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Invited review

The rapid spread of carbapenem-resistant Enterobacteriaceae

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ABSTRACT

Carbapenems, our one-time silver bullet for multidrug resistant bacterial infections, are now threatened by widespread dissemination of carbapenem-resistant Enterobacteriaceae (CRE). Successful expansion of Enterobacteriaceae clonal groups and frequent horizontal gene transfer of carbapenemase expressing plasmids are causing increasing carbapenem resistance. Recent advances in genetic and phenotypic detection facilitate global surveillance of CRE diversity and prevalence. In particular, whole genome sequencing enabled efficient tracking, annotation, and study of genetic elements colocalized with carbapenemase genes on chromosomes and on plasmids. Improved characterization helps detail the co-occurrence of other antibiotic resistance genes in CRE isolates and helps identify pan-drug resistance mechanisms. The novel β-lactamase inhibitor, avibactam, combined with ceftazidime or aztreonam, is a promising CRE treatment compared to current colistin or tigecycline regimens. To halt increasing CRE-associated morbidity and mortality, we must continue quality, cooperative monitoring and urgently investigate novel treatments.

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1. Introduction

Carbapenems are the favored last resort drugs for treatment of multidrug resistant (MDR) bacterial infections. Accordingly, spreading carbapenem resistance is a global health crisis. Carbapenems are β-lactam antibiotics that bind to penicillin binding proteins and inhibit cell wall synthesis. Meropenem, doripenem, ertapenem, and imipenem are the four most clinically used carbapenems (Nicolau, 2008).

Enterobacteriaceae are a family of diverse Gammaproteobacteria which include common (*Klebsiella pneumoniae*, *Escherichia coli*, *Salmonella enterica*) and rare (*Proteus mirabilis*, *Raoultella planticola*, *Citrobacter freundii*) human pathogens with increasing antibiotic resistance. The Clinical Laboratory Standards Institute defines Enterobacteriaceae as carbapenem-resistant if they have minimum inhibitory concentrations (MICs) of ≥2 μg/ml against ertapenem and ≥4 μg/ml against doripenem, meropenem, or imipenem (Patel, 2015). In a 2013 US Centers for Disease Control and Prevention (CDC) report, carbapenem-resistant Enterobacteriaceae (CRE) were listed as one of the three most urgent antimicrobial resistant threats. CREs received this highest threat level due to rapidly increasing global spread, propensity for multidrug resistance, and high mortality during blood stream infections (BSI) (Bell et al., 2013).

Carbapenem resistance can arise from β-lactam ring hydrolysis by dedicated carbapenemase enzymes or from changes in membrane permeability via mutations in efflux pumps or porins coupled with extended spectrum β-lactamase (ESBL) expression. Carbapenemases come from ambler Class A or D serine β-lactamases and ambler class B metallo-β-lactamases (MBLs). *K. pneumoniae* carbapenemase (KPC-Class A), New Delhi metallo-β-lactamase (NDM-Class B), Verona integron-encoded metallo-β-lactamase (VIM-Class B), Imipenemase metallo-β-lactamase (IMP-Class B), and Oxacillinase-48 (OXA-48-Class D) variants are the most common carbapenemases in carbapenemase producing Enterobacteriaceae (CPE) and thus our focus in this review, but several emerging Class A enzymes are also described (Meletis, 2016). Carbapenemase production is concerning given high occurrence of carbapenemase genes on MDR plasmids transferred both within Enterobacteriaceae and to other bacterial families (Harmer and Hall, 2015).

This review highlights recent work documenting CRE prevalence, detecting CRE, and describing MDR patterns to optimize therapeutic strategy.

2. Class A β-lactamases

The first Class A carbapenemase was reported in 1990 in a *Serratia marcescens* isolate from the United Kingdom (Yang et al., 1990). Many Class A carbapenemases were identified after the discovery of *S. marcescens* enzyme one (bla_{SME-1}), including Guiana extended-spectrum two (bla_{GES-2}), *K. pneumoniae* carbapenemase (bla_{KPC}), imipenemase/non-metallocarbapenemase-A ($bla_{IMI/NMC}$), *Serratia fonticola* carbapenemase one (bla_{SFC-1}), and bla_{SHV-38} (Henriques et al., 2004; Poirel et al., 2003, 2001; Rasmussen et al., 1996; Yigit et al., 2001). Many bla_{GES} variants are only ESBLs but frequent point mutations confer increased hydrolytic properties against carbapenems for specific variants (Dang et al., 2016a,b). Phylogenetic alignment of Class A carbapenemase genes determined that bla_{SME}, bla_{GES}, bla_{KPC}, and $bla_{IMI/NMC}$ constitute a separate group from bla_{SFC-1} and bla_{SHV-38} (Walther-Rasmussen and Hoiby, 2007). Similar to other Class A β-lactamases, Class A carbapenemases are inhibited by clavulanic acid and tazobactam (Bush and Jacoby, 2010). While KPC is the most common Class A carbapenemase in Enterobacteriaceae, sporadic cases of previously discovered enzymes such as SME and NMC and new gene discoveries necessitate molecular characterization to identify potentially pandemic carbapenemases before they spread (Nordmann et al., 2011; Poirel et al., 2007).

2.1. KPC

As reported in 2001, bla_{KPC} was discovered in carbapenem resistant *K. pneumoniae* from the United States and it is largely responsible for conferring carbapenem resistance in CRE infections in the western hemisphere (Gaiarsa et al., 2015; Yigit et al., 2001). Unlike the previously characterized Class A carbapenemases (bla_{NMC} and bla_{SME}), bla_{KPC} is plasmid borne which facilitated its rapid appearance in non-*K. pneumoniae* Enterobacteriaceae (Hossain et al., 2004; Miriagou et al., 2003; Yigitet al., 2003). KPC's efficient carbapenem hydrolysis confers high levels of carbapenem resistance in the absence of complementary membrane permeability changes or ESBL expression, setting it apart from other serine β-lactamases (Poirel et al., 2007). In the UCLA Hospital system from January 2011 to January 2013, a few (0.73%) Enterobacteriaceae isolates were CRE, but an overwhelming proportion of those isolates (78.3%) had KPC associated carbapenem resistance (Pollett et al., 2014).

Regardless of location, 97% of whole-genome sequenced, KPC-producing *K. pneumoniae* belong to the clonal complex 258, demonstrating the global dissemination of member sequence types (Gaiarsa et al., 2015). Analysis of ST258 isolates identified two clades due to divergence in capsular polysaccharide synthesis (cps) genes (Deleo et al., 2014). Association of cps-1 with bla_{KPC-2} and cps-2 with bla_{KPC-3} suggests that variation in KPC is due to point mutations following cps recombination, rather than horizontal gene transfer via Tn4401 (Bowers et al., 2015). However, a two year-long study of admitted patients in five Colombian hospitals found a majority (62%, 120/193) of carbapenem-resistant *K. pneu-*

Table 1
Newly reported Class A carbapenemases.

Gene	Enterobacteriaceae	Year reported	Country	Plasmid	Accession number	Activity	References
bla_{BKC-1}	*K. pneumoniae*	2015	Brazil	IncQ	KP689347	Carbapenems, monobactams, penicillins, cephalosporins	Nicoletti et al. (2015)
bla_{FRI-1}	*E. cloacae*	2015	France	Untypeable	KT192551	Carbapenems, monobactams, aztreonam, penicillins	Dortet et al. (2015a)

moniae isolates were non-258 group members, but overall, KPC was the predominant carbapenemase (Ocampo et al., 2016). ST258 was identified for the first time in a collection of CPE Isolates from Taiwan. Although KPC was the most common (85.8%, 157/183) carbapenemase found, it was largely associated with *K. pneumoniae* ST11 (Tseng et al., 2015). Since ST258 is a hybrid strain of ~80% ST11, there is potential for rapid proliferation of the clone throughout the region (Chen et al., 2014). Overall percentage of CPE dropped in Israeli post-acute-care hospitals from 2008 (16%, 184/1147) to 2013 (9.9%, 127/1287), but ST258 increased compared to all KPC producing *K. pneumoniae* (65%, 120/184 in 2008 to 80%, 91/113 in 2013) (Adler et al., 2015a,b).

