Tigecycline-induced acute pancreatitis in a renal transplant patient: a case report and literature review

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Abstract

Background: The purpose of this case report is to increase the awareness of tigecycline-induced pancreatitis specifically in renal transplant patients predisposed to the condition.

Case presentation: A 48-year-old woman developed a donor-derived infection after kidney transplantation, resulting in a ruptured graft renal artery, followed by peritoneal drainage, blood and urine culture infections. Due to multiple drug resistance Acinetobacter baumannii cultured from the preservation fluid and blood, she was treated with tigecycline at the 8th post-transplant day combined with other antibiotics. After 15 days of tigecycline treatment, she was observed with recurrent fever and abdominal distension with a rise in pancreatic enzymes. CT scans showed acute pancreatitis with grade D on Balthazar score, no necrosis visible without contrast injection. These facts were sufficient to hint that pancreatitis was slowly becoming prominent. After withdrawal of tigecycline, CT scans showed that exudation around the pancreas were relieved, and blood amylase returned to the normal range in a week.

Conclusions: Clinicians should pay attention to clinical signs and symptoms and the level of serum pancreatic enzymes in order to monitor the development of pancreatitis. If necessary, abdominal CT scans should be performed regularly when given tigecycline.

Keywords: Tigecycline, Pancreatitis, Adverse events, Kidney transplantation

Background

Tigecycline was the first member in the glycyclcycline class of antibacterial agents to be used clinically. It was approved by the US Food and Drug Administration (FDA) for the treatment of complicated skin and skin-structure infections (cSSSIs). Furthermore, it can be used for the treatment of complicated intra-abdominal infections (CIAI) caused by susceptible Gram-positive, Gram-negative and anaerobic organisms [1]. Tigecycline is a structural derivative of minocycline sharing similar pharmacokinetic properties and adverse effects with tetracyclines. The most common adverse effects associated with tigecycline are nausea, vomiting and diarrhea. Pancreatitis has been found to be associated with tetracycline. However, it was not listed as an adverse drug reaction in the product label when tigecycline was originally approved. A subsequent retrospective cohort analysis and a review of phase 3 and 4 comparative studies of tigecycline have also been performed with mixed conclusions [2, 3]. As tigecycline has a broad spectrum, it has been used as part of the antimicrobial regimen for complicated infections in patients who had received an organ transplant. We report a case of tigecycline-induced acute pancreatitis after kidney transplantation and review the relevant literature.

Case presentation

A 48-year-old woman with end-stage renal disease (ESRD) due to chronic glomerulonephritis received a kidney transplant from a donor with DCD (donated cardiac death). The kidney was successfully transplanted to the recipient and normal serum creatinine levels were observed after 7 days. On the fourth day after transplantation, the patient was treated with teicoplanin, cefoperazone, sulbactam and...
etimicin due to the development of multiple drug resistance Acinetobacter baumannii in both organ preservation solution and drainage fluid. Tigecycline was administered intravenously at 100 mg for the first dose and was given at 50 mg every 12 h from the eighth day after the operation because of persistent abdominal infection. She felt pain at the transplant kidney area and then the blood pressure dropped to 88/61 mmHg on the twentieth day after transplantation. Emergency ultrasound showed two huge hematomas around the graft. Graft pain relieved after emergency treatment including transplanted kidney exploration, renal hematoma removal, renal vascular reconstruction and ureteral reimplantation. The treatment with tigecycline was continued based on the results of the peritoneal drainage, blood and urine culture. The patient did not worsen until approximately 15 days after being initially administered. The patient presented with fever, nausea, vomiting and moderate abdominal pain. Physical examination found moderate tenderness in the upper abdomen. Laboratory analyses were remarkable for leukocytosis and the level of lipase raised to 156 U/L. Other results such as serum amylase level was 424 U/L and drainage amylase was 554 U/L, despite the aminotransferase and alkaline phosphatase were within the normal range. CT scans (Fig. 1a) suggested acute pancreatitis (AP) with grade D on Balthazar score, no necrosis visible without contrast injection. There was no sign of dilated biliary ducts according to the abdominal ultrasound examination. Since those findings were considered to be related to drug-induced pancreatitis, it was recommended that tigecycline should be discontinued on the 16th day following exposure. Shortly after tigecycline discontinuation, the patient's symptoms gradually improved. Blood amylase and lipase returned to baseline levels in a week. CT scans (Fig. 1b) showed a basically normal after tigecycline discontinuation for 14 days. She was discharged from the hospital with a low-fat diet for 3 weeks. One month later, abdominal CT scans on follow-up did not find any abnormalities and showed as normal (Fig. 1c). Throughout the course of treatment, the immunosuppressive regimen was a triple therapy based on recommended doses including tacrolimus, mycophenolate mofetil and prednisone. Serum tacrolimus concentration was maintained at 6–8 ng/ml. The patient received these medications over the next 6 months, with no discomfort and relapse after stopping tigecycline. Timeline of disease was shown in Additional file 1: Figure S1.

