Case Report: Treatment of Recurrent Urosepsis Caused by ESBL-Producing *Escherichia coli* with Tigecycline

**JCM01340-07 – REVISED VERSION**

Wolfgang A. Krueger, MD* 1; Volkhard A. J. Kempf, MD 2; Manou Peiffer, MD 1; Udo Nagele, MD 3; Klaus E. Unertl, MD 1; Torsten H. Schroeder, MD 1;

Tübingen University Hospital, Dept. of Anesthesiology and Intensive Care Medicine 1, Hoppe-Seyler-Str. 3, 72076 Tübingen; Dept. of Medical Microbiology and Hygiene 2, Elfriede-Aulhorn-Str. 6, 72076 Tübingen; Dept. of Urology 3, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany;

**RUNNING HEAD: TREATMENT OF ESBL UROSEPSIS WITH TIGECYCLIN**

Corresponding author:

Wolfgang A. Krueger, MD

Tübingen University Hospital, Dept. of Anesthesiology and Intensive Care Medicine
Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany
Tel: ++49 – 7071 – 298-6622; Fax: ++49 – 7071 – 29-5533
E-mail: wolfgang.krueger@uni-tuebingen.de

E-mail addresses of co-authors:

volkhard.kempf@med.uni-tuebingen.de; peiffer.manou@web.de; udo.nagele@med.uni-tuebingen.de; ksunertl@med.uni-tuebingen.de; torsten.schroeder@uni-tuebingen.de;
Treatment of Recurrent Urosepsis Caused by ESBL-Producing *Escherichia coli* with Tigecycline

Abstract

A 25-year old female was admitted to our ICU in septic shock and multi-organ failure caused by ESBL-producing *E. coli* originating from the right renal pelvis. A 16-day treatment course of meropenem reversed the septic condition, but the infection recurred thereafter. The patient fully recovered after changing therapy to tigecycline.

Key Words: urosepsis, multiple-organ failure, ARDS, ESBL, *E. coli*, meropenem, tigecycline.
Case report

A 25-year-old female presented at a private practice with lower abdominal pain. She was suspected for urinary tract infection and was started on levofloxacin. Three days later, she presented with increasing abdominal pain at a municipal hospital, where she was diagnosed to suffer from urosepsis. She was immediately admitted to the ICU and the antibiotic treatment was switched to intravenous piperacillin-tazobactam.

Her past medical history was remarkable, since she was born with lumbar meningomyelocele and paraparesis below the 2\textsuperscript{nd} lumbar segment. She also suffered from neurogenic impairment of bladder emptying leading to chronic reflux into the renal pelvis. She had suffered from repeated episodes of pyelonephritis, which had caused cirrhosis of the kidneys and chronic renal impairment. She had not been on dialysis with the exception of a short period, that was already nine years ago. Furthermore, the following surgical procedures had been performed on her in the past: implantation of ventriculo-atrial shunt for treatment of hydrocephalus, bladder augmentation plasty, osteotomy at the left hip, and correction of pes equinus by achilles tendon plasty.

Despite treatment with piperacillin-tazobactam, the condition of the patient rapidly and dramatically deteriorated and she was intubated one day after ICU admission due to respiratory failure and development of septic shock. She required mechanical ventilation with 70\% oxygen and noradrenalin was applied up to 0.2 μg/kg/min. Antibiotic therapy was changed to cefotaxime and amikacin. Her platelet counts fell to 20,000/μL, which was interpreted as septic thrombocytopenia, and the patient developed anuric renal failure. A urinary sample obtained one day after ICU-admission grew \textit{E. coli}, but antibiotic susceptibility testing was still pending.
this situation, the patient was transferred by helicopter to the University Hospital of Tübingen, which is a tertiary care hospital, for further treatment of the life-threatening condition.

A CT-scan performed upon admission showed severe alterations of the lung tissue, that confirmed the diagnosis of ARDS. Additionally, pneumonic infiltrates were suspected on both sides in the dorsobasal regions. The kidney tissues showed chronic alterations, and the picture was compatible with pyelonephritis and several smaller renal abcesses (Figure 1).

After CT-scan, the patient was transferred immediately to our ICU, where blood cultures and tracheal aspirate were obtained, followed by immediate start of antimicrobial therapy with meropenem, linezolid, and voriconazole. Noradrenalin and dobutamine were given at 0.45 µg/kg/min and 5 µg/kg/min, respectively, and continuous infusion of hydrocortisone (200 mg/d) was started after an initial bolus of 100 mg. According to current guidelines, the patient was ventilated in a lung-protective manner applying a PEEP-level of 13 mbar with limitation of tidal volumes to 6 ml/kg body weight (1). The patient was then transferred into the operating room. Cystoscopy showed status post bladder augmentation plasty with a dilated left ureter without obstruction and with clear urine in the left renal pelvis. The right ureter was kinked and there was heavy discharge of pus from the right renal pelvis. Urinary samples were obtained from both sides for microbiological examination. Two mono-J-catheters were inserted for drainage of both renal pelvises. After this procedure, the patient was still anuric and continuous veno-venous hemofiltration was started.

