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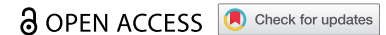


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REVIEW



All-cause mortality rates in adults with carbapenem-resistant Gram-negative bacterial infections: a comprehensive review of pathogen-focused, prospective, randomized, interventional clinical studies

Thomas P. Lodise^a, Matteo Bassetti^b, Ricard Ferrer^c, Thierry Naas^d, Yoshihito Niki^e, David L. Paterson^f, Markus Zeitlinger^g and Roger Echols^h

^aDepartment of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, NY, USA; ^bInfectious Diseases Clinic, Department of Health Science, University of Genova and Policlinico San Martino IRCCS Hospital, Genova, Italy; ^cDepartment of Intensive Care, Hospital Universitari Vall d'Hebron, Barcelona, Spain; ^dHôpital Bicetre, Bacteriology-Hygiene Unit, APHP-, University Paris-Saclay, Paris, France; ^eDivision of Clinical Infectious Diseases, Showa University, Tokyo, Japan; ^fUQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Herston, Australia; ^gDepartment of Clinical Pharmacology, Medical University, Vienna, Austria; ^hInfectious Disease Drug Development Consulting, LLC, Easton, CT, USA

ABSTRACT

Introduction: Pathogen-focused, randomized, controlled trials (PF-RCT) are important in the fight against carbapenem-resistant (CR) Gram-negative infections. Some recently approved antibiotics and older generic antibiotics with activity against CR Gram-negative bacteria were investigated in PF-RCTs in a variety of infections.

Areas covered: We searched Pubmed, Cochrane database and international clinical trial databases for PF-RCTs for the period between 2005 and 2020 and compared the study designs, patient populations, infection types, pathogens, and Day-28 all-cause mortality (ACM).

Expert opinion: PF-RCTs are particularly challenging to quantitatively assess and compare due to the heterogeneity in infection types, pathogens, CR mechanism, inclusion/exclusion criteria, and endpoints. Data interpretation is further complicated by lack of formal statistical analysis plans and/or non-inferiority design, and limited power across most PF-RCTs. The studies with new antibiotics (i.e. plazomicin, meropenem/vaborbactam, cefiderocol) ranked lower regarding feasibility, with relatively small sample sizes (analyzed: 37–118) versus the comparative effectiveness studies of older generic drugs (analyzed: 94–406). ACM ranged between 11.8% and 40% for CR Enterobacterales, 17.7% and 57.4% for CR *Acinetobacter* spp., and 20.0% and 30.8% for CR *Pseudomonas aeruginosa*. The information gathered must be considered carefully alongside the study limitations and caution should be exercised when making direct comparisons across trials.

PLAIN LANGUAGE SUMMARY

New antibiotics to treat multidrug-resistant Gram-negative bacterial infections are needed because antimicrobial resistance has become a global threat. In recent years, several pathogen-focused, randomized, controlled clinical trials were conducted to test new antibiotics or combinations of older generic antibiotics in the fight against resistant bacteria. However, these trials were exceptionally challenging and most of them enrolled relatively few patients. These studies were highly heterogeneous in terms of species, antibiotics, infection site, mechanism of resistance, endpoints and patient factors. In these trials, all-cause mortality at Day 28 or Day 30 were numerically lower with the new antibiotics in infections caused by carbapenem-resistant (CR) Enterobacterales. However, in the trials which investigated CR *Acinetobacter* spp. infections, there was no reduction in all-cause mortality at Day 28 or Day 30 with combinations of older generic antibiotics compared with colistin monotherapy. Limited information was available for CR *Pseudomonas aeruginosa*. More pathogen-focused, randomized, controlled clinical trials with more feasible design and higher patient numbers are needed to demonstrate clinical benefit in drug-resistant infections.

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Carbapenem resistance; critically ill; day 28 all-cause mortality; Gram-negative; imipenem/cilastatin/relebactam; meropenem/vaborbactam; plazomicin; cefiderocol; colistin; pathogen-focused randomized controlled trial


1. Introduction

Carbapenem-resistant (CR) Gram-negative pathogens, including Enterobacterales and non-fermenters such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, have spread alarmingly in recent years, leading to their inclusion on the World Health Organization (WHO) global critical priority list of antibiotic-

resistant bacteria [1]. These CR pathogens carry a higher risk of morbidity and mortality relative to their carbapenem-susceptible counterparts [2–5].

About 10 years ago, initiatives in the USA and Europe set out plans to stimulate the development of new antimicrobial agents, with a particular focus on drug-resistant pathogens [6–10]. The

CONTACT Thomas P. Lodise  Thomas.Lodise@acphs.edu  Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, 106 New Scotland Avenue, Albany, NY, 12208-2392, USA

 Supplemental data for this article can be accessed [here](#).

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Article highlights

- Carbapenem-resistant (CR) Gram-negative pathogens carry a high risk of morbidity and mortality and are on the World Health Organization's global critical priority list of antibiotic-resistant bacteria.
- Patients with infections due to these difficult-to-treat CR pathogens are often excluded from clinical trials of new antibiotics, even when the product is intended to be used to treat antibiotic-resistant infections. Regulatory agency guidance for the development of new antimicrobial agents has provided the possibility of using pathogen-focused trial approvals as an alternative to the traditional infection site-specific approach.
- We conducted a literature search and subsequent narrative analysis of pathogen-focused, randomized, controlled clinical trials (PF-RCTs) of new and older generic antibiotics that were conducted in seriously ill, hospitalized patients with CR Gram-negative infections.
- Eight PF-RCTs were identified: three involved only CR Enterobacterales ([CRE]; CARE, TANGO II, Ji et al. study), two involved only CR *Acinetobacter baumannii* (Durante-Mangoni and Sirijatuphat studies), three studies included different CR Gram-negative infections: CREs, carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and CR *Acinetobacter* spp. in AIDA and CREDIBLE-CR studies, and CREs and CR *P. aeruginosa* in RESTORE-IMI 1 study.
- Three new antibiotics (meropenem/vaborbactam, cefiderocol, and plazomicin) were investigated against CRE infections, while colistin with or without meropenem and cefepime with amoxicillin/clavulanic acid were also investigated against CRE infections. Against CR *Acinetobacter* spp. infections, the older generic antibiotics studied were colistin monotherapy or the combination of colistin plus meropenem or rifampicin or fosfomycin, whereas cefiderocol was investigated mainly as monotherapy. Against CRPA, studies investigated cefiderocol and imipenem/relebactam as new antibiotics, and colistin with or without a carbapenem as older generic antibiotics.
- Day 28 all-cause mortality (ACM) rates in CR *Acinetobacter* spp. infections were generally higher than in CRE or CRPA infections, and were consistent with rates in previous prospective or retrospective observational studies of CR *Acinetobacter* spp. There was no evidence for benefit of colistin combination therapy over colistin monotherapy. Limited information is available against CRPA from PF-RCTs regarding Day 28 ACM. Day 28 ACM rates in the CRE studies broadly matched those in observational studies and mortality appeared numerically lower with newer agents.
- These pathogen-focused studies provide clinically relevant information to guide clinical decisions on antibiotic treatment in target populations with CR Gram-negative infections.

traditional approach to the investigation of new antibiotics utilized non-inferiority clinical trials, which centered on a specific infection site such as urinary tract, intra-abdominal or lung, rather than a specific pathogen or group of pathogens defined by antibiotic susceptibility phenotype (e.g. carbapenem resistance) [11]. Despite the increased public health burden of CR pathogens, patients with suspected or documented CR pathogens at randomization have been excluded from recent infection site-specific trial designs due to the limited activity of the control drugs, which were mainly carbapenems [12–20]. As set out by guidance, these Phase 2 or Phase 3 registrational, randomized, non-inferiority studies enrolled a large number of patients over a 2–3-year time frame because the burden of these infections is significant worldwide [21–23]. However, they often excluded patient populations with severe illnesses or comorbidities and drug-resistant infections [12–20].

