



Successful treatment of hypervirulent *Klebsiella pneumoniae* bacteremia with combination carbapenem and rifampicin



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ABSTRACT

Hypervirulent *Klebsiella pneumoniae* (hvKP) with a high mucus phenotype, can cause liver abscess and extrahepatic invasive infection. The morbidity of hvKP infections has increased recently. Here we describe a case report of septicemia caused by hvKP due to the term septic arthritis of right knee joint in a 29-year-old male. The patient was persistent fever with a peak temperature at 40.6 °C. However, based on the drug sensitivity, the treatment failed frequently. The patient did not improve clinically on susceptible monotherapy antimicrobial. Combination therapy with meropenem and rifampicin (RFP) lead to clinical improvement and discharge.

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Case report

A 29-year-old male with previous history of right knee fracture was admitted to our intensive care unit because of persistent fever for 2 weeks as well as swelling and pain of right knee joint for 10 days. Two weeks before admission, the patient developed fever with chills after being drenched in the rain. After taking 999® cold particles (antipyretic and analgesic; for headache and fever caused by cold) orally, the patient felt a drop in body temperature, although specific temperature was unknown. About ten days before hospitalization, the patient developed swelling and pain of right knee joint, accompanied by shortness of breath and fatigue after physical activity. The patient complained of oliguria and having frothy and foul-smelling urine.

When the patient was initially admitted to the department of Rheumatology and Immunology (day 1), his vital signs were as follows: hypothermia 37 °C, heart rate 100 beats/min, respiratory rate 20 breaths/min and blood pressure 138/80 mmHg. Laboratory test results upon admission were indicative of infection (Table 1). An ultrasound color doppler showed cavity effusion and synovial thickening in right knee joint, and thoracic CT showed pneumonia

and hepatic cyst in S7 segment (Fig. 1A). An empiric antibiotic therapy (intravenous (IV) piperacillin/tazobactam) was started right after collecting blood cultures. On the second day, cavity effusion sample of right knee joint was obtained through puncture for culture. The results about cavity effusion sample showed that color of cavity effusion was yellow, and white blood count (WBC)(+++/HP), red blood count (RBC)(1–3/HP) and transparency (turbidity) were positive. On day 3, the patient was still persistent fever (with a peak temperature at 39.5 °C) after the original treatment. Considering little clinical improvement, the treatment was upgraded to carbapenems(biapienem). At the same time, empiric gram positive coverage was added with IV vancomycin for pneumonia. On day 5, Blood culture was positive for *Klebsiella pneumoniae*, and microbiology laboratory tests (the string test in Fig. 1B) for hvKP turned out to be positive [1–3]. However, right knee effusion culture was negative. The antibiotic sensitivity testing (Table 2) showed the strain was sensitive to levofloxacin, cefotaxime, piperacillin/tazobactam and carbapenems, etc. The results of drug sensitivity were consistent with those reported in relevant literature. For example, Patel et al. and Chi-Tai Fang et al. reported that antimicrobial susceptibility patterns of hvKP remains largely pan-sensitive for now, usually only resistant to ampicillin [4,5]. We kept the same empiric coverage. Afterwards, the antifungal drugs (voriconazole 0.4 g q12h) was also combined because of urine culture *Candida albicans*, but the patient was still persistent fever with a peak temperature at 40.6 °C during two weeks. Meanwhile, inflammatory markers were still elevated. Hence, we changed the antimicrobial therapy to meropenem (2 g q8h) combined with RFP (0.6 g q12h), and both of vancomycin and voriconazole were discontinued. The patient

Abbreviations: hvKP, hypervirulent *Klebsiella pneumoniae*; RFP, Rifampicin; Hs-CRP, hypersensitive C-reactive protein; CK, creatine kinase; CK-MB, MB isoenzyme of creatine kinase; GLU, glucose in the blood; rmpA, regulator of mucoid phenotype A; magA, mucus related gene A; BSIs, bloodstream infections; KPLA, *Klebsiella pneumoniae* liver abscess

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Table 1
Clinical laboratory findings.

