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Annals of Clinical Pathology

Research Article

KPC-Producing *Klebsiella pneumoniae* Strains: A Threat to our Therapeutic Arsenal

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Submitted: 01 August 2016

Accepted: 20 November 2016

Published: 23 November 2016

ISSN: 2373-9282

Keywords

- *K. pneumoniae*
- KPC
- Epidemiology

Abstract

In the last decade, extremely drug-resistant KPC-producing *Klebsiella pneumoniae* strains have emerged in the USA and sequentially in other parts of the world. In particular, *K. pneumoniae* producing carbapenemase (KPC) has been identified as a major public health threat because of the rapid plasmid mediated spread of resistance and limited available therapeutic options. These strains are resistant to almost all available antibiotics and are associated with high morbidity and mortality. Reported rates of mortality associated with KPC-Kp infections vary widely from 22% to 72%. The detection of KPC-2-producing *K. pneumoniae* strains belonging to CC11 in urban rivers is epidemiological evidence demonstrating that the environmental dissemination of high-risk multiresistant bacteria is ongoing in Brazil and other countries.

INTRODUCTION

In a recent report, WHO highlights the emergence of carbapenem resistance among Enterobacteriaceae as the harbinger for a potential post-antibiotic era, once bacteria have become resistant to carbapenems, very few treatment options remain [1].

Klebsiella pneumoniae carbapenemase (KPC) enzymes are, by far, the most common class A carbapenemases generally plasmid encoded within the Tn3-based transposon Tn4401, which has five known isoforms (a, b, c, d and e) as defined by insertions or deletions within a polymorphic region immediately upstream of *bla*KPC [2], and KPC-producing isolates are usually resistant to non-β-lactam antibiotics such as fluoroquinolones, aminoglycosides and co-trimoxazole [3].

Bacteria producing these enzymes are generally only susceptible to a few antibiotics, and there is high mortality among patients with bloodstream infections caused by these organisms [4]. For instance, the overall mortality in patients with KPC-associated infections has been estimated to be between 22% and 72% [1,5-7].

Substantial percentages of hospitalized patients are colonized by these microorganisms, which have caused several outbreaks of severe nosocomial infections, including bacteraemia and ventilator-associated pneumonia, since 2010 [8].The aim of this review is to summaries the epidemiology of *K. pneumoniae* producing carbapenemase across continents circulating and discuss possible therapeutic options.

METHODS

Literature Search in Databases

It is a literary review of articles related to the subject published in the database of Scielo, Pubmed, EBSCOhost, Scopus and Web of Science being selected only articles in which the focus was *Klebsiella pneumoniae* carbapenemases producers. In addition, the African Journals Online database was searched using the keywords 'β-lactamase in Africa'.

Class A Carbapenemases

KPC families of carbapenemases are plasmid encoded and have the greatest potential for spread due to its location on plasmids. The KPC carbapenemases differ from the other functional Group 2f enzymes by two important characteristics. First is the presence of the KPC enzymes on transferable plasmids. The second, their substrate hydrolysis spectrum includes the aminothiazole oxime cephalosporins, such as cefotaxime. Although, the KPC beta-lactamases are predominantly found in *K. pneumoniae*, there have been reports of these enzymes in Enterobacter species and in Salmonella spp [9,10]. However the *bla*KPC genes are flanked by the same transposon Tn4401 located on conjugative plasmids and are horizontally transferred [11]. This gives to this enzyme an extraordinary spreading capacity (Naas et al., 2014)[12]. They have been detected more often in *Klebsiella* spp. [13], but have also been reported in other *Enterobacteriaceae* [14]. Thirteen variants of KPC are known so far; KPC-2 and KPC-3 are the most frequent worldwide variants [15,16].

