Imipenem/Relebactam

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Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections

Yohei Doi[1,2]

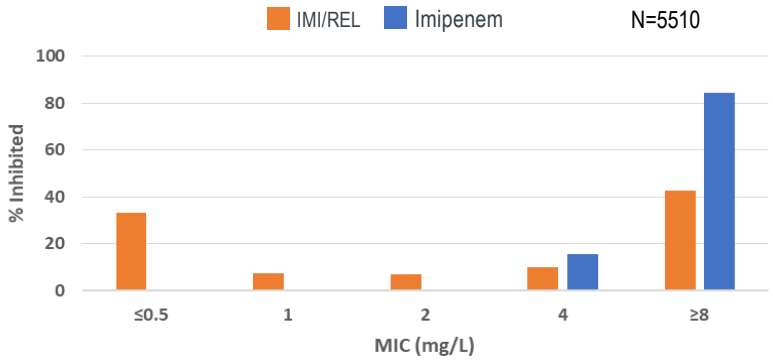
Table 1. Activity and Indications of New Agents Against Carbapenem-resistant Gram-negative Pathogens

	Activity							
	Enterobacteriaceae							
Agent	Class A Carbapenemase (eg, KPC)	Class B Carbapenemase (eg, NDM)	Class D Carbapenemase (eg, OXA-48)	*P. aeruginosa*	*A. baumannii*	*S. maltophilia*	Indications (Including Expected)	Pathogen-directed Trial (Including Expected)
Ceftazidime-avibactam	Yes	No	Yes	Yes	No	No	cUTI/AP, cIAI, HABP/VABP	No
Ceftolozane-tazobactam	No	No	No	Yes	No	No	cUTI/AP, cIAI, NP	No
Meropenem-vaborbactam	Yes	No	No	No[a]	No	No	cUTI/AP	Yes
Imipenem-cilastatin-relebactam	Yes	No	No	Yes	No	No	cUTI/AP, cIAI, HABP/VABP	Yes
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	cUTI/AP, HABP/VABP	Yes
Plazomicin	Yes	Variable[b]	Yes	Variable	No	No	cUTI/AP	Yes
Eravacycline	Yes	Yes	Yes	No	Yes	Yes	cIAI	No
Fosfomycin	Yes	Yes	Yes	Variable	No	No	cUTI/AP	No

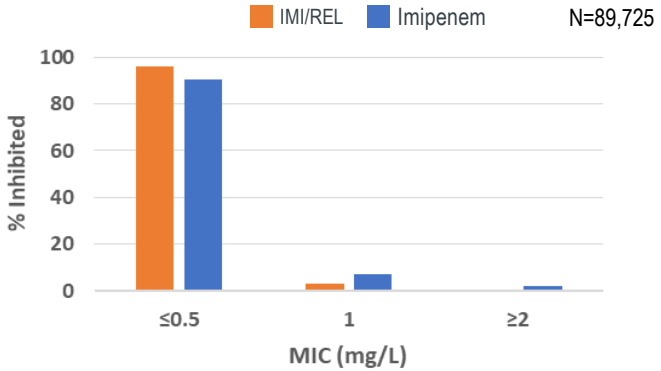
Effect of Relebactam on Imipenem activity Among Enterobacterales

Activity of Imipenem (IMI) among Enterobacterales is enhanced by Relebactam (REL)

Imipenem-Nonsusceptible (MIC >2 mg/L) Enterobacterales*



Imipenem-Susceptible (MIC ≤2 mg/L) Enterobacterales*



- For **imipenem-nonsusceptible isolates**, the addition of relebactam increases the proportion of susceptible isolates from 0% to 48%
  - This shift is largely due to relebactam inhibition of KPC, carried by ~42% of imipenem-nonsusceptible isolates
  - Isolates that remain IMI/REL-nonsusceptible include those that carry genes encoding MBL (~37%) or OXA-48 enzymes (~26%)
- Among **imipenem-susceptible isolates**, the addition of relebactam causes a small but perceptible shift, increasing the proportion of isolates with MIC ≤0.5 mg/L from 90% to 96%

*Enterobacterales includes the following species: *E. coli*, *K. pneumoniae*, *E. cloacae*, *S. marcescens*, *K. oxytoca*, K. aerogenes, *C. freundii* and *C. koseri*.
Figure adapted from: Hilbert D, et al. ECCMID 2021; Poster #1590

Hilbert D, et al. ECCMID 2021; Poster #1590

Inhibition of KPC by Relebactam in Enterobacterales

Relebactam Inhibits KPC: An Important Carbapenemase in Enterobacterales

- Inhibition of KPC by relebactam allows imipenem to reach its PBP target, leading to disruption of the bacterial cell wall and cell death
- Neither imipenem nor relebactam is subject to efflux

