Carbapenems are potent and broad-spectrum β-lactam antibiotics traditionally reserved for the treatment of the most serious infections (El-Gamal and Oh, 2010). The emergence and dissemination of carbapenem-resistant Gram-negative pathogens including Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae is a significant contributor to patient morbidity and mortality (Patel et al., 2008; Schwaber et al., 2008; Lautenbach et al., 2009, 2010; Marchaim et al., 2011). Despite heavy reliance on these agents, carbapenem resistance has become widespread and with the paucity of reliable antimicrobials available or in development, international focus has shifted to early detection and infection control. However, as reports of Klebsiella pneumoniae carbapenemases, New Delhi metallo-β-lactamase-1, and more recently OXA-48 (oxacillinase-48) become more common and with the conveniences of travel, the assumption that infections with highly resistant Gram-negative pathogens are limited to the infirmed and the heavily antibiotic and healthcare exposed are quickly being dispelled. Herein, we provide a status report describing the increasing challenges clinicians are facing and forecast the “stormy waters” ahead.

Carbapenem resistance among Gram-negative bacteria results from one or more of the following mechanisms: (i) overproduction or derepression of Ambler class C β-lactamases (AmpC β-lactamases) or ESBLs (e.g., sulhydryl variable (SHV), temsonia (TEM), cefotaxime (CTX-M) type β-lactamases) with loss or alteration in outer membrane porins; (ii) augmented drug efflux; (iii) alterations in penicillin binding proteins (PBPs); (iv) carbapenemase production (Patel and Bonomo, 2011). Carbapenemases belong to three molecular classes of β-lactamases, Ambler class A, B, and D (Ambler, 1980; Bush and Jacoby, 2010). Our aim is to provide a status report of the molecular diversity and epidemiology of carbapenemases as well as current and future therapeutics. The increasing public safety concerns associated with organisms harboring these enzymes has created significant turmoil. Regrettably, the situation is critical and our patients are in peril.

**AMBLER CLASS A CARBAPENEMASES**

Few Ambler class A β-lactamases demonstrate carbapenem-hydrolyzing activity and, up until a decade ago, these were rarely recovered. Class A carbapenemases include: K. pneumoniae carbapenemase (KPC), Guiana extended-spectrum (GES), non-metallo-carbapenemase-A (Nmc-A)/(imipenem-resistant (IMI), Serratia marcescens enzyme (SME), serratia fonticola carbapenemase (SFC), and BIC-β-lactamases (Table 1; Wüthrich-Rasmussen and Hasib, 2007). With the notable exception of KPCs, the clinical isolation of these types of carbapenemases is relatively limited.
**Table 1 | Class A carbapenemases**.

| Enzyme | Year isolated or described | Organism(s) | Origin and geographic distribution | Location | Reference |
|--------|----------------------------|-------------|------------------------------------|----------|-----------|
| Nmc-A  | 1990                       | Enterobacter cloacae | France, Argentina, USA | Chromosomal | Nordmann et al. (1993) |
| IMI-1  | 1984                       | Enterobacter cloacae | USA | Chromosomal | Rasmussen et al. (1986) |
| IMI-2  | 1999                       | Enterobacter asburiae, Enterobacter cloacae | USA, China | Plasmid | Aubron et al. (2005), Yu et al. (2008) |
| SME-1  | 1982                       | S. marcescens | USA, UK | Chromosomal | Naas et al. (1994) |
| SME-2  | 1992                       | S. marcescens | USA, Canada, Switzerland | Chromosomal | Deshpande et al. (2006a), Poirel et al. (2007), Carrer et al. (2008) |
| SME-3  | 2003                       | S. marcescens | USA | Chromosomal | Quevran et al. (2006) |
| SFC-1  | 2003                       | S. fonticola | Portugal | Chromosomal | Henriques et al. (2004) |
| GES-2  | 2000                       | P. aeruginosa | South Africa | Plasmid | Vourli et al. (2004) |
| GES-4  | 2002                       | K. pneumoniae | Japan | Plasmid | Wachino et al. (2004) |
| GES-5  | 2001                       | K. pneumoniae, E. coli, P. aeruginosa | Greece, Korea, worldwide | Plasmid | Jeong et al. (2005), Vial et al. (2012) |
| GES-6  | 2003                       | K. pneumoniae | Greece | Plasmid | Vial et al. (2012) |
| GES-11 | 2008                       | Acinetobacter baumannii | France | Plasmid | Mouflin et al. (2009) |
| GES-14 | 2010                       | A. baumannii | France | Plasmid | Boogaerts et al. (2010) |
| KPC-1  | 1996                       | K. pneumoniae | USA | Plasmid | Yigit et al. (2001) |
| KPC-2  | 1998                       | Enterobacteriaceae, P. aeruginosa, Acinetobacter spp. | USA and worldwide | Plasmid | Yigit et al. (2001) |
| KPC-3  | 2000                       | Enterobacteriaceae, Acinetobacter spp. | USA and worldwide | Plasmid | Woodford et al. (2004) |
| KPC-4  | 2003                       | Enterobacter cancerogenus, K. pneumoniae, Acinetobacter spp. | Scotland, Puerto Rico | Plasmid | Palepou et al. (2005), Robledo et al. (2007) |
| KPC-5  | 2006                       | P. aeruginosa | Puerto Rico | Plasmid | Wolter et al. (2009) |
| KPC-6  | 2003                       | K. pneumoniae | Puerto Rico | Plasmid | Bartual et al. (2005), Robledo et al. (2008) |
| KPC-7  | 2007                       | K. pneumoniae | USA | Plasmid | Perez et al. (2010a) |
| KPC-8  | 2008                       | K. pneumoniae | Puerto Rico | Plasmid | Dencová et al. (2010) |
| KPC-9  | 2009                       | E. coli | Israel | Plasmid | Grossio et al. (2011) |
| KPC-10 | 2009                       | Acinetobacter spp. | Puerto Rico | Plasmid | Robledo et al. (2010) |
| KPC-11 | 2009                       | K. pneumoniae | Greece | Unknown | Da Silva et al. (2004) |
| KPC-12 | 2010                       | E. coli | China | Unknown | |
| KPC-13 | 2010                       | Enterobacteriaceae | Thailand | Unknown | |
| BIC-1  | 2009                       | P. fluorescens | France | Chromosomal | Girlich et al. (2010) |

