

Management of infections due to KPC-producing *Klebsiella pneumoniae*

Stanley C Deresinski^{1,2*} and Patricia Schirmer^{1,3}

Addresses: ¹Division of Infectious Disease and Geographic Medicine, Department of Medicine, Stanford University, 300 Pasteur Drive, Stanford, CA 94305-5107, USA; ²2900 Whipple Avenue, Suite 115, Redwood City, CA 94062, USA; ³Department of Veterans Affairs, 3801 Miranda Ave (132), Palo Alto, CA 94304, USA

* Corresponding author: Stanley C Deresinski (polishmd@stanford.edu)

F1000 Medicine Reports 2009, 1:79 (doi:10.3410/M1-79)

This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<http://creativecommons.org/licenses/by-nc/3.0/legalcode>), which permits unrestricted use, distribution, and reproduction in any medium, for non-commercial purposes provided the original work is properly cited. You may not use this work for commercial purposes.

The electronic version of this article is the complete one and can be found at: <http://F1000.com/Reports/Medicine/content/1/79>

Abstract

The emergence of the *Klebsiella pneumoniae* carbapenemases in *K. pneumoniae* and other Gram-negative bacteria, usually on a background of multidrug resistance, has led to difficult therapeutic choices. Among available antibiotics, tigecycline and the polymyxins are the most frequently active against these organisms *in vitro*. Optimal therapy of infections due to these bacteria may involve maximization of antibiotic dose as well as their use in combination.

Introduction and context

A novel class A serine carbapenemase detected in North Carolina in 1996 was given the designation KPC-1 because it was first identified in *Klebsiella pneumoniae* [1]. Since then, a number of variants of this enzyme (currently up to KPC-8) have been identified and have spread globally [2]. The mobile nature of the genetic element encoding KPC, *Tn4401*, which is carried on a plasmid, has contributed to the spread of this enzyme, which has now been identified in many of the Enterobacteriaceae as well as in *Pseudomonas* and *Salmonella* [2]. Strain dissemination, however, appears to be of greater importance than plasmid dissemination as evidenced by the fact that almost 70% of strains in a US Centers for Disease Control and Prevention collection are of a single lineage, sequence type (ST) 258 [3].

KPCs hydrolyze all β -lactam antibiotics and are not significantly inhibited by clavulanic acid, sulbactam, or tazobactam [2]. Detection of KPCs in the clinical laboratory may be difficult and many bacteria producing this enzyme appear to be susceptible to anti-pseudomonal carbapenems by routine testing [4]. Resistance to ertapenem may be a more sensitive (albeit less specific) indicator of the possible presence of KPC than resistance to other carbapenems. Because of the insensitivity of current

breakpoints in detecting the presence of KPC, it is suggested that isolates of *K. pneumoniae* with a minimal inhibitory concentration (MIC) of at least 1 $\mu\text{g}/\text{mL}$ to imipenem, meropenem, or doripenem undergo further testing designed to detect the presence of carbapenemases, including KPC [4-6]. The importance of detection resistance in these organisms is evidenced by the fact that the use of imipenem or meropenem in patients with infections due to KPC-producing *K. pneumoniae* that appear to be susceptible to these carbapenems is associated with frequent therapeutic failure [7].

KPCs are often accompanied by additional β -lactamases within individual isolates [4]. A survey of 42 KPC-producing *K. pneumoniae* isolates in the Eastern US found that each isolate carried a mean of 3.5 β -lactamases [4]; one KPC-producing *K. pneumoniae* isolate has been reported to contain seven extended spectrum β -lactamases [8]. *K. pneumoniae* isolates producing both KPC-2 and VIM-1 enzymes (the latter of which are class B metallo-carbapenemases) have been detected in Greece [9].

Recent advances

KPC-producing bacteria are often resistant to a broad range of antibiotics beyond the β -lactams. In fact, the

plasmids that carry the KPC gene may also contain genes encoding aminoglycoside-modifying enzymes and some have also been reported to encode QnrA and QnrB, resulting in reduced susceptibility to fluoroquinolones [4,10]. An evaluation of 104 carbapenemase-producing Enterobacteriaceae, 70% of which produced KPC-2 or KPC-3, found that the most active agent tested was tigecycline, to which all isolates were susceptible [11]. Among antibiotics other than β -lactams that were tested, tigecycline was followed (in decreasing order of susceptibility) by polymyxin B (88% susceptible), amikacin (73.0%), gentamicin (50.0%), tetracycline (35.6%), and ciprofloxacin (32.1%). A similar evaluation of 96 carbapenemase-resistant *K. pneumoniae* from 10 Brooklyn hospitals (82% of a single ribotype) also found that all were susceptible to tigecycline [12]. Ninety-one percent were considered susceptible to polymyxin B, 66% to doxycycline, 61% to gentamicin, 45% to amikacin, and 2-7% to chloramphenicol, rifampin, tobramycin, and ciprofloxacin. Time-kill studies found that tigecycline was bacteriostatic whereas gentamicin and polymyxin B were bactericidal. Killing by polymyxin B was concentration-dependent.

