CASE REPORT

High-dose tigecycline and colistin for successful treatment of disseminated carbapenem-resistant *Klebsiella pneumoniae* infection in a liver transplant recipient

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SUMMARY

Solid organ transplantation (SOT) is a risk factor for the acquisition of carbapenem-resistant *Klebsiella pneumoniae*. This infection is associated with a high mortality rate given the limited armamentarium of antibiotics for multidrug-resistant organisms along with continued immunosuppression to prevent graft rejection. We report a case of carbapenem-resistant *K. pneumoniae* pneumonia, bacteraemia and intra-abdominal infection in a newly transplanted liver recipient. The patient was successfully treated with a long course of high-dose tigecycline and colistin, along with surgical drainage. We discuss SOT-relevant epidemiology, therapeutic options and the rationale for our treatment choice.

BACKGROUND

Klebsiella pneumoniae carbapenemases are β -lactamases produced by Gram-negative bacteria that hydrolyse penicillins, cephalosporins, monobactams, carbapenems and β -lactamase inhibitors. The increasing prevalence of these organisms has become a worldwide problem with pockets of endemicity reported in the northeastern USA, Latin America, Italy, Greece, Poland and China. In a recent report from the Centers for Disease Control, there are an estimated 9300 infections annually due to carbapenem-resistant Enterobacteriaceae, 85% of which are due to *K. pneumoniae*.¹ Infections from carbapenem-resistant *K. pneumoniae* (CR Kp) are associated with more intensive and invasive care, as well as crude mortality rates ranging from 40% to 72%.^{2–3} Treatment options are limited to tigecycline and polymyxins (either as monotherapy or in combination) along with potential additional use of carbapenems, aminoglycosides and other agents.

We report a case of disseminated CR Kp infection during the postoperative course of a new orthotopic liver transplant recipient successfully treated with a combination of high-dose tigecycline and colistin.

CASE PRESENTATION

A 47-year-old man with end-stage liver disease secondary to alcoholic cirrhosis had undergone liver transplantation in October 2012. His physiological Model for End-Stage Liver Disease (MELD) score was 17 at the time of transplant (Child class C,

Child Pugh Score of 10). His medical history was significant for hepatopulmonary syndrome requiring 3–6 L of home oxygen for the past 1.5 years with a room air PO₂ of 40 mm Hg, and splenectomy at age 9 secondary to trauma. The patient was hospitalised earlier in the year for a pan-sensitive *K. pneumoniae* peritonitis and bacteraemia. There was no pertinent social or family history.

The patient was in his usual state of health when he presented for transplant surgery. The surgery was complicated by dense vascularised adhesions from his prior splenectomy requiring extensive dissection and cauterisation of large raw surface areas. He received 12 units of packed red blood cells (PRBCs), 12 units of fresh frozen plasma (FFP), 2 units of cryoprecipitate and 2 units of platelets during surgery. The postoperative course was complicated by coagulopathy, initial graft dysfunction with peak serum aminotransferase on postoperative day 1 of 1700 IU/mL, and hypotension requiring blood products and vasopressors. The patient required two further operations due to bleeding from the diaphragm. These surgeries occurred 12 and 24 h following the initial transplant surgery. At the third surgery, an incidental hard 1 cm lesion was noted close to the ligament of Treitz for which he had undergone a 3 cm jejunal resection with end-to-end anastomosis (pathology revealed vessel dilated by thrombus). He required multiple blood products during the time period following the initial surgery: 22 units PRBCs, 6 units FFP, 22 units cryoprecipitate and 7 units of platelets. Table 1 delineates a timeline for the clinical course of the patient.

The patient received perioperative ampicillin-sulbactam for each surgery; this was continued for 24 h after the third surgery. He was continued on immunosuppression consisting of methylprednisolone (tapered to prednisone), mycophenolate mofetil and tacrolimus. He was also started on prophylactic trimethoprim-sulfamethoxazole, valganciclovir and fluconazole (later changed to micafungin).