*Adapted from Walther-Rasmussen and Høiby (2007).

1 Environmental isolates.

‡ KPC-1 was later found to be the same enzyme as KPC-2 (Higgins et al., 2012a).

§ Chromosomal expression of blaKPC-2 has been described in P. aeruginosa (Villegas et al., 2007).

Non-metallo-carbapenemase-A is a chromosomal carbapenemase originally isolated from *Enterobacter cloacae* in France (Nordmann et al., 1993). Currently, reports of this particular β-lactamase are still rare (Poturnaury et al., 2003; Castanheira et al., 2008; Osterblad et al., 2012). IMI-1 was initially recovered from the chromosome of an *Enterobacter cloacae* isolate in the southwestern USA (Rasmussen et al., 1996). A variant of IMI-1, IMI-2, has been identified on plasmids isolated from environmental strains of *Enterobacter asburiae* in USA rivers (Aubron et al., 2005). SME-1 (S. marcescens enzyme) was originally identified in an isolate of *S. marcescens* from a patient in London in 1982 (Yang et al., 1990). SME-2 and SME-3 were subsequently isolated in the USA, Canada, and Switzerland (Naas et al., 1994; Quevran et al., 2000, 2006; Deshpande et al., 2006b; Poirel et al., 2007; Carrer et al., 2008). Chromosomally encoded SME-type carbapenemases continue to be isolated at a low frequency in North America (Deshpande et al., 2008a,b, Fairfax et al., 2011; Masaue et al., 2012). Both SFC-1 and BIC-1 are chromosomal serine carbapenemases recovered from environmental isolates. The former from...
a *S. fonticola* isolate in Portugal (Henriques et al., 2004) and the latter from *Pseudomonas fluorescens* isolates recovered from the Sasse River (Córůlich et al., 2010).

The GES-type β-lactamases are acquired β-lactamasers recovered from *P. aeruginosa*, Enterobacteriaceae, and *A. baumannii* (Poirel et al., 2008a; Castanheira et al., 2004a). The genes encoding these β-lactamase have often, but not exclusively, been identified within class 1 integrons residing on transferable plasmids (Bonnin et al., 2013; Walther-Rasmussen and Høiby, 2007). GES-1 has a similar hydrolysis profile to other ESBLs, although they essentially spare monobactams. Several GES β-lactamases are described with *i.e.*, GES-2, GES-4, GES-5, GES-6, GES-11, and GES-14, demonstrating detectable carbapenemase activity in the setting of amino acid substitutions at their active sites (specifically at residue 184 and 170; Walther-Rasmussen and Høiby, 2007; Kotsakis et al., 2010). These GES-type carbapenemases have been described in Europe, South Africa, Asia, and the Middle East (Poirel et al., 2002; Jeong et al., 2005; da Fonseca et al., 2007; Moubareck et al., 2009; Nordmann et al., 2009; Gupta et al., 2011; Schwaber et al., 2011). Congruent pulsed-field gel electrophoresis (PFGE) patterns also suggest a clonal relationship between outbreak-associated strains of KPC-producing *K. pneumoniae* recovered from different areas that are endemic (Navon-Venezia et al., 2009; Wolter et al., 2009; Gregory et al., 2010) have been reported with the vast majority of isolated expressing either KPC-2 or KPC-3.

The *blaKPC* gene has been mapped to a highly conserved Tn3-based transposon, Tn4401 (Figure 1A), and five isoforms of Tn4401 are described (Niaa et al., 2008; Cuzon et al., 2010; Kitchel et al., 2010). Plasmids carrying *blaKPC* are of various sizes and many carry additional genes conferring resistance to fluoroquinolones and aminoglycosides thus limiting the antibiotics available to treat infections with KPC-producing pathogens (Endimiani et al., 2008; Rice et al., 2008). *blaKPC* has rarely been mapped to a chromosomal location (Villegas et al., 2007; Castanheira et al., 2009).

A predominant strain of *K. pneumoniae* appears responsible for outbreaks and the international spread of KPC-producing *K. pneumoniae* (Woodford et al., 2008; Kitchel et al., 2009a; Samulsen et al., 2009). Carbapenem resistance secondary to KPC production was first described in a *K. pneumoniae* recovered in North Carolina in 1996 (Yigit et al., 2001). To date 12 KPC subtypes (KPC-2 to KPC-13; Robledo et al., 2008; Kitchel et al., 2009a; Navon-Venezia et al., 2009; Wolter et al., 2009; Gregory et al., 2010) have been reported with the vast majority of analyzed isolates expressing either KPC-2 or KPC-3.