WGS identified a novel KPC encoding mosaic plasmid, pKp28, associated with an outbreak from an endoscope at a single hospital in the United States from January 2011 to July 2013. bla_{KPC-2} was found on a Tn4401 transposon with 99.99% nucleotide identity to pKpQIL, while a downstream region had 99.99% identity to pHg, another plasmid associated with ST258 (Marsh et al., 2015). bla_{KPC-2} was also discovered in the canonical hypervirulent *K. pneumoniae* ST23 (Cejas et al., 2014). Focused genomic analyses demonstrated that CG258 isolates cluster separately from ST23, and broader results confirm that multidrug resistant isolates have little overlap with hyper-virulent ones. However, this does not preclude the possibility of plasmid exchange leading to hypervirulent and multidrug resistant *K. pneumoniae* expressing KPC (Bialek-Davenet et al., 2014; Struve et al., 2015). bla_{KPC-2} was also identified in *K. pneumoniae* ST1797, a new hypervirulent strain associated with surgical wound infection in China in 2013 (Zhang et al., 2016). Successful transfer of bla_{KPC} containing plasmids throughout established nosocomial Enterobacteriaceae strains led to outbreaks in the United States in 2002–2003, and in Nepal in 2012 (Bratu et al. 2005; Chung The et al., 2015). A comparative study of hospitals in the United States and Pakistan from February 2012 to March 2013 showed that carriage of both bla_{KPC} and bla_{NDM} in the same isolate is rare, but similarity in genetic background between both locations make the possibility of horizontal gene transfer likely (Pesesky et al., 2015).

Active surveillance methods should be undertaken to quickly identify KPC producers and reduce infection prevalence.

2.2. Sequence-divergent Class A carbapenemases

A novel Class A carbapenemase with 63% sequence identity to an environmental β-lactamase and encoding broad activity against the penicillins, cephalosporins, carbapenems, and monobactams was discovered in three carbapenem-resistant *K. pneumoniae* ST1781 isolates from Brazil in 2008 (Nicoletti et al., 2015). The Brazilian Klebsiella Carbapenemase-1 (bla_{BKC-1}) gene was found on a non-conjugative IncQ plasmid with aph3A-VI, a novel variant of the aminoglycoside resistance gene aph3 (Nicoletti et al., 2015). In 2015 another novel Class A carbapenemase was identified in France from a carbapenem-resistant *Enterobacter cloacae* that produced a tazobactam-inhibitable carbapenemase negative for bla_{KPC}, bla_{GES}, bla_{SFC-1}, bla_{IMI}, and bla_{NMC-A}. The identified French imipenemase-1 (FRI-1) has significant activity against carbapenems and aztreonam, but not broad-spectrum cephalosporins; the low GC content (39%) of bla_{FRI-1} compared to the *E. cloacae* genome (55%) suggests acquisition via horizontal gene transfer (Dortet et al., 2015a,b). Surveillance of CPE carriage at a hospital in Italy identified an *Enterobacter ludwigii* in August 2014 with a chromosomally integrated bla_{NMC-A} complexed by a novel Xer-dependent integrative mobile element. Examination of publically available whole genome sequencing (WGS) data found that the element was associated with bla_{IMI} and bla_{NMC-A} in other members of the *E. cloacae* clonal complex, indicating the possibility of dissemination throughout Enterobacteriaceae (Antonelli et al., 2015) (Table 1).

3. Class B β-lactamases

MBLs can be differentiated from Class A and D β-lactamases by their use of zinc instead of a catalytic serine in the active site mediated hydrolysis of β-lactams (Pitout et al., 2015). Accordingly, MBLs are inhibited by metal chelators such as Ethylenediaminetetraacetic acid (EDTA) and dipicolinic acid (DPA) but not clavulanic acid or other clinically used β-lactamase inhibitors (Pitout et al., 2015). They often have hydrolysis profiles against all β-lactams except monobactams and can confer high level of resistance when combined with changes in membrane permeability and ESBL production (Pitout et al., 2015).

3.1. NDM

NDM is endemic to parts of Asia and is responsible for sporadic outbreaks around the globe (Zmarlicka et al., 2015). As of August 2016 when we accessed the NCBI database, 16 variants of NDM were identified on a variety of plasmid types, corresponding to the high diversity of Enterobacteriaceae species shown to express it (NCBI, 2016; Zmarlicka et al., 2015). A comprehensive study from 2012 to 2014 of 38,266 Enterobacteriaceae isolates collected from 40 countries spanning every inhabited continent found that global incidence of MBL presence is low (0.5%, 163/38,266), but dissemination is high (85%, 34/40 countries). bla_{NDM-1} was the most common gene (36.8%, 60/163) in Enterobacteriaceae (Kazmierczak et al., 2015). The Study for Monitoring Antimicrobial Resistance Trends identified bla_{NDM-1} (96.3%, 130/135) as the most common variant in NDM associated infections from 2008 to 2012 across geographically diverse countries.

Population migration will undoubtedly contribute to future global spread of CRE as evidenced by the prevalence of bla_{NDM} (59.3%, 19/32) among *K. pneumoniae* and *E. coli* isolates from Syrian patients displaced by civil strife in Europe (Lerner et al., 2016). Co-presence of ESBLs and NDM in the same isolate was high (78.5%, 106/135), but dual carbapenemase prevalence was fortunately low (1/135 with bla_{VIM-1} + *blaNDM*, 2/135 with $bla_{OXA-181}$ + bla_{NDM}) (Biedenbach et al., 2015a,b). A nosocomial outbreak declared in March 2014 of 19 *K. pneumoniae* ST10 in the neonatal intensive care unit of a Chinese hospital found that all isolates harbored bla_{NDM-1} on conjugative IncFI plasmids and that co-production of bla_{IMP-4} was common (36.8%, 7/19) but fortunately so was tigecycline, amikacin, and ciprofloxacin susceptibility (Zheng et al., 2016). *K. pneumoniae* was overwhelmingly responsible for NDM production in CRE colonized patients (370/374 patients) from Poland, a non-endemic area, during a 2012–2014 outbreak (Baraniak et al., 2016a,b). ST11 was the dominant sequence type and bla_{NDM-1} was

the most common variant, while a mix of IncR, IncFII, and undetermined plasmids were responsible for spread (Baraniak et al., 2016a,b). Tn3000, a novel transposon, was responsible for proliferation of bla_{NDM-1} among IncX3 and IncFIIk plasmids extracted from *E. coli* and *Enterobacter hormaechei*, respectively, in 2013 (Campos et al., 2015). Whole plasmid sequencing revealed high levels of intrapatient diversity for bla_{NDM-1} plasmid types and host species for Enterobacteriaceae and *Acinetobacter baumannii* isolates obtained in Pakistan during 2010 (Wailan et al., 2015).

Recently, bla_{NDM-13}, a chromosomally integrated NDM variant discovered in *E. coli* ST101 from Nepal in 2013, was found with a spectrum of action similar to bla_{NDM-1} but with increased cefotaxime affinity due to D95N and M154L mutations (Shrestha et al., 2015). Carbapenemase production in *Salmonella enterica* is rare but documented for KPC and NDM (Miriagou et al., 2003; Savard et al., 2011). bla_{NDM-1} was found on a conjugative IncA/C plasmid with bla_{CMY} (Class C plasmid-mediated AmpC beta-lactamase) in an extensively drug resistant *S. enterica* serovar Senftenberg isolate obtained from a pediatric outpatient in India in 2012. The plasmid had multiple mobile gene elements, complicating precise determination of the genetic events that led to bla_{NDM-1} acquisition (Sarkar et al., 2015). A study published in August 2014 identified two bla_{NDM-1} positive *S. enterica* serovar Agona isolates obtained from pediatric gastroenteritis infections in Pakistan (Irfan et al., 2015). These examples demonstrate need for carbapenemase gene surveillance in *S. enterica* serovars, especially for MBL endemic regions.

3.2. IMP

IMP, the first identified acquired MBL, was found in a *S. marcescens* isolate from Japan in 1991 (Ito et al., 1995). They are most common in China, Japan, and Australia (Nordmann et al., 2011). Contrasting global trends, bla_{IMP-4} was the most common carbapenemase (82.7%, 48/58) found in July 2009 to March 2014 from hospitals in Australia. 10 Enterobacteriaceae species produced bla_{IMP-4}, but *E. cloacae* was the most frequent (60.4%, 29/48) and possessed bla_{IMP-4} on conjugatable HI2 (22/29 or L/M (7/29)) plasmids demonstrating a plausible mechanism for bla_{IMP-4} proliferation throughout the region (Sidjabat et al., 2015). A pediatric patient in China in June 2014 had seven closely related bla_{IMP-4} producing *Raoultella ornithinolytica* isolated from an infected surgical wound, including the first observation of an *R. ornithinolytica* in China producing bla_{IMP-4} and bla_{KPC-2} (Zheng et al., 2015). Analysis of mobile genetic elements surrounding MBLs in Enterobacteriaceae collected in Spain from February to July 2009 found that all 14 bla_{VIM-1} genes were associated with class 1 integrons but a mixture of genetic backgrounds (2/14 bla_{VIM-1}, IncU and 12/14 unidentified plasmid type) (Zamorano et al., 2015).

