruginosa*	Pseudomonas: Amikacin-S Cefepime-R	Ceftazidime-I Ceftriaxone-R Cipro/Levo-R	Meropenem-R
5	• *Pseudomonas aeruginosa*	Pseudomonas: Amikacin-S Cefepime-I Ceftazidime-I	Ceftaz-Avi-S Ceftriaxone-R Gent/Tobra-S Imi-Rel-S[2,3]	Meropenem-I Pip-tazo-I Polymyxin B-S
6	• *Pseudomonas aeruginosa*	Pseudomonas: Amikacin-S Cefepime-I	Ceftazidime-I Ceftaz-Avi(Etest)-R Ceftriaxone-R	Cipro/Levo-R Gent/Tobra-S Meropenem-R
7	• *Pseudomonas aeruginosa*	Pseudomonas: Amikacin(DD)-S Aztreonam(Etest)-R Cefepime(DD)-R	Ceftazidime(DD)-R Ceftaz-Avi(Etest)-R Cipro/Levo(DD)-R Colistin(Etest)-S	Gent/Tobra(DD)-R Imi-Rel(Etest)-S[2,3] Meropenem(DD)-R Pip-tazo(DD)-S
8	• *Pseudomonas aeruginosa*	Pseudomonas: Amikacin-S Aztreonam-R Cefepime-R Ceftazidime-R Ceftaz-Avi-R	Ceftolo-tazo-R Ceftriaxone-R Cipro/Levo-R Colistin-S Gent/Tobra-S	1. Imipenem-S 2. Imipenem(Etest)-R Imi-Rel(Etest)-R[2,3] Meropenem-R Mero-Vabor-R Pip-tazo-I
9	• *Pseudomonas aeruginosa*	Pseudomonas: Ceftazidime-I	Cipro/Levo-R Gent/Tobra-S	Imipenem-R
10	• *Pseudomonas aeruginosa*	Pseudomonas: Cefepime-R	Ceftazidime-R Cipro/Levo-R	Gent/Tobra-S Imipenem-R
11	• *Pseudomonas aeruginosa*	Pseudomonas: Cefepime-R Ceftazidime-R	Cipro/Levo-R Gent/Tobra-S	Imipenem-R Pip-tazo-R
12	• *Pseudomonas aeruginosa*	Pseudomonas: Amikacin-S(16) Cefepime-R Ceftazidime-R	Ceftaz-Avi(Etest)-R Ceftriaxone-R Cipro/Levo-R Gent/Tobra-S	Imipenem-R Meropenem-R Mero-Vabor(Etest)-SDD Pip-tazo-R
13	• *Pseudomonas aeruginosa*	Pseudomonas: Amikacin-I Aztreonam-R Cefepime-R	Cefiderocol-S Cipro/Levo-I Colistin(BMD)-I Gent-I/Tobra-S	Imi-Rel(BMD)-S[2,3] Meropenem-R Pip-tazo-R
14	• *Pseudomonas aeruginosa* • *Stenotrophomonas maltophilia*	Pseudomonas: Amikacin-S Cefepime-S(8)	Ceftazidime-R Ceftaz-Avi(Etest)-R Ceftriaxone-R	Cipro/Levo-R Gent/Tobra-S Meropenem-R
15	• *Pseudomonas aeruginosa* • *Serratia marcescens* • *Acinetobacter baumanii*	Pseudomonas: Amikacin-S Aztreonam(DD)-R Ceftazidime-R Cefepime(DD)-R	Cefiderocol(BMD)-S Cipro/Levo-R Ceftolo-tazo-S Gent-I/Tobra-S	Imipenem-R Imi-Rel(Etest)-R[2,3] Meropenem-R Pip-tazo(DD)-R
16	• *Klebsiella oxytoca* • *Pseudomonas aeruginosa* • *Enterococcus faecalis* • Group B *Streptococcus*	Klebsiella (ESBL+): Aztreonam-R Ceftriaxone-R Cipro/Levo-S Gent/Tobra-S Meropenem-S Pip-tazo-R	Pseudomonas: Aztreonam-I Cefepime-S(8) Ceftazidime-S	Cipro/Levo-R Gent/Tobra-S Meropenem-I Pip-tazo-S

