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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.

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].

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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 $\mu\text{g/ml}$ against ertapenem and ≥ 4 $\mu\text{g/ml}$ 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 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.

Class A β -lactamases

The first class A carbapenemase was reported in 1990 in a *Serratia marcescens* isolate from the United Kingdom [Yang 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-metallo carbapenemase-A (*bla_{IMI/NMC}*), *Serratia fonticola* carbapenemase one (*bla_{SFC-1}*), and *bla_{SHV-38}* [Henriques 2004, Poirel 2003, Poirel 2001, Rasmussen 1996, Yigit 2001]. Many *bla_{GES}* variants are only ESBLs but frequent point mutations confer increased hydrolytic properties against carbapenems for specific variants [Dang 2016]. 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 2011, Poirel 2007].

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 2015, Yigit 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 2004, Miriagou 2003, Yigit 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 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 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 2015]. Analysis of ST258 isolates identified two clades due to divergence in capsular polysaccharide synthesis (*cps*) genes [Deleo 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 2015]. However, a two year-long study of admitted patients in five Colombian hospitals found a majority (62%, 120/193) of carbapenem-resistant *K. pneumoniae* isolates were non-258 group members, but overall, KPC was the predominant carbapenemase [Ocampo 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 2015]. Since ST258 is a hybrid strain of ~80% ST11, there is potential for rapid proliferation of the clone throughout the region [Chen 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 2015].

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 2015]. *bla*_{KPC-2} was also discovered in the canonical hypervirulent *K. pneumoniae* ST23 [Cejas 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 2014, Struve 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 2016]. Successful transfer of *bla*_{KPC} containing plasmids throughout established nosocomial Enterobacteriaceae strains led to outbreaks in the United States in 2002 to 2003, and in Nepal in 2012 [Bratu 2005, Chung The 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 2015].

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

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 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 2015]. In 2015 another novel Class A carbapenemase was identified in France from a carbapenem-resistant *E. 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 2015]. 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 2015].

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 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 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 2015].

NDM

NDM is endemic to parts of Asia and is responsible for sporadic outbreaks around the globe [Zmarlicka 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 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 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 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} + *bla*_{NDM}, 2/135 with *bla*_{OXA-181} + *bla*_{NDM}) [Biedenbach 2015]. 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 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 2016]. 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 2016]. 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 2015]. Whole plasmid sequencing revealed high levels of inpatient diversity for *bla*_{NDM-1} plasmid types and host species for Enterobacteriaceae and *Acinetobacter baumannii* isolates obtained in Pakistan during 2010 [Wailan 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 2015]. Carbapenemase production in *Salmonella enterica* is rare but documented for KPC and NDM [Miriagou 2003, Savard 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 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 2015]. These examples demonstrate need for carbapenemase gene surveillance in *S. enterica* serovars, especially for MBL endemic regions.

IMP

IMP, the first identified acquired MBL, was found in a *S. marcescens* isolate from Japan in 1991 [Ito 1995]. They are most common in China, Japan, and Australia [Nordmann 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 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 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 2015].

VIM

VIM is largely found in Italy and Greece [Pitout 2015]. VIM-1 has the closest amino acid sequence identity (32.4%) to NDM-1 [Pitout 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 2015]. 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* DH5 α [Papagiannitsis 2015]. 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 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 2016].

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 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 2016]. *bla*_{OXA-48} was identified in a *K. pneumoniae* isolate from Turkey in 2001 and remains the most common CHDL detected [Poirel 2004]. 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 2004]. Analysis of the flanking sequences between *bla*_{OXA-48} and

*bla*_{OXA-54} suggest that *bla*_{OXA-48} originated in *Shewanella* spp [Poirel 2004]. *bla*_{OXA-48}-like family members cleave carbapenems weakly, which can lead to phenotypic susceptibility against carbapenems and therefore complicate treatment options [Bakthavatchalam 2016]. Excepting OXA-163, OXA-48-like family members have little to no activity against Ceftazidime and Cefotaxime but phenotypic resistance to cephalosporins can occur in isolates co-expressing CHDLs and cephalosporin cleaving β -lactamases [Oueslati 2015].

