Il ruolo di Ceftolozano/tazobactam e di Imipenem/relebactam nel contrasto all'AMR

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MSD

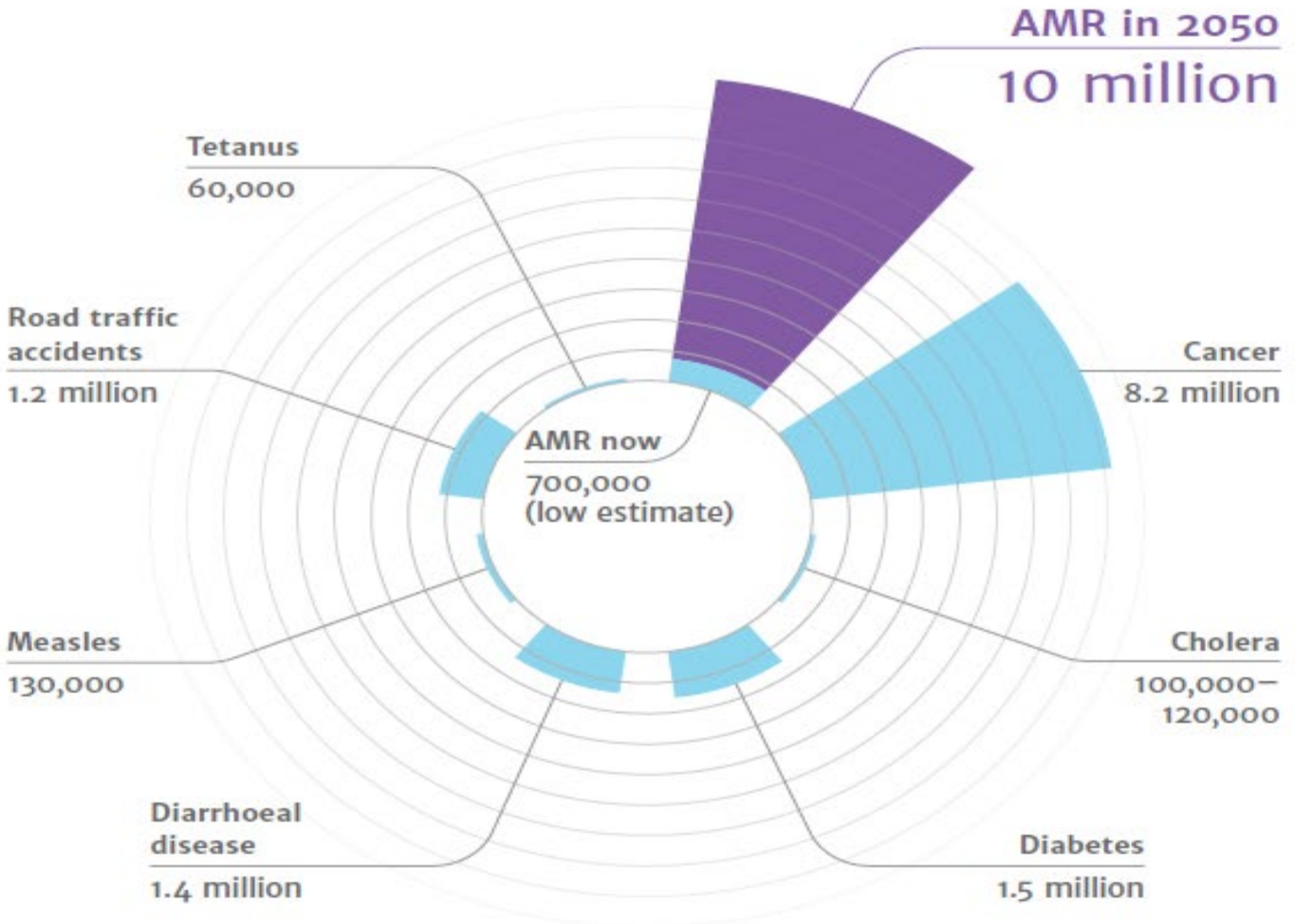
Disclosures
Past 6 years

- **MSD**

AGENDA

- Contesto AMR
- Imipenem/relebactam
- Ceftolozano/tazobactam
- Linee Guida IDSA

La resistenza antimicrobica è una delle principali sfide per la sanità pubblica e sarà la principale causa di morte entro il 2050 [1]

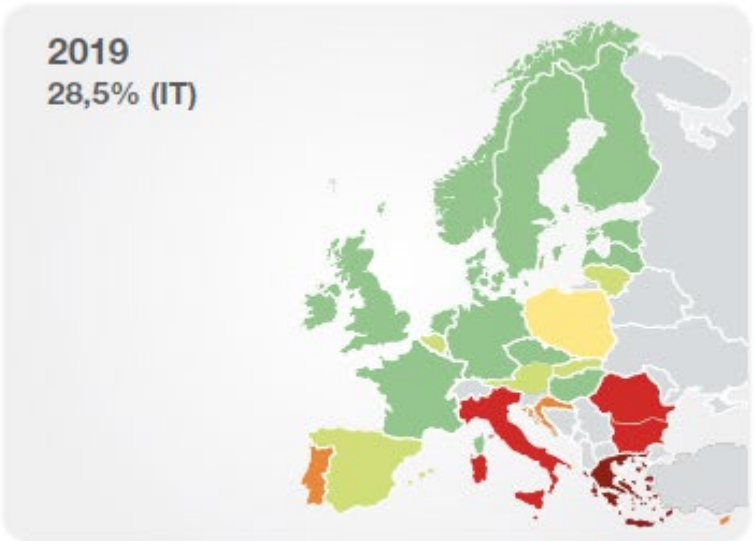


Fonte: Tackling drug-resistant infections globally: final report and recommendations. The review on antimicrobial resistance chaired by Jim O'Neill. May 2016

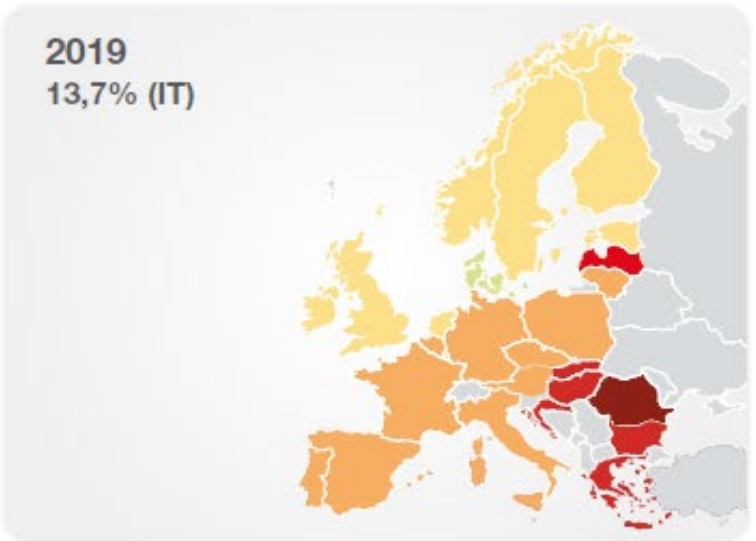
Dagli ultimi dati dell'ECDC, l'Italia si conferma tra i primi Paesi europei con le infezioni sostenute da Enterobacteriaceae produttrici di carbapenemasi (CPE). [4]

- in *K. Pneumoniae*, il tasso di resistenza ai carbapenemi (28,5%) è quasi quattro volte superiore alla media europea (7,3%), in aumento rispetto all'anno precedente;
- il tasso di resistenza dello *P. Aeruginosa* MDR si attesta attorno al 14%, in diminuzione rispetto agli anni precedenti.

Inoltre, la resistenza ai carbapenemi insorge spesso in ceppi già resistenti ad altre classi di antibiotici, rendendo quindi ancora più limitate le opzioni terapeutiche disponibili. Questo quadro evidenzia la necessità di nuove opzioni terapeutiche per il trattamento delle infezioni sostenute da questi patogeni che restano ad oggi un importante causa del prolungamento della degenza ospedaliera e del conseguente e significativo incremento dei costi correlati.