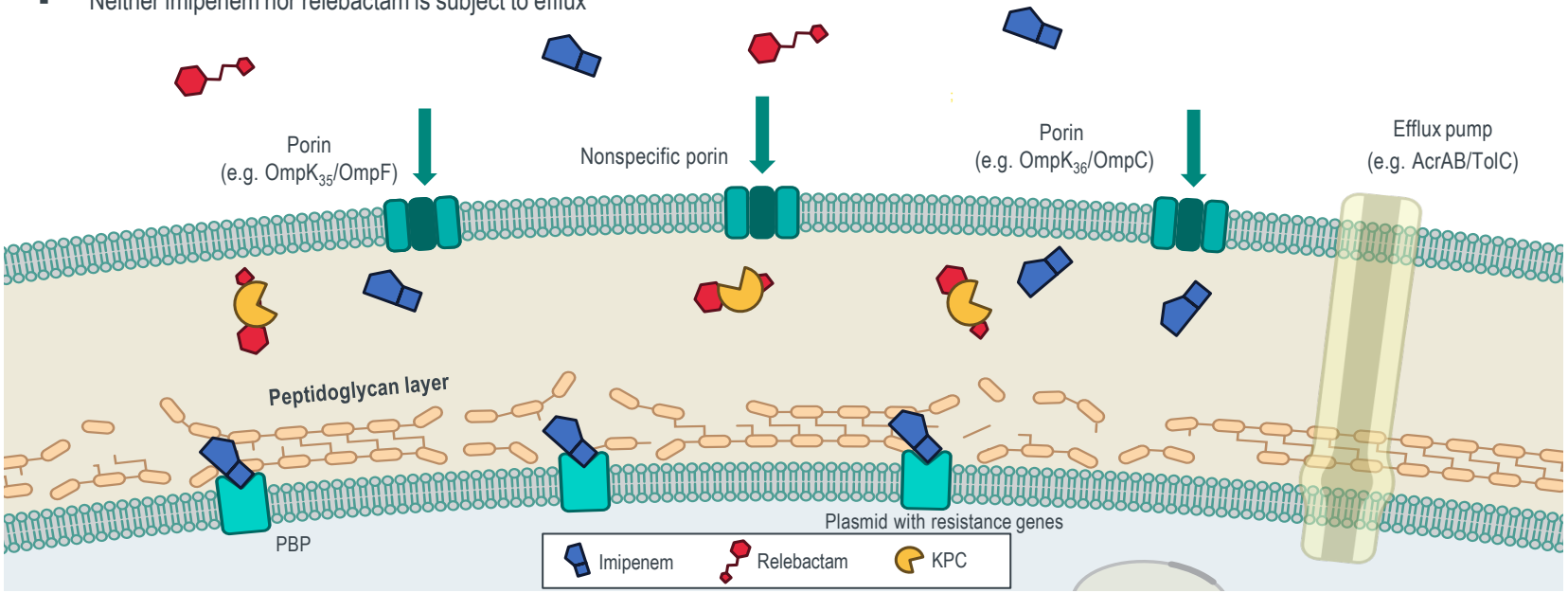


Figure adapted from: Hilbert D, et al. ECCMID 2021; Poster #1590.
Hilbert D, et al. ECCMID 2021; Poster #1590; Young K, et al. ECCMID 2020; Poster #4436; Horner C, et al. J. *Antimicrob Chemother* 2019;74:1940–4

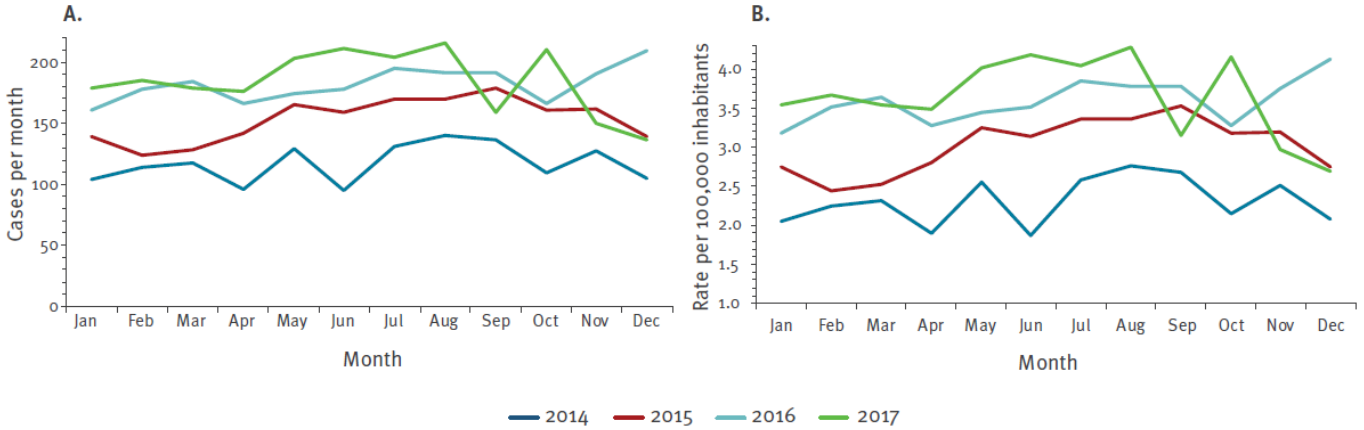
Bloodstream infections due to carbapenemase-producing Enterobacteriaceae in Italy: results from nationwide surveillance, 2014 to 2017

Simone Iacchini[1], Michela Sabbatucci[1,2], Carlo Gagliotti[3], Gian Maria Rossolini[4,5], Maria Luisa Moro[3], Stefania Iannazzo[6], Fortunato D'Ancona[1], Patrizio Pezzotti[1], Annalisa Pantosti[1]

Carbapenemase enzyme	*Klebsiella pneumoniae*		*Escherichia coli*		Total	
	N	%	N	%	N	%
KPC	4,323	95.2	57	81.4	4,380	95.0
MBL[a]	87	1.9	12	17.1	99	2.1
KPC + MBL[b]	43	0.9	0	0.0	43	0.9
OXA-48	55	1.2	1	1.4	56	1.2
MBL[c] + OXA-48	15	0.3	0	0.0	15	0.3
KPC + OXA-48	3	0.1	0	0.0	3	0.1
ND[d]	16	0.4	0	0.0	16	0.3
Not indicated	2,948	–	72	–	3,020	–
Total	7,490	–	142	–	7,632	–

