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Case Report

Multi-Drug-Resistant *Klebsiella pneumoniae* Pancreatitis: A New Challenge in a Serious Surgical Infection

Derin Tugal,[1,4] Melanie Lynch,[2] Andrea M. Hujer,[3,4] Susan Rudin,[3,4] Federico Perez,[3,4] and Robert A. Bonomo[3–6]

Abstract

Background: *Klebsiella pneumoniae* is an important cause of nosocomial infections, but its role in severe acute pancreatitis (SAP) is not well defined. Few cases of *K. pneumoniae* associated SAP have been reported. Due to the emergence of extended-spectrum beta-lactamases (ESBLs) and carbapenemases, treatment of multidrug-resistant (MDR) *K. pneumoniae* presents a challenge. Tigecycline and colistin have gained recent attention for their broad-spectrum antimicrobial activity.

Methods: We describe a case of SAP due to *K. pneumoniae* bearing *K. pneumoniae* carbapenemase (KPC) treated successfully with colistin plus tigecycline and offer a review of similar experiences published in the literature.

Results: The case reported herein required surgical drainage of multiple pancreatic abscesses and treatment with tigecycline and colistin. Our comparative analysis revealed a number of unique features associated with SAP due to *K. pneumoniae*: 1) underlying pancreatic injury, 2) multiple drug resistance determinants and virulence factors that complicate treatment, and 3) surgical debridement as a requirement for cure.

Conclusion: As the prevalence of *K. pneumoniae* bearing KPC continues to increase in the healthcare setting, SAP caused by this MDR pathogen will become more common. Tigecycline plus colistin was a successful antibiotic regimen for the treatment of SAP due to *K. pneumoniae* bearing KPC.

The emergence of antibiotic resistance in Enterobacteriaceae mediated by extended-spectrum β-lactamases (ESBLs), first recognized in the 1980s and more common after the 1990s, led to the establishment of carbapenems for the treatment of serious infections caused by these organisms. However, during the past decade, carbapenem resistance has emerged in Enterobacteriaceae. For instance, the retrospective analysis of approximately one-half million isolates from almost three hundred clinical laboratories throughout the United States revealed that the proportion of carbapenem-resistant *Klebsiella pneumoniae* increased from less than 0.1% in 2002 to 4.5% in 2010 [1]. *Klebsiella pneumoniae* carbapenemase (KPC) is the most common mechanism of carbapenem resistance in the United States, and clonally related strains carrying bla_{KPC} are identified throughout the world [2]. The evolution and spread of KPC is a worrisome harbinger of increased mortality and longer-duration and higher-cost hospitalizations, and underscores the exhaustion of our current antimicrobial armamentarium [3].

Necrotizing pancreatitis is complicated frequently with infection caused by gram-negative bacteria. However, KPC-producing *K. pneumoniae* infection has been associated only rarely with necrotizing pancreatitis [4,5]. Acute pancreatitis results in gland necrosis in 10–20% of patients and is associated with mortality rates of 10–25%. Secondary bacterial infection of necrotizing pancreatitis confers even higher mortality (40–70%), emphasizing the need for early effective antibiotic therapy and appropriate surgical debridement [6,7]. Although the benefit of antibiotic prophylaxis in necrotizing

[1]Department of Medicine, University Hospitals Case Medical Center, Cleveland, Ohio.
[2]General Surgery Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio.
[3]Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio.
[4]Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio.
[5]Department of Pharmacology, Case Western Reserve University School of Medicine, Cleveland, Ohio.
[6]Department of Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, Ohio.

pancreatitis is dubious, it remains common practice to implement empiric carbapenem therapy (imipenem-cilastatin or meropenem) until culture results are available from fine-needle aspiration biopsy or open debridement of the pancreas [8]. Regrettably, the emergence of multi-drug-resistant (MDR) organisms has become an impediment to effective empiric antibiotic therapy in this syndrome.

