AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

MINIREVIEW

Treatment of Infections by OXA-48-Producing *Enterobacteriaceae*

Adam Stewart,[a] Patrick Harris,[a] Andrew Henderson,[a] David Paterson[a]

[a]Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Royal Brisbane and Women's Hospital Campus, Brisbane, Australia

ABSTRACT Carbapenemase-producing *Enterobacteriaceae* (CPE) contribute significantly to the global public health threat of antimicrobial resistance. OXA-48 and its variants are unique carbapenemases with low-level hydrolytic activity toward carbapenems but no intrinsic activity against expanded-spectrum cephalosporins. bla_{OXA-48} is typically located on a plasmid but may also be integrated chromosomally, and this gene has progressively disseminated throughout Europe and the Middle East. Despite the inability of OXA-48-like carbapenemases to hydrolyze expanded-spectrum cephalosporins, pooled isolates demonstrate high variable resistance to ceftazidime and cefepime, likely representing high rates of extended-spectrum beta-lactamase (ESBL) coproduction. *In vitro* data from pooled studies suggest that avibactam is the most potent beta-lactamase inhibitor when combined with ceftazidime, cefepime, aztreonam, meropenem, or imipenem. Resistance to novel avibactam combinations such as imipenem-avibactam or aztreonam-avibactam has not yet been reported in OXA-48 producers, although only a few clinical isolates have been tested. Although combination therapy is thought to improve the chances of clinical cure and survival in CPE infection, successful outcomes were seen in ~70% of patients with infections caused by OXA-48-producing *Enterobacteriaceae* treated with ceftazidime-avibactam monotherapy. A carbapenem in combination with either amikacin or colistin has achieved treatment success in a few case reports. Uncertainty remains regarding the best treatment options and strategies for managing these infections. Newly available antibiotics such as ceftazidime-avibactam show promise; however, recent reports of resistance are concerning. Newer choices of antimicrobial agents will likely be required to combat this problem.

KEYWORDS *Enterobacteriaceae*, Gram-negative bacteria, antibiotic resistance, carbapenems

Infection due to carbapenemase-producing *Enterobacteriaceae* (CPE) carries a significantly high attributable mortality (1). CPE infections are steadily increasing worldwide and spreading to several countries (2). Moreover, they are increasing as a proportion of the total *Enterobacteriaceae* infections, with *Klebsiella* species being the predominant type (3). OXA-48 is a carbapenemase produced by a growing number of CPE isolates (4). Plasmid-mediated spread has led it to become a growing problem in the Middle East, North Africa, and Europe, especially in the Mediterranean (2, 4). Turkey, the Middle East, and North African countries (mainly Morocco, Tunisia, Egypt, and Libya) are considered the principal reservoirs (5). OXA-181 appears to be unique in having India as its main reservoir (6). There have been OXA-48-like producing isolates reported in Lebanon, the Sultanate of Oman, Saudi Arabia, Kuwait, and recently in European countries, including France, Germany, The Netherlands, Italy, Belgium, the United Kingdom, Ireland, Slovenia, Switzerland, and Spain (5). Although thought to be almost absent from the Americas, reports have revealed their slow emergence (3). Australia

Accepted manuscript posted online 13 August 2018

Citation Stewart A, Harris P, Henderson A, Paterson D. 2018. Treatment of infections by OXA-48-producing *Enterobacteriaceae*. Antimicrob Agents Chemother 62:e01195-18. https://doi.org/10.1128/AAC.01195-18.

Address correspondence to Adam Stewart, adm_stewart@hotmail.com.

and New Zealand have both reported sporadic cases (7). A recent community-acquired urinary tract infection in Algeria has raised concerns regarding community reservoirs of bla_{OXA-48} (8). Hospital outbreaks involving OXA-48-producing *Enterobacteriaceae* have been reported in France, Germany, Switzerland, the Netherlands, and the United Kingdom (9). The clonal expansion of *Escherichia coli* ST38 carrying a chromosomally integrated bla_{OXA-48} has also been documented (10). The OXA-48 enzyme is an Ambler class D beta-lactamase that hydrolyzes carbapenems but shows very weak activity against extended-spectrum cephalosporins such as cefepime and ceftazidime (2), although isolates are frequently multidrug resistant as they combine multiple resistance mechanisms (11). The gene encoding OXA-48, bla_{OXA-48}, appears to have originated from *Shewanella oneidensis* that naturally harbors bla_{OXA-54}, which has a 92% amino acid sequence homology with bla_{OXA-48} (12).

The first identification of OXA-48-producing *Enterobacteriaceae* was from an isolate in Turkey in 2001 (13). Shortly thereafter, there was an outbreak of OXA-48-producing *Klebsiella pneumoniae* isolates reported in Istanbul in 2006 (14). Since its recognition, there have been increasing numbers of reports of OXA-48-producing organisms worldwide, particularly in Europe (2). OXA-48 carbapenemases appear to be uncommon in the United States, with the first reported OXA-48-producing isolate identified in 2009 (5, 15). Of 52 identified isolates producing OXA-48-like carbapenemases in the United States between 2010 and 2015, two-thirds were acquired from outside the United States (most frequently India), and the majority of these involved patients hospitalized while overseas (3). OXA-48-like carbapenemases have also been subsequently described, which include OXA-181 and OXA-163 (2). The OXA-181 variant, which differs from OXA-48 by four amino acid substitutions, is prominent in India and has been associated with other carbapenemase genes, including bla_{NDM-1} and bla_{VIM-5} (16). OXA-181 has a similar pattern of resistance to OXA-48; however, OXA-163 hydrolyzes extended-spectrum cephalosporins but has only weak activity against carbapenems (2). Reviewing the treatment efficacy of different antimicrobials is somewhat challenging due to a paucity of clinical data, often related to the inherent difficulties in laboratory detection of OXA-48 producers due to many of the isolates falling within the susceptible range for carbapenems. The challenge of detecting OXA-48 producers is outside the scope of this review and the authors direct the readers to other reviews on this topic (6). Currently, there is a lack of evidence and data on treating infections due to OXA-48 producers, as recent CPE literature has focused more on *Klebsiella pneumoniae* carbapenemase (KPC)-producers.