Biochemical indexes	Reference range	Upon admission	Without RFP	With RFP
White cell count ($\times 10^9/L$)	4.00–10.00	13.5	23.84	9.5
Neutrophil (%)	50–70	85.9	94.2	76.3
Hemoglobin (g/L)	120–160	129	117	97
Platelet count ($\times 10^9/L$)	100–300	316	441	399
Hs-CRP (mg/L)	0–3	177.07	103.23	49.19
Procalcitonin (ng/ml)	0–0.5	0.919	2.33	<0.08
Alanine aminotransferase (U/L)	9–50	19.95	48	19
Albumin (g/L)	35–55	30.4	33.5	30.1
Total bilirubin ($\mu\text{mol/L}$)	5.1–17.2	9.1	13.8	11.6
GLU (mmol/L)	3.6–6.1	15.37	10.33	5.62
CK (U/L)	25–200	55.59	73.03	41.16
CK-MB (U/L)	1.00–25.00	8.9	14.3	26.6
Creatinine ($\mu\text{mol/L}$)	44–133	39	293.03	47

Notes: Hs-CRP = hypersensitive C-reactive protein; CK = creatine kinase; CK-MB = MB isoenzyme of creatine kinase; GLU = glucose in the blood; Without RFP = the results after 2 weeks treatment; With RFP = the results after 3 days with Meropenem and RFP combinations treatment.

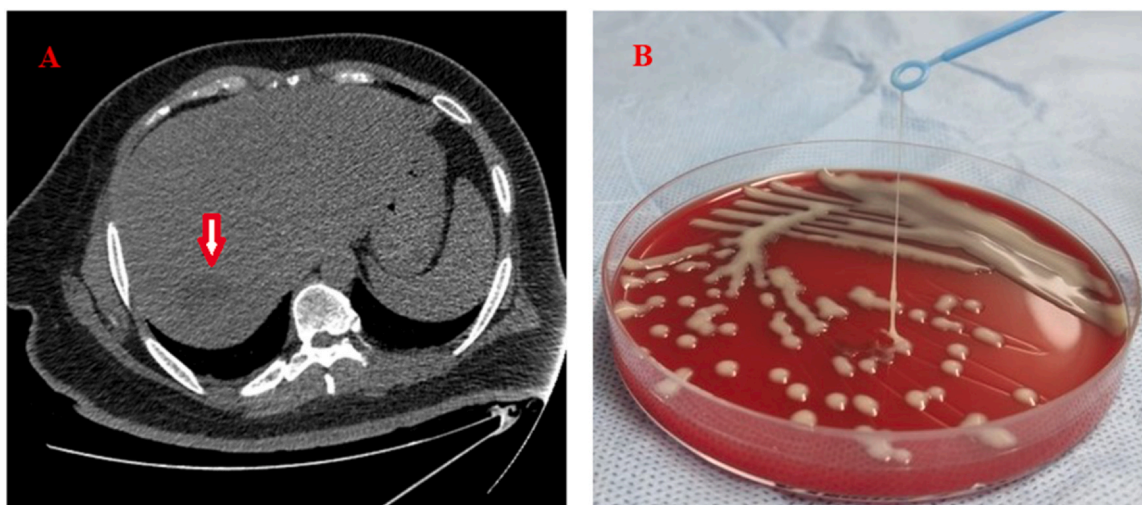


Fig. 1. (A) Thoracic CT scan showed hepatic cyst in S7 segment; (B) The string test prompted hypermucoviscosity phenotype.

Table 2
The drug sensitivity for *Klebsiella pneumoniae* from blood culture.

Antibiotics	Sensitivity	MIC	Antibiotics	Sensitivity	MIC
Ceftazidime	S	≤ 1	Ciprofloxacin	S	≤ 0.5
Polymyxin	S	1	Cefotaxime	S	≤ 1
Cefazolin	S	≤ 4	Cefepime	S	≤ 2
Gentamicin	S	≤ 2	Imipenem	S	≤ 1
Levofloxacin	S	≤ 1	Meropenem	S	≤ 1
Piperacillin	S	8	Ampicillin/sulbactam	S	$\leq 4/2$
Compound Sulfanilamide	S	$\leq 0.5/9.5$	Tetracycline	S	≤ 2
Piperacillin/tazobactam	S	$\leq 4/4$	Ampicillin	R	> 16
Amoxicillin/clavulanic acid	S	$\leq 4/2$	Amikacin	S	≤ 8
Aztreonam	S	≤ 2	Cefoperazone/sulbactam	S	$\leq 4/4$

