Tigecycline Lock Therapy for Catheter-Related Bloodstream Infection Caused by KPC-Producing *Klebsiella pneumoniae* in Two Pediatric Hematological Patients

Sergio Foresti,^a Stefano Di Bella,^a Attilio Rovelli,^b Alessandra Sala,^b Marta Verna,^b Luca Bisi,^a Carla Nisii,^c Andrea Gori^a

Infectious Diseases Division, San Gerardo de' Tintori Hospital, Monza, Italy^a; BMT Unit, Pediatric Department, San Gerardo de' Tintori Hospital, Monza, Italy^b; Laboratory of Microbiology, National Institute for Infectious Diseases L. Spallanzani, Rome, Italy^c

Catheter-related bacteremias carry high mortality rates in hematological patients. When a multidrug-resistant microorganism is involved, the catheter should ideally be removed; however, this approach is not always possible. Tigecycline lock therapy was used in two pediatric oncohematological patients with intravascular catheter-related infection due to KPC-producing *Klebsiella pneumoniae*. The catheter was salvaged in both cases, and the patients were later discharged. Our experience suggests the usefulness of this approach in treating this type of infection.

Infections due to *Klebsiella pneumoniae* carbapenemase (KPC)-producing bacteria represent an emerging problem. In tackling these infections, clinicians are confronted with the scarcity of therapeutic options, due to the high antibiotic resistance of these bacteria. The associated mortality is high, reaching 65% in patients receiving allogeneic hematopoietic stem cell transplantation (HSCT) (1).

Adding to the urgency of the problem, KPC-producing *K. pneumoniae* infections are currently on the rise in the pediatric population as well. Most pediatric oncohematological patients carry intravascular catheters, which are often implantable or semi-implantable. In such patients, if an intravascular catheter-related infection occurs during the critical phases which follow HSCT (often characterized by cytopenia), the procedure of replacing the infected catheter carries the risks posed by sedation, general anesthesia, bleeding, and further infection; moreover, obtaining alternative venous access in pediatric patients is often difficult. The antibiotic lock technique can be attempted to prevent these complications (2). This procedure targets the bacterial biofilm lining the lumen of the infected catheter through the instillation of solutions with antibiotic concentrations severalfold higher than the MIC (3).

Tigecycline has a good potential for this use (3): it is a lipophilic antibiotic with good biofilm penetration and appeared to be superior to vancomycin in eradicating experimental catheter-related infections from *Staphylococcus epidermidis* (4). It has been increasingly used for treating KPC-producing *K. pneumoniae*, usually as part of a multiple antibiotic regimen; however, data reporting its use as a lock therapy agent for Gram-negative infections are lacking.

We describe here two cases of catheter-related bloodstream infection (CRBSI) in pediatric hematological patients treated with tigecycline as a lock solution alongside systemic therapy. These patients survived the bacteremic episodes, and catheter salvage was possible.

Case 1. A 1-year-old female underwent HSCT from an HLA-matched unrelated donor for congenital aplastic anemia. The conditioning regimen included fludarabine and cyclophosphamide, and prophylaxis for graft-versus-host disease (GvHD) included cyclosporine, antithymocyte globulin, and methotrexate.

The patient carried a long-term venous line (Browiac catheter) for chemotherapy and had been empirically treated for fever with vancomycin, amikacin, and ceftazidime during the conditioning regimen and subsequently with vancomycin plus meropenem. A computed tomography chest scan revealed an infiltrate in the inferior left lobe. The latter therapy was continued until day +5 after HSCT, when the patient again developed fever (39°C); cultures from the catheter and peripheral vein grew KPC-producing *K. pneumoniae*. Antimicrobial susceptibility tests revealed MICs of 2 mg/liter for gentamicin, 0.25 mg/liter for colistin, 1 mg/liter for tigecycline, and >32 mg/liter for meropenem. A difference in time to positivity of >2 h was recorded for the paired blood cultures; therefore, a diagnosis of catheter-related bloodstream infection was made, in accordance with international guidelines (5). Systemic therapy with colistin (150,000 IU every 8 h), gentamicin (35 mg every 24 h), and tigecycline (25 mg every 12 h) was commenced, accompanied by lock therapy with tigecycline: 50 mg was diluted in 0.9% normal saline solution for a final concentration of 10 mg/ml, and 3 ml was injected in the catheter lumen. The solution was replaced every 8 h. Cultures of blood from the catheter and from a peripheral vein taken after 72 h were sterile. The therapy was continued for 14 days.

A KPC-producing *K. pneumoniae* isolate was grown from rectal swabs, and decontamination therapy with oral gentamicin was also introduced. After 15 days, test results for blood cultures and rectal swabs were negative.

The patient was discharged on day +67 and was afebrile, with normal inflammatory markers. The catheter was electively re-

Received 30 July 2015 Returned for modification 16 August 2015

Accepted 3 October 2015

Accepted manuscript posted online 12 October 2015

Citation Foresti S, Di Bella S, Rovelli A, Sala A, Verna M, Bisi L, Nisii C, Gori A. 2015. Tigecycline lock therapy for catheter-related bloodstream infection caused by KPC-producing *Klebsiella pneumoniae* in two pediatric hematological patients. *Antimicrob Agents Chemother* 59:7919–7920. doi:10.1128/AAC.01855-15.

Address correspondence to Stefano Di Bella, stefano932@gmail.com.

Copyright © 2015, American Society for Microbiology. All Rights Reserved.

moved 3 months after the discharge, with no further infective episodes experienced. The patient is still alive.