One day after admission to our ICU, the antibiogram of *E. coli* isolated from urine 3 days before at the transferring hospital was sent by fax from an external microbiological laboratory. The pathogen turned out to be an extended spectrum beta-lactamase (ESBL)-producing *E. coli* resistant to piperacillin-tazobactam, fluoroquinolones, and trimethoprim-sulfamethoxazole. It was susceptible to imipenem and amikacin, with intermediate susceptibility to gentamicin and
tobramycin. The triple-combination of meropenem, linezolid, and voriconazole was continued, as long as the results from microbiological samples obtained in our hospital were still pending. Meropenem was given at 2 x 1g, as recommended for patients receiving continuous hemofiltration (3, 4). Linezolid was stopped on day 4, since the microbiological samples obtained upon admission showed uniform growth of *E. coli* in blood cultures, tracheal aspirate, and the sample obtained from the right renal pelvis. Antibiotic resistance pattern was similar to that obtained at the external microbiological laboratory, but the pathogen was tested susceptible to cefotaxime and was thus not classified as-ESBL producing. There was no bacterial growth in the sample from the left renal pelvis, but additional growth of *Candida glabrata* from the right renal pelvis. Therapy with voriconazole was therefore continued for a total of 10 days.

Meanwhile, the patient’s condition ameliorated: catecholamines were stopped on day 5 after admission to our hospital and the patient was changed from continuous veno-venous hemofiltration to intermittent dialysis on day 8. She was weaned from the respirator and extubated on day 12. Meropenem was stopped after a total of 16 days. Leucocytes, that had been elevated up to 30,720 / µL on admission were back to normal levels (8,100 / µL); CRP came down from 20,0 mg / dL to 12,9 mg / dL, and the body temperature was 37°C.

One day after stop of meropenem, the patient developed tachycardia (140 / min), the temperature rapidly increased to 39.0°C, and CRP increased to 21.8 mg / dL. Oxygen was administered via a rebreathing face mask with 8 L / min. A CT-scan showed dislocation of the ureter catheter on the left side (Figure 2). A new finding was cavernous destruction of the lower lobe of the right lung, but the CT-scan did not reveal any infectious focus in the thorax. Lower respiratory tract samples were not obtained, since non-invasive ventilatory support was applied in order to avoid re-intubation of the patient. Blood cultures were drawn but turned out negative later. Urinary samples were also without bacterial growth, but the value of this negative result...
was questionable in the presence of high antibiotic concentrations in urine. Thus, the most likely source of the repeated infection was again the urinary tract. Meropenem was started again and the double-J-catheter was repositioned, but the patient continued to have fever spikes up to 39.5°C. After two days, therapy was therefore switched to tigecycline. Within the next day, body temperature fell to normal levels and CRP fell to 6.9 mg/dL within 5 days. Furthermore, the patient produced sufficient amounts of urine, and blood urea and creatinine levels returned to normal ranges, which obviated the need for further dialysis.

The two mono-J-catheters were changed to double-J-catheters on day 24 after admission. The patient was transferred to the intermediate care unit on day 28 and one day later for another 7 days to the general ward. Tigecycline was stopped after a total of 13 days and the patient was discharged from our hospital in good clinical condition with stable renal and respiratory function after a total of 38 days.

Compared to sepsis from other sources, the prognosis of urosepsis is generally considered to be more favorable. Most antibiotics are excreted by the kidneys, which means that antibiotic concentrations are exceedingly high at the focus of sepsis and may even be therapeutically active in pathogens with less antibiotic susceptibility. Surgical drainage of the infected area can usually effectively be accomplished by relatively less invasive means. Finally, microbiological samples for identification of the pathogens and for targeting antibiotic therapy may also easily be obtained. In our young patient, pyelonephritis rapidly progressed despite prompt antibiotic treatment, causing life-threatening septic shock and multiple organ failure. Furthermore, the infection recurred despite 16 days of pathogen-targeted antibiotic therapy and surgical drainage of the initial focus, which was the right renal pelvis.
In our patient, pre-existent neurogenic impairment of bladder emptying had already caused repeated episodes of urinary tract infections and had previously necessitated several antibiotic treatment cycles, which certainly contributed to this overwhelming *E. coli* urosepsis described here. The empirical treatment with levofloxacin initiated in a private practice was not effective, since the pathogen turned out to be resistant to fluoroquinolones. However, resistance to the other antibiotics used in our patient remains not completely clear. The patient’s clinical condition rapidly deteriorated despite treatment with piperacillin-tazobactam, which was changed to cefotaxime and amikacin. This is consistent with the microbiological cultures obtained from a urinary sample in the transferring hospital, which showed *E. coli* with resistance to piperacillin-tazobactam and to 3rd generation cephalosporins due to ESBL production. In contrast, the pathogen isolated from blood culture, renal pelvis, and tracheal secretions upon admission to our hospital was not classified as ESBL, when tested according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Surgical drainage of the main focus in the right renal pelvis was certainly crucial for improvement of our patient. However, the fact that the pathogen was recovered from blood cultures and spread to the lung during ongoing antibiotic treatment documented therapeutic failure and is highly suggestive of ESBL-producing pathogens.