Characteristics		N	%
Pathogen	*Klebsiella pneumoniae*	7,490	98.1
	Escherichia coli	142	1.9
Sex[a]	Female	2,817	37.3
	Male	4,731	62.7
Age group (years)[a]	0–19	101	1.4
	20–39	411	5.6
	40–59	1,642	22.2
	60–79	3,677	49.7
	≥ 80	1,569	21.2
Nationality	Italian	7,631	96.4
	Other	271	3.6
Patient location at symptom onset[a]	Hospital	6,386	87.2
	Other[b]	937	12.8
Total		**7,632**	**100**

(A) Frequency and (B) incidence rate per 100,000 inhabitants by month and year of bloodstream infections due to carbapenemase-producing Enterobacteriaceae reported to the national surveillance system, Italy, 2014–2017



AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

RESEARCH ARTICLE

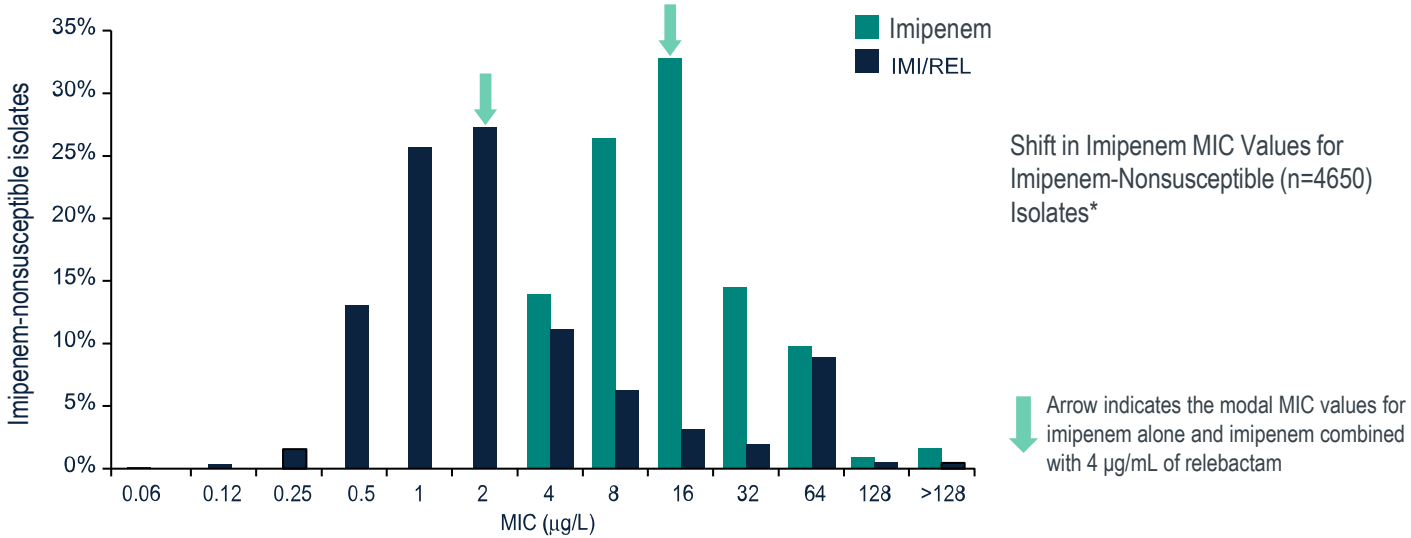
Imipenem-Relebactam Susceptibility in *Enterobacterales* Isolates Recovered from ICU Patients from Spain and Portugal (SUPERIOR and STEP Studies)

Marta Hernández-García,[a,b] María García-Castillo,[a] Germán Bou,[b,c] Emilia Cercenado,[d] Mercedes Delgado-Valverde,[e,b] Antonio Oliver,[b,f] Cristina Pitart,[g] Jesús Rodríguez-Lozano,[h] Nuria Tormo,[i] José Melo-Cristino,[j] Margarida F. Pinto,[k] Elsa Gonçalves,[l] Valquíria Alves,[m] Ana Raquel Vieira,[n] Elmano Ramalheira,[o] Luísa Sancho,[p] José Diogo,[q] Rui Ferreira,[r] Hugo Cruz,[s] Catarina Chaves,[t] Joana Duarte,[u] Leonor Pássaro,[u] Jazmín Díaz-Regañón,[v] Rafael Cantón,[a,b] on behalf of the SUPERIOR and STEP study groups

Multidrug resistance in *Enterobacterales* that cause severe infections in ICUs remains a serious challenge worldwide and requires different interventions, including stewardship programs, implementation of infection control measures, rapid diagnostic tools, and also the development of novel therapeutic options. Imipenem-relebactam is positioned as a treatment option against KPC-producing *K. pneumoniae* isolates frequently detected in ICU patients with complicated infections in which few or no other treatment options are available. Despite the elevated susceptibility rate detected in this study, OXA-48-producing *K. pneumoniae* high-risk clones widely disseminated in hospital settings in Spain are the main contributor to imipenem-relebactam resistance among multidrug-resistant *Enterobacterales* isolates causing complicated infections in ICU patients.