The *blaKPC* gene has been mapped to a highly conserved Tn3-based transposon, Tn4401 (Figure 1A), and five isoforms of Tn4401 are described (Niaa et al., 2008; Cuzon et al., 2010; Kitchel et al., 2010). Congruent pulsed-field gel electrophoresis (PFGE) patterns also suggest a clonal relationship between outbreak-associated strains of KPC-producing *K. pneumoniae* recovered from different areas that are endemic (Navon-Venezia et al., 2009; Woodford et al., 2011). The Centers for Disease Control and Prevention (CDC) performed PFGE and multilocus sequence typing (MLST) on isolates submitted to their reference laboratory from 1996 to 2008. A dominant PFGE pattern was observed and noted to be of a specific MLST type, ST 258 (Kitchel et al., 2009a). A second sequence type, ST 14, was common in institutions in the Midwest (Kitchel et al., 2009b). These findings implied that certain strains of *K. pneumoniae* may be more apt to obtain and retain the *blaKPC* gene. Another study, however, analyzing 16 KPC-2 producing *K. pneumoniae* isolates from different geographic regions demonstrated diverse PFGE patterns and MLST types. This included four
different MLST types in Colombia (ST 14, ST 337, ST 338, and ST 339) and two in Israel (ST 227 and ST 340). Although this study analyzed a smaller number of isolates, these findings suggest that the global propagation of KPC-2 is more complicated than the successful expansion of a fixed number of clones (Cazon et al., 2010; Qi et al., 2011). More recently, a study evaluating the MLST types associated with widespread KPC-2 production in K. pneumoniae in Greece suggested that although ST 258 predominates at least 10 additional sequence types were found to carry blakPC-2. Of note there (i.e., ST 147, ST 323, and ST 383) carried both KPC-2 as well as genes encoding VIM-type MBLs (Giaikoupi et al., 2011; Woodford et al., 2011). A retrospective study in Cleveland documented the presence of ST 36 in a long-term care facility for children (Vissà et al., 2012).

Klebsiella pneumoniae carbapenemases—production can confer variable levels of carbapenem resistance with reported minimum inhibitory concentrations (MICs) ranging from susceptible to $\geq 16 \mu g/mL$. Analysis of isolates displaying high-level carbapenem resistance demonstrated that increased phenotypic resistance may be due to increased blakPC-2 gene copy number or the loss of an outer membrane porin, OmpK35 and/or OmpK36. The highest level of imipenem resistance was seen with isolates lacking both porins and with augmented KPC enzyme production (Kitchel et al., 2010).

**AMBLER CLASS B CARBAPENEMASES:**

**METALLO-ß-LACTAMASES**

Class B ß-lactamases (Table 2) are referred to as MBLs and require a metal ion, usually zinc, for ß-lactam hydrolysis (Walsh et al., 2005). Due to the dependence on Zn$^{2+}$, catalysis is inhibited in the presence of metal-chelating agents like ethylenediaminetetraacetic acid (EDTA). MBL expression in Gram-negative bacteria confers resistance to penicillins, cephalosporins, and carbapenems. MBLs are not inhibited by the presence of commercially available ß-lactamase inhibitors and susceptibility to monobactams (e.g., aztreonam) appears to be preserved in the absence of concomitant expression of other resistance mechanisms (e.g., ESBL production). The more geographically widespread MBLs include IMP (imipenem-resistant), VIM, and New Delhi metallo-ß-lactase (NDM).

Chromosomal MBLs were the first to be identified and are the cause of carbapenem resistance observed in Bacillus cereus, Aeromonas spp., and Stenotrophomonas maltophilia (Walsh et al., 2005). However, of growing concern are the “mobile” MBLs that have been reported since the mid-1990s. Although most frequently found in carbapenem-resistant isolates of P. aeruginosa and occasionally Acinetobacter spp., there is growing isolation of these enzymes in Enterobacteriaceae.

Prior to the description of NDM-1, frequently detected MBLs include IMP-type and VIM-type with VIM-2 being the most prevalent. These MBLs are embedded within a variety of genetic structures, most commonly integrons. When these integrons are associated with transposons or plasmids they can readily be transferred between species.

In 1991, IMP-1, a plasmid-mediated MBL, was identified in an isolate of S. marcescens from Japan (Ito et al., 1995). Since then plasmid-mediated carbapenem resistance secondary to IMP-1 spread widely in Japan, Europe, Brazil, and other parts of Asia and in several species of Gram-negative bacilli including Acinetobacter spp. and Enterobacteriaceae. At the present time, 42 variants of IMP have been identified with most cases of IMP-mediated carbapenem resistance being reported from Asia and among P. aeruginosa (Bush and Jacoby, 2010).

**Table 2 | Metallo-ß-lactamases.**

| Enzyme | Year isolated or described | Organism(s) | Geographic distribution | Location | Reference |
|--------|-----------------------------|-------------|-------------------------|----------|-----------|
| IMP-1 to IMP-42 | 1988 | Enterobacteriaceae, Pseudomonas spp., Acinetobacter spp. | Worldwide | Plasmid or chromosomal | Osano et al. (1994), Rico et al. (2000) |
| VIM-1 to VIM-37 | 1997 | Enterobacteriaceae, Pseudomonas spp., Acinetobacter spp. | Worldwide | Plasmid or chromosomal | Lauretti et al. (1999), Pfaller et al. (2000a) |
| SPM-1 | 2001 | P. aeruginosa | Brazil* | Chromosomal | Telemans et al. (2002) |
| GIV-1 | 2002 | P. aeruginosa | Germany | Plasmid | Castanheira et al. (2004b) |
| SIM-1 | 2003–2004 | A. baumannii | Korea | Chromosomal | Lee et al. (2005) |
| NDM-1 to NDM-7 | 2006 | Enterobacteriaceae, Acinetobacter spp., Vibrio cholerae | Worldwide | Plasmid or chromosomal | Wong et al. (2009), Kaase et al. (2011), Nordmann et al. (2012a) |
| AIM-1 | 2007 | P. aeruginosa | Australia | Chromosomal | Kinh et al. (2007) |
| KH-1 | 1997 | C. freundii | Japan | Plasmid | Sekiguchi et al. (2008) |
| DHA-1 | 2007 | P. stutzeri | Netherlands | Plasmid | Pfaller et al. (2010a) |
| SMM-1 | 2010 | S. marcescens | Japan | Chromosomal | Wachino et al. (2011) |
| TMB-1 | 2011 | Achromobacter xylosidans | Libya | Chromosomal | El Sabti et al. (2012) |
| FIM-1 | 2007 | P. aeruginosa | Italy | Chromosomal | Polivka et al. (2012) |