Our initial extremely broad therapy, which consisted of meropenem, linezolid, and voriconazole was started as a consequence of the treatment failure of the previous antibiotics. Furthermore, it was unclear whether *E. coli* isolated from a urinary sample upon admission in the municipal hospital would suffice to explain the progression of life-threatening septic shock despite antibiotic therapy. Linezolid was chosen for treatment of resistant Gram-positive bacteria that could have infected the ventriculo-atrial shunt. After foreign body infections had been ruled out, the empirical therapy with linezolid was stopped.
Treatment with voriconazole was justified later by the fact that *C. glabrata* was isolated from the right renal pelvis. Even though this is a relevant finding, one may well assume that progression to septic shock and multiple-organ failure was mainly caused by *E. coli*, and the contribution of *C. glabrata* to the overall clinical picture remains rather vague.

More important is the aspect, that treatment with meropenem together with surgical drainage of the renal pelvis reversed the clinical progress of the disease, but there was recurrent infection, when meropenem was stopped after 16 days. For severe infections, especially when caused by bacteria of intermediate susceptibility (2), continuous infusion of time-dependent antibiotics such as carbapenems has been suggested to improve clinical outcome (6). Thus, one might argue, whether continuous infusion of meropenem rather than twice daily bolus infusions would have been a more favorable mode of administration in our patient. On the other hand, the half-life of meropenem is prolonged at least 4-fold in anuric patients treated with continuous hemofiltration (4). This means that there is prolonged time above the minimal inhibitory concentration of the infecting pathogens and the pharmacokinetic profile of meropenem in such situations meets the pharmacodynamic requirements, even without using continuous infusions (3).

Our decision for switching therapy to tigecycline was based on its antibiotic activity against *E. coli* including ESBL-producing strains, and on the fact that approximately 30% of the dose of tigecycline are eliminated as parent drug by the kidneys (5). This means that high levels in the urinary system may be expected, even though to our knowledge there are no publications on using tigecycline for treatment of urinary tract infections. Furthermore, we wanted to avoid further prolongation of carbapenem therapy, given the risk of selecting for fungal infections (7), especially since our patient had already been co-infected by *C. glabrata*. After switch to
treatment with tigecycline, the patient’s condition improved rapidly and finally obviated the need for renal replacement therapy and for further treatment in our ICU.

Our case report has several limitations. The recurrent episode of urosepsis after stop of meropenem was not bacteriologically proven. However, other infectious foci were excluded by thorough clinical workup including repeated CT-scan. Urine cultures were negative, but such cultures are difficult to interpret, when obtained during ongoing antibiotic treatment. One might also argue, whether the fever spikes were simply caused by dislocation of the mono-J-catheter on the left side. On the other hand, the main focus had previously been the right renal pelvis, and the patient continued to have fever spikes even after repositioning of the left ureter catheter and after therapy with meropenem had been started again.

In conclusion, our patient suffered from life-threatening *E. coli* urosepsis, that rapidly progressed to multiple-organ failure despite antibiotic therapy. The microbiological results obtained from different laboratories were not completely consistent, but the clinical course strongly supported the finding of ESBL-producing *E. coli*. Even though septic shock and multiple-organ failure were reversed during prolonged treatment with meropenem, the infection was completely cured only after subsequently using tigecycline. Here, the 30% renal excretion of tigecycline may have contributed to the favorable outcome in our patient. We therefore conclude that tigecycline may be a useful treatment option for serious urinary tract infections caused by multi-resistant pathogens, but more clinical data supporting this hypothesis are needed.
References


Figure Legends

Figure 1
CT-scan on admission to our hospital showing chronic alterations of the kidneys and several smaller renal abcesses, which were compatible with acute pyelonephritis.

Figure 2
Dislocation of the ureter catheter on the left side. Cirrhosis of the kidneys with large hypodense areas.
Figure 1

Figure 2