3.3. VIM

VIM is largely found in Italy and Greece (Pitout et al., 2015). VIM-1 has the closest amino acid sequence identity (32.4%) to NDM-1 (Pitout et al., 2015). A multinational European survey of MBL-producing Enterobacteriaceae isolates collected between 2008 and 2011 found universal expression of bla_{VIM-1} type members (98.9%, 93/94) in nine different Enterobacteriaceae species but disproportionately high representation of *K. pneumoniae* ST147, ST36, and ST383 (60.6%, 57/94) from Greece (Papagiannitsis et al., 2015a,b,c). VIM-39 is a novel bla_{VIM-1} type member identified in the previous study; it was found to hydrolyze meropenem, doripenem, and imipenem more efficiently than VIM-1 and conferred greater resistance to those carbapenems than bla_{VIM-1} in *E. coli* DH5α (Papagiannitsis et al., 2015a,b,c). A pediatric patient from the United States was colonized by a MBL producing *K. pneumoniae* and later infected by a clone of the isolate in May 2014. The isolate transferred an IncA/C replicon 188-kb plasmid containing bla_{VIM-4} and bla_{CMY-4} to a recipient *E. coli* strain (Tamma et al., 2016). Additionally, eight VIM-producing CRE isolates were found on six patients in the same tertiary care hospital in the United States during August 2015. Fortunately, VIM colonization was not linked with infection, but the diversity of Enterobacteriaceae species (one *Raoultella* spp., four *E. cloacae*, one *E. coli*, and two *K. pneumoniae*) and patient location (6 neonatal intensive care unit, 2 adult intensive care unit) combined with the unidentified VIM-producing source warrant further investigation of bla_{VIM} containing plasmids (Yaffee et al., 2016).

4. Class D β-lactamases

Class D β-lactamases were named oxacillinases (OXA) because they cleave oxacillin in addition to penicillin, distinguishing them from Class A β-lactamases. Although first characterized as extended spectrum β-lactamases, OXA-23 was found to confer resistance against imipenem in an *A. baumannii* isolate from the United Kingdom in 1985 (Donald et al., 2000). Additional carbapenem-hydrolyzing class D β-lactamases (CHDLs) have also been discovered. Since 2001 OXA-23-like, OXA-40-like, OXA-51-like, OXA-58-like, and OXA-48-like family members have been found in the Enterobacteriaceae (Evans and Amyes, 2014). CHDLs are increasing in global frequency more than the Class A and B carbapenemases (Bakthavatchalam et al., 2016). bla_{OXA-48} was identified in a *K. pneumoniae* isolate from Turkey in 2001 and remains the most common CHDL detected (Poirel et al., 2004a,b). A chromosomally encoded CHDL, bla_{OXA-54}, from the environmental bacteria *Shewanella oneidensis* had a 92% amino acid similarity with bla_{OXA-48} and comparable catalytic activity against imipenem (Poirel et al., 2004a,b). Analysis of the flanking sequences between bla_{OXA-48} and bla_{OXA-54} suggest that bla_{OXA-48} originated in *Shewanella* spp. (Poirel et al., 2004a,b). $bla_{OXA-48-like}$ family members cleave carbapenems weakly, which can lead to phenotypic susceptibility against carbapenems and therefore complicate treatment options (Bakthavatchalam et al., 2016). Excepting OXA-163, OXA-48-like family members have little to no activity against Ceftazidine and Cefotaxime but phenotypic resistance to cephalosporins can occur in isolates co-expressing CHDLs and cephalosporin cleaving β-lactamases (Oueslati et al., 2015).

4.1. OXA-48-like family members

A survey of CRE in Moscow from January 2013 to October 2014 found examples of bla_{OXA-48} spreading from *K. pneumoniae* to *Proteus mirabilis*, with both pathogens having nearly universal resistance (99% and 100% respectively) to three or more functional drug classes (Fursova et al., 2015). The majority (71.9%, 87/121) of carbapenem-resistant, carbapenemase producing *E. coli* obtained from 2012 to 2014 in Spain possess bla_{OXA-48} but in a less diverse population compared to bla_{VIM-1} expressing isolates (Ortega et al., 2016). Conjugatable bla_{OXA-48} (9/11) was the most prevalent carbapenemase detected in CPE from a hospital in Morocco collected in June to August 2011 (Barguigua et al., 2015). The first documented instance of a community acquired UTI due to an $bla_{OXA-48-like}$ producing Enterobacteriaceae was in Greece in January 2010 when a recovered *K. pneumoniae* ST11 isolate was found with carbapenem resistance due to $bla_{OXA-162}$ (Voulgari et al., 2015). Multiple studies identified bla_{OXA-48} as the most prevalent carbapenemase in Spain, and this is associated with successful spread of *K. pneumoniae*, particularly ST11 (Branas et al., 2015; Oteo et al., 2015). OXA-48 in the absence of other ESBLs is difficult to detect using traditional phenotypic methods due to low level of resistance

against cephalosporins or carbapenems. Molecular characterization of $bla_{\text{OXA-48-like}}$ variants is recommended, as expression of $bla_{\text{OXA-48}}$ in *E. coli* does not always yield carbapenem resistance in vitro, but it can prevent clearance of infections (Haverkate et al., 2015). Emerging cases of $bla_{\text{OXA-48}}$ in Taiwan from January 2012 to May 2014 suggest expanding ability to confer carbapenem resistance in the Enterobacteriaceae (Ma et al., 2015). $bla_{\text{OXA-48}}$ was responsible for carbapenem resistance in a collection of *Raoultella planticola* isolates from January 2011 to December 2015 at a Turkish hospital (Demiray et al., 2016). A plasmid borne $bla_{\text{OXA-48}}$ contained on Tn1999.2 was reported in a *R. ornithinolytica* clinical isolate from Lebanon in 2016 (Al-Bayssari et al., 2016).

Within $bla_{\text{OXA-48-like}}$ members, carbapenemase activity varies significantly despite few sequence changes. Purified OXA-163 was shown to hydrolyze carbapenems at efficiencies far lower than several other OXA-48-like members. When $bla_{\text{OXA-163}}$ was expressed in *E. coli* TOP10, this correlated with MICs below the clinical breakpoint for Enterobacteriaceae carbapenem susceptibility (Oueslati et al., 2015). However, MIC values for *E. coli* lacking OmpF and OmpC were above the susceptibility cut off for meropenem, doripenem, and ertapenem (Oueslati et al., 2015). OXA-405 is a $bla_{\text{OXA-48}}$ type carbapenemase without carbapenemase activity discovered in a *S. marcescens* isolate from France in January 2011 (Dortet et al., 2015a,b). Similar to OXA-163, it conferred increased resistance to extended-spectrum cephalosporins and aztreonam compared to OXA-48. Rapid global spread of $bla_{\text{OXA-48-like}}$ expressing Enterobacteriaceae necessitates molecular detection for informed patient treatment options and documentation of epidemiological occurrences to prevent nosocomial outbreaks (Poirel et al., 2012a,b).

5. Non-carbapenemase resistance mechanisms

Resistance-nodulation-division (RND) efflux pumps including the AcrAB-TolC system are a common resistance mechanism for Enterobacteriaceae and other Gram-negative bacteria against multiple antibiotic classes. Counterintuitively, KPC-2 production coupled with a loss-of-function AcrAB mutant in *K. pneumoniae* ECL-8 and *E. coli* BW25113 resulted in increased resistance against ertapenem and meropenem. Similarly, *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. treated with the efflux pump inhibitor, phenylalanine-arginine β-naphthylamide (PABN), down-regulated *ompF* expression and had increased ertapenem resistance (Saw et al., 2016). RND efflux pump inhibition holds promise as synergistic treatment against MDR Gram-negative bacteria, but these results indicate that pump inhibition cannot be broadly applied across antibiotic classes (Aparna et al., 2014). Single nucleotide polymorphism (SNP) analysis between carbapenem-resistant, non-carbapenemase producing *E. cloacae* found that most SNPs are attributable to natural phylogenetic variation. However, SNPs in *ampD* leading to increased bla_{ampC} expression combined with mutations lowering expression of *ompC*, *ompF*, or both, thus increasing carbapenem resistance as well (Babouee Flury et al., 2016). As reported in 2015, *K. pneumoniae* clinical isolates from the United States and Israel with intermediate carbapenem susceptibility but lacking carbapenemase genes had more frequent porin nonsense mutations (*ompK35*, *ompK36*, and *ompK37*) and greater ESBL expression compared to *K. pneumoniae* with carbapenemases (Adler et al., 2015a,b).