KLEBSIELLA PNEUMONIAE
CARBAPENEMS RESISTANT

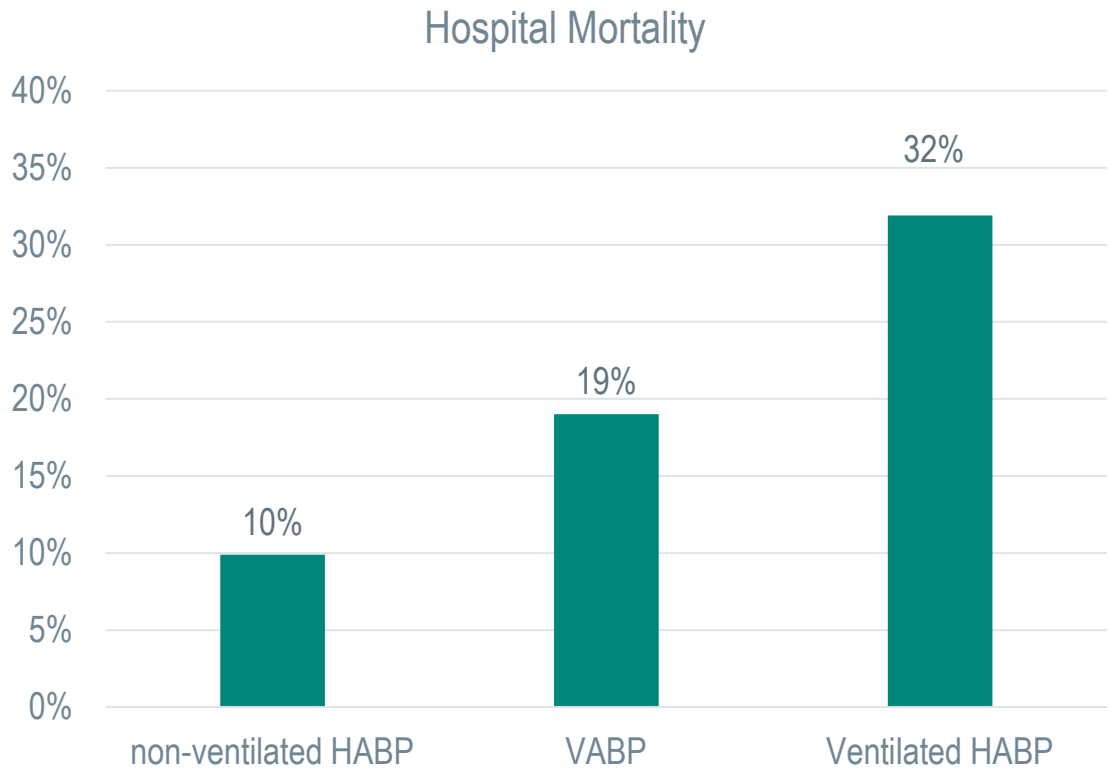


PSEUDOMONAS AERUGINOSA
CARBAPENEMS RESISTANT

http://atlas.ecdc.europa.eu/public/index.aspx

Difference in All Cause Mortality in VAP and Ventilated HAP

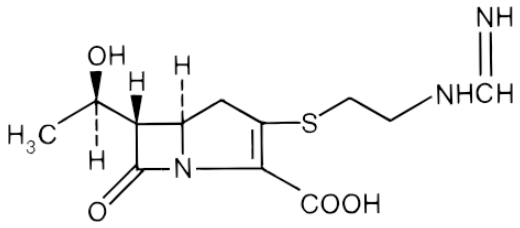
- FDA analysis of 4 trials submitted after the 2014 guidance for HABP/VABP
- Trials focused on treatment of gram-negative organisms
- Hospital mortality was highest among patients with ventilated HABP and lowest in non-ventilated HABP



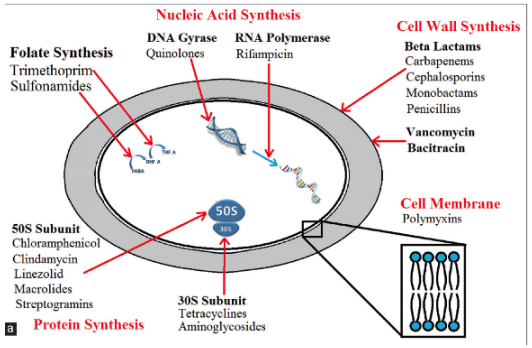
ICU = intensive care unit; HABP = hospital-acquired bacterial pneumonia; VABP = ventilator associated bacterial pneumonia

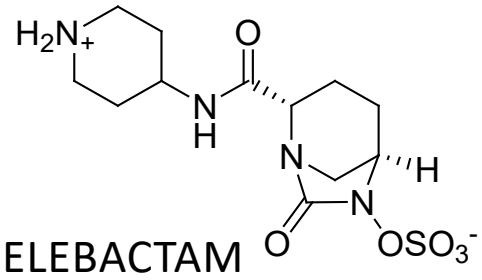
Bart SM et al. Clin Infect Dis 2021;73(3):e602–8

Imipenem-Relebactam

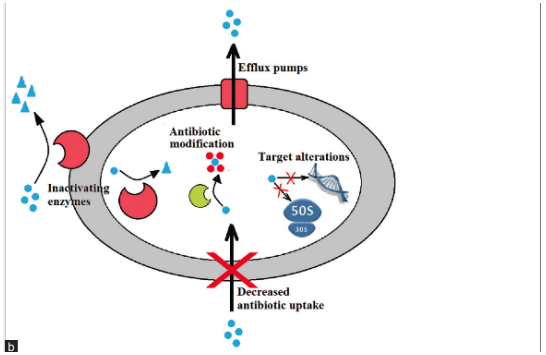


IMIPENEM





RELEBACTAM



Well established carbapenem with broad Gram-negative, Gram-positive and anaerobic activity, including ESBLs

Bactericidal

Inhibits cell-wall synthesis (by inactivating essential penicillin-binding proteins [PBPs])

Not subject to efflux in organisms with up-regulated efflux pumps as a mechanism of resistance

Novel β-lactamase inhibitor

Inhibits Ambler Class A (e.g., KPC) and class C β-lactamases (e.g., AmpC)

Enhances activity of imipenem against Enterobacteriaceae and Pseudomonas aeruginosa

No activity against metallo-beta-lactamases (MBLs)

DEVELOPED AS FIXED-DOSE COMBINATION (2:1) WITH INTENDED ADULT DOSE OF 500 MG IMIPENEM / 250 MG RELEBACTAM Q6H, **INFUSED OVER 30 MINUTES**
UNDER REVIEW IN US (CUTI & CIAI CASED BY SUSCEPTIBLE GRAM-NEGATIVES WITH LIMITED OR NO ALTERNATIVES)
AND EU (BACTERIAL INFECTIONS DUE TO GRAM-NEGATIVE ORGANISMS IN ADULTS WITH LIMITED TREATMENT OPTIONS)

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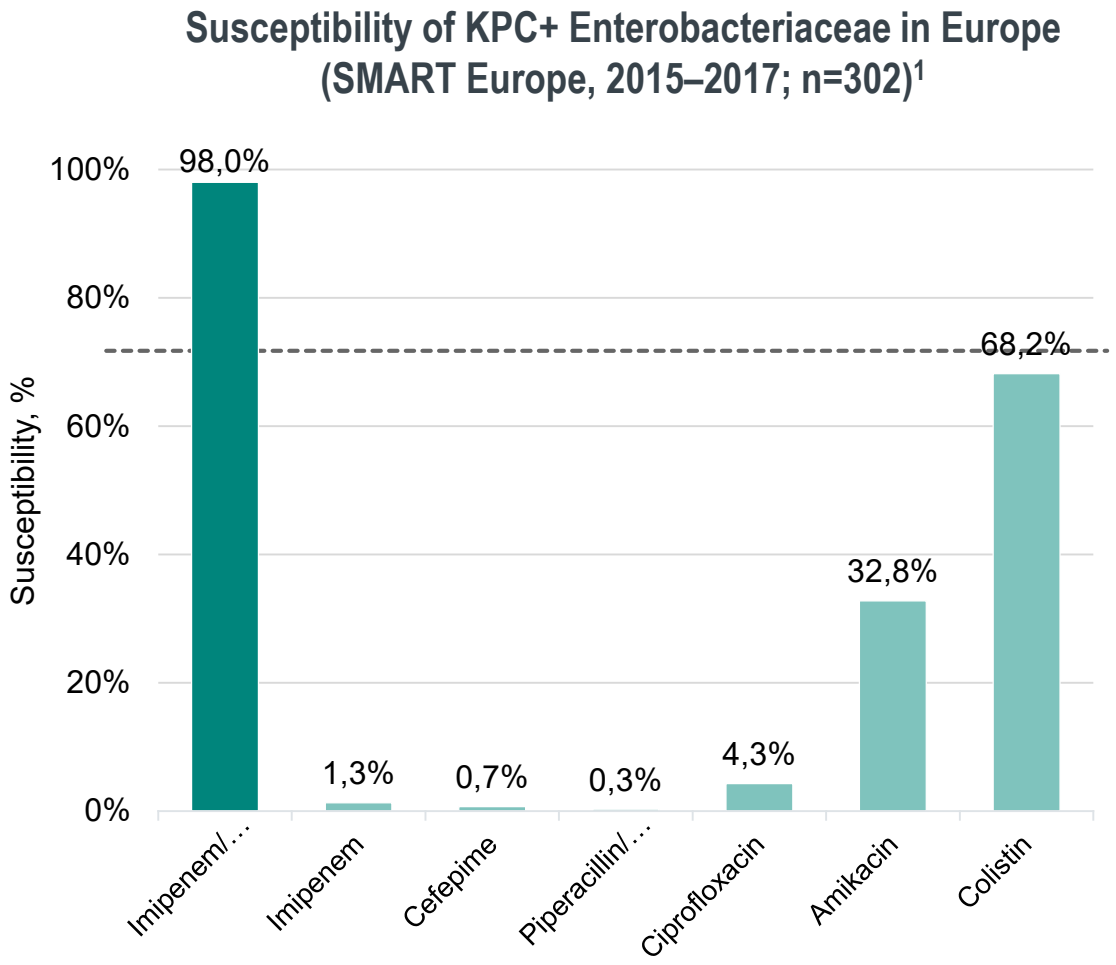
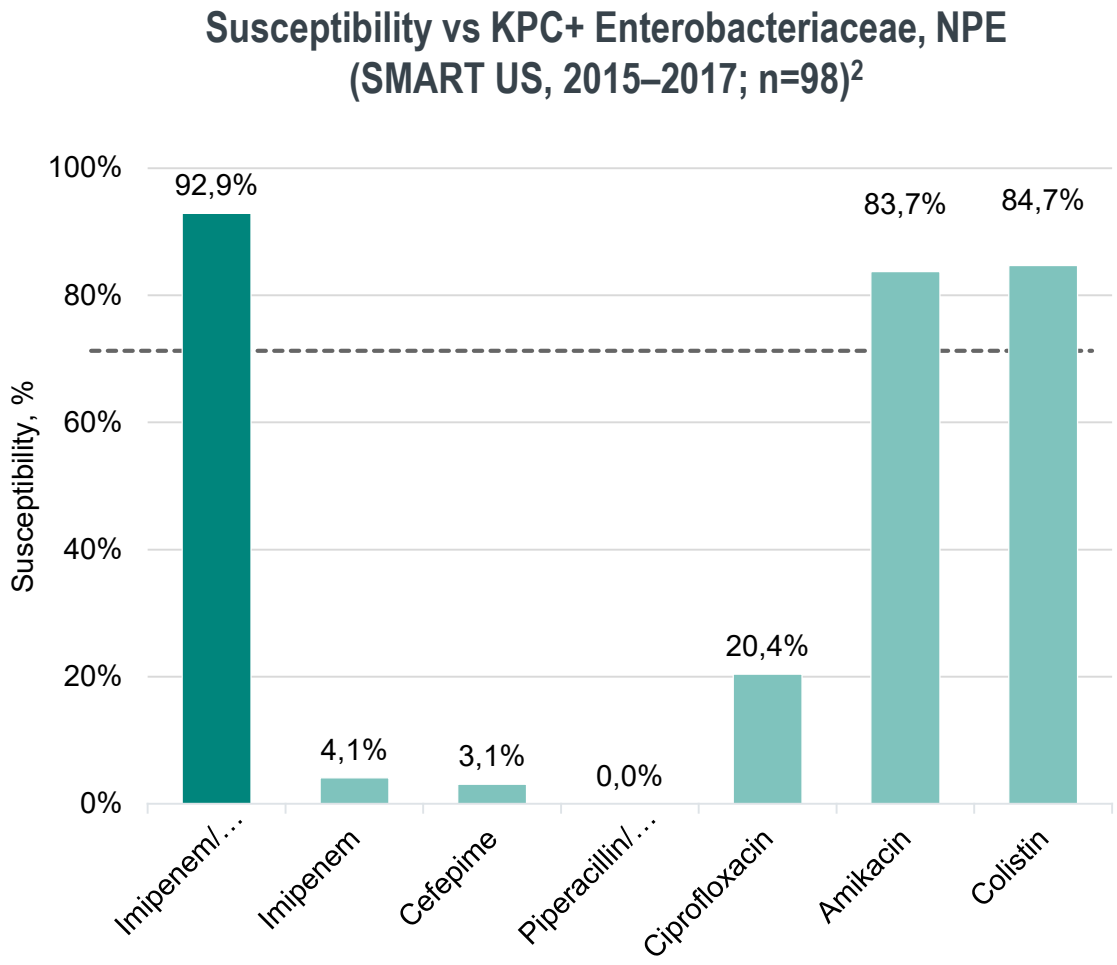
Imipenem-relebactam Has Potent Activity Against KPCs