*Single report of SPM-1 in Europe linked to healthcare exposure in Brazil (Giaikoupi et al., 2011).
A more commonly recovered MBL is the VIM-type enzyme. VIM-1 was first described in Italy in 1997 in P. aeruginosa (Laurent et al., 1999). VIM-2 was next discovered in southern France in P. aeruginosa cultured from a neutropenic patient in 1996 (Poirel et al., 2000b). Although originally thought to be limited to non-fermenting Gram-negative bacilli, VIM-type MBLs are being increasingly identified in Enterobacteriaceae as well (Giaidouki et al., 2005; Kassis-Chikhani et al., 2006; Morfin-Otero et al., 2009; Canton et al., 2012). To date, 37 variants of VIM have been described with VIM-2 being the most common MBL recovered worldwide.

Other more geographically restricted MBLS include SPM-1 (Sao Paulo MBL), which has been associated with hospital outbreaks in Brazil (Tolentino et al., 2002; Rossi, 2011); GIM-1 (German imipenemase) isolated in carbapenem-resistant P. aeruginosa isolates in Germany (Castanheira et al., 2004b); SIM-1 (Seoul imipenemase) isolated from A. baumannii isolates in Korea (Lee et al., 2005); KHM-1 (Kyorin Health Science MBL) isolated from a C. freundii isolate in Japan (Sekiguchi et al., 2008); AIM-1 (Australian imipenemase) isolated from P. aeruginosa in Australia (Yong et al., 2007); DIM-1 (Dutch imipenemase) isolated from a clinical P. stutzeri isolate in the Netherlands (Poirel et al., 2010c); SMB-1 (S. marcescens MBL) in S. marcescens in Japan (Wachino et al., 2011); TMB-1 (Tripoli MBL) in Acinetobacter xylosoxidans in Libya (El Salibi et al., 2012), and FIM-1 (Florence imipenemase) from a clinical isolate of P. aeruginosa in Italy (Pollini et al., 2012). With the notable exception of SPM-1, these MBLs have remained confined to their countries of origin (Salabi et al., 2010).

NDM-1 was first identified in 2008. Due to its rapid international dissemination and its ability to be expressed by numerous Gram-negative pathogens, NDM is poised to become the most commonly isolated and distributed carbapenemase worldwide. Initial reports frequently demonstrated an epidemiologic link to the Indian subcontinent where these MBLs are endemic (Kumarasamy et al., 2010). Indeed, retrospective analyses of stored isolates suggest that NDM-1 may have been circulating in the subcontinent as early as 2006 (Castanheira et al., 2011). Despite initial controversy, the Balkans may be another area of endemicity for NDM-1 (Struelens et al., 2010; Iovcic et al., 2011; Livermore et al., 2011c; Halaby et al., 2012). Sporadic recovery of NDM-1 in the Middle East suggests that this region may be an additional reservoir (Poirel et al., 2010a, 2011d; Nordmann et al., 2011; Ghazawi et al., 2012).

Like KPCs, the conveniences of international travel and medical tourism have quickly propelled this relatively novel MBL into a formidable public health threat. Gram-negative bacilli harboring blaNDM-1 have been identified worldwide with the exception of Central and South America. NDM-1 was first identified in Sweden in a patient of Indian descent previously hospitalized in India (Yong et al., 2009). The patient was colonized with a K. pneumoniae and an E. coli carrying blaNDM-1 on transferable plasmids. In an increase in the number of clinical isolates of carbapenem-resistant Enterobacteriaceae was seen in both 2008 and 2009. A UK reference laboratory reported that at least 17 of 29 patients found to be harboring NDM-1 expressing Enterobacteriaceae had a history of recent travel to the Indian subcontinent with the majority having been hospitalized in those countries (Kumarasamy et al., 2010).

European reports suggest that horizontal transfer of blaNDM-1 exists within hospitals outside endemic areas. Of overwhelming concern are the reported cases without specific contact with the healthcare system locally or in endemic areas suggesting autochthonous acquisition (Kumarasamy et al., 2010; Kus et al., 2011; Arpin et al., 2012; Bogaia et al., 2012; Nordmann et al., 2012b).

Surveillance of public water supplies in India indicates that exposure to NDM-1 may be environmental. Walsh et al. (2011) analyzed samples of public tap water and sewage water from sites around New Delhi. The results were disheartening in that blaNDM-1 was detected by PCR in 4% of drinking water samples and 30% of sewage samples. In this survey, carriage of blaNDM-1 was noted in 11 species of bacteria not previously described, including virulent ones like Shigella boydii and Vibrio cholaeae.