Here we describe a case of necrotizing pancreatitis infected with KPC-producing *K. pneumoniae* associated with failure of antibiotic therapy with imipenem-cilastatin. We compare it to other reported cases in the literature, and introduce the use of colistin and tigecycline as a useful tactic in patients with infected necrotizing pancreatitis who fail empiric antibiotic treatment due to the presence of MDR organisms.

Case Report

A 79-year-old Caucasian male with a history of coronary artery disease who had undergone four-vessel coronary artery bypass grafting, with a left ventricular ejection fraction of 60%, hypertension, moderate aortic stenosis, obstructive sleep apnea, and prostate cancer, presented to the hospital with abdominal pain. He was diagnosed with severe acute pancreatitis (SAP) secondary to gallstones and was managed with intravenous fluids and opiods for pain control. His early hospital course was complicated by respiratory distress requiring intensive care management, and ileus requiring nasogastrictube placement and total parenteral nutrition (TPN). On day 18 of hospitalization, he was transferred to a long-term acute care facility for rehabilitation while still on TPN. On day 40, he was readmitted for worsening abdominal pain and found to have leukocytosis (18,000 white blood cell count). Computed-tomography (CT) of the abdomen and pelvis revealed formation of two pancreatic pseudocysts in the mid-abdomen and inferior to the splenic flexure of the colon. Due to concern for infection, piperacillin-tazobactam was initiated. Leukocytosis initially improved to 12,000 white blood cell count; however, on day 51, the patient developed fever and tachycardia with worsening abdominal pain and leukocytosis to $29{,}000 \times 10^9$cells/L. A repeat CT of the abdomen (Fig. 1A) showed a 10×19 cm pancreatic pseudocyst and loculated fluid collections inferior to the splenic flexure (9.3×4.2 and 8×4.2 cm). The patient was transferred to the medical intensive care unit (MICU) where a central venous catheter was placed for aggressive fluid resuscitation; imipenem-cilastatin was started while piperacillin-tazobactam was discontinued. On day 52, he underwent CT-guided drainage of the pancreatic pseudocysts; cultures were sterile. He was stabilized and transferred to the medicine ward on day 57; due to persistence of the mid-abdominal pseudocyst, a retroperitoneal drain was left in place. On day 61, the patient again developed leukocytosis to $15{,}000 \times 10^9$cells/L, although transient; culture of a sample obtained on that day from the proximal aspect of the retroperitoneal drain grew *K. pneumoniae* resistant to all beta-lactams, including carbapenems, and to trimethoprim-sulfamethoxazole, fluoroquinolones, and amikacin. The isolate was only susceptible to tigecycline (minimum inhibitory concentration [MIC] = 2 mcg/mL), colistin (MIC = 2 mcg/mL), and gentamicin (MIC = 2 mcg/mL). No additional bacterial isolates were identified. Fever and leukocytosis recurred on day 68, and treatment was initiated with tigecycline (100 mg IV initially, then 50 mg IV q 12 h) and colistin (75 mg IV q 12 h); carbapenem-resistant *K. pneumoniae* was isolated again from samples of abdominal fluid obtained from the retroperitoneal drain and CT imaging demonstrated enlargement of the pancreatic pseudocyst with formation of gas bubbles (Fig. 1B). This prompted surgical debridement on day 70; behind the stomach, a collection of purulent fluid was drained revealing a necrotic mass (Fig. 2). Cultures obtained from surgical specimens also grew carbapenem-resistant *K. pneumoniae*. Polymerase chain reaction (PCR) detected the presence of bla_{KPC} in these MDR *K. pneumoniae* isolates, and DNA sequencing of the amplicon identified it further as $bla_{\text{KPC-3}}$.

