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Successful Treatment of Extended-Spectrum β-Lactamase-Producing *Klebsiella pneumoniae* Recurrent Urinary Tract Infection with High Doses of Amoxicillin with Clavulanic Acid in a Kidney Transplant Recipients: A Case Report

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Abstract

Introduction: An increase in the number of infections with *Klebsiella pneumoniae* producing Extended-Spectrum β-Lactamase (ESBL+) is a clinical issue, because there are no guidelines regarding the correct choice of an antibiotic and duration of treatment in kidney transplant recipients. The bacterial capacity to degrade almost all β-lactam antibiotics, except carbapenems, causes resistance to standard treatment and makes long-term intravenous antibiotic therapy necessary.

Case Presentation: This report describes the case of a 44-year-old patient after kidney transplantation, who developed recurrent urinary tract infections (UTIs) caused by ESBL-producing *K. pneumoniae* despite prolonged antibiotic targeted treatments with imipenem/cilastatin, meropenem, imipenem/cilastatin with amikacin and oral phosphomycin for UTI prophylaxis. Ineffectiveness of previous treatments caused the necessity to use a non-standard therapy of the consecutive UTI episode with high doses of amoxicillin combined with standard doses of clavulanic acid to break the bacteria's resistance. There was no recurrence of UTI and control urine cultures were sterile over the entire course of treatment, lasting 165 days, and throughout the follow-up period of more than 1 year.

Conclusions: It has been shown in this case that UTI with the aetiology of *K. pneumoniae* could be treated on an outpatient basis with high doses of amoxicillin in combination with standard doses of clavulanic acid followed by prolonged antibiotic prophylaxis.

Keywords: Amoxicillin, Clavulanic Acid, Drug Resistance, Bacterial, Beta-Lactamases, Urinary Tract Infections, Kidney Transplantation, *Klebsiella pneumoniae*, *Klebsiella* Infections

1. Introduction

Infections caused by extended spectrum β-lactamase ESBL-producing *Klebsiella pneumoniae* are one of the major therapeutic and epidemiologic problems in kidney transplant recipients (1, 2). The bacterial capacity to degrade almost all β-lactam antibiotics, except carbapenems, causes resistance to standard treatment and makes long-term intravenous antibiotic therapy necessary. The growing problem of bacterial resistance and lack of efficacy of standard antibiotic treatment led to the implementation of a non-standard therapies (3, 4). Several reports confirm observations that high doses of beta-lactam antibiotics could overcome bacterial resistance *in vivo*. In the literature, there are cases describing the use of high doses of amoxicillin to effectively treat drug-resistant strains of pneumococcal carriage (5), community-acquired pneumonia (6), inflammation of the middle ear (5), and even in combined therapy with a high dose of esomeprazole to eradicate *Helicobacter pylori*. This report describes a case of a 44-year-old kidney transplant recipient, who, despite several prolonged, intravenous, targeted antibiotic therapies, developed recurrent urinary tract infection (UTI) caused by ESBL-producing *K. pneumoniae*. In an attempt to overcome bacterial resistance, high doses of amoxicillin in combination with standard doses of clavulanic acid were administered on an outpatient basis.

2. Case Presentation

A 44-year-old male had undergone kidney transplant surgery on 15th of May, 2014 due to kidney failure in course

of hypertensive nephropathy. On the eighth day after the surgery, he underwent a second operation due to ureteral stenosis, and soon after UTI, caused by ESBL-producing *K. pneumoniae*, was diagnosed (Table 1, culture 1). Treatment with imipenem/cilastatin 500/500 mg t.i.d. was administered for 14 days till the patient's discharge. One week later, the patient was admitted again with symptoms of UTI and positive urine culture for ESBL-producing *K. pneumoniae* (Table 1, culture 2). Treatment with meropenem was administered at a dose adjusted for kidney graft function for 21 days and phosphomycin was prescribed (3 g for 2 days, then 3 g per week) after the patient was discharged from the hospital to prevent recurrence of the infection. One week later, the patient was admitted to the hospital for the third time with massive pyuria and highly elevated inflammatory parameters: C-reactive protein (CRP) 423.2 mg/dL (normal range: 0 to 9 mg/dL) and procalcitonin 91.26 ng/mL (normal range: 0 to 0.5). Blood and urea cultures were positive for *K. pneumoniae* (Table 1, culture 3 and 4).