KPC carbapenemases hydrolyse beta-lactams of all classes, with the most efficient hydrolysis observed for nitrocefin, cephalothin, cephaloridine, benzylpenicillin, ampicillin, and piperacillin. Imipenem, meropenem, cefotaxime, and aztreonam, are hydrolyzed 10-fold-less efficiently than the penicillins and early cephalosporins. Weak but measurable hydrolysis is observed for cefoxitin and ceftazidime, giving the KPC family a broad hydrolysis spectrum that includes most beta-lactam antibiotics. The KPC family can spread easily due to its location on plasmids. It is the most often present in *K. pneumoniae*, an organism known for its ability to accumulate and transfer resistance determinants. The treatment of infections caused by these organisms is extremely difficult because of their multidrug resistance and hence results in high mortality rates [9].

EPIDEMIOLOGY

The first isolate of KPC-producing bacteria was discovered through the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) surveillance program in a clinical specimen of *K. pneumoniae* from North Carolina in 1996 [17]. Soon after, KPC-producing organisms spread rapidly along the east coast and then became widely disseminated westward and throughout the country [17,4] (Figure 1). have now been reported almost in all States of the US except, Idaho and Maine [54].

The first KPC-producing organism detected outside of the United States occurred in in Paris, France [18]. Interestingly, the patient was hospitalized in a New York City hospital 2 months prior, suggesting that the resistant organism was imported from the USA [17]. The European Centre for Disease Control and Prevention in 2015 reported highest prevalence of carbapenem-resistant *K. pneumoniae* in three countries (Greece, Italy and Romania) reported carbapenem resistance percentages considerably higher than any other country (62.3%, 32.9% and 31.5%, respectively). These countries also reported the highest percentages of polymyxin-resistant *K. pneumoniae*, indicating an especially worrisome situation [17].

The first KPC-positive isolate recorded in Warsaw (Poland) from the urine of an inpatient without relevant travel history [19]. By the end of 2008, the national reference laboratory had identified 32 additional cases in five hospitals of this city [20].

In South America, the first report of KPC was detectedin Colombia in 2006, since then, has become widespread in different parts of this country [21]. KPC-producing *K. pneumoniae* was first described as occurring in Brazil in 2006, isolates in an intensive care unit [21] and since then its incidence has greatly increased [22,23], observed the presence of the *bla*KPC-2 gene in *K. pneumoniae* strains isolated in five states from 2006 through to 2009. In 2010, however, a great dispersion of this gene was observed in this country, with the spread of carbapenem-resistant *K. pneumoniae* observed in several hospitals in different Brazilian cities and states [24]. Nevertheless, detection of KPC-2-producing *K. pneumoniae* strains in urban rivers [25] and in hospital wastewater [26], is epidemiological evidence demonstrating that the environmental dissemination of high-risk multiresistant bacteria is ongoing in Brazil. Similarly, Argentina have reported sporadic cases and clusters of infections with KPC-mediated resistance in different types of Gram-negative pathogens, including *K. pneumoniae* [27,28].

The first report of KPC in Middle East (Israel) was in a returned traveler who received health care in New York in 2005. However, since the first reported case, have firmly established endemic status in Israel [29]. The most common clinical site was the urinary tract, although several body sites have been involved in clinical infections [30].

