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OXA-48-Like *β*-Lactamases: Global Epidemiology, Treatment Options, and Development Pipeline

Sara E. Boyd,[a,b,c] Alison Holmes,[b,d] Richard Peck,[a,e] David M. Livermore,[f] William Hope[a]

aAntimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom
bNational Institute for Health Research, Health Protection Research Unit in Healthcare Associated Infection and Antimicrobial Resistance, Imperial College London, London, United Kingdom
cChelsea and Westminster NHS Foundation Trust, London, United Kingdom
dCentre for Antimicrobial Optimisation, Imperial College London, London, United Kingdom
ePharma Research & Development (pRED), Roche Innovation Center, Basel, Switzerland
fNorwich Medical School, University of East Anglia, Norwich, United Kingdom

ABSTRACT Modern medicine is threatened by the rising tide of antimicrobial resistance, especially among Gram-negative bacteria, where resistance to *β*-lactams is most often mediated by *β*-lactamases. The penicillin and cephalosporin ascendancies were, in their turn, ended by the proliferation of TEM penicillinases and CTX-M extended-spectrum *β*-lactamases. These class A *β*-lactamases have long been considered the most important. For carbapenems, however, the threat is increasingly from the insidious rise of a class D carbapenemase, OXA-48, and its close relatives. Over the past 20 years, OXA-48 and "OXA-48-like" enzymes have proliferated to become the most prevalent enterobacterial carbapenemases across much of Europe, Northern Africa, and the Middle East. OXA-48-like enzymes are notoriously difficult to detect because they often cause only low-level *in vitro* resistance to carbapenems, meaning that the true burden is likely underestimated. Despite this, they are associated with carbapenem treatment failures. A highly conserved incompatibility complex IncL plasmid scaffold often carries *bla*OXA-48 and may carry other antimicrobial resistance genes, leaving limited treatment options. High conjugation efficiency means that this plasmid is sometimes carried by multiple *Enterobacterales* in a single patient. Producers evade most *β*-lactam–*β*-lactamase inhibitor combinations, though promising agents have recently been licensed, notably ceftazidime-avibactam and cefiderocol. The molecular machinery enabling global spread, current treatment options, and the development pipeline of potential new therapies for *Enterobacterales* that produce OXA-48-like *β*-lactamases form the focus of this review.

KEYWORDS OXA-48 *β*-lactamase, treatment, pharmacology, drug development, OXA-48, beta-lactamases, epidemiology

An estimated 4.95 million deaths associated with bacterial antimicrobial resistance (AMR) in 2019 make it a leading cause of mortality worldwide and a serious threat to modern medicine (1). The rise in resistance to carbapenems—until recently the last-resort *β*-lactams—is a particular concern. OXA-48-like *β*-lactamases, including OXA-48 itself, are important because they hydrolyze carbapenems, readily transmit among a wide range of *Enterobacterales* (2), frequently associate with other resistances, and have recently (though rarely) been identified among *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (3, 4).

OXA-48-like *β*-lactamases are notoriously difficult to detect in the clinical laboratory, impeding implementation of infection control and facilitating their stealthy rise.

TABLE 1 Proposed division of class D β-lactamases by Poirel et al. (19)

Group	Examples	Host
Acquired narrow-spectrum β-lactamases	OXA-1, OXA-2, and OXA-10 subgroups; OXA-20, OXA-21, OXA-22, OXA-29, and OXA-30	Mainly identified from *Enterobacterales* and *P. aeruginosa*
Acquired expanded-spectrum β-lactamases	OXA-11, OXA-14, OXA-15, OXA-16, OXA-17, OXA-18, OXA-19, OXA-28, OXA-31, OXA-32, OXA-35, OXA-45, and OXA-53	Mainly identified from *P. aeruginosa*
Acquired carbapenem-hydrolyzing β-lactamases	OXA-23, OXA-40, OXA-58, and OXA-97	Mainly identified from *Acinetobacter* spp.
	OXA-48 and OXA-48-like	Mainly identified from *Enterobacterales*
Naturally occurring types	OXA-10	*Acinetobacter baumannii*
	OXA-12	*Aeromonas jandaei*
	OXA-23	*Acinetobacter radioresistans*
	OXA-61	*Campylobacter jejuni*
	OXA-42 and OXA-43	*Burkholderia pseudomallei*
	OXA-50	*Pseudomonas aeruginosa*
	OXA-51	*Acinetobacter baumannii*
	OXA-54	*Shewanella oneidensis*
	OXA-57	*Burkholderia pseudomallei*

Since around 2010, nosocomial spread and outbreaks have increased worldwide (5–12). This has merged into endemicity among a range of *Enterobacterales* across much of Eurasia and Africa (13).

Therapeutic options remain limited (14), though promising agents have been recently licensed (ceftazidime-avibactam and cefiderocol) or are progressing through development (various β-lactam inhibitor combinations and monobactams). The utility of older therapies remains debatable.

Here, we review the structure and function of OXA-48-like β-lactamases, how their genetic support allowed proliferation engendering a serious threat to health care systems, their current epidemiology and, lastly, current and emerging treatment options.

CLASSIFICATION

OXA-48-like enzymes are serine β-lactamases (SBLs) (15, 16) belonging to molecular class D. This family is the most diverse of the four β-lactamase classes defined by Ambler et al., who divide these enzymes based on their amino acid sequences (17, 18).

SBLs hydrolyze their substrates by forming an acyl intermediate through the active-site serine, and class D β-lactamases (DBLs) or "OXA types" have oxacillin as their preferred substrate in terms of k_{cat}/K_m, which measures catalytic efficiency. DBLs vary greatly in both sequence and substrate spectrum. Some (e.g., OXA-1 and -2) are primarily penicillinases, others (e.g., OXA-11 and -14) have an extended spectrum (extended-spectrum β-lactamases [ESBLs]), and a few, including OXA-48 and most OXA-48-like enzymes, are carbapenemases. Each has a unique number assigned based on the chronological order of first description.

Bush and Jacoby's functional β-lactamase classification (18) places OXA-48 β-lactamases, along with the carbapenemases of *Acinetobacter* spp. (OXA-23 and similar) in group 2 (subgroup 2df), where the defining characteristics are the ability to hydrolyze cloxacillin, oxacillin, and carbapenems, with no inhibition by EDTA. Alternatively, in 2010, Poirel et al. (19) proposed a division of DBLs into four groups: (i) acquired narrow-spectrum β-lactamases, (ii) acquired expanded-spectrum β-lactamases, (iii) acquired carbapenem-hydrolyzing β-lactamases, and (iv) naturally occurring (chromosomal) types (Table 1). A complexity is that the "acquired" types are escaped chromosomal types from other species, blurring that distinction. For example, OXA-23 originated from *Acinetobacter radioresistens* (20) and OXA-48 from *Shewanella* spp. (see below). A second complexity is diversity among acquired class D carbapenemases comprising group 3: OXA-48 types attack penicillins but mostly not extended-spectrum cephalosporins, whereas the *Acinetobacter* OXA types attack both penicillins and cephalosporins (19).

Since OXA-48 enzyme was first described, several variants have been observed, collectively forming the "OXA-48-like" subfamily. Variants differ from OXA-48 by one to five amino acid substitutions and/or deletions (21). More-prevalent members include OXA-181 (four substitutions at Thr104Ala, Asn110Asp, Glu168Gln, and Ser171Ala) (22), OXA-232 (single substitution at Arg214Ser) (23), OXA-204 (two substitutions at Gln98His and Thr99Arg) (24), OXA-162 (single substitution at Thr213Ala) (25), OXA-244 (single substitution at Arg214Gly), OXA-163 (four deletions at Arg214, Ile215, Glu216, and Pro217 and a single substitution at Ser220Asp) (26) OXA-245 (single substitution at Glu125Tyr) (27), OXA-370 (single substitution at Gly220Glu) (28), and OXA-405 (four deletions at Thr213 to Glu216) (29). Almost all are carbapenemases unable to hydrolyze cephalosporins, but some, including OXA-163, OXA-405 (29), and OXA 247 (30), show the converse pattern.