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 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*_{TEM-1} expressing isolates [Ortega 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 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 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 2015, Oteo 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*_{OXA-48}-like variants is recommended, as expression of *bla*_{OXA-48} in *E. coli* does not always yield carbapenem resistance *in vitro*, but it can prevent clearance of infections [Haverkate 2015]. Emerging cases of *bla*_{OXA-48} in Taiwan from January 2012 to May 2014 suggest expanding ability to confer carbapenem resistance in the Enterobacteriaceae [Ma 2015]. *bla*_{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 2016]. A plasmid borne *bla*_{OXA-48} contained on Tn1999.2 was reported in a *R. ornithinolytica* clinical isolate from Lebanon in 2016 [Al-Bayssari 2016].

Within *bla*_{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*_{OXA-163} was expressed in *E. coli* TOP10, this correlated with MICs below the clinical breakpoint for Enterobacteriaceae carbapenem susceptibility [Oueslati 2015]. However, MIC values for *E. coli* lacking OmpF and OmpC were above the susceptibility cut off for meropenem, doripenem, and ertapenem [Oueslati 2015]. OXA-405 is a *bla*_{OXA-48} type carbapenemase without carbapenemase activity discovered in a *S. marcescens* isolate from France in January 2011 [Dortet 2015]. Similar to OXA-163, it conferred increased resistance to extended-spectrum cephalosporins and aztreonam compared to OXA-48. Rapid global spread of *bla*_{OXA-48}-like expressing Enterobacteriaceae necessitates molecular detection for informed patient treatment options and documentation of epidemiological occurrences to prevent nosocomial outbreaks [Poirel 2012].

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 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 2014]. Single nucleotide polymorphism (SNP) analysis between carbapenem-resistant, non-carbapenemase producing *Enterobacter 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 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 2015].

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 2013]. However, OmpK35/36 loss combined with expression of *bla_{CTX-M-15}* ESBL or the plasmid-mediated β -lactamase *bla_{DHA-1}* and its regulator *ampR* led to clinical resistance against ertapenem, meropenem, doripenem, and imipenem [Tsai 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 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 2016]. Meropenem but not ertapenem passaging caused mutations in stringent response regulator enzymes, *spoT*, *thrS*, and *tufA* [Adler 2016]. Increased stringent response activity is believed to contribute to carbapenem resistance but at a substantial fitness cost [Adler 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* [Alekhshun 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 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 2013]. ^{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 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.

Detection

Initial CRE detection is often by analysis of susceptibility testing results from automated systems, broth microdilution assays, and Kirby-Bauer disk diffusion [Nordmann 2012]. Further characterization is done to differentiate carbapenemase producers from non-producers [Nordmann 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 2016, Poirel 2012]. PCR-based and phenotypic assays are the two detection methods for identifying CRE and CPE [Nordmann 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 2016].