As a region, Asia has widely disseminated KPC resistance

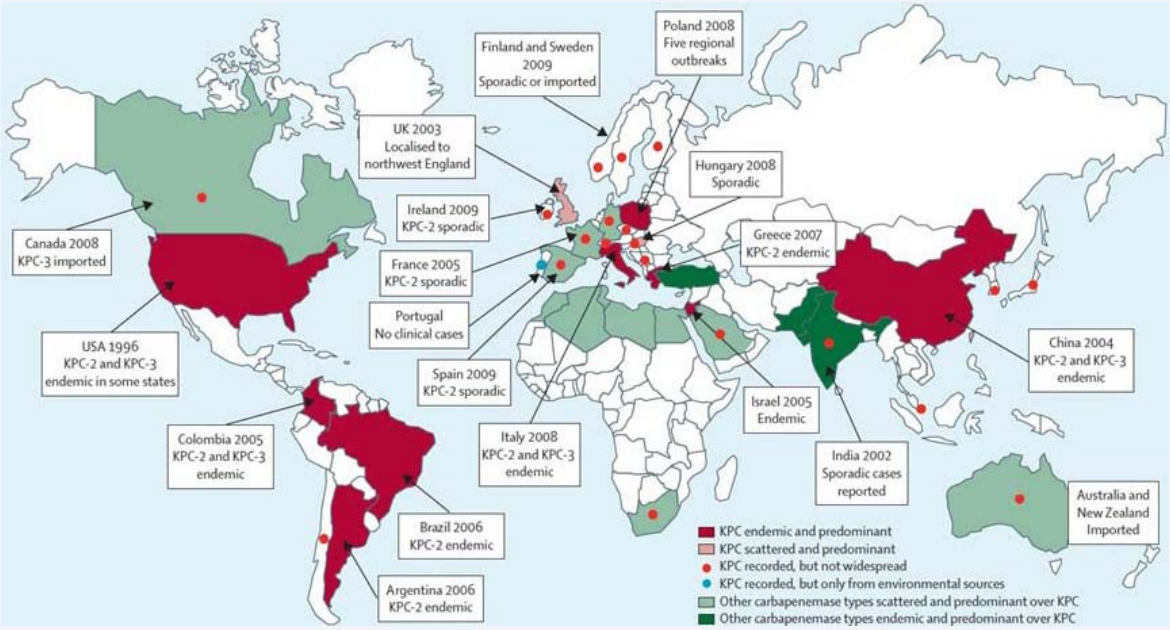

Figure 1 Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin. Other carbapenemase types include VIM, OXA-48, or NDM (Munoz- Price et al., 2013)[4].

elements [31]. The first KPC-positive organisms recorded in India were clinical isolates of *E. coli*, *K. pneumoniae*, and Proteus mirabilis recovered from patients enrolled in clinical trials (2002–2006) [32]. From 2007 to 2010, nine further patients with bacteria that carried *bla*KPC were identified in an active microbiological surveillance study [33]. The first KPC-positive *K. pneumoniae* isolate recorded in China was identified in 2004 from a 75-year-old ICU patient in Zhejiang, and this province appears to be the epicenter for KPC-producing organisms in China [34,35]. Screening in nine Chinese cities, all 95 *K. pneumoniae* found that were not susceptible to carbapenem [36].

In Australia, the first report of KPC was detected in an isolate of *K. pneumoniae* from a returned traveler who was hospitalized during a holiday to Greece in the prior year [37]. Similarly, the first isolate of KPC in New Zealand was *K. pneumoniae* resistance obtained from a patient repatriated from a Chinese hospital [17].

In Portugal, there have been no reports of clinical cases involving KPC-positive isolates, but a KPC-2-positive *E. coli* strain was recently recovered from river water [38]. In 2009, an old Spanish man was the first of eight cases colonized with KPC positive *K. pneumoniae* to occur in a health-care facility in Madrid, Spain. These patients were in five different wards in the hospital, and none had recently travelled to KPC-endemic countries [39].

In June 2013, a 6-month-old child with hydrocephalus was admitted to neurosurgery ward of Sétif University Hospital, Algeria. After analysis of a cerebrospinal fluid sample was determinated first case of infection by *K. pneumoniae* carrying the *bla*KPC gene isolated from a child in the North African [40]. In the year 2011 in Egypt, with a total of 45 samples of *K. pneumoniae*, 31.1% were positive KPC [41]. In the same year in South Africa were isolated 4 *K. pneumoniae* producing KPC [42], and in Tanzania between 2007-2012 were isolated and identified 8 KPC positive [43].

In Mozambique was isolated from *Lactuca sativa* (Lettuce) and *Allium fistulosum* L. (Welsh onion) carbapenem-resistant Enterobacteriaceae, believing that the contamination was due to the water used for irrigation.Molecular experiments had to be performed to better characterize these bacteria [44].