Case 2. A 14-year-old female with aplastic anemia was admitted to the Pediatric Hematology Department to receive HSCT from an unrelated matched donor. The conditioning regimen included fludarabine, cyclophosphamide, and total body irradiation. Cyclosporine and antithymocyte globulin were also administered to prevent GvHD. The day prior to the transplantation, she experienced fever and diarrhea. Blood cultures yielded an extended-spectrum- β -lactamase-producing *Escherichia coli* isolate; the patient was treated with meropenem with progressive resolution of signs and symptoms, and blood cultures taken in the following days were negative. Surveillance rectal swabs grew KPC-producing *K. pneumoniae*, and decontamination with oral amikacin was attempted without success.

The patient, who carried a tunneled venous line (Hickman catheter) for chemotherapy, experienced a new febrile episode during her stay (day +15), and a KPC-producing *K. pneumoniae* strain grew from catheter and peripheral vein blood cultures. The antibiogram showed MICs of 16 mg/liter for meropenem, 0.125 mg/liter for colistin, and 2 mg/liter for tigecycline. A catheter-related bloodstream infection was diagnosed based on the differential time to positivity of >2 h between the paired blood cultures. Systemic antibiotic therapy with colistin (3,000,000 IU every 8 h), meropenem (2 g every 8 h), and tigecycline (100 mg every 12 h) plus lock therapy with tigecycline (the solution was prepared as described above but was replaced every 24 h in this case) was performed for 16 days; the fever subsided, and procalcitonin results became negative. The patient developed a mild renal impairment, likely due to colistin nephrotoxicity. Repeated cultures from both catheter and peripheral vein were negative at 72 h.

The patient did not present other febrile episodes and was discharged on day +40. The catheter remained *in situ* until 5 months after the discharge, when it was removed because of colonization by *Candida parapsilosis*.

Although reports on the use of other drugs such as colistin or aminoglycosides have been published (6, 7), there was no previous experience of the use of lock therapy for treating CRBSI caused by KPC-producing *K. pneumoniae*. Tigecycline was considered a lock therapy agent because of its lipophilic nature, which enables it to penetrate the biofilm, reaching the bacteria embedded in it, and because of its stability at concentrations that confer bactericidal activity (we used a concentration 10,000-fold higher than the MIC, and no precipitation of the molecule occurred). In both cases, a single lumen catheter was involved, and the volume used

(3 ml) was determined on the basis of the specifications of the catheter manufacturers. Blood draws were performed mainly from the catheter for patient 1, because venous access was extremely difficult, and from the peripheral vein for patient 2.

Given the limited therapeutic options for intravascular catheter-related infections caused by Gram-negative bacteria, our recent experience (although limited to two patients) suggests that tigecycline could represent a valuable option for selected cases when the causative agent is a multidrug-resistant (MDR) Gram-negative strain and removing the catheter presents difficulties and risks.

ACKNOWLEDGMENTS

S.F., A.S., A.R., and M.V. managed the clinical cases. S.D.B. and L.B. collected patient data and wrote the manuscript. C.N. and A.G. made a critical revision of the manuscript.

We declare that we have no conflict of interest.

We received no funding for the study.

REFERENCES

- Girmenia C, Viscoli C, Piciocchi A, Cudillo L, Botti S, Errico A, Sarmati L, Ciceri F, Locatelli F, Giannella M, Bassetti M, Tascini C, Lombardini L, Majolino I, Farina C, Luzzaro F, Rossolini GM, Rambaldi A. 10 April 2015, posting date. Management of carbapenem resistant *Klebsiella pneumoniae* infections in stem cell transplant recipients: an Italian multidisciplinary consensus statement. *Haematologica* <http://dx.doi.org/10.3324/haematol.2015.125484>.
- Simon A, Bode U, Beutel K. 2006. Diagnosis and treatment of catheter-related infections in paediatric oncology: an update. *Clin Microbiol Infect* 12:606–620. <http://dx.doi.org/10.1111/j.1469-0691.2006.01416.x>.
- Vassallo M, Dunais B, Roger PM. 6 February 2015, posting date. Antimicrobial lock therapy in central-line associated bloodstream infections: a systematic review. *Infection* <http://dx.doi.org/10.1007/s15010-015-0738--1>.
- Aybar Y, Ozaras R, Besirli K, Engin E, Karabulut E, Salihoglu T, Mete B, Tabak F, Mert A, Tahan G, Yilmaz MH, Ozturk R. 2012. Efficacy of tigecycline and vancomycin in experimental catheter-related *Staphylococcus epidermidis* infection: microbiological and electron microscopic analysis of biofilm. *Int J Antimicrob Agents* 39:338–342. <http://dx.doi.org/10.1016/j.ijantimicag.2012.01.001>.
- Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK. 2009. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 49:1–45. <http://dx.doi.org/10.1086/599376>.
- Justo JA, Bookstaver PB. 2014. Antibiotic lock therapy: review of technique and logistical challenges. *Infect Drug Resist* 7:343–363. <http://dx.doi.org/10.2147/IDR.S51388>.
- Ozbek B, Mataraci E. 2013. In vitro effectiveness of colistin, tigecycline and levofloxacin alone and combined with clarithromycin and/or heparin as lock solutions against embedded *Acinetobacter baumannii* strains. *J Antimicrob Chemother* 68:827–830. <http://dx.doi.org/10.1093/jac/dks472>.