Relebactam Effect on Imipenem-nonsusceptible *P. aeruginosa*

Relebactam Restores Susceptibility in Imipenem Nonsusceptible P. aeruginosa



- Isolates were obtained from four separate sources: 1) challenge panel of imipenem-nonsusceptible isolates curated at Merck & Co., Inc. (n=108); 2) challenge panel of imipenem-nonsusceptible isolates curated at Eurofins (Chantilly, VA, USA) (n=185); 3) Global SMART database (2009; 2011; 2015–16) (n=14,813); 4) all imipenem-nonsusceptible isolates from a previously published surveillance study from NY, NY, USA (n=144); all sources

*Excludes SMART surveillance data from China and India (2015 and 2016) and Vietnam (2015) due to late inclusion of the data in the analysis.

Young K, et al. *BMC Microbiol* 2019;19:150

Relebactam Mechanism of Action in Imipenem-Nonsusceptible *P. aeruginosa*

Relebactam Restores Susceptibility in Imipenem Non-susceptible *P. aeruginosa*

- Relebactam restores the activity of imipenem vs *P. aeruginosa* with loss of OprD protein
- Relebactam inhibits hydrolysis of imipenem by AmpC ß-lactamase, restoring imipenem activity against imipenem-nonsusceptible *P. aeruginosa*
- Imipenem and relebactam are not subject to *P. aeruginosa* efflux pumps

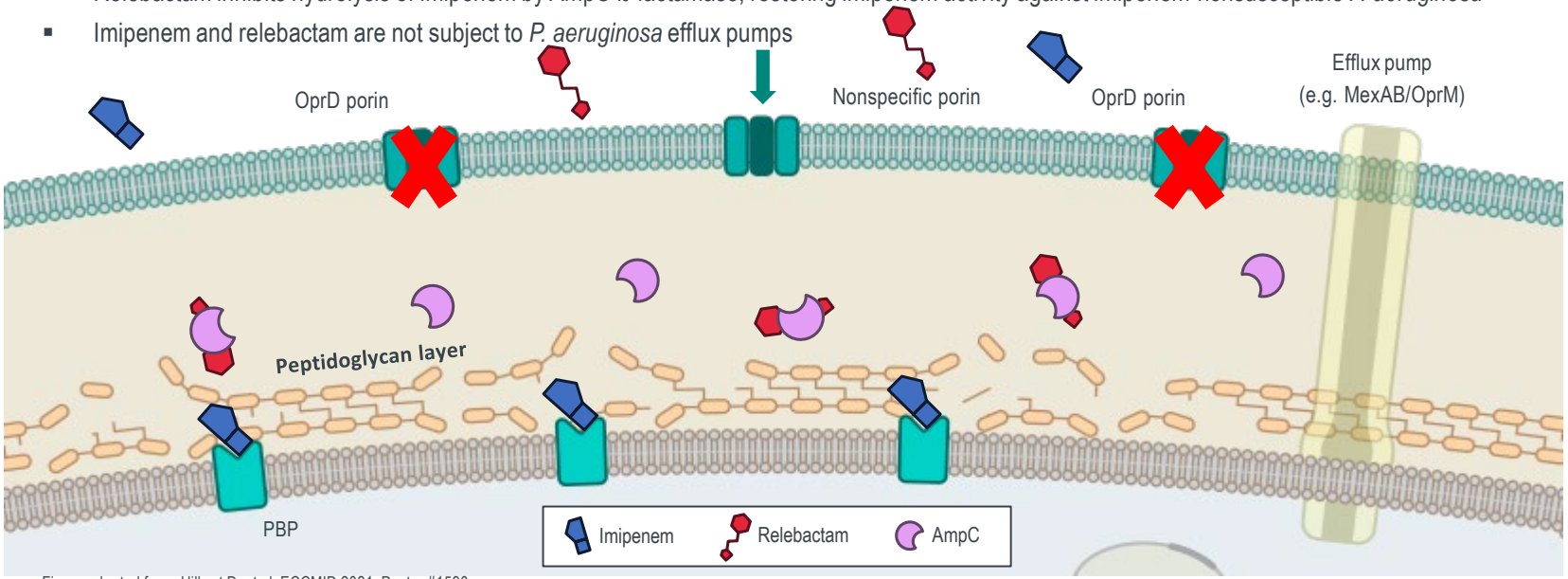


Figure adapted from: Hilbert D, et al. ECCMID 2021; Poster #1590.

Hilbert D, et al. ECCMID 2021; Poster #1590; Young K, et al. *BMC Microbiol* 2019;19:150; Livermore DM. *Antimicrob Agents Chemother* 1992;36:2046–8; Livermore DM, et al. J.Antimicrob. Chemother 2013;68:2286–90; Horner C, et al. J Antimicrob Chemother 2019;74:1940–44

J Antimicrob Chemother. 2022 Oct 28;77(11):3163-3172. doi: 10.1093/jac/dkac298.