Notes: Results from Central People's Hospital of Zhanjiang. Report date: February 8, 2021 (day 4). MIC: minimum inhibitory concentration; R: resistant; S: sensitive.

improved clinically (Fig. 2) three days after changing the antimicrobials to meropenem and RFP. He became afebrile and was discharged after two weeks. During the treatment, meropenem combined with RFP was treated for 10 days.

Discussion

HvKP, which causes community-acquired liver abscess, was first reported in Taiwan in 1986 [6]. It can cause serious disseminated infections in young and healthy hosts [7–9], especially in the diabetic patients. Over the past few decades, because of its increasing emergence rate and its capacity to cause serious and metastatic infections, hvKP has gradually attracted scientists' attention

worldwide. The detection rate of hvKP in China is the highest, reaching over 80%, whilst it is less than 10% in other regions such as United States, Britain, Spain and Canada [6,10,11]. The prevalence of hvKP infection ranges from 8.33% to 73.9% in China [7]. The main associated infection of hvKP is liver abscess combined with multiple invasive infections, namely invasive *Klebsiella pneumoniae* liver abscess syndrome. Hiroki Namikawa et al. reported that the independent predictors of hvKP bacteremia were abscess and no antibiotic exposure. Therefore, early assessment of these factors is important. For patients with a history of abscess but no antibiotic exposure, it is necessary to apply anti-infection in which anti-hvKP methods should be considered [12]. Compared with *Klebsiella pneumoniae*, mortality of infection by hvKP is much higher, which is

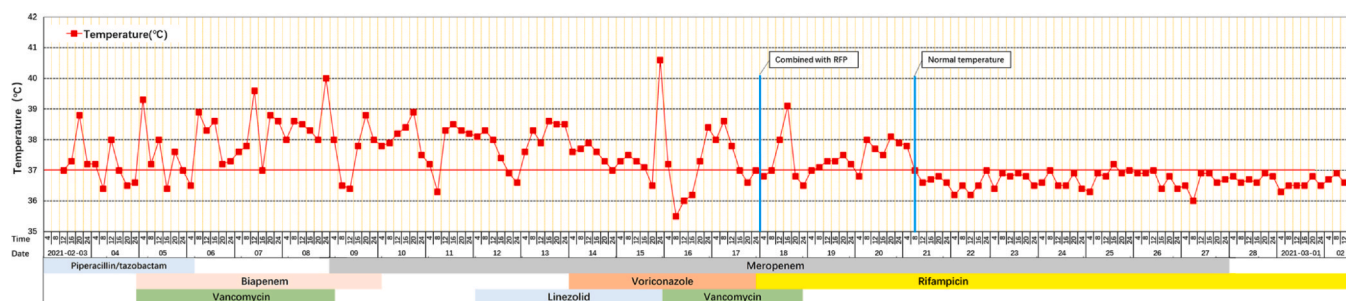


Fig. 2. Body temperature and antibiotic therapy use during hospitalization. Body temperature: measured every 4 h; Antibiotic use: Piperacillin/tazobactam 4.5 g q8h (day 1–4), Biapenem 0.3 g q6h (day 4–7) and vancomycin 1 g q12h (day 4–6 and day 14–17), Meropenem 2 g q8h (day 7–25), Linezolid 0.6 g q12h (day 10–14), Voriconazole 0.4 g q12h (day 12–14), Rifampicin 0.6 g q12h (day 16–27).