Forty-eight hours after the third laparotomy, the patient developed a right middle and lower lobe infiltrate on chest X-ray (figure 1A) accompanied by a leukocytosis (white cell count, WCC, 18.5×10^3 cells/mL) and bandemia of 14%. He was empirically started on vancomycin and piperacillin-

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Table 1 Sequence of events and relevant cultures during the case patient's clinical course following orthotopic liver transplantation

Procedure	Postoperative day after transplant	Culture	Minimum inhibitory concentration
Liver Transplant	Day 0	–	–
Exploratory laparotomy for bleeding	Day 1	–	–
Exploratory laparotomy for bleeding; jejunal resection	Day 1	–	–
Pneumonia	Day 3	Tracheal aspirate: CR Kp	Tigecycline: 2 µg/mL Colistin: 2.5 µg/mL
Surgical site infection and bacteraemia	Day 8	Blood: CR Kp Abdominal wound culture: CR Kp	Tigecycline: 2 µg/mL Colistin: 0.6 µg/mL (susceptibilities not done)
Percutaneous drainage of abdominal abscess	Day 9	Abscess fluid: CR Kp	Hodge test for KPC was positive. Susceptibilities for tigecycline/colistin not done
Surgical drainage and washout of abdominal abscesses/peritonitis	Day 29	Peritoneal fluid: CR Kp	Tigecycline: 2 µg/mL Colistin: 10 µg/mL
Hospital discharge	Day 38		
Readmission for failure to thrive	Day 40–47		
Readmission for fall	Day 48–60		

Susceptibility testing was conducted via E-test for tigecycline and agar dilution for colistin. CR Kp, carbapenem-resistant *Klebsiella pneumoniae*; KPC, *K. pneumoniae* carbapenemases.

tazobactam while awaiting culture results. The piperacillin-tazobactam was broadened to meropenem 2 days later as the WCC increased to 31×10^3 cells/mL and his tracheal aspirate culture grew *K. pneumoniae*. Susceptibilities returned the following day and revealed resistance to aminoglycosides, cephalosporins, quinolones and carbapenems. At this time, we discontinued the vancomycin and meropenem, and started the patient on high-dose tigecycline 100 mg every 12 h and colistin loading dose of 350 mg (5 mg/kg ideal body weight) followed by 90 mg every 12 h (2.5 mg/kg daily) and requested susceptibilities to these two drugs. As shown in table 1, the CR Kp isolate had a tigecycline minimum inhibitory concentration (MIC) of 2 µg/mL via E-test and the colistin MIC was 2.5 µg/mL via agar dilution.

Two days after initiating tigecycline and colistin (8 days after liver transplantation), purulent drainage was noted from the abdominal incision. This was opened at bedside and sent for culture. The wound culture and concomitant blood culture grew CR Kp as well (same MIC to tigecycline as earlier but the colistin MIC was 0.6 µg/mL in the blood isolate). A CT scan revealed two loculated heterogeneously enhancing fluid collections located medial and lateral to the stomach, 9×5 cm and 8×4 cm, respectively (figure 1B). At this time, the patient remained afebrile, haemodynamically stable and had a minimal cough. He did not require further circulatory or ventilatory support.

The abdominal abscesses were drained percutaneously and abscess fluid culture grew the same organism. The colistin dose was increased to 180 mg every 12 h (5 mg/kg/day) and high-dose tigecycline was continued. He was transferred out of the intensive care unit (ICU) 13 days after liver transplantation. Blood cultures were negative at time of transfer and pneumonia had resolved.

Two weeks into therapy, the patient developed acute renal insufficiency thought to be secondary to colistin. Hence, the colistin dose was decreased to 3 mg/kg daily adjusted for creatinine clearance. Despite clinical improvement, the patient's WCC remained elevated (ranging from 24 to 32×10^3 cells/mL). Repeat abdominal imaging revealed re-accumulation of abdominal abscess fluid (figure 1C). He eventually returned to the operating room 29 days after liver transplantation for abdominal washout with murky peritoneal fluid growing CR Kp. Six days after abdominal washout, the tigecycline dose was lowered to 50 mg every 12 h due to recent development of nausea and emesis. Prior to this he had no nausea or vomiting with high-dose tigecycline.