To address the problem of drug-resistant organisms, modifications to clinical trial requirements for new antibacterial

drugs were introduced by the US Food and Drug Administration and European Medicines Agency, which led to the possibility of pathogen-focused investigations [24,25]. As a result, several pathogen-focused, randomized clinical trials (PF-RCTs) have been conducted in an attempt to gauge the clinical efficacy of new and older generic antibiotics in specific CR pathogen-associated infections [26–36]. In contrast to Phase 2 or Phase 3 registrational, randomized, non-inferiority studies, the pathogen-focused studies allowed for the enrollment of patients with more severe illnesses and previously excluded comorbidities to explore further the efficacy of the new agents and effectiveness of older approved agents in special patient populations [23]. As a result, these CR pathogen-focused studies were highly heterogeneous and enrolled patients with a variety of clinical diagnoses, including bloodstream infections (BSI), sepsis, urinary tract infection (UTI), skin and soft tissue infection, and nosocomial pneumonia, representing the most common clinical illnesses. While the broad enrollment criteria in the CR pathogen-focused studies result in more heterogeneous study populations, limiting the data interpretation [26,37,38], they are important in gaining a better understanding of the efficacy of new antibiotics, as well as the effectiveness of older approved agents, where they are intended to be used [26,37]. To gain an overview and understanding of the totality of the data generated by pathogen-focused, multicenter trials, we conducted a literature and database search in order to review data from randomized, prospective, interventional, pathogen-focused trials in patients with CR Gram-negative infections. Our evaluation included studies of approved older generics and new antibiotics, and considered baseline patient demographics, infection types, and outcome of Day 28 or Day 30 all-cause mortality (ACM).

2. Methods

2.1. Database and literature search strategy

We sought to identify prospective, randomized, controlled, interventional studies in hospitalized adult patients (≥ 18 years old) focusing on a single species or group of species based on their antibiotic resistance profiles. Phase 2, 3, and 4 studies, and those from which phase information was not available, in patients with a laboratory-confirmed CR Gram-negative pathogen (Enterobacterales, especially *Klebsiella* spp., *Acinetobacter* spp., or *Pseudomonas* spp.), registered from 2005 in clinical trial registries and with outcome data (including Day 28 or Day 30 ACM) reported from 2010, were included.

The following sources were searched: ClinicalTrials.gov registry database, European Union Drug Regulating Authorities Clinical Trials Database, WHO International Clinical Trials Registry Platform, Cochrane database, and PubMed. Infection-related search terms were: 'carbapenem resistance,' 'carbapenem-resistant *Acinetobacter*,' 'carbapenem-resistant Enterobacteriaceae,' 'carbapenem-resistant *Klebsiella*,' 'carbapenem-resistant *Pseudomonas*,' 'randomized study,' 'prospective trial,' and/or 'pathogen-focused' (Supplementary Table S1). The following types of study were excluded: 1) those investigating aerosolized, inhaled, nebulized, or dry-powder

inhalation antibiotics; 2) pediatric, children studies; 3) prophylaxis antibiotic studies; 4) topical agent or scrub use studies; 5) oral, bowel, digestive, perioperative decontamination studies; 6) antiseptic agent or scrub use decolonization studies; 7) fecal transplantation studies; 8) outbreak reports; 9) infection site-specific studies; 10) retrospective studies (any); 11) prospective observational (case-control, cohort, cross-sectional) or non-interventional, non-randomized, or single-arm studies (any); 12) mixed Gram-negative/Gram-positive infections; 13) studies not reporting Day 28 or Day 30 ACM; 14) studies not reporting pathogen-focused Day 28 or Day 30 ACM; 15) fewer than 50 patients enrolled; 16) Phase 1 studies; 17) studies published on a non-English language platform. Clinical studies registered on the WHO register in English were reviewed for inclusion. International, multicenter trials were cross-checked in each clinical trial registry and were counted only once.

Reference titles and abstracts available before 1 December 2020, were screened and reviewed by the authors. Peer-reviewed publications of primary clinical study results, secondary publications, systematic reviews (to ensure that all randomized clinical trials had been included), and congress abstracts and/or posters were reviewed for availability of outcomes and patient characteristics and to confirm eligibility for inclusion.

2.2. Primary analysis outcomes

Each study identified was described according to a number of categories. Study design features recorded were: study dates; number of patients screened/enrolled and randomization ratio; number of study sites and geographical locations; antibiotics and dose regimens used; study design and development phase; treatment duration; target pathogens; key inclusion and exclusion criteria; study endpoints and the primary analysis population. Intervention treatments were described as either older generic or new antibiotics.

Patient populations were presented according to age, sex, baseline diagnosis, target pathogens involved, sites of infections, and severity of illness propensity scores (Charlson Comorbidity Index [CCI], Acute Physiology and Chronic Health Evaluation II, and/or intensive care unit [ICU] admission). The Day 28 (or Day 30) ACM rates reported for each study were collated and summarized by pathogen group (carbapenem-resistant Enterobacterales [CRE] or CR *Acinetobacter* spp. or CR *P. aeruginosa* [CRPA]).

Data summarized from the analyses were descriptive and no formal statistical analysis plan was utilized. Day 28 (or Day 30) ACM rates were analyzed by treatment arm; point estimate and within-arm 95% confidence intervals (CIs) calculated by the Clopper-Pearson test are presented.

3. Results

3.1. Trials included in the analysis

A total of 931 entries were identified in the search, of which 883 were excluded on the basis of duplication or non-relevant information (Supplementary Figure S1). After author screening

of the study designs, titles, abstracts, and full articles, 41 of the remaining 48 studies were excluded because they contained data from retrospective or prospective, observational, or single-arm studies, systematic reviews or meta-analyses, lacked mortality data required for inclusion in the analysis, or lacked pathogen-specific Day 28 mortality data (Supplementary Figure S1, Supplementary Table S1, Supplementary Table S2). We identified eight PF-RCTs; however, pathogen-specific ACM data were available in seven studies. In one of these studies (RESTORE-IMI 1), pathogen-focused ACM data were not available to compare with other studies [36]. For one small, single-center, open-label, randomized, controlled study in infections caused by *Klebsiella pneumoniae* carbapenemase (KPC)-producing CR *K. pneumoniae*, limited inclusion and exclusion criteria were available for comparison with the other studies [35].

Seven trials meeting the inclusion criteria for mortality analysis were open-label studies [29–35] (Table 1). Three were national trials, two involving one site [34,35] and one involving five sites [33], and the remaining four trials were international, involving 5–95 sites in 3–16 countries (Table 1). In accordance with the inclusion criteria, all studies required patients to be hospitalized. Some of the studies specifically excluded patients with endocarditis [29–31], meningitis and other central nervous system infections [29–31], bone and joint infections [29–31], and intra-abdominal infections [30].