IN VITRO ACTIVITY AGAINST OXA-48 PRODUCERS

OXA-48 producers display a unique *in vitro* susceptibility pattern, often making detection difficult with phenotypic methods alone (17). Initial early descriptions of the dissemination of OXA-48 enzymes were linked to a single IncL/M-type plasmid not containing any other resistance genes (5). However, more recently, epidemiologic studies have demonstrated a strong association with other beta-lactamase genes, in particular, extended-spectrum beta-lactamases (ESBLs) (18). OXA-48 is known to hydrolyze penicillins at a high level and carbapenems at a low level, sparing expanded-spectrum cephalosporins (5). Most current available beta-lactamase inhibitors (BLI) act only against class A beta-lactamases, remaining ineffective against OXA-48 producers. This has led to a recent surge in research evaluating the *in vitro* effectiveness of new BLI and beta-lactam–BLI combinations. Ceftazidime, cefepime, and aztreonam are not substrates for the OXA-48 beta-lactamase (19, 20). Numerous studies have demonstrated ceftazidime *in vitro* efficacy against OXA-48 producers, in the absence of ESBL coproduction (18, 21–23). Aztreonam, a member of the monobactam class of antibiotics, is stable from hydrolysis by OXA-48 enzymes and also demonstrates activity against metallo-beta-lactamase (MBL)-producing organisms (20, 24). There appears to be variability in the levels of hydrolysis among the different carbapenem antimicrobials. Carbapenems have been evaluated both *in vitro* and in a murine peritonitis model (20, 25). Doripenem and imipenem, despite testing susceptible *in vitro*, were not efficacious

in an *in vivo* murine model; ertapenem displayed little activity *in vivo* and *in vitro* with an MIC of 3 mg/liter (20). Moreover, all 30 OXA-48 isolates characterized in a recent study from the United States were ertapenem resistant (26). There have been a number of case reports and series describing treatment failures with carbapenem-containing regimens in the treatment of OXA-48-producing bacterial infections (4, 27–29). Dual carbapenem combinations, particularly those with imipenem, have shown synergy *in vitro* against both OXA-48 and KPC producers (30, 31). Although, only some study isolates (*K. pneumoniae* but not recombinant *E. coli*) showed this result and produced values close to the cutoff value for defining synergy (30). Interestingly, levofloxacin exhibited activity against isogenic OXA-48 strains, but demonstrated little activity against clinical isolates and failed to suppress infection in an *in vivo* mouse model. Temocillin, a carboxypenicillin used to treat multiresistant Gram-negative organisms, is hydrolyzed efficiently by OXA-48 and failed to demonstrate efficacy in a mouse model (20). Moreover, high-level temocillin resistance has been included in algorithms to aid in OXA-48 recognition (32). Amdinocillin, an old extended-spectrum penicillin, had *in vitro* activity in 48% of OXA-48 producers in one study when using an extrapolated urinary breakpoint MIC of 8 mg/liter (33). Polymyxins, namely, colistin, have shown inconsistent and variable results in *in vitro* studies, with many reporting resistance in *K. pneumoniae*, *E. coli*, and *Enterobacter* species clinical isolates found to produce OXA-48 (11, 34). Colistin resistance, likely mediated by alterations in the *mgrB* gene, was probably acquired after clonal dissemination of an OXA-48-producing isolate identified during an outbreak in France in 2014 (34). Moreover, the addition of fosfomycin to colistin was found to be antagonistic against 12 OXA-48 strains (11). This finding was not statistically significant and it is unclear whether it is specific to OXA-48-producing *K. pneumoniae* isolates, as there were no controls used in the study (11). Inconsistencies with regard to *in vitro* susceptibility have been observed with the glycylcycline antibiotic tigecycline, with a broad range of percentages for susceptible isolates identified across different studies (35–38). Table 1 lists MICs for a variety of these drugs.

Novel beta-lactamase inhibitors. New and established beta-lactamase inhibitors have been extensively studied for their activity against OXA-48-producing *Enterobacteriaceae*. OXA-48 carbapenemases are not effectively inhibited by commonly used BLI such as clavulanic acid, tazobactam, and sulbactam, which mainly inhibit class A beta-lactamases (21). Avibactam is a diazabicyclooctane (DBO), a non-beta-lactam BLI which may have the ability to inhibit OXA-48 beta-lactamase by forming a stable covalent complex (21). In one study, it improved the efficacy of imipenem against OXA-48-producing *K. pneumoniae* isolates with an MIC_{50} of 0.016 mg/liter, equating to a 500-fold reduction in the MIC_{50} value. It also demonstrates inhibition of class A and C beta-lactamases, making its combination with cefepime and ceftazidime effective against OXA-48–ESBL-coproducing organisms, resulting in 266- and 1,000-fold reductions in MIC_{50} value, respectively (21, 23). Avibactam has also been combined with aztreonam, exhibiting a stability from hydrolysis with OXA-48, MBLs, ESBLs, AmpC, and KPC (33). Vaborbactam, a cyclic boronic acid BLI, exhibited no activity against isolates harboring bla_{OXA-48} when combined with meropenem (39). Moreover, relebactam, another novel BLI, also showed no activity when combined with imipenem (23). It is unclear whether the novel DBO BLI zidebactam is effective at inhibiting OXA-48 due to it being combined in one study with cefepime, which is known to be stable against OXA-48 (22). Compound CB-618 is another novel DBO BLI that has shown promise, with *in vitro* susceptibility of OXA-48 producers when combined with meropenem (40). Compound ETX2514 is yet another broad-spectrum DBO with activity against class D beta-lactamases and is currently in clinical development in combination with sulbactam for the treatment of *Acinetobacter baumannii* infections (41). ETX2514 also potently inhibits penicillin-binding proteins, resulting in intrinsic antibacterial activity that has confounded its analysis as a novel BLI (42). WCK 234 is a DBO that displayed uniquely high activity against strains with class D carbapenemases when paired with imipenem and meropenem in one study. It is a pure BLI and is not known to display direct

TABLE 1 *In vitro* activity against OXA-48 producers

Drug	Reference(s)	Total no. of isolates tested across all studies	MIC (mg/liter)			% susceptible
			50%	90%	Range	
Ceftazidime	18, 21, 23, 26, 33, 35, 36, 37, 62, 70	674	0.12 to 256	128 to 512	0.06 to 512	8 to 40
Cefepime	18, 21, 22, 26, 46, 50, 70	242	0.25 to 32	16 to 512	0.12 to >512	0 to 46
Aztreonam	18, 33, 35, 36, 37, 70	599	128	128 to >512	<0.015 to >512	12.2 to 27
Meropenem	18, 26, 35, 36–40, 50, 62, 71	734	0.06 to 128	0.25 to 256	2 to 256	0 to 87.8
Doripenem	18, 26, 70	170	>4	0.5 to >4	0.25 to >4	10 to 83.3
Ertapenem	18, 26, 35, 36	373	>1	1 to >8	>1	0 to 4.1
Imipenem	18, 23, 26, 35, 36, 72	781	0.12 to 32	8 to 256	1 to 256	0 to 74.8
Levofloxacin	18, 70	140	>4	>4	0.03 to >4	0 to 20.9
Amdinocillin	33	14	—[a]	—	—	43
Plazomicin (ACHN-490)	73, 74	19	<0.12 to 64	—	<0.12 to 64	—
Amikacin	18, 26, 35, 36, 37, 73	628	1 to 8	2 to >64	0.5 to >64	36.7 to 100
Gentamicin	73	19	0.25 to 128	—	0.25 to >128	68
Colistin	18, 26, 34–36, 38	520	<0.12 to 0.25	1 to 128	0.015 to 128	75.4 to 100
Tigecycline	18, 26, 35, 36–38	649	0.25 to 1	2	0.12 to 8	36 to 91
Fosfomycin	35, 36	281	—	—	—	44.8 to 82
Piperacillin-tazobactam	18, 62, 70	155	128	128 to 256	32 to 256	0
Ceftazidime-avibactam	18, 19, 21, 23, 33, 37, 62	705	0.03 to 1	0.5 to 256	<0.008 to 256	80 to 100
Cefepime-avibactam	21	26	0.016 to 0.12	0.5	<0.008 to 0.5	100
Cefepime-zidebactam	22	15	<0.03	—	—	100
Cefepime-tazobactam	46	25	1 to 8	—	1 to 8	80
Imipenem-avibactam	21	26	0.016 to 0.5	0.5	<0.008 to 2	100
Imipenem-relebactam	23	4	1 to 8	—	1 to 8	25
Aztreonam-avibactam	24, 33	71	0.12 to 0.25	0.25 to 1	0.12 to 1	100
Meropenem-vaborbactam	39, 71	62	16	≥32	0.12 to >32	0 to 3.8
Ceftolozane-tazobactam	19, 47	21	1 to >256	>256	0.5 to >256	13 to 50
Cefiderocol (S-649266)	50	6	0.25	2	0.125 to 2	—
Meropenem–CB-618	40	2	0.25 to 0.5	—	0.25 to 0.5	—