The infection slowly resolved following definitive drainage surgery. The patient was discharged from the hospital 38 days after his liver transplantation to complete a 4-week course of colistin 75 mg every 12 h and tigecycline 50 mg every 12 h in a rehabilitative facility. However, the patient was readmitted

Figure 1 Radiographic imaging of carbapenem-resistant *Klebsiella pneumoniae* infected sites. (A) Initial chest X-ray and CT scan showing right-sided pneumonia. (B) CT of the abdomen and pelvis showing loculated intra-abdominal fluid collections, measuring 9×4 cm and 8×4 cm. (C) CT of the abdomen and pelvis showing peritoneal fluid collection, measuring 12.8 cm×4.9 cm.

2 days later with shortness of breath and worsening acute kidney injury (creatinine of 1.94 mg/dL at admission). Colistin was discontinued (as recent susceptibility results indicated that the isolate from the abdominal surgery was now resistant to colistin, MIC 10 µg/mL) and the patient was discharged 7 days later on tigecycline 50 mg twice daily to complete a 4-week course from the most recent abdominal surgery. In total, the patient received high-dose tigecycline for the first 30 days of the treatment course followed by de-escalation to 50 mg twice daily dose for the remaining 23 days.

OUTCOME AND FOLLOW-UP

We have now followed the case patient for 21 months following liver transplant. The patient has done well clinically with excellent liver function, normalisation of his pulmonary function and no signs of recurrent infection.

DISCUSSION

Solid organ transplantation (SOT) is a known risk factor for the acquisition of multidrug-resistant organisms, including CR Kp.⁴ This may be related to multiple courses of antibiotics in these patients, length of stay in the ICU, poor functional status and severity of underlying conditions.⁵ SOT recipients have high mortality rates from drug-resistant infections, especially when due to carbapenem resistance. In particular, liver transplant recipients with CR Kp infections have a reported mortality rate of 71–100%.^{6–7} Almost all of these infections occurred within the first month following liver transplant. A MELD score ≥ 30 and infection with CR Kp in the post-transplant period independently predicted mortality in these patients.⁶ Interestingly, there are few studies demonstrating a correlation with infection due to the encapsulated bacterium *K. pneumoniae* and prior splenectomy.

Treatment options for CR Kp infections include use of polymyxins, tigecycline and aminoglycosides, either as monotherapy or in combination. Use of inadequate initial antimicrobial therapy was associated with increased 30-day mortality in a study of 125 patients with CR Kp bacteraemia.⁸ In this study, the lowest mortality of 12.5% (2 patients died) was seen in a subgroup of 16 patients who were treated with a combination of tigecycline, colistin and meropenem. Appropriate antimicrobial therapy for at least 48 h was an independent predictor of survival in another study as well.⁹ Physical removal of a probable focus of infection, such as catheter removal, surgical drainage, etc, is independently associated with patient survival.^{9–10}

Owing to poor outcomes when liver transplant recipients with CR Kp infections are treated with conventionally dosed tigecycline (100 mg loading dose followed by 50 mg twice daily) either alone or in combination with polymyxin B, we chose to treat our patient with high-dose tigecycline combined with colistin.⁶ This is particularly relevant since the Food and Drug Authority (FDA) released a black box warning in 2010 for tigecycline due to increased all-cause mortality in patients receiving conventional dose tigecycline as seen in a meta-analysis of clinical trials.¹¹ The cause of death in these patients had not been established and may possibly be related to worsening infection. Since then, a recent clinical trial demonstrated higher cure rates in ventilator and hospital-acquired pneumonia when tigecycline 100 mg twice daily was used instead of the conventional 50 mg twice daily dose.¹² There is evidence that a combination of agents has better outcomes than monotherapy for CR Kp infections even when monotherapy is with an agent that has documented susceptibility for the isolate.^{8–9–13} The use of high-dose tigecycline was based on a

recent case report that demonstrated successful treatment of a CR Kp bloodstream infection with high-dose tigecycline combined with colistin and amikacin.¹⁴ We believe that use of an unconventional antimicrobial regimen in addition to surgical drainage of abdominal abscesses contributed to the successful outcome in this patient who had multiple abdominal surgeries, prolonged ICU stay, immunosuppression for liver transplant and a prior splenectomy, among other risk factors for poor outcome.