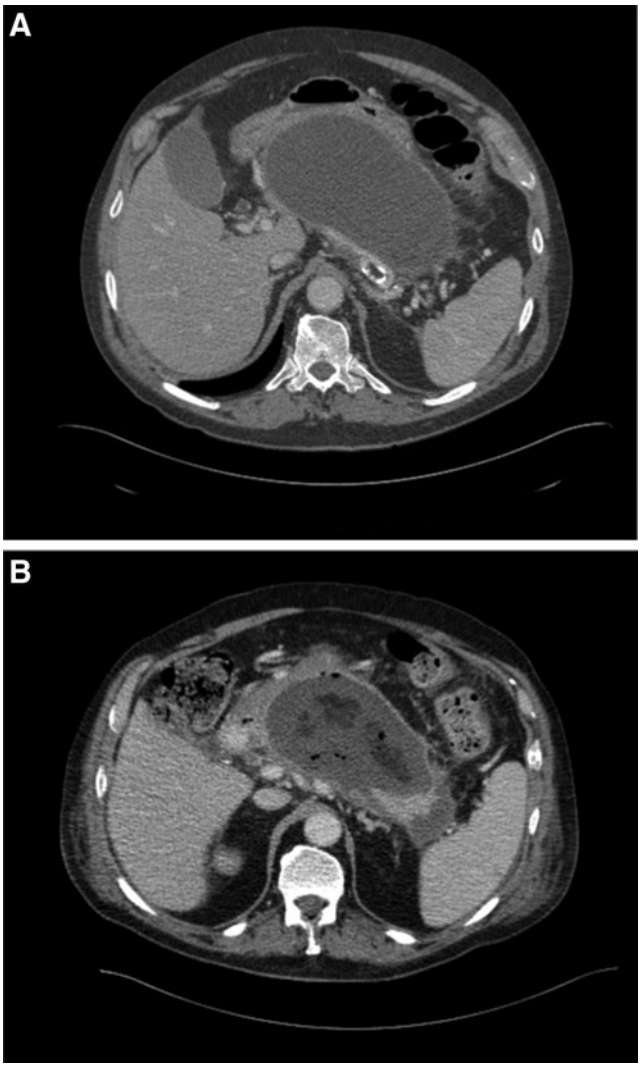

FIG. 1. **(A)** Computed tomography of abdomen on day 50 after presentation showing a large cystic lesion replacing most of the pancreas and measuring approximately 19×10 cm in diameter. **(B)** Computed tomography of abdomen obtained on day 69 revealing fluid collection with presence of gas bubbles, suggesting infection.

Discussion

The rate of infectious complications in SAP is 40–70% in the first three weeks of disease. Most cases are due to a bacterial species found frequently in the gastrointestinal

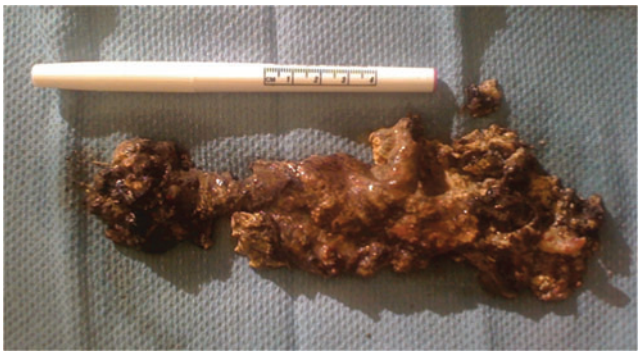

FIG. 2. Necrotic pancreas removed surgically from our patient on day 70. Color images available online at www.liebertpub.com/sur

tract including *Escherichia coli, Pseudomonas aeruginosa, Enterococcus* spp., and *Staphylococcus aureus* [9]. Bacterial infection is a late-stage complication of necrotizing pancreatitis that occurs generally after the second week of an acute episode, and is belived to be secondary to bacterial translocation from the small bowel and colon [6,7]. Infection of the necrotic pancreas with enteric organisms is the most common cause of death in patients with SAP. Mortality rates average 30% (range 14–62%), triple the rate of death in sterile SAP [8]. These complications are likely to increase further in patients infected with MDR bacteria, such as KPC-bearing *K. pneumoniae,* and in the presence of increasing age, mechanical ventilation, malignant disease, cardiac disease, and intensive care. Whereas the use of antimicrobial prophylaxis in SAP is debated, timely diagnosis of bacterial infection and identification of the infecting organism is necessary for targeted therapy [7]. Few reported cases of *K. pneumoniae*-infected pancreatitis are documented in the literature. We were prompted to perform a case review of the published literature to identify patients with *K. pneumoniae*-infected pancreatitis [5,10–12] (Table 1).

