Journal of Infectious Diseases and Therapy
ISSN: 2332-0877

Odio, et al., J Infect Dis Ther 2015, 3:1
DOI: 10.4172/2332-0877.1000200

Short Communication Open Access

Carbapenem-Resistant Klebsiella Pneumoniae Osteomyelitis and Soft Tissue Infections: A Descriptive Case Series

Camila D Odio[1], David van Duin[2], Eric Cober[2,3], Lucileia Teixeira-Johnson[2,3], Steven Schmitt[2,3] and Jorgelina de Sanctis[4*]

[1]*Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Cleveland Clinic Foundation, Cleveland, OH, USA*

[2]*Division of Infectious Diseases, UNC School of Medicine, Chapel Hill, NC, USA*
[3]*Department of Infectious Diseases, Cleveland Clinic Foundation, Cleveland, OH, USA*

[4]*Division of Infectious Disease, Spectrum Health Medical Group, Grand Rapids, MI, USA*

[*]**Corresponding author**: Jorgelina De Sanctis, MD, Department of Infectious Diseases, Spectrum Health, 230 Michigan Ave, NE, Grand Rapids, MI 49503, USA, Tel: 616-633-1433, Fax: 616-391 8665; E-mail: Jorgelina.deSanctis@spectrumhealth.org

Rec date: Nov 26, 2014; **Acc date:** Dec 16, 2014; **Pub date:** Jan 07, 2015

Abstract

Antimicrobial therapies for Carbapenem-resistant Klebsiella pneumoniae (CR-KP) infections are limited. We examine the presentation of and response to therapy in CR-KP osteomyelitis and soft tissue infections. Tigecycline monotherapy cured mild infections; the addition of amikacin and colistimethate did not increase survival in dire cases. The 45% mortality rate underscores the gravity of these infections.

Keywords: Carbapenem-resistant *Klebsiella pneumoniae*; *Klebsiella pneumoniae* carbapenemase; Carbapenem-resistant enterobacteriaceae; Osteomyelitis; Soft tissue infection

Abbreviations

CR-KP: Carbapenem-resistant Klebsiella pneumoniae; STIs: soft tissue infections; DOI: duration of illness; LOS: Length of hospital Stay; WBC: White Blood Cell count; CRP: C-Reactive Protein; MRSA: Methicillin-resistant Staphylococcus aureus; VRE: Vancomycin-Resistant Enterococci

Short Communication

Carbapenem-resistant Klebsiella pneumoniae (CR-KP) are multi-drug resistant organisms that cause infections associated with dire morbidity and mortality. These microbes produce enzymes that degrade carbapenems, a treatment of last resort for other infections. CR-KP infections are commonly treated with tigecycline and colistimethate, with an estimated 70% response rate [1,2]. Because colistimethate and tigecycline have low bone distribution [2,3] and only four CR-KP osteomyelitis cases have been reported [4-6], we describe an additional four cases. Moreover, we report 14 CR-KP soft tissue infections (STIs) and compare therapeutic responses to those observed in animal studies [7]. Our experience may inform therapeutic approaches and outcomes.

This IRB approved study was conducted at a 1400 bed academic medical center and consisted of a retrospective review of all adult patients with CR-KP positive clinical specimens of bone or soft tissue from March 2006-January 2011. CR-KP positive was defined as *K. pneumoniae* isolates with MIC ≥ 2 mcg/mL against ertapenem, meropenem, or imipenem and a positive modified Hodge test (CLSI 2009).

Osteomyelitis was defined by CR-KP positive isolates from bone biopsies. Samples to identify soft tissue infections were collected from soft tissue wounds that had no X-ray and/or clinical evidence of osteomyelitis including no exposed bone or positive probe to bone test. Soft tissue infections were defined as positive CR-KP isolates from these samples coupled with positive clinical findings including edema, erythema, and/or purulent drainage from the wound as well as fever and/or leukocytosis. CR-KP colonization was defined as positive skin and/or soft tissue isolates from dry wounds with no edema, erythema, pain, leukocytosis or fever. Sepsis was defined by a clinical and/or expiratory note describing sepsis in the patient. Other evidence of sepsis included two or more positive blood cultures, fever of greater than 100.4 F, and WBC >12,000 or <4,000. The primary outcome examined was overall survival, and secondary outcomes included days to mortality or treatment cessation, length of hospital stay (LOS) related to CR-KP infection, and antibiotic regimens. The antibiotic side effects examined were a positive *C. difficile* culture with diarrhea and nephrotoxicity as noted by the initiation of dialysis therapy and/or by a change in antibiotic regimen secondary to decreasing renal function. Comorbidity scores were calculated using the Charlson Comorbidity Index [8].