ENZYME STRUCTURE AND FUNCTION

OXA-48 has a dimeric structure, similar to OXA-10 (31), OXA-13 (32), and OXA-46 (33), comprising two identical subunits. The active site is in a narrow crevice presenting three motifs typical of DBLs in addition to the carbamylated side chain of Lys73 (34). These elements (notably Arg214) are critical for substrate recognition and for catalysis (15, 35). OXA-48-like enzymes have a unique β-5–β-6 loop conformation, which extends to the outer portion of the active-site crevice, modifying the charge distribution and narrowing the active site compared with more remote DBLs, such as OXA-10 (31, 36). This loop is considered important for carbapenem hydrolysis, although there is a different conformation in *A. baumannii* OXA enzymes (i.e., OXA-23, -24, and -58) (37–39). OXA-48 preferentially hydrolyzes imipenem (k_{cat}, 5 s^{-1}) compared with the 1-β-methyl-carbapenems, meropenem and ertapenem, whose k_{cat} values are $\leq$1 s^{-1} (34, 40); the k_{cat} for oxacillin, for comparison, is 25 s^{-1} (41). Nonetheless, ertapenem MICs are raised more than for other carbapenems, including imipenem.

Efficient hydrolysis relies on rotation of the carbapenem's alpha-hydroxyethyl group, as promoted by the conformation of residues located in or close to the β-5–β-6 loop, which subsequently allows for the deacylating water molecule to access the acylated serine residue (34). Sequence modifications in OXA-163 (see above) correspond to positions belonging to, or close to, the β-5 strand (34), explaining spectrum changes compared with other OXA-48-like enzymes. Specifically, the lack of Arg214 in OXA-163 disturbs the active-site conformation and compromises interactions with carbapenems (26), whereas cephalosporin breakdown is efficient due to control of active-site solvation requiring orientation of Leu158 in the Ω loops (42).

Of significant concern is the recent prediction that a single mutation in the OXA-48 β-5–β-6 loop (Arg214Ser) would increase the efficiency of ceftazidime deacylation relative to that of OXA-163 (42), though the authors do not speculate on how this might affect carbapenemase activity.

MOLECULAR MACHINERY: MOBILIZATION AND GLOBAL SPREAD

The original reservoir of bla_{OXA-48} was demonstrated to be the waterborne Gram-negative saprophyte *Shewanella oneidensis*, which has a chromosomal β-lactamase gene, bla_{OXA-54}. bla_{OXA-54} has genetic components upstream and downstream similar to those of bla_{OXA-48}, and its product has 92% amino acid identity to plasmid-associated OXA-48 (41). Other *Shewanella* species have been sequenced, and their role as progenitors of $bla_{OXA-48-like}$ genes has been confirmed (43), although the relative importance of new escapes versus postescape mutations is uncertain.

Plasmids are the primary vehicle for the transmission and propagation of $bla_{OXA-48-like}$ genes. Several plasmid types have been observed to host $bla_{OXA-48-like}$ genes, including IncL, IncA/C, IncF, ColKP3, ColE2, IncX3, IncN1, and IncT plasmids (13). The most frequent hosts for bla_{OXA-48} itself are self-conjugative 60- to 70-kb plasmids with an IncL scaffold (13, 44, 45) also encoding the replicon protein RepP (46). IncA/C plasmids often carry $bla_{OXA-204}$

(47), whereas $bla_{OXA-181/232}$ are predominantly associated with IncX3 and ColKP3 plasmids (44, 48, 49).

In contrast to many other oxacillinase determinants, $bla_{OXA-48-like}$ genes are not associated with class 1 integrons (50, 51). Rather, the "typical" IncL plasmid harbors bla_{OXA-48} via acquisition of transposon Tn*1999* with an upstream, and often a downstream, IS*1999* insertion sequence (52). Expression is driven by the outward-directed promoter P_{out}, located in IS*1999* (53). When bla_{OXA-48} was originally described from *Klebsiella pneumoniae* in Turkey in 2001, IS*1999* was immediately upstream of the enzyme's gene (50) and the transposon had integrated within the *tir* gene, which is recognized as key for high conjugation and transfer frequency (54, 55). This Tn*1999* transposon structure has several variants, designated Tn*1999.2*, Tn*1999.3*, Tn*1999.4*, and Tn*1999.5* (46, 56, 57). IncL plasmids with embedded Tn*1999.2* were critical to the dissemination of bla_{OXA-48} across Libya, Turkey, and the Netherlands (58).

OXA-181 has been identified among diverse sequence types (STs) but with nearly identical IncX3 plasmids responsible for spread in different countries, including Jordan, Egypt, Turkey, South Korea, Thailand, South Africa, and Kuwait (59). Furthermore, although superclone *K. pneumoniae* ST307 was implicated as an OXA-181 producer in a large outbreak across hospitals in South Africa, the IncX3 plasmid was universally identified and found to be identical to others reported with $bla_{OXA-181}$ from China and Angola (48). Plasmid-borne OXA-48-like carbapenemases have been observed in high-risk international clones, including *K. pneumoniae* ST147 (12), ST307 (48), ST15 (13), ST14 (51), ST23 (60), and ST405 (61) and *Escherichia coli* ST38 and ST410 (13), but these are not the major factor behind the enzymes' global spread (46). Thus, *E. coli*, *K. pneumoniae*, and *Enterobacter cloacae* were the predominant $bla_{OXA-48-like}$ hosts in the United Kingdom; these were polyclonal, and the common denominator was that many harbored a disseminated IncL plasmid carrying the carbapenemase gene (62).

Inevitably, exceptions to these generalizations occur. Clones with OXA-48-like enzymes do, of course, cause local and regional outbreaks; examples are given (see above and below). Furthermore, while plasmids are the principal mechanism responsible for global dissemination (13, 55), a chromosome-integrated $bla_{OXA-48-like}$ gene has been observed in emerging clones such as *E. coli* ST38 with OXA-244 β-lactamase, which has spread across several European countries (63). Last, there is a growing problem, internationally, with *K. pneumoniae*, commonly of ST14 (an anyway frequent lineage) carrying OXA-48-like (often OXA-232) enzymes together with NDM (New Delhi metallo-β-lactamase) types (64–66). These points should not, however, detract from the great importance of plasmids for the dissemination of $bla_{OXA-48-like}$ and the overall diversity of producers. This contrasts with KPC carbapenemases, where the *K. pneumoniae* ST258 has been a considerable vector of global dissemination.

CHALLENGES IN THE CLINICAL MICROBIOLOGICAL LABORATORY

A wide range of *Enterobacterales* can carry bla_{OXA-48} and its variants, with a few reports also for *P. aeruginosa* (3). In principle, biochemical or genetic detection can be achieved by immunochromatography, multiplex PCR, or matrix-assisted laser desorption ionization–time of flight (MALDI-TOF), among other assays. However, the practical difficulties for OXA-48-like β-lactamases are greater than for other carbapenemases. These challenges have recently been reviewed (67, 68) and are not discussed in detail here. Briefly, they include the following: (i) that carbapenem resistance is often low level, meaning that a high level of suspicion is required to ensure that all likely producers are recognized and examined further; (ii) that unlike for KPC carbapenemases and metallo-β-lactamases (MBLs), there are no simple synergy tests to aid detection; (iii) that owing to weak expression, biochemical tests (e.g., Carba-NP) have a greater risk of false-negative results, and finally (iv) that some variants (including OXA-163, OXA-405, and OXA-247) with increased expanded-spectrum cephalosporin hydrolysis may be incorrectly identified as class A, although these are rare. These challenges mean that OXA-48-like enzymes often pass undetected, impacting our understanding
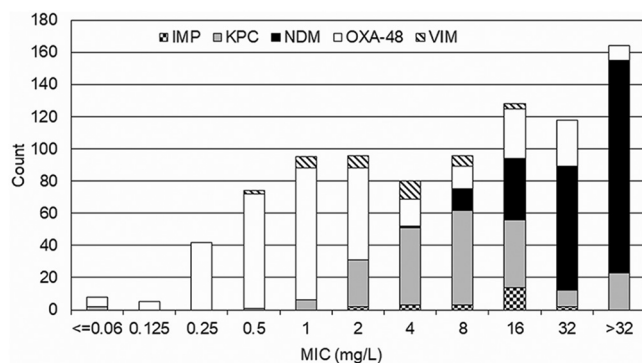
FIG 1 MIC distribution of meropenem for *Enterobacterales*. MIC distributions of meropenem for *Enterobacterales* that were submitted to United Kingdom Health Security Agency (previously Public Health England) Antimicrobial Resistance and Healthcare Associated Infection Reference Unit from July 2015 to July 2016 are shown. (Reproduced from reference 69 with permission of the Infectious Diseases Society of America.)

of their global epidemiology, burden of associated infection, and current treatment outcomes.