Three of the trials involved a new antibiotic: CARE (plazomicin) [29], TANGO II (meropenem/vaborbactam) [30], and CREDIBLE-CR (cefiderocol) [31]. Two new antibiotics, plazomicin and meropenem/vaborbactam, were investigated against CRE infections only [29,30], whereas cefiderocol was investigated in infections caused by either CREs or CR non-fermenters, including CR *Acinetobacter* spp [31]. The remaining four studies involved older generic antibiotics, including colistin monotherapy or colistin in combination with meropenem (AIDA) [32], rifampicin [33], or fosfomycin [34], or cefepime combined with amoxicillin/clavulanic acid versus tigecycline-based therapy [35].

In two trials, the control arm was not a specified antibiotic regimen but rather best available therapy (BAT). In the TANGO II study, BAT included any of the following as monotherapy or in combination: polymyxins, carbapenems, aminoglycosides, or tigecycline; or monotherapy with ceftazidime-avibactam [30]. Treatment selection was confirmed by the investigator based on institutional standards of care, patient characteristics, and local regulatory approval. In the CREDIBLE-CR study, BAT comprised a maximum of three systemic antibiotics with Gram-negative activity, dosed according to the country's label and local clinical practice, and most patients (65%) received colistin-based combination therapy [31], primarily for CR *Acinetobacter* spp. infections (Supplementary Table S3, Supplementary Table S4). In the CARE study, colistin monotherapy was selected as the control antibiotic [29].

In terms of the target pathogens involved, three of the trials focused on CREs: the CARE trial (primary analysis population, $n = 37$ [randomized $n = 69$]) [29], the TANGO II trial ($n = 47$ [randomized $n = 77$]) [30] and the study by Ji et al. ($n = 51$ [randomized $n = 62$]) [35]. Two trials enrolled patients with extensively drug-resistant and/or CR *A. baumannii*

Table 1. Study characteristics and inclusion and exclusion criteria of studies investigating carbapenem-resistant Gram-negative infections.

	CARE ^a	TANGO II	CREDIBLE-CR	AIDA	Durante-Mangoni	Srijatiuphat	Ji et al. IRB approved [35]	RESTORE-IMI 1
	NCT01970371 [29]	NCT02168946 [30]	NCT02714595 [31]	NCT01732250 [32]	NCT01577862 [33]	NCT01297894 [34]	2011–2012	NCT02452047 [36]
Study period	2014–2016	2014–2017	2016–2019	2013–2016	2008–2011	2010–2011	2011–2012	2015–2017
No. of screened patients	>2000	85	257	802	449	NA	Unknown	65
No. of enrolled patients	69	77	152	406	210	99	62	50
No. (location) of study site(s)	5 (Brazil, Greece, Italy, Turkey, USA)	27 (Argentina, Brazil, Colombia, Greece, Israel, Italy, UK, USA)	95 (16 countries) ^b	6 (Israel, Greece, Italy)	5 (Italy)	1 (Thailand)	1 (China)	35 (17 countries)
Antibiotic	PLAZ	MEM/VAB	BAT	COL + MEM	COL + RIF	COL + FOS	FEP + AMC	IMI/REL
Dose	5 mg/kg	2 g/2 g, q8h	2 g, q8h	9 MIU loading dose + 4.5 MIU q12h + 2 g q8h	2 MIU q8h + 600 mg q12h	5 mg/kg BW + 4 g q12h	1 g q6h + 1.2 g q6h	500 mg/250 mg q6h + 300 mg loading dose + 150 mg q12h
Design	Open label ^d	Open label	Open label	Open label	Open label	Open label	Open label	Double blind
Phase	3	3	3	4	3	3	4	3
Randomization	1:1	2:1	2:1	1:1	1:1	1:1	1:1	2:1
Treatment duration, days	7–14	7–14	7–14	7–14	10–21	7–14	NA	5–21
Pathogen focus	CR Enterobacteriales	CR Enterobacteriales	CR Enterobacteriales and CR non-fermenters	CR Enterobacteriales and CR non-fermenters	XDR/CR A. baumannii	CR A. baumannii	CR Klebsiella pneumoniae	CR Enterobacteriales, CR P. aeruginosa
Key inclusion criteria	<ul style="list-style-type: none"> Hospitalized adults 18–85 years • BSI, HAP/VAP, or cUTI/AP caused by suspected/confirmed CRE infection 	<ul style="list-style-type: none"> Hospitalized adults ≥18 years • cUTI, HAP/VAP, BSI, or cIAI • Suspected/confirmed CRE infection 	<ul style="list-style-type: none"> Hospitalized adults ≥18 years • HAP/VAP/HCAP, BSI, or cUTI caused by CR GN bacteria 	<ul style="list-style-type: none"> Hospitalized adults with severe infections caused by CR NS, COL-susceptible, GN bacteria • BSI, HAP/VAP, or cIAI • Life-threatening nosocomial infection due to XDR A. baumannii 	<ul style="list-style-type: none"> Hospitalized adults ≥18 years • BSI, HAP/VAP, or cIAI • Life-threatening nosocomial infection requiring COL therapy 	<ul style="list-style-type: none"> Hospitalized adults in the ICU • Pneumonia, cIAI, BSI, cUTI, and other sites 	<ul style="list-style-type: none"> Hospitalized adults ≥18 years • HAP/VAP, cUTI, or cIAI caused by IMI-non-susceptible, IMI/RELE-susceptible, colistin-susceptible organisms • Failure on prior antibiotic therapy 	
Key exclusion criteria	<ul style="list-style-type: none"> Antibiotic therapy for >72 h (HAP/VAP) or <48 h (cUTI) before enrollment • CRE pathogen resistance to colistin 	<ul style="list-style-type: none"> Antibiotic therapy for >24 h before enrollment • Confirmed CRE-producing NDM, VIM, or OXA-encoded beta-lactamases • APACHE II score >30 	<ul style="list-style-type: none"> Antibiotic therapy <72 h before enrollment with a continuous duration of >24 h for cUTI or >36 h for other infections • APACHE II score >30 	<ul style="list-style-type: none"> Prior COL for >96 h • Polymicrobial CS GN bacteria 	<ul style="list-style-type: none"> Prior treatment with COL or RIF during the index hospitalization • Infections caused by CS pathogens 	<ul style="list-style-type: none"> No criteria specified • APACHE II score >30 	<ul style="list-style-type: none"> APACHE II score >30 	

(Continued)

Table 1. (Continued).