Most published experience of treatment of infection due to KPC-producing organisms is with tigecycline, a polymyxin (polymyxin B or colistin), or their combination, with variable reported outcomes. Monotherapy, however, may be associated with persistent infection and the emergence of antibiotic resistance. Recurrence of an empyema due to a KPC-producing *K. pneumoniae* during treatment with tigecycline was associated with an increase in MIC from 0.75 to 2.0 $\mu\text{g}/\text{mL}$ [13]. Elemam and colleagues [14] recently reported two patients with infections due to *K. pneumoniae* isolates resistant to all antibiotics tested, including tigecycline and polymyxin B, with both isolates having developed progressive increases in the MIC to polymyxin B during treatment with this antibiotic. Similarly, of 16 patients with infection due to carbapenemase-resistant *K. pneumoniae* carrying a KPC gene who had persistently positive cultures, 12 were treated with polymyxin B alone whereas 4 received this polypeptide antibiotic in combination with tigecycline for at least a portion of their therapy [15]. Blood cultures, though initially positive in only 12, subsequently yielded the organism in all 16. Marked increases in the polymyxin B MIC were observed in 3 of the 12 given that antibiotic alone and in 0 of 4 who also received tigecycline. The development of resistance during therapy may be due to the presence of heteroresistant subpopulations, a phenomenon observed with colistin (polymyxin E) in 15 of 16 multidrug-resistant *K. pneumoniae* isolates considered susceptible to colistin by MIC testing, a result consistent

with the very high mutant prevention concentration/MIC ratios observed [16]. Although polymyxin B causes concentration-dependent killing, this is accompanied by rapid regrowth of resistant subpopulations with little or no postantibiotic effect [16], consistent with the clinical observation of treatment-emergent resistance. It should be noted that resistance has also been reported to emerge in *Acinetobacter* during treatment with tigecycline [17].

This problem may require optimization of dosage regimens to overcome some of these characteristics of polymyxins, combination therapy, or both. Very limited published clinical experience suggests that combination therapy may prove to be more successful than polymyxin monotherapy. Neither antagonism nor synergy was detected with the combination of tigecycline and polymyxin B tested against three isolates of *K. pneumoniae in vitro* [18]. In one series, only 1 of 3 patients with bacteremia due to a KPC-2-producing *K. pneumoniae* had a favorable outcome after treatment with polymyxin B, whereas another patient, treated with a combination of tetracycline and an aminoglycoside, survived [19]. As indicated above, resistance to polymyxin B occurred in 0 of 4 patients given this antibiotic in combination with tigecycline, whereas resistance occurred in 3 of 12 given polymyxin B monotherapy [15]. Other combinations, such as those including an active aminoglycoside, may also have promise: a patient with endocarditis due to KPC-3-producing *K. pneumoniae* was successfully treated with a combination of colistin and gentamicin [20]. Another agent for consideration in combination therapy is rifampin; polymyxin B and rifampin were synergistic *in vitro* against 15 of 16 isolates of carbapenemase-resistant *K. pneumoniae* [12].

Implications for clinical practice

The optimal therapy for infections due to these multi-drug-resistant pathogens is not well defined and depends upon the susceptibilities of individual isolates, and the choices are often severely limited. The most frequently active antibiotics *in vitro* are tigecycline and colistin (or polymyxin B) and these may often be the only choices based on susceptibility test results. The pharmacodynamics of the polymyxins remain poorly defined, and optimal dosing regimens have not yet been determined [21]. It is possible that doses higher than those currently approved by the US Food and Drug Administration may provide improved therapeutic results. Concerns about toxicity of the polymyxins (which may have previously been overestimated) have limited the attempts at significantly increasing the dose of these agents. In cases of ventilator-associated

pneumonia, consideration could be given to adjunctive administration of colistin by aerosolization [22].