Treatment with imipenem/cilastatin 500/500 mg t.i.d. for 20 days and amikacin 500 mg once a day for 13 days resulted in quick clinical improvement and normalization of inflammatory parameters. Blood and urine cultures were negative during the treatment. At the discharge, phosphomycin was prescribed (3 g for 2 days, then 3 g 2 x per week) for the prevention of recurrence. After 3 weeks, the patient returned to the outpatient clinic with fever, pyuria, blood CRP elevation and positive urine culture for ESBL-producing *K. pneumoniae* strain with intermediate susceptibility to amoxicillin and clavulanic acid (Table 1, culture 5). The patient refused another hospital treatment due to problems he had with absence from his work.

Taking into account the ineffectiveness of previous treatments, despite various combinations of targeted antibiotics, it was decided to try breaking the bacteria's resistance with the use of high doses of amoxicillin combined with standard doses of clavulanic acid (total dose of 5750 mg amoxicillin plus 250 mg of clavulanic acid). After 7 days of treatment, the patient's symptoms were alleviated, CRP decreased, leukocyturia normalized and urine culture was sterile. The daily dose of amoxicillin was gradually reduced to 3750 mg/day in the second week, 1750 mg/day after the third week, then to 500 mg of amoxicillin and 125 mg of clavulanic acid twice daily and finally to a single dose overnight (Table 2). There was no recurrence of UTI during the 165 days of treatment and over the 1-year follow-up. On routine check-ups, the patient had stable kidney graft function, normal urine test, and sterile urine culture.

2.1. Microbiologic Testing

Blood samples were collected using an aseptic technique, then an automated blood culture system BacT/ALERT (bioMerieux, Marcy l'Etoile, France) was used. Samples were incubated in sets of 2 bottles for anaerobic and aerobic bacteria. All positive samples underwent the procedure of bacterial identification and antimicrobial susceptibility testing performed using the Vitek2 system (bioMerieux, Marcy l'Etoile, France), according to standard laboratory procedures. Midstream urine samples or catheterized urine samples were collected and transported to the laboratory within 2 hours and cultured on MacConkey agar and CPS agar (bioMerieux, Marcy l'Etoile, France). The plates were incubated at 37°C for 24 hours under aerobic conditions. Bacterial identification and antimicrobial susceptibility were performed using the Vitek2 system (bioMerieux, Marcy l'Etoile, France).

3. Discussion

The ESBL-producing *K. pneumoniae* originally belonged to the group of nosocomial pathogens, however, its spread into the general population became a cause of community-acquired infections (7). Genes encoding ESBLs are located on large plasmids, allowing the transfer of genetic material among gram-negative bacteria. Extended spectrum β-lactamases have the ability to degrade the β-lactam ring of pencillins (except temocillin), cephalosporins (without cephamycins), and monobactams (6). The individual groups and types of ESBLs differ in their activity. In accordance to the definition, ESBLs are inhibited by classic β-lactamase inhibitors (e.g. clavulanic acid), however, resistance due to other mechanisms could be observed (5).

In this case, the researchers decided to use higher that usual doses of amoxicillin due to its low toxicity despite the bacterial strain being intermediately susceptible to combination of amoxicillin and clavulanic acid *in vitro*. Taking into account previous infections caused by the same strain in this patient, it could be suspected that differences in the minimum inhibitory concentration (MIC) between resistant-intermediate, if it is the same strain, may result from error in the antimicrobial susceptibility testing (it is called small mistake). One of the possible reasons could be that the differences between MIC arise even in small changes in the inoculum (more inoculum - higher MIC). The highest recommended dose of amoxicillin is 6.0 g/day in the treatment of late stage of Lyme disease, however, a prospective study of 51 pediatric patients at a poison-control Centre suggested that over dosage of less than 250 mg/kg of amoxicillin is not associated with significant clinical symptoms.

Table 1. Antimicrobial Susceptibility (MIC values) of *K. pneumoniae* Isolates from Blood and Urine of the Patient