In vitro activity of imipenem/relebactam against Pseudomonas aeruginosa isolates recovered from ICU patients in Spain and Portugal (SUPERIOR and STEP studies)

Marta Hernández-García [1 2], María García-Castillo [1], José Melo-Cristino [3], Margarida F Pinto [4], Elsa Gonçalves [5], Valquíria Alves [6], Ana Raquel Vieira [7], Elmano Ramalheira [8], Luísa Sancho [9], José Diogo [10], Rui Ferreira [11], Hugo Cruz [12], Catarina Chaves [13], Germán Bou [2 14], Emilia Cercenado [15 16], Mercedes Delgado-Valverde [2 17], Antonio Oliver [2 18], Cristina Pitart [19], Jesús Rodríguez-Lozano [20], Nuria Tormo [21], Jazmín Díaz-Regañón [22], Leonor Pássaro [23], Joana Duarte [23], Rafael Cantón [1 2], STEP and SUPERIOR study groups

Collaborators, Affiliations + expand

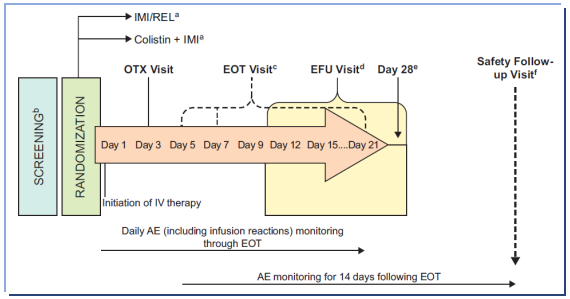
PMID: 36059128 DOI: 10.1093/jac/dkac298

Conclusions: Microbiological results reinforce imipenem/relebactam as a potential option to treat cUTI, cIAI and LRTI caused by MDR/XDR P. aeruginosa isolates, except for GES-13 and VIM producers.

Clinical Infectious Diseases
MAJOR ARTICLE

RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections

Johann Motsch,[1] Cláudia Murta De Oliveira,[2] Viktor Stus,[3] Ittihar Köksal,[4] Olexiy Lyulko,[5] Helen W. Boucher,[6] Keith S. Kaye,[7] Thomas M. File Jr,[8] Michelle L. Brown,[9] Ireen Khan,[9] Jiejun Du,[9] Hee-Koung Joeng,[9] Robert W. Tipping,[9] Angela Aggrey,[9] Katherine Young,[9] Nicholas A. Kartsonis,[9] Joan R. Butterton,[9] and Amanda Paschke[9]



Pseudomonas aeruginosa (77%), *Klebsiella* spp. (16%), other Enterobacteriaceae (6%)

31 patients received imipenem/relebactam and 16 colistin+imipenem

Favorable overall response was observed in 71% imipenem/relebactam and 70% colistin+imipenem patients, day 28 favorable clinical response in 71% and 40%, and 28-day mortality in 10% and 30%, respectively. Serious adverse events occurred in 10% of imipenem/relebactam and 31% of colistin+imipenem patients,

Table 2. Primary and Secondary Prospective Efficacy Endpoints (in the Modified Microbiologic Intent-to-Treat Population) and Secondary Prospective Safety Endpoints (in the Safety Population)

	IMI/REL (n = 21)		Colistin + IMI (n = 10)		Unadjusted Difference	Adjusted Difference[a]	
Endpoint	n	% (95% CI)[b]	n	% (95% CI)[a]	%	%	90% CI
Primary endpoint							
Favorable overall response[c]	15	71.4 (49.8, 86.4)	7	70.0 (39.2, 89.7)	1.4	−7.3	(−27.5, 21.4)
Hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia	7/8	87.5 (50.8, 99.9)	2/3	66.7		20.8	
Complicated intraabdominal infection	0/2[d]	0.0	0/2[e]	0.0		0.0	
Complicated urinary tract infection	8/11	72.7 (42.9, 90.8)	5/5	100.0 (51.1, 100.0)		−27.3 (−52.8, 12.8)	
Secondary endpoints							
Favorable clinical response (day 28)	15[f]	71.4 (49.8, 86.4)	4[g]	40.0 (16.7, 68.8)	31.4	26.3	(1.3, 51.5)
28-day all-cause mortality	2	9.5 (1.4, 30.1)	3	30.0 (10.3, 60.8)	−20.5	−17.3	(−46.4, 6.7)
Treatment-emergent nephrotoxicity[h]	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)		−45.9 (−69.1, −18.4)	

RESTORE-IMI-1: Qualifying Baseline Pathogens with IMI/REL and Colistin + Imipenem

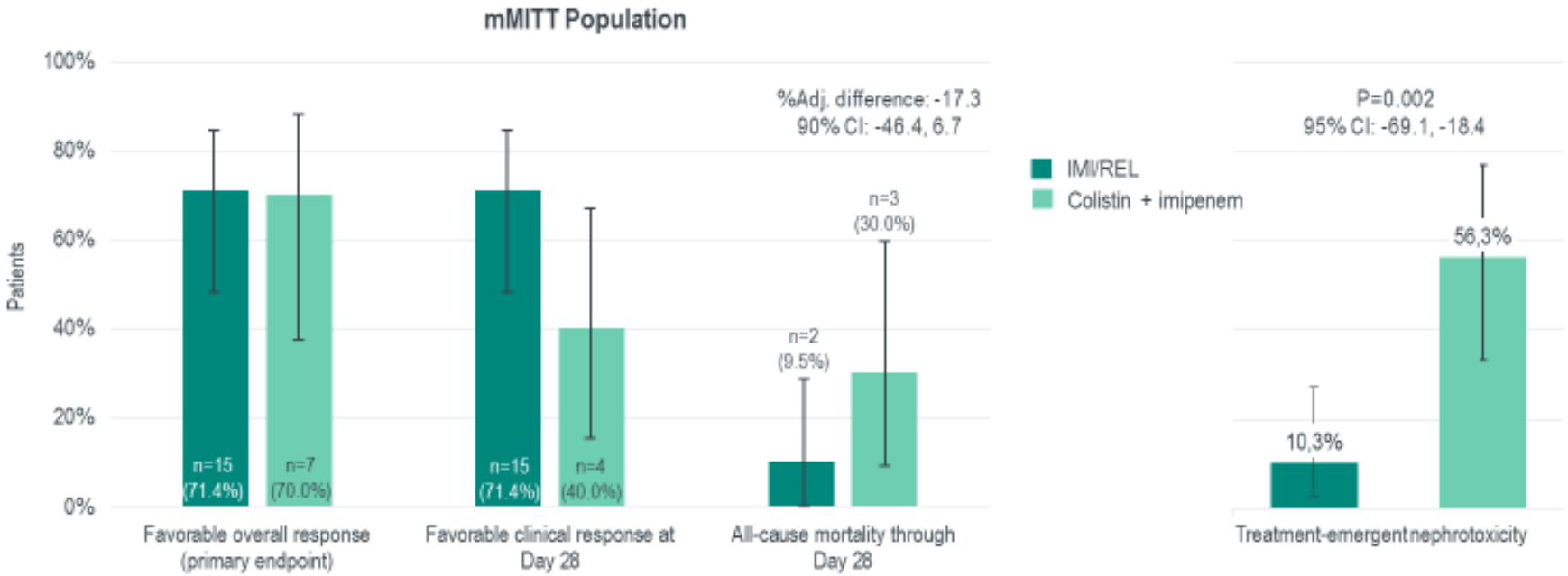
- The distribution of species within qualifying baseline pathogens for the mMITT population was similar in both treatment arms

