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Prolonged Meropenem Infusion Therapy for Multidrug Resistance (MDR) *Klebsiella pneumoniae* Infection Following Liver Transplantation: A Pediatric Case Report

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ABSTRACT: In this case report, we present a 2-year-old child treated with long-term meropenem infusion for multidrug-resistant (MDR) Klebsiella pneumoniae bacteremia after liver transplantation. The patient underwent transplantation due to Progressive Familial Intrahepatic Cholestasis Type 2 (PFIC-2). MDR Klebsiella pneumoniae was detected in blood cultures on the 18th postoperative day. Since no clinical response was observed to the empirical amikacin treatment, the treatment was switched to colistin and meropenem combination. Upon recurrence of the infection, meropenem was administered as a 3-hour long-term infusion by increasing the dose. Following this approach, significant clinical improvement was observed, with a marked decrease in inflammatory markers. Importantly, liver function tests remained stable throughout the treatment period. This case highlights that extended meropenem infusion may be a valuable therapeutic option in the management of MDR Gram-negative infections in pediatric liver transplant recipients and highlights its potential efficacy and safety in such high-risk patient populations

Keywords: Liver transplantation, Meropenem, Prolonged infusion, MDR, *Klebsiella pneumoniae*

1 INTRODUCTION

Bacteria are responsible for 95% of infections observed in solid organ transplant (SOT) recipients, and it is estimated that approximately 60% of bacterial infections after SOT are caused by multidrug-resistant (MDR) bacteria [1]. Liver transplant recipients, in particular, have a high incidence of MDR colonization and infection due to factors such as immunosuppression, prolonged hospital stay, multiple hospitalizations, invasive devices, frequent antibiotic use, renal failure, and malnutrition [2,3]. Meropenem, a broad-spectrum beta-lactam antibiotic, is commonly used in critically ill patients for treating serious

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infections, including those caused by MDR bacteria [4]. In liver transplant recipients, various levels of inflammation and oxidative stress post-transplantation significantly influence the pharmacokinetics and pharmacodynamics of antibiotics by altering the liver regeneration, graft characteristics, functional hepatocyte count, and liver enzyme activity [5]. However, limited data are available on the pharmacokinetics of meropenem following liver transplantation [6].

As with other antibiotics in the beta-lactam group, the bactericidal activity of meropenem is time-dependent. Therefore, both microbiologic and clinical outcomes rely on the dosing interval during which free drug concentrations remain above the pathogen's minimum inhibitory concentration (%fT>MIC) [7]. Optimal antibacterial activity in non-serious infections occurs when the %fT>MIC is ≥40% of the dosing interval. However, a higher proportion %fT>MIC (70% to 80%) is required in critically ill patients**.** Due to its time-dependent activity, it has been suggested that prolonging the infusion time and/or increasing the dosing frequency increases the likelihood of reaching the target (%fT>MIC) set for meropenem, leading to improved clinical outcomes [8]. The aim of this case report is to demonstrate the efficacy of extended meropenem infusion in the treatment of MDR Klebsiella pneumoniae infection after liver transplantation.

2 CASE

In 2023, a 2-year-old girl who was diagnosed with Progressive Familial Intrahepatic Cholestasis subtype 2 (PFIC-2) and suffering liver failure for the past year underwent liver transplantation on day 0. Postoperatively, the patient weighed 11 kg. On postoperative day 1, intravenous (IV) methylprednisolone was initiated at a dose of 11 mg/day (1 mg/kg/day), and on postoperative day 4, IV tacrolimus (Prograf) was started at a dose of 2x0.55 mg (0.05 mg/kg/dose, every 12 hours) as immunosuppressive therapy. For prophylaxis, pediatric patients received, 1x275 mg (25 mg/kg/day) IV sultamycillin, 1x66 mg (6 mg/kg/day) IV fluconazole and 2x55 mg (5 mg/kg/dose every 12 hours) IV ganciclovir according to protocols determined by the Liver Transplant Institute affiliated with the university hospital.