up to 29.2% [12]. Among hvKP infection, 30-day mortality for hvKP-induced bloodstream infections even reached 37.1% [13]. Diabetes mellitus is an independent risk factor not only for hvKP induced bloodstream infections (hvKP-BSIs) [13], but also for *Klebsiella pneumoniae* liver abscess (KPLA). In the present case, the young patient was persistent fever (with a peak temperature at 40.6 °C) with chills and the laboratory examination revealed high blood glucose concentration (15.37 mmol/L on admission) which might be a risk factor. Tian et al. reported that hyperglycemia in diabetic patients can inhibit the chemotaxis and adhesion of leukocytes, which damaged the function of intestinal barrier so intestinal flora are displaced, and promoted the formation of liver abscess [14]. Further, hyperglycemia can lead to change in the structure and function of vascular intima, *Klebsiella pneumoniae* can be transported to the blood and cause liver abscess. These pathophysiologic changes can lead to poor efficacy of conventional anti-infective therapy. As is known, capsular polysaccharide, which was mediated in part by regulator of mucoid phenotype A (*rmpA*) gene and/or mucus related gene A (*magA*), not only increases the virulence but also protects the strain against human defense activities [4]. As it is reported in relevant literature, capsular polysaccharide is the most important virulence factor of hvKP, which is related to the migration, adhesion and proliferation of hvKP in the host [15]. Compared with *Klebsiella pneumoniae*, hvKP is able to produce more capsular polysaccharide. This could explain why the treatment was not effective in the case. Yi-Hsiang Cheng et al. identified alterations in the *rmpA* as a mechanism of in-vivo tigecycline resistance development in a hvKP strain [16]. And Hiroki Namikawa et al. reported that RFP, which inhibits not only transcription of the *rmpA* gene but also capsular polysaccharide biosynthesis to reduce capsular thickness, may serve as potential anti-virulence agent for hvKP infection. Besides, RFP exerts strong mucoviscosity-suppressing activity against hvKP [17]. The above characteristics possibly enabled RFP to fight against hvKP effectively and potentially benefited our patient. This could possibly explain why the treatment was not effective prior to the combination therapy with RFP.

In summary, we present a case of 29-year-old male with hyperglycemia with hypervirulent *Klebsiella pneumoniae* bacteremia, pneumonia and septic knee arthritis. Initially, the patient did not improve clinically on susceptible monotherapy antimicrobial. Combination therapy with meropenem and RFP lead to clinical improvement and discharge. This case report provides foundation and reference for RFP combination treatment for hvKP infection, but identifies the lack of studies on sequence identification, typing and drug resistance mechanism.

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Ethics approval

Not applicable.

Consent for publication

Written and signed consent for publication from the patient was acquired prior to the submission.

Authors' contributions

Yong-Chun Lin, Xi Cao and Yun-Chao Mo oversaw the therapeutic decisions during the patient's treatment. Xi Cao and Yong-Chun Lin drafted and wrote the manuscript. Yun-Chao Mo and Cai-Peng Xie critically revised the manuscript. Yong-Fang Zhang, Na Li and Hua-Ling Chen processed the data and plotting. All authors read and approved the final manuscript.

CRediT authorship contribution statement

Yong-Chun Lin: Conceptualization, Methodology, Writing – original draft. **Xi Cao:** Conceptualization, Methodology, Software, Writing – review & editing, Visualization. **Yun-Chao Mo:** Conceptualization, Writing – original draft. **Cai-Peng Xie:** Formal analysis, Writing – review & editing. **Yong-Fang Zhang:** Data curation. **Na Li:** Data curation. **Hua-Ling Chen:** Data curation.

Conflicts of interest

None of the authors reported any conflict of interests regarding this manuscript.

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References

- [1] Sun B, Singhal S, Winslow DL. Suppurative lymphadenitis caused by hypermucoid variant *Klebsiella* in a Polynesian woman: a case report. *Diagn Microbiol Infect Dis* 2020;98(4):115166.
- [2] Fang CT, Chuang YP, Shun CT, Chang SC, Wang JT. A novel virulence gene in *Klebsiella pneumoniae* strains causing primary liver abscess and septic metastatic complications. *J Exp Med* 2004;199(5):697–705.
- [3] Gunnarsson GL, Brandt PB, Gad D, Struve C, Justesen US. Monomicrobial necrotizing fasciitis in a white male caused by hypermucoviscous *Klebsiella pneumoniae*. *J Med Microbiol* 2009;58(11):1519–21.
- [4] Patel PK, Russo TA, Karchmer AW. Hypervirulent *Klebsiella pneumoniae*. *Open Forum Infect Dis* 2014;1(1):1–3.
- [5] Fang CT, Lai SY, Yi WC, Hsueh PR, Liu KL, Chang SC. *Klebsiella pneumoniae* genotype K1: an emerging pathogen that causes septic ocular or central nervous system complications from pyogenic liver abscess. *Clin Infect Dis* 2007;45(3):284–93.