Table 2. Continued

ID #	Index Organism(S)	MIC Resistance Profile[a]		
17	• *Klebsiella pneumoniae* • *Acinetobacter baumanii* • *Proteus mirabilis* • *Stenotrophomonas maltophilia*	Klebsiella: Amikacin-R Cefazolin-R Cefepime-SDD Cefiderocol(DD)-S Ceftazidime-I	Ceftriaxone-R Cipro/Levo-R Gent-S/Tobra-R Imipenem(Etest)-S Imi-Rel(Etest)-S[2,3]	Meropenem(Etest)-S Minocycline(Etest)-I Pip-tazo-R Tetracycline-R
18	• *Klebsiella pneumoniae* • *Enterococcus avium*	Klebsiella: Amikacin-S(16) Cefazolin-R Cefepime-R Ceftazidime-R Ceftriaxone-R	Ceftaz-Avi-S Cipro/Levo-R Colistin-S Eravacycline-2 Ertapenem-R Gent-S/Tobra-R Imi-Rel-S[2,3]	Meropenem-R Mero-Vabor-S Pip-tazo-R Tetracycline-R TMP/SMX-R
19	• *Enterobacter cloacae* • *Klebsiella pneumoniae*	Enterobacter: Amikacin-S Aztreonam(DD)-R Cefepime(DD)-R Ceftazidime-R	Ceftaz-Avi(Etest)-R Ceftriaxone-R Cipro/Levo-R Colistin(BMD)-S Gent/Tobra-S	Imi-Rel(Etest)-S[2,3] Meropenem-R Mero-Vabor(Etest)-S Tigecycline(DD)-R TMP/SMX-R
20	• *Burkholderia cepacia* complex • *Enterobacter cloacae*	Burkholderia: Cefiderocol(BMD)-0.25 Ceftazidime-S Ceftaz-Avi(BMD)-3 Cipro/Levo-R Imi-Rel(Etest)-2[2,3] Meropenem-I Minocycline-I TMP/SMX-R	Enterobacter: Amikacin-S Aztreonam-R Cefazolin-R Cefepime-I Cefiderocol(BMD)-S Cefpodoxime-R Ceftazidime-R	Ceftaz-Avi-S Cipro/Levo-S Gent/Tobra-S Imi-Rel(BMD)-S[2,3] Meropenem-S Pip-tazo-R TMP/SMX-R
21	• *Escherichia coli*	Escherichia: Amikacin-S Cefepime-S Cefoxitin-R	Ceftazidime-S Ceftriaxone-S Cipro/Levo-R	Gent/Tobra-S Meropenem-S TMP/SMX-R

Abbreviations: BMD, Broth Microdilution; CLSI, Clinical and Laboratory Standards Institute; DD, Disk Diffusion; ESBL, extended-spectrum β-lactamase; EUCAST, European Committee on Antimicrobial Susceptibility Testing; IMI/REL, imipenem-cilastatin-relebactam; MIC, minimum inhibitory concentration; R, resistant; S, susceptible; SDD, susceptible dose-dependent; TMP/SMX, trimethoprim/sulfamethoxazole.

[a]CLSI breakpoints used for determinations of S, SDD, I, and R. Where I or SDD has multiple MIC breakpoints or MICs are significantly discrepant between CLSI and EUCAST, the specific MIC is listed in parentheses after the CLSI classification [31]. Parentheses after the antibiotic specify susceptibility method if not automated (ie, Disk Diffusion, Etest, or Broth Microdilution).

[b]CLSI susceptibility breakpoints for IMI/REL are ≤1/4 mg/L for *Enterobacterales* and ≤2/4 for *P. aeruginosa*. EUCAST breakpoints are ≤2/4 for *P. aeruginosa* and *Enterobacterales*.

[c]For susceptibility testing purposes, the concentration of relebactam is fixed at 4 mg/L.

addition, we observed a mortality rate of 33%. However, it is worth noting that the patients receiving I-R often have high APACHE II scores associated with mortality rates around 40% [28]. The patients here have higher APACHE-II scores than the RESTORE-IMI 1 trial did, with slightly lower clinical cure rates and higher mortality, as expected [15].

In our experience, I-R was utilized for a variety of infections including PNA, UTI, and IAI caused by MDR gram-negative bacteria. However, the treatment niche for I-R seems to be in MDR *P. aeruginosa* due to relebactam's activity against AmpC hyperproduction, resistance to efflux, and porin channel–mediated resistance in *P. aeruginosa* [9, 16, 18]. This place in therapy may have been further emphasized with an ongoing drug shortage and recall of ceftolozane/tazobactam (C/T), a principal agent used against MDR *P. aeruginosa*, since January 4, 2021 [29]. I-R also seems to have a place in polymicrobial-resistant infections with *Enterococcus faecalis* given that CZA and C/T have no activity against this bacterium.

The most common clinical reasoning for I-R selection was "no other active agent for infection" and may explain its relatively infrequent current use. Of note, I-R requires renal dosage adjustment below a CrCl of 90 mL/min. This is a higher threshold than other antibiotics; yet, appropriate dose adjustments for I-R were often implemented (14/21, 67%), with some departure from listed adjustments likely due to age or clinical status. A significant limitation of this report is its observational nature, which limits controlled experimental analyses. There are many antimicrobials, patient statuses, durations of therapy, and infection types that may impact the results and effectiveness of the antibiotic. MICs for I-R were only acquired in just over half of cases making it difficult to assess I-R activity in the unreported cases. Also, while adverse effects were reported, it is difficult to link them directly to I-R use as Naranjo Adverse Drug Reaction Probability scores were not calculated [30]. However, I-R seems to be utilized effectively in these patients with limited available antibiotic options and with limited adverse effects. Given its spectrum of activity, I-R may remain a viable option for infections caused by MDR *P. aeruginosa,* other nonlactose fermenters, and CRE, in addition to potential use in polymicrobial infections with *Enterococcus faecalis*. Therefore, I-R provides another useful

tool to the antibiotic repertoire in the fight against antimicrobial resistance.

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Patient consent. This study does not include factors necessitating patient consent. Furthermore, the design and reporting of this study have been approved by local institutional review boards.

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