Review of these cases suggests that pancreatic injury contributes to infection with *K. pneumoniae*. One of the features of the observed cases of *K. pneumoniae* pancreatitis is the prolonged duration of illness; in this patient series we observed an illness lasting greater than two weeks. Patient 1 reported two months of abdominal pain before his presentation and diagnosis of *K. pneumoniae*-infected pancreatitis. Patients 2 and 4 were hospitalized with pancreatitis for two weeks and four months, respectively, before diagnosis of *K. pneumoniae*-infected pancreatitis. Our patient had been hospitalized for 61 days at the time that *K. pneumoniae* was isolated from a pancreatic pseudocyst. In addition to acute injury, chronic pancreatic injury contributes to bacterial infection. Our search revealed three patients who suffered from chronic alcoholism; two of these patients (patients 3 and 4) had a history of chronic pancreatitis, one of whom (patient 4) had radiographic evidence thereof. This suggests that loss of pancreatic parenchymal integrity facilitates infection with *K. pneumoniae,* consistent with previous observations of secondary bacterial infection of the necrotic pancreas.

All of these patients, including our patient (Fig. 1), demonstrated CT evidence of pancreatic mass(es), which drained purulent material on aspiration biopsy. The degree of necrosis correlates with the risk for bacterial infection; >50% necrosis of the pancreas is associated with an eight-fold increase in infection rate compared to less severe involvement [13]. The CT severity index created by Balthazar et al. combines the percentage of necrosis with a grade of its severity to predict mortality and morbidity; these scores are comparable to the Ranson criteria and the APACHE II score [7,14]. As expected, survival is best when the focus of infection is removed via catheter-guided drainage (in selected cases), or surgical debridement and open drainage. In the absence of drainage, the mortality of patients with infected pancreatic necrosis approaches 100% [13]. Before surgical drainage, empiric antibiotics are employed to treat the expected pathogen. Antimicrobial agents including carbapenems, fluoroquinolones, and nitroimidazoles are used often. Although their use for prophylaxis is not of benefit, empiric therapy is appropriate for patients who have a clinical picture of infection suggested by fever, leukocytosis, and hemodynamic instability [6].

Multi-drug resistant strains of *K. pneumoniae* often carry plasmids that confer resistance to multiple classes of antibiotics, including cephalosporins, aminoglycosides, tetracyclines and trimethoprim-sulfamethaxazole. Interestingly, independent of ESBL-containing plasmids, resistance to beta-lactam/beta-lactamase inhibitor combinations and extended-spectrum cephalosporins has also been described. Fluoroquinolone resistance is well established with a 10–20% overall prevalence, and 50% in ESBL-containing strains [15]. Whereas carbapenems have been the agents of choice for ESBL-producing organisms, *K. pneumoniae* resistant to carbapenems has unfortunately emerged, mediated frequently by the presence of $bla_{\text{KPC,}}$ a widespread carbapenemase. Patient 4 was infected with KPC carrying the $bla_{\text{KPC-3}}$ gene, therefore necessitating treatment with alternate classes of antimicrobials. As was our patient, she was treated with colistin and tigecycline.

The spread of MDR organisms is a formidable threat for patients and emphasizes the need for new antimicrobial agents. As a result of this peril, tigecycline and colistin have gained attention for their antimicrobial activity against MDR organisms. Shortly before Di Carlo et al. first described the treatment of *K. pneumoniae* pancreatitis with tigecycline and colistin, we treated our patient successfully with this regimen [5]. Further experience in intra-abdominal infections, and recent studies of bacteremia due to *K. pneumonia* containing $bla_{\text{KPC,}}$ also demonstrated successful therapy with a combination of colistin and tigecycline [3,16–18]