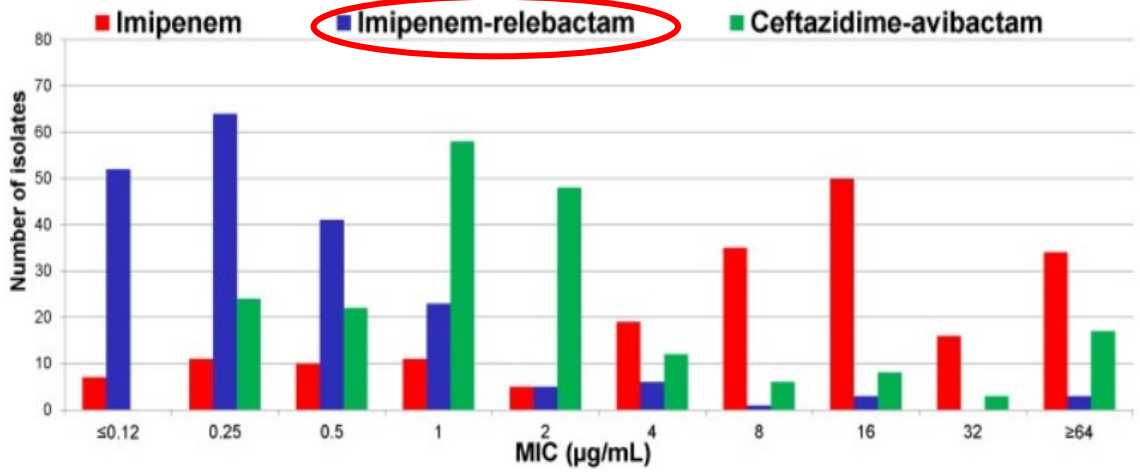
KPC = *Klebsiella pneumoniae* carbapenemase.

1. Lob S et al. Presented at ECCMID Annual Meeting; April 13–16, 2019; Amsterdam, Netherlands. Abstract P1161. **2.** Lob S et al. Presented at ASM Microbe Annual Meeting; June 8–10, 2018; Atlanta, GA. Abstract 650.

In vitro Activity in Isolates Resistant to Existing Agents

- IMI/REL demonstrated potent *in vitro* activity against diverse CRE, including CZA-resistant isolates
- IMI/REL MICs are higher against clinical KPC-Kp with *ompK36* mutations, which also arose during passage experiments
- Selection for IMI/REL resistance against KPC-Kp may occur at lower frequencies than CZA
- In another study, IMI/REL exhibited activity against known (D179N) and emerging (D179Y) variants of KPC-2 conferring resistance to marketed agents CZA and IMI

Figure 1. Comparison of imipenem, imipenem-relebactam, and ceftazidime-avibactam MICs



B) MICs (mg/L) for *E. coli* strains expressing selected KPC-2 D179 variants.

Strain	IMI	IMI/REL	CAZ	CZA
E. coli DH10B	0.5	0.25	0.5	0.25
E. coli DH10B pBR322 bla_{KPC-2}	8	0.5	64	1
E. coli DH10B pBR322 $bla_{KPC-2\ D179N}$	4	0.5	512	16
E. coli DH10B pBR322 $bla_{KPC-2\ D179Y}$	0.5	0.5	512	64

Kline E, Jones C, Mettus R et al. O0287 presented at ECCMID. Amsterdam, Netherlands. April 13-16, 2019
Barnes M, Rutter J, Papp-Wallace K et al. O0284 presented at ECCMID. Amsterdam, Netherlands. April 13-16, 2019

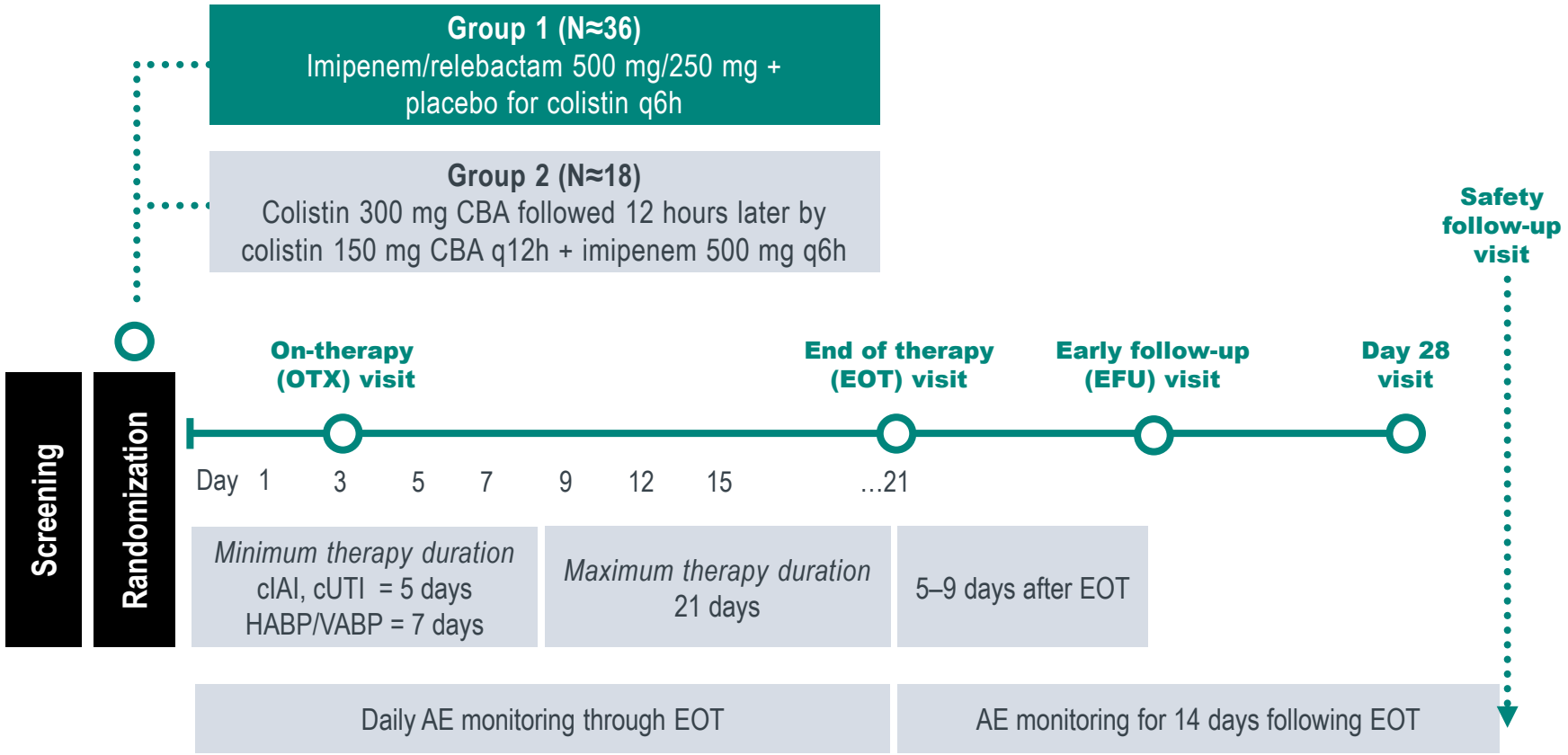
Imipenem-Relebactam Among *P. aeruginosa*

