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Emergence of Carbapenemase Producing Pathogens in Animals

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Abstract

Carbapenems are beta (β)-lactam antibiotics active against wide range of bacteria. Carbapenem resistance may be outcome of efflux pump activation, alteration in protein binding proteins, production of carbapenemases which degrade carbapenems. There are number of bacteria producing different types of carbapenemases like NDM (Enterobacteriaceae), IMP (*Pseudomonas aeruginosa*), IMI (*Enterobacter cloacae*), KPC (*Klebsiella pneumonia*), OXA-23, OXA-24/40, OXA-58-type (*Acinetobacter baumannii*), VIM (*Acinetobacter baumannii*) etc. Carbapenem resistance is emerging throughout the world due to interspecies transfer of genetic elements carrying genes for carbapenemase production. It is very difficult to control spread of resistant strains because of the continuous threshold of selection present in forms of presence of carbapenems in environment created through wide spread clinical use. To control infection of carbapenem resistant bacteria there are limited options available for treatment. Many a time carbapenem resistant bacteria show pan-resistance and such bacterial infection become life-threatening and cannot be treated with available last resort antibiotics like polymin B, tigecyclin and colistin. Infection of carbapenem resistant bacteria can be controlled using two or more antibiotics or antibiotic+ herbal drug combination or herbal drugs like (carvacrol, cinnamon, holy-basil oil, lemon grass oil) etc. The herbal drugs may be used as first line of treatment against carbapenem resistant bacteria instead of antibiotics. But, how? It is still not very lucid. Besides it, probiotics and homeopathic therapy has also been recommended with no sufficient data to establish their efficacy.

Keywords: Carbapenem; Carbapenemase; Resistance; Animals; Herbal drugs; Mobile genetic elements; NDM; VIM; OXA; KPC

Introduction

Carbapenems are broad-spectrum beta (β)-lactam antibiotics used for treatment of serious infections. They are considered as the last-line therapy against multidrug-resistant (MDR) Gram-negative bacterial infections like extended spectrum β-lactamase (ESBL) producing Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp. Etc [1-5]. If a bacterial strain carries carbapenemase production potential there are only few or sometimes no options to treat the infection. Carbapenems are used extensively due to increased prevalence of cephalosporin-resistant pathogens. Because of the emergence of bacterial strains producing carbapenemases, resistance to carbapenems is increasing throughout the world that may seriously limits the clinical efficacy of carbapenam antibiotics [6-13]. Patients infected with carbapenem resistant Enterobacteriacae are not easy to treat due to limited available options.

Carbapenem resistant bacteria mostly carry genes responsible for resistance to the antibiotics like fluoroquinolones, trimethoprim-sulfamethoxazole and aminoglycosides on same transposon [14]. There are different types of carbapenemases produced by different bacteria like SME (*Serratia marcescens*), NMC and IMI (*Enterobacter cloacae*), KPC (*Klebsiella pneumonia*), GES (*Pseudomonas aeruginosa*), SFC (*Serratia fonticola*), OXA-23, OXA-24/40, OXA-58-type (*Acinetobacter baumannii*), OXA-48-type (*Klebsiella pneumoniae*), OXA-54 (*Acinetobacter baumannii*), OXA-55 (*Shewanella oneidensis*), VIM (*Acinetobacter baumannii*), NDM (Enterobacteriaceae), IMP(*Pseudomonas aeruginosa*) and many more. These enzymes are responsible for reduced susceptibility/ resistance to carbapenems.

Carbapenem hydrolyzing enzymes are broadly classified into two types on the basis of reactive site of the enzymes: serine carbapenemases and metallo-β-lactamases. Both the types of enzymes are inducible through exposure of bacteria to β-lactams. Beta lactamases are produced by number of bacteria, genes encoded may house either on chromosome or on plasmid(s). The first few metallo-β-lactamases, chromosomally encoded, enzymes were detected in *Bacillus cereus* (BCI, BCII) (15-16), *Stenotrophomonas maltophilia* (L1) [17] and *Aeromonas spp* (CphA) [18]. In case of plasmid borne MBLs, gene cassettes possess mobile MBL genes viz., *bla*VIM, blaIMP, *bla*GIM, *bla*SIM and *bla*KMH. Magiorakos and coworkers [19] revealed that many carbapenemase-producing (CP) strains may carry additional resistance determinants to other non-β-lactam antibiotics also; those organisms are called as pan drug-resistant (PDR) or extensively drug-resistant (XDR).