As reported in 2013, loss of OmpK35 and OmpK36 porins in a *K. pneumoniae* isolate from Taiwan resulted in a 32-, 8-, and 4-fold increase in the MIC to ertapenem, meropenem, and doripenem respectively, but only ertapenem was beyond the clinical resistance breakpoint (Tsai et al., 2013). However, OmpK35/36 loss combined with expression of $bla_{CTX\text{-}M\text{-}15}$ ESBL or the plasmid-mediated β-lactamase $bla_{DHA\text{-}1}$ and its regulator *ampR* led to clinical resistance against ertapenem, meropenem, doripenem, and imipenem (Tsai et al., 2013). This combination of ESBL production and porin loss is believed to have contributed to dissemination of carbapenem-resistant *K. pneumoniae* within a tertiary-care hospital in South Korea from 2007 to 2008 (Shin et al., 2012).

Stepwise-carbapenem resistance in the absence of a carbapenemase or β-lactamase was reported in Sweden in 2016 when an *E. coli ompC* and *ompF* double-deletion mutant was passaged in meropenem or ertapenem for ~60 generations (Adler et al., 2016). Meropenem but not ertapenem passaging caused mutations in stringent response regulator enzymes, *spoT*, *thrS*, and *tufA* (Adler et al., 2016). Increased stringent response activity is believed to contribute to carbapenem resistance but at a substantial fitness cost (Adler et al., 2016).

Multiple antibiotic resistance protein A (*marA*) is an AraC-type transcriptional regulator (TR) responsible for antibiotic resistance in the Enterobacteriaceae primarily by controlling outer membrane permeability in coordination with two other AraC-type TRs, *rob* and *soxS* (Alekshun and Levy, 1999). Overexpression of an additional AraC-type TR, *ramA*, in the *K. pneumoniae* NCTC 5055 reference strain increased growth around an imipenem Kirby-Bauer disk, suggesting a role in regulating carbapenem resistance (Jimenez-Castellanos et al., 2016). As reported in 2013, an *E. coli* isolate from China lacked OmpF and OmpC porins and had a *marA* mutation which resulted in expression of the previously classified pseudogene *yedS* (Warner et al., 2013). $_{\text{G42R}}$MarA facilitated expression of the YedS porin which is believed to contribute to *E. coli* isolate survival in the absence of OmpF and OmpC (Warner et al., 2013). These examples indicate that changing membrane permeability by altering efflux pumps and porin expression can confer carbapenem resistance alone or synergistically with ESBLs in the absence of a carbapenemase.

6. Detection

Initial CRE detection is often by analysis of susceptibility testing results from automated systems, broth microdilution assays, and Kirby-Bauer disk diffusion (Nordmann et al., 2012). Further characterization is done to differentiate carbapenemase producers from non-producers (Nordmann et al., 2012). The poor hydrolytic ability of some carbapenemases for carbapenems, most notably OXA-48-like enzymes and KPC variants, makes the appearance of carbapenem susceptible, carbapenemase producers also possible (Gagetti et al., 2016; Poirel et al., 2012a,b). PCR-based and phenotypic assays are the two detection methods for identifying CRE and CPE (Nordmann et al., 2012).

Screening breakpoints for CPE detection are recommended by CLSI and EUCAST, but there is no consensus on the optimal breakpoints (CLSI, 2016; EUCAST, 2013). A 2016 study suggested that CLSI screening breakpoints for CPE detection are missing carbapenem susceptible carbapenemase producers in carbapenemase isolates 14% (26/188) including 25% (14/63) of KPC producers and 40% (12/30) of OXA-48-like producers (Fattouh et al., 2016).

The diversity of OXA-48-like carbapenemases makes precise molecular determination difficult (Hemarajata et al., 2015). However, a PCR-based assay using high-resolution melt time analysis can differentiate seven $bla_{\text{OXA-48-like}}$ family members as well as bla_{KPC}, $bla_{\text{NDM-1}}$, bla_{IMP}, bla_{VIM}, and bla_{SME} (Hemarajata et al., 2015). A multiplex PCR assay using peptide nucleic acid probes reported high sensitivity and specificity (both above 99.0%) in identifying bla_{KPC}, $bla_{\text{OXA-48}}$, bla_{GES}, bla_{IMP}, bla_{VIM}, and bla_{NDM} from a mixture of Enterobacteriaceae isolates (Jeong et al., 2015). One assay combined nested PCR, rtPCR, and microfluidics to obtain class level identification of carbapenemases (bla_{KPC}, bla_{VIM}, $bla_{\text{OXA-23}}$, $bla_{\text{OXA-48}}$, $bla_{\text{OXA-51}}$) and ESBLs for rapid detection of diverse mul-

tidrug resistant organisms including CRE (Walker et al., 2016). A PCR-based assay for rectal swabs had high sensitivity (96.6%) and specificity (98.6%) at identifying bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{OXA-48}, and bla_{IMP-1} on a rapid time-scale (32–48 min) (Tato et al., 2016).

A comparison of disk diffusion assay detection of OXA-48-like carbapenemase producing Enterobacteriaceae from 2014 demonstrated that temocillin disk detection had similar sensitivity (all above 98%) to meropenem and piperacillin/tazobactam disk detection (Huang et al., 2014). Use of temocillin disk detection dramatically increased specificity (92.0% for *K. pneumoniae* and 89.3% for other species with temocillin compared to 46.0% for meropenem and 60.5% for piperacillin/tazobactam) using modified detection cut-offs of 29 mm, 16 mm, and 12 mm for meropenem, piperacillin/tazobactam, and temocillin respectively (Huang et al., 2014). Temocillin can also be used for detection of MBL and KPC using Disks or tablets if synergy is not detected (EUCAST, 2013).

The Modified Hodge Test (MHT) is a phenotypic assay for detection of CPE by inactivation of carbapenems allowing increased growth of an indicator strain (Girlich et al., 2012). However, the MHT has poor sensitivity for class B carbapenemases (sensitivity <50%) which is marginally improved by addition of $ZnSO_4$ (sensitivity 87%) (Girlich et al., 2012). As reported in Argentina in 2016, addition of 0.2% Triton X-100 [vol/vol] to Mueller Hinton Agar plates improved sensitivity (97–100%) for detecting Class B carbapenemase expressing CPE (Pasteran et al., 2016). The proposed mechanism relies on the anionic detergent disturbing the hydrophobic interactions between the lipoprotein carbapenemases and the outer membrane (Gonzalez et al., 2016; Pasteran et al., 2016).

Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) has become an essential tool within Clinical microbiology laboratories for rapid identification of bacterial pathogens as well as their resistance mechanisms by comparing a clinical isolate's peptide mass fingerprint with known databases (Bohme et al., 2012). Additionally, MALDI-TOF MS can be adapted to study small molecules. As reported in France in 2015, a MALDI-TOF MS analysis of imipenem hydrolysis by cell supernatants had 100% specificity and sensitivity at differentiating CPE (OXA-48 variants, KPC, NDM, VIM, IMI, IMP, and NMC-A) from CRE that lack carbapenemases (Lasserre et al., 2015). The low cost per test (<0.10 USD) and rapid protocol (~20 min) holds promise for widespread adoption by clinical microbiology labs (Lasserre et al., 2015).

The easily interpretable Rapidec Carba NP Test showed high sensitivity and specificity (both 96%) at detecting CPE (in addition to *A. baumannii* and *Pseudomonas aeruginosa*) with an under 30-min incubation time (Poirel and Nordmann, 2015). A phenotypic assay using imipenem, EDTA, and EDTA plus phenylboronic acid had high sensitivity (96.3%) and specificity (97.7%) in identifying OXA-48-like family members within genetically characterized CRE (Tsakris et al., 2015). A novel colorimetric assay for carbapenemase detection showed high sensitivity (97.8%) and specificity (98.5%) at differentiating carbapenem-resistant, carbapenemase producers from non-producers (Kabir et al., 2016). An electrochemical assay using imipenem hydrolysis to drive redox changes was capable of detecting CPE in less than 35 min with high sensitivity (95%) and perfect specificity (100%) (Bogaerts et al., 2016). The carbapenem inactivation method is an efficient phenotypic assay that has high concordance with PCR-based detection of carbapenemase production in Enterobacteriaceae as well as *Acinetobacter* and *Pseudomonas* species. The simple protocol and required materials makes it promising for widespread adoption by clinical microbiology labs (van der Zwaluw et al., 2015). An immunochromatographic assay had perfect sensitivity (100%) and specificity (100%) at detecting OXA-48-like CPE compared to isolates possessing OXA-48-like variants lacking carbapenemase activity or Class A and B carbapenemases (Dortet et al., 2016). Accurate detection methods are important for developing ideal patient treatment options and surveillance of carbapenemases. In a study done between June 2010 to January 2014, an Italian hospital demonstrated that identification of carbapenemases by disk diffusion synergy and quarantine of CRE carriers significantly reduces incidence of high mortality BSIs (Viale et al., 2015).