Clinical isolates from 11 Queens and Brooklyn hospitals, but not tested at the same time
Carbapenems tested at 2-fold dilutions, with 4 µg/ml relebactam

	$MIC_{50/90}$ µg/mL	
Organism (n)	**Imipenem**	**IMI + REL (REL 4 µg/ml)**
K. pneumoniae KPC (n=111)	16/>16	0.25/1
***P. aeruginosa* IMI-R (n=144)**	**8/>16**	**1/2**

Lapuebla et al. AAC 2015 59; 4856
Lapuebla et al. AAC 2015 59: 5029

Phase 3 Non-Inferential Study (RESTORE-IMI 1): Study Design
Imipenem/relebactam vs. Colistin + Imipenem in Patients With Imipenem-resistant HABP/VABP, cIAI, and cUTI[1]



Primary efficacy end point
- Overall response, based on:
  - Survival (all-cause mortality) through day 28 postrandomization (HABP/VABP)
  - Clinical response at day 28 postrandomization (cIAI)
  - Composite clinical and microbiological response at EFU at days 5–9 following completion of therapy (cUTI)

Secondary efficacy end points
- Clinical response at 28 days following initiation of IV study therapy
- All-cause mortality through day 28 postrandomization
- Safety

Study Limitations
- This was a non-inferential, descriptive, estimation trial without formal statistical testing for efficacy endpoints. The trial had several limitations, including the small sample size.
- The trial was intended to generate limited clinical data in a target population as part of a streamlined drug development program. Sample size was based on logistical feasibility and not statistical considerations.

AE = adverse event; cIAI = complicated intra-abdominal infection; CBA = colistin base activity; cUTI = complicated urinary tract infection; EFU = early follow-up; EOT = end of therapy; HABP/VABP = hospital-acquired/ventilator-associated pneumonia; IV = intravenous; OTX = on-therapy; q6h = every 6 hours; q12h = every 12 hours.

1. Motsch J et al. *Clin Infect Dis*. 2019.

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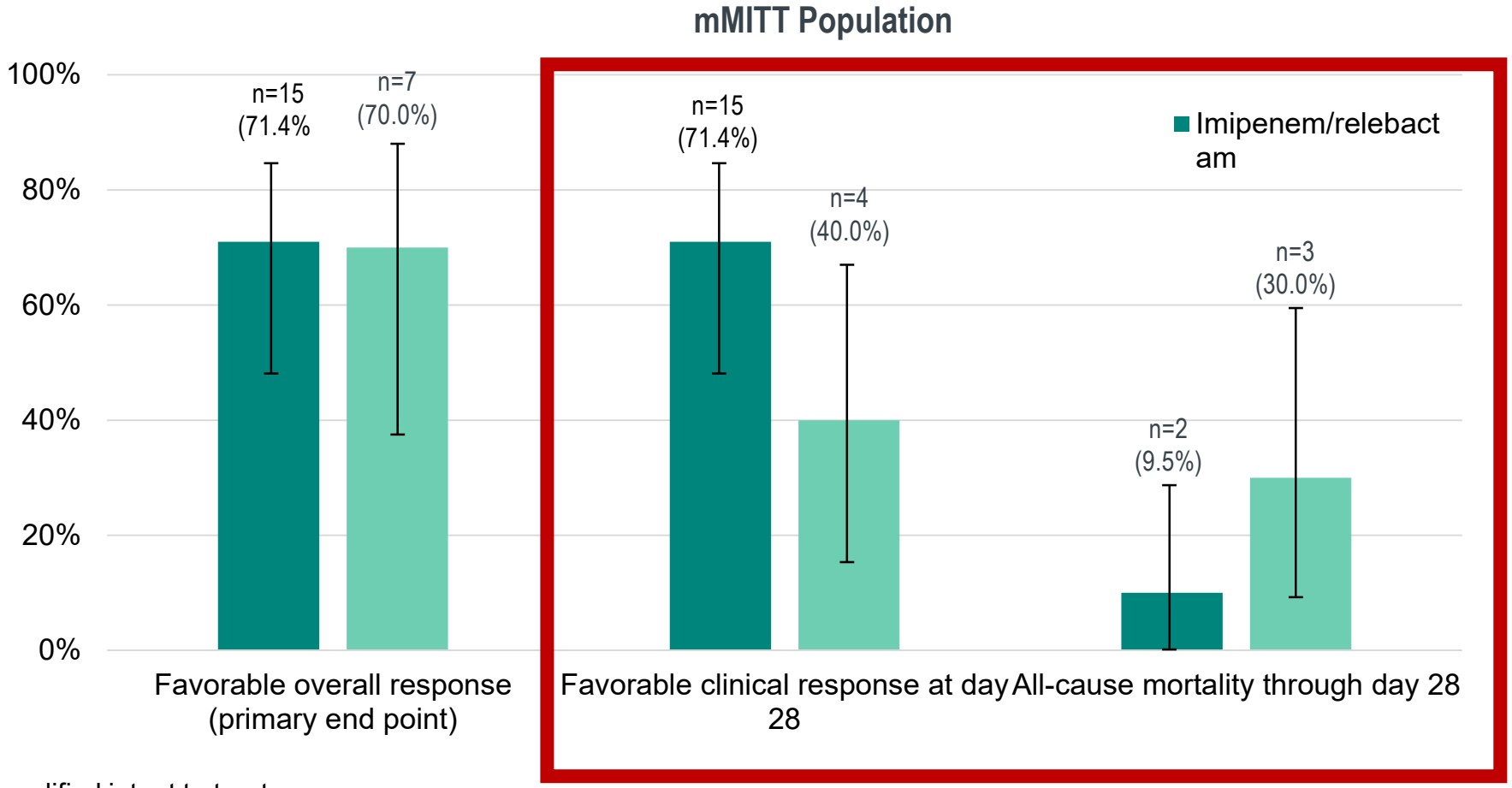
Phase 3 Study (RESTORE-IMI 1): Favorable Response to Imipenem/relebactam in the mMITT Population[1]

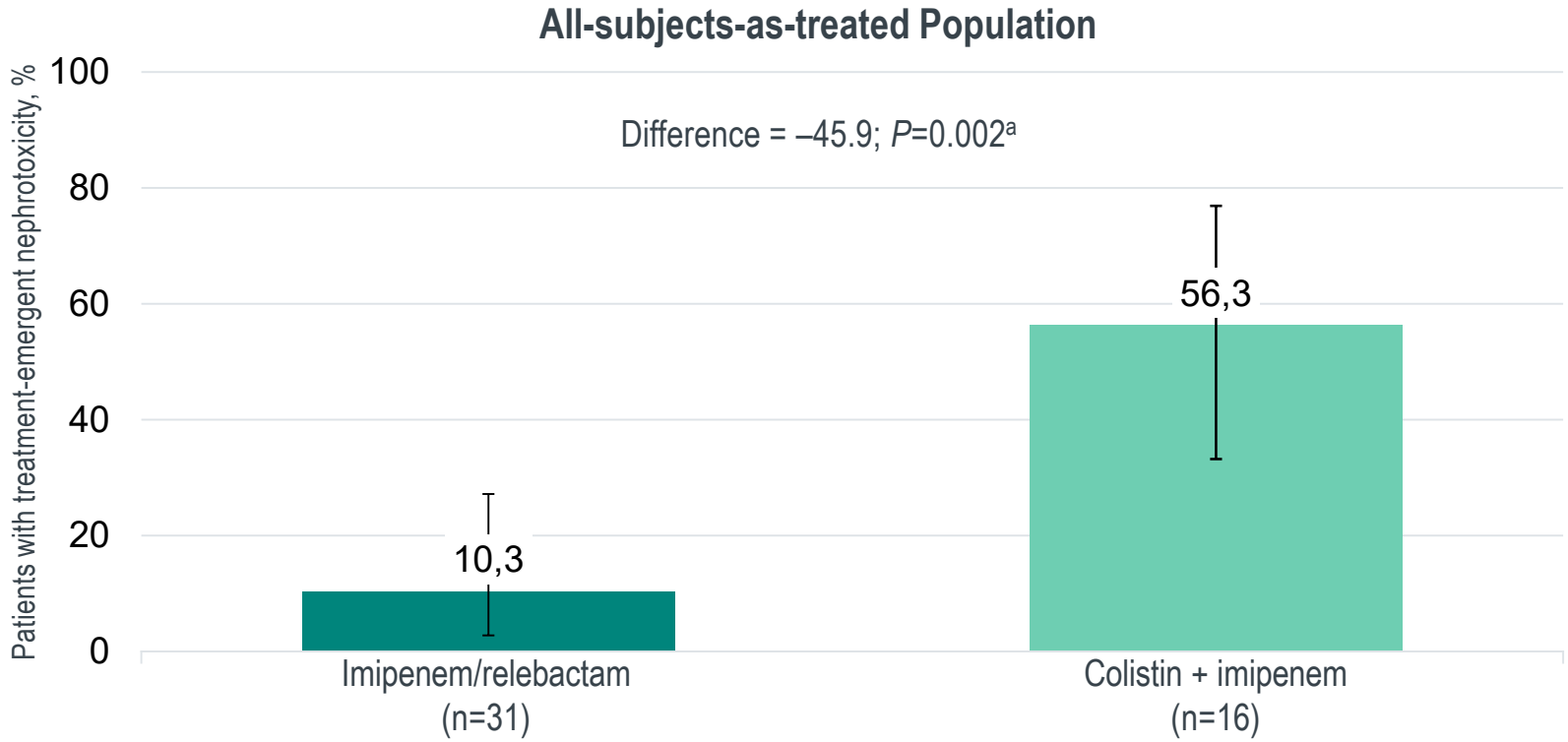


mMITT = microbiological modified intent to treat.