mMITT Population

	IMI/REL (n=21) n (%)	Colistin + imipenem (n=10) n (%)
All pathogens	21	10
Aerobic gram-negative bacillus	21 (100.0)	10 (100.0)
C. freundii	1 (4.8)	0 (0.0)
E. cloacae	1 (4.8)	0 (0.0)
K. oxytoca	0 (0.0)	1 (10.0)
K. pneumoniae	3 (14.3)	1 (10.0)
P. aeruginosa	16 (76.2)	8 (80.0)

Motsch J, et al. *Clin Infect Dis* 2020;70:1799–808 (RESTORE-IMI-1)

RESTORE-IMI-1: Response to IMI/REL in mMITT Population



Motsch J, et al. *Clin Infect Dis* 2020;70:1799–808 (RESTORE-IMI-1)

Clinical Infectious Diseases
MAJOR ARTICLE

A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety of Imipenem/Cilastatin/Relebactam Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study)

264 imipenem/cilastatin/relebactam and 267 piperacillin/tazobactam;
48.6% had ventilated HABP/VABP, 66.1% were in the ICU.
The most common pathogens were *K. pneumoniae* (25.6%) and *P. aeruginosa* (18.9%).

Table 2. Primary, Key Secondary, and Other Prespecified Secondary Efficacy Endpoints

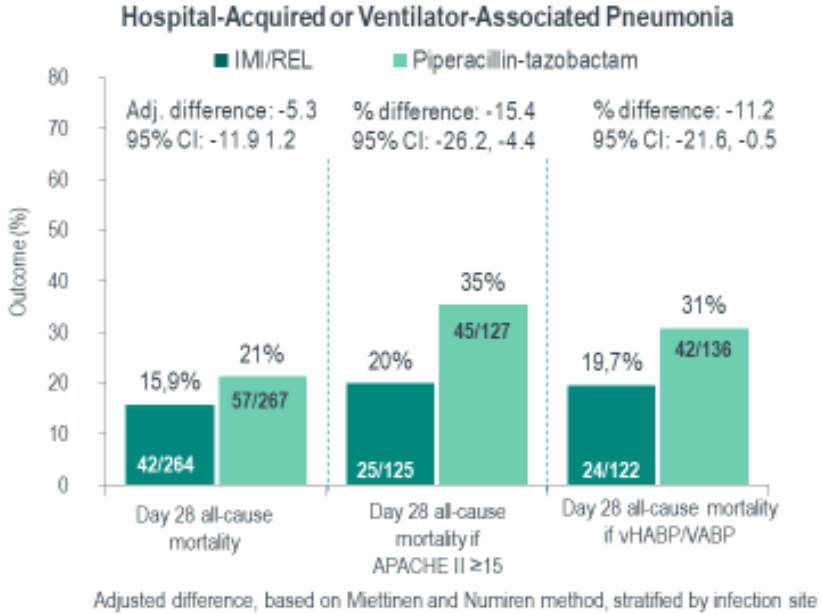
Endpoint	IMI/REL, no./No. (%)[a]	PIP/TAZ, no./No. (%)[a]	Adjusted Difference[b], % (95% CI)
Primary endpoint			
Day 28 all-cause mortality (MITT)	42/264 (15.9)	57/267 (21.3)	−5.3 (−11.9 to 1.2)[c]
Key secondary endpoint			
Favorable clinical response at EFU (MITT)	161/264 (61.0)[d]	149/267 (55.8)[d]	5.0 (−3.2 to 13.2)[e]
Other secondary endpoints			
Day 28 all-cause mortality (mMITT)	36/215 (16.7)	44/218 (20.2)	−3.5 (−10.9 to 3.6)
Favorable microbiologic response at EFU (mMITT)	146/215 (67.9)[d]	135/218 (61.9)[d]	6.2 (−2.7 to 15.0)
Favorable clinical response at EFU (CE)	101/136 (74.3)	100/126 (79.4)	−3.7 (−13.6 to 6.4)

Imipenem/cilastatin/relebactam was noninferior ($P < .001$) to piperacillin/tazobactam for both endpoints: day 28 all-cause mortality and favorable clinical response at early follow-up.