Emergence of Antimicrobial Drug Resistance

Emergence of antimicrobial drug resistance (ADR) and multiple ADR (MDR) in microbes has been discussed and reviewed extensively over the time [20-25]. Several reasons have been attributed for emergence of ADR and MDR but no cure has still been possible to reverse this process. Scientists fear that if the process is not reversed in time than the day is not far away when number of incurable cases will be out of clinical control and beyond reach of health management agencies [24-26]. Bacteria develop ADR through complex interactions within their community, through de-novo mutation under clinical antibiotic use and through acquisition of genes under antibiotic stress [20-25] and even under natural environmental stresses [26,27]. However, the spread of ADR and MDR usually occurs through selection under nonclinical and clinical antibiotic stresses or through

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acquisition of mobile genes that have evolved over the time in bacteria and in their environment [20,26]. The reservoir of resistance genes in the environment exists since time immemorial due to a mix of naturally occurring resistance and those natural antimicrobials present in animal and human waste, and the selective effects of environmental pollutants [22,24,26]. It is not necessary that only antibiotic stress will be responsible for emergence and spread of ADR, natural stress arising from global warming as a result of pollution may be an instrumental factor. In recent studies [27] it has been shown that *Escherichia coli* may evolve resistance when grown at elevated temperature. Now, we understand that of most of the reasons behind emergence and spread of ADR and MDR are anthropogenic activities, more important than any other single factor [26]. Therefore, our future is in our hands and self-regulation might be the key for the still unresolved riddle of ADR evolution and spread in microbes.

History of Carbapenem Resistance

Guiana extended spectrum (GES) β-lactamase was first observed in a *Klebsiella pneumoniae* isolate from French Guiana in 2000. Soon after in 2001, *Klebsiella pneumoniae* carbapenemase designated as KPC was identified from a *Klebsiella* isolate [28]. The KPC was encoded by a highly transmissible gene, spread widely throughout world. Verona integron encoded metallo-β-lactamase (VIM) was first metallo-β-lactamase identified from a *P. aeruginosa* isolated in 1997 in Italy. VIM-2 was detected from an isolate of *P. aeruginosa* again from a strain isolated in France in year 1996. Again from *P. aeruginosa* one more β-lactamase, Sao Paulo metallo-β-lactamases (SPM-1) was identified from Sao Paulo, Brazil. In year 2002, German imipenemase (GIM-1) was first detected in bacteria in Germany. However, transferable carbapenem resistance due to IMP was first detected in a *P. aeruginosa* isolate from Japan in 1990. Besides it, IMP-2 was observed in *A. baumannii* in Italy. Next, from Seoul, Seoul imipenemase (SIM-1) was detected in *P. aeruginosa* and *A. baumannii* from imipenem resistant isolates. New Delhi metallo-β-lactamase (NDM-1) was first reported from a *K. pneumoniae* isolate obtained from a Swedish patient in year 2009. NDM-1 was initially identified in *Klebsiella pneumoniae* [29] and then in *E .coli*. Gene responsible for it, *bla*NDM-1 was housed in 180 kb plasmid. The gene product confers high level resistance to all penicillins, cephalosporins, cefoxitin, carbapenems, ciprofloxacin and aztreonam. In 1985, first OXA enzyme with carbapenemase activity was identified in *A. baumannii* from Scotland in a previously known imipenem resistant *Acinetobacter* (ARI-1) and since then it is detected all over the world in many bacteria.

Epidemiology of Carbapenam Resistant Pathogens

Carbapenem resistance due to production of carbapenemases has increased in different countries around the world [30,23]. This is mainly due to travelling across the countries while being infected with antibiotic-resistant organisms and global open trade of animals, their products, goods and foods. The highest infection rate is detected among the travelers to Indian subcontinent and African countries. *Klebsiella pneumoniae* carbapenemase (KPC) has been reported in number of countries like India, China, Turkey, Israel, United Kingdom and United States. The KPC enzymes have been observed in *K. pneumoniae, K. oxytoca, P. aeruginosa, E. coli, Enterobacter cloacae, E. aerogenes, Salmonella enterica, Serratia marcescens* and *Citrobacter freundi*. KPC-2 producing *K. pneumoniae* were isolated from Israel and Columbia.

In case of GES enzymes, they have been identified across Asian, Europeon and African countries. VIM and IMP enzymes are also detected in pathogens all over the world. Since the year 2009, NDM MBL detection was considered as more common over VIM-2. The gene encoding NDM-1 is located on mobile genetic element, thus results in rapid spread across the species and countries. Many variants of NDM (>12) have been identified in last few years and NDM-5 has been even detected in several non-clinical bacterial isolates from animals. On other hand, GIM, SIM and SPM enzymes remained restricted to countries of their origin. Regarding OXA-48, it is now reported from Turkey, China, India, and the United Kingdom. OXA-58 was isolated from *Acinetobacter* spp. in France, Greece, Romania, Italy, Turkey, Kuwait and Argentina. Fischer *et al.* [31-34] speculated that wild birds and animals may act as a reservoir for strains possessing carbapenemase encoding genes, as *Salmonella* producing NDM-1 has been isolated from a black kite and E. coli having NDM-5 has been isolated from Thamin dear (unpublished data from our lab).