Between 2006 and 2011, four bone and fourteen soft tissue CR-KP infections occurred at our hospital, and the all cause mortality was 50% and 43% respectively. Although the classical definition of attributable mortality is less than 30 days post infection, several non-survivors, who exceeded this time period, are retained to illustrate infection progression.

Patients with osteomyelitis had a median age of 69 (67–74) years, spent a median of 24 (7–43) days in the hospital, and had a median of 41 (32–204) days until mortality or treatment cessation (Table 1). Median peak WBC count and CRP were 12.88 (10.31–25.31) K/μL and 12.8 (2.7–19.6) mg/dL respectively. Three of the four osteomyelitis patients had polymicrobial infections, and the two non-survivors were treated with debridement and antibiotics while the two survivors were treated with amputation and antibiotics. One patient had nephrotoxicity and *C. difficile* infection secondary to antibiotic use. Osteomyelitis patients had a median Charlson comorbidity score of 7 (4.75–7.75), and non-survivors had slightly more comorbidities. Both of the patients that died had intermediate resistance to at least 1/3 of

the antimicrobials used and developed sepsis secondary to underlying decubitus ulcers.

Among patients with soft tissue infections (STIs), survivors and non-survivors had similar ages, comorbidity scores, and rates of immune suppression (Table 2). However, longer hospital stays, higher peak WBC and CRP, and a higher incidence of polymicrobial infections (83% vs. 63%) and sepsis (67% vs. 13%) suggest more severe infections in non-survivors. Three of the sepsis cases (one survivor and two non-survivors) were caused by CR-KP and two were caused by unidentified organisms. Co-infecting organisms in the soft tissue included P.aeruginosa (33% vs. 0%, non-survivors vs. survivors), methicillin resistant S. aureus (17% vs. 0%), and vancomycin resistant enterococci (17% vs. 13%). In both groups, the majority of patients were treated with debridement and antibiotics, followed by treatment with amputation and antibiotics, and treatment with antibiotics alone. The three patients treated with amputation and antibiotics had stumps infected with CR-KP. In all three cases, the stumps were revised because of worsening necrosis of the incision wounds and concern for osteomyelitis. However, these were considered soft tissue infections because pre-surgical imaging did not suggest osteomyelitis in any of the cases, and bone cultures, performed in only one case, were negative.

	Patient 1	Patient 2	Patient 3	Patient 4
Survivor	No	No	Yes	Yes
Demographics				
Gender	M	M	F	M
Race	White	White	Black	White
Age, years	68	75	70	67
Location of Infection	Pressure ulcer	Pressure ulcer	Diabetic wound	Diabetic wound
Source of isolate	Sacral bone	Sacral tissue and MRI showed evidence of sacral OM	Metatarsal bone	Bone from TMA site
MIC				
Tigecycline	2 S	4 I	N/A	0.25 S
Amikacin	32 I	16 S	16 S	16 S
Colistimethate	N/A	N/A	N/A	8 U
Polymicrobial infection	Yes	Yes	Yes	No
Co-infecting organisms	*C. freundii, E. faecalis, E. coli, P. vulgaris*	VRE	*C. koseri*	None
Sepsis	Yes–organism not identified	Yes- coagulase negative staphylococcus	No	No
Infection characteristics				
Hospital LOS, days	8	40	6	44
Days to mortality or treatment cessation	257	39	34	49
Peak WBC count (K/μL)	10.01	28.9	11.21	14.55
Peak CRP (mg/dL)	9.7	19.6	12.8	N/A
Comorbidities	Diabetes mellitus, chronic kidney disease, organ transplant	Diabetes mellitus, chronic kidney disease, CHF	Diabetes mellitus, CAD, CHF	Diabetes mellitus, chronic kidney disease, CAD
Charlson comorbidity score	7	8	4	7
Course of action	Debridement and antibiotics	Debridement and antibiotics	Amputation and antibiotics	Amputation and antibiotics
Antibiotic therapy	Imipenem, ciprofloxacin	Tigecycline, colistimethate, amikacin	Tigecycline	Tigecycline and colistimethatea,b

Abbreviations: CAD, coronary artery disease; CHF: Congestive Heart Failure; I: Intermediate susceptibility; LOS, Length of Stay; MIC: Minimum Inhibitory Concentration; N/A, not available; OM: osteomyelitis; S: Susceptible; TMA: Transmetatarsal Amputation; U: Unknown susceptibility