Tigecycline is a bacteriostatic antimicrobial agent that interferes with protein synthesis by binding to the 30S ribosomal subunit. Tigecycline is excreted mainly in feces via bile, which may have been a unique advantage in this case. However, little tigecycline, is excreted in the urine. The pharmocokinetics and pharmacodynamics (PK/PD) of this antibiotic have been evaluated mainly in complicated skin and skin structure infections (cSSSI) and complicated intra-abdominal infections (cIAI) in both the community and nosocomial setting; these studies demonstrate that tigecycline has a large volume of distribution, a long elimination half-life, and a low total clearance. It is recognized that tigecycline elimination is greater in males and correlates with weight and creatinine clearance; overweight patients and patients with renal dysfunction have reduced tigecycline clearance. Despite differences in drug clearance, the

Table 1. Review of Characteristics of Five Cases of *Klebsiella pneumoniae*-Associated Pancreatitis

Case	*Reference*	*Age*	*Sex*	*Comorbidities*	*Presentation*	*CT imaging*	*Diagnosis*	*Antibiotics used*	*Outcome*
1	Chong [11]	72	Male	Poorly controlled type 2 diabetes mellitus, dyslipidemia, depression	Two months of abdominal pain, distension, anorexia, weight loss	Two-centimeter mass at pancreatic head	*K. pneumoniae* cultured from percutaneous aspiration biopsy	Imipenem-cilastatin	Clinical improvement
2	Orzechowska [12]	49	Male	Chronic alcoholism	Impaired consciousness, rigors and fever two weeks following hospitalization with fever, anorexia and abdominal pain	Pancreatic pseudocyst	*K. pneumoniae* (K2) cultured from blood, post-mortem pancreatic pseudocyst and meninges	Amoxicillin-clavulanic acid, metronidazole, gentamicin, followed by piperacillin-tazobactam	Death
3	Bhasin [10]	35	Male	Chronic alcoholism, chronic calcific pancreatitis, complete pancreas divisum	Abdominal pain and fever	Communicating intrasplenic pancreatic abscess	*K. pneumoniae* cultured from percutaneous aspiration biopsy	Cefotaxime and amikacin	Clinical improvement
4	Di Carlo [5]	50	Female	Chronic alcoholism, chronic pancreatitis, tobacco dependence	Fever and leukocytosis four months after hospitalization with abdominal pain anorexia, chills, abdominal distension and weight loss	Mass of pancreatic head	*K. pneumoniae* belonging to sequence type 258 and harboring $bla_{\text{KPC-3}}$ cultured from percutaneous aspiration biopsy	Tigecycline and colistin	Clinical improvement
5	This article	79	Male	Gallstone pancreatitis, prostate cancer, coronary artery disease with coronary artery bypass grafts, hypertension, aortic stenosis	Abdominal pain	Two pancreatic pseudocysts	*K. pneumoniae* harboring $bla_{\text{KPC-3}}$ cultured from pseudocyst drainage and surgical specimen two months after admission	Tigecycline and colistin	Clinical improvement

modest variations do not compel adjustment in drug dosing [19–22].

Presently, clinicians are concerned with reports of a higher risk of death among patients receiving tigecycline compared to other antibacterial drugs [23]. Based on those reports, the U.S. Food and Drug Administration issued a new ''black box'' warning recommending restriction of tigecycline to situations where suitable alternative treatments are not available [24]. Yet therapy with this drug may still be the only option in cases of MDR infections. Furthermore, in some reports of serious blood stream infection, regimens containing tigecycline have proved superior to other regimens; as mentioned, tigecycline may play an important role in the treatment of carbapenem-resistant *K. pneumoniae* as part of combination regimens including colistin and carbapenems [3,17,18].