**Discussion**

Infection from DCD donors is a major challenge in China. A recent study from China showed that 19.4% of donor blood cultures showed blood infection, consistent with the literature that about 5% -11.3% of donors did not find bacteremia on donation. Data from this single-center showed that the incidence of donor-derived bacterial infection was 4.5% [4, 5]. Because this patient’s donor-associated pathogen was multidrug-resistant Acinetobacter baumannii, we added tigecycline to the antibiotic regimen based on Chinese expert consensus [6].

Tigecycline is the first member of a new class of antibiotics called glycylcyclines which was licensed by the US FDA in June 2005 for intravenous (IV) use in adults [7]. It inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit with a five-fold higher affinity than tetracycline [8]. Tigecycline is a derivative of minocycline, with a 9-t-butylglycylamido group added to the 1st carbon on the D ring of minocycline and it possesses a broad spectrum range. In 2008, tigecycline received FDA approval for the treatment of adult patients with community-acquired bacterial pneumonia [9]. In vitro studies demonstrated that tigecycline exhibits a high level of antimicrobial activity against many common types of respiratory bacteria, including multiple resistant Gram-positive, Gram-negative, anaerobic, as well as multi-drug-resistant (MDR) pathogens, such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus [10], penicillin-resistant Streptococcus pneumoniae (PRSP), methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus [10], penicillin-resistant Streptococcus pneumoniae (PRSP), methicillin-resistant

![Fig. 1](image1.png) Image of CT scan during the whole course of AP. a Twenty-five days post transplantation, the CT scan of abdomen showed pancreatic swelling, peripheral exudate effusion, considered acute pancreatitis (grade D on Balthazar score, no necrosis visible without contrast injection) after tigecycline treatment for 20 days. b Scan showed a basically normal after tigecycline discontinuation for 14 days. c CT reported a normal finding after tigecycline discontinuation for 58 days.
**Staphylococcus epidermidis** (MRSE) and β-lactamase-producing *Haemophilus influenzae* [11].

The most common adverse effects associated with tigecycline are nausea, vomiting and diarrhea. Pancreatitis has been reported that it could be induced by tetracycline, but it was not listed as an adverse drug reaction in the product label when tigecycline was originally approved. Concerns about tigecycline-induced AP have been raised by the clinicians in nearly 10 years [12–14]. Therefore, the former manufacturer of tigecycline, Wyeth, updated the product label including AP as one of the post-marketing adverse events in July 2006 [1]. Interestingly, although tigecycline was registered as a treatment for CIAI, it should be used causally when infectious complications were associated with acute pancreatitis because of the possible tigecycline–induced pancreatitis. This exclusion criteria might have emerged due to the similarities between tigecycline and other tetracyclines.

Biliary tract disease (40%) and alcohol exposure (35%) are common causes of AP. Other etiologies include idiopathic.