[a]Patient had *C. difficile* infection

[b]Patient had acute, antibiotic induced nephrotoxicity

Table 1: Characterization of patients with osteomyelitis

	Soft tissue non-survivors (n=6)	Soft tissue survivors (n=8)
Demographics		
Gender, Female	4 (67)	4 (50)
Race, Caucasian	3 (60)	3 (38)
Age, years, median (IQR)	58 (47 - 74)	58 (48.5–66.5)
Location of Infection, n (%)		
Post-operation wound	2 (33)	5 (63)
Pressure ulcer	2 (33)	2 (25)
Diabetic wound	0 (0)	1 (13)
Miscellaneous[*]	2 (33)	0 (0)
Polymicrobial, n (%)	5 (83)	5 (63)
Developed sepsis, n (%)	4 (67)	1 (13)
Infection characteristics, median (IQR)		
Hospital LOS, days	18 (11–59)	9.5 (4.5–22)
Days to final outcome	18 (12–130)	27 (12–78)
Peak WBC count (K/μL)	17.47	11.1 (7.91–16.49)
	(12.88–32.01)	
Peak CRP (mg/dL)	24.8, n=1	3.1 (1.15–4.75), n = 4
Comorbidities, n (%)		
Diabetes mellitus	4 (67)	6 (75)
Chronic kidney disease	3 (50)	6 (75)
CAD	4 (67)	4 (50)
CHF	1 (17)	4 (50)
Organ transplant	2 (33)	2 (25)
Other immune suppression	1 (17)	0 (0)
Charlson comorbidity score, median (IQR)	6.5 (2.75–7.5)	5 (3.25–6)
Course of action, n (%)		
Amputation+antibiotics	2 (33)	1 (13)
Debridement+antibiotics	3 (50)	6 (75)
Antibiotics alone	1 (17)	1 (13)
MIC, median (IQR; n)		
Tigecycline	1.5 (0.63–6.5; 4)	1 (0.5–1.5; 5)
Colistimethate	5 (2–8; 2)	5 (2 – 8.75; 4)
Amikacin	16 (12.5–28; 6)	16 (13–64; 6)
Antibiotic therapy, n (%)		
Monotherapy		
Tigecycline	1 (17)[a]	4 (50)
Colistimethate	1 (17)	1 (13)
Dual therapy		
Tigecycline and:		
Gentamicin	0 (0)	2 (25)
Amikacin	1 (17)	0 (0)
Meropenem	0 (0)	1 (13)
Triple therapy		
Tigecycline, colistimethate, amikacin	3 (50)[b]	0 (0)

Abbreviations: LOS: Length of Stay; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure;

[a]*C. difficile* infection in one patient of the cohort.

[b]Acute, antibiotic induced nephrotoxicity in one patient of the cohort.

[*]Miscellaneous location of infection: One patient had a superficial left shin abrasion of unknown origin that developed CR-KP infection. The second patient developed a sudden onset erythematous lesion in the left middle thigh and perineum in the setting of neutropenia that became infected with CR-KP.

Table 2: Characterization of patients with soft tissue infections

Tigecycline mono or dual therapy was used in 100% of survivors and 50% of non-survivors. Tigecycline, colistimethate, and amikacin triple therapy was utilized in half of the non-survivors and none of the survivors. The organisms affecting survivors and non-survivors did not differ in their sensitivities to tigecycline, colistimethate, and amikacin. Seven percent of STI patients experienced *C. difficile* infection or nephrotoxicity secondary to antibiotic use.

The overall 45% mortality rate underscores the gravity of these infections and is consistent with previous reports [9]. Although a previous study reported 22% mortality in CR-KP patients with sepsis [10], 100% of the osteomyelitis patients and 80% of the STI patients with sepsis died. This high mortality may be due to the diminished general health of our patients. Notably, both of the osteomyelitis and 33% of the STI non-survivors developed CR-KP secondary to pressure ulcers, which are common in debilitated individuals. Further, the two osteomyelitis non-survivors were treated with debridement and antibiotics, while the two survivors were treated with amputation and antibiotics. Although this is a small sample size, our findings support aggressive treatment CR-KP osteomyelitis, and we recommend serious consideration of surgical management (amputation) in these cases.

Among patients with soft tissue infections, non-survivors had longer hospital stays, higher peak WBC and CRP counts, and increased rates of polymicrobial infections and sepsis. These clinical

findings may be more consistent with patient outcomes than comorbidity scores. Further, non-survivors were more likely to have co-infections with P.aeruginosa, MRSA, and/or VRE, suggesting that co-infecting virulent and/or drug resistant organisms may exacerbate disease. It should be noted that two patients had CR-KP positive isolates from dry wounds with no other symptoms of infection. These patients were not treated with antibiotics or any other therapy and were not included in this analysis as they were considered cases of colonization rather than infection. The possibility of CR-KP colonization should be considered in dry, non-symptomatic wounds.

Two osteomyelitis and eleven STI patients were treated with tigecycline mono or dual therapy, and there was 100% and 73% survival among these patients respectively. This is consistent with an animal study that found tigecycline was a highly effective monotherapy against CR-KP [7] as well as case studies that have reported the successful use of tigecycline in CR-KP osteomyelitis [5] and STIs [11]. However, meta-analyses have reported increased mortality in patients treated with tigecycline [12]. Our success with tigecycline mono and dual therapy may be related to its effective anti – CR-KP activity and milder infections among survivors.