1. Motsch J et al. *Clin Infect Dis*. 2019 Aug 10. pii: ciz530. doi: 10.1093/cid/ciz530. [Epub ahead of print].

Phase 3 Study (RESTORE-IMI 1): Treatment-emergent Nephrotoxicity[1]

A smaller percentage of patients receiving imipenem/relebactam experienced treatment-emergent nephrotoxicity than with colistin + imipenem (*P*=0.002) during on-study treatment and the 14-day follow-up period



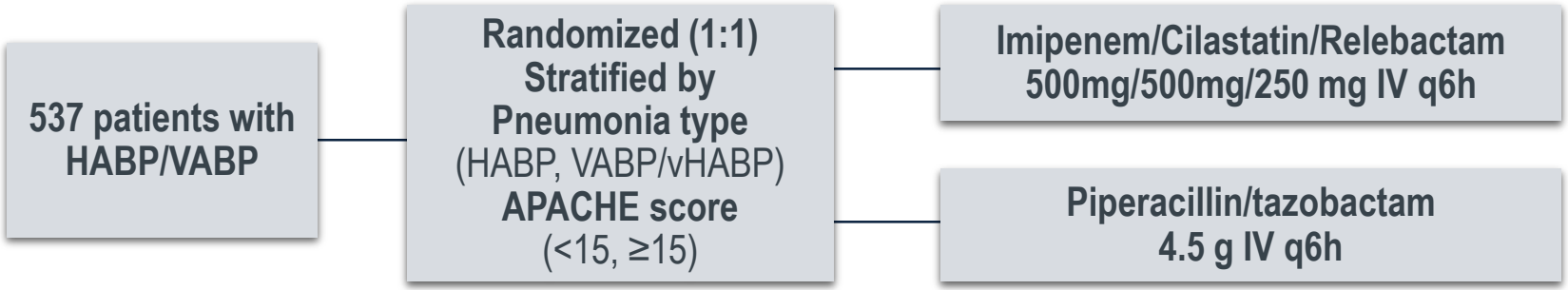
[a]*P* value is based on Fisher's Exact Test

1. Motsch J et al. *Clin Infect Dis*. 2019 Aug 10. pii: ciz530. doi: 10.1093/cid/ciz530. [Epub ahead of print].

RESTORE-IMI-2: Study Design

Hospital-Acquired Bacterial Pneumonia (HABP) or Ventilator-Associated Bacterial Pneumonia (VABP)

Phase 3, randomized, controlled, double-blind, multicenter trial in adult patients with HABP or VABP



Duration of treatment: 7-14 days* of IV study drug (no oral switch)

Adjunctive Therapy

- Linezolid 600 mg IV 1 h infusion, q12h was required for all patients until baseline LRT cultures confirmed absence of MRSA

Primary & Key Secondary Endpoints & Assumptions

	Primary Endpoint	Primary Population	NI Margin	Anticipated Outcome	Power
Primary	**Day 28 all-cause mortality**	**MITT**	**10% (95 CI)**	**15%**	**90%**
Key Secondary	**Clinical Response at Early Follow Up (EFU) visit**	**MITT**	**12.5% (95 CI)**	**60%**	**84%**

*Participants with evidence of concurrent bacteremia or with P. aeruginosa infection were to receive 14 days of IV trial treatment

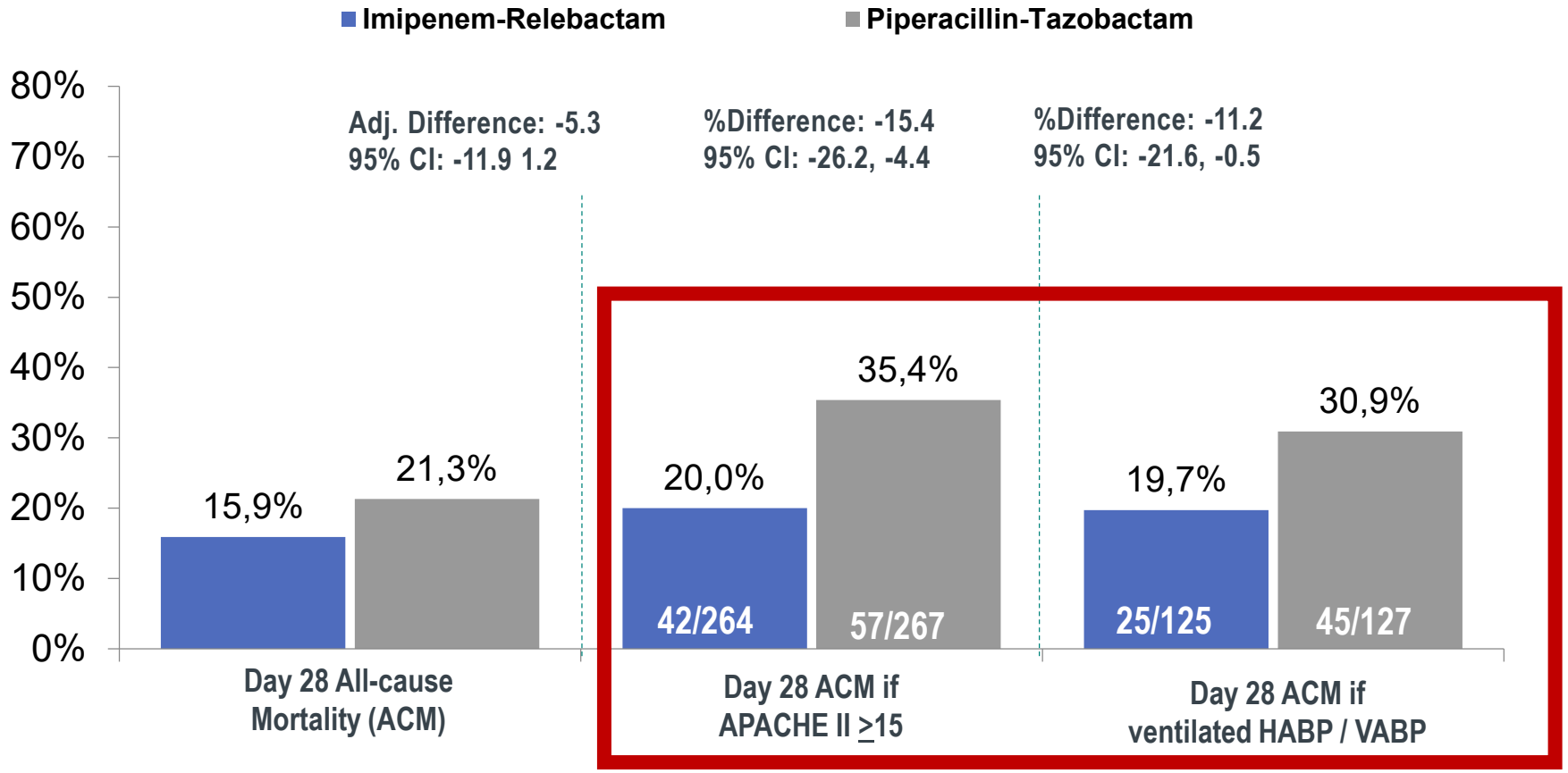
HABP=hospital-acquired bacterial pneumonia; VABP=ventilator-associated bacterial pneumonia; vHABP=ventilated hospital-acquired bacterial pneumonia; NI = non-inferior; CI = confidence interval

Dose adjustments were made based on renal function; all infusions were IV over 30 minutes

Imipenem/Relebactam Phase 3 Data Summary in High-Risk Patients: High Risk Due to Resistance & High Risk of Mortality

RESTORE-IMI-2:

Hospital-Acquired or Ventilator-Associated Pneumonia



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

Titov I et al. Clin Infect Dis 2020 [Online ahead of print]