Why would tigecycline be effective in our patient? In cSSSI, an area-under-the-curve:mean inhibitory concentration ratio (AUC:MIC) of 20–25 predicts 0.95 probability of cure. In cIAI, an AUC:MIC of 20–25 anticipates 0.90 probability of cure. Recent analysis of two randomized, controlled trials by Rubino et al. assessed the PK/PD of tigecycline in community-acquired pneumonia and found that $fAUC_{20-24}$:MIC > 12.8 is associated with faster resolution of infection. Whereas area-under-the-curve and mean inhibitory concentrations ratios correlate well with microbial eradication, surgery is central to the management of cIAI [19–21]. Likely, we were able to achieve these important pharmacologic parameters in our patient due to the dosing we employed and penetration of tigecycline into abdominal and pancreatic tissues [21]. Of note, nausea and vomiting occur commonly in patients treated with tigecycline, approximately 40% and 20%, respectively, which may complicate the treatment of pancreatitis where these symptoms are prominent. Less common, but equally relevant, are reports of tigecycline-induced acute pancreatitis, typically occurring during the second or third week of therapy [25].

We also added colistin methanesulfonate (CMS) to our patient's antibiotic regimen; CMS, a polymyxin antibiotic, is administered as an inactive prodrug that is converted in vivo to the active form. Colistin methanesulfonate is used in the treatment of infections caused by MDR gram-negative bacteria including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *K. pneumoniae*, especially when carbapenems are not an option. A bactericidal antimicrobial agent, colistin acts as a ''surface detergent'' that damages cell membranes, promoting the leakage of cellular proteins and cell death. The conversion of CMS to colistin is relatively inefficient and much of the inactive prodrug is eliminated in urine; it is notable that < 1% of colistin is excreted renally owing to tubular reabsorption. Nephrotoxicity is likely mediated by the complex handling of both forms of the drug in renal tubules. Neurotoxicity, although rare, has also been associated with its use [26]. We took advantage of colistin's unique PK/PD to dose it so that time (T) > MIC was achieved to further enhance the efficacy of tigecycline by allowing even greater bacterial penetration thereby avoiding the emergence of resistance to colistin. Importantly, in critically ill patients, renal insufficiency affects steady-state concentrations, making alterations in dosing important to achieve therapeutic success with minimal side effects.

The combination of a bactericidal cell wall active agent, such as colistin, which enhances the effect of a bacteriostatic drug that interferes with protein synthesis, such as tigecycline, may have been advantageous in the treatment of our patient. Although we do not advocate the empiric use of colistin and tigecycline in all cases of infected pancreatic necrosis, the judicious use of this regimen in patients with documented MDR infection may prove beneficial. As stated above, patients at risk for toxicity, particularly with colistin, should be monitored carefully or alternative regimens should be considered.

In summary, our patient illustrates the risk factors that contribute to the development of *K. pneumoniae* bearing bla_{KPC-3}, including exposure to multiple antibiotics, intensive care stay, indwelling catheter placement (bladder catheter and central venous catheter), prolonged hospitalization, and poor functional status. Increasing rates of KPC-producing *K. pneumoniae* in North America and its potential for horizontal transmission should lead clinicians to consider the presence of this pathogen in patients with severe intra-abdominal infection, especially in the intensive care setting. Infection control procedures are imperative to prevent further nosocomial spread. Despite concerns about increased mortality with tigecycline and the toxicity of colistin, in intra-abdominal infections where surgical drainage and adequate tissue concentrations of antibiotics are essential, this combination may offer an advantage when other therapies are not effective.

Conclusion

Far less common than infection with other gastrointestinal pathogens, pancreatic infection with *K. pneumoniae* is indeed a cause of substantial morbidity. Identification of patients at particular risk for infection with *K. pneumoniae* bearing KPC is imperative for the timely initiation of appropriate antibiotic therapy coupled with adequate surgical drainage. In the case of severe acute pancreatitis, we describe successful treatment with drainage, tigecycline, and colistin. The use of both tigecycline and colistin appears to be an important ''last line'' choice of therapy for SAP and may be considered further in the future.

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Author Disclosure Statement

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Department of Veterans Affairs.

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Address correspondence to:
Dr. Robert A. Bonomo
Louis Stokes Cleveland Veterans Affairs Medical Center
10701 East Blvd.
Cleveland, OH 44106

E-mail: robert.bonomo@va.gov