Figure 1 shows a meropenem susceptibility distribution for 906 carbapenemase-producing *Enterobacterales* (CPEs) submitted to Public Health England (PHE), illustrating how MICs for OXA-48 producers are mainly ≤2 mg/L and lower than those for *Enterobacterales* with other carbapenemases (69, 70). Consequently, many producers count as "susceptible" based on current EUCAST (≤2 mg/L) and CLSI (≤1 mg/L) clinical breakpoints (71, 72).

Two useful indicators in a clinical laboratory workflow are that producers of OXA-48-like enzymes reliably display high-level resistance to piperacillin-tazobactam (MIC, >64 mg/L) and temocillin (MIC, >128 mg/L), though the latter drug has limited availability and so is not widely tested (62). Ertapenem resistance (MIC, >0.5 mg/L) provides a useful clue, even when imipenem and meropenem still appear active, but is also seen in isolates with combinations of ESBL or AmpC activity and impermeability. Most producers should be identified when screening breakpoints for meropenem (MIC, >0.12 mg/L) trigger subsequent biochemical or genotypic testing (73). Rare producers are susceptible to meropenem at ≤0.12 mg/L and/or temocillin at ≤32 mg/L (69).

A diagnostic trap is that most OXA-48-like carbapenemases do not hydrolyze third- and fourth-generation cephalosporins, meaning that producers lacking ESBLs remain susceptible to these agents (67). The unwary easily dismiss carbapenem-borderline-resistant, cephalosporin-susceptible isolates as test failures, when the phenotype should prompt suspicion of an OXA-48-like β-lactamase.

EPIDEMIOLOGY

OXA-48 itself was initially identified from a carbapenem-resistant *K. pneumoniae* isolate from a patient in Istanbul, Turkey, in 2001 (50). OXA-48-like β-lactamases have subsequently disseminated to every inhabited continent (Fig. 2) (59, 74). Turkey remains an important reservoir for OXA-48-like producers, with OXA-48, OXA-181, OXA-232, and increasing reports of OXA-48-like/NDM coproducers linked with different hosts and various STs (59, 64, 75, 76).

Aside from human clinical samples, OXA-48-like enzymes have been widely detected among different bacterial species and in different countries globally from the environment, particularly from water (Table 2). The potential role of monitoring hospital sewage as an early warning system for clinical outbreaks (77) is of interest, but false positives from environmental *Shewanella* spp. may ensue if PCR is simply performed on sewage or hospital wastewater. Different niches have been reviewed (21) and updated here. The dissemination of OXA-48-like carbapenemases (particularly OXA-181) among nonhuman settings in Switzerland (78), including in companion animal clinics (Table 3) (79, 80) and

A
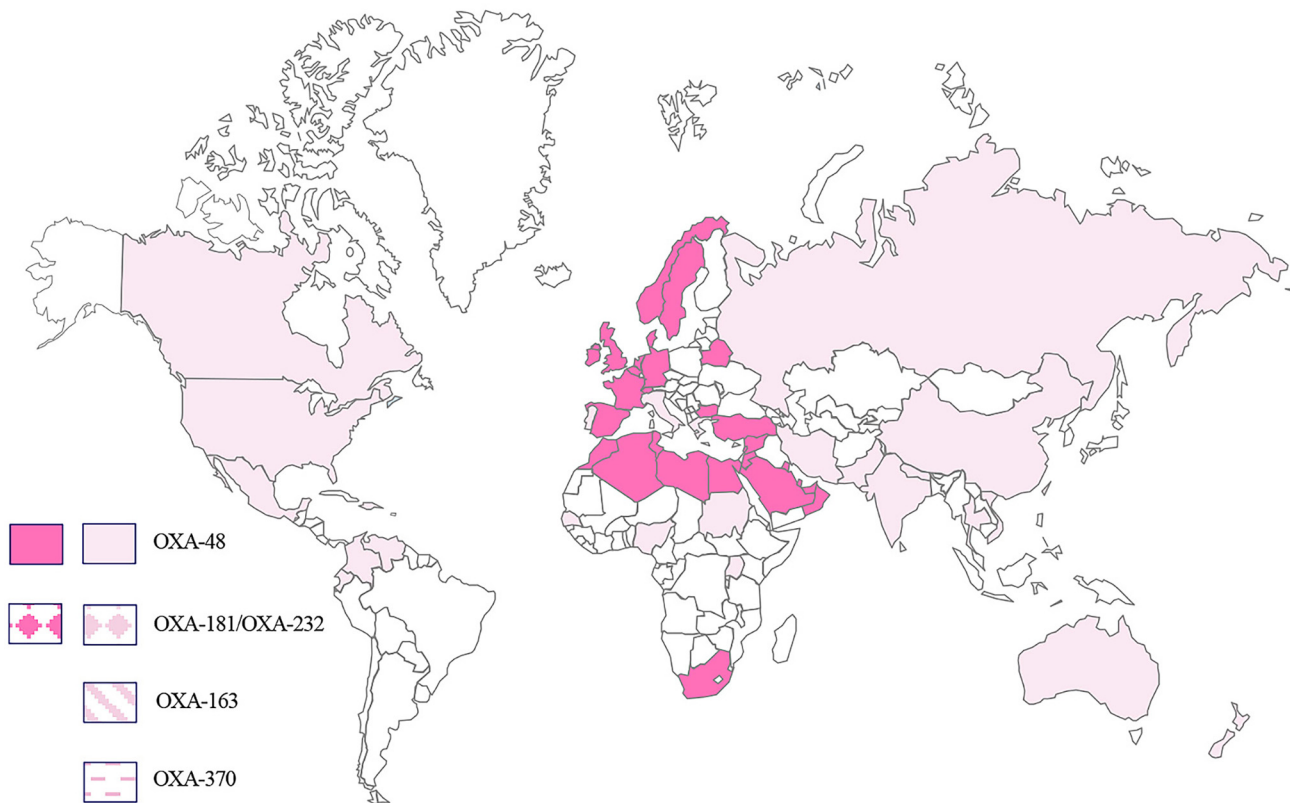
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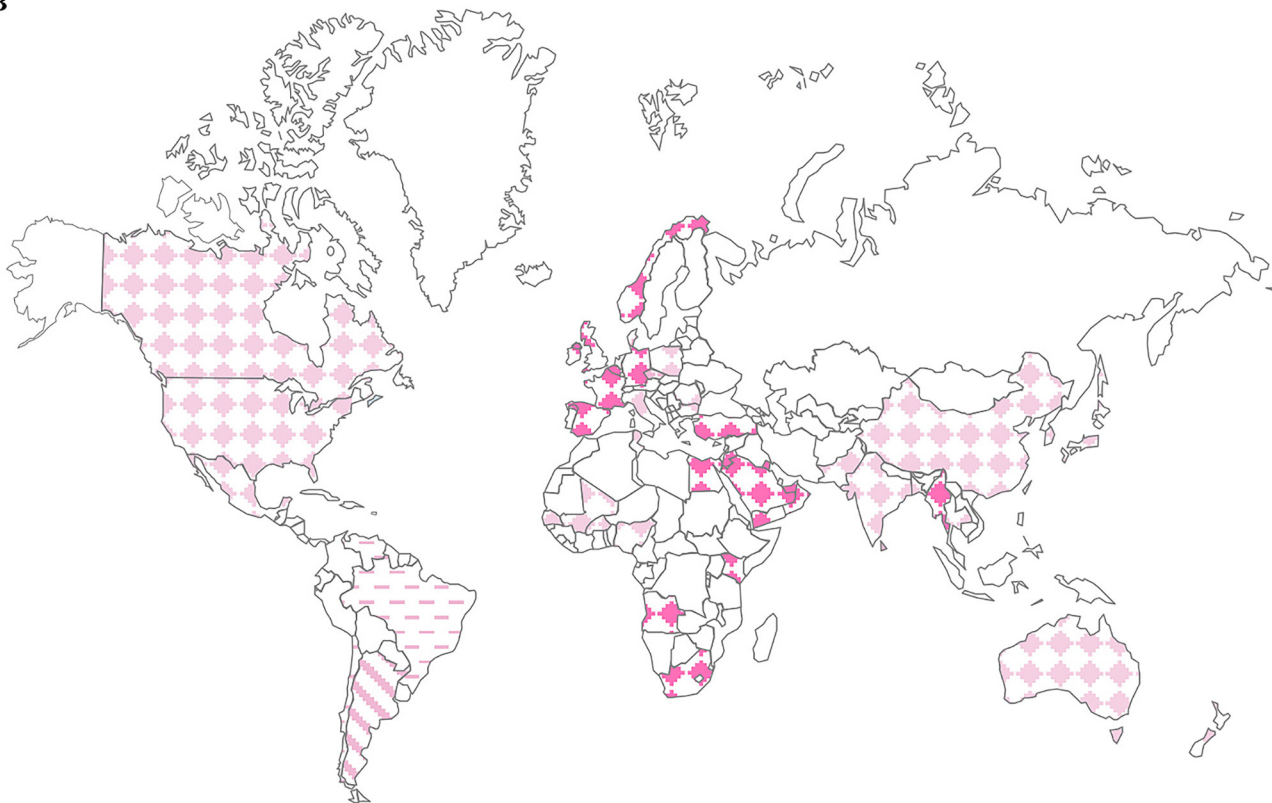
FIG 2 Global distribution of acquired OXA-48-like β-lactamases among *Enterobacterales*. (A) OXA-48; (B) prevalent OXA-48-like variants. Full-tone color is used to indicate where OXA-48-like enzymes are reported as the most prevalent carbapenemases in the country. Lighter-tone color is used to indicate countries where OXA-48-like enzymes are reported in outbreaks but where other carbapenemases (KPC or metalloenzymes) are more prevalent or the most prevalent carbapenemase is unclear.

