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Case Report

Successful treatment of extreme drug resistant *Acinetobacter baumannii* infection following a liver transplant

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Abstract

Orthotopic liver transplantation is a life-saving procedure for patients with end-stage liver failure. However, *Acinetobacter baumannii* infections and acute rejection are important causes of morbidity and mortality following transplants. Here we present a case report of a cadaveric donor liver transplantation with infectious complications detected after transplantation.

The patient was a 64-year-old female. Because of non-alcoholic steatohepatitis due to hepatic insufficiency (model for end-stage liver disease (MELD): 12; Child-Pugh: 9B), liver transplantation from a cadaveric donor was performed. Following the transplantation, the patient developed a blood stream infection, urinary tract infection (UTI) and postoperative wound infection from biliary leakage. *A. baumannii* was isolated from blood, urine and wound cultures. Imipenem (4×500 mg), tigecycline (2×50 mg) and phosphomycin (4×4 g) were administered intravenously (IV). On the 14th day of treatment, the bile fistula closed and there was no bacterial growth in blood and urine cultures. The patient was discharged with full recovery.

The duration of a transplant patient's hospital stay, intensive care unit stay, invasive interventions, blood transfusions and immunosuppressive treatments cause an increased risk of extensively drug-resistant (XDR) *A. baumannii* infections, and a high mortality rate is seen despite antibiotic treatment. Phosphomycin, used in combination therapy, may be an alternative in the treatment of XDR pathogens in organ transplant patients, due to its low side effect profile and lack of interaction with immunosuppressives.

Key words: liver transplantation; *Acinetobacter baumannii*, phosphomycin.

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Introduction

Orthotopic liver transplantation is a life-saving procedure for patients with end-stage liver failure. In patients undergoing liver transplantation, 80% of post-infectious complications occur in the first year [1]. The incidence of infections due to *Acinetobacter baumannii* is 1.4–6.1% in patients who undergo liver transplantation, with a mortality rate of 39–80% for those infected [2].

Case Presentation

The patient was a 64-year-old female with diabetes mellitus, hypertension and coronary artery disease. Because of non-alcoholic steatohepatitis due to hepatic insufficiency (model for end-stage liver disease (MELD): 12; Child-Pugh: 9B), liver transplantation from cadaveric donor was performed. Piperacillin tazobactam (3×4.5 g IV, 48 hours) and fluconazole (1×100 mg IV, seven days) were given in prophylaxis. Trimethoprim/sulfamethoxazole and valganciclovir prophylaxis were started postoperatively within the first 10 days. The standard immunosuppressive treatment protocol was tacrolimus, mycophenolate mofetil and methyl prednisolone for the first three months and then tacrolimus. Due to a femoral fracture on the postoperative 82nd day and due to leakage of bile anastomosis on the 94th day, reoperations were performed. On physical examination, the patient's body temperature was 38°C, blood pressure was 81/53 mmHg, pulse was 143/min and respiration was tachypnoeic. There was discharge due to bile stasis on the operation scar. Haemoglobin = 10.7 g/dL, white blood cells (WBCs) = 12,890/mm^3 (78% polymorphonuclear leukocytes (PMNL)), C-reactive protein (CRP) = 25 mg/dL, procalcitonin = 0 ng/mL, alanine aminotransferase (ALT) = 10 IU/L, aspartate aminotransferase (AST) = 20 IU/L, blood urea nitrogen (BUN) = 78 mg/dL and creatinine = 1.75 md/dL were found in laboratory tests. Meropenem (3×1 g IV) and teicoplanin (2×400 mg IV) were started. Bacterial

growth in the wound culture showed extensively drug-resistant (XDR) (penicillin, ampicillin/sulbactam, third-generation cephalosporin, co-trimoxazole, aminoglycoside, fluoroquinolone and carbapenem-resistant) but only colistin-susceptible (minimum inhibition concentration (MIC) < 2 μg/mL) *A. baumannii*. After loading 300 mg/day, colistin (2×150 mg IV) was started and the meropenem dose was increased to 3×2 g. After 72 hours, BUN = 89 mg/dL and creatinine = 2.54 mg/dL were found. Colistin treatment was discontinued and tigecycline (2×50 mg) maintenance treatment was started after 100 mg loading.

On the 23rd day of the antibiotic therapy, bile leakage continued at the wound site. XDR *A. baumannii* was found in blood and urine cultures and lab tests showed WBCs = 6770/mm^3, CRP = 10.3 mg/dL and procalcitonin = 1 ng/mL. Imipenem (4×500 mg) and phosphomycin (4×4 g IV) were started. After 48 hours, due to CRP increase (CRP = 17.6 mg/dL), tigecycline (50 mg/q12h IV) was added after 100 mg loading. On the 14th day of treatment, the bile fistula closed, and there was no bacterial growth in blood and urine cultures. Laboratory tests showed WBCs = 5320/mm^3, CRP = 2.9 mg/dL and procalcitonin = 0 ng/mL. The patient was discharged with full recovery.