Endpoints	CARE ^a NCT01970371 [29]	TANGO II NCT02168946 [30]	CREDIBLE-CR NCT02714595 [31]	AIDA NCT01732250 [32]	Durante-Mangoni NCT01577862 [33]	Sirijatuphat NCT01297894 [34]	Ji et al. IRB approved [35]	RESTORE-IMI 1 NCT02452047 [36]
	Day 28 ACM	Clinical and microbiological cure, Day 28 ACM	1°: clinical and microbiological outcome 2°: Day 14 and 28 ACM and others	1°: clinical success at Day 14 and 28 ACM and others	1°: Day 30 mortality 2°: infection-related death, microbiological eradication	1°: favorable clinical response 2°: microbiological eradication, Day 28 ACM	1°: Day 28 ACM 2°: microbiological eradication, clinical efficacy, cost of antibiotic treatment, duration of hospital length of stay	1°: Day 28 ACM (HAP/VAP); Day 28 clinical response (cIAI); composite clinical and microbiological response at EFU visit (cUTI) 2°: clinical response, Day 28 ACM
Primary analysis population	Microbiological modified ITT (confirmed CRE and ≥1 dose of study drug)	Microbiological CRE-modified ITT (confirmed CRE and ≥1 dose of study drug)	CR microbiological ITT (confirmed CR GN pathogen and ≥1 dose of study drug)	ITT	ITT	ITT	Not specified (includes all randomized + treated patients)	Microbiological modified ITT (confirmed qualifying CR GN pathogen and ≥1 dose of study drug)

ACM: all-cause mortality, AMC: amoxicillin/clavulanic acid, AP: acute pyelonephritis, APACHE II: Acute Physiology and Chronic Health Evaluation II, BAT: best available therapy, BSI: bloodstream infection, BW: body weight, CFDC: cefiderocol, cIAI: complicated intra-abdominal infection, COL: colistin, CR: carbapenem resistant, CRE: carbapenem-resistant Enterobacteriales, CS: carbapenem susceptible, cUTI: complicated urinary tract infection, EFU: early follow-up, FEP: cefepime, FOS: fosfomicin, GN: Gram-negative, HAP: hospital-acquired pneumonia, IMI: imipenem, IRB: institutional review board, ITT: intention-to-treat population, MEM: meropenem, NDM: New Delhi metallo-beta-lactamase, MIU: million unit, NA: not available, NS: non-susceptible, OXA: oxacillinase, PLAZ: plazomicin, q6h: every 6 hours; q8h: every 8 hours, q12h: every 12 hours, REL: relebactam, RIF: rifampicin, TIG: tigecycline, VAB: vaborbactam, VAP: ventilator-associated pneumonia, VIM: Verona integron-encoded metallo-beta-lactamase, XDR: extensively drug resistant, -: not applicable.

^aThe trial was stopped prematurely due to slow enrollment.

^bUSA 9; Brazil 9; Guatemala 2; Italy 6; Spain 12; Greece 7; France 2; Turkey 4; Germany 3; Israel 10; Croatia 5; UK 5; Japan 3; Taiwan 7; South Korea 8; Thailand 3.

^cAs monotherapy or in combination with amikacin + levofloxacin, meropenem, fosfomicin, cefepime, ceftoperazone/sulbactam.

^dThe study was open label, but the sponsor remained blinded to the results throughout its course.

infections only: Durante-Mangoni et al. (n = 209 [randomized n = 210]) [33] and Sirijatuphat et al. (n = 94 [randomized n = 99]) [34]. The AIDA trial (n = 406 [randomized n = 406]) [32] and the CREDIBLE-CR trial (n = 118 [randomized n = 150]) [31] included both CRE infections and CR non-fermenters, among which CR *Acinetobacter* spp. was the most frequent. In these two studies, CRPA was also investigated and analyzed [31,32].

In four trials, CARE, TANGO II, CREDIBLE-CR and Ji et al. study [29–31,35], the primary analysis population was the microbiological modified intention-to-treat (mITT) population, which included patients with a confirmed qualifying CR pathogen who received at least one dose of study drug. In these four trials 53.6% [CARE], 61.0% [TANGO II], 78.7% [CREDIBLE-CR] and 82.3% [35] of randomized patients were included in the primary analysis. For the remaining trials, the primary analysis population was the ITT population [32–34] and almost all enrolled patients were analyzed (e.g. patients were excluded in the AIDA [32] study from the analysis if they died within 48 hours). Two of the trials, CARE and TANGO II, underwent significant protocol amendments in order to address enrollment feasibility [29,30]. For the original analyses, the AIDA and Durante-Mangoni trials had adequate enrollment to support a prior statistical hypothesis [32,33]; the remaining trials used descriptive statistics only [29–31,34,35].

Definitions of carbapenem resistance used in the different trials are shown in Supplementary Table S5. The definition for carbapenem resistance differed to some extent between studies, but generally coincided with the consensus definition and minimum inhibitory concentration interpretive criteria available at the time of the studies and according to the geographical location [39].

3.2. Patient demographics and baseline characteristics

Demographics and baseline characteristics of patients in the primary analysis populations are shown in (Table 2). A total of 962 patients were included (range 37–406) and the mean age ranged from 60.2 to 69.2 years. The studies enrolling patients with CR *Acinetobacter* spp. were larger than studies with CRE infections and enrolled primarily patients with pneumonia, whereas patients with BSI were more frequent in studies investigating CRE infections. Within studies, the most frequent infections were hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) in four studies (CREDIBLE-CR [31], AIDA [32], and trials reported by Durante-Mangoni et al. [33] and Sirijatuphat et al. [34]), and BSI in two studies (CARE [29] and TANGO II [30]). The TANGO II trial [30] included a notable proportion of patients (i.e. 34%) with complicated UTI (cUTI), and the trial from Durante-Mangoni et al. [33] included fewer patients with BSI relative to HAP/VAP; both factors might be expected to influence mortality (Table 2).

A. baumannii was the predominant baseline pathogen in four studies [31–34] (Table 2). *K. pneumoniae* was the predominant baseline pathogen in the CRE-focused CARE, TANGO II and Ji et al. studies [29,30,35]. In terms of comorbidities, two of the trials reported that 60–93% of the patients had a CCI score ≥ 2 [30,33], with similar proportions of patients between treatment arms within each study. In CREDIBLE-CR [31] and

AIDA [32], the median CCI scores in both treatment arms were around 5.0 and 2, respectively (Table 2). Where reported, the proportion of patients in ICU varied between studies, being highest in the study by Ji et al. (cefepime arm 73%, tigecycline arm 72%) [35], the CREDIBLE-CR study (cefiderocol 65%, BAT 50%) [31] and the study reported by Durante-Mangoni et al. (colistin + rifampicin 60%; colistin 62%) [33] and lowest in the TANGO II trial (meropenem/vaborbactam 16%; BAT 20%) [30].

3.3. Day 28 or Day 30 ACM

Data for Day 28 (or Day 30) ACM rates were mainly available for CRE and CR *Acinetobacter* spp. infections, and only in two studies for CRPA infections.

For CRE infections, the combined Day 28 ACM rate across the new and comparator arms of all studies was 25.0% (62/248). In three studies with the new antibiotics [29–31], the Day 28 ACM was numerically lower in the new antibiotic arms (range: 11.8%–15.6%) compared with the comparator arms (range: 27.3%–40.0%) (Figure 1). In the study conducted by Ji et al. [35], the combination of cefepime with amoxicillin/clavulanic acid resulted in a numerically lower ACM versus tigecycline-based therapy (23.1% vs 36.0%) (Figure 1). In the AIDA study, the combination of colistin with meropenem also resulted in numerically lower mortality than colistin monotherapy in CRE infections (combination 20.5% and monotherapy 35.3%) [32]. The sample sizes were similar, but relatively small, across studies and treatment arms (range: 11–39 patients), which led to wide 95% CIs.