TABLE 2 Examples of environmental reservoirs of OXA-48-like enzymes globally

Yr isolated	OXA-48-like enzyme	Host	Reservoir	Country	Reference
2011	OXA-48	*E. coli* and *Serratia marcescens*	Puddles in and around Marrakech	Morocco	231
2011–2012	OXA-48	*E. coli*	Domestic sewage and hospital wastewater treatment plant	Austria	232
2015	OXA-48	*Enterobacterales* (mainly *E. coli*)	River water	Algeria	233
2015–2016	OXA-48-like[a]	Host species not defined[b]	Hospital wastewater effluent	Tunisia	234
2015–2017	OXA-48	*E. coli* and other coliforms	Hospital sewage	Sweden	77
2015–2021	OXA-48	*E. cloacae* (mainly ST66)	Hospital (shower drains)	Germany	235
2016	OXA-48-like[a]	Bacteriophages and unspecified bacterial hosts[b]	Wastewater, river water, and irrigation water	USA	236
2016–2017	OXA-48	*S. marcescens*	Hospital wastewater (sink trap)	Israel	237
2016–2019	OXA-48	*Citrobacter freundii*	Hospital wastewater (toilets)	France	238
2017	OXA-48	ST131 *E. coli* and ST101 *K. pneumoniae*	Seawater bathing site	Ireland	239
2018	OXA-48-like[a]	*Enterobacterales* (mainly *Klebsiella* spp.)	River water and farm soil	South Africa	240
2019	OXA-48	*K. pneumoniae* and *Raoultella ornithinolytica*	Hospital wastewater treatment plant	United Kingdom	241
2019–2020	OXA-48	*Enterobacterales*	Municipal wastewater treatment plant	Romania	242
2020	OXA-48	*Enterobacterales* (mainly *E. coli*)	Municipal wastewater treatment plant	Croatia	243
2020	OXA-48	*K. pneumoniae*	Hospital wastewater treatment plant	Mexico	244
Sampling date not specified	OXA-48-like (including OXA-48, OXA-181, OXA-199, and OXA-204, among others)	Host species not defined[b]	Estuarine water with flow from domestic, agricultural, and domestic origin	Portugal	245

[a]Specific variant not specified.
[b]Where host species are not defined among water reservoirs, caution must be used to interpret data due to the naturally occurring chromosomally encoded OXA-54 in *Shewanella* spp. (as described in the text).

in the food chain (Table 4), is a concern. These new data enhance our understanding of important links between humans and other reservoirs for OXA-48-like carbapenemases, which remains poorly understood, with uncertainty on whether the predominant direction of spread is from animals to humans or *vice versa*.

International travel is well known to facilitate the spread of carbapenemases. This is better documented for bla_{NDM} than for bla_{OXA-48}, but nonetheless, some data are available. Among early (2007 to 2014) United Kingdom patients colonized or infected with bacteria producing OXA-48-like enzymes, a travel history was available for 24%, of whom 42% had documented travel to 17 different countries, several of which had previously reported outbreaks involving bacteria with OXA-48-like enzymes (62). Casualties from the Libyan conflict were a source of export of OXA-48-like producers to Germany (81), Denmark (82), United Kingdom, the Netherlands, and Malta (83, 84). Notably, a polytrauma patient from Libya was the source of OXA-48-producing *Salmonella enterica* serovar Kentucky ST198 into Switzerland in 2011 (85). The recent COVID pandemic has greatly reduced travel and, no doubt, reduced the international spread of resistance. Nevertheless, case reports continue to appear that highlight the importation of OXA-48-like carbapenemases by way of repatriation of patients; one such example was the transfer of a patient colonized with an *E. coli* carrying $bla_{OXA-484}$ from India to Switzerland (86).

Europe and Russia. OXA-48-like enzymes are the most prevalent carbapenemases among *Enterobacterales* in much of Western Europe (87). They are most frequently detected in *K. pneumoniae* and *E. coli* but may be associated with other *Enterobacterales*.

One of the first cases outside Turkey was reported from Belgium in 2007. Notably, this imipenem-susceptible, ertapenem-resistant *K. pneumoniae* isolate was cultured from a patient who had no connection to Turkey (88). France reported its first OXA-48 outbreak in 2010, involving a *K. pneumoniae* strain (89). As in Belgium, those affected had not travelled to anywhere the enzyme had previously been recorded, suggesting

TABLE 3 Dissemination of OXA-48-like enzymes among animals globally

Yr isolated	OXA-48-like enzyme	Host	Reservoir	Country	Reference
2009–2011	OXA-48	*Enterobacterales* (mainly *E. coli* and *K. pneumoniae*)	Companion animals (dogs, cats, horses)	Germany	246
2009–2013	OXA-48	*E. coli*	Companion animals (dogs and cats)	U.S.A.	247
2009–2016	OXA-48-like[a]	*Enterobacterales* (mainly *K. pneumoniae*)	Companion animals (dogs, cats, guinea pig, rat, mouse, rabbit)	Germany	248
2013	OXA-48	*E. coli* and *K. pneumoniae*	Companion animals (dog)	Germany	249
2014–2015	OXA-48	*E. coli*	Companion animals (dogs and cats)	Algeria	250
2015	OXA-48	*E. cloacae*	German cockroaches	Algeria	251
2015	OXA-48	*E. coli*	Companion animals (dog)	France	252
2015–2016	OXA-48	*Enterobacterales* (mainly *E. cloacae* ST527)	Companion animals (dogs, cats, horses, pet birds)	Algeria	253
2016	OXA-48-like (OXA-181, OXA-232)	*E. coli*, *K. pneumoniae*, *E. cloacae*	Cockroaches, ants, moths, spiders, flies in human hospital setting	Pakistan	254
2016–2019	OXA-48-like (OXA-181)	*E. coli* ST410	Companion animals postdischarge from veterinary hospital (dog)	Portugal	49
2018	OXA-48-like (OXA-181)	*E. coli*	Companion animals postdischarge from veterinary hospital (dogs, cats)	Switzerland	80

[a]Specific variant not specified.

that *bla*$_{OXA-48}$ was already endemic in these regions (89). OXA-48-like enzymes have become the most prevalent carbapenemase group in France (90) and Spain (55, 91, 92) although KPC types remain more prevalent in Italy and Greece. Colistin resistance among OXA-48-producers was first reported from France in 2014, likely mediated by *mgrB* gene alterations (93), and cocarriage with plasmid-mediated *mcr-1* has also been reported (see below). *Enterobacterales* producing OXA-48-like carbapenemases appear to have been introduced to Israel—a country where KPC otherwise dominates among carbapenemases—first by medical tourism in 2007 (6) and then by wounded Syrian nationals, transferred for medical care, in 2013 (94).

Elsewhere in Europe, away from the Mediterranean, OXA-48 types are now the most prevalent carbapenemases in Germany (45, 95), the Netherlands (7), Switzerland (96), and the United Kingdom (97, 98). *E. coli* ST38 with *bla*$_{CTX-M-27/14b}$ together with *bla*$_{OXA-48/244}$ has spread across Germany and Switzerland (99, 100), precluding the use of unprotected third- or fourth- generation cephalosporins. The case is similar in the United Kingdom and Spain, where clonally diverse isolates with OXA-48-like carbapenemases often also produce CTX-M-15 enzyme, narrowing the therapeutic options (27).