- [6] Siu LK, Yeh KM, Lin JC, Fung CP, Chang FY. Klebsiella pneumoniae liver abscess: a new invasive syndrome. *Lancet Infect Dis* 2012;12(11):881–7.
- [7] Zhang Y, Zhao C, Wang Q, Wang X, Chen H, Li H, et al. High prevalence of hypervirulent Klebsiella pneumoniae infection in China: geographic distribution, clinical characteristics, and antimicrobial resistance. *Antimicrob Agents Chemother* 2016;60(10):6115–20.
- [8] Lee CR, Lee JH, Park KS, Jeon JH, Kim YB, Cha CJ, et al. Antimicrobial resistance of hypervirulent Klebsiella pneumoniae: epidemiology, hypervirulence-associated determinants, and resistance mechanisms. *Front Cell Infect Microbiol* 2017;7:1–13.
- [9] Chang L, Bastian I, Warner M. Survey of Klebsiella pneumoniae bacteraemia in two South Australian hospitals and detection of hypermucoviscous phenotype and magA/rmpA genotypes in K. pneumoniae isolates. *Infection* 2013;41(2):559–63.
- [10] Yu F, Lv J, Niu S, Du H, Tang YW, Pitout J, et al. Multiplex PCR analysis for rapid detection of Klebsiella pneumoniae carbapenem-resistant (Sequence Type 258 [ST258] and ST11) and hypervirulent (ST23, ST65, ST86, and ST375) Strains. *J Clin Microbiol* 2018;56(9). JCM.00731-18.
- [11] Russo TA, Olson R, Fang CT, Stoesser N, Miller M, MacDonald U, et al. Identification of biomarkers for differentiation of hypervirulent Klebsiella pneumoniae from classical K. pneumoniae. *J Clin Microbiol* 2018;56(9). JCM.00776-18.
- [12] Namikawa H, Yamada K, Sakiyama A, Imoto W, Yamairi K, Shibata W, et al. Clinical characteristics of bacteremia caused by hypermucoviscous Klebsiella pneumoniae at a tertiary hospital. *Diagn Microbiol Infect Dis* 2019;95(1):84–8.
- [13] Li J, Ren J, Wang W, Wang G, Gu G, Wu X, et al. Risk factors and clinical outcomes of hypervirulent Klebsiella pneumoniae induced bloodstream infections. *Eur J Clin Microbiol Infect Dis* 2018;37(4):679–89.
- [14] Tian LT, Yao K, Zhang XY, Zhang ZD, Liang YJ, Yin DL, et al. Liver abscesses in adult patients with and without diabetes mellitus: an analysis of the clinical characteristics, features of the causative pathogens, outcomes and predictors of fatality: a report based on a large population, retrospective study in China. *Clin Microbiol Infect* 2012;18(9):E314–30.
- [15] Choby JE, Howard-Anderson J, Weiss DS. Hypervirulent Klebsiella pneumoniae – clinical and molecular perspectives. *J Intern Med* 2020;287(3):283–300.
- [16] Cheng YH, Huang TW, Juan CH, Chou SH, Tseng YY, Chen TW, et al. Tigecycline-non-susceptible hypervirulent Klebsiella pneumoniae strains in Taiwan. *J Antimicrob Chemother* 2019;75(2):309–17.
- [17] Namikawa H, Oinuma KI, Sakiyama A, Tsubouchi T, Tahara YO, Yamada K, et al. Discovery of anti-mucoviscous activity of rifampicin and its potential as a candidate antivirulence agent against hypervirulent Klebsiella pneumoniae. *Int J Antimicrob Agents* 2019;54(2):167–75.