The rapid spread of NDM-1 highlights the fluidity and rapidity of gene transfer between bacterial species. Although blaNDM-1 was initially and repeatedly mapped to plasmids isolated from carbapenem-resistant E. coli and K. pneumoniae, reports of both plasmid and chromosomal expression of blaNDM-1 has been noted in other species of Enterobacteriaceae as well as Acinetobacter spp. and P. aeruginosa (Moughareb et al., 2009; Bagarett et al., 2010; Bonnaire et al., 2011; Nordmann et al., 2011; Patel and Bonomo, 2011). Recently, bacteremia with a NDM-1 expressing V. cholaeae has been described in a patient previously hospitalized in India colonized with a variety of Enterobacteriaceae previously known to be capable of carrying plasmids with blaNDM-1 (Darley et al., 2012).

In contrast to KPCs, the presence of a dominant clone among blaNDM-1 carrying isolates remains elusive (Poirel et al., 2011c). NDM-1 expression in E. coli has been noted among sequence types previously associated with the successful dissemination of other β-lactamases including ST 101 and ST 131 (Mushitq et al., 2011). Mushitq et al. (2011) analyzed a relatively large group of blaNDM-1 expressing E. coli from the UK, Pakistan, and India in order to potentially identify a predominant strain responsible for the rapid and successful spread of NDM-1. The most frequent sequence type identified was ST 101. Another study examining a collection of carbapenem-resistant Enterobacteriaceae from India demonstrates the diversity of strains capable of harboring blaNDM-1. Carriage of blaNDM-1 was confirmed in 10 different sequence types of K. pneumoniae and 5 sequence types of E. coli (Lascols et al., 2011). This multiplicity was confirmed in a study looking at a collection of blaNDM-1 expressing Enterobacteriaceae from around the world (Poirel et al., 2011c). Of most concern is that NDM-1 has been identified in E. coli ST 131, the strain of E. coli credited with the global propagation of CTX-M-15 ESBLs (Mushitq et al., 2011; Petrino et al., 2011; Pfeifer et al., 2011b; Woodford et al., 2011). Similar to KPCs, NDM-1 expression portends variable levels of carbapenem resistance and there is often concomitant carriage of a myriad of resistance determinants including other β-lactamases and carbapenemases as well as genes associated with resistance to fluoroquinolones and aminoglycosides (Nordmann et al., 2011).
NDM-1 shares the most homology with VIM-1 and VIM-2. It is a 28-kDa monomeric protein that demonstrates tight binding to both penicillins and cephalosporins (Zhang and Hao, 2011). Binding to carbapenems does not appear to be as strong as other MBLs, but hydrolysis rates appear to be similar. Using ampicillin as a substrate, allowed for detailed characterization of the interactions between NDM’s active site and β-lactams as well as improved evaluation of MBLs unique mechanism of β-lactam hydrolysis. More recent crystal structures of NDM-1 reveal the molecular details of how carbapenem antibiotics are recognized by dizinc-containing MBLs (Kung et al., 2012).

To date, NDM-1 remains the most common NDM variant isolated. Seven variants (NDM-1 to NDM-7) exist (Kaase et al., 2011; Nordmann et al., 2012a). It is currently held that NDM-1 is a chimeric gene that may have evolved from A. baumannii (Toleman et al., 2012). Contributing to this theory is the presence of complete or variations of the insertion sequence, ISAba125, upstream to the NDM-1 gene in both Enterobacteriaceae and A. baumannii (Pfeifer et al., 2011a; Poirel et al., 2011a; Dortet et al., 2012; Toleman et al., 2012). This insertion sequence has primarily been found in A. baumannii.

A recent evaluation of the genetic construct associated with blaNDM-1 (Figure 1B) has led to the discovery of a new bleomycin resistance protein, BRFABM. Evaluation of 23 isolates of blaNDM-1 harboring Enterobacteriaceae and A. baumannii noted that the overwhelming majority of them possessed a novel bleomycin resistance gene, bmbA (Dortet et al., 2012). Co-expression of blaNDM-1, and bmbA appear to be mediated by a common promoter (P_blaNDM-1) which includes portions of ISAba125. It is postulated that BRFABM expression may contribute some sort of selective advantage allowing NDM-1 to persist in the environment.

A contemporary evaluation of recently recovered NDM-1 producing A. baumannii isolates from Europe demonstrates that blaNDM-1 and blaBMB, genes are situated on the same chromosomally located transposon, Tn125 (Bonnin et al., 2012). Dissemination of bmbA in A. baumannii seems to be due to different strains carrying Tn125 or derivatives of Tn125 rather than plasmid-mediated or clonal (Bonnin et al., 2013; Poirel et al., 2012a).

CARBAPENEM-HYDROLYZING CLASS D β-LACTAMASES

Oxacillinases comprise a heterogeneous group of class D β-lactamases which are able to hydrolyze amino- and carbapenem-β-lactamases are not inhibited by commercially available β-lactamase inhibitors but are inhibited in vitro by NaCl. Over 250 types of oxacillinases are reported with a minority demonstrating low levels of carbapenem-hydrolyzing activity. This select group of enzymes is also referred to as the carbapenem-hydrolyzing class D β-lactamases (CHDLs; Table 3). CHDLs have been identified most often in organisms demonstrating higher levels of phenotypic carbapenem resistance. These include expression of other carbapenemases, alterations in outer membrane proteins (e.g., OmpK36; Perez et al., 2007; Gulmez et al., 2008; Pfeifer et al., 2012), increased transcription mediated by IS elements functioning as promoters, increased gene copy number, and amplified drug efflux (Poirel and Nordmann, 2006; Perez et al., 2007). Many subgroups of CHDLs have been described. We will focus on those found in A. baumannii and Enterobacteriaceae: OXA-23 and OXA-27, OXA-24/40, OXA-25, and OXA-26, OXA-48 variants; OXA-51, OXA-66, OXA-69, OXA-99, and OXA-143.