Culture No	1	2	3	4	5
Date	31.05.2014	25.06.2014	23.07.2014	23.07.2014	2.09.2014
Specimen	urinary catheter	urine	blood	urine	urine
ESBL	+	+	+	+	+
Antibiotic name	MIC	MIC	MIC	MIC	MIC
Amoxiclin/ clavulanic acid	≥ 32 R	= 16 R	≥ 32 R	≥ 32 R	= 8 I
Piperacillin /tazobactam	≥ 128 R	≥ 128 R	≥ 128 R	≥128 R	≥ 128 R
Ampicillin	≥ 32 R	≥ 32 R	≥ 32 R	≥ 32 R	≥ 32 R
Cefuroxime	≥ 64 R	≥ 64 R	≥ 64 R	≥ 64 R	≥ 64 R
Cefotaxime	≥ 64 R	≥ 64 R	≥ 64 R	≥ 64 R	≥ 64 R
Ceftazidime	≥ 64 R	≥ 64 R	≥ 64 R	≥ 64 R	≥ 64 R
Cefalexin	≥ 64 R	≥ 64 R	≥ 64 R	≥ 64 R	≥ 64 R
Cefepime	= 16 R	= 16 R	≥ 64 R	= 16 R	= 16 R
Ertapenem	≤ 0.5 S	≤ 0.5 S	≤ 0.5 S	≤ 0.5 S	≤ 0.5 S
Imipenem	≤ 0.25 S	≤ 0.25 S	≤ 0.25 S	≤ 0.25 S	≤ 0.25 S
Meropenem	S	S	= 0.064 S	S	S
Gentamicin	≥ 16 R	≥ 16 R	≥ 16 R	≥ 16 R	≥ 16 R
Amikacin	= 8 I	≤ 2 S	= 4 S	= 4 S	≤ 2 S
Ciprofloxacin	≥ 4 R	≥ 4 R	≥ 4 R	≥ 4 R	≥ 4 R
Norfoxacin	≥ 16 R	≥ 16 R	≥ 16 R	≥ 16 R	≥ 16 R
Trimethoprim/sulfamethoxazole	≥ 320 R	≥ 320 R	≥ 320 R	≥ 320 R	≥ 320 R
Treatment	Imipenem/ cilastatin (14 days)	Meropenem (21 days)	Imipenem/cilastatin (20 days) + Amikacin (13 days)	Amoxiclin/ clavulanic acid (165 days)	

Abbreviations: ESBL, Extended-Spectrum Ƀ-Lactamase; I, Intermediate Susceptibility; MIC, Minimal Inhibitory Concentration; R, Resistant Organism; S, Susceptible Organism.

Table 2. Summary of the Treatment

Visit Number	Treatment Day	Dose of Amoxicillin, mg/day	Dose of Clavulanic Acid, mg/day	CRP, mg/L (Normal Range: 0 - 9)	Leukocyturia, cells/HPF
1	0	3750	250	19.4	75
2	2	5750	250	6.7	11 - 18
3	6	5750	250	1.3	1 - 5
4	14	3750	250	0.3	1 - 5
5	21	1750	250	0.5	1 - 5
6	35	1750	250	0.7	1 - 5
7	49	1000	250	0.6	1 - 5
8	84	500	125	1.2	1 - 5
9	136	500	125	0.7	5 - 10
10	153	500	125		1 - 5

Abbreviations: CRP, C Reactive Protein; HPF, High-Power Field; WBC, White Blood Cell Count.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after over dosage with amoxicillin. Adjustment of the dose is necessary in chronic renal disease with eGFR < 30 mL/min and it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. Concurrent administration of allopurinol, the drug often used after kidney transplantation, during treatment with amoxicillin, could increase the risk of allergic skin reactions. Due to the potential toxicity of clavulanic acid, only the maximum recommended dose was used in the treatment. In the presented case, treatment quickly resulted in clinical improvement and eradication of pathogenic bacterial strain. The dose of medication was gradually reduced yet the treatment was continued with low-dose ampicillin for 6 months to prevent the recurrence of infection. The important aspect of such therapy was the outpatient basis that gave the patient the opportunity to go back to work after a few days. It is also worth mentioning that the success of the treatment reported in this case was the basis for the start of the use of high dose of amoxicillin in renal transplant patients with recurrent ESBL-producing *K. pneumoniae*.

4. Conclusions

Urinary tract infections caused by ESBL-producing *K. pneumoniae* could be effectively treated with a long-term therapy with high doses of amoxicillin in combination with standard doses of clavulanic acid, despite low bacterial susceptibility to these agents. Such treatment may be the only effective therapeutic option for patients with recurrent infections when other methods fail.

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Footnotes

Authors' Contribution: Study concept and design, Michal Ciszek, Leszek Paczek, Piotr Wilkowski; acquisition of data: Piotr Wilkowski, Kornelia Dobrzaniecka, Monika Wojtowicz, Dariusz Wasiak, Grazyna Mlynarczyk; analysis and interpretation of data, Michal Ciszek, Leszek Paczek, Piotr Wilkowski, Kornelia Dobrzaniecka, Monika Wojtowicz, Dariusz Wasiak, Grazyna Mlynarczyk; drafting of the manuscript: Michal Ciszek, Leszek Paczek, Piotr Wilkowski, Kornelia Dobrzaniecka, Monika Wojtowicz; critical revision of the manuscript for important intellectual content, Michal Ciszek, Leszek Paczek, Piotr Wilkowski, Dariusz Wasiak; study supervision, Leszek Paczek, Michal Ciszek, Grazyna Mlynarczyk.

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