[a]—, data not available.

antibacterial activity (43). LN-1-255 is a penicillin sulfone derivative highly effective at inhibiting OXA-48, as demonstrated in clinical isolates and in porin-deficient transformed *K. pneumoniae*. It has a 33-fold higher inhibition efficiency than tazobactam and binds OXA-48 very effectively (44). A focused fragment library has been set up to examine the *in vitro* inhibitory activity of 49 benzoic acid derivative fragments against OXA-48 as well as to observe their binding pockets and conformations (45). This approach shows promise in identifying new molecules for building novel BLIs.

Novel antibiotics. The MIC values for ceftazidime-resistant OXA-48 producers, presumably due to the coproduction of ESBLs, to the new antibiotic ceftolozane-tazobactam are mostly higher than for cefepime-tazobactam (46). In a study of 353 OXA-48-producing isolates, 81.9% of those with a ceftazidime MIC of ≤4 mg/liter were susceptible (EUCAST and CLSI breakpoint, ≤1 mg/liter) to ceftolozane-tazobactam (C/T), with only 8.1% of those with an MIC of ≥4 mg/liter to ceftazidime reported as susceptible to C/T (47). The mechanism for this observation is unknown and needs further investigation; however, explanations include the carriage of additional porin mutations or the possibility of OXA-48 overwhelming tazobactam, rendering it unable to protect ceftolozane against AmpC or ESBL enzymes. The next-generation aminoglycoside plazomicin inhibited all carbapenemase-producing *K. pneumoniae* isolates (MIC < 1 mg/liter) (48). As with other aminoglycosides, its *in vitro* activity is compromised by the presence of ribosomal methylases, including ArmA and RmtC. The frequency of these resistance determinants in OXA-48 producers is uncertain but understood to be significant (49). Plazomicin showed activity against all CPE isolates irrespective of species, carbapenemase production, or level of resistance to antibiotics. In addition, synergy was observed at physiologically attainable concentrations when plazomicin was combined with colistin, meropenem, and fosfomycin (48). A new siderophore cephalosporin, cefiderocol (S-649266), demonstrated activity against OXA-48-producing strains of *K. pneumoniae* and *Enterobacter cloacae*,

with MIC values between <0.125 and 2 mg/liter (50). The novel fluorocycline antibiotic eravacycline demonstrated *in vitro* efficacy against CPE isolates and carbapenem-nonsusceptible *Acinetobacter baumannii* (51, 52). It has demonstrated noninferiority to ertapenem in the treatment of complicated intraabdominal infection (cIAI) and is awaiting planned clinical trials assessing its utility in complicated urinary tract infections (cUTIs) (53). Although efficacy in OXA-48-like producers has not been specifically evaluated, eravacycline remains a possible candidate for future treatment options for nosocomial and infections due to multidrug-resistant (MDR) pathogens.

RISK FACTORS FOR OXA-48-PRODUCING ORGANISM COLONIZATION AND INFECTION

Identifying patient risk factors for colonization and infection is of great importance in relation to the timely institution of effective therapy. In areas where OXA-48-producing organisms are rarely encountered, recent travel to an area with a high prevalence provides a significant risk for acquisition (3). The identified risk factors for colonization of OXA-48-producing organisms include previous intraabdominal surgery, gastrointestinal or biliary endoscopy, hospitalization and intensive care unit (ICU) admission, and antibiotic intake (54). Male sex and advanced age were identified as factors in another study (55). A multivariate analysis identified the prior administration of a third- or fourth-generation cephalosporin ($P < 0.001$) and beta-lactam–BLI combination ($P < 0.001$) as strong risk factors for colonization (54). An estimated 10% to 30% of patients who are colonized with OXA-48-producing CPE will develop infections (56). Another study identified a modest <10% infection rate in colonized patients (57). The risk factors for infection are previous interhospital transfers, admission to an ICU within the previous 3 months, invasive procedures during hospitalization (including the insertion of a central venous line), and mechanical ventilation (56). In addition, the cumulative infection risk was found to progressively increase during the first 100 days in the hospital. Overall, higher rates of colonization and/or infection were seen with other multidrug-resistant Gram-negative organisms than with OXA-48-producing CPE.

TREATMENT OPTIONS

An ideal antimicrobial therapy for OXA-48-producing *Enterobacteriaceae* infection has not been established. A scarcity of clinical data, the heterogeneity in pathogen genotypes assessed, and the nonrandomization and retrospective nature of most studies have contributed to our inability to answer critical questions. Extended-spectrum cephalosporin monotherapy has been used successfully in two case reports for presumed ESBL-negative OXA-48-positive infection, although this is uncommon (58, 59). Carbapenem monotherapy has been used, with various reported rates of success. Meropenem and imipenem were the only carbapenems used as monotherapies in confirmed infections with OXA-48-producing organisms, with clinical cure and survival rates ranging between 0% and 66% (4, 27–29). Most cases were bloodstream infections, often complicating intravenous catheter placement. The treatment failure of carbapenem monotherapy is likely higher, as many treatment successes involved the removal of the central venous catheters. Amikacin has also been used with moderate success, with two successful outcomes in catheter-related bloodstream infections; however, a death was observed in a case of complicated urinary tract infection (27). Its success is likely also related to the prevalence of alternative mechanisms of resistance in local isolates. Colistin monotherapy resulted in a clinical cure in one case of OXA-48-producing *K. pneumoniae* bacteremia (27). Tigecycline has been used as a single-agent therapy in two cases of bacteremia secondary to a complicated intraabdominal and soft tissue infection (27). Although surgical intervention was a key component of their management, both patients had successful outcomes with tigecycline (27). Ceftazidime-avibactam as a salvage therapy for CPE infection has shown promise in a case series. In hematology patients with CPE bacteremia, 28/38 patients (73.7%) achieved clinical and/or microbiological cure with ceftazidime-avibactam as a

monotherapy or in combination with another antimicrobial, with a delay in therapy being associated with worse outcomes (60). For infections caused by OXA-48 producers, salvage ceftazidime-avibactam produced clinical cure, microbiological cure, and survival to discharge in 8/13 (61.5%), 6/13 (46%), and 5/13 (38.5%) cases, respectively (60). In comparison, in those infected with KPC-producing *Enterobacteriaceae*, the treatment yielded rates of 17/23 (74%), 18/23 (78%), and 17/23 (74%), respectively. Of all CPE organisms, clinical cure occurred among 68% and 32% of KPC and OXA-48 producers, respectively, suggesting an advantage of ceftazidime-avibactam against this type of carbapenemase (60). Castón et al. reported a higher probability of clinical cure with ceftazidime-avibactam in CPE bacteremia; however, no significant difference in mortality was noted compared to that with other antimicrobial regimens (61). Although the majority of CPE isolates included in that study produced an OXA-48 carbapenemase (61.3%), a significant number produced a *Klebsiella pneumoniae* carbapenemase (KPC) (61). Surveillance data have suggested that resistance to ceftazidime-avibactam among CPE isolates (excluding those producing Ambler class B beta-lactamases) is rare. A recent case report documented the genetic evidence for MIC elevations resulting in full nonsusceptibility emerging *in vivo* through the evolution of $bla_{\text{CTX-M-14}}$ in a OXA-48-producing *K. pneumoniae* strain (62).