CHDLs can be intrinsic or acquired. A. baumannii does not appear to be increased in the presence of specific insertion sequences promoting gene expression (Figueiredo et al., 2009; Culebras et al., 2010). Additional resistance to extended-spectrum cephalosporins can be seen in the setting of co-expression of ESBLs and/or other carbapenemases (Castanheira et al., 2011; Mathers et al., 2012; Pfeifer et al., 2012; Vougiaris et al., 2012; Potron et al., 2013).

The first reported “acquired” oxacillinase with appreciable carbapenem-hydrolyzing activity was OXA-23. OXA-23, or ARI-1, was identified from an A. baumannii isolate in Scotland in 1993 (the isolate was first recovered in 1985; Paton et al., 1993). Subsequently, OXA-23 expression has been reported worldwide (Mugnier et al., 2010) and both plasmid and chromosomal carriage of blaOXA-23 is described. The OXA-23 group includes OXA-27, found in a single A. baumannii isolate from Singapore (Afzal-Shah et al., 2011). With the exception of an isolate of Proteus mirabilis identified in France in 2002, this group of β-lactamases has been exclusively recovered from Acinetobacter species (Bonnet et al., 2002). Increased expression of OXA-23 has been associated with the presence of upstream insertion sequences (e.g., ISAba1 and ISAba2) acting as strong promoters (Corvec et al., 2007).

Another group of CHDLs include OXA-24/40, OXA-25, and OXA-26 (Bou et al., 2000b; Afzal-Shah et al., 2001). OXA-24 and OXA-40 differ by a few amino acid substitutions and OXA-25 and OXA-26 are point mutation derivatives of OXA-40 (Afzal-Shah et al., 2001). Although primarily linked with clonal outbreaks in Spain and Portugal (Bou et al., 2000a; Lopez-Otin et al., 2002; Du Silva et al., 2004; Acosta et al., 2011), OXA-24/40 β-lactamases has been isolated in other European countries and the USA (Lolans et al., 2006). OXA-40 was in fact the first CHDL documented in the USA (Lolans et al., 2006).

OXA-58 has also been detected in Acinetobacter spp. initially identified in France (Héritier et al., 2005a; Poirel et al., 2005). OXA-58 has been associated with institutional outbreaks and has been recovered from clinical isolates of A. baumannii worldwide (Goulielmos et al., 2006; Mendes et al., 2009; Cailes et al., 2012). As civilian and military personnel began returning from Afghanistan and the Middle East, practitioners noted increasing
recovery of A. baumannii from skin and soft tissue infections. Drug resistance was associated with expression of both OXA-23 and OXA-58 (Haux et al., 2006; Scott et al., 2007; Ferez et al., 2010b). Many isolates carrying the blaOXA−58 gene concurrently carry insertion sequences (e.g., ISaba1, ISaba2, or ISaba3) associated with increased carbapenem production and thus higher levels of carbapenem resistance. In one report increased gene copy number was also associated with a higher level of enzyme production and increased phenotypic carbapenem resistance (Bertini et al., 2007).

Spread of OXA-type carbapenemases among A. baumannii appears to be clonal and in depth reviews of the molecular epidemiology and successful dissemination of these clones have been published (Woodford et al., 2011; Zarrilli et al., 2013). Two MLST schemes with three loci in common exist for A. baumannii – the PubMLST scheme (Bartual et al., 2005) and the Pasteur scheme (Diancourt et al., 2010). Both schemes assign different – the PubMLST scheme (Bartual et al., 2005) and the Pasteur scheme (Diancourt et al., 2010). Both schemes assign different clonal complexes (CC). Sequence types and related to international clones I, II, and III. It should be noted, however, that the molecular taxonomy of A. baumannii continues to evolve (Higgins et al., 2012a). OXA-23 producing A. baumannii predominantly belong to international clones I and II with a notable proportion being part of CC92 (PubMed; Mugnier et al., 2010; Adams-Hadjuch et al., 2011). Similarly, A. baumannii isolates associated with epidemic spread of OXA-24/40

| Enzyme group | Year isolated or described | Organism(s) | Geographic distribution | Location | Reference |
|--------------|---------------------------|-------------|------------------------|----------|-----------|
| OXA-23/27    | 1985–                      | Acinetobacter baumannii, Proteus mirabilis* | Europe, USA, Middle East, Asia, Australia | Plasmid, chromosomal | Atta-Shah et al. (2001), Gogou et al. (2011) |
| OXA-24/40    | 1997                      | A. baumannii | Europe and USA         | Plasmid, chromosomal | Bou et al. (2000b), Lopez-Otin et al. (2002) |
| OXA-25       | –                         | A. baumannii | Spain                  | Chromosomal | Atta-Shah et al. (2001) |
| OXA-26       | 1996                      | A. baumannii | Belgium                | Chromosomal | Atta-Shah et al. (2001) |
| OXA-48       | 2001                      | K. pneumoniae | Turkey, Middle East, Northern Africa, Europe, India, USA | Plasmid | Poirol et al. (2004b) |
| OXA-51/66/69 | 1993                      | A. baumannii | Worldwide              | Chromosomal | Brown et al. (2005), Evans et al. (2007) |
| OXA-58       | 2003                      | A. baumannii | Europe, USA, Middle East, South America | Plasmid | Poirol et al. (2005) |
| OXA-143      | 2004                      | A. baumannii | Brazil                 | Plasmid | Higgins et al. (2009) |
| OXA-162      | 2004                      | Enterobacteriaceae | Germany | Plasmid | Pfeifer et al. (2012) |
| OXA-163      | 2008                      | K. pneumoniae, E. coli | Argentina and Egypt | Plasmid | Poirol et al. (2011b), Abdelaziz et al. (2012) |
| OXA-181      | 2006                      | K. pneumoniae, E. coli | India | Plasmid | Castanheira et al. (2011) |
| OXA-232      | 2012                      | K. pneumoniae | Tunisia | Plasmid | Poiron et al. (2013) |
| OXA-204      | 2012                      | K. pneumoniae | France | Plasmid | Poirol et al. (2012b) |