For CR *Acinetobacter* spp. infections [31–34], the combined Day 28 ACM rate (46.3% [311/671]; Figure 2) across both arms of all studies was higher than for CRE infections (25.0%). Among studies of older generic antibiotics for CR *Acinetobacter* spp., the combination of colistin with rifampicin, fosfomycin or meropenem did not reduce the Day 28 ACM (range: 43.3%–52.2%) compared with colistin alone (range: 42.9%–57.4%). In the CREDIBLE-CR study [31], ACM was 38.5% (15/39) with cefiderocol treatment and 17.7% (3/17) with BAT treatment (Figure 2). The small sample size of *A. baumannii* infections in the CREDIBLE-CR study (39 patients in the cefiderocol arm and 17 patients in the BAT arm) resulted in 95% CIs that were wider than those seen in the larger AIDA [32], Durante-Mangoni [33], and Sirijatuphat [34] studies, particularly for the BAT arm.

ACM data for CRPA infections were limited in the studies due to small number of enrolled patients. In the AIDA study [32], Day 28 ACM was reported for 30.8% (4/13) and 25.0% (2/8) for patients with CRPA in the colistin and colistin + meropenem treatment arms, respectively. In the CREDIBLE-CR study, among those with CRPA infections, 25.0% (3/12) of patients in the cefiderocol arm and 20.0% (2/10) of patients in the BAT arm died by Day 28 (unpublished data). The RESTORE-IMI 1 study was a pathogen-focused RCT to investigate the efficacy of imipenem/cilastatin/relebactam and imipenem/cilastatin + colistin against imipenem-non-susceptible infections (Table 1) [36]. In this study, patients with CRE or CRPA infections were enrolled and randomized (Table 2); however, pathogen-focused Day 28 (or Day 30) ACM was not

Table 2. Demographic and baseline details in the primary analysis populations of recent studies in adult patients with infections caused by carbapenem-resistant Gram-negative pathogens.

Arm	CARE [29]			TANGO II [30]			CREDIBLE-CR [31]			AIDA [32]			Durante-Mangoni [33]			Sirijatuphat [34] ^a			Ji et al. [35]			RESTORE-IMI 1 [36]	
	PLAZ	COL	MEM/VAB	BAT	CFDC	BAT	BAT	CFDC	BAT	COL + MEM	COL	COL + RIF	COL	COL + FOS	COL	FEP + AMC	TIG-based therapy	IMI + COL	IMI/REL	IMI + COL			
No. of analyzed patients	17	20	32	15	80	38	38	80	208	198	104	105	47	47	26	25	21	10					
Patient population	12 (70.6)	10 (50.0)	14 (43.8)	10 (66.7)	55 (69)	29 (76)	29 (76)	55 (69)	76 (37)	75 (38)	67 (64.4)	70 (66.7)	20 (42.6)	24 (51.1)	18 (39.2)	13 (52.0)	13 (61.9)	7 (70.0)					
Male, n (%)	66.7	63.1	63.5	60.2	63.1	62.1	62.1	63.1	66	66	62	61	67.4	69.2	67.1	63.6	59 ^b	61 ^b					
Age (mean), years	NA	NA	8 (25.0)	3 (20.0)	50 (63)	17 (45)	17 (45)	50 (63)	NA	NA	NA	NA	NA	NA	NA	NA	6 (28.6)	5 (50.0)					
Age ≥65 years, n (%)	14 (82.4)	15 (75.0)	14 (43.8)	8 (53.3)	23 (29) ^c	14 (37) ^c	14 (37) ^c	23 (29) ^c	97 (47)	76 (38)	21 (20.2)	21 (20.0)	2 (4.3)	3 (6.4)	4 (15)	2 (8)	8 (38.1)	3 (30.0)					
Baseline diagnosis, n (%)	3 (17.6)	5 (25.0)	4 (12.5)	1 (6.7)	40 (50) ^d	19 (50) ^e	19 (50) ^e	40 (50) ^d	99 (48)	108 (55)	81 (77.9)	81 (77.1)	37 (78.7)	35 (74.5)	8 (31)	5 (20)	11 (52.4)	5 (50.0)					
BSI	–	–	12 (37.5)	4 (26.7)	17 (21)	5 (13)	5 (13)	17 (21)	12 (6)	14 (7)	NA	NA	3 (6.4)	2 (4.3)	1 (4)	0	2 (9.5)	2 (20.0)					
HAP/VAP	–	–	2 (6.3)	2 (13.3)	–	–	–	–	NA	NA	2 (1.9)	3 (2.9)	2 (4.3)	4 (8.5)	3 (12)	10 (40)	–	–					
cUTI	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0	1 (4)	–	–					
cIAI	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0	–	–	–					
Other	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–					
Baseline pathogens, n (%)	16 (94.1)	20 (100)	29 (90.6)	12 (80.0)	27 (34)	12 (32)	12 (32)	27 (34)	39	34	–	–	2 (4.3)	6 (12.8)	26 (100)	25 (100)	5 (23.8)	2 (20.0)					
Enterobacteriales	1 (5.9)	0	5 (15.6)	6 (40.0)	4 (5)	1 (3)	1 (3)	4 (5)	NA	NA	NA	NA	NA	NA	26 (100)	25 (100)	3 (14.3)	1 (10.0)					
<i>K. pneumoniae</i>	NA	NA	NA	NA	37 (46)	17 (45)	17 (45)	37 (46)	161 (77)	151 (76)	104 (100)	105 (100)	47 (100)	47 (100)	NA	NA	NA	NA					
Non-fermenters	NA	NA	NA	NA	12 (15)	10 (26)	10 (26)	12 (15)	8 ^f	13 ^f	0	0	3 (6.4)	1 (2.1)	NA	NA	16 (76.2)	8 (80.0)					
<i>A. baumannii</i>	NA	NA	NA	NA	7 (8.8)	0	0	7 (8.8)	0	0	0	0	0	0	NA	NA	NA	NA					
<i>P. aeruginosa</i>	NA	NA	28 (87.5) ^g	14 (93.3) ^g	5.5 (3–8) ^h	5.0 (3–7) ^h	5.0 (3–7) ^h	5.5 (3–8) ^h	2 (0–4) ^h	2 (0–3) ^h	64 (61.5)	63 (60.0)	NA	NA	NA	NA	NA	NA					
Other	NA	NA	NA	NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–					
CCI ≥2, n (%) or Median (IQR)	0	0	NA	NA	41 (51)	21 (55)	21 (55)	41 (51)	NA	NA	NA	NA	23.0 (±6.4) ^j	21.9 (±7.9) ^j	16.0 (±8.8) ^j	17.1 (±9.3) ^j	7 (33.3)	8 (80.0)					
APACHE II score, n (%) or Mean (±SD)	17 (100) ⁱ	20 (100) ⁱ	NA	NA	39 (49)	17 (45)	17 (45)	39 (49)	NA	NA	NA	NA	NA	NA	NA	18 (72.0)	14 (66.7)	2 (20.0)					
≤15	NA	NA	5 (15.6)	3 (20.0)	52 (65)	19 (50)	19 (50)	52 (65)	71 (34) ^k	77 (39) ^k	62 (59.6) ^j	65 (61.9) ^j	NA	NA	19 (73.1)	18 (72.0)	NA	NA					
>15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA					
ICU admission, n (%)	NA	NA	5 (15.6)	3 (20.0)	52 (65)	19 (50)	19 (50)	52 (65)	71 (34) ^k	77 (39) ^k	62 (59.6) ^j	65 (61.9) ^j	NA	NA	19 (73.1)	18 (72.0)	NA	NA					

AMC: amoxicillin/clavulanic acid; APACHE II: Acute Physiology and Chronic Health Evaluation II; BAT: best available therapy; BSI: bloodstream infection; CCI: Charlson Comorbidity Index; CFDC: ceftiderocol, cIAI: complicated intra-abdominal infection, COL: colistin, cUTI: complicated urinary tract infection, FEP: fosfomicin, HAP: hospital-acquired pneumonia, HCAP: healthcare-associated pneumonia, ICU: intensive care unit, IMI: imipenem, IQR: interquartile range, MEM: meropenem, NA: not available, PLAZ: plazomicin, REL: relebactam, RIF: rifampicin, SD: standard deviation, TIG: tigecycline; VAB: vaborbactam, VAP: ventilator-associated pneumonia, –: not applicable.