7. Plasmid replicons

Plasmids are extrachromosomal DNA elements that often contain genes which confer fitness to specific extracellular stressors (Carattoli, 2013). Certain plasmids are conjugative and can be passed between members of the Enterobacteriaceae and with other gram negative pathogens such as *A. baumannii* and *P. aeruginosa* (Vilacoba et al., 2014). Class A, B, and D carbapenemases contained on mobile gene elements within these plasmids is a core factor in the rapid spread of CRE (Mathers et al., 2015).

7.1. IncL/M

IncL/M plasmids are self-transmissible replicons common among Enterobacteriaceae (Carattoli et al., 2015). Genomic characterization of IncL and IncM plasmid identified high nucleotide conservation (~94%) but two distinct branches when clustered for sequence similarity (Carattoli et al., 2015). Of 20 IncL/M plasmids sequenced by 2015, 18 harbored β-lactamases from ambler Classes A–D including KPC, NDM, VIM, and OXA carbapenemases (Adamczuk et al., 2015). These plasmid types were originally endemic to the Mediterranean region but have become globally disseminated (Adamczuk et al., 2015). IncL/M plasmids containing bla_{OXA-48} were demonstrated to have a 40-fold higher transfer efficiency compared to plasmids with bla_{NDM-1} due to insertion of bla_{OXA-48} and its flanking transposon Tn1999 into the transfer inhibition protein gene (Potron et al., 2014). Genetic analysis of the plasmid containing bla_{OXA-48} determined the absence of other antibiotic resistance genes but the presence of a Tn1999 composite transposon on the common IncL/M type backbone (Poirel et al., 2012a,b). Given widespread dissemination of the IncL/M type plasmids among Enterobacteriaceae and presence of multiple mobile genetic elements, threat of additional antibiotic resistance genes associating with bla_{OXA-48} is constant but currently undocumented (Manageiro et al., 2015).

7.2. IncX3

A single IncX3 plasmid with two bla_{KPC-3} copies, both associated with Tn4401, was recovered from an XDR *K. pneumoniae* ST512 isolate in Italy in 2014. The MICs for carbapenems were identical between the IncX3-*K. pneumoniae* ST512 and a *K. pneumoniae* ST512 with KPC on the canonical pkpQIL plasmid. IncX3 *E. coli* transformants had greater carbapenem resistance than the pkpQIL, but this could be due to differences in plasmid copy number or KPC expression in addition to the two bla_{KPC-3} genes (Fortini et al., 2016). An *E. coli* ST 3835 isolate obtained in November 2012 from China contained bla_{NDM-1} and bla_{SHV-12} on the IncX3 plasmid backbone (Feng et al., 2015a,b). This narrow-spectrum plasmid was found harboring bla_{NDM-1} in several Enterobacteriaceae isolates in China, suggesting a possible role in global dissemination of bla_{NDM-1} (Feng et al., 2015a,b). A comparison of CPE collected from 2013 to 2014 in a Canada found that bla_{NDM-7} was harbored on an identical IncX3 plasmid across *K. pneumoniae*, *E. coli*, *E. hormaechei*, and *S. marcescens*, indicating frequent horizontal gene transfer events within Enterobacteriaceae (Chen et al., 2015a,b). Five CRE collected at a hospital in China from January to September 2013 possessed bla_{NDM-1} on an IncX3 plasmid with high similarity in the immediate region surrounding bla_{NDM-1}, but one plasmid was twice as

large (104.5–138.9 kb) as the other four (33.3–54.7 kb), indicating genetic exchanges during horizontal gene transmission between Enterobacteriaceae (Yang et al., 2015).

7.3. IncF

IncFII-type plasmids (7/12) were the most common background carrying NDM in a cohort of NDM positive isolates obtained in Australia from 2012 to 2014. IncX3 (4/12) and IncHI1B (1/12) were also identified, but every NDM variant was within Tn125 (Wailan et al., 2016a,b). bla_{NDM-5} on an IncFII plasmid was found on two *K. pneumoniae* ST147 isolates in a suspected nosocomial transmission event at a hospital in South Korea in 2014 (Shin et al., 2016). A *K. pneumoniae* isolate obtained from China in October 2010 expressed bla_{KPC-2} on a IncFIIK conjugative plasmid in association with a different transposon, Tn1772, indicating carriage plasticity by mobile gene elements (Wang et al., 2015). As reported in 2015, a patient from Spain with no recent travel history had a urine culture positive for *E. coli* ST448 with bla_{NDM-5} on a conjugatable IncFII-type plasmid (Pitart et al., 2015). The first MBL expressing Enterobacteriaceae isolate obtained from Poland in August 2011, an *E. coli* ST410, was found to carry bla_{NDM-1} on a IncFII plasmid (Fiett et al., 2014). An IncFIIy type plasmid containing NDM and three ESBLs (bla_{TEM}, $bla_{CTX-M-1}$, and bla_{OXA-1}) together was isolated from the first instance of a carbapenem-resistant *Leclercia adecarboxylata* from China in August 2012 (Sun et al., 2015). In Europe, clonal group 258 is the primary source of KPC producing *K. pneumoniae*, with the eponymous ST258 being the most common (69.1%, 76/110) followed by ST512 (19.1%, 21/110) (Baraniak et al., 2016a,b). Both predominantly possess IncFIIB and IncFIBK, contrasting with non-CG258 *K. pneumoniae* and other CPE species which mostly possess IncN plasmids (Baraniak et al., 2015).

7.4. IncA/C

Chromosomally integrated bla_{NDM-1} expressing *P. aeruginosa* and bla_{NDM-1} on IncA/C plasmid in *E. coli* were obtained from the same patient (Mataseje et al., 2016). As reported in 2016, IncA/C2 and IncFIIy plasmids carrying NDM in Enterobacteriaceae from Australia and New Zealand all had segments with high sequence similarity to *Acinetobacter* plasmids, further documenting frequent genetic exchange with non-Enterobacteriaceae members (Wailan et al., 2016a,b). Multidrug resistant IncA/C plasmids containing integrons In4863 (bla_{VIM-19}) were identified in two carbapenem-resistant *K. pneumoniae* ST383 isolates with suspected origin from Greece in 2009 to 2011 (Papagiannitsis et al., 2016). Multidrug resistant, conjugative IncA/C plasmids were recovered from two *K. pneumoniae* ST11 isolates obtained from a hospital in Bulgaria in 2014. The larger (176-kb) plasmid possessed bla_{NDM-1} with bla_{CMY-4}, $bla_{CTX-M-15}$, bla_{TEM-1b}, and *qnrB* while the smaller (86-kb) plasmid had bla_{NDM-1} with bla_{TEM-1}, and *aac(6')-Ib* (Todorova et al., 2016). bla_{OXA-48} has additionally been identified on an IncA/C plasmid in Taiwan (2015) and Tunisia (2011) (Ktari et al., 2011).

7.5. Other

A *K. pneumoniae* ST25 isolate obtained from a Portuguese ICU in 2009 possessed bla_{IMP-8} on a ColE1-like plasmid in association with a novel class 3 integron that also contained the weak carbapenemase bla_{GES-5}, *aacA4*, and bla_{BEL-1}, an ESBL only identified in *P. aeruginosa* previously. Formerly, these genes were found solely on class 1 integrons; this suggests a resistance cassette exchange between class 1 and 3 integrons, with potential IncQ plasmid involvement, may be responsible (Papagiannitsis et al., 2015a,b,c).

bla_{NDM-1} was discovered on a BJ01-like plasmid in an *E. aerogenes* isolate from China in June 2012 (Chen et al., 2015a,b). Since previous reports of pNDM-BJ01 have exclusively been in *Acinetobacter*, this identification confirms that horizontal gene transfer between Gammaproteobacteria is a continual occurrence (Chen et al., 2015a,b).