*Single isolate described in France.
single 62 kb self-conjugative Inc/M-type plasmid has contributed to a large proportion of the distribution of blaOXA-48 in Europe (Potron et al., 2011a). Sequencing of this plasmid (POXA-48a) notes that blakxenensis -lactamase -lactamase is unique in that it has activity against extended-spectrum cephalosporins (Cantón et al., 2012). A variant of Tn1999, blaOXA-48 had been integrated through the acquisition of a Tn1999 composite transposon (Figure 1C; Poirel et al., 2012b). blaOXA-48 appears to be associated with a specific insertion sequence IS1999 (Poirel et al., 2006c, 2012b). A variant of Tn1999, Tn1999.2, has been identified among isolates from Turkey and in Europe (Carrer et al., 2010; Potron et al., 2011a). Tn1999.2 harbors an IS50R element within the IS1999. OXA-48 appears to have the highest affinity for imipenem of the CHDLs specifically those harboring blaOXA-48 within a Tn1999.2 composite transposon (Dousquet et al., 2009). Three isoforms of the Tn1999 transposon have been described (Giani et al., 2012).

Although much of the spread of OXA-48 is attributed to a specific plasmid, outbreak evaluations demonstrate that a variety of strains have contributed to dissemination of this emerging carbapenemase in K. pneumoniae. The same K. pneumoniae sequence type, ST 395, harboring blaOXA-48 was identified in Morocco, France, and the Netherlands (Cantón et al., 2011; Potron et al., 2011a). ST 353 was associated with an outbreak of OXA-48 producing K. pneumoniae in London (Woodford et al., 2011) and ST 221 with an outbreak of OXA-48 in Ireland (Cantón et al., 2012). OXA-48 production in K. pneumoniae, like KPC-expressing K. pneumoniae, has also been associated with ST 14 (Poirel et al., 2004c) and a recent outbreak in Greece was associated with ST 11 (Voulgaris et al., 2012).

OXA-163, a single amino acid variant of OXA-48, was identified in isolates of K. pneumoniae and Enterobacter cloacae from Argentina and is unique in that it has activity against extended-spectrum cephaporphins (Poirel et al., 2011b). OXA-163 also has been identified in Egypt, which has a relatively prevalence of OXA-48, in patients without epidemiologic links to Argentina (Abdelaziz et al., 2012).

Tigecycline remains untested in prospective trials and reports of resistance are increasing (Navon-Venezia et al., 2007; Anthony et al., 2008; Wang and Dowzicky, 2010). The role of tigecycline in treating primary bloodstream infections or urinary tract infections remains undefined due less than therapeutic concentrations of drug achieved in the serum (Rodvold et al., 2006) and urine (Satin et al., 2011). We also note that meta-analyses of pooled data from trials evaluating the use of tigecycline for a variety of indications suggest there is a excess mortality associated with the use of tigecycline over comparator regimens (Cai et al., 2011; Tasina et al., 2011; Yahav et al., 2011; Verde and Cucitrino, 2012). However, in the absence of other tested regimens tigecycline may be an appropriate or perhaps the only therapeutic option.

Growing resistance to both the polymyxins and tigecycline has resulted the revisiting of older drugs including chloramphenicol, nitrofurantoin, and tobramycin (Livermore et al., 2010). Fosfomycin is also one of these earlier antibiotics being reassessed...
Avibactam in combination with aztreonam, however, does seem to demonstrate activity against non-urinary pathogens. Fosfomycin demonstrated activity against only 30.2% of 1069 multidrug-resistant (MDR) P. aeruginosa isolates and 3.5% of 85 MDR A. baumannii isolates (Falagas et al., 2009). The individual studies included in this review did not employ uniform MDR definitions or consistent susceptibility breakpoints. Moreover, access to the parenteral fosfomycin is limited and the threshold for resistance is low (Rodríguez-Rojas et al., 2010; Karamagopoulos et al., 2012). Concerns regarding the emergence of resistance have lead to an increasing interest in the utility of combination therapy (Michalopoulos et al., 2010; Bercoff et al., 2011; Souli et al., 2011).

Few agents are in the advanced stages of development with demonstrable in vitro activity against carbapenemase-producing organisms. These include β-lactamase inhibitors, aminoglycoside derivatives, polymyxin derivatives, and novel monobactams and monobactams-β-lactamase inhibitor combinations.