In 2018, there was a remarkable increase in *K. pneumoniae* producing OXA-48 or OXA-244 enzymes across Russia (75). In Moscow, reports describe an outbreak of infection in a neurosurgical intensive care unit (ICU) caused by hypermucoviscous virulent *K. pneumoniae* ST23 isolates harboring both *bla*$_{OXA-48}$ and *bla*$_{CTX-M-15}$ (101, 102). This is

TABLE 4 Dissemination of OXA-48-like enzymes in the food chain

Yr isolated	OXA-48-like enzyme	Host	Reservoir	Country	Reference
2013	OXA-48	*E. coli* ST38	Fowl	Lebanon	255
2015	OXA-48-like (OXA-181)	*Klebsiella variicola*	Coriander herb	Import from Thailand, Vietnam, and India to Switzerland	256
2018	OXA-48	*K. pneumoniae*	Retail pork meat in farmers' market	China	257
2018	OXA-48	*E. cloacae*	Retail pork meat in supermarket chain	China	257
2018–2019	OXA-48	*E. coli*	Poultry in foodchain	Nepal	131
2019	OXA-48	*E. coli*	Fattening pig	Germany	258

worrisome owing to the clone's propensity to cause severe metastatic infection, and this concern is redoubled by subsequent detections of the lineage in Sweden (2019), Ireland and France (2020) (103), and then Switzerland (104).

Surveillance across 31 countries from 2016 to 2018 revealed 40/354 isolates with second carbapenemases in addition to their OXA-48-like-enzymes. Most of these were from Europe (75). Twenty carried NDM-1 plus OXA-232 (United Kingdom), 16 had NDM-1 plus OXA-48 (Germany, Belarus, Greece, Turkey), two had NDM-5 plus OXA-232 (United Kingdom), and one had NDM-1 plus OXA-181 (Turkey) (75). The Middle East, where double carbapenemase producers may be particularly prevalent (105), was not represented.

Africa. Tunisia was another country with early reports of OXA-48-like enzymes (87, 106). Subsequently, OXA-48-like carbapenemases proliferated in neighboring North African countries, including Egypt (107), Algeria (106, 108), and Morocco and Libya (46, 109, 110).

A lack of health care infrastructure, limited molecular diagnostics, and a paucity of skilled scientists mean that the epidemiology of $bla_{\text{OXA-48-like}}$ is poorly understood across much of Africa. Nonetheless, a study conducted from 2015 to 2016 examined 117 clinical *K. pneumoniae* isolates from Sudan; 44/117 produced a carbapenemase, and most were NDM types but seven had OXA-48-like enzymes (111). On the other side of the continent, in Senegal, OXA-48 was reported among hospital and community *Enterobacterales* as early as 2011 (112). More recently, a systematic review reported OXA-48-like carbapenemases in human samples from Algeria, Nigeria, Libya, São Tomé and Principe, Tunisia, South Africa, and Uganda, though not in environmental or animal samples (113).

OXA-48-like enzymes are dominant among carbapenemases in South Africa (114), with at least one early case having been imported from Egypt (115). Colistin resistance emerged from a *K. pneumoniae* strain producing OXA-181 during selective digestive decontamination (11), while *K. pneumoniae* ST307 with OXA-181 enzymes have spread across several private hospitals in South Africa, concurrent with a period of high carbapenem use (116).

Middle East, Gulf region, and the Levant. *Enterobacterales* producing OXA-48-like β-lactamases have swiftly become endemic in the Gulf and non-Mediterranean Middle East, with startling high prevalence rates reported in several studies (117–120). Surveillance of ICU patients in Bahrain, Kuwait, Saudi Arabia, Oman, and the United Arab Emirates in 2019 reported $bla_{\text{OXA-48}}$ to be the most prevalent carbapenemase gene in isolates from rectal swab samples (representing colonization), being present in 15% of all specimens screened and up to 51% of those in Saudi Arabia (121). Risk factors for colonization included being on antibiotics at admission to ICU, age of >65 years, and prolonged stay. Travel was not associated with increased risk (121). In Saudi Arabia, 81.5% of carbapenem-resistant *K. pneumoniae* isolates collected across two large hospitals produced OXA-48. The authors attributed this prevalence to large numbers of migrant workers from Turkey, India, and Pakistan (122), though the latter two countries are more associated with NDM carbapenemases, which were much less prevalent. Of particular concern is the emergence of *Enterobacterales* that harbor both $bla_{\text{OXA-48-like}}$ and bla_{NDM} in Iran (123), Saudi Arabia (124), and Oman (125) from as early as 2010. OXA-48 types dominate in the Levant, including Lebanon (126), Jordan (127, 128), and Syria, as well Turkey (see above).

Indian subcontinent, East Asia, and Australasia. In India, OXA-48-like enzymes are the second-most-prevalent carbapenemases among *Enterobacterales* after New Delhi metallo-β-lactamases (NDM) and are often represented by OXA-181 (87, 129) and OXA-232 (130). Surveillance and reports show increasing numbers of *Enterobacterales* that coproduce both OXA-48-like and NDM enzymes in hospital settings across the Indian subcontinent and in Thailand (51, 75, 129). Cocarriage of $bla_{\text{OXA-48}}$ and plasmid-mediated *mcr-1*, encoding colistin resistance, has been identified in *E. coli* from clinical and poultry isolates in Nepal (131) and in *K. pneumoniae* from pediatric patients in

Vietnam (132). These patients had no epidemiological link to each other, further indicating that reservoirs are poorly understood.

Enterobacterales producing OXA-48-like enzymes remain sporadic in China (12, 133) and are (or, pre-COVID, were) occasionally linked to isolates from Western European travelers (134). *K. pneumoniae* ST15 isolates producing OXA-232 have caused several hospital outbreaks in the country (135–137), as have, less frequently, *K. pneumoniae* ST11 strains coproducing KPC-2 and OXA-48 enzymes (133). In Singapore, OXA-181 producers appear increasingly important (138). In Japan, producers of OXA-48-like enzymes are still uncommon and most often from patients transferred for medical care from elsewhere, including India (139) and Kuwait (140).

In Australia and New Zealand, reports are few and sporadic (14). From 2009 to 2017, 9% of cases with OXA-48-like producers in New Zealand had no history of travel, suggesting local transmission (8).

North America. The first reports of OXA-48-like carbapenemases in North America were published in 2013 and included retrospectively identified isolates from 2009 (141). From 2010 to 2015, the Centers for Disease Control and Prevention (CDC) received reports of 52 *Enterobacterales* that produced OXA-48-like enzymes; international travel was the predominant risk factor (66% of cases, frequently India) in addition to hospitalization abroad (55% of cases) (142). U.S. surveillance of OXA-48-like producers from 2010 to 2014 across 12 states showed several variants represented (OXA-181, 43%; OXA-232, 33%; OXA-48, 23%) (143). From 2016 to 2018, *Enterobacterales* expressing OXA-232 alone or together with NDM-1 were the second-largest group of carbapenemase producers (75), although they remain considerably rarer than those with KPC types.

OXA-48-like (OXA-181, 52.2%; OXA-48, 31.3%) enzymes are reported to be emerging in Canada, with recent international travel reported for 40% of cases identified between 2011 and 2014 and IncL plasmids implicated (44), although this trend has likely been disrupted by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced travel restrictions.

Latin America. Reports of *Enterobacterales* producing OXA-48-like β-lactamases remain relatively scarce in Latin America, where KPC enzymes dominate (144). Nevertheless, a case series from Mexico in 2014 reported the first finding of *Enterobacterales* producing OXA-232 (145), followed by a 2016 study reporting classical OXA-48 (146). In Argentina, OXA-163 has spread extensively among *Enterobacterales* (147, 148) and is exceptional among OXA-48-like enzymes (see above) in not attacking carbapenems. Other variants, including OXA-247, have also emerged here (147). The OXA-370 variant has been recorded in Brazil (28, 149), spreading also into Chile (150) and conferring small rises in carbapenem MICs. This variant coproduced with NDM-1 by *K. pneumoniae* was first isolated from a patient transferred from Brazil to Chile (150), although there is no current evidence of ongoing spread in Chile within the published literature. There is little evidence of wide dissemination of OXA-48-like enzymes in human samples in Latin America, although there remain questions on the reliability of detection and on environmental, animal, or food chain reservoirs.

TREATMENT OPTIONS

Much of the available data relate to infections involving strains with classical OXA-48 enzymes. This is assumed to extend to other prevalent variants, including OXA-181 and OXA-232, which are associated with similar phenotypes. Data on noncarbapenemase variants such as OXA-163 remain scant.