The first instance of the narrow-spectrum plasmid, IncT, containing bla_{NDM-1} was from a *Providencia rettgeri* isolate colonizing a patient in Canada who received medical care in India in 2015 (Mataseje et al., 2016).

8. Non-infectious surveillance

Prediction of carbapenemase dissemination is complicated by the discovery of new reservoirs for antibiotic resistance genes. An *E. coli* CMUL 64 specimen isolated from domesticated chickens in Lebanon in December 2013 contained bla_{OXA-48} in addition to two ESBLs (Al Bayssari et al., 2015). Surveillance of Silver Gull (*Chroicocephalus novaehollandiae*) excrement from South-East Australia in October 2012 found that CPE carriage was alarmingly high (71.8%, 120/167) and almost completely due to bla_{IMP-4} (96.7%, 116/120), but bla_{IMP-26} (1.67%, 2/120) and bla_{IMP-38} (5.83%, 7/120; 5/7 in *E. coli* ST58 co-producing bla_{IMP-4}) were also detected (Dolejska et al., 2016). This agrees with clinical observations reporting bla_{IMP-4} as the most prevalent gene from CPE clinical isolates in Australia, indicating either high transmission frequency of bla_{IMP-4} to human pathogens or that these CPE environmental isolates can be infectious agents (Dolejska et al., 2016). Contrasting with the seemingly high carriage of CPE in birds, CPE are absent (0.6%, 1/160) from studied companion dog fecal microbiota in Madrid, Spain from October 2014 to January 2015 excepting one *K. pneumoniae* ST2090 expressing bla_{VIM-1} on an untyped plasmid (Gonzalez-Torralba et al., 2016). Similarly, WGS analysis of fecal microbiota collected from dairy cows in the southwestern United States from May to July 2014 failed to detect any CRE, though it did find other carbapenem-resistant Gram-negative bacteria (Webb et al., 2016).

Assessment of individual carriage potential demonstrated that recent antibiotic therapy, immunosuppression, and a Charlson Comorbidity Index >4 are all significant predictors of CRE infection (Miller and Johnson, 2016). A US case report from February 2016 indicates that the Middle East may be another reservoir for bla_{NDM} genes in addition to the Indian subcontinent and the Balkans (Li et al., 2016). Identifying intra-hospital carriage of CRE is important given the high fatality rate from CRE infections in patients with solid organ transplants from endemic areas (Satlin et al., 2014).

A study published in 2016 identified bla_{IMI-3} on a IncFIIY plasmid obtained from sediment at the Haihe River in China showed high genetic similarity with IncF plasmids from pathogenic Enterobacteriaceae (Dang et al., 2016a, 2016b). As reported in 2016, an IncP-1β plasmid also obtained from sediment at the Haihe River contained a bla_{GES-5} variant with several amino acid substitutions that led to loss of carbapenemase activity (Dang et al., 2016a, 2016b). Two *E. coli* isolates expressing bla_{IMP-8} and two *E. coli* isolates expressing bla_{VIM-1} and bla_{VIM-34} were obtained in February 2015 from the Ave river in northern Portugal. bla_{IMP-8} and bla_{VIM-1} were found on IncFIB type plasmids capable of transconjugation while bla_{VIM-34} was suspected to be chromosomally integrated (Kieffer et al., 2016). As reported in 2016, water collected from Rio De Janeiro yielded many bla_{KPC} producing Enterobacteriaceae as well as bla_{GES}, $bla_{OXA-48-like}$, and bla_{NDM} genes amplified directly from aquatic microbial communities (de Araujo et al., 2016). Routine environmental sampling could prove advantageous in anticipating spread of novel antibiotic resistance genes into clinical pathogens (Table 2).

Table 2
Environmental CRE surveillance.

Source	Enterobacteriaceae	Carbapenem resistance	Year reported	Country	References
Chicken	*E. coli*	bla_{OXA-48}	2015	Lebanon	Al-Bayssari et al. (2016)
Silver Gull	*E. coli*, *Escherichia fergusonii*, *K. pneumoniae*, *Kluyvera georgiana*, *E. aerogenes*, *E. cloace*, *C. freundii*, *Citrobacter braakii*, *P. mirabilis*, *Proteus penneri*	bla_{IMP-4}, bla_{IMP-26}, bla_{IMP-38}	2016	Australia	Dolejska et al. (2016)
Companion dog	*K. pneumoniae*	bla_{VIM-1}	2016	Spain	Gonzalez-Torralba et al. (2016)
Dairy cow	*E. coli*, *Aeromonass veronii*, *Aeromonas allosaccharophila*	ESBL + Porin mutation	2016	United States	Webb et al. (2016)
Ave River	*E. coli*	bla_{VIM-1}, bla_{VIM-34}, bla_{IMP-8}	2016	Portugal	Kieffer et al. (2016)
Carioca River	*E. cloace/asburiae*, *K. pneumoniae*, *Klebsiella* spp., *E. kobei*	bla_{KPC}	2016	Brazil	de Araujo et al. (2016)

9. Contribution of carbapenemases to MDR/XDR Enterobacteriaceae

9.1. Dual carbapenemases

Presence of multiple carbapenemase genes in one isolate is concerning given the possibility of different carbapenemase genes crossing onto the same plasmid. A *K. pneumoniae* isolate obtained in the United States in 2013 from the high risk ST258 clade expressed plasmid borne bla_{KPC-2} and bla_{VIM-4} (Castanheira et al., 2016). An *E. cloacae* ST231 from China in 2012 was found to harbor bla_{NDM-1} on IncA/C2 mosaic plasmid and bla_{KPC-3} on a novel IncX6 plasmid (Du et al., 2016a, 2016b). These same resistance genes were found on two different IncF plasmids in an *E. cloacae* isolate from China in April 2014, further increasing the likelihood that a recombination event could create a dual carbapenemase plasmid (Wu et al., 2015). In April 2014 a *K. pneumoniae* ST147 strain possessing bla_{NDM-5} and $bla_{OXA-181}$ was isolated at a hospital in South Korea from a patient native to the United Arab Emirates (Cho et al., 2015). Four months later, a *K. pneumoniae* isolate with identical ST, $bla_{OXA-181}$, and bla_{NDM-5} genes was obtained from a patient native to South Korea with no history of travel abroad (Cho et al., 2015). The patients did not overlap temporally or spatially, which suggests extended surface survival of *K. pneumoniae* (Cho et al., 2015). This occurrence is also documented outside of *K. pneumoniae*; in 2016 an *E. coli* ST410 isolate from Egypt was found to have bla_{NDM-5} and $bla_{CTX-M-15}$ on a transmissible ~100 kb plasmid with 99% similarity to pHC105 and $bla_{OXA-181}$ on a 48.5 kb plasmid that did not transform a recipient strain (Gamal et al., 2016a,b). A *C. freundii* isolate from China in July 2013 possessed bla_{NDM-1} on an IncX3 type plasmid and bla_{KPC-2} on an untypable plasmid that is notable for a region with genes conferring resistance to macrolides (*mphA-mrx-mphR* operon), quinolones (*aac(6′)-Ib-cr*), rifampin (*arr-3*), chloramphenicol (*catB3*), sulfonamides (*sul1*), cephalosporins (bla_{OXA-1}), quaternary ammonium compounds (*qacEΔ1*), chromate (*chrA*), and fosfomycin (*fosA3*) (Feng et al., 2015a,b).

9.2. Tigecycline resistance

Tigecycline is a tetracycline derivative and one of the few remaining drugs for treating CRE infections. 56 tigecycline non-susceptible *K. pneumoniae* from South Korean hospitals in 2012 showed that co-resistance with carbapenems is low (2/56) compared to ceftazidime, ceftriaxone, and aztreonam (37/56, 36/56, and 35/56 respectively) (Ahn et al., 2016). But prior admission to a skilled nursing facility was significantly associated with tigecycline non-susceptible, carbapenem-resistant *K. pneumoniae* cultures in hospitalized patients (van Duin et al., 2015). Additionally, tigecycline resistance in carbapenem-resistant *K. pneumoniae* bacteriuria occurred significantly following tigecycline monotherapy in a multicenter, prospective study from December 2011 to October 2013 in the United States (van Duin et al., 2014). Clinical resistance to Tigecycline was associated with increased expression of *AcrAB* by *marA* mutations in KPC-producing *K. pneumoniae* isolates from China collected between January 2010 and December 2013 (Hemarajata et al., 2015).