TREATMENT OPTIONS

Carbapenems have been widely used in many countries due to the increasing rate of ESBL-producing Enterobacteriaceae, resulting in the emergence of resistance to these agents, especially in *K. pneumoniae*. Very few therapeutic options are left for patients infected with multidrug-resistant *K. pneumoniae* with additional resistance to carbapenems, and mortality is therefore high [45]. Furthermore, KPC producers frequently carry additional genetic determinants, which confer resistance to other antibiotics, such as fluoroquinolones, aminoglycosides, and cotrimoxazole [46,48,17].

Most study demonstrated that the vast majority of isolates were susceptible to amikacin, tigecycline, gentamicin or colistin [49,50,17,46]. This leaves colistin as the sole therapeutic alternative. Usage of colistina should be limited due to their neurotoxicity and nephrotoxicity [45]. [8], demonstrate also during the study period, rates of non-susceptibility to each of these drugs increased alarmingly among study isolates: from 6% (gentamicin), 11% (colistin) and 9% (tigecycline) in 2010 to 21%, 27% and 25%, respectively, in 2013. Emergence of resistance to polymyxins, especially in countries with already high percentages of multidrug and carbapenem resistance is another step towards pandrug resistance [17].

Fosfomycinhas been used successfully to treat KPC-producing organisms that still showed in vitro susceptibility [17]. A study showed that fosfomycin retained in vitro activity against 93% of KPC-producing isolates collected in the USA in 2009 [50]. Notably, five out of six extremely drug-resistant KPC producers nonsusceptible to tigecycline and colistin were susceptible to fosfomycin. This drug causes very little toxicity and penetrates tissues readily; the concern with fosfomycin, however, is the propensity for resistance to rapidly develop when it is used in monotherapy [51,17]. Thus, many investigators have proposed using fosfomycin in combination with other agents, such as aminoglycosides, since synergism has been demonstrated [51].

Combination therapies may be an attractive option based on some in-vitro data, but clinical data supporting such recommendations are lacking [52]. One study has reported in-vitro synergy between colistin and rifampicin against KPC-2-producing- *K. pneumoniae* isolates [53].Oral treatments such as fosfomycin and nitrofurantoin should be evaluated. In addition, β lactam and β-lactamase inhibitor combinations (carbapenem or cephalosporins, and clavulanic acid, sulbactam, or tazobactam) should at least be evaluated in animal models of urinary tract infections [45]. Recent findings suggest that combination treatment with colistin, tigecycline, and meropenem might improve survival among bacteraemic patients, but none is ideal for empirical use because colistin are nephrotoxic [5].

PREVENTION AND INFECTION CONTROL

The updated guidance for control of carbapenem-resistant Enterobacteriaceae (CRE) of Centers for Disease Control and Prevention recommends a set of core measures for all acute and long-term care facilities: first, sanitizing hands; second, minimize use of invasive medical devices and isolating CRE–infected patients; third, promotion of antibiotic stewardship and screening for patients with risks for CRE (CDC, 2012). Nevertheless, findings from several studies emphasize the importance of early identification of asymptomatic carriers and their subsequent grouping, and this factor was a key part of the successful national intervention in Israel [54,55].

[56], propose use a combination of the above interventions to curtail an outbreak of multidrug-resistant bacteria that included KPCs in their intensive care unit performing rectal swab screening for all new admissions to the intensive care unit and repeated the surveillance cultures weekly. KPC-infected or colonized patients were cohorted and were assigned dedicated nurses to care for them. Daily environmental cleaning was performed with a quaternary ammonium compound on all work surfaces in clinical areas.

Furthermore, a recent study in New York (USA) compared infection control practices among nine neighbouring hospitals and found that those that used active surveillance cultures had most success in decreasing the acquisition rate of KPC-positive

organisms [57].

CONCLUSION

Since their discovery 16 years ago, KPC-positive Gram-negative organisms have spread worldwide; however, their local epidemiology and clinical characteristics vary. Some countries have experienced endemicity whereas others largely continue to have only imported cases [4].