The diversity of OXA-48-like carbapenemases makes precise molecular determination difficult [Hemarajata 2015]. However, a PCR-based assay using high-resolution melt time analysis can differentiate seven *bla*_{OXA-48-like} family members as well as *bla*_{KPC}, *bla*_{NDM-1}, *bla*_{IMP}, *bla*_{VIM}, and *bla*_{SME} [Hemarajata 2015]. A multiplex PCR assay using peptide nucleic acid probes reported high sensitivity and specificity (both above 99.0%) in identifying *bla*_{KPC}, *bla*_{OXA-48}, *bla*_{GES}, *bla*_{IMP}, *bla*_{VIM}, and *bla*_{NDM} from a mixture of Enterobacteriaceae isolates [Jeong 2015]. One assay combined nested PCR, rtPCR, and microfluidics to obtain class level identification of carbapenemases (*bla*_{KPC}, *bla*_{VIM}, *bla*_{OXA-23}, *bla*_{OXA-48}, *bla*_{OXA-51}) and ESBLs for rapid detection of diverse multidrug resistant organisms including CRE [Walker 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 minutes) [Tato 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 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 29mm, 16mm, and 12mm for meropenem, piperacillin/tazobactam, and temocillin respectively [Huang 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 2012]. However, the MHT has poor sensitivity for class B carbapenemases (sensitivity <50 %) which is marginally improved by addition of ZnSO₄ (sensitivity 87%) [Girlich 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 2016]. The proposed mechanism relies on the anionic detergent disturbing the hydrophobic interactions between the lipoprotein carbapenemases and the outer membrane [Gonzalez 2016, Pasteran 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 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 2015]. The low cost per test (< 0.10 USD) and rapid protocol (~20 minutes) holds promise for widespread adoption by clinical microbiology labs [Lasserre 2015].

The easily interpretable Rapidec Carba NP Test showed high sensitivity and specificity (both 96%) at detecting CPE (in addition to *A. baumannii* and *P. aeruginosa*) with an under 30-minute 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 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 2016]. An electrochemical assay using imipenem hydrolysis to drive redox changes was capable of detecting CPE in less than 35 minutes with high sensitivity (95%) and perfect specificity (100%) [Bogaerts 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 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 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 2015].

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 *Pseudomonas aeruginosa* [Vilacoba 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 2015].

IncL/M

IncL/M plasmids are self-transmissible replicons common amongst Enterobacteriaceae [Carattoli 2015]. Genomic characterization of IncL and IncM plasmid identified high nucleotide conservation (~94%) but two distinct branches when clustered for sequence similarity [Carattoli 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 2015]. These plasmid types were originally endemic to the Mediterranean region but have become globally disseminated [Adamczuk 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 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 2012]. 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 2015].

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 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 2015]. 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 2015]. 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*, *Enterobacter hormaechei*, and *S. marcescens*, indicating frequent horizontal gene transfer events within Enterobacteriaceae [Chen 2015]. 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 to 138.9 kb) as the other four (33.3 to 54.7 kb), indicating

genetic exchanges during horizontal gene transmission between Enterobacteriaceae [Yang 2015].

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 2016]. *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 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 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 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 [Fielt 2014]. An IncFII 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 adedecarboxylata* from China in August 2012 [Sun 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 2016]. Both predominantly possess IncFIIB and IncFIBK, contrasting with non-CG258 *K. pneumoniae* and other CPE species which mostly possess IncN plasmids [Baraniak 2015].

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 2016]. As reported in 2016, IncA/C2 and IncFII type 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 2016]. 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 2009–2011 [Papagiannitsis 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 2016]. *bla*_{OXA-48} has additionally been identified on an IncA/C plasmid in Taiwan (2015) and Tunisia (2011) [Ktari 2011].

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 2015].

*bla*_{NDM-1} was discovered on a BJ01-like plasmid in an *E. aerogenes* isolate from China in June 2012 [Chen 2015]. 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 2015].

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 2016].

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 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 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 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 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 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 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 2014].

A study published in 2016 identified *bla*_{IMI-3} on a IncFIY plasmid obtained from sediment at the Haihe River in China showed high genetic similarity with IncF plasmids from pathogenic Enterobacteriaceae [Dang 2016]. As reported in 2016, an IncP-1 β 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 2016]. 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 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 2016]. Routine environmental sampling could prove advantageous in anticipating spread of novel antibiotic resistance genes into clinical pathogens.

Contribution of Carbapenemases to MDR/XDR Enterobacteriaceae

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 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 2016]. 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 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 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 2015]. The patients did not overlap temporally or spatially, which suggests extended surface survival of *K. pneumoniae* [Cho 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 pH105 and *bla*_{OXA-181} on a 48.5 kb plasmid that did not transform a recipient strain [Gamal 2016]. 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 (*sulI*), cephalosporins (*bla*_{OXA-1}), quaternary ammonium compounds (*qacE1*), chromate (*chrA*), and fosfomycin (*fosA3*) [Feng 2015].