The currently approved dose of tigecycline results in low serum and urine concentrations, raising concern about the efficacy of this agent in the treatment of bacteremia and urinary tract infections as well as about the emergence of resistance [17]. Inadequate tissue concentrations may have accounted for the failure of tigecycline relative to comparator therapy in the treatment of patients with ventilator-associated pneumonia due to a variety of organisms [23]. Cunha [24] has reported administering tigecycline in a 400 mg loading dose followed by 200 mg every 24 hours – a dose four times higher than currently approved – without eliciting nausea or vomiting, frequent adverse reactions seen with standard dosing regimens. However, he provides little specific information in regard to the use of these doses.

Although higher doses of tigecycline or a polymyxin may be beneficial, lack of knowledge in regard to tolerability and safety may limit their current acceptance by clinicians. Combination therapy of serious infections due to KPC-producing organisms would, however, appear to be warranted. The combination to be used depends on the antibiotic susceptibilities of the isolated pathogen but most often would be tigecycline with a polymyxin, perhaps at escalated dosages. Limited *in vitro* data suggest that co-administration of rifampin may have a role in such cases. Repeated cultures during therapy should be performed with monitoring for emergence of resistance.

The future of therapy for infections caused by multidrug-resistant aerobic Gram-negative bacilli appears bleak as a result of the paucity of development of new drugs targeting these organisms [25]. One potential exception is the development of β -lactamase inhibitors active against carbapenemases, such as NX104, a potent inhibitor of KPC-2 [26]. It can be hoped that the attitude of the pharmaceutical industry toward antibiotic development will soon change and that additional candidates will be developed.

Abbreviations

KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimal inhibitory concentration; ST, sequence type.

Competing interests

SCD has served on the advisory panel and/or speaker's bureau of Pfizer Incorporated (New York, NY, USA), Johnson & Johnson (New Brunswick, NJ, USA), Merck & Co, Incorporated (Whitehouse Station, NJ, USA), and Wyeth (Madison, NJ, USA).

References

1. Yigit H, Queenan AM, Anderson GJ, Domenech-Sanchez A, Biddle JW, Steward CD, Alberti S, Bush K, Tenover FC: **Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae***. *Antimicrob Agents Chemother* 2001, **45**:1151-61.
 2. Nordmann P, Cuzon G, Naas T: **The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria**. *Lancet Infect Dis* 2009, **9**:228-36.
 3. Kitchel B, Rasheed JK, Patel JB, Srinivasan A, Navon-Venezia S, Carmeli Y, Brolund A, Giske CG: **Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* isolates in the United States: clonal expansion of multilocus sequence type 258**. *Antimicrob Agents Chemother* 2009, **53**:3365-70.
 4. Endimiani A, Hujer AM, Perez F, Bethel CR, Hujer KM, Kroeger J, Oethinger M, Paterson DL, Adams MD, Jacobs MR, Diekema DJ, Hall GS, Jenkins SG, Rice LB, Tenover FC, Bonomo RA: **Characterization of blaKPC-containing *Klebsiella pneumoniae* isolates detected in different institutions in the Eastern USA**. *J Antimicrob Chemother* 2009, **63**:427-37.
 5. Queenan M, Bush K: **Carbapenemases: the versatile β -lactamases**. *Clin Microbiol Rev* 2007, **20**:440-58.
 6. Clinical and Laboratory Standards Institute: *M100-S19: Performance Standards for Antimicrobial Susceptibility Testing; 19th Informational Supplement*. Wayne, PA, USA: Clinical and Laboratory Standards Institute; 2009.
 7. Weisenberg SA, Morgan DJ, Espinal-Witter R, Larone DH: **Clinical outcomes of patients with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* after treatment with imipenem or meropenem**. *Diagn Microbiol Infect Dis* 2009, **64**:233-5.
 8. Moland ES, Hong SG, Thomson KS, Larone DH, Hanson ND: ***Klebsiella pneumoniae* isolate producing at least eight different β -lactamases, including AmpC and KPC β -lactamases**. *Antimicrob Agents Chemother* 2007, **51**:800-1.
 9. Giakkoupi P, Pappa O, Polemis M, Vatopoulos AC, Miriagou V, Zioga A, Papagiannitsis CC, Tzouveleki LS: **Emerging *Klebsiella pneumoniae* isolates co-producing KPC-2 and VIM-1 carbapenemases**. *Antimicrob Agents Chemother* 2009, **53**:4048-50.
- F1000 Factor 6.0 Must Read
Evaluated by Karen Bush 29 Sep 2009
10. Chmelnitsky I, Naven-Venezia S, Strahilevitz J, Carmeli Y: **Plasmid-mediated qnrB2 and carbapenemase gene bla(KPC-2) carried on the same plasmid in carbapenem-resistant ciprofloxacin-susceptible *Enterobacter cloacae* isolates**. *Antimicrob Agents Chemother* 2008, **52**:2962-5.
 11. Castanheira M, Sader HS, Deshpande LM, Fritsche TR, Jones RN: **Antimicrobial activities of tigecycline and other broad-spectrum antimicrobials tested against serine carbapenemase- and metallo-beta-lactamase-producing Enterobacteriaceae: report from the SENTRY Antimicrobial Surveillance Program**. *Antimicrob Agents Chemother* 2008, **52**:570-3.
 12. Bratu S, Tolaney P, Karumudi U, Quale J, Mooty M, Nichani S, Landman D: **Carbapenemase-producing *Klebsiella pneumoniae* in Brooklyn, NY: molecular epidemiology and *in vitro* activity of polymyxin B and other agents**. *J Antimicrob Chemother* 2005, **56**:128-32.
- F1000 Factor 6.0 Must Read
Evaluated by Kenneth Thomson 27 Jun 2006
13. Daly MW, Riddle DJ, Lebedoe NA, Dunne WM, Ritchie DJ: **Tigecycline for treatment of pneumonia and empyema caused by carbapenemase-producing *Klebsiella pneumoniae***. *Pharmacotherapy* 2007, **27**:1052-7.
 14. Elemam A, Rahimian J, Mandell W: **Infection with panresistant *Klebsiella pneumoniae*: a report of 2 cases and a brief review of the literature**. *Clin Infect Dis* 2009, **49**:271-4.
 15. Lee J, Patel G, Huprikar S, Calfee DP, Jenkins SG: **Decreased susceptibility to polymyxin B during treatment for**