Polymyxins, such as colistinandpolymyxin B, are another class of drugs that have been used successfully to treat KPC-producers. These drugs are active against most genera of Gram-negative aerobic bacilli [17]. Polymyxin B and colistina have been increasingly used, but they are associated with high rates of nephrotoxicity and have been considered drugs of last resort [17]. There are recent data to show that the polymyxins may not be as nephrotoxic as previously thought; however, optimal dosing of polymyxinsis not known. The optimal dosing regimens for colistin are under evaluation [58].

REFERENCES

1. Bathoorn E, Tsioutis C, da Silva Voorham JM, Scoulica EV, Ioannidou E, Zhou K, et al. Emergence of pan-resistance in KPC-2 carbapenemase-producing *Klebsiella pneumoniae* in Crete, Greece: a close call. J AntimicrobChemother. 2016; 71: 1207-1212.

2. Naas T, Cuzon G, Truong HV, Nordmann P. Role of ISKpn7 and deletions in *bla*KPC gene expression. Antimicrob Agents Chemother. 2012; 56: 4751-4759.

3. Alexandre K, Chau F, Guérin F, Massias L, Lefort A, Cattoir V, et al. Activity of temocillin in a lethal murine model of infection of intra-abdominal origin due to KPC-producing *Escherichia coli*. J AntimicrobChemother. 2016; 71: 1899-1904.

4. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. Lancet Infect Dis. 2013; 13: 785-796.

5. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase producing *K. pneumoniae*: importance of combination therapy. Clin Infect Dis. 2012; 55: 943-950.

6. Sbrana F, Malacarne P, Viaggi B, Costanzo S, Leonetti P, Leonildi A, et al. Carbapenem-sparing antibiotic regimens for infections caused by *Klebsiella pneumoniae* carbapenemase producing *K. pneumoniae* in intensive care unit. Clin Infect Dis. 2013; 56: 697-700.

7. Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psichogiou M, Argyropoulou A, et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother. 2014; 58: 2322-2328.

8. Tumbarello M, Trecarichi EM, De Rosa FG, Giannella M, Giacobbe DR, Bassetti M, et al. Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study. J Antimicrob Chemother. 2015; 70: 2133-2143.

9. Dahiya S, Singla P, Chaudhary U, SinghB. Carbapenemases: A Review. Int J Adv Health Sci. 2015; 2.

10. Queenan AM, Bush K. Carbapenemases: The versatile betalactamases. Clin Microbiol Rev. 2007; 20: 440-458.

11. Gaëlle Cuzon, Thierry Naas, HaVy Truong, Maria-Virginia Villegas, Karin T. Wisell, Yehuda Carmeli, et al. Worldwide diversity of *Klebsiella pneumoniae* that produces β-lactamase blaKPC-2 Gene. Emerg Infect Dis. 2010; 16: 1349-1356.

12. Naas T, Cuzon G, Villegas MV, Lartigue MF, Quinn JP, Nordmann P. Genetic structures at the origin of acquisition of the β-lactamase *bla*KPC gene. Antimicrob Agents Chemother. 2014; 52: 1257-1263.

13. Patrice Nordmann, Thierry Naas, Laurent Poirel. Global spread of carbapenemase producing *Enterobacteriaceae*. Emerg Infect Dis. 2011; 17: 1791-1798.

14. L.M. Deshpande, P. R. Rhomberg, H. S. Sader, R. N. Jones. Emergence of serine carbapenemases (KPC and SME) among clinical strains of Enterobacteriaceae isolated in the United States Medical Centers: report from the MYSTIC Program (1999–2005). Diag Microbiol Infect Dis.2006; 56: 367-372.

15. Y. Pfeifer, A.Cullik, W.Witte. Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. Int J Med Microbiol. 2010; 300: 371-379.

16. Djahmi N, Dunyach-Remy C, Pantel A, Dekhil M, Sotto A, Lavigne JP. Epidemiology of carbapenemase-producing Enterobacteriaceae and Acinetobacter baumannii in Mediterranean countries. Biomed Res Int. 2014; 2014: 305784.