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 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 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 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 2015].

Aminoglycoside Resistance

Gentamicin, amikacin, and tobramycin are aminoglycosides occasionally used to treat CRE [Morrill 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 2008, Yu 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 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 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 2013]. 20 of the 34 *rmtF* expressing Enterobacteriaceae also contained NDM-1 [Hidalgo 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 2016].

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 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]. 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]. A third (32/97) of carbapenem-resistant *K. pneumoniae* found in Italy from December 2010 to May 2011 displayed a colistin MIC of 16 µg/mL, which was associated with higher mortality compared to infection by colistin susceptible, carbapenem-resistant *K. pneumoniae* [Capone 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 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 2016]. 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 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

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 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 *mcrB* allele. Tigecycline resistance was attributed to an inactivating mutation in *ramR* allowing for increased expression of *acrAB* [Zowawi 2015].

Treatment Options

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 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 $0.5 \times \text{MIC}$, with MICs of 32, 128, and 256 $\mu\text{g/ml}$ respectively [Oliva 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 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 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 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 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 2015, Pal 2015, Roemer and Boone 2013].

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 2013].

Avibactam is a recent non- β -lactam, β -lactamase inhibitor with broad efficacy against serine β -lactamases, particularly KPC [Krishnan 2015]. Structural analysis showed that avibactam covalently binds to the S70 residue in the active site of two class A β -lactamases, KPC-2 and SHV-1 [Krishnan 2015]. Combining avibactam with ceftazidime, a third generation cephalosporin, shows promise as treatment for non-MBL expressing CRE [Castanheira 2015, Zhanel 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 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 μ g/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 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 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 2011]. An aztreonam-avibactam combination inhibited 99.9% (n=23,516) of Enterobacteriaceae species at 4/4 μ g/mL. The combination was particularly effective against Enterobacteriaceae isolates possessing a MBL in addition to serine β -lactamases [Biedenbach 2015]. 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 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 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 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.

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 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 2014]. Emerging synthetic tools are being used to identify genetic cytotoxicity loci that can augment or replace antibiotic treatment [Vercoe 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 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 MIC₉₀ of 256, 64, and 16 µg/ml for gentamicin, tobramycin, and amikacin respectively [Rodriguez-Avil 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 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 2015].

FMTs are a promising alternative to antibiotics for treatment of inflammatory bowel disorders and active *Clostridium difficile* infections [Surawicz 2013, Wang 2014]. Commensal gut flora is believed to outcompete enteric pathogens and then establish further colonization resistance [Wang 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 2015]. Pre-colonization with one pathogen does not prevent the colonization by the other, but FMT administration reduced levels of both species [Caballero 2015]. This suggests the use of fecal microbiota transplants as a putative clearance method for non-infected, CRE colonized patients [Caballero 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-log₁₀ reduction of bacterial CFU [Citorik 2014]. The proposed mechanism relies on an increase in dsDNA breaks leading to activation of the SOS response and antibiotic independent cell death [Citorik 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 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 2014]. Further work is needed to characterize additional vulnerabilities in CRE.

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 9,000 cases of healthcare-associated Enterobacteriaceae infections [Yaffee 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 2014, Viau 2016]. The diversity of plasmids containing carbapenemase 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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Table 1

Newly reported class A carbapenemases.

Gene	Enterobacteriaceae	Year Reported	Country	Plasmid	Accession number	Activity	Reference
<i>bla_{BKC-1}</i>	<i>K. pneumoniae</i>	2015	Brazil	IncQ	KP689347	Carbapenems, monobactams, penicillins, cephalosporins	120
<i>bla_{qRI-1}</i>	<i>E. cloacae</i>	2015	France	Untypeable	KT192551	Carbapenems, monobactams, aztreonam, penicillins	61

Table 2

Environmental CRE surveillance.