Combination therapy. Until recently, the treatment of infections due to carbapenemase producers was mostly with polymyxins, tigecycline, aminoglycosides, and fosfomycin, often in combination and often together with carbapenems.

A systematic review in 2014 concluded that combination therapy reduced mortality for infections involving carbapenemase-producing *Enterobacterales* (CPE), with fewer treatment failures than with monotherapy (151). However, only one study represented patients infected by OXA-48 producers. This was a cohort of 34 elderly patients with bloodstream infection (BSI) among whom the 30-day mortalities were 52.4% (11/21) for those treated with $\geq$2 active drugs (mostly including colistin) but not including a

carbapenem, 33.3% (2/6) in patients receiving ≥2 "active" drugs including a carbapenem, and 33.3% (1/3) in patients receiving amikacin monotherapy (152). While this study was prospective, the numbers were tiny, the patient population heterogenous, and the infection sources diverse. Moreover, numerous antimicrobial combinations were reported, and tigecycline susceptibility was judged by FDA interpretive criteria, with a breakpoint 4-fold higher than that of EUCAST criteria, meaning that definitive conclusions cannot be drawn.

Following this, a prospective multicenter randomized controlled trial in 2017 (INCREMENT) showed that patients who received "appropriate" combination therapy (based on *in vitro* susceptibilities) for infections caused by CPE had reduced mortality compared with those receiving appropriate monotherapy only when their pretreatment mortality hazard score was high (153). Colistin monotherapy was concluded to be adequate for those with a low-mortality risk. A caveat is that KPC carbapenemases were heavily represented and OXA-48-like carbapenemases were underrepresented.

In an observational study of bacteremia involving OXA-48-producing *Enterobacterales*, a triple combination (colistin-aminoglycoside-ceftazidime/cefepime) was associated with slightly better 28-day survival than that with colistin-based dual combinations ($P = 0.075$), although the authors failed to comment on the incidence of renal toxicity with aminoglycoside-colistin combinations (154).

Based on these data, it remains unclear whether and when there is a benefit to colistin-based combination therapy versus monotherapy for patients with infections due to bacteria with OXA-48-like enzymes. Increasingly, though, this debate is being overtaken by the availability of ceftazidime-avibactam and cefiderocol (discussed below). Scenarios that may still necessitate consideration of a colistin-based combination include (i) patients showing an anaphylaxis risk with cephalosporins, or (ii) patients already receiving a high-dose central nervous system (CNS)-penetrating β-lactam, e.g., for concurrent pneumococcal meningitis, precluding further cephalosporin coadministration. In such cases, the neurotoxicity of colistin-based regimens should also be considered.

Ceftazidime, cefepime, and aztreonam. Ceftazidime, cefepime, and aztreonam evade hydrolysis by OXA-48-like enzymes (with the exceptions noted above). Ceftazidime activity was demonstrated in a *K. pneumoniae* murine peritonitis model when the challenge strain produced OXA-48 without accompanying ESBL or AmpC enzymes (155). However, these drugs lack efficacy against strains that coexpress ESBLs and, for ceftazidime and aztreonam, also those with derepressed AmpC. Since as many as 80% of OXA-48-positive isolates (rates vary by country) coproduce ESBLs (7, 61), sometimes with $bla_{CTX-M-15}$ contained within a mosaic Tn*1999.4* transposon (156, 157), neither unprotected ceftazidime, cefepime, nor aztreonam is a reliable option for monotherapy.

Ceftazidime-avibactam. The ceftazidime-avibactam combination protects ceftazidime with a novel diazabicyclooctane β-lactamase inhibitor, avibactam, which binds covalently and reversibly to serine β-lactamases, including ESBLs and AmpC enzymes. Inhibition of OXA-48 enzyme is weak, but this matters little given ceftazidime's stability to this carbapenemase.

Nonrandomized controlled trials and registry-based analyses suggest that ceftazidime-avibactam is an effective therapy for a range of infections due to pathogens with OXA-48-mediated resistance to carbapenems (158). It displays *in vitro* activity against most *Enterobacterales* producing OXA-48-like enzymes at the EUCAST and FDA susceptibility breakpoints (8 + 4 mg/L) (159–163). Case series suggest better clinical outcomes than when colistin- or carbapenem-based regimens are used against OXA-48 producers (164–167), though further *in vivo* data and prospective outcome studies are required.

Emerging resistance to ceftazidime-avibactam was documented in one patient infected with a *K. pneumoniae* strain producing OXA-48 enzyme. However, this individual was first treated with unprotected ceftazidime, and resistance emerged via Pro170Ser and Thr264Ile substitutions to a coproduced CTX-M-14 enzyme, with OXA-48 remaining unaltered (70).

An *in vitro* exploration revealed that Pro68Ala and Pro68Ala,Tyr211Ser amino acid substitutions in OXA-48 resulted in an increased ability to hydrolyze ceftazidime and a

decreased ability to withstand inhibition by avibactam, respectively (168). Although this has not been reported in clinical practice, and unlike for KPC carbapenemases, emerging mutational resistance appears rare (169).

Further pharmacokinetics/pharmacodynamics (PK/PD) and clinical outcome data, for specific OXA-48-like carbapenemase variants, would be welcomed; nonetheless, ceftazidime-avibactam appears widely effective for infections involving OXA-48-like-β-lactamase-producing *Enterobacterales* and should be seen as a therapy of choice.

Cefepime-tazobactam and ceftolozane-tazobactam. A cefepime-tazobactam (1 g + 0.125 g) combination is available in India and China (170). While positive series have been described (171), the low tazobactam dose is contentious and appears to be predicated upon the 8:1 ratio of piperacillin to tazobactam [4 g to 0.5 g] rather than robust PK/PD data. There is concern that the low tazobactam concentrations achieved are insufficiently reliable to protect cefepime from hydrolysis by ESBL enzymes. A higher dose combination (2 g + 2 g) is currently in development (172). Tazobactam is a weaker inhibitor of ESBLs than enmetazobactam (below), but the higher dose combination may render this difference insignificant.

Around two-thirds (90/136) of ceftazidime-resistant (i.e., ESBL-producing) OXA-48-producing *Enterobacterales* were inhibited by cefepime-tazobactam at 8 + 8 mg/L along with almost all (113/114) ceftazidime-susceptible OXA-48-producing *Enterobacterales* (173).

A phase 3 clinical trial to compare cefepime-tazobactam to meropenem for complicated urinary tract infections (cUTI) is planned (174).

Ceftolozane, like cefepime and ceftazidime, must approach stability to OXA-48-like enzymes, since it has low MICs for producers that lack ESBLs. Wide activity against OXA-48-like producers would therefore be anticipated for ceftolozane-tazobactam, given tazobactam's ability to inhibit coproduced ESBLs. Nonetheless, MICs of tazobactam-protected ceftolozane are consistently high for ceftazidime-resistant OXA-48 producers, indicating that ESBLs are being poorly inhibited in practice (175). A simple explanation—that OXA-48 might hydrolyze tazobactam—is refuted by the observation that cefepime-tazobactam MICs are much lower than those of ceftolozane-tazobactam (173). Unlike cefepime-tazobactam, ceftolozane-tazobactam should not be seen as a potential option against OXA-48 β-lactamase producers.

Cefiderocol. Cefiderocol is a siderophore cephalosporin with a catechol moiety on the 3 position of the R2 side chain (176). It exploits the iron uptake pathway to permeate Gram-negative bacteria and binds mainly to PBP3; moreover, it is stable to most β-lactamases, including ESBLs and OXA-48-like enzymes (177, 178), with low induction of chromosomal AmpC (179).

Despite this potential, preclinical animal models of infection assessing efficacy against *Enterobacterales* with OXA-48 enzymes are limited. Moreover, although cefiderocol demonstrated efficacy and safety in a phase 3 clinical trial for infections due to carbapenem-resistant pathogens, (CREDIBLE CR), it is unclear how many patients had OXA-48-like producers (180). Its role against producers of more globally prevalent variants, including OXA-181 and OXA-232, requires further investigation. Clarification of these aspects is needed, along with a fuller understanding of the hazard of selecting mutants with reduced CirA-mediated uptake (181); nonetheless, it is likely that cefiderocol will find a role in treating infections due to producers as an alternative to ceftazidime-avibactam.

Aminoglycosides. Aminoglycosides may be used for the treatment of infections due to *Enterobacterales* that produce OXA-48-like enzymes, provided that *in vitro* susceptibility is confirmed. Except in UTI, they would not ordinarily be considered for monotherapy.