- carbapenem-resistant *Klebsiella pneumoniae* infection.** *J Clin Microbiol* 2009, **47**:1611-2.
16. Poudyal A, Howden BP, Bell JM, Gao W, Owen RJ, Turnidge JD, Nation RL, Li J: **In vitro pharmacodynamics of colistin against multidrug-resistant *Klebsiella pneumoniae*.** *J Antimicrob Chemother* 2008, **62**:1311-815.
 17. Anthony KB, Fishman NO, Linkin DR, Gasink LB, Edelstein PH, Lautenbach E: **Clinical and microbiological outcomes of serious infections with multidrug resistant gram-negative organisms treated with tigecycline.** *Clin Infect Dis* 2008, **46**:567-70.
 18. Petersen PJ, Labthavikul P, Jones CH, Bradford PA: **In vitro antibacterial activities of tigecycline in combination with other antimicrobial agents determined by checkerboard and time-kill kinetic analysis.** *Antimicrob Agents Chemother* 2006, **57**:573-6.
 19. Nadkarni AS, Schliep T, Khan L, Zeana CB: **Cluster of bloodstream infections caused by KPC-2 carbapenemase-producing *Klebsiella pneumoniae* in Manhattan.** *Am J Infect Control* 2009, **37**:121-6.
 20. Benenson S, Navon-Venezia S, Carmeli Y, Adler A, Strahilevitz J, Moses AE, Block C: **Carbapenem-resistant *Klebsiella pneumoniae* endocarditis in a young adult. Successful treatment with gentamicin and colistin.** *Int J Infect Dis* 2009, **13**:e295-8.
 21. Landamn D, Georgescu C, Martin DA, Quale J: **Polymyxins revisited.** *Clin Microbiol Rev* 2008, **21**:449-65.
 22. Michalopoulos A, Fotakis D, Virtzili S, Vletsas C, Raftopoulou S, Mastora Z, Falagas ME: **Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: a prospective study.** *Respir Med* 2008, **102**:407-12.
 23. **Tygacil® (Tigecycline) for injection.** [http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021821s0161bl.pdf].
 24. Cunha B: **Pharmacokinetic considerations regarding tigecycline for multidrug-resistant (MDR) *Klebsiella pneumoniae* or MDR *Acinetobacter baumannii* urosepsis.** *J Clin Microbiol* 2009, **47**:1613.
 25. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J: **Bad bugs, no drugs: no ESCAPE! An update from the Infectious Diseases Society of America.** *Clin Infect Dis* 2009, **48**:1-12.
 26. Stachyra T, Levasseur P, Pêchereau MC, Girard AM, Claudon M, Miossec C, Black MT: **In vitro activity of the {beta}-lactamase inhibitor NXLI04 against KPC-2 carbapenemase and Enterobacteriaceae expressing KPC carbapenemases.** *J Antimicrob Chemother* 2009, **64**:326-9.