### Table 1: Review of cases report of tigecycline-induced acute pancreatitis — demographic data and drug characteristics

| Author         | Country       | Number of cases | Year of report | Age of patient | Gender | Indication of tigecycline                                                                 | Culture of specimens                                                                 | Duration of tigecycline (days) | Daily dose (mg) | Combination drug                                                                 | History of liver disease |
|----------------|---------------|-----------------|----------------|----------------|--------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------|-----------------|--------------------------------------------------------------------------------------|--------------------------|
| Gilson M       | France        | 1               | 2008           | 35             | Male   | Chronic osteitis complicated by pseudarthrosis                                            | Enterobacter cloacae with broad-spectrum beta lactamase                               | 15                           | 100             | Imipenem, amikacin                                                                     | None                     |
| Lipshitz J     | USA           | 1               | 2009           | 64             | Female | Prosthetic joint infection                                                                | NA                                                                                   | 14                           | 100             | Levothyroxine, Pantoprazole, and hydromorphone.                                       | None                     |
| Marshall RS    | USA           | 1               | 2009           | 55             | Female | Soft Tissue Infection                                                                     | Enterococcus faecalis, Pseudomonas aeruginosa, and Staphylococcus hominis             | 14                           | NA              | Pantoprazole, and hydromorphone.                                                       | None                     |
| Hung WY        | USA           | 1               | 2009           | 69             | Female | Soft tissue infection/vascular graft infection                                              | Coagulase-negative Staphylococcus, *Staphylococcus epidermidis* and diphtheroids, Clostridium difficile | 8                            | 100             | Meropenem, vancomycin, clindamycin                                                    | None                     |
| Prot-Labarthe S| France        | 1               | 2010           | 9              | Male   | Bacteremia / arthritis                                                                    | Enterobacter cloacae producing extended spectrum beta lactamase                        | 56                           | 100             | Colistin, amikacin and rifampin                                                       | None                     |
| Otero RS       | Mexico        | 1               | 2010           | 27             | Female | Acute pneumonia                                                                          | NA                                                                                   | 7                            | 100             | Amikacin, oseltamivir                                                                  | None                     |
| Mascarello M   | Italy         | 1               | 2012           | NA             | NA     | Chronic osteomyelitis                                                                     | methicillin-resistant *Staphylococcus aureus*, multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* | 12                           | 100             | Amikacin, propofol                                                                    | None                     |
| Hemphill MT    | USA           | 1st             | 2015           | 22             | Male   | Acute bronchitis                                                                          | *M. chelonae*                                                                         | 14                           | NA              | Tobramycin, meropenem, and vancomycin                                                  | None                     |
| Hemphill MT    | USA           | 2nd             | 2015           | 22             | Male   | Acute bronchitis                                                                          | *M. chelonae*                                                                         | 3                            | NA              | Amikacin, clarithromycin                                                               | None                     |
| Marot JC       | Belgium       | case 1          | 2012           | 64             | Male   | Soft tissue infection                                                                     | *Staphylococcus aureus*                                                                | 6                            | 100             | None                                                                                  | None                     |
| Marot JC       | Belgium       | case 2          | 2012           | 58             | Male   | Soft tissue infection/osteomyelitis                                                       | *Staphylococcus schleiferi* methicillin-resistant and *Staphylococcus lugdunensis methicillin-sensitive | 8                            | 100             | Piperacillin-Tazobactam, Vancomycin                                                   | None                     |
| Davido B       | France        | Case 1          | 2016           | 70             | Male   | Pyelonephritis                                                                           | ESBL *Escherichia coli*                                                                | 6                            | 100             | None                                                                                  | None                     |
| Davido B       | France        | Case 2          | 2016           | 50             | Female | Femoral osteomyelitis                                                                     | EBSL *E. coli*                                                                         | 20                           | 100             | None                                                                                  | None                     |

NA not available
pancreatitis, post-endoscopic retrograde cholangiopancreatoxygraphy, trauma, medications, infection, hypercalcemia, hypertriglyceridemia, tumor and autoimmune diseases. Several drugs are associated with AP. The overall incidence of drug-induced AP is 0.1% ~ 2% [15]. Medications associated with pancreatitis include tetracyclines, isoniazid, macrolides, metronidazole, propofol, angiotensin-converting enzyme inhibitors (ACEI), etc. [16].