All of the patients treated with tigecycline, colistimethate, amikacin triple therapy died (one osteomyelitis and three STI patients). This high mortality may be associated with more severe disease in these patients. However, tigecycline and colistimethate were somewhat antagonistic in a murine thigh model of CR-KP [7], and amikacin may be less active in bone because of the acidic environment of synovial fluid [13]. Moreover, a case series of CR-KP prosthetic joint infections reported the emergence of colistimethate and amikacin resistance on therapy, suggesting that these may not be the best choice for severe CR-KP infections [14].

Because there is no optimal treatment for CR-KP infections, a number of therapeutic combinations are reported here. We found that tigecycline monotherapy and dual therapy was associated with survival in cases of mild to moderate infection, consistent with animal studies and case reports. However, tigecycline, amikacin, and colistimethate triple therapy was not efficacious in more severe CR-KP osteomyelitis and STIs. Our observations are limited by the small number of occurrences and the retrospective nature of the data, and the choice of antibiotics tended to follow the severity of illness. However, the high mortality highlights the need for novel antibiotics.

Competing Interests

CO, EC, LTJ, SS, and JS do not have any potential, perceived, or real conflict of interest. DVD is a consultant for Sanofi and has received research funds from Steris. More remotely, he has served on DSMB for Pfizer and on the speaker's bureau for Astellas.

Authors Contribution

All authors made substantial contributions to the acquisition of data. CO and JD worked together on data gathering and drafting the manuscript. All authors read and approved the final manuscript prior to publication.

Acknowledgment

A summary of this work was presented as a poster at ID Week, San Francisco, California, October 2-5, 2013. This work was not supported by funding.

References

1. Hirsch EB, Tam VH (2010) Detection and treatment options for Klebsiella pneumoniae carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. J Antimicrob Chemother 65: 1119-1125.
2. Michalopoulos AS, Falagas ME (2011) Colistin: recent data on pharmacodynamics properties and clinical efficacy in critically ill patients. Ann Intensive Care 1: 30.
3. Ji AJ, Saunders JP, Amorusi P, Wadgaonkar ND, O'Leary K, et al. (2008) A sensitive human bone assay for quantitation of tigecycline using LC/MS/MS. J Pharm Biomed Anal 48: 866-875.
4. Babouee B, Widmer AF, Dubuis O, Ciardo D, Droz S, et al. (2011) Emergence of four cases of KPC-2 and KPC-3-carrying Klebsiella pneumoniae introduced to Switzerland, 2009-10. Euro Surveill 16.
5. Chen P-L, Yan J-J, Wu C-J, Lee H-C, Chang C-M, et al. (2010) Salvage therapy with tigecycline for recurrent infection caused by ertapenem-resistant extended-spectrum ß-lactamase-producing Klebsiella pneumoniae. Diagn Microbiol Infect Dis, 68: 312–314.
6. Schelenz S, Bramham K, Goldsmith D (2007) Septic arthritis due to extended spectrum beta lactamase producing Klebsiella pneumoniae. Joint Bone Spine 74: 275-278.
7. Michail G, Labrou M, Pitiriga V, Manousaka S, Sakellaridis N, et al. (2013) Activity of Tigecycline in combination with Colistin, Meropenem, Rifampin, or Gentamicin against KPC-producing Enterobacteriaceae in a murine thigh infection model. Antimicrob Agents Chemother 57: 6028-6033.
8. Hall WH, Ramachandran R, Narayan S, Jani AB, Vijayakumar S (2004) An electronic application for rapidly calculating Charlson comorbidity score. BMC Cancer 4: 94.
9. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, et al. (2013) Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect Dis 13: 785-796.
10. Corcione S, Cardellino CS, Calcagno A, Fossati L, Costa C, Cavallo R, Perri GD, Rosa FGD: Healthcare-Associated Klebsiella pneumoniae carbapenemase Producing K. pneumoniae Bloodstream Infection: The Time Has Come. Clin Infect Dis 2014:ciu294.
11. Du X, Fu Y, Yu Y (2013) Tigecycline treatment of infection caused by KPC-producing Escherichia coli in a pediatric patient. Ann Clin Microbiol Antimicrob 12: 19.
12. Prasad P, Sun J, Danner RL, Natanson C (2012) Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis 54: 1699-1709.
13. Darley ES, MacGowan AP (2004) Antibiotic treatment of gram-positive bone and joint infections. J Antimicrob Chemother 53: 928-935.
14. De Sanctis J, Teixeira L, van Duin D, Odio C, Hall G, et al. (2014) Complex prosthetic joint infections due to carbapenemase-producing Klebsiella pneumoniae: a unique challenge in the era of untreatable infections. Int J Infect Dis 25:73–78.