Carbapenem Resistance

Emergence of acquired carbapenemases and their worldwide dissemination is a major global threat to antibiotic era [30,33,35-39]. Carbapenem resistance is either due to production of β-lactamases, or activation of efflux pumps, and or mutations that alter expression of porins and penicillin binding proteins (PBPs). The combination of these mechanisms results in increased resistance to carbapenems in bacterial species such as *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* [40-42].

Carbapenem resistance is of two types: intrinsic and acquired. Intrinsic resistance to carbapenems is because of inherent properties like low permeability of bacterial membranes, low affinity of penicillin binding proteins (PBPs), presence of species-specific carbapenem-inactivating enzymes and presence of multidrug efflux pumps and is common in enterococci [43]. Acquired carbapenem resistance is due to presence of exogenous genetic material such as plasmids, transposons and insertion sequence common region (ISCR) elements containing genes coding for carbapenemase production. It is common in Enterobacteriaceae members [44].

Mechanism of resistance to carbapenems is different for Gram-positive cocci and Gram-negative rods. In case of Gram-positive cocci, carbapenem resistance is due to substitutions in amino acid sequences of PBPs or production of a new carbapenem-resistant PBP [45-47]. In case of Gram-negative rods, porin loss, alterations in PBPs, expression of β-lactamases and efflux pumps are responsible for carbapenem resistance [11,48].

Carbapenam Resistance in Animal Pathogens

Carbapenemase producing (CP) bacteria has been reported in food-producing animals and their environment [44,49-54]. *Salmonella* Paratyphi B variant Java, *S.* Saintpaul and *S.* Virchow with CP potential have been reported from buffalo calves and beef in India [55]. The CP *E. coli* from oysters, water, shrimps and pond environment have been reported in Brazil [56-57]. The CP *Salmonella* Corvallis isolated from a wild bird has also been reported in Germany [34]. NDM-1-producing *E. coli* were reported from companion animals (cats and dogs) in USA [58]. Wang and coworkers [52] found *bla*NDM-1 gene in *A. lwoffii* isolated from a chicken in a broiler farm. Stolle *et al.* [59] reported OXA-48 in *E. coli* and *K. pneumoniae* from dogs. Kempf *et al.* [60] described OXA-23-like CP *A. baumannii* from human head lice in Senegal. Poirel *et al.* [51] detected 9 CP isolates of *Acinetobacter* genomospecies on a dairy cattle farm in France in 2010. The carbapenemase resistance in these isolates was due to OXA-23 enzyme encoded by the gene *bla*OXA-23. The same gene was also detected in *Acinetobacter* spp. from two horses in Belgium [61]. Fischer *et al.* [49] described three CP

Salmonella spp. isolates from two fattening pig farms and one broiler farm in Germany.

Kumsa *et al.* [62] conducted search for CP strains in Ethiopia to determine the presence of *Acinetobacter* species in lice and *Melophagus ovinus* (sheep ked) of animals in year 2011. During the study the isolates were tested for carbapenemase resistance-encoding genes like *bla*OXA-58, *bla*OXA-23, *bla*OXA-24, *bla*OXA-51 and *bla*NDM-1. However, no positive result was recorded in their study. Stolle *et al.* [59] described transmission of a *K. pneumoniae* strain having OXA-48 carbapenemase to several dogs in a veterinary clinic. It suggests that hand hygiene is as important here as in human medicine to prevent and control infections and to limit the spread of resistant bacteria.

In India, in a recent study on 279 *E. coli* isolates from calves, 80 isolates were found resistant to carbapenem drugs. These isolates were subjected to PCR targeting NDM, VIM, OXA, KPC and IMP genes. One isolate was producing the metallo beta lactamase enzyme VIM - genotypically confirmed by PCR [63]. Besides, several CP strains possessing VIM, NDM and OXA genes have been recently reported from dears, tigers, diarrhoeic as well as healthy pigs and aborting cows (Research Advisory Committee meeting of IVRI, 21-23 April, 2015, unpublished).

Control of Carbapenem Resistant Infections

Though options available are few still we are not away of hope, some of alternative strategies for control of CP bacterial infection are:

Alternative antibiotic

Polymyxin B: It is considered as last-line antibiotics for multidrug-resistant *A. baumanni* and *P. aeruginosa*. Polymixin B can be used at high doses regardless of the presence of renal dysfunction [64]. But polymyxins can only achieve limited bacterial killing against isolates with high minimal inhibitory concentrations (MICs), though considerably high concentrations of unbound polymyxin are achievable in patients [65-66].