The cause of drug-induced pancreatic injury is unknown. By using the classification of Zimmerman originally described for drug hepatotoxicity, drugs associated with tissue-specific injury can be divided into those with intrinsic toxicity in the organ involved and those that cause injury as a result of host idiosyncrasy [17]. As opposed to intrinsic toxicity, idiosyncratic reaction appears to be the mechanism of drug injury in the vast majority of cases. It is known that

### Table 2 Review of cases report of tigecycline-induced acute pancreatitis — Clinical findings of cases

| Author          | Onset of symptoms | Clinical manifestation                  | Amylase/Lipase levels (u/L) | CRP (mg/l) | CT scan | AP severity | Time to symptoms relieved (days) | Time to recovery of enzymes (days) |
|-----------------|-------------------|----------------------------------------|-----------------------------|------------|---------|------------|----------------------------------|----------------------------------|
| Glison M        | 13 days, abdominal pain | Acute abdominal ‘stab-like’ pain       | (−)/1000                    | 35         | Pancreatic oedema without any necrotic flows (Balthazar Stage 1). | Mild | 2 | 43 |
| Lipshitz J      | 14 days, epigastric pain | Nausea, vomiting, abdominal pain       | 806/1406                    | NA         | Mild inflammatory stranding about the duodenum and minimal fluid in the left retroperitoneum. | Mild | 3 | 5 |
| Marshall RS     | 3 days, uncontrolled emesis | Nausea, vomiting, fever and loss of appetite | 180/156                     | NA         | Acute pancreatitis | Mild | 2 | 7 |
| Hung WY         | 3 days, nausea and vomiting | Persistent and worsening nausea and vomiting, abdominal pain | 926/749                    | NA         | NA | NA | 3 | 5 |
| Prot-Labarthe S | 14 days, abdominal pain | Abdominal pain, recurrent vomiting     | (−)/603                     | NA         | Inflammation involving pancreas and peripancreatic fat without necrosis (Ranson Score 2 and Balthazar stage 2). | Mild | 3 | 5 |
| Otero RS        | 7 days             | Nausea, vomiting, epigastric pain, distention | 255/424                     | NA         | Pancreatic enlargement, low density shadow of pancreas tail (grade D on Balthazar score) | Mild | 3 | 12 |
| Mascarello M    | 12 days            | Nausea, vomiting and acute severe upper abdominal pain | 312/382                     | 131        | Inflammation of the pancreas and peripancreatic fat, necrosis of 40% of the pancreatic gland, peripancreatic stranding, and fluid collection (Balthazar CT severity index 7). | severe | $\leq$10 | $\leq$10 |
| Hemphill MT     | 10 days            | Abdominal pain                         | NA/732                      | NA         | Acute pancreatitis | Mild | 6 | 6 |
| Hemphill MT     | 3 days             | Mild nausea, epigastric tenderness     | 381/268                     | NA         | Acute pancreatitis | Mild | 5 | 5 |
| Marot JC        | 6 days, epigastric pain | Nausea, epigastric pain               | 750/936                     | NA         | An oedematous pancreatitis (grade D on Balthazar score) | Mild | 4 | 18 |
| Marot JC        | 7 days, abdominal pain on day 8 | Nausea, vomiting and loss of appetite | 552/1660                    | NA         | Acute pancreatitis, no necrosis visible without contrast injection (grade D on Balthazar score) | Mild | 5 | 4 |
| Davido B        | 6 days             | Anorexia, vomiting and abdominal discomfort | NA/ 2460                    | NA         | Typical oedematous infiltrate (Balthazar A). | Mild | 2 | 2 |
| Davido B        | 20 days            | Nausea, abdominal discomfort           | NA/ 1340                    | NA         | NA | NA | 1 | 1 |

*CT Computerized Tomography, AP Acute Pancreatitis, CRP C-Reactive Protein*
pancreatitis was associated with propofol combination therapy. Our patient was taking several additional drugs possibly. However, during treatment or ceasing of tigecycline, she has been taking these medications at recommended dose which were associated with pancreatitis and classified as group III (prednisone) and group IV (tacroli-mus), respectively (low risk) [18]. Therefore, we do not think that combination therapy in this situation may lead to acute pancreatitis.