RESTORE-IMI-2: Efficacy of IMI/REL in Hospital-Acquired or Ventilator-Associated Pneumonia

Favorable clinical response at EOT Comparable between treatment arms among clinically relevant subgroups

- Of 537 randomized patients, the mITT population comprised 264 IMI/REL- and 267 piperacillin/tazobactam-treated patients
  - 48.6% had vHABP/VABP, 47.5% APACHE II score ≥15
  - 24.7% moderate/severe RI, 42.9% were ≥65 years old
  - 66.1% were in the intensive care unit
- The most common baseline pathogens were *K. pneumoniae* (25.6%) and *P. aeruginosa* (18.9%)



Adjusted difference, based on Miettinen and Nurminen method, stratified by infection site

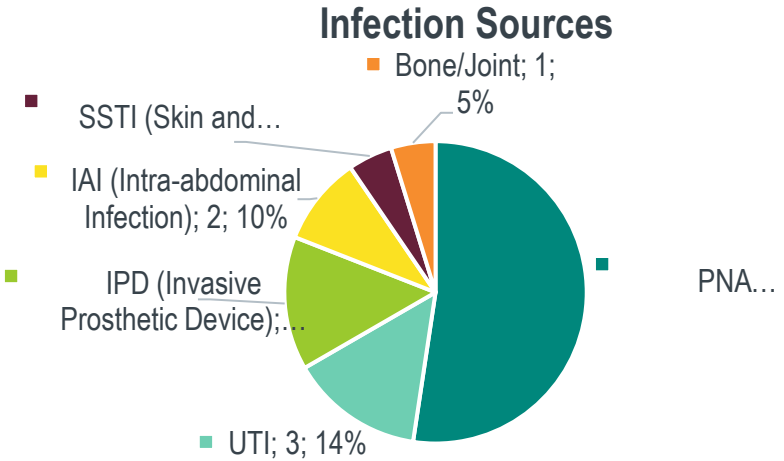
Open Forum Infectious Diseases

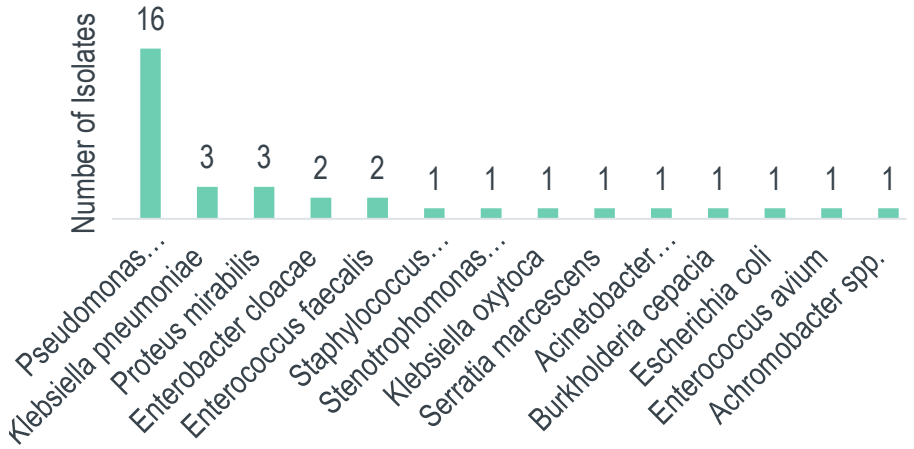
BRIEF REPORT

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

Nicholas Rebold,[1] Taylor Morrisette,[1,2,3] Abdalhamid M. Lagnf,[1] Sara Alosaimy,[1] Dana Holger,[1] Katie Barber,[4,5] Julie Ann Justo,[6,7] Kayla Antosz,[7] Travis J. Carlson,[8] Jeremy J. Frens,[9] Mark Biagi,[10,11] Wesley D. Kufel,[12,13] William J. Moore,[14] Nicholas Mercuro,[15,16] Brian R. Raux,[2] and Michael J. Rybak[1,17,18]

- Multicenter, retrospective, observational case series
- 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.

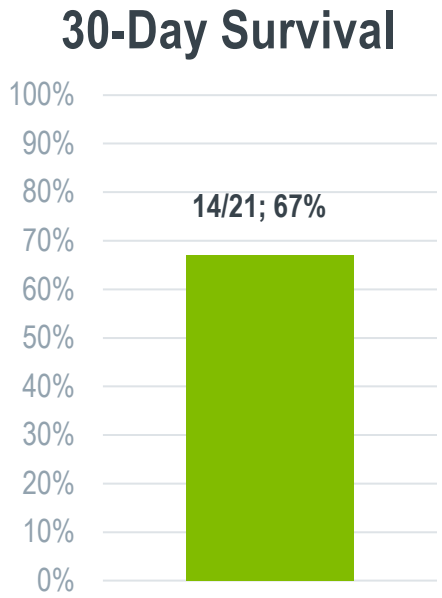


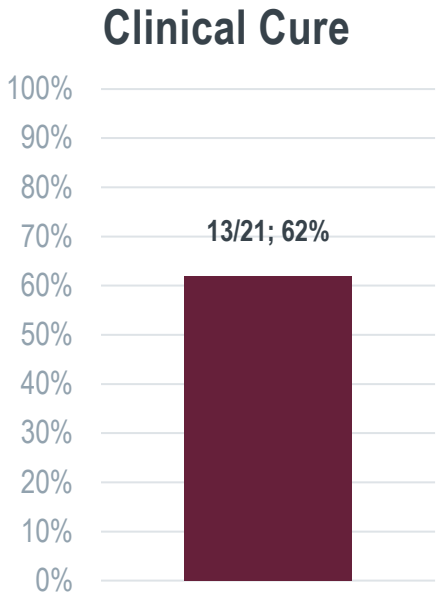


Additional Notes

- Bacteremia occurred in 29% of patients
- 16 PSA – all were meropenem I or R or imipenem R
- All PSA were carbapenem non-susceptible
- 3/8 patients with Enterobacterales had a CRE infection