Colistin: Colistin is a polypeptide antibiotic, consists of colistin A and B. The antibiotic came in use in the 1960s. It is again becoming common for use against multidrug resistant bacteria as alone or in combination form with other antibiotic [67-69]. But at effective doses colistin can cause nephrotoxicity. Colistin methane sulphonate sodium (CMS) is converted to colistin in urine leading to high urinary concentrations [65]. In India, colistin resistance is quite common in bacteria isolated from animals [70].

Tigecycline: Tigecycline was approved by the Food and Drug Administration (FDA) in year 2005 [71-72]. The antibiotic is used against polymixin B resistant carbapenem resistant Enterobacteriaceae and *A. baumannii*. The clinical use of antibiotic is limited for controlling infection in urinary tract and for primary blood-stream infections. Tigecycline is not very active against *P. aeruginosa* [73].

Fosfomycin: Fosfomycin, a phosphonic acid derivative, used as an alternative against carbapenem resistant Enterobacteriaceae [74-78]. Fosfomycin is used for the treatment of non-complicated urinary tract infections because it rapidly reaches high urinary concentrations [79]. It shows excellent activity *in vitro* against strains resistant to both colistin and tigecycline. The antibiotic is less frequently used against *P. aeruginosa* because of higher MICs and a higher potential for development of resistance against it [80-82]. Some other antibiotics are also recommended like aminoglycosides, quinolones, trimethoprim, chloramphenicol and temocillin but only after their proper MIC determination to the pathogen.

Combinational therapy

Antibiotic combinations have been proposed as the best way to treat carbapenem resistant organisms like colistin along with tigecycline, colistin with a carbapenem, carbapenem along with fosfomycin, carbapenem with an aminoglycoside [83-86] and fosfomycin with an aminoglycoside [87]. Gentamicin is the recommended antibiotic which can be used against KPC and VIM-producing Enterobacteriaceae with the highest *in vitro* activity [88-89]. Aztreonam, ceftazidime can also be combined with aminoglycoside like amikacin or genatmicin for use in combination therapy against carbapenem resistant bacteria [70].

Probiotics

Probiotics are used to alter the gut microflora so that carbapenem resistant bacteria cannot colonize in it [23,24]. There are number of commercial supplements, enough to boost immune system and help to protect from developing a serious infection. These strains include *Lactobacillus casei, Lactobacillus plantarum, Lactobacillus salivarius, Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium breve* and *Bifidobacterium lactis*.

Alternative therapies

Herbal drugs: Oregano oil (containing carvacrol) disrupts the protective cell membrane of the carbapenemase resistant bacteria. Olive leaf extract is also considered as natural antibacterial agent against antibiotic resistant isolates. According to Jazani group's studies [90] fennel essential oil extracts has antimicrobial activity against multi-drug resistant *A. baumannii*. Fahey *et al.* [91] found that pomegranate rind extract has antimicrobial activity against multi-drug resistant *P. aeruginosa*. Khan *et al.* [92] found that cinnamon and clove extract has antibacterial activity against multi-drug resistant strains of *E. coli* and *Klebsiella*. Herbal drugs can modulate the effect of antibiotics available against carbapenem resistant bacteria. Colistin antibacterial activity can be enhanced by cinnamon oil as well as carvacrol [70]. The herbal drugs namely holy basil oil (MIC 20 mcg to >2560 mcg mL^{-1}), lemon grass oil (MIC 5 mcg to >5000 mcg mL^{-1}), cinnamon oil (MIC 10 mcg to > 1280 mcg mL^{-1}), and carvacrol (MIC 5mcg to >5000mcg mL^{-1}) have shown potential for use to control CP strains of bacteria at least *in vitro* [70].

Homeopathy

Veterinary homeopathy is use of homeopathy in animals. The homeopathic products are not recommended veterinary medicine in the US. The field can be explored in future to treat against carbapenem resistant bacteria.

Conclusions

The emergence and rapid spread of carbapenem resistance bacteria is an important threat to public health. Antibiotic options currently in use against carbapenemase producer microbes include tigecycline, colistin, polymyxin B, fosfomycin, and aminoglycosides. There are number of limitations associated with these drugs like increase in resistance, less efficacy and toxicity. So, these antibiotics have been used as combination therapy to reduce the side effects. Moreover, carbapenems are considered as last line of treatment for resistant bacteria but due to production of carbapenemases, the carbapenems are not effective against multidrug resistant bacteria. Due to limited therapeutic options more emphasis should be laid on control strategies for preventing their spread. Also, carriers of resistant isolates should be identified at early stages. Excessive use of broad-spectrum antibiotics

should be controlled. For the treatment of carbapenem resistant bacteria some alternatives should be used with limited side effects like herbal drugs.

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