The tigecycline MIC remained at 2 µg/mL during the treatment course. This MIC is considered susceptible by the FDA criteria, though it is considered resistant according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, which considers isolates with MIC ≤ 1 µg/mL as susceptible. Given the relatively high MIC, use of high-dose tigecycline is expected to have contributed to a higher area under the curve (AUC) characteristic (though we did not specifically measure drug levels), which is especially important since AUC/MIC ratio is predictive of efficacy.

The CR Kp isolate developed colistin resistance while on treatment; even though the initial sputum isolate had an MIC of 2.5 µg/mL, a blood culture a few days later had an MIC of 0.6 µg/mL. The final isolate tested from the patient's last abdominal surgery had an MIC of 10 µg/mL. The FDA no longer lists colistin for routine susceptibility testing and thus breakpoints are not reported. EUCAST considers a colistin MIC >2 µg/mL for any Enterobacteriaceae as resistant. The patient had a relatively high colistin MIC based on the agar dilution method, which has been associated with more consistent susceptibility rates than the E-test. The FDA recommended dosage for colistin is 2.5–5 mg/kg/day divided into 2–4 doses based on normal renal function. Although colistin's bactericidal activity is concentration dependent, the optimal dose is unclear. A better indicator of antibiotic efficacy may be monitoring the ratio of maximum colistin plasma concentration to the MIC of the

Patient's perspective

I was diagnosed with end stage cirrhosis of the liver in 2012. Three weeks after being placed on a transplant list, I was selected to receive a donor liver. I was called at 22:00 and instructed to arrive at UCSD Hillcrest Medical Center at 5:00 the following morning. Three hours after arriving, I was prepped and taken into the operating room where a sizable surgical staff introduced themselves one at a time in a friendly, comforting manner. I was given an IV sedative and drifted off peacefully within minutes. I awoke in the ICU some 48 h later. As I became more and more alert, I experienced discomfort in my upper abdomen. A dull, generalized ache soon became a sharp pain specific to the area of my surgical incision. Also, the area felt unusually warm. My doctors informed me that my white count was elevated, possibly due to a post-op infection. I was sent back into surgery to remove infected fluid. A few days later, I was worked on again to lower the infection levels and several days later, I was taken into surgery for what I believe was called a "washout" procedure. Eventually, my pain and elevated white count subsided. I remained hospitalized at UCSD for roughly 6 weeks. In the 18 months following my liver transplant, I have stayed on my medication, abstained from alcohol and, aside from substantial weight gain, am in what appears to be full recovery.

organism.¹⁵ Our patient required frequent dose adjustment of the colistin secondary to worsening renal function. Additionally, there may have been inadequate penetration of colistin into the abdominal abscesses, thus increasing the risk of development of resistance.

In summary, this is an unusual case of a successful outcome of CR Kp pneumonia, bacteraemia, surgical site infection, abdominal abscess and peritonitis in a recipient of liver transplant. The use of high-dose tigecycline and colistin along with surgical drainage most likely contributed to the patient's positive outcome.

Learning points

- ▶ Solid organ transplant recipients have high mortality rates when infected by carbapenem-resistant *Klebsiella pneumoniae*.
- ▶ High-dose tigecycline along with a second agent may lead to better treatment outcomes when treating carbapenem-resistant *K. pneumoniae* infection in an immunosuppressed patient.
- ▶ Removal of the infection source, if possible, should be attempted for clinical cure.

Competing interests None.

Patient consent Obtained.

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