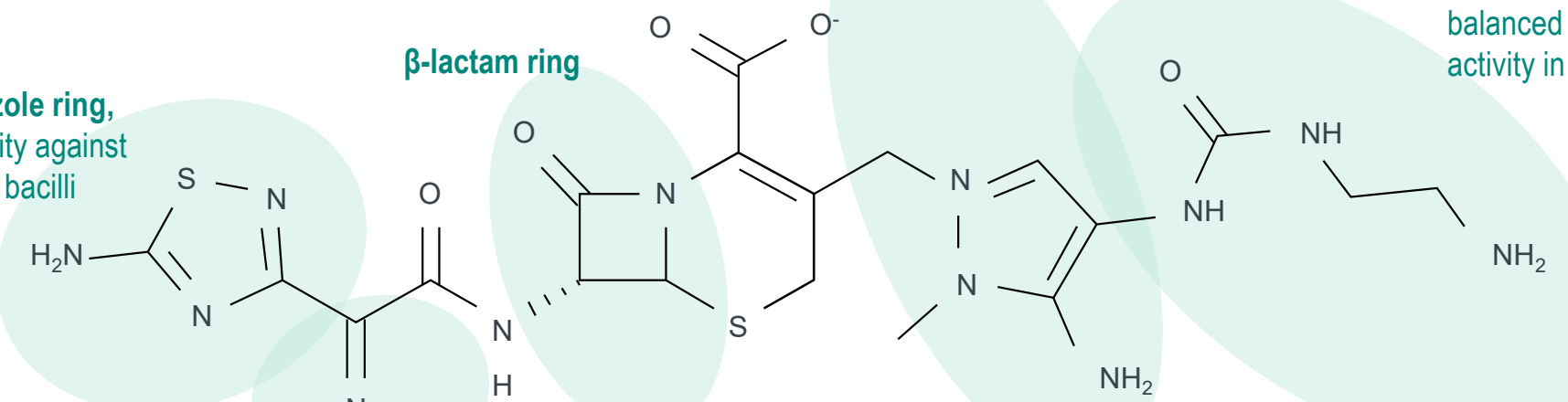
Ceftolozane Is an Antipseudomonal Cephalosporin Designed to be Stable Against Common *P. aeruginosa* Resistance Mechanisms, Like AmpC Production[1–3]

Pyrazole ring, provides steric hindrance preventing ceftolozane from entering active site of AmpC

2-aminoethylureido group, balanced to exhibit optimal AmpC activity in *P. aeruginosa*

β-lactam ring

Aminothiadiazole ring, enhances activity against Gram-negative bacilli



Oxime, confers β-lactamase stability

2-methylpyrazole group, shown to have the best activity against *P. aeruginosa*

Dimethylacetic acid moiety, enhances antipseudomonal activity

P. aeruginosa = *Pseudomonas aeruginosa*.

1. Murano K et al. *Bioorg Med Chem.* 2008;16(5):2261–2275. **2.** van Duin D et al. *Clin Infect Dis.* 2016;63(2):234–241. **3.** Xipell M et al. *Int J Antimicrob Agents.* 2017;49(2):266–268.

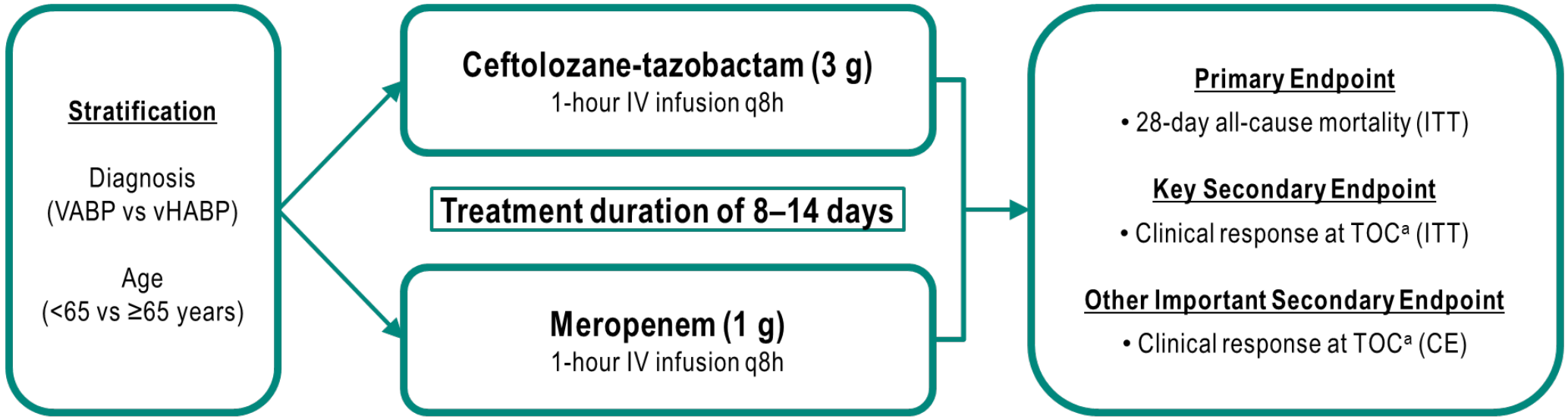
- Stable against common *P. aeruginosa* resistance mechanisms, including loss of outer membrane porin (OprD), Chromosomal AmpC, and up-regulation of efflux pumps (MexXY, MexAB)[1]
- Isolates resistant to other cephalosporins may be susceptible, although cross-resistance may occur[2]

Resistance Mechanisms	OprD Loss	β-lactamase Enzyme	Efflux Pump	Efflux Pump
	OprD	AmpC	MexXY	MexAB
Ceftolozane*	●	●	●	●
Ceftazidime**	◐	○	●	○
Cefepime	●	○	○	○
Piperacillin/tazobactam	●	○	●	○
Imipenem	○	●	●	●
Meropenem	◐	●	○	◐

○ Activity greatly decreased >> ● Retains activity

Lapuebla et al. AAC 2015 59: 5029
Castanheira M, et al. Antimicrob Agents Chemother 2014;58:6844–6850. 2. ZERBAXA™ [prescribing information]
2015. Whitehouse Station, NJ: Merck Sharp & Dohme., a subsidiary of Merck & Co., Inc.

ASPECT-NP Study Design



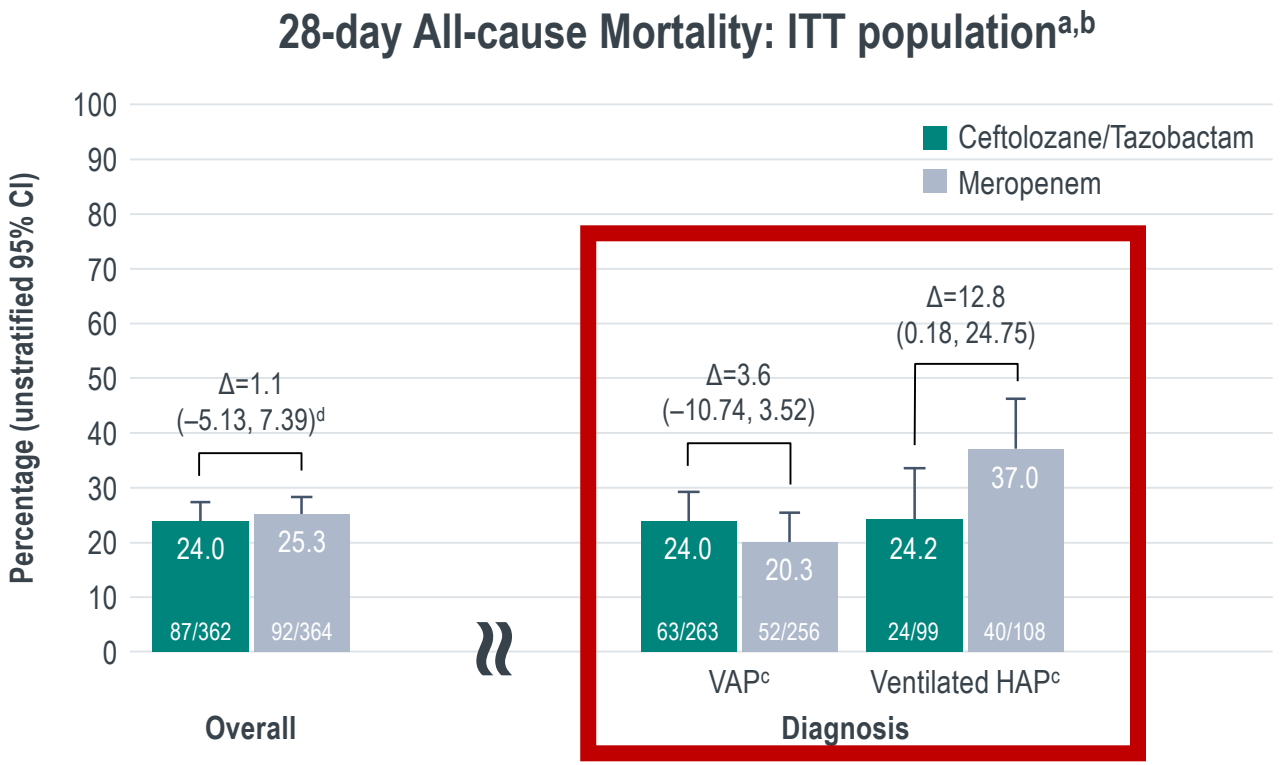
- Ceftolozane-tazobactam and meropenem doses were reduced for patients with CrCL ≤50 mL/min. Patients with ARC received the same dose (3 g ceftolozane-tazobactam [2 g ceftolozane and 1 g tazobactam] or 1 g meropenem) as patients with normal renal function
- Adjunctive gram-positive therapy with linezolid was required for all patients until baseline lower respiratory tract cultures confirmed absence of *Staphylococcus aureus*
- Adjunctive gram-negative therapy with amikacin was permitted for the first 72 hours at study sites with ≥15% meropenem-resistant *Pseudomonas aeruginosa*
- Plasma pharmacokinetic data was collected from all patients enrolled in the ASPECT-NP trial

CE, clinically evaluable; ITT, intention-to-treat; IV, intravenous; q8h, every 8 hours; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia; vHABP, ventilated hospital-acquired bacterial pneumonia.
[a]TOC was defined as 7 to 14 days after the end of therapy.