Combination therapy is often used for CPE infections and is proposed to offer reduced mortality and fewer treatment failures (63). A large international prospective study noted an improved survival within combination therapy, but only in those with high mortality scores (64). In infections involving OXA-48 carbapenemases, dual- and triple-therapy regimes containing various combinations of a carbapenem, aminoglycoside, colistin, tigecycline, and fosfomycin have been used with moderate success. A carbapenem, either imipenem or meropenem, plus colistin has been used in seven cases involving catheter-related bloodstream infections, pneumonia, and intraabdominal infection (4, 27, 29, 65). Only 3/7 (42.8%) patients treated with this regimen achieved a clinical cure and survived. However, the addition of amikacin to a carbapenem, when there is susceptibility to amikacin, achieved better outcomes, with 3/4 (75%) patients with OXA-48 bloodstream infections treated with this regimen surviving (27, 66). Colistin has been used in combination with both tigecycline and fosfomycin in six and four patients, respectively, in a large retrospective case series by Navarro-San Francisco et al. which documented survival rates of 5/6 (83%) and 3/4 (75%) (27). Non-carbapenem- and non-colistin-based dual therapies with tigecycline and amikacin were used in four patients in the same case series, which reported survival in 50% (27). Treatment failure and mortality were lower among those who received colistin, carbapenem, and/or an aminoglycoside in a combination regimen, although the combination of colistin and an aminoglycoside was noted to be significantly nephrotoxic (63). An increase in survival was noted with carbapenem-containing regimens when meropenem MIC values were $<$4 mg/liter (63).

Conversely, another study documenting an outbreak of OXA-48-producing CPE reported an increase in mortality associated with imipenem-containing therapy (4). A lack of adequate detection of OXA-48-producing strains was noted in this case series, attributed to low-level resistance to carbapenems and a lack of additional ESBLs, which may have contributed to the higher mortality rate. In bloodstream infections due to OXA-48-producing *Enterobacteriaceae*, a non-colistin-based combination regimen was found to be an independent risk factor for death in one study (67). When colistin was used, the survival rates were not significantly different when it was combined with either a carbapenem, a aminoglycoside, or a broad-spectrum cephalosporin in the setting of bacteremia (27). Interestingly, colistin has been reported as the least effective when used as a monotherapy (67).

Ceftazidime-avibactam combined with aztreonam *in vitro* demonstrated a synergistic effect against MBL-coproducing *Enterobacteriaceae* in two reports, being particularly effective against *K. pneumoniae* isolates, again highlighting the need to assess additional mechanisms of carbapenem resistance in OXA-48-carrying strains (68). Lastly, nonantibiotic options have been explored with an OXA-48-type carbapenemase-

TABLE 2 Treatment options for OXA-48 producers

Drug regimen	Reference(s)	No. of patients	Type of infection (*n*)	Microbiological cure (%)	Survival at 14–30 d (%)
Ceftriaxone	27, 59	2	Endometritis (1) Bloodstream infection (1)	—[a]	100
Carbapenem	4, 27–29	10	Pneumonia (1) Bloodstream infection (9)	—	0–66
Amikacin	27	3	Bloodstream infection (3)	—	66
Colistin	27	1	Bloodstream infection (1)	—	100
Tigecycline	27	2	Bloodstream infection (2)	—	100
Ceftazidime-avibactam	60, 61	18	Bloodstream infection (5)	25	22.7–70.6
Ceftazidime plus colistin	58	1	Catheter-related bloodstream infection (1)	—	100
Carbapenem plus amikacin	27, 66	4	Bloodstream infection (4)	—	66–100
Carbapenem plus colistin	4, 27, 29, 65	7	Catheter-related bloodstream infection (1) Bloodstream infection (4) Pneumonia (1) Intraabdominal infection (1)	—	0–100
Colistin plus fosfomycin	27	4	Bloodstream infection (4)	—	75
Colistin plus amikacin	27	1	Bloodstream infection (1)	—	100
Tigecycline plus amikacin	27	4	Bloodstream infection (4)	—	50
Tigecycline plus fosfomycin	27	1	Bloodstream infection (1)	—	100
Tigecycline plus colistin	27	6	Bloodstream infection (6)	—	83
Carbapenem plus amikacin plus colistin	4	2	Catheter-related bloodstream infection (1) Pneumonia (1)	—	50
Colistin plus amikacin plus tigecycline	27	2	Bloodstream infection (2)	—	50

[a]—, data not available.

producing *K. pneumoniae* diabetic foot osteomyelitis acquired in Tunisia, which was successfully treated with hyperbaric oxygen therapy alone (69). Overall, these observations highlight the variability and unpredictability of appropriate therapeutic options for this type of infection. Table 2 lists the treatment options for OXA-48 producers.

TREATMENT STRATEGIES

An approach to treating infections due to OXA-48-producing *Enterobacteriaceae* is undefined and yet to be rigorously studied. Given the unavailability of a single effective antibiotic, multiple strategies have been proposed and advocated for in various retrospective studies involving low patient numbers. Combination therapies using two or three agents with demonstrated activities against an OXA-48-producing isolate have demonstrated a mortality benefit compared with that for monotherapy, in a systematic review (63). No difference was noted between dual and triple-therapy regimens. Another study reported greater survival and microbiological cure of patients with OXA-48-producing *Enterobacteriaceae* bacteremia than in those treated with a single agent; however, this was attributed to greater source control and catheter removal (67). Despite a theoretical benefit, there are no clinical data to support the notion that combination therapy reduces the emergence of resistance (63).

CONCLUSION

Patients with infection due to OXA-48-producing *Enterobacteriaceae* experience high mortality, as evidenced by a 30-day mortality rate of 50% in patients with bacteremia (27). The progressive spread of bla_{OXA-48}-containing organisms has been clearly documented in Africa, the Middle East, and Europe, particularly in the Mediterranean, and is an active threat to the rest of the world (2, 3). OXA-48 has low-level carbapenem hydrolytic activity and resistance, making it difficult to detect by standard laboratory methods and making treatment failure common. A number of antibiotics have shown *in vitro* activity against OXA-48-producing *Enterobacteriaceae*; however, the results have been largely inconsistent. In addition, colistin-based regimens are toxic and not well tolerated (63). Ceftazidime-avibactam perhaps has proven to be most successful according to available *in vitro* and clinical data; however, reports of resistance are emerging. New BLIs, paired with appropriate beta-lactams, are being developed which may provide a solution in the future. New antibiotic choices and randomized controlled

trials are needed to inform future decision making and increase the armamentarium used to treat these difficult infections.