9.3. Aminoglycoside resistance

Gentamicin, amikacin, and tobramycin are aminoglycosides occasionally used to treat CRE (Morrill et al., 2015). *rmtB* is a 16s rRNA methylase conferring high level aminoglycoside resistance that is commonly found on IncF, IncA/C, IncK, and IncN plasmids (Kang et al., 2008; Yu et al., 2010). These plasmids are common in Enterobacteriaceae and indeed *rmtB* was found in 34% (25/74) of *K. pneumoniae* ST11 isolates from China in 2012 to 2014 with 97% (72/74) positive for bla_{KPC-2} and the remainder (2/74) positive for bla_{NDM-1} (Cheng et al., 2016). Quinolone resistance genes *oqxA*, *oqxB*, and *qnrB* were also common in 81% (60/74), 76% (56/74), and 8% (6/74) of isolates, respectively (Cheng et al., 2016). *rmtF* is a novel 16S rRNA methyltransferase which was found to confer high aminoglycoside resistance in Enterobacteriaceae isolates collected from 2009 to 2011 in India and the United Kingdom (Hidalgo et al., 2013). 20 of the 34 *rmtF* expressing Enterobacteriaceae also contained NDM-1 (Hidalgo et al., 2013). Two ST11 *K. pneumoniae* isolated from a tertiary care hospital in Egypt from September 2013 to December 2014 possessed bla_{NDM-1} and *rmtF* on the same untypeable 170 kb plasmid (Gamal et al., 2016a,b).

9.4. Colistin resistance

Colistin is an old and rarely used (due to severe nephrotoxicity) polymyxin antibiotic that has emerged as a CRE treatment, making co-resistance concerning. Until the discovery of the plasmid-mediated colistin resistance gene, *mcr-1*, resistance was attributed to chromosomal modification of the LPS biosynthesis pathway (Liu et al., 2016). *Mcr-2*, a colistin resistance gene with 76.7% nucleotide identity to *mcr-1*, was discovered on a conjugatable IncX4 plasmid in *E. coli* ST10 and ST167 from Belgium in July 2016 (Xavier et al., 2016). The IncX4 plasmid did not contain any additional resistance genes, but *mcr-2* was contained within an IS element from the IS1595 superfamily, which was associated with the carbapenemase bla_{OXA-23} in *Acinetobacter radioresistens* (Higgins et al., 2013). A third (32/97) of carbapenem-resistant *K. pneumoniae* found in Italy from December 2010 to May 2011 displayed a colistin MIC

Table 3
Co-occurrence of antibiotic resistance genes in CPE isolates.

Isolate	Carbapenemase	Identified Antibiotic resistance genes	Method	Year reported	Country	References
K. pneumoniae	$bla_{OXA-181}$	*rmtF, aac(6′)-Ib-cr,* $bla_{CTX-M-15}$, *gyrA, parC, qnrB, afrA12, drfA14, acrAB,* bla_{SHV-36}, *catB1, fosA, tetC*	WGS	2015	United Arab Emirates	Zowawi et al. (2015)
K. pneumoniae	bla_{NDM-5}, $bla_{OXA-181}$	bla_{TEM-1}, bla_{SHV-11}, $bla_{CTX-M-15}$, *rmtB*	PCR	2015	South Korea	Cho et al. (2015)
E. coli	bla_{NDM-5}, $bla_{OXA-181}$	$bla_{CTX-M-15}$, bla_{CMY-2}, *aac(3)-IIa, aac(6′)-Ib-cr*	PCR	2016	Egypt	Gamal et al. (2016a)
C. freundii	bla_{KPC-2}, bla_{NDM-1}	*aac(6′)-Ib-cr,* bla_{OXA-1}, *catB3, arr-3, sul1, ampR, qnr,* $bla_{CTX-M-14}$, *fosA3,* bla_{SHV-12}	PCR	2015	China	Feng et al. (2015a)
E. cloacae	bla_{IMI-1}	bla_{AmpC}, *ampR, ampD, fosA, cat, emrB, macB, mexE, mexX, acrAB, tolC, robA, msbA, ompL, oprD, ompC, phoP, phoQ*	WGS	2015	United States	Norgan et al. (2016)

of 16 μg/ml, which was associated with higher mortality compared to infection by colistin susceptible, carbapenem-resistant *K. pneumoniae* (Capone et al., 2013). The first characterization of a bla_{IMI-1} producing, colistin resistant *E. cloacae* from the United States in February 2015 showed absence of *mcr-1* and canonical chromosomal modifications, suggesting that Enterobacteriaceae contain other colistin resistance mechanisms (Norgan et al., 2016). A retroactive study on colistin-resistant Enterobacteriaceae isolates obtained from January 2013 to November 2015 at a hospital in China found two *K. pneumoniae* harboring *mcr-1* and bla_{NDM-5} (Du et al., 2016a,b). Four bla_{KPC-2} producing *K. pneumoniae* ST101 from a cohort of nosocomial CRE obtained in Italy from November 2013 to August 2014 had colistin resistance (MIC 16–125 μg/ml) through an unidentified mechanism (Del Franco et al., 2015).

A *K. pneumoniae* ST147 isolated from patient urine in the United Arab Emirates in April 2014 was phenotypically pan drug resistant by the Vitek 2 semi-automated system (Zowawi et al., 2015). Resistance to carbapenems is derived from the OXA-48-like family member, $bla_{Oxa-181}$, with contributions from an inactivating mutation in OmpK36 (Zowawi et al., 2015). The isolate was resistant to many antibiotics by acquired genes, but colistin resistance was conferred through a chromosomal copy of the $bla_{OXA-181}$ transposon disrupting the *mgrB* allele. Tigecycline resistance was attributed to an inactivating mutation in *ramR* allowing for increased expression of acrAB (Zowawi et al., 2015) (Table 3).

10. Treatment options

10.1. Antibiotic combinations

Therapeutic potency of antibiotics can be increased (synergy), decreased (antagonism), or unaffected (additivity) when combined with other each other as determined by their fractional inhibitory concentration index (Doern, 2014). Most widely used combinations were formulated from clinical observations of effectiveness but not heavily scrutinized for mechanistic basis of synergy (Baym et al., 2016). Understanding how commonly used CRE infection antibiotic treatments affect each other and identifying new combinations is necessary to optimize CRE treatment.

As reported in 2015, a regimen of intravenous colistin, meropenem, and ertapenem successfully treated a bacteremic, multidrug resistant, KPC expressing *K. pneumoniae* infection in an elderly patient from Italy. In vitro analysis indicated synergy of colistin/ertapenem/meropenem when each antibiotic is 0.5 × MIC, with MICs of 32, 128, and 256 μg/ml respectively (Oliva et al., 2015). A retrospective study of patients who received ertapenem-containing double-carbapenem therapy from October 2013 to November 2014 at a hospital in the United States also supported the efficacy of dual carbapenem treatment regimens, finding that ertapenem treatment followed by doripenem or meropenem had promising microbiological success (79%, 11/14) (Cprek and Gallagher, 2016).

Resurgence of polymyxins as a CRE treatment motivated further study of other antibiotics with historically limited use, such as chloramphenicol (Abdul Rahim et al., 2015). Colistin and chloramphenicol were synergistic in 89% (25/28) of cases against three NDM-producing MDR *K. pneumoniae* clinical isolates and the *K. pneumoniae* NDM reference strain BAA-ATCC-2146 in vitro. All chloramphenicol resistant isolates were determined by PCR to use efflux pumps, so further research is needed to see if the combination is synergistic against bacteria with carbapenemases and chloramphenicol acetyltransferases (Abdul Rahim et al., 2015). Polymyxin B and tigecycline together and in triple combination with meropenem significantly increased rat survival during systemic infection with bla_{KPC-2} expressing *K. pneumoniae*, but the double combination had superior in vitro activity. This could be explained by antagonistic effects between polymyxin B and meropenem (Toledo et al., 2015). While empiric antibiotic therapy has led to development of clinically useful combinations, most notably trimethoprim-sulfamethoxazole and β-lactam/β-lactamase inhibitor combinations, immediate benefits from synergy may be countered by quicker evolution of resistance to these pairings (Yeh et al., 2009). Applying systems biology to understand how antibiotic combinations interact with isolate resistomes is necessary to mechanistically understand the increased effectiveness and design collaterally sensitive formulations (Gonzales et al., 2015; Pal et al., 2015; Roemer and Boone, 2013).