17. Chen YT, Lin JC, Fung CP, Lu PL, Chuang YC, Wu TL, Siu LK.. KPC-2-encoding plasmids from Escherichia coli and Klebsiella pneumoniae in Taiwan. J AntimicrobChemother. 2014; 69: 628–631.

18. Naas T, Nordmann P, Vedel G, Poyart C. Plasmid-mediated carbapenem-hydrolyzing beta-lactamase KPC in a *Klebsiella pneumoniae* isolate from France. Antimicrob Agents Chemother. 2005; 49: 4423-4424.

19. Baraniak A, Izdebski R, Herda M, Fiett J, Hryniewicz W, Gniadkowski M, et al. Emergence of *Klebsiella pneumoniae* ST258 with KPC-2 in Poland. Antimicrob Agents Chemother. 2009; 53: 4565-4567.

20. Baraniak A, Grabowska A, Izdebski R, Fiett J, Herda M, Bojarska K, et al. Molecular characteristics of KPC-producing *Enterobacteriaceae* at the early stage of their dissemination in Poland, 2008–2009. Antimicrob Agents Chemother. 2011; 55: 5493-5499.

21. Monteiro J, Santos AF, Asensi MD, Peirano G, Gales AC. First report of KPC-2-producing *Klebsiella pneumoniae* strains in Brazil. Antimicrob Agents Chemother. 2009; 53: 333-334.

22. Seki LM, Pereira PS, de Souza Mda P, Conceição Mde S, Marques EA, Porto CO, et al. Molecular epidemiology of KPC-2- producing *Klebsiella pneumoniae* isolates in Brazil: the predominance of sequence type 437. Diagn Microbiol Infect Dis. 2011; 70: 274-247.

23. Peirano G, Seki LM, Val Passos VL, Pinto MC, Guerra LR, Asensi MD. Carbapenem-hydrolysing beta-lactamase KPC-2 in *Klebsiella pneumoniae* isolated in Rio de Janeiro, Brazil. J Antimicrob Chemother. 2009; 63: 265-268.

24. Perez F, Endimiani A, Ray AJ, Decker BK, Wallace CJ, Hujer KM, et al. Carbapenem-resistant Acinetobacter baumannii and *Klebsiella pneumoniae* across a hospital system: impact of post-acute care facilities on dissemination. J Antimicrob Chemother. 2010; 65: 1807-1818.

25. Oliveira S, Moura RA, Silva KC, Pavez M, McCulloch JA, Dropa M, et al. Isolation of KPC-2-producing *Klebsiella pneumoniae* strains belonging to the high-risk multiresistant clonal complex 11 (ST437 and ST340) in urban rivers. J Antimicrob Chemother. 2014; 69: 849-852.

26. Chagas TP, Seki LM, da Silva DM, Asensi MD. Occurrence of KPC-2-producing *Klebsiella pneumoniae* strains in hospital wastewater. J Hosp Infect. 2011; 77: 281.

27. Pasteran F, Faccone D, Gomez S, De Bunder S, Spinelli F, Rapoport M,

et al. Detection of an international multiresistant clone belonging to sequence type 654 involved in the dissemination of KPC-producing *Pseudomonas aeruginosa* in Argentina. J Antimicrob Chemother. 2012; 67:1291-1293.

28. Gales AC, Castanheira M, Jones RN, Sader HS. Antimicrobial resistance among Gram-negative bacilli isolated from Latin America: results from SENTRY Antimicrobial Surveillance Program (Latin America, 2008–2010). Diagn Microbiol Infect Dis. 2012; 73: 354-360.

29. Leavitt A, Navon-Venezia S, Chmelnitsky I, Schwaber MJ, Carmeli Y. Emergence of KPC-2 and KPC-3 in carbapenem-resistant *Klebsiella pneumoniae* strains in an Israeli hospital. Antimicrob Agents Chemother. 2007; 51: 3026-3029.

30. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother. 2008; 52: 1028-1033.

31. Jean SS, Hsueh PR. High burden of antimicrobial resistance in Asia. Int J Antimicrob Agents. 2011; 37: 291-295.

32. Jones CH, Tuckman M, Keeney D, Ruzin A, Bradford PA. Characterization and sequence analysis of extended-spectrum-{beta}-lactamase-encoding genes from *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* isolates collected during tigecycline phase 3 clinical trials. Antimicrob Agents Chemother. 2009; 53: 465-475.

33. Munoz-Price LS, Hayden MK, Lolans K, Won S, Calvert K, Lin M, et al. Successful control of an outbreak of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* at a long-term acute care hospital. Infect Control Hosp Epidemiol. 2010; 31: 341-347.

34. Wei ZQ, Du XX, Yu YS, Shen P, Chen YG, Li LJ. Plasmid-mediated KPC-2 in a *Klebsiella pneumoniae* isolate from China. Antimicrob Agents Chemother. 2007; 51: 763-765.

35. JF Sheng, JJ Li, S Tu, ZK Sheng, S Bi, MH Zhu, et al. *bla*KPC and rmtB on a single plasmid in *Enterobacter amnigenus* and *Klebsiella pneumoniae* isolates from the same patient. Eur J ClinMicrobiol Infect Dis. 2012; 31: 1585-1591.

36. Qi Y, Wei Z, Ji S, Du X, Shen P, Yu Y. ST11, the dominant clone of KPC-producing *Klebsiella pneumoniae* in China. J AntimicrobChemother. 2011; 66: 307-312.

37. Huntington P, Coatsworth N, Hardiman R, Hudson B, Kotsiou G, Fernandes C. *Klebsiella pneumoniae* carbapenemase in Australia: detection of a KPC-producing clinical isolate at a Sydney hospital. The Australian Society for Microbiology (ASM) 2011 Annual Conference. Hobart, Tasmania, Australia; 2011.

38. Poirel L, Barbosa-Vasconcelos A, Simoes RR, Da Costa PM, Liu W, Nordmann P. Environmental KPC-producing *Escherichia coli* isolates in Portugal. Antimicrob Agents Chemother. 2012; 56: 1662-1663.

39. Curiao T, Morosini MI, Ruiz-Garbajosa P, Robustillo A, Baquero F, Coque TM, et al. Emergence of *bla*KPC-3-Tn4401a associated with a pKPN3/4-like plasmid within ST384 and ST388 *Klebsiella pneumoniae* clones in Spain. J Antimicrob Chemother. 2010; 65: 1608-1614.

40. Bakour S, Sahli F, Touati A, Rolain JM. Emergence of KPC-producing *Klebsiella pneumoniae* ST512 isolated from cerebrospinal fluid of a child in Algeria. New Microbes and New Infections. 2015; 3: 34-36.

41. Metwally L, Gomaa N, Attallah M, Kamel N. High prevalence of *Klebsiella pneumoniae* carbapenemase-mediated resistance in *K. pneumoniae* isolates from Egypt. East Mediterr Heal J. 2013; 19: 947-952.

42. Adrian J Brink, Jennifer Coetzee, Cornelis G Clay, Sindi Sithole, Guy A Richards, Laurent Poirel, et al. Emergence of New Delhi metallo-b-lactamase (NDM-1) and Klebsiella pneumoniae carbapenemase (KPC-2) in South Africa. J ClinMicrobiol. 2012; 50: 525-527.

43. Mushi MF, Mshana SE, Imirzalioglu C, Bwanga F. Carbapenemase genes among multidrug resistant Gram negative clinical isolates from a tertiary hospital in Mwanza, Tanzania. Biomed Res Int. 2014; 2014: 303104.

44. Salvador E, Chaúque A, Irá T, Monteiro M. Potential Risk for Spread Multidrug Resistant Enterobacteriaceae through *Lactuca sativa* (Lettuce) and *Allium fistulosum L.* (Welsh onion) from Infulene Valley, Maputo City, Mozambique. J Appl Environ Microbiol. 2016; 4: 21-24.

45. Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. Lancet Infect Dis. 2009; 9: 228-236.

46. Endimiani A, Carias LL, Hujer AM, Bethel CR, Hujer KM, Perez F, et al. Presence of plasmid-mediated quinolone resistance in *Klebsiella pneumoniae* isolates possessing *bla*KPC in the United States. Antimicrob Agents Chemother. 2008; 52: 2680-2682.

47. Zagorianou A, Sianou E, Iosifidis E, Dimou V, Protonotariou E, Miyakis S, et al. Microbiological and molecular characteristics of carbapenemase-producing *Klebsiella pneumoniae* endemic in a tertiary Greek hospital during 2004-2010. Euro Surveill. 2012; 17.

48. Hu YY, Cai JC, Zhang R, Zhou HW, Sun Q, Chen GX. Emergence of *Proteus mirabilis* harboring *bla*KPC-2 and qnrD in a Chinese Hospital. Antimicrob Agents Chemother. 2012; 56: 2278-2282.

49. Pereira RS, Dias VC, Ferreira-Machado AB, Resende JA, Bastos AN, Andrade Bastos LQ, et al. Physiological and molecular characteristics of carbapenem resistance in *Klebsiella pneumoniae* and *Enterobacter aerogenes*. J InfectDevCtries. 2016; 10: 592-599.

50. Andrea Endimiani, Gopi Patel, Kristine M. Hujer, Mahesh Swaminathan, Federico Perez, Louis B. Rice, et al. In vitro activity of fosfomycin against *bla*KPC-containing *Klebsiella pneumoniae* isolates, including those nonsusceptible to tigecycline and/or colistin. Antimicrob Agents Chemother. 2010; 54: 526-529.

51. Cai Y, Fan Y, Wang R, An MM, Liang BB. Synergistic effects of aminoglycosides and fosfomycin on *Pseudomonas aeruginosa* in vitro and biofilm infections in a rat model. J Antimicrob Chemother. 2009; 64: 563-566.

52. Zavascki AP, Goldani LZ, Li J, Nation RL. Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. J Antimicrob Chemother. 2007; 60: 1206-1215.

53. Bratu S, Tolaney P, Karumudi U, Quale J, Mooty M, Nichani S, et al. Carbapenemase-producing *Klebsiella pneumoniae* in Brooklyn, N.Y.: molecular epidemiology and in vitro activity of polymyxin B and other agents. J Antimicrob Chemother. 2005; 56: 128-132.

54. Borer A, Eskira S, Nativ R, Saidel-Odes L, Riesenberg K, Livshiz-Riven I, et al. A multifaceted intervention strategy for eradication of a hospital-wide outbreak caused by carbapenem-resistant *Klebsiella pneumoniae* in Southern Israel. Infect Control Hosp Epidemiol. 2011; 32: 1158-1165.

55. Ciobotaro P, Oved M, Nadir E, Bardenstein R, Zimhony O. An effective intervention to limit the spread of an epidemic carbapenem-resistant *Klebsiella pneumoniae* strain in an acute care setting: from theory to practice. Am J Infect Control. 2011; 39: 671-677.

56. Kochar S, Sheard T, Sharma R, Hui A, Tolentino E, Allen G, et al. Success of an infection control program to reduce the spread of carbapenem-resistant Klebsiella pneumoniae. Infect Control Hosp Epidemiol. 2009; 30: 447-452.

57. Landman D, Babu E, Shah N, Kelly P, Olawole O, Bäcker M, et al. Transmission of carbapenem-resistant pathogens in New York City hospitals: progress and frustration. J AntimicrobChemother. 2012; 67: 1427-1431.

58. Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother. 2011; 55: 3284-3294.

Cite this article

Pereira RS, Daniel JB (2016) KPC-Producing Klebsiella pneumoniae Strains: A Threat to our Therapeutic Arsenal. Ann Clin Pathol 4(8): 1097.