REFERENCES

1. Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. 2014. Deaths attributable to carbapenem-resistant *Enterobacteriaceae* infections. Emerg Infect Dis 20:1170–1175. https://doi.org/10.3201/eid2007.121004.
2. Mairi A, Pantel A, Sotto A, Lavigne JP, Touati A. 2017. OXA-48-like carbapenemases producing *Enterobacteriaceae* in different niches. Eur J Clin Microbiol Infect Dis 37:587–604. https://doi.org/10.1007/s10096-017-3112-7.
3. Lyman M, Walters M, Lonsway D, Rasheed K, Limbago B, Kallen A. 2015. Notes from the field: carbapenem-resistant *Enterobacteriaceae* producing OXA-48-like carbapenemases–United States, 2010–2015. MMWR Morb Mortal Wkly Rep 64:1315–1316. https://doi.org/10.15585/mmwr.mm6447a3.
4. Cuzon G, Ouanich J, Gondret R, Naas T, Nordmann P. 2011. Outbreak of OXA-48-positive carbapenem-resistant *Klebsiella pneumoniae* isolates in France. Antimicrob Agents Chemother 55:2420–2423. https://doi.org/10.1128/AAC.01452-10.
5. Poirel L, Potron A, Nordmann P. 2012. OXA-48-like carbapenemases: the phantom menace. J Antimicrob Chemother 67:1597–1606. https://doi.org/10.1093/jac/dks121.
6. Bakthavatchalam YD, Anandan S, Veeraraghavan B. 2016. Laboratory detection and clinical implication of oxacillinase-48 like carbapenemase: the hidden threat. J Glob Infect Dis 8:41–50. https://doi.org/10.4103/0974-777X.176149.
7. Howard JC, Anderson T, Creighton J, Freeman JT. 13 July 2018. Geographical and temporal clustering of OXA-48-producing *Escherichia coli* ST410 causing community-onset urinary tract infection in Christchurch, New Zealand. J Antimicrob Chemother https://doi.org/10.1093/jac/dky269.
8. Loucif L, Chelaghma W, Helis Y, Sebaa F, Baoune RD, Zaatout W, Rolain JM. 2018. First detection of OXA-48-producing *Klebsiella pneumoniae* in community-acquired urinary tract infection in Algeria. J Glob Antimicrob Resist 12:115–116. https://doi.org/10.1016/j.jgar.2017.12.017.
9. Nordmann P, Poirel L. 2014. The difficult-to-control spread of carbapenemase producers among *Enterobacteriaceae* worldwide. Clin Microbiol Infect 20:821–830. https://doi.org/10.1111/1469-0691.12719.
10. Turton JF, Doumith M, Hopkins KL, Perry C, Meunier D, Woodford N. 2016. Clonal expansion of *Escherichia coli* ST38 carrying a chromosomally integrated OXA-48 carbapenemase gene. J Med Microbiol 65:538–546. https://doi.org/10.1099/jmm.0.000248.
11. Evren E, Azap OK, Colakoglu S, Arslan H. 2013. *In vitro* activity of fosfomycin in combination with imipenem, meropenem, colistin and tigecycline against OXA 48-positive *Klebsiella pneumoniae* strains. Diagn Microbiol Infect Dis 76:335–338. https://doi.org/10.1016/j.diagmicrobio.2013.04.004.
12. Poirel L, Heritier C, Nordmann P. 2004. Chromosome-encoded ambler class D beta-lactamase of *Shewanella oneidensis* as a progenitor of carbapenem-hydrolyzing oxacillinase. Antimicrob Agents Chemother 48:348–351. https://doi.org/10.1128/AAC.48.1.348-351.2004.
13. Poirel L, Heritier C, Tolun V, Nordmann P. 2004. Emergence of oxacillinase-mediated resistance to imipenem in *Klebsiella pneumoniae*. Antimicrob Agents Chemother 48:15–22. https://doi.org/10.1128/AAC.48.1.15-22.2004.
14. Carrër A, Poirel L, Eraksoy H, Cagatay AA, Badur S, Nordmann P. 2008. Spread of OXA-48-positive carbapenem-resistant *Klebsiella pneumoniae* isolates in Istanbul, Turkey. Antimicrob Agents Chemother 52:2950–2954. https://doi.org/10.1128/AAC.01672-07.
15. Humphries RM, Yang S, Hemarajata P, Ward KW, Hindler JA, Miller SA, Gregson A. 2015. First report of ceftazidime-avibactam resistance in a KPC-3-expressing *Klebsiella pneumoniae* isolate. Antimicrob Agents Chemother 59:6605–6607. https://doi.org/10.1128/AAC.01165-15.
16. Potron A, Nordmann P, Lafeuille E, Al Maskari Z, Al Rashdi F, Poirel L. 2011. Characterization of OXA-181, a carbapenem-hydrolyzing class D beta-lactamase from *Klebsiella pneumoniae*. Antimicrob Agents Chemother 55:4896–4899. https://doi.org/10.1128/AAC.00481-11.
17. van Dijk K, Voets GM, Scharringa J, Voskuil S, Fluit AC, Rottier WC, Leverstein-Van Hall MA, Cohen Stuart JW. 2014. A disc diffusion assay for detection of class A, B and OXA-48 carbapenemases in *Enterobacteriaceae* using phenyl boronic acid, dipicolinic acid and temocillin. Clin Microbiol Infect 20:345–349. https://doi.org/10.1111/1469-0691.12322.
18. de Jonge BL, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. 2016. *In vitro* susceptibility to ceftazidime-avibactam of carbapenem-nonsusceptible *Enterobacteriaceae* isolates collected during the INFORM Global Surveillance Study (2012 to 2014). Antimicrob Agents Chemother 60:3163–3169. https://doi.org/10.1128/AAC.03042-15.
19. Alatoom A, Elsayed H, Lawlor K, AbdelWareth L, El-Lababidi R, Cardona L, Mooty M, Bonilla MF, Nusair A, Mirza I. 2017. Comparison of antimicrobial activity between ceftolozane-tazobactam and ceftazidime-avibactam against multidrug-resistant isolates of *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Int J Infect Dis 62:39–43. https://doi.org/10.1016/j.ijid.2017.06.007.
20. Wiskirchen DE, Nordmann P, Crandon JL, Nicolau DP. 2014. Efficacy of humanized carbapenem and ceftazidime regimens against *Enterobacteriaceae* producing OXA-48 carbapenemase in a murine infection model. Antimicrob Agents Chemother 58:1678–1683. https://doi.org/10.1128/AAC.01947-13.
21. Aktas Z, Kayacan C, Oncul O. 2012. *In vitro* activity of avibactam (NXL104) in combination with beta-lactams against Gram-negative bacteria, including OXA-48 beta-lactamase-producing *Klebsiella pneumoniae*. Int J Antimicrob Agents 39:86–89. https://doi.org/10.1016/j.ijantimicag.2011.09.012.
22. Livermore DM, Mushtaq S, Warner M, Vickers A, Woodford N. 2017. *In vitro* activity of cefepime/zidebactam (WCK 5222) against Gram-negative bacteria. J Antimicrob Chemother 72:1373–1385. https://doi.org/10.1093/jac/dkw593.
23. Haidar G, Clancy CJ, Chen L, Samanta P, Shields RK, Kreiswirth BN, Nguyen MH. 2017. Identifying spectra of activity and therapeutic niches for ceftazidime-avibactam and imipenem-relebactam against carbapenem-resistant *Enterobacteriaceae*. Antimicrob Agents Chemother 61:e00642-17. https://doi.org/10.1128/AAC.00642-17.
24. Sader HS, Mendes RE, Pfaller MA, Shortridge D, Flamm RK, Castanheira M. 2018. Antimicrobial activities of aztreonam-avibactam and comparator agents against contemporary (2016) clinical *Enterobacteriaceae* isolates. Antimicrob Agents Chemother 62:e01856-17. https://doi.org/10.1128/AAC.01856-17.
25. Krishnappa LG, Marie MA, Al Sheikh YA. 2015. Characterization of carbapenem resistance mechanisms in *Klebsiella pneumoniae* and in vitro synergy of the colistin-meropenem combination. J Chemother 27:277–282. https://doi.org/10.1179/1973947814Y.0000000197.
26. Lutgring JD, Zhu W, de Man TJB, Avillan JJ, Anderson KF, Lonsway DR, Rowe LA, Batra D, Rasheed JK, Limbago BM. 2018. Phenotypic and genotypic characterization of *enterobacteriaceae* producing oxacillinase-48-like carbapenemases, United States. Emerg Infect Dis 24:700–709. https://doi.org/10.3201/eid2404.171377.
27. Navarro-San Francisco C, Mora-Rillo M, Romero-Gomez MP, Moreno-Ramos F, Rico-Nieto A, Ruiz-Carrascoso G, Gomez-Gil R, Arribas-Lopez JR, Mingorance J, Pano-Pardo JR. 2013. Bacteraemia due to OXA-48-carbapenemase-producing *Enterobacteriaceae*: a major clinical challenge. Clin Microbiol Infect 19:E72–E79. https://doi.org/10.1111/1469-0691.12091.
28. Balkan II, Aygun G, Aydin S, Mutcali SI, Kara Z, Kuskucu M, Midilli K, Semen V, Aras S, Yemisen M, Mete B, Ozaras R, Saltoglu N, Tabak F, Ozturk R. 2014. Blood stream infections due to OXA-48-like carbapenemase-producing *Enterobacteriaceae*: treatment and survival. Int J Infect Dis 26:51–56. https://doi.org/10.1016/j.ijid.2014.05.012.
29. Ahn C, Butt AA, Rivera JI, Yaqoob M, Hag S, Khalil A, Pitout M, Doi Y. 2015. OXA-48-producing *Enterobacteriaceae* causing bacteremia, United Arab Emirates. Int J Infect Dis 30:36–37. https://doi.org/10.1016/j.ijid.2014.11.008.
30. Poirel L, Kieffer N, Nordmann P. 2016. *In vitro* evaluation of dual carbapenem combinations against carbapenemase-producing *Enterobacteriaceae*. J Antimicrob Chemother 71:156–161. https://doi.org/10.1093/jac/dkv294.
31. Galani I, Nafplioti K, Chatzikonstantinou M, Souli M. 21 March 2018. *In*