Avibactam, or NXL104, is a β-lactamase inhibitor which has been tested in combination with ceftazidime, ceftaroline, and aztreonam against several carbapenemase-producing Enterobacteriaceae if the infection is localized to the genitourinary tract. Unfortunately, fosfomycin does not demonstrate reliable activity against non-urinary pathogens. Fosfomycin demonstrated activity against only 30.2% of 1069 multidrug-resistant (MDR) P. aeruginosa isolates and 3.5% of 85 MDR A. baumannii isolates (Falagas et al., 2009). The individual studies included in this review did not employ uniform MDR definitions or consistent susceptibility breakpoints. Moreover, access to the parenteral fosfomycin is limited and the threshold for resistance is low (Rodríguez-Rojas et al., 2010; Karamagopoulos et al., 2012). Concerns regarding the emergence of resistance have lead to an increasing interest in the utility of combination therapy (Michalopoulos et al., 2010; Bercoff et al., 2011; Souli et al., 2011).

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A combination of fosfomycin and rifampicin or clarithromycin demonstrated synergistic activity against seven strains of carbapenemase-producing Gram-negative bacilli including one polymyxin-resistant strain (Väara et al., 2010). It remains unclear what role these agents will play in the setting the increasing burden of infections with carbapenemase-producing Enterobacteriaceae.

The activity of the siderophore monosulfactam, BAL30072, has been against non-fermenting carbapenemase-producing Gram-negative bacilli (Page et al., 2010). In one study, susceptibility to BAL30072 was noted in 73% of 200 isolates of carbapenemase-producing A. baumannii, the majority of which were of the same OXA-23 producing clone (Mustaq et al., 2010a). In that same study, smaller percentages of susceptibility were noted in a selection of carbapenem-resistant Burkholderia cepacia and P. aeruginosa isolates. Recent evaluations of BAL30072 confirm that there may be a role for this agent in the treatment of resistant A. baumannii infections (Russo et al., 2011; Higgins et al., 2012b). BAL 30376 is a combination of a siderophore monosulfactam with clavulanic acid. In two studies, this combination demonstrated reasonable in vitro activity against CHDL, including OXA-48, and MBLs but not KPCs (Livermore et al., 2010; Page et al., 2011).

In an in vitro evaluation of 68 KPC-expressing K. pneumoniae isolates, fosfomycin demonstrated in vitro activity against 87% of tigecycline and/or polymyxin non-susceptible isolates and 85% of isolates that were resistant to both (Endimiani et al., 2010b). Fosfomycin may be a potential therapeutic option for patients infected with carbapenemase-producing Enterobacteriaceae if the infection is localized to the genitourinary tract. Unfortunately, fosfomycin does not demonstrate reliable activity against non-urinary pathogens. Fosfomycin demonstrated activity against only 30.2% of 1069 multidrug-resistant (MDR) P. aeruginosa isolates and 3.5% of 85 MDR A. baumannii isolates (Falagas et al., 2009). The individual studies included in this review did not employ uniform MDR definitions or consistent susceptibility breakpoints. Moreover, access to the parenteral fosfomycin is limited and the threshold for resistance is low (Rodríguez-Rojas et al., 2010; Karamagopoulos et al., 2012). Concerns regarding the emergence of resistance have lead to an increasing interest in the utility of combination therapy (Michalopoulos et al., 2010; Bercoff et al., 2011; Souli et al., 2011).

In one evaluation, 48% of 25 tested isolates were susceptible to amikacin, 44% to gentamicin, and 8% to tobramycin. Plazomicin demonstrated an MIC90 significantly lower than that of amikacin (Endimiani et al., 2009c). In vitro studies also indicate that depending on the aminoglycoside resistance mechanisms present, Plazomicin may have activity against select isolates of P. aeruginosa and A. baumannii (Aggen et al., 2010; Landman et al., 2011). Susceptibility to plazomicin in the setting of resistance to other aminoglycosides appears to be dependent on the mechanism of aminoglycoside resistance (Livermore et al., 2011a).

NAB739 and NAB7061 are polymyxin derivatives that may be less nephrotoxic than commercially available polymyxins. In a small in vitro study, NAB739 displayed activity against nine carbapenemase-producing polymyxin-susceptible isolates of Enterobacteriaceae (Väara et al., 2010). A contemporary evaluation of NAB739 demonstrated higher MICs compared to those of polymyxin B in a collection of polymyxin-susceptible and non-susceptible Enterobacteriaceae, P. aeruginosa, and A. baumannii (Väara et al., 2012). NAB7061 when used in combination with rifampicin or clarithromycin demonstrated synergistic activity against seven strains of carbapenemase-producing Gram-negative bacilli including one polymyxin-resistant strain (Väara et al., 2010). It remains unclear what role these agents will play in the setting the increasing burden of infections with carbapenemase-producing Enterobacteriaceae.
CONCLUDING REMARKS

In the last 5 years, we have witnessed the global spread of carbapenem resistance among Gram-negative organisms. The notion that multidrug resistance among these pathogens is limited to isolated outbreaks among the critically ill has met the ultimate challenge with NDMA-1 (Kumarasamy et al., 2010). The conveniences of travel and medical tourism have introduced resistance mechanisms across states, countries, and even continents at an alarming rate (Rogers et al., 2011; van der Bij and Pitout, 2012). Rates of resistance in some countries may be underestimated due to the lack of organized reporting structures and limited resources.

Long-term healthcare facilities are now recognized reservoirs for the continued propagation of MDR organisms (Urban et al., 2008; Acosta et al., 2012). Preventing the spread of MDR organisms is crucial in these settings, and the future savings of investing in prevention is not as tangible as the immediate capital investment required to allot appropriate resources including advanced laboratory platforms, experienced laboratory personnel, dedicated nursing staff, and infection control personnel (Balsavský et al., 2010). Expanding these efforts to non-acute healthcare settings is recommended to begin to stem the evolving pandemic of carbapenem resistance (Castaño et al., 2013).

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