Historically, most resistance has been mediated by aminoglycoside-modifying enzymes (182), with amikacin evading more of these than gentamicin and tobramycin. Cocarriage of methyltransferases, which alter rRNA and prevent binding of 3-ring aminoglycosides, is an emerging issue (183). These confer resistance to plazomicin as well as to long-established analogues such as amikacin, gentamicin, and tobramycin. In Greece, most isolates with both NDM and OXA-48-like carbapenemases also had these methyltransferases (183). Notably, *armA* was observed together with OXA-48 and CTX-

M in the absence of NDM enzymes in both Greece (184) and Oman (125). In the United Kingdom, pan-aminoglycoside resistance (to amikacin, tobramycin, and gentamicin), as is typical of methyltransferase production, was seen in 14.8% to 15.9% of *Enterobacterales* with OXA-48-like carbapenemases sent to the reference laboratory in 2018 and 2021, respectively (S.E.B., personal correspondence with United Kingdom Health Security Agency). Rates vary globally although with much higher resistance due to associated *aac (6′)-Ib* (185, 186) and/or *rmtB* and *armA* (187) genes having been observed in Egypt.

Polymyxin B and colistin. Although most *Enterobacterales* with OXA-48-like carbapenemases are susceptible to polymyxins, susceptibility is not universal, with resistance reported in *K. pneumoniae*, *E. coli*, and *Enterobacter* spp. (93, 188). Much of this resistance is likely mediated by *mgrB* gene alterations (93) but cocarriage of *bla*$_{OXA-48-like}$ with plasmid-mediated *mcr-1* has also been reported (see above).

A combination of azithromycin and colistin has recently been proposed to treat infections caused by *K. pneumoniae* producing OXA-48-like enzymes, based on *in vitro* synergism but without supportive *in vivo* or clinical data (189). However, the approach is potentially undermined by genes increasing resistance to macrolides [e.g., *mph*(A), *erm*(B)], which are commonly carried by the plasmids of Gram-negative bacteria. These genes were identified alongside *bla*$_{OXA-181}$ in *K. pneumoniae* isolates from septic neonates in India (51) and alongside *bla*$_{OXA-48}$ among different *Enterobacterales* associated with outbreaks in China (133).

Tigecycline and eravacycline. Tigecycline is a glycylcycline with *in vitro* activity against *Enterobacterales* except *Proteeae* (190, 191) but not against *Pseudomonas* spp. It is generally used in combination, often with colistin, but was successfully used as monotherapy against OXA-48-β-lactamase-producing *K. pneumoniae* in two patients with bacteremia secondary to intra-abdominal or skin and soft tissue sources (152).

Caution is advocated in sepsis because of bacteriostatic activity, the low plasma levels of the currently recommended regimen, and disagreement concerning the appropriate breakpoint (EUCAST susceptibility breakpoint, ≤0.5 mg/L for *E. coli* only; FDA, ≤2 mg/L for all *Enterobacterales*; CLSI, no values). Mixed trial outcomes and excess mortality contributed to an FDA black box warning in 2013 (192). Time-kill curve assays support its use with ceftazidime-avibactam as synergistic against OXA-48 producers, but clinical data are lacking (193).

Eravacycline is a fluorocycline which, like classical tetracyclines, inhibits protein synthesis by binding to the 30S ribosomal subunit. Like tigecycline, it evades acquired efflux pumps (194); potential advantages over tigecycline are that it has slightly lower MICs for *Enterobacterales* (195), achieves higher serum levels (196), and induces less nausea and vomiting (197). Consequently, it may be a preferable combination agent to tigecycline, but clinical data are scant. In 2019, the FDA approved eravacycline for use in complicated intra-abdominal infections based on data from the IGNITE4 clinical trial (198), with subsequent United Kingdom and European Union (EU) licenses. Eravacycline was not approved for cUTI, where it failed to achieve noninferiority to fluoroquinolone and carbapenem comparators (199). Clinical outcome data against OXA-48-like producers remain unavailable, but evidently, the carbapenemase itself will not compromise activity.

Fosfomycin. Fosfomycin inhibits cell wall synthesis by a unique irreversible mechanism, inactivating UDP *N*-acetylglucosamine-GlcNAc enolpyruvyl transferase (MurA) (200). Despite having been available for over 50 years, its intravenous (i.v.) formulation has garnered interest as a treatment for severe infections only in the past decade; it is available in the United Kingdom, much of Europe, and Japan, but approval remains pending in the United States.

Fosfomycin retains *in vitro* activity against many multidrug-resistant (MDR) *Enterobacterales*, including most with OXA-48-like enzymes (201). Synergy, defined by a fractional inhibitory concentration index (FICI) of ≤0.5, has been reported *in vitro* for combinations with imipenem, meropenem, and tigecycline, whereas antagonism (FICI, >0.5 to 4) has been observed with colistin (188).

A multicenter, noninterventional, prospective clinical registry (FORTRESS) across Europe is in progress to evaluate the clinical outcomes of severely infected patients

treated with i.v. fosfomycin and is expected to complete recruitment in 2023 (202), although how well OXA-48-like producers will be represented is unclear.

An oral fosfomycin formulation is widely available, including in the United States, but its utility is limited to uncomplicated lower UTI, with EUCAST and CLSI breakpoints only for *E. coli* among Gram-negative bacteria. It may be useful in *E. coli* cystitis involving carbapenemase producers, including those with OXA-48-like enzymes.

Carbapenems. Carbapenems are often considered in combination regimens against infections due to "carbapenem-resistant *Enterobacterales*" (CRE) (203), particularly if the MIC is low (69) or if ceftazidime-avibactam and cefiderocol are unavailable. However, clinical studies investigating treatments for CRE infections often include pathogens with mixed mechanisms of resistance (180, 204), and a growing body of evidence from animal models, small trials, and case series suggests that the type of carbapenemase is as important as the MIC (69).

Uncertainty surrounds the utility of carbapenems for infections involving *Enterobacterales* with OXA-48-like enzymes: clinical cure and survival rates ranged from 0 to 66% with meropenem or imipenem monotherapy (61, 89, 154, 205). True figures are likely to be lower, as some "successes" involved source control by line removal (14). Clinical outcomes were poor when carbapenems were used to treat patients infected with *Enterobacterales* producing both OXA-48 and CTX-M-15 enzymes, despite low imipenem and meropenem MICs (89).

Crucially, and despite these poor outcomes, many OXA-48-like-positive isolates are categorized as susceptible according to EUCAST and CLSI breakpoints (69, 70). It may be that under challenge, the bacteria swiftly accumulate secondary mechanisms precluding carbapenem efficacy. When meropenem was administered to recapitulate humanized PK in a hollow fiber model of infection with a "EUCAST and CLSI susceptible" challenge strain (*E. cloacae*; meropenem MIC, 1 mg/L), the total bacterial population expanded and a drug-resistant population emerged. The drug-resistant population had reduced permeability via inactivation of OmpC rather than increased expression of OXA-48 (206). Likewise, (i) doripenem, administered to simulate a humanized regimen, failed to achieve efficacy in a murine thigh infection model where the strain produced OXA-48 β-lactamase despite a doripenem MIC of only 0.38 mg/L (versus EUCAST and CLSI susceptible breakpoints of $\leq$1 mg/L) (207), and (ii) imipenem-cilastatin had little or no impact on lethality in a *K. pneumoniae* murine peritonitis model where the challenge strain, with an imipenem MIC of 0.5 mg/L (versus the CLSI susceptibility breakpoint of $<$1 mg/L and the EUCAST susceptibility breakpoint of $\leq$2 mg/L) produced OXA-48 enzyme with no associated ESBL or AmpC β-lactamase (155). Synergy has been reported *in vitro* with a dual-carbapenem combination for OXA-48 producers (208, 209), but this is not an approach supported by current clinical safety or outcome data. In particular, it may be precluded by central nervous system toxicity.

Carbapenems combined with β-lactamase inhibitors. The β-lactamase inhibitors vaborbactam and relebactam do not inhibit OXA-48-like enzymes and do not potentiate partner carbapenems against producers (67); rather, they are specific inhibitors of KPC and other class A carbapenemases. Consequently, meropenem-vaborbactam and imipenem-relebactam-cilastatin are not options against infections with OXA-48-like producers.