vitro evaluation of double-carbapenem combinations against OXA-48-producing *Klebsiella pneumoniae* isolates using time-kill studies. J Med Microbiol https://doi.org/10.1099/jmm.0.000725.
32. Woodford N, Pike R, Meunier D, Loy R, Hill R, Hopkins KL. 2014. *In vitro* activity of temocillin against multidrug-resistant clinical isolates of *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp., and evaluation of high-level temocillin resistance as a diagnostic marker for OXA-48 carbapenemase. J Antimicrob Chemother 69:564–567. https://doi.org/10.1093/jac/dkt383.
33. Vasoo S, Cunningham SA, Cole NC, Kohner PC, Menon SR, Krause KM, Harris KA, De PP, Koh TH, Patel R. 2015. *In vitro* activities of ceftazidime-avibactam, aztreonam-avibactam, and a panel of older and contemporary antimicrobial agents against carbapenemase-producing Gram-negative bacilli. Antimicrob Agents Chemother 59:7842–7846. https://doi.org/10.1128/AAC.02019-15.
34. Jayol A, Poirel L, Dortet L, Nordmann P. 2016. National survey of colistin resistance among carbapenemase-producing *Enterobacteriaceae* and outbreak caused by colistin-resistant OXA-48-producing *Klebsiella pneumoniae*, France, 2014. Euro Surveill 21:pii=30339. https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2016.21.37.30339.
35. Oteo J, Ortega A, Bartolome R, Bou G, Conejo C, Fernandez-Martinez M, Gonzalez-Lopez JJ, Martinez-Garcia L, Martinez-Martinez L, Merino M, Miro E, Mora M, Navarro F, Oliver A, Pascual A, Rodriguez-Bano J, Ruiz-Carrascoso G, Ruiz-Garbajosa P, Zamorano L, Bautista V, Perez-Vazquez M, Campos J, Geih G, Reipi. 2015. Prospective multicenter study of carbapenemase-producing *Enterobacteriaceae* from 83 hospitals in Spain reveals high *in vitro* susceptibility to colistin and meropenem. Antimicrob Agents Chemother 59:3406–3412. https://doi.org/10.1128/AAC.00086-15.
36. Samuelsen O, Overballe-Petersen S, Bjornholt JV, Brisse S, Doumith M, Woodford N, Hopkins KL, Aasnaes B, Haldorsen B, Sundsfjord A, Norwegian Study Group on, CPE. 2017. Molecular and epidemiological characterization of carbapenemase-producing *Enterobacteriaceae* in Norway, 2007 to 2014. PLoS One 12:e0187832. https://doi.org/10.1371/journal.pone.0187832.
37. García-Castillo M, Garcia-Fernandez S, Gomez-Gil R, Pitart C, Oviano M, Gracia-Ahufinger I, Diaz-Reganon J, Tato M, Canton R, iCREST Study Group. 2018. Activity of ceftazidime-avibactam against carbapenemase-producing *Enterobacteriaceae* from urine specimens obtained during the infection-carbapenem resistance evaluation surveillance trial (iCREST) in Spain. Int J Antimicrob Agents 51:511–515. https://doi.org/10.1016/j.ijantimicag.2018.01.011.
38. Ozbek B, Mataraci-Kara E, Er S, Ozdamar M, Yilmaz M. 2015. *In vitro* activities of colistin, tigecycline and tobramycin, alone or in combination, against carbapenem-resistant *Enterobacteriaceae* strains. J Glob Antimicrob Resist 3:278–282. https://doi.org/10.1016/j.jgar.2015.09.001.
39. Castanheira M, Huband MD, Mendes RE, Flamm RK. 2017. Meropenem-vaborbactam tested against contemporary Gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant *Enterobacteriaceae*. Antimicrob Agents Chemother 61:e00567-17. https://doi.org/10.1128/AAC.00567-17.
40. VanScoy BD, Trang M, McCauley J, Conde H, Bhavnani SM, Friedrich LV, Alexander DC, Ambrose PG. 2016. Pharmacokinetics-pharmacodynamics of a novel beta-lactamase inhibitor, CB-618, in combination with meropenem in an *in vitro* infection model. Antimicrob Agents Chemother 60:3891–3896. https://doi.org/10.1128/AAC.02943-15.
41. Shapiro AB. 2017. Kinetics of sulbactam hydrolysis by beta-lactamases, and kinetics of beta-lactamase inhibition by sulbactam. Antimicrob Agents Chemother 61:e01612-17. https://doi.org/10.1128/AAC.01612-17.
42. Durand-Réville TF, Guler S, Comita-Prevoir J, Chen B, Bifulco N, Huynh H, Lahiri S, Shapiro AB, McLeod SM, Carter NM, Moussa SH, Velez-Vega C, Olivier NB, McLaughlin R, Gao N, Thresher J, Palmer T, Andrews B, Giacobbe RA, Newman JV, Ehmann DE, de Jonge B, O'Donnell J, Mueller JP, Tommasi RA, Miller AA. 2017. ETX2514 is a broad-spectrum beta-lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including *Acinetobacter baumannii*. Nat Microbiol 2:17104. https://doi.org/10.1038/nmicrobiol.2017.104.
43. Mushtaq S, Vickers A, Woodford N, Livermore DM. 2017. WCK 4234, a novel diazabicyclooctane potentiating carbapenems against *Enterobacteriaceae*, *Pseudomonas* and *Acinetobacter* with class A, C and D beta-lactamases. J Antimicrob Chemother 72:1688–1695. https://doi.org/10.1093/jac/dkx035.