Kollef, Marin H., et al. "Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial." *The Lancet Infectious Diseases* (2019

ASPECT-NP: 28-day All-cause Mortality in Patients With Ventilated HAP (vHAP) and VAP[1]

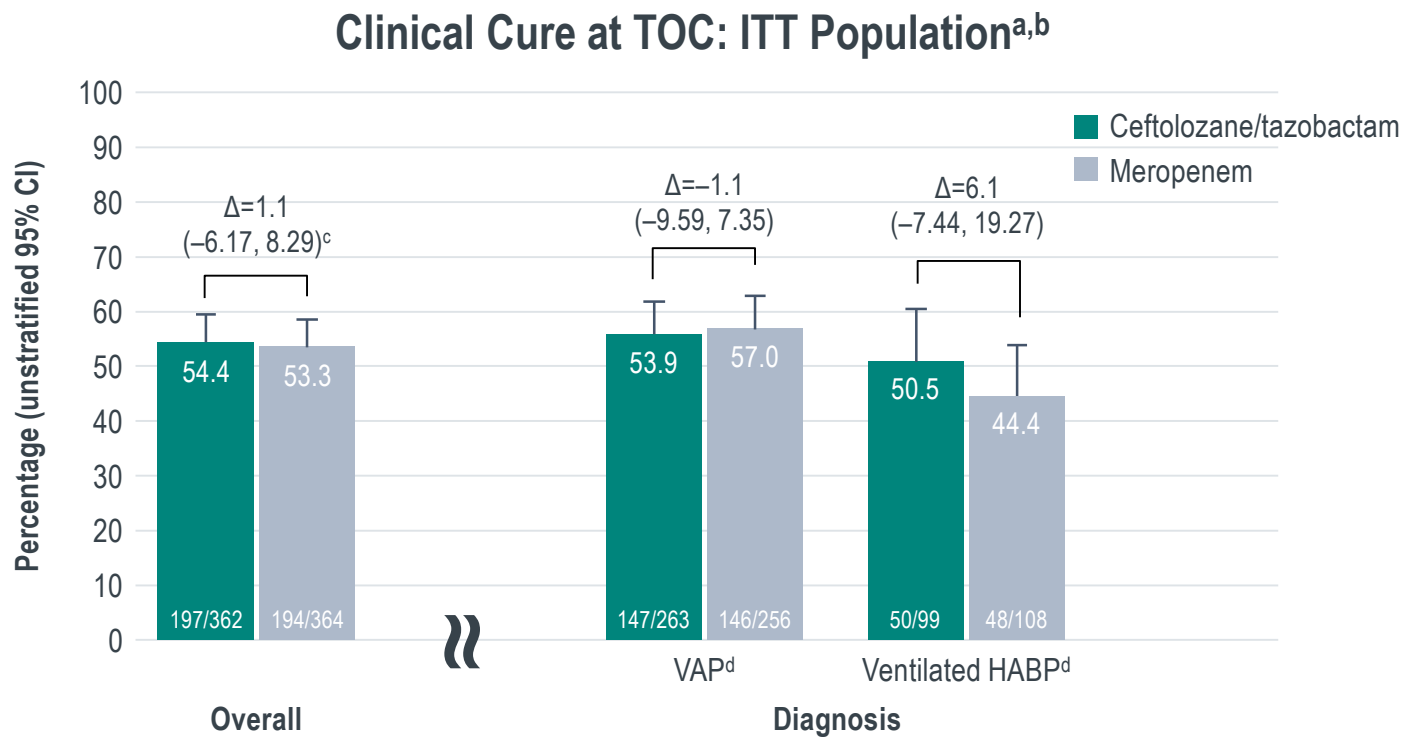
- Met prespecified noninferiority criterion for primary end point in ITT population
  - In ventilated HABP, there was a favorable response as the mortality rate was approximately 13% lower with ceftolozane/tazobactam.
    - The 95% CI of between-group difference did not cross zero
  - In VABP, mortality rates were comparable between study arms
- Mortality rates in key ITT subgroups were comparable between treatments



[a]Positive differences are in favor of ceftolozane/tazobactam; negative differences are in favor of meropenem. [b]Weighted proportion difference stratified by diagnosis (VABP, ventilated HABP), with stratified Newcombe CIs. [c]Unstratified Newcombe CIs. [d]Stratified 95% CI.
ASPECT = Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam; CI = confidence interval; HABP = hospital-acquired bacterial pneumonia; ITT = intent-to-treat. NP = nosocomial pneumonia; VABP = ventilator-associated bacterial pneumonia.

1. Kollef M et al. *Lancet Infect Dis.* 2019;19(12):1299-1311.

ASPECT-NP: Clinical Cure at TOC in Patients With Ventilated HAP (vHAP) and VAP[1]



- Ceftolozane/tazobactam was noninferior to meropenem for clinical cure at TOC in the ITT population, including key subgroups

[a]Positive differences are in favor of ceftolozane/tazobactam; negative differences are in favor of meropenem. [b]Weighted proportion difference stratified by diagnosis (VAP, ventilated HAP) and age (<65 years, ≥65 years), with stratified Newcombe CIs. [c]Stratified 95% CI. [d]Unstratified Newcombe CIs.
ASPECT = Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam; CI = confidence interval; HABP = hospital-acquired bacterial pneumonia; ITT = intent-to-treat. NP = nosocomial pneumonia; TOC = test of cure;
VABP = ventilator-associated bacterial pneumonia.

1. Kollef M et al. *Lancet Infect Dis*. 2019;19(12):1299-1311.

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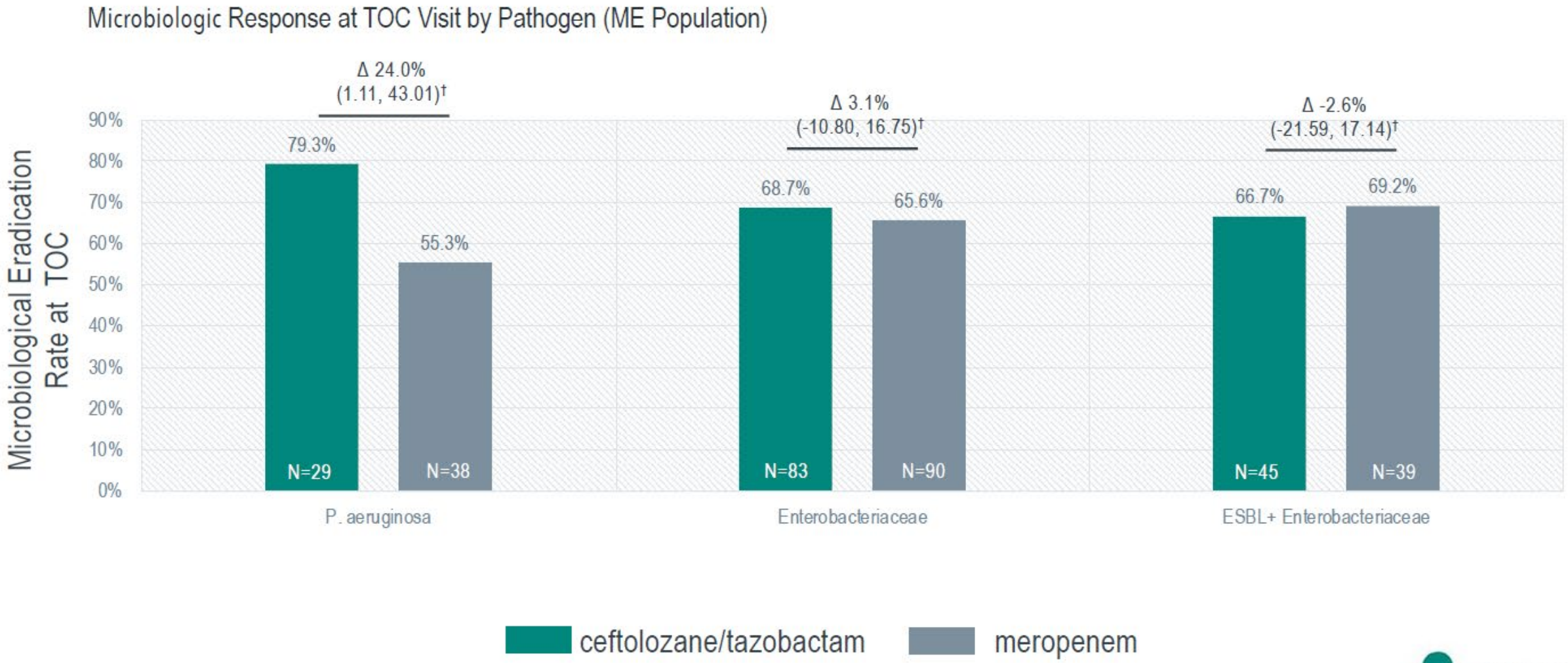
Per-Pathogen Microbiologic Response at Test of Cure (TOC)



† Stratified 95% CI

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INVENTING FOR LIF

ASPECT-NP: Safety Profile in Patients With Ventilated HAP (vHAP) and VAP

- Incidence of AEs was generally similar across treatment groups
- Treatment Relevant Adverse Events leading to discontinuation were rare