Discussion

The risk of infection with multidrug-resistant (MDR)/XDR bacteria is increased in solid organ transplantation (SOT) recipients because of long-term hospitalization (especially in intensive care), invasive procedures, comorbidities and immunosuppressives. As a result, mortality risk was increased, graft survival was reduced, and antibiotic use in SOT recipients was investigated in 54%, and it was found that this resulted in a 3.5-fold increase in mortality [1,2]. Early treatment can reduce bacteraemic infections by 15% and severe sepsis and septic shock-related mortality by 50% [3].

The risk of biliary complications after liver transplantation has been reported in the range of 5–30%. Biliary leaks cause opportunistic infections, bile duct necrosis and prevention of arterial collateralisation [3,4]. Metallo-beta-lactamase-, oxacillinase- and carbapenem-resistant MDR and XDR *A. baumannii* species are increasing [5]. Bacterial resistance to beta-lactams, aminoglycosides, fluoroquinolones and tetracyclines, such as broad-spectrum antibiotics, has also increased. Colistin is the cornerstone of carbapenemase-producing *Acinetobacter* treatment [5,6]. Combinations with tigecycline, sulbactam, aminoglycosides, rifampicin, phosphomycin and/or carbapenems have been tried because of the increasing number of MDR and XDR pathogens and the lack of new antibiotics [6,7].

Phosphomycin is a phosphonic acid derivative that inhibits UDP-N-acetyl glucosamine (MurA). Thus, it inhibits the first step of bacterial cell wall synthesis [8,9]. It has remained active against both Gram-positive and Gram-negative MDR and XDR bacteria. It prevents bacterial invasion into the urinary and respiratory epithelium. Phosphomycin has an immunomodulating effect, effective on a biofilm structure, that increases neutrophilic phagocytosis even in patients with chronic renal failure and in transplant patients [8]. *In vitro* studies with XDR *A. baumannii* producing OXA-23 demonstrated the combinations of imipenem+phosphomycin, meropenem+amikacin, imipenem+amikacin and imipenem+colistin had synergistic effects of 65.2%, 46.2%, 30.8% and 17.4%, respectively [10,11]. In another study, aminoglycoside, sulbactam or colistin and phosphomycin were found to be synergistic combinations [10,11]. In addition, the combinations prevented the development of resistance to phosphomycin [10-12]. In 94 patients infected with carbapenem-resistant *A. baumannii*, when colistin and colistin + phosphomycin treatments (7–14 days) were compared, there was a significantly better microbiological response and better clinical outcome compared to monotherapy [13]. In the meta-analysis results of clinical studies using the results of 128 studies and including 5527 patients and using phosphomycin +colistin combination was found to be more effective for carbapenem-resistant *A.baumannii* than colistin treatment alone [14]. According to meta-analysis of 23 studies examining pneumonia due to resistant Acinetobacter, clinical cure rate was found to be more effective in combination of inhaler colistin+IV colistin+sulbactam, and microbiological eradication rate in phosphomycin+intravenous colistin+sulbactam combination compared to colistin treatment alone [15]. The risk of renal toxicity is increased in patients undergoing solid organ transplantation due to reduced glomerular perfusion and the use of nephrotoxic agents (such as calcineurin inhibitors). In these patients, aminoglycosides and colistin used in the treatment of infections with resistant microorganisms due to increase the risk of renal toxicity. In animal studies, histamine release from aminoglycoside-associated mast cells was inhibited by phosphomycin and was shown to be protective against nephrotoxic effect [9]. No interactions related to immunosuppressives have been described. The most common side effects of intravenous phosphomycin-disodium are

hypernatremia and hypokalemia, resulting in edema, acid and heart failure [15]. No side effects were seen in our case.

As a result; In the treatment of infections in solid organ transplant recipients, treatment decision should be made according to the place of infection, liver and kidney function values, comorbidities and resistance profile of regional strains. phosphomycin may be an alternative in the treatment of XDR pathogens in organ transplant patients, in combination therapy due to its low side effect profile and lack of interaction with immunosuppressives.

Authors' Contributions

TS wrote the article, organized the data and prepared the manuscript. MRA and SY organized the data and prepared the manuscript. TS and MRA revised the manuscript. All authors contributed to analysis and interpretation of the data, read and approved the final version of the manuscript.

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