Source	Enterobacteriaceae	Carbapenem Resistance	Year Reported	Country	Reference
Chicken	<i>E. coli</i>	<i>bla_{OXA-48}</i>	2015	Lebanon	8
Silver Gull	<i>E. coli</i> , <i>Escherichia fergusonii</i> , <i>K. pneumoniae</i> , <i>Kluyvera georgiana</i> , <i>E. aerogenes</i> , <i>E. cloace</i> , <i>C. freundii</i> , <i>Citrobacter braakii</i> , <i>P. mirabilis</i> , <i>Proteus penneri</i>	<i>bla_{IMP-4}</i> , <i>bla_{IMP-26}</i> , <i>bla_{IMP-38}</i>	2016	Australia	57
Companion dog	<i>K. pneumoniae</i>	<i>bla_{NDM-1}</i>	2016	Spain	81
Dairy Cow	<i>E. coli</i> , <i>Aeromonas veronii</i> , <i>Aeromonas allosaccharophila</i>	ESBL+Porin mutation	2016	United States	197
Ave River	<i>E. coli</i>	<i>bla_{NDM-1}</i> , <i>bla_{NDM-34}</i> , <i>bla_{NDM-8}</i>	2016	Portugal	99
Carioca River	<i>E. cloace/asburiae</i> , <i>K. pneumoniae</i> , <i>Klebsiella spp.</i> , <i>E. kobei</i>	<i>bla_{KPC}</i>	2016	Brazil	51

Table 3

Co-occurrence of antibiotic resistance genes in CPE isolates.

Isolate	Carbapenemase	Identified Antibiotic resistance genes	Method	Year Reported	Country	Reference
<i>K. pneumoniae</i>	<i>bla_{OXA-181}</i>	<i>rmtF</i> , <i>aac(6')-Ib-cr</i> , <i>bla_{CTX-M-15}</i> , <i>gyrA</i> , <i>parC</i> , <i>qnrB</i> , <i>afrA12</i> , <i>drfA14</i> , <i>acrAB</i> , <i>bla_{SHV-36}</i> , <i>catB1</i> , <i>fosA</i> , <i>tetC</i>	WGS	2015	United Arab Emirates	213
<i>K. pneumoniae</i>	<i>bla_{NDM-5}</i> , <i>bla_{OXA-181}</i>	<i>bla_{TEM-1}</i> , <i>bla_{SHV-11}</i> , <i>bla_{CTX-M-15}</i> , <i>rmtB</i>	PCR	2015	South Korea	44
<i>E. coli</i>	<i>bla_{NDM-5}</i> , <i>bla_{OXA-181}</i>	<i>bla_{CTX-M-15}</i> , <i>bla_{CMY-2}</i> , <i>aac(3)-IIa</i> , <i>aac(6')-Ib-cr</i>	PCR	2016	Egypt	76
<i>C. freundii</i>	<i>bla_{KPC-2}</i> , <i>bla_{NDM-1}</i>	<i>aac(6')-Ib-cr</i> , <i>bla_{OXA-1}</i> , <i>catB3</i> , <i>arr-3</i> , <i>sul1</i> , <i>ampR</i> , <i>qnr</i> , <i>bla_{CTX-M-14}</i> , <i>fosA3</i> , <i>bla_{SHV-12}</i>	PCR	2015	China	69
<i>E. cloacae</i>	<i>bla_{IMP-1}</i>	<i>bla_{AmpC}</i> , <i>ampR</i> , <i>ampD</i> , <i>fosA</i> , <i>cat</i> , <i>emrB</i> , <i>macB</i> , <i>mexE</i> , <i>mexX</i> , <i>acrAB</i> , <i>tolC</i> , <i>roxA</i> , <i>msbA</i> , <i>ompL</i> , <i>oprD</i> , <i>ompC</i> , <i>phoP</i> , <i>phoQ</i>	WGS	2015	United States	123