44. Vallejo JA, Martinez-Guitian M, Vazquez-Ucha JC, Gonzalez-Bello C, Poza M, Buynak JD, Bethel CR, Bonomo RA, Bou G, Beceiro A. 2016. LN-1-255, a penicillanic acid sulfone able to inhibit the class D carbapenemase OXA-48. J Antimicrob Chemother 71:2171–2180. https://doi.org/10.1093/jac/dkw105.
45. Akhter S, Lund BA, Ismael A, Langer M, Isaksson J, Christopeit T, Leiros HS, Bayer A. 2018. A focused fragment library targeting the antibiotic resistance enzyme - oxacillinase-48: synthesis, structural evaluation and inhibitor design. Eur J Med Chem 145:634–648. https://doi.org/10.1016/j.ejmech.2017.12.085.
46. Livermore DM, Mushtaq S, Warner M, Turner SJ, Woodford N. 2018. Potential of high-dose cefepime/tazobactam against multiresistant Gram-negative pathogens. J Antimicrob Chemother 73:126–133. https://doi.org/10.1093/jac/dkx360.
47. Livermore DM, Mushtaq S, Meunier D, Hopkins KL, Hill R, Adkin R, Chaudhry A, Pike R, Staves P, Woodford N, Committee BRSS. 2017. Activity of ceftolozane/tazobactam against surveillance and "problem" *Enterobacteriaceae*, *Pseudomonas aeruginosa* and non-fermenters from the British Isles. J Antimicrob Chemother 72:2278–2289. https://doi.org/10.1093/jac/dkx136.
48. Rodríguez-Avial I, Pena I, Picazo JJ, Rodriguez-Avial C, Culebras E. 2015. *In vitro* activity of the next-generation aminoglycoside plazomicin alone and in combination with colistin, meropenem, fosfomycin or tigecycline against carbapenemase-producing *Enterobacteriaceae* strains. Int J Antimicrob Agents 46:616–621. https://doi.org/10.1016/j.ijantimicag.2015.07.021.
49. Galani I, Anagnostoulis G, Chatzikonstantinou M, Petrikkos G, Souli M. 2016. Emergence of *Klebsiella pneumoniae* co-producing OXA-48, CTX-M-15, and ArmA in Greece. Clin Microbiol Infect 22:898–899. https://doi.org/10.1016/j.cmi.2016.08.002.
50. Kohira N, West J, Ito A, Ito-Horiyama T, Nakamura R, Sato T, Rittenhouse S, Tsuji M, Yamano Y. 2016. *In vitro* antimicrobial activity of a siderophore cephalosporin, S-649266, against *Enterobacteriaceae* clinical isolates, including carbapenem-resistant strains. Antimicrob Agents Chemother 60:729–734. https://doi.org/10.1128/AAC.01695-15.
51. Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. 2018. *In vitro* activity of the novel fluorocycline eravacycline against carbapenem non-susceptible *Acinetobacter baumannii*. Int J Antimicrob Agents 51:62–64. https://doi.org/10.1016/j.ijantimicag.2017.06.022.
52. Zhanel GG, Baxter MR, Adam HJ, Sutcliffe J, Karlowsky JA. 2017. *In vitro* activity of eravacycline against 2213 Gram-negative and 2424 Gram-positive bacterial pathogens isolated in Canadian hospital laboratories: CANWARD surveillance study 2014–2015. Diagn Microbiol Infect Dis 91:51–62. https://doi.org/10.1016/j.diagmicrobio.2017.12.013.
53. Sutcliffe JA, O'Brien W, Fyfe C, Grossman TH. 2013. Antibacterial activity of eravacycline (TP-434), a novel fluorocycline, against hospital and community pathogens. Antimicrob Agents Chemother 57:5548–5558. https://doi.org/10.1128/AAC.01288-13.
54. Maseda E, Salgado P, Anillo V, Ruiz-Carrascoso G, Gomez-Gil R, Martin-Funke C, Gimenez MJ, Granizo JJ, Aguilar L, Gilsanz F. 2017. Risk factors for colonization by carbapenemase-producing enterobacteria at admission to a surgical ICU: a retrospective study. Enferm Infecc Microbiol Clin 35:333–337. https://doi.org/10.1016/j.eimc.2016.02.017.
55. Dautzenberg MJ, Ossewaarde JM, de Greeff SC, Troelstra A, Bonten MJ. 2016. Risk factors for the acquisition of OXA-48-producing *Enterobacteriaceae* in a hospital outbreak setting: a matched case-control study. J Antimicrob Chemother 71:2273–2279. https://doi.org/10.1093/jac/dkw119.
56. Madueño A, Gonzalez Garcia J, Aguirre-Jaime A, Lecuona M. 2017. A hospital-based matched case-control study to identify risk factors for clinical infection with OXA-48-producing *Klebsiella pneumoniae* in rectal carriers. Epidemiol Infect 145:2626–2630. https://doi.org/10.1017/S095026881700142X.
57. Semin-Pelletier B, Cazet L, Bourigault C, Juvin ME, Boutoille D, Raffi F, Hourmant M, Blancho G, Agard C, Connault J, Corvec S, Caillon J, Batard E, Lepelletier D. 2015. Challenges of controlling a large outbreak of OXA-48 carbapenemase-producing *Klebsiella pneumoniae* in a French university hospital. J Hosp Infect 89:248–253. https://doi.org/10.1016/j.jhin.2014.11.018.
58. Goren MG, Chmelnitsky I, Carmeli Y, Navon-Venezia S. 2011. Plasmid-encoded OXA-48 carbapenemase in *Escherichia coli* from Israel. J Antimicrob Chemother 66:672–673. https://doi.org/10.1093/jac/dkq467.
59. Levast M, Poirel L, Carrer A, Deiber M, Decroisette E, Mallaval FO, Lecomte C, Nordmann P. 2011. Transfer of OXA-48-positive