On the day of transplantation (day 0), the patient's C-reactive protein (CRP) level was 0.63 mg/dL (reference range: 0–0.351 mg/dL), and the procalcitonin (PCT) level was 0.003 ng/mL (reference range: 0–0.5 ng/mL). In the biochemical evaluation

performed on the same day, the serum creatinine level was 0.30 mg/dL, and accordingly, the estimated glomerular filtration rate (eGFR) value calculated according to the Schwartz formula was found to be approximately 117 mL/min/1.73 m². No microorganism growth was detected in the culture samples taken from the patient on postoperative days 1 and 2. On postoperative day 3, CRP and PCT increased to 1.79 mg/dL and 1800 ng/mL, respectively, and the patient developed a fever. Empirical sultamicillin treatment was discontinued and IV meropenem at a dose of 3x220 mg (20 mg/kg /dose, every 8 hours) and IV teicoplanin were initiated. Teicoplanin was administered as a loading dose of 10 mg/kg /dose, given in 3 doses, followed by a maintenance dose of 1x 66 mg (6 mg/kg /dose every 24 hours), and this regimen was continued for 14 days. On postoperative day 18, *MDR Klebsiella pneumoniae* growth was detected in blood cultures obtained from the patient and CRP and PCT levels elevated to 18 mg/dL and 6880 ng/mL, respectively. Based on the antibiotic susceptibility results, IV amikacin (Susceptible=S) at a dose of 1x165 mg (15 mg/kg/day) was administered on day 18. Considering the presence of a central venous catheter and a history of invasive intervention, the infection was suspected to be catheter-associated bloodstream infection. On postoperative day 18, the patient's serum creatinine level was 0.40 mg/dL, and the (eGFR) was approximately 88 mL/min/1.73 m². On postoperative day 20, CRP was 9.58 mg/dL, and PCT was 4730 ng/mL. Due to worsening tachycardia, amikacin treatment was discontinued. On the same day, IV colistin (Susceptible=S, MIC=0.5) was started at a dose of 2x55 mg (5 mg/kg/dose every 12 hours, administered as a short-term infusion) and IV meropenem was continued at a dose of 3x220 mg (20 mg/kg/dose every 8 hours) despite being resistant (R) with a MIC of 16 to prevent resistance to colistin. In the biochemical evaluation performed on the same day, serum creatinine level was found to be 0.45 mg/dL and glomerular filtration rate (eGFR) was approximately 78 mL/min/1.73 m². On postoperative day 25, it was found that the same pathogen grew again in the blood culture obtained from the patient and CRP was 15.9 mg/dL, while PCT was 2680 ng/mL. In this case, although tigecycline was sensitive (S) in the pediatric patient, it could not be administered due to her age and the potential side effects it may cause on the liver. Instead, colistin (2 × 55 mg, administered via short-term infusion) and meropenem (3 × 220 mg, administered via 3-hour prolonged infusion) were initiated. On postoperative day 25, the patient's serum

creatinine level was 0.35 mg/dL, and the eGFR was approximately 100 mL/min/1.73 m². By postoperative day 27, CRP had decreased to 13 mg/dL, and PCT to 1820 ng/mL. Based on these laboratory findings, the meropenem dose was increased on day 27 and the patient received 3x440 mg (40 mg/kg/dose every 8 hours) as a 3-hour infusion. CRP and PCT levels and the patient's complaints of tachycardia started to decrease on the postoperative day 29, the patient's serum creatinine level was 0.32 mg/dL, and the eGFR was approximately 110 mL/min/1.73 m². CRP and PCT levels of the patient are given in Figure 1 and 2, respectively. By postoperative day 35, CRP and PCT levels had decreased to 1.42 mg/dL and 0.206 ng/mL, respectively. Additionally, the patient's complaints of tachycardia disappeared, and as a result the antibiotic regimen was discontinued. Throughout the treatment there was no observed deterioration in liver enzymes. After stabilization in the intensive care unit, the patient was transferred to the ward and discharged in a clinically stable condition after a 20-day follow-up period. Informed consent was obtained from the legal guardian for the publication of this case report.