^an numbers calculated from percentages provided.
^bMedian.
^cSepsis included in BSI category.
^dIncludes 1 patient with HCAP.
^eIncludes 2 patients with HCAP.
^f*Pseudomonas* and others.
^gCCI >2.
^hMedian (IQR).
ⁱAPACHE II score ≥15.
^jMean (±SD).
^kAcquisition of infection in the ICU.
^lEmergency/ICU admission.

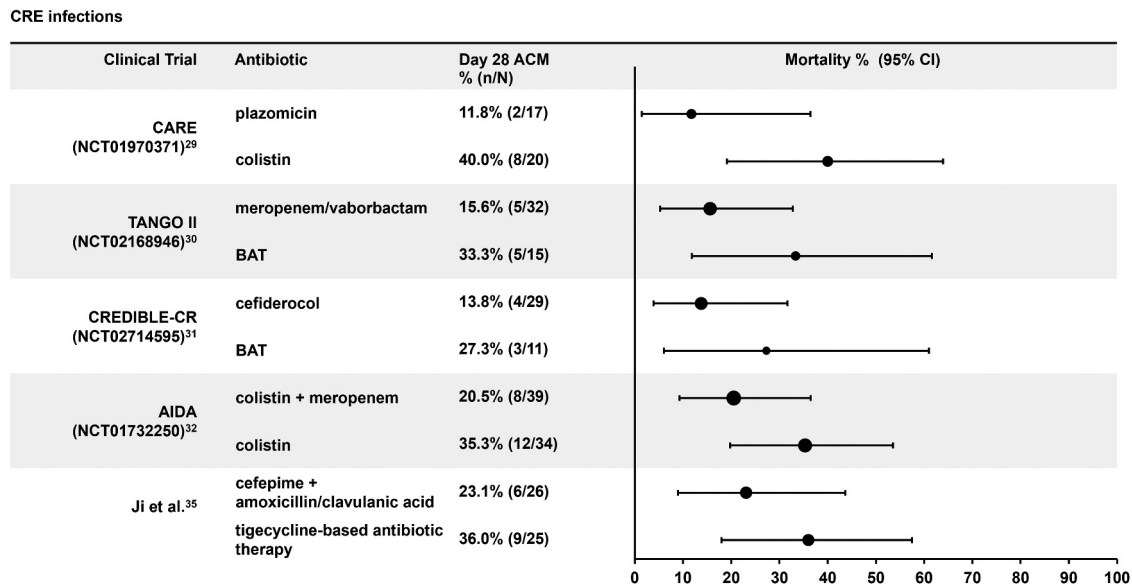


Figure 1. Day 28 all-cause mortality rates in carbapenem-resistant Enterobacterales infections. ACM: all-cause mortality, BAT: best-available therapy, CI: confidence interval, CR: carbapenem resistant. In the TANGO II and CREDIBLE-CR studies, patients were randomized 2:1 (investigational therapy:control).

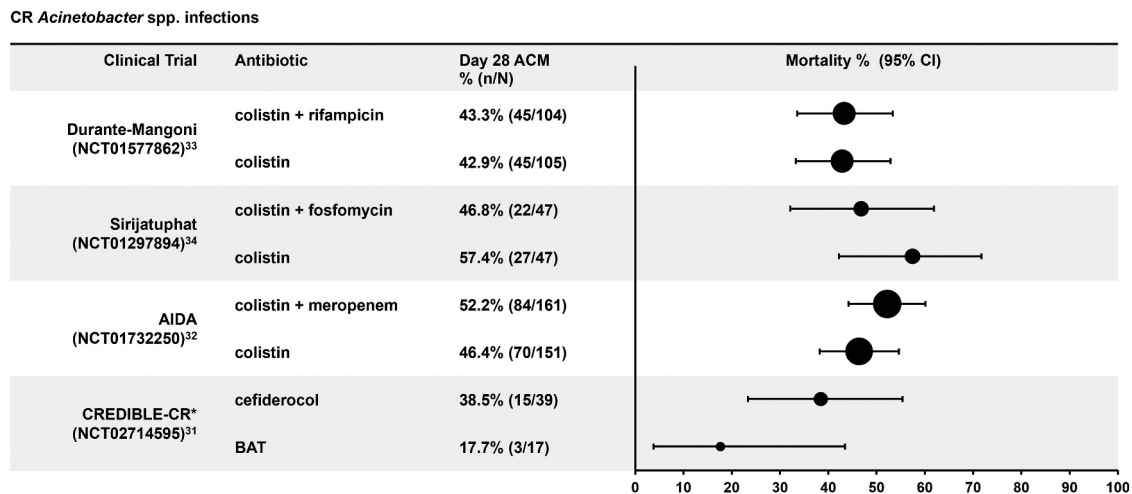


Figure 2. Day 28 all-cause mortality rates in carbapenem-resistant *Acinetobacter* spp. infections. ACM: all-cause mortality, BAT: best-available therapy, CI: confidence interval, CR: carbapenem resistant. In the CREDIBLE-CR study, patients were randomized 2:1 (cefiderocol:BAT). *Acinetobacter* spp. include: *A. baumannii*; *A. nosocomialis*.

reported (for either CRE or CRPA) [36]. In this study, 50 patients were enrolled overall, and CRPA infections were reported for 24 of 31 patients across the two arms (11 with HAP/VAP, 3 with complicated intra-abdominal infections, and 10 with cUTI) in the primary analysis population, and only seven patients had CRE infections. Day 28 ACM overall was 9.5% (2/21) and 30% (3/10) in the imipenem/relebactam and colistin + imipenem arms, respectively [36].