carbapenem-resistant *Klebsiella pneumoniae* from Turkey to France. J Antimicrob Chemother 66:944–945. https://doi.org/10.1093/jac/dkq504.
60. Temkin E, Torre-Cisneros J, Beovic B, Benito N, Giannella M, Gilarranz R, Jeremiah C, Loeches B, Machuca I, Jimenez-Martin MJ, Martinez JA, Mora-Rillo M, Navas E, Osthoff M, Pozo JC, Ramos Ramos JC, Rodriguez M, Sanchez-Garcia M, Viale P, Wolff M, Carmeli Y. 2017. Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. Antimicrob Agents Chemother 61:e01964-16. https://doi.org/10.1128/AAC.01964-16.
61. Castón JJ, Lacort-Peralta I, Martin-Davila P, Loeches B, Tabares S, Temkin L, Torre-Cisneros J, Pano-Pardo JR. 2017. Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing *Enterobacteriaceae* in hematologic patients. Int J Infect Dis 59:118–123. https://doi.org/10.1016/j.ijid.2017.03.021.
62. Livermore DM, Meunier D, Hopkins KL, Doumith M, Hill R, Pike R, Staves P, Woodford N. 8 December 2017. Activity of ceftazidime/avibactam against problem *Enterobacteriaceae* and *Pseudomonas aeruginosa* in the UK, 2015–16. J Antimicrob Chemother https://doi.org/10.1093/jac/dkx438.
63. Falagas ME, Lourida P, Poulikakos P, Rafailidis PI, Tansarli GS. 2014. Antibiotic treatment of infections due to carbapenem-resistant *Enterobacteriaceae*: systematic evaluation of the available evidence. Antimicrob Agents Chemother 58:654–663. https://doi.org/10.1128/AAC.01222-13.
64. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Pano-Pardo JR, Venditti M, Tumbarello M, Daikos G, Canton R, Doi Y, Tuon FF, Karaiskos I, Perez-Nadales E, Schwaber MJ, Azap OK, Souli M, Roilides E, Pournaras S, Akova M, Perez F, Bermejo J, Oliver A, Almela M, Lowman W, Almirante B, Bonomo RA, Carmeli Y, Paterson DL, Pascual A, Rodriguez-Bano J, REIPI/ESGBIS/INCREMENT Investigators. 2017. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing *Enterobacteriaceae* (INCREMENT): a retrospective cohort study. Lancet Infect Dis 17:726–734. https://doi.org/10.1016/S1473-3099(17)30228-1.
65. Ouertani R, Limelette A, Guillard T, Brasme L, Jridi Y, Barguellil F, El Salabi A, de Champs C, Chouchani C. 2016. First report of nosocomial infection caused by *Klebsiella pneumoniae* ST147 producing OXA-48 and VEB-8 beta-lactamases in Tunisia. J Glob Antimicrob Resist 4:53–56. https://doi.org/10.1016/j.jgar.2015.10.002.
66. Hajjej Z, Gharsallah H, Naija H, Boutiba I, Labbene I, Ferjani M. 2016. Successful treatment of a carbapenem-resistant *Klebsiella pneumoniae* carrying bla OXA-48, bla VIM-2, bla CMY-2 and bla SHV- with high dose combination of imipenem and amikacin. IDCases 4:10–12. https://doi.org/10.1016/j.idcr.2016.01.003.
67. Balkan II, Batirel A, Karabay O, Agalar C, Akalin S, Alici O, Alp E, Altay FA, Altin N, Arslan F, Aslan T, Bekiroglu N, Cesur S, Celik AD, Dogan M, Durdu B, Duygu F, Engin A, Engin DO, Gonen I, Guclu E, Guven T, Hatipoglu CA, Hosoglu S, Karahocagil MK, Kilic AU, Ormen B, Ozdemir D, Ozer S, Oztoprak N, Sezak N, Turhan V, Turker N, Yilmaz H. 2015. Comparison of colistin monotherapy and non-colistin combinations in the treatment of multi-drug resistant *Acinetobacter* spp. bloodstream infections: a multicenter retrospective analysis. Indian J Pharmacol 47:95–100. https://doi.org/10.4103/0253-7613.150383.
68. Jayol A, Nordmann P, Poirel L, Dubois V. 2018. Ceftazidime/avibactam alone or in combination with aztreonam against colistin-resistant and carbapenemase-producing *Klebsiella pneumoniae*. J Antimicrob Chemother 73:542–544. https://doi.org/10.1093/jac/dkx393.
69. Goerger E, Honnorat E, Savini H, Coulange M, Bergmann E, Simon F, Seng P, Stein A. 2016. Anti-infective therapy without antimicrobials: apparent successful treatment of multidrug resistant osteomyelitis with hyperbaric oxygen therapy. IDCases 6:60–64. https://doi.org/10.1016/j.idcr.2016.09.008.
70. Karlowsky JA, Kazmierczak KM, Bouchillon SK, de Jonge BLM, Stone GG, Sahm DF. 2018. *In vitro* activity of ceftazidime-avibactam against clinical isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* collected in Asia-Pacific countries: results from the INFORM Global Surveillance Program, 2012 to 2015. Antimicrob Agents Chemother 62:e02569-17. https://doi.org/10.1128/AAC.02569-17.
71. Pfaller MA, Huband MD, Mendes RE, Flamm RK, Castanheira M. 2018. *In vitro* activity of meropenem-vaborbactam and characterization of carbapenem resistance mechanisms among carbapenem-resistant *Enterobacteriaceae* from the 2015 meropenem-vaborbactam surveillance program. Int J Antimicrob Agents 52:144–150. https://doi.org/10.1016/j.ijantimicag.2018.02.021.
72. Karlowsky JA, Lob SH, Kazmierczak KM, Badal RE, Young K, Motyl MR, Sahm DF. 2017. *In vitro* activity of imipenem against carbapenemase-positive *Enterobacteriaceae* isolates collected by the SMART Global Surveillance Program from 2008 to 2014. J Clin Microbiol 55:1638–1649. https://doi.org/10.1128/JCM.02316-16.
73. Livermore DM, Mushtaq S, Warner M, Zhang JC, Maharjan S, Doumith M, Woodford N. 2011. Activity of aminoglycosides, including ACHN-490, against carbapenem-resistant *Enterobacteriaceae* isolates. J Antimicrob Chemother 66:48–53. https://doi.org/10.1093/jac/dkq408.
74. Martins AF, Bail L, Ito CAS, da Silva Nogueira K, Dalmolin TV, Martins AS, Rocha JLL, Serio AW, Tuon FF. 2018. Antimicrobial activity of plazomicin against *Enterobacteriaceae*-producing carbapenemases from 50 Brazilian medical centers. Diagn Microbiol Infect Dis 90:228–232. https://doi.org/10.1016/j.diagmicrobio.2017.11.004.