10.2. Avibactam

β-Lactamase inhibitors have extended the spectrum and efficacy of several β-lactam antibiotics, and a few β-lactam/β-lactamase inhibitor combinations have gained widespread clinical use (Drawz and Bonomo, 2010). Unfortunately, our current β-lactamase inhibitors are ineffective against Class B β-lactamases; this is especially concerning given the global dissemination of NDM positive Enterobacteriaceae and regional prevalence of VIM and IMP enzymes (Watkins et al., 2013).

Avibactam is a recent non-β-lactam, β-lactamase inhibitor with broad efficacy against serine β-lactamases, particularly KPC (Krishnan et al., 2015). Structural analysis showed that avibac-

tam covalently binds to the S70 residue in the active site of two Class A β-lactamases, KPC-2 and SHV-1 (Krishnan et al., 2015). Combining avibactam with ceftazidime, a third generation cephalosporin, shows promise as treatment for non-MBL expressing CRE (Castanheira et al., 2015; Zhanel et al., 2013). KPC-2 engineered to be avibactam resistant had increased ceftazidime susceptibility, suggesting collateral sensitivity as an explanation for the combination's clinical efficacy (Papp-Wallace et al., 2015). However, in a United States hospital in 2015, *K. pneumoniae* isolated from a patient not previously exposed to ceftazidime-avibactam treatment showed resistance to the combination (MIC 32/4 μg/ml). The only identified carbapenemase was a bla_{KPC-3} with 100% identity to previously sequenced variants. Additionally, the ceftazidime-avibactam resistance mechanism does not appear efflux based because treatment with PABN did not decrease the MIC. The isolate was multidrug resistant, but was susceptible to aminoglycosides, colistin, and trimethoprim-sulfamethoxazole (Humphries et al., 2015). In vitro studies suggest decreased membrane permeability via OmpK36 mutation, and the expression of an ESBL in conjunction with KPC-2, or expression of KPC-3 instead of KPC-2 correlated with increased ceftazidime-avibactam resistance (Shields et al., 2015).

The monobactam aztreonam is resistant to inactivation by NDM, but not serine β-lactamases. Accordingly, high levels of NDM and serine β-lactamase co-occurrence reduces the clinical utility of aztreonam monotherapy (Shakil et al., 2011). An aztreonam-avibactam combination inhibited 99.9% (n = 23,516) of Enterobacteriaceae species at 4/4 μg/ml. The combination was particularly effective against Enterobacteriaceae isolates possessing a MBL in addition to serine β-lactamases (Biedenbach et al., 2015a,b). Aztreonam-avibactam activity had broader efficacy than ceftazidime-avibactam against a panel of CPE species possessing a variety of Class A, B, and D carbapenemases (Vasoo et al., 2015). An *E. cloacae* ST88 isolate from a hospital in the United States with chromosomally integrated bla_{KPC-18} and bla_{VIM-1} on a 58-kb multidrug resistant IncN plasmid was reported in 2016. The *E. cloacae* was highly resistant to ceftazidime-avibactam (MIC->256/4) but not aztreonam-avibactam as (MIC-0.5/4) (Thomson et al., 2016).

In 2015, avibactam-ceftazidime combined with ertapenem successfully treated a patient infected with bla_{NDM-1} expressing pan drug resistant *K. pneumoniae* at a hospital in the United States. Avibactam has not demonstrated activity against class B β-lactamases, but it showed *in vitro* synergy with ceftazidime and carbapenems (Camargo et al., 2015). These current investigations demonstrate the utility of avibactam to extend the effectiveness of aztreonam and ceftazidime against CRE, judicious use will hopefully preserve this efficacy.

10.3. Emerging options

In addition to exploring combinations of antibiotic and resistance inhibitors, urgent work is needed to develop novel antimicrobial therapeutics to treat CRE infections and eliminate colonization. Medicinal chemistry to develop new antibiotic classes and modify current compounds to evade resistance mechanisms is key to revitalizing our arsenal against CRE (Pucci and Bush, 2013). Immune based therapies augmenting endogenous innate and adaptive effector mechanisms are being investigated as alternatives to traditional broad spectrum antibiotics (DiGiandomenico and Sellman, 2015; Li et al., 2014). Restoration of diverse gut microbiota by fecal microbiota transplant (FMT) is being used to restore colonization resistance against MDR enteric pathogens following antibiotic treatment (Allen et al., 2014). Emerging synthetic tools are being used to identify genetic cytotoxicity loci that can augment or replace antibiotic treatment (Vercoe et al., 2013).

A novel cephalosporin with a 3-position catechol moiety that acts as a siderophore to sequester ferric iron displayed low MIC values against a diverse group of CRE species and carbapenemase genes (Kohira et al., 2015). The next generation aminoglycoside, plazomicin, had an MIC90 value of 1 μg/ml against 164 Enterobacteriaceae isolates expressing Class A (bla_{KPC-2}, n = 34), Class B (bla_{VIM-1}, n = 125; bla_{IMP-22}, n = 1), or Class D (bla_{OXA-48}, n = 4) carbapenemases compared to MIC_{90} of 256, 64, and 16 μg/ml for gentamicin, tobramycin, and amikacin respectively (Rodriguez-Avial et al., 2015).

Monoclonal antibodies targeting poly-(β-1,6)-*N*-acetyl glucosamine, a polysaccharide implicated as an *E. cloacae* and *K. pneumoniae* virulence factor, showed significant in vivo protection against NDM-1 producing Enterobacteriaceae in a mouse peritonitis model. This target is a promising new vaccine candidate against invasive infection (Skurnik et al., 2016). Cationic antimicrobial peptides (AMPs) are an ancient feature of multicellular immune systems that hold potential for novel bacterial infection treatments. Two piscidin family AMPs isolated from tilapia (*Oreochromis niloticus*) in Taiwan in 2012 exhibited in vivo bacteriostatic effects yielding superior survival outcomes compared to tigecycline and imipenem in a mouse sepsis model infected with bla_{NDM-1} producing *K. pneumoniae* (Pan et al., 2015).

FMTs are a promising alternative to antibiotics for treatment of inflammatory bowel disorders and active *Clostridium difficile* infections (Surawicz et al., 2013; Wang et al., 2014). Commensal gut flora is believed to outcompete enteric pathogens and then establish further colonization resistance (Wang et al., 2014). As reported in 2015 from the United States, antibiotic administration to mice perturbs the intestinal microbiota enough to lose colonization resistance against vancomycin resistant *E. faecium* and carbapenem resistant *K. pneumoniae* (Caballero et al., 2015). Pre-colonization with one pathogen does not prevent the colonization by the other, but FMT administration reduced levels of both species (Caballero et al., 2015). This suggests the use of fecal microbiota transplants as a putative clearance method for non-infected, CRE colonized patients (Caballero et al., 2015).

Transduction of carbapenem resistant bla_{NDM-1} *E. coli* with CRISPR/Cas9 based RNA guided nucleases for bla_{NDM-1} resulted in a three-$\log_{10}$ reduction of bacterial CFU (Citorik et al., 2014). The proposed mechanism relies on an increase in dsDNA breaks leading to activation of the SOS response and antibiotic independent cell death (Citorik et al., 2014). A combinatorial TR overexpression screen in bla_{NDM-1} *E. coli* identified many gene pairs that induced lethality in the presence or absence of ceftriaxone (Cheng et al., 2014). These results support the notion that antibiotic cytotoxicity is a result of target specific inhibition coupled to increased redox activity via a global stress response (Dwyer et al., 2014). Further work is needed to characterize additional vulnerabilities in CRE.

11. Conclusion

Although individual resistance gene presence varies by geography, CRE represents a worsening global threat that ignores national borders. Within the United States, CRE are suspected to cause over 9000 cases of healthcare-associated Enterobacteriaceae infections (Yaffee et al., 2016). Predictions indicate that infections caused by MDR bacteria will increase substantially, with MDR *E. coli* expected to cause 3 million deaths each year by 2050 (O'Neill, 2016). In-depth characterization of clinical CRE isolates is necessary to identify carbapenemase burden and distribution in endemic and non-endemic areas (Lutgring and Limbago, 2016). Additionally, surveillance of CRE in patients, the environment, and animals should be continued to identify reservoirs for carbapenemase genes (Guerra et al., 2014; Viau et al., 2016). The diversity of plasmids containing car-

bapenemase genes and propensity of these plasmids to contain multiple antibiotic resistance genes and mobile gene elements foreshadows increasing incidence of extensively drug resistant Enterobacteriaceae (Tangden and Giske, 2015). Though avibactam with ceftazidime or aztreonam is a promising CRE treatment, developing novel antibiotic combinations and revamping the antibiotic development pipeline is required to suppress the worsening CRE threat.

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