Interpretive pitfalls arise owing to the different breakpoints for meropenem and meropenem-vaborbactam. EUCAST defines *Enterobacterales* as susceptible to meropenem when the MIC is $\leq$2 mg/L, based upon 1 g every 8 h (q8h) dosing, "susceptible, increased exposure" when the MICs are 4 to 8 mg/L with 2 g q8h dosing, and resistant when MICs are $>$8 mg/L. For meropenem-vaborbactam, the breakpoints are for susceptible, $\leq$8 plus 8 mg/L, and for resistant, $>$8 plus 8 mg/L, based on the sole licensed regimen of 2 g + 2 g q8h administered over a 3-h infusion (71). CLSI criteria for meropenem are for susceptible, $\leq$1 mg/L, for intermediate, 2 mg/L, and for resistant, $\geq$4 mg/L; those for meropenem-vaborbactam are for susceptible, $\leq$4 + 8 mg/L, for intermediate, 8 + 8 mg/L, and for resistant, $\geq$16 + 8 mg/L (72).

Consequently, an isolate with MICs of 4 mg/L meropenem and 4 + 4 mg/L meropenem-vaborbactam would count as meropenem resistant based on CLSI criteria,

"susceptible–increased exposure" based on EUCAST criteria, and fully susceptible to meropenem-vaborbactam based on both sets of criteria, despite vaborbactam not inhibiting OXA-48-like enzymes. As already highlighted, no data exist to show that an increased dosage of meropenem (alone or combined as in meropenem-vaborbactam) will overcome reduced susceptibility associated with OXA-48 β-lactamases in clinical settings.

Flomoxef and other 7-α-methoxy (oxa)cephems. Flomoxef is an off-patent 7-α-methoxy oxacephem β-lactam drug, developed in the 1980s. It is stable to ESBLs, though not AmpC enzymes (210). It may retain activity against isolates with DBLs, including OXA-48-like enzymes, but further research is required. It is licensed in China, South Korea, Taiwan, and Japan, where OXA-48-like producers are sporadic, perhaps explaining the lack of data thus far. Other 7-α-methoxy (oxa)cephems, moxalactam and cefotetan, also deserve fuller investigation; published data on their interactions are scant, and the drugs themselves have largely fallen into disuse.

Cefoxitin MICs for producers of OXA-48-like enzymes are widely scattered, from 4 to >64 mg/L, with low values for some that coproduce ESBLs (D.M.L., data on file), but there is a general acceptance that activity is marginal against MDR *Enterobacterales*, and mutational resistance readily arises via porin loss.

DEVELOPMENT PIPELINE

The development pipeline includes several cefepime-based β-lactamase inhibitor combinations. Given cefepime's stability to prevalent OXA-48-like enzymes (see above), the key issue is whether the inhibitor inactivates coproduced ESBLs (also NDM types, coproduced in around 5 to 10% of United Kingdom isolates with OXA-48-like enzymes) (62).

Cefepime-taniborbactam. Taniborbactam is a boronic acid β-lactamase inhibitor able to inactivate many class A (ESBL, KPC), class B (VIM, NDM, SPM-1, GIM-1), class C (AmpC), and class D (OXA-48-like) β-lactamases (211); IMP metallo-carbapenemases are not inhibited. The inhibition of serine β-lactamases involves covalent binding to the active-site serine. Activity at likely breakpoints (4 or 8 mg/L) includes *Enterobacterales* with OXA-48 carbapenemases (212).

A randomized, double-blind, phase 3 noninferiority trial (CERTAIN-1) has completed recruitment, comparing cefepime-taniborbactam with meropenem for the treatment of complicated urinary tract infection (cUTI) in adults (213). Given the comparator, it is unlikely that this trial will inform on efficacy against carbapenemase producers.

Cefepime-zidebactam. Cefepime-zidebactam is widely active against *Enterobacterales* that produce class A (ESBL, KPC), class B (IMP, VIM, NDM), class C (AmpC), and class D (OXA-48-like) β-lactamases and retains activity against *P. aeruginosa* with multiple modes of resistance (214). Direct inhibition of OXA-48-like enzymes by zidebactam is limited; rather, activity depends substantially (i) on the stability of cefepime (see above), (ii) on the ability of zidebactam to inhibit coproduced ESBLs, and (iii) on zidebactam's direct antibacterial activity and ability to potentiate PBP3-targeted β-lactams by binding PBP2 (215).

A phase 3, randomized, double-blind, multicenter noninferiority clinical trial evaluating the efficacy, safety, and tolerability of cefepime-zidebactam versus meropenem in the treatment of hospitalized adults with cUTI is planned (216). As with cefepime-taniborbactam, the design and comparator mean that few conclusions will be drawn for the treatment of infections caused by carbapenemase producers.

Cefepime-enmetazobactam. Enmetazobactam is a methylated analog of tazobactam with potent activity against class A (ESBL) enzymes (217–219). Eight of 10 *Enterobacterales* producing OXA-48 carbapenemases were inhibited at 8 + 8 mg/L cefepime-enmetazobactam compared to 4/10 with cefepime-tazobactam at 8 + 4 mg/L (220); this suggests an advantage, but further data are needed (219).

The ALLIUM phase 3 clinical trial recently demonstrated cefepime-enmetazobactam's superiority over piperacillin-tazobactam for cUTI at the primary efficacy endpoint (221), but given the comparator, this trial is unlikely to contain any data relevant to efficacy against OXA-48-like producers. At a dose of 2 g + 0.5 g q8h infused over 2 h, a

probability of target attainment is achieved for >90% *Enterobacterales* with MICs of ≤8 mg/L (222).

Aztreonam-avibactam. Aztreonam-avibactam is active, at a prospective breakpoint of 8 + 4 mg/L, against *Enterobacterales* with class A (ESBL, KPC), class B (MBLs), class C (AmpC), and class D (OXA-48-like) enzymes but not against *P. aeruginosa* (223). This combination is attractive, especially given the growing numbers of isolates that coproduce NDM and OXA-48-like carbapenemases reported across India, the United Kingdom, Thailand, Turkey, Germany, the United States, and Belarus (75).

Nonetheless, the emergence of aztreonam-avibactam resistance via PBP3 modifications in *E. coli* is a concern. This is documented mostly for strains with NDM carbapenemases alone and is particularly prevalent in India (224) but was also seen for isolates producing both OXA-48-like and NDM-type carbapenemases in Germany (225). These modifications also compromise cefiderocol and ceftazidime-avibactam, though not cefepime-zidebactam (226, 227).

Other therapies. Ancremonam (formerly LYS228 or BOS228) is a monobactam antibiotic currently in phase 2 development (Boston Pharmaceuticals). It is stable to class A (ESBL, KPC), B (IMP, VIM, NDM), C (AmpC), and D (OXA-48-like) enzymes but is not active against *P. aeruginosa*.

QPX7728 is a novel cyclic boronic acid inhibitor of class A (ESBLs, KPC), B (NDM, VIM, IMP), C (AmpC), and D enzymes, including OXA-48-like enzymes from *Enterobacterales* and OXA types from *A. baumannii* (228). Its future partner β-lactam remains uncertain (229), and it may instead be developed as a "stand-alone" inhibitor (230). Direct comparison with taniborbactam remains to be published.

CONCLUSIONS

The spread and threat of OXA-48-like producers have been underappreciated for the last 2 decades. Patchy data on epidemiology undoubtedly reflect diagnostic difficulties. Consequently, it is likely that the published literature reflects only the tip of the iceberg. Several treatment options (ceftazidime-avibactam, cefiderocol, tigecycline, eravacycline) have been licensed since 2001, when these enzymes first began to spread. Unfortunately, data on their merits and limitations remain scantier than those for KPC producers, despite OXA-48-like β-lactamases being more prevalent globally. A limited appetite to generate specific PK/PD or clinical outcome data for newer agents, let alone for repurposed older drugs, means it is difficult to definitively guide treatment practice.

Despite these limitations, it seems reasonable to now consider ceftazidime-avibactam, followed (simply because there are fewer data) by cefiderocol, as first-choice options if *in vitro* susceptibility allows. While "OXA-48-like" enzymes currently fall under the same umbrella, we are continuously developing our understanding of how broad and unique these enzymes are. A concerted effort is required to ensure that new epidemiological, PK/PD, and clinical outcome data are deeply understood, so that differences in the therapeutics for specific OXA-48-like variants can be explored. The development pipeline includes promising new agents, notably cefepime combined with taniborbactam and zidebactam, but it is unlikely that licensing trials will provide extensive information on activity against pathogens with OXA-48-like enzymes. Assuming that these combinations proceed to licensure, an urgent need will arise to evaluate efficacy against cefiderocol and ceftazidime-avibactam and to monitor the impact of evolution within the OXA-48 family, the incidence of coproduction with metallo-carbapenemases, and the spread of reduced susceptibility owing to PBP3 inserts.

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