4. Discussion

This analysis of seven pathogen-focused randomized, interventional trials provides important, largely descriptive information about antibiotic regimens used to treat CR Gram-

negative infections from different infection sites. Only three studies were designed with inferential hypothesis testing (CARE, AIDA, and Durante-Mangoni) [29,32,33]. Perhaps unsurprisingly, the analysis highlights considerable inter-study heterogeneity, in terms of the number of patients screened and enrolled, infection sites, the individual pathogens and pathogen types investigated and, consequently, the control antibiotics used, the proportion of patients in ICU, severity of illness (e.g. varying APACHE II scores across PF-RCTs), and the geographical location for patient enrollment. Due to the limited sample sizes and inclusion of multiple infection types, patients were not consistently stratified in PF-RCTs based on specific factors related to severity of illness, which further complicates inferences across PF-RCTs. There were also differences in the

primary analysis populations. Three of the approved antibiotic studies consisted of older generic agents and allowed for a longer period of time prior to study drug treatment to confirm carbapenem resistance; thus, randomized patients with only confirmed CR pathogens were investigated [32–34]. In the Ji et al. study, patients with confirmed CR *K. pneumoniae* were enrolled, which were also tested for the presence of *bla_{KPC}* suggesting a 48–72-hour time window, although information was not available [35]. Hence, their focus was on comparative effectiveness. In the new antibiotic studies, the focus was on efficacy; the study protocols following regulatory guidance were more restrictive in terms of the time window permitted for potentially effective antibiotics, and patients with infections due to suspected, but not confirmed, CR pathogens could have been randomized [29–31]. The CRE-focused investigations of Day 28 ACM involved fewer patients in each treatment arm than the *Acinetobacter* spp. studies. Despite allowing more infection types for new treatments, the CRE studies often enrolled patients with BSI or cUTI. In contrast, pneumonia was more frequent in the CR *A. baumannii* studies.

Among the CRE-focused studies, mortality rates were high and consistent, and broadly match those reported in non-randomized cohort studies [3,40]. Although mortality was numerically lower in each study with new agents compared with standard-of-care regimens, patient numbers in all studies were small and 95% CIs overlapped. In the studies analyzed, Enterobacterales mainly expressed KPC in the TANGO II study [30] and the Ji et al. study [35], whereas in the CREDIBLE-CR study both KPC and metallo-beta-lactamases (MBLs) were identified [31,41]. Of note, TANGO II and RESTORE-IMI 1 excluded patients with confirmed MBL-expressing CREs, respectively [30,36]. No information was provided in the CARE or AIDA studies on mechanism of carbapenem resistance [29,32].

Studies investigating only CR *Acinetobacter* spp. infections assessed a relatively large number of patients (up to 161 patients per treatment arm) mainly with nosocomial pneumonia, representing a population at high risk of mortality. As with CRE, mortality rates were consistently high and are similar to those reported in prospective or retrospective observational, cohort studies [40,42,43]. In the three large studies (AIDA, Durante-Mangoni, Sirijatuphat), the combination treatment arms did not reduce ACM [32–34]. The exception to this was the mortality rate in the BAT arm of the smaller CREDIBLE-CR study, which was considerably lower than generally reported in larger studies using the same antibiotics (colistin monotherapy or combination therapy) [31]. Most of the BAT regimens in the CREDIBLE-CR study used to treat CR *A. baumannii* were colistin-based combinations and nearly all 17 patients had an individual antibiotic regimen. In the CREDIBLE CR study, imbalances were found at randomization in some demographic parameters and patient factors for patients with CR *A. baumannii* infection (e.g. age, renal function, ICU location at randomization, and prior/ongoing shock) [31]. This highlights the need for additional large RCTs to investigate the role of cefiderocol in patients with CR *A. baumannii*. Of note, the recent APEKS-NP Phase 3 non-inferiority RCT, which compared cefiderocol

with high-dose, extended-infusion meropenem for patients with nosocomial pneumonia caused by a Gram-negative pathogen, included 36 patients with CR *A. baumannii* as their baseline Gram-negative pathogen [20]. In APEKS-NP, carbapenem resistance was based on EUCAST high-dose susceptibility breakpoint (i.e. resistant with meropenem MIC >8 µg/mL) [20]. No difference in ACM at Day 28 was observed in the subgroup of patients with CR *Acinetobacter* spp. between cefiderocol or high-dose, extended-infusion meropenem (cefiderocol 33%, meropenem 39%) [20].

The treatment patterns observed across these trials are reflective of current practice. A recent Europe-wide survey highlighted that physicians consider three main factors when selecting antibiotics for the treatment of CR infections: *in vitro* susceptibility, severity of illness, and infection site [44]. Patients with CR cUTI are usually treated with monotherapy, whereas patients with pneumonia, BSI, or intra-abdominal infections are treated mainly with combination therapy with the anticipation of antibiotic synergism against CR Gram-negative pathogens, despite the lack of rigorous clinical evidence [44]. In the PF-RCTs with BAT as the comparator arm [30,31], a high variability in antibiotic agents was found and these agents could have been given as either monotherapy or combination therapy. Although extreme caution should be exercised when making direct comparisons across trials due to heterogeneity in patients, infection sites, and pathogens, our current analysis suggests that monotherapy and combination therapy in severely ill patients resulted in similar Day 28 ACM rates. ACM rates were numerically lower with the newer antibiotics relative to colistin-based therapies for CRE infections [29–31]. A post-hoc analysis of the AIDA study highlighted a favorable trend in ACM for colistin plus meropenem combination in patients with CRE but not with CR *A. baumannii* infections [32]. However, ACM rates were largely equivocal, as reflected in the overlapping 95% CIs, across all combination and monotherapy regimens assessed for CR *A. baumannii* infections. The lack of mortality benefit with any studied combination or monotherapy regimen in CR *Acinetobacter* spp. infections potentially reflects the fact that patient factors substantially contribute to the observed ACM rates, and these are more difficult to balance when designing PF-RCTs of limited sample size.

It should be noted that the efficacy of the various new antibiotics was driven in part by their activity against different carbapenem resistance mechanisms. The mechanisms of carbapenem resistance are variable and frequently mixed in Gram-negative pathogens. Carbapenem resistance in Enterobacterales is driven mainly by the production of carbapenemase enzymes [45]. Among the non-fermenter species, carbapenemases are rarely expressed in CRPA, and carbapenem resistance is often the result of porin channel mutations or upregulated efflux pumps as well as overexpression of AmpC, whereas CR *A. baumannii* often expresses Ambler Class D carbapenemases such as oxacillinases OXA-23, OXA-24, or OXA-151 [46].

Several additional items should be considered when reviewing the findings across studies. The findings of our analysis are limited by the minimal information on CRPA for

which the search retrieved suitable data from the AIDA study, and information was subsequently obtained for the CREDIBLE-CR study. In the RESTORE-IMI 1 PF-RCT, ACM data for patients with CRPA infections were not reported separately, despite 77% of the patients having CRPA infections [36]. The small size and descriptive nature of the trials included in our analysis precludes a formal meta-analysis and the drawing of definitive conclusions. Interpretation of the results can be challenging when these small studies are conducted with high degree of heterogeneity and risk of bias [37,38]. Of note, the degree of heterogeneity and risk of bias were not assessed in this review as it was not a full systematic review, and it was not registered in the PROSPERO database. Instead, a comprehensive review of the registered studies and the available literature to identify studies with Day 28 ACM result in CR Gram-negative infections was conducted. However, two recently published review papers included quality appraisal of six of the analyzed studies included in our review. Five of the analyzed studies in this review were assessed in a systematic literature review conducted by Savoldi et al. [38]. According to their assessment, the AIDA study had low risk of bias in all six domains, the Durante-Mangoni study had moderate or critical risk of bias, the Sirijatuphat, TANGO II, and CARE studies had low, moderate and critical risk of bias. The second review paper by Hsueh et al. provides a meta-analysis of randomized, controlled studies investigating cefiderocol and assessed the risk of bias [47]. The assessment of the CREDIBLE-CR study found low or critical risk of bias across all six domains.