Results
Primary Endpoints





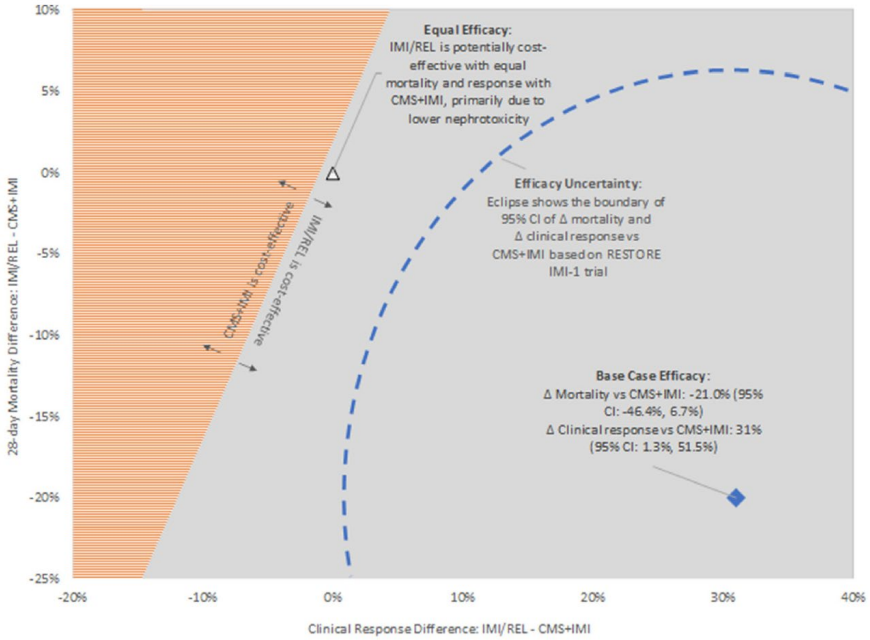
- **30-day microbiological recurrence: 5/21 (24%) patients**
  - 2 recurrent isolates found IMI/REL resistant on MIC testing
- 2 adverse events occurred (neither led to drug discontinuation):
  - Gastrointestinal: Nausea, vomiting, diarrhea
  - Encephalopathic: Altered mental status, somnolence, new onset seizures

Infect Dis Ther
https://doi.org/10.1007/s40121-022-00607-x

ORIGINAL RESEARCH

Cost-Effectiveness of Imipenem/Cilastatin/Relebactam Compared with Colistin in Treatment of Gram-Negative Infections Caused by Carbapenem-Non-Susceptible Organisms

Joe Yang · Jaesh Naik · Matthew Massello · Lewis Ralph · Ryan James Dillon



Why carry out this study?

Carbapenem-non-susceptible (CNS) gram-negative infections (GNIs) continues to grow globally and have very limited treatment options

This study assessed cost and clinical effectiveness of imipenem/cilastatin/relebactam (IMI/REL) in treating confirmed CNS GNIs, compared to colistin plus imipenem (CMS + IMI)

What was learned from the study?

Higher drug acquisition cost for IMI/REL over CMS + IMI may be offset by savings from hospital resource use due to reduced nephrotoxicity risk of IMI/REL

For treatment of confirmed CNS GNIs, IMI/REL could be cost-effective or even cost-saving for the US payers compared to CMS + IMI

MBL ?

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Aztreonam in combination with imipenem-relebactam against clinical and isogenic strains of serine and metallo-β-lactamase-producing enterobacterales

Mark Biagi[a], Michelle Lee[a], Tiffany Wu[a], Aisha Shajee[b], Shitalben Patel[a], Lalitagauri M. Deshpande[c], Rodrigo E. Mendes[c], Eric Wenzler[a,*]

- The objective was to evaluate the in vitro activity of aztreonam plus imipenem-relebactam against strains of Escherichia coli and Klebsiella pneumoniae co-harboring NDM and >1 serine b-lactamase. Thirteen isolates were included
- All isolates were resistant to imipenem and imipenem-relebactam, and 85% were aztreonam-resistant.
- The combination of aztreonam+imipenem was bactericidal and synergistic against 7/13 and 10/13 isolates. The addition of relebactam to this combination resulted in synergy against all 11 aztreonam-resistant clinical isolates.
- Aztreonam plus imipenem-relebactam may be a viable treatment option for aztreonam-non-susceptible NDM and serine b-lactamase-producing E. coli and K. pneumoniae.

Imipenem-relebactam has a strong activity against KPC-producing Enterobacterales and many MDR Pseudomonas.

PK / PD characteristics suggests that imipenem-relebactam may be an important treatment option for both ICU and non-ICU HP, including VAP, caused by Enterobacterales (in regions with a high prevalence of KPCs) and by MDR Pseudomonas.

The activity of imipenem-relebactam would not be expected to differ from that of imipenem alone in the presence of MBL and/or oxacillinase producers.

The activity of imipenem-relebactam against Acinetobacter spp. appears to be similar to that of imipenem alone.