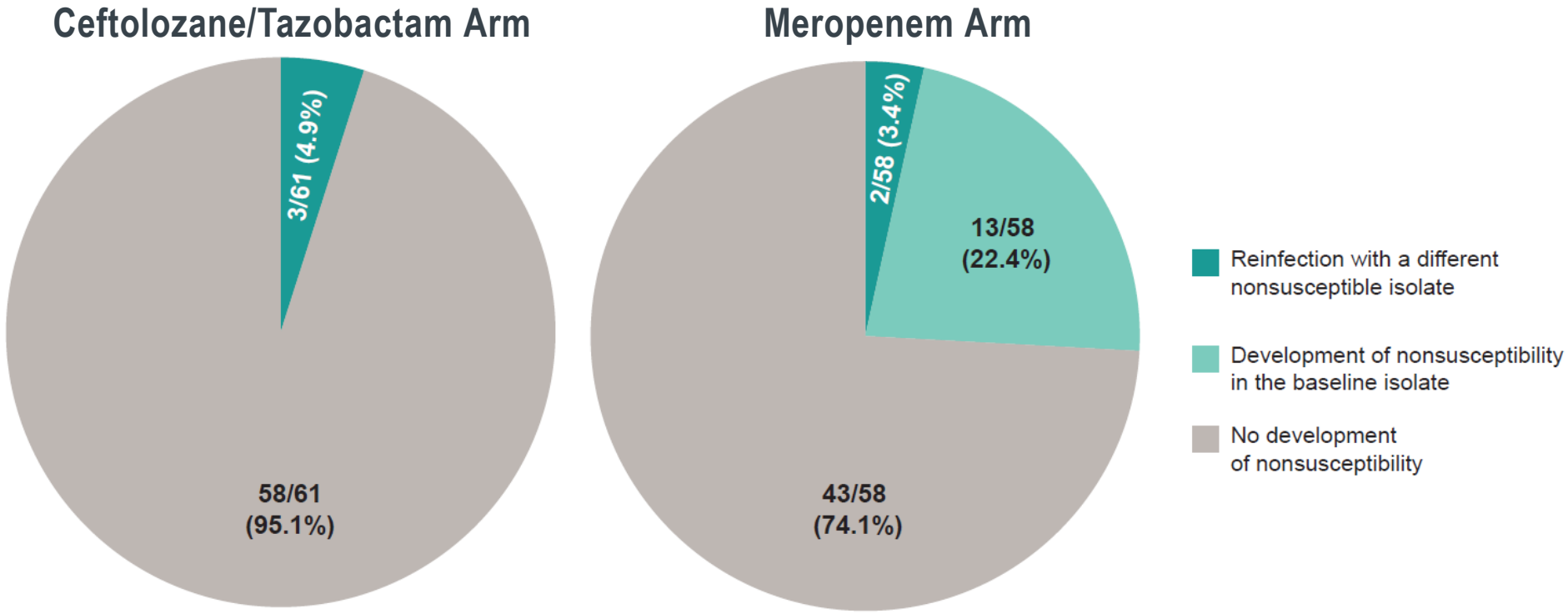
Summary of AEs in the Safety Population

AE category, n (%)	Ceftolozane/tazobactam N=361	Meropenem N=359
≥1 AE	310 (85.9)	299 (83.3)
Severe	143 (39.6)	136 (37.9)
Serious	152 (42.1)	129 (35.9)
Leading to discontinuation	37 (10.2)	42 (11.7)
Resulting in death	105 (29.1)	101 (28.1)
≥1 TRAE	38 (10.5)	27 (7.5)
Severe	5 (1.4)	3 (0.8)
Serious	8 (2.2)	2 (0.6)
Leading to discontinuation	4 (1.1)	5 (1.4)
Resulting in death	0	0

AE = adverse event [illegible] P = ventilator-associated bacterial pneumonia.

1. Kollef M et al. *Lancet Infect Dis*. 2019;19(12):1299-1311.

ASPECT-NP Sub Analysis: Emergence of Nonsusceptibility in Baseline *P aeruginosa* Lower Respiratory Tract Isolates

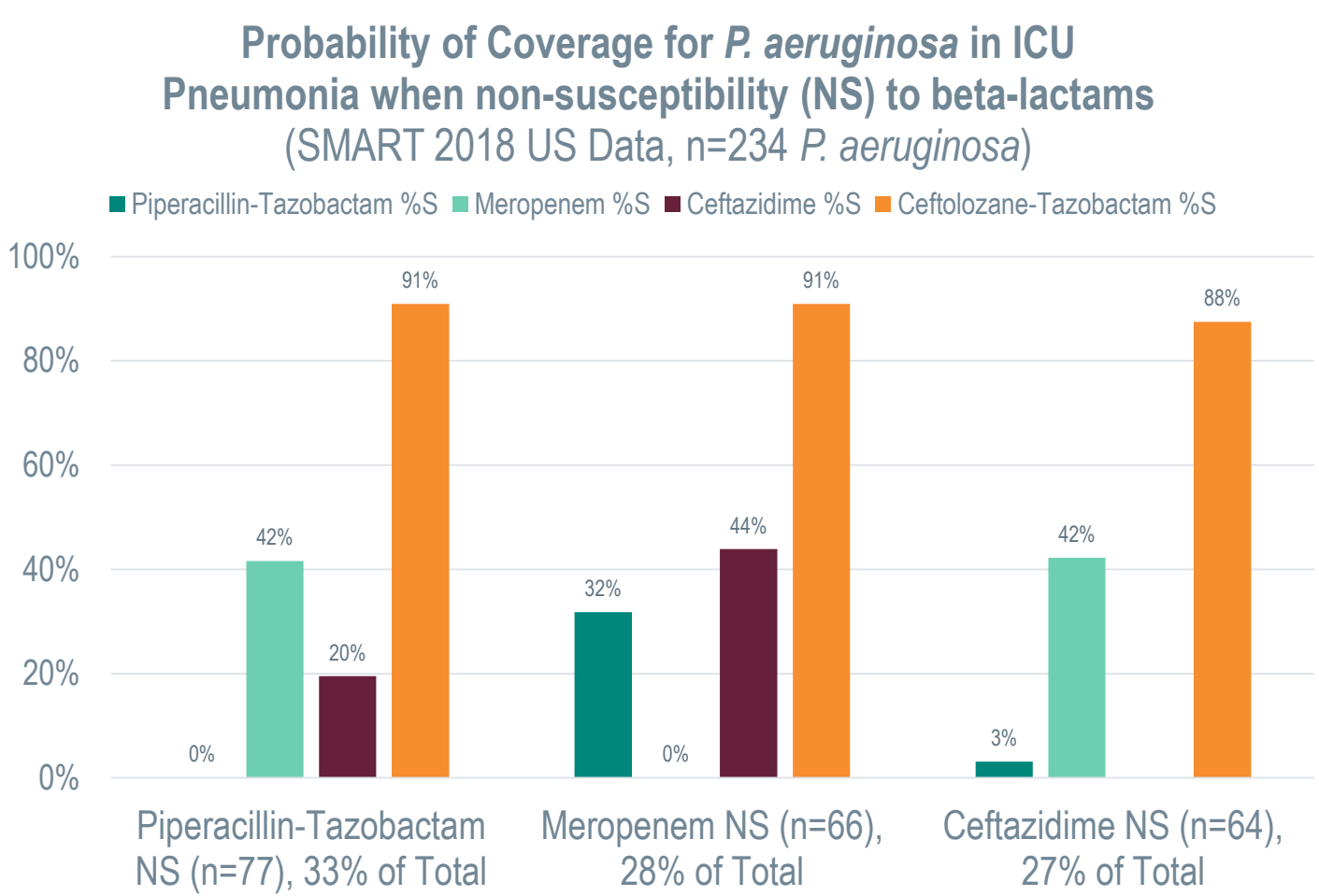


No baseline *P aeruginosa* isolates in the ceftolozane/tazobactam arm developed nonsusceptibility, compared with 22.4% in the meropenem arm

M.G. Johnson *et al*. International Journal of Antimicrobial Agents 57 (2021)

Co-Resistance among Commonly Prescribed 1st line Beta-Lactams, but not Ceftolozane/Tazobactam: Potential Implications

- When patients with *P. aeruginosa* pneumonia fail to improve on initial therapy, clinicians frequently escalate therapy.
- However, *P. aeruginosa* co-resistance may be common among 1st line β-lactams
  - For example, if *P. aeruginosa* was non-susceptible to a traditional 1st-line β-lactam, such as piperacillin-tazobactam, only ~40% were susceptible to meropenem and only 20% to ceftazidime. Hence, switching to another commonly prescribed antibiotics would offer limited additional coverage.
  - In contrast, switching to ceftolozane/tazobactam could offer additional coverage



Moise PM *et al.* JAC Antimicrob Resist

Update IDSA Guidelines

Which are the current treatment options for **definitive treatment** of drug resistant Gram negative infections?

	First line regimen	Alternative
ESBL-E	Carbapenems	*BL/BLI?*
CR-E	Ceftazidime/avibactam Meropenem/vaborbactam Imipenem/relebactam	Cefiderocol Colistin
DTR *P. aeruginosa*	Ceftolozane/tazobactam Ceftazidime/avibactam Imipenem/relebactam	Cefiderocol Colistin

Tamma PD et al. Clin Infect Dis 2021

DOMANDE?

GRAZIE