5. Conclusion

Pathogen-focused trials are vital to provide clinicians with guidance on the efficacy and safety of new antibiotics in their critically ill patients, for whom limited treatment options are available due to antimicrobial resistance. Understanding how to utilize new antibiotics once they are approved is of paramount importance to preserve their efficacy against difficult-to-treat and/or CR Gram-negative pathogens. Our analysis of seven recent randomized trials confirmed the value of these types of studies in generating clinically useful information.

6. Expert opinion

There is still a clear need for well-designed, larger pathogen-focused clinical studies [48]. PF-RCTs are challenging but necessary to gain a better understanding on the efficacy or effectiveness of antibiotics against the WHO priority pathogens. Although several antibiotics have recently been approved with activity against CR bacteria, they have varying *in vitro* activity against CR pathogens and stability against common carbapenemases. Of the new treatment options reviewed, cefiderocol has the broadest spectrum of activity against CR lactose- and non-lactose fermenters, such as *A. baumannii* or *P. aeruginosa*. To move away from the polymyxin-based therapies with increased toxicity, new treatment options are still needed, supported by prospective RCTs enrolling the type of patients in whom these agents are likely to be utilized.

In principle, pathogen-focused studies can either support regulatory approval of new antibiotics or provide complementary information on comparative effectiveness for antibiotics already used in clinical practice. Ideally, a single, prospective PF-RCT could address both objectives. The new antibiotics that are being developed to treat multidrug-resistant pathogens will certainly be restricted for use in specific patients infected by the target pathogens. The currently approved new beta-lactam/beta-lactamase inhibitors or the single agents plazomicin and cefiderocol can be selected, depending on the target species and mechanism of resistance, as control agents in future PF-RCTs. Notably, no uniform standard of care is available against CR infections [37].

Both pathogen-focused and double-blind, non-inferiority RCTs investigating new antibiotics with *in vitro* activity against the WHO priority pathogens are currently ongoing [45,48–51] and face many challenges. Undoubtedly, the design and execution of pathogen-focused studies can be (and should be) improved to facilitate enrollment and increase the sample size as studies may require a large number of investigation sites to enroll a limited number of patients for new antibiotics, particularly for pathogens with low and variable prevalence [29,50,51]. However, it will require a combined and maximized effort from regulatory agencies, diagnostic device manufacturers, and clinical investigators. Within the context of regulatory clinical trial requirements, rapid diagnostic tests, especially direct specimen polymerase chain reaction (PCR), could greatly facilitate the screening to randomization process. Rapid diagnostic tests are particularly useful in confirming MBL-producing pathogenic bacteria, which have very few treatment options. However, incorporation of rapid diagnostics in PF-RCTs is logistically challenging as the commercially available rapid diagnostic products are not approved for use in all the countries and hospitals that participate in PF-RCTs, and currently these tools are not part of routine microbiological testing. Target pathogen-focused studies are important to understand the usefulness of any new antibiotic being developed to address antimicrobial resistance, but these studies are often too confounded to be suitable for regulatory approval. Furthermore, it needs to be considered that the current reimbursement model for new antibiotics is insufficient to support robust post-marketing, comparative effectiveness studies. Government-funded agencies should be involved to fund RCTs in order to support organized efforts by expert clinicians.

The key to improvement in efficiency of pathogen-focused clinical trials is the utilization of rapid diagnostics during screening for the desired pathogen. Direct specimen (e.g. blood, respiratory specimen, or urine) or culture-derived PCR or other nucleic acid amplification test, as well as easy biochemical tests, can identify the specific genes or phenotype for carbapenem resistance within a few hours. Unfortunately, such tests may have their own regulatory hurdles and, depending on the country and investigation site, these tests may be considered experimental requiring an additional time-consuming informed consent prior to screening of patients. Alternatively, expanding the use of local surveillance cultures and colonization status,

before the patient develops an infection, could be considered to enrich the patient population [52].

Although mortality has traditionally been used in certain infection site-specific trials among severely ill patients with infections in the critical care setting, it is often related to underlying illnesses and disease severity [53,54]. In addition, the detection of inter-treatment differences in mortality rates requires larger patient numbers [53], which may not be achievable in pathogen-focused studies [26,37]. Consideration should instead be given to composite endpoints (i.e. desirability of outcome ranking [DOOR]) [55], nested trial designs, and safety endpoints, along with improved statistical analysis approaches [52]. Endpoints more proximal to the treatment intervention, and 'soft' but still clinically meaningful endpoints, such as ICU-free or ventilator-free days, may be useful alternatives [54,56]. While there is increased interest in examining composite DOOR endpoints, they should be carefully discussed for their suitability prior to incorporation into the design of PF-RCTs, which are heterogeneous in terms of infection sites and pathogens. Once a heterogeneous patient population is enrolled with various infection types, one composite endpoint may not be suitable. The uniform, most objective endpoint across antibiotic trials is all-cause mortality with dichotomous results and its combination with another endpoint prerequisites that the patient is alive. Depending on the comparator arm, a safety endpoint, such as acute kidney injury, may be combined with mortality or a clinical outcome [53]. However, it is known that composite endpoints are challenging to interpret if clinically more important effects (e.g. mortality) are hidden by less important components [53]. Better delineations of regulatory pathways to investigate certain CR pathogens, and standardization of BAT, infection sites, and definitions of carbapenem resistance and treatment response are also required to facilitate cross-study comparisons.

We need to identify ways to enhance enrollment of sufficient patient numbers to these types of studies, which may require broader collaborations such as ECRAID or COMBACTE, innovative study designs, and more suitable study endpoints [57,58]. Until such innovative clinical trials become available, real-world evidence from post-marketing prospective or retrospective observational studies will provide additional information [59]. For example, adaptive and hybrid clinical trial designs may enable prompt enrollment as soon as CR Gram-negative infection is confirmed [27,60]. In addition, rapid diagnostic testing can facilitate patients being enrolled into studies earlier, reducing the confounding effects of prior antibiotic treatment. Finally, the inclusion of pharmacokinetic/pharmacodynamic data may enable refinement of exposure-response analyses.

Both types of studies, such as those for regulatory approval of new agents and those investigating comparative effectiveness, will improve our understanding in the treatment of multi-drug-resistant and/or CR Gram-negative infections. Their success relies on the combination of inter-related factors such as global epidemiology, local antibiotic resistance, evolving mechanism of resistance, understanding of risk factors, patient factors, physicians' experience with and availability of control agents, and regulatory requirements, study design, sample size,

selected outcomes, and robustness of analysis. Nevertheless, they are equally important to combat antimicrobial resistance.

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Author contributions

All authors had substantially contributed to the conception and design of the review article, interpretation of the relevant literature, drafting the review article and/or revising it for intellectual content.

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Geolocation information

The reviewed studies enrolled patients globally.

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Data availability

Details of best available therapy and unpublished mortality in the CREDIBLE-CR study included in the current manuscript were provided by Shionogi & Co., Ltd., Osaka, Japan, on request from the authors. All other data included in the manuscript were available in the full-text articles of the studies.

ORCID

Ricard Ferrer  <http://orcid.org/0000-0002-4859-4747>
Thierry Naas  <http://orcid.org/0000-0001-9937-9572>

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