The increasing degree of amylase and lipase is not directly related to the severity of AP. Lipshitz J et al. reported the serum lipase and the amylase were as high as 806 UI/L and 1406 UI/L in patients with abdominal pain associated with nausea and vomiting, while CT scans showed duodenal mild inflammation and left posterior abdominal effusion [13]. However, Mascarello M et al. reported that serum lipase and amylase were 382 UI/L and 1406 UI/L in patients with abdominal pain associated with nausea and vomiting, while CT scans showed severe pancreatitis inflammation with 40% pancreatic and peripancreatic necrosis and fluid retention, and the Balthazar classification was E level with CTSI score 7 points. It should be noted that the final time to normalize serum lipase and amylase was not directly related to serum lipase and amylase levels.

Finally, tigecycline induced AP is still considered to be a rare phenomenon. However, serum amylase and lipase levels should be closely monitored if any symptomatic abdominal pain suggests AP during treatment. In addition, the mechanism of tigecycline-induced AP and the possibility of cross-reactivity with tetracycline in patients with AP induced by tigecycline should be given more attention. Whether tigecycline increases the risk of pancreatitis in immunosuppressed recipients requires more research data.

Conclusions
Clinicians should pay attention to clinical signs and symptoms and the level of pancreatic enzymes in the blood in order to monitor the development of pancreatitis. Abdominal CT images should be taken on a regular basis when necessary for the administration of tigecycline.

Additional file

**Additional file 1: Figure S1.** Timeline. (DOC 70 kb)

**Abbreviations**
ACEI: Angiotensin-converting enzyme inhibitors; AP: Acute pancreatitis; CIAI: Complicated intra-abdominal infection; cSSSIs: Complicated skin and skin-structure infections; CT: Computed Tomography; CTSI: CT severity index; DCD: Donation Cardiac Death; ERCP: Endoscopic retrograde cholangiopancreatography; ESRD: End-stage renal disease; FDA: Food and Drug Administration; IV: Intravenous; MDR: Multidrug-resistant; MRSA: Methicillin-resistant *Staphylococcus aureus*; MRSR: Methicillin-resistant *Staphylococcus epidermidis*; PRSP: Penicillin-resistant *Streptococcus pneumoniae*; VRE: Vancomycin-resistant *Enterococcus*
Availability of data and materials
Ct scan images of case were obtained from the First Affiliated Hospital, College of Medicine, Zhejiang University.

Authors' contributions
JWL and RDW searched the database for the literature and drafted the manuscript. JHC submitted case report and provided guidance for drafting the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate
Written informed consent for publication of their clinical details and clinical images was obtained from the patient. This case report was a retrospective investigation and was not necessary for ethics approval. Ethics approval is not applicable.

Consent for publication
All named authors have read the manuscript and have agreed to submit the paper to BMC Infectious Disease in its present form. The research has not been and will not be submitted simultaneously to another journal, in whole or in part. The paper reports previously unpublished work. All those named as authors have made a sufficient contribution to the work. Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Competing interests
The authors declare that they have no competing interests.

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References
1. Wyeth Pharmaceuticals. Tygacil® (package insert). Philadelphia: Wyeth Pharmaceuticals. Tigecycline is a structural derivative of minocycline and shares similar pharmacokinetic and properties and most of the adverse effects with tetracyclines; 2009.
2. Okon E, Engel C, van Manen R, Brown J. Tigecycline-related pancreatitis: a review of spontaneous adverse event reports. Pharmacotherapy. 2013;33:63–8.
3. McGovern PC, Wible M, Korth-Bradley JM, Quintana A. Pancreatitis in tigecycline phase 3 and 4 clinical studies. J Antimicrob Chemother. 2014;69:773–8.
4. Ye QF, Zhou W, Wan QQ. Donor-derived infections among Chinese donation after cardiac death liver recipients. World J Gastroenterol. 2017;23: 5809–16.
5. González-Segura C, Pascual M, García Huete L, Canizares R, Torres J, Corral L, Santos P, Ramos R, Pujol M. Donors with positive blood culture: could they transmit infections to the recipients? Transplant Proc. 2005;37:3664–6.
6. Chen BY, He LX, Hu BJ. Consensus of the Chinese specialists for diagnosis, treatment & control of acinetobacter baumannii infection. Zhonghua Yi Xue Za Zhi. 2012;92:76–85.
7. Mullangi PK, Pankey GA. Tigecycline in critical care. Crit Care Clin. 2008;24: 365–75.