3 DISCUSSION

In the treatment of serious infections in pediatric patients, studies have demonstrated that administering beta-lactam antibiotics via prolonged infusion significantly reduces all-cause mortality rates in children and leads to earlier microbiological elimination [9,10]. However, this approach has not yet been widely recommended in guidelines, as there are still insufficient randomized controlled studies on this topic. Therefore, all studies, including case reports, that demonstrate the effectiveness of extended infusion applications will contribute to the literature. A 2-year-old girl who underwent liver transplantation was initially treated with amikacin for MDR *Klebsiella pneumoniae* grown in blood culture. However, due to a lack of improvement in clinical and laboratory findings, the patient's treatment was changed to receive colistin (short-term infusion) and meropenem (short-term infusion) to prevent the development of resistance to colistin. Despite this combination therapy, upon regrowth of the causative pathogen, meropenem was administered as a 3-hour prolonged infusion together with colistin. Although CRP and PCT levels decreased initially, the meropenem dose was increased and administered as a 3-hour prolonged infusion to achieve a significant decrease. Prolonging both the dose and duration of administration of meropenem resulted in an improvement in the patient's clinical

findings and a significant decrease in laboratory parameters.

There are limited studies demonstrating the effectiveness of prolonged infusion of meropenem in pediatric patients undergoing liver transplantation. The study conducted by Morales Junior et al. in 2023 aimed to determine the optimal infusion time of meropenem in this patient population, marking the first investigation of its kind in the literature [5]. In this study, patients receiving meropenem (40 mg/kg/dose, every 8 hours) were divided into two groups. The first group received meropenem as a 15-minute short-term infusion, while the second group received it as a 3-hour prolonged infusion. In both groups, the therapeutic target was achieved 100% against pathogens with MIC ≤ 8 mg/L. In the study, the authors did not report any toxicity in the group treated with the 15-minute infusion; however, they noted that higher peak and trough plasma meropenem levels were detected in these patients, which may lead to unnecessary total drug exposure (overexposure). This safety assessment is based not only on peak and trough concentrations but also on the 24-hour area under the curve ($AUC_{(24)}$) data reported in the study. Indeed, $AUC_{(24)}$ is one of the pharmacokinetic parameters that best reflects total drug exposure. In the study by Morales Junior et al. $AUC_{(24)}$ was reported as 5318.5 mg/h/L in the short infusion group and 2041.9 mg/h/L in the extended infusion group, and this difference was found to be statistically significant ($p< 0.05$). This result suggests that extended infusion administration provides therapeutic effect with lower drug exposure and reduces the risk of potential toxicity. The present case agrees with the findings of Morales Junior et al. In our study, there was no response to the initial short-term meropenem infusion; however, significant improvement in laboratory values and clinical stabilization were achieved with the prolonged infusion regimen.

In the study conducted by Cies et al. in 2018, an attempt was made to determine an appropriate meropenem regimen based on pharmacokinetic parameters in pediatric patients aged 1-9 years with sepsis and septic shock [11]. The study revealed that the meropenem regimen administered via short-term infusion at doses of 20-40 mg/kg/dose every 8 hours failed to achieve the desired pharmacodynamic target in critically ill children aged 1-9 years. According to the findings, only extended infusion durations of 3 to 4 hours and continuous infusion over 24 hours were deemed capable of achieving the optimal target of 40%fT>MIC against all susceptible Gram-negative bacteria in

critically ill children. Additionally, Cies et al. suggested that dosage regimens of 120 and 160 mg/kg/day could be administered as continuous infusion regimens to potentially attain the optimal target for meropenem against all susceptible Gram-negative bacteria, achieving an %fT>MIC of 80% in critically ill children.

In a study conducted by Wang et al. in 2020 based on pharmacokinetic analyses to optimize the meropenem treatment regimen in 57 pediatric patients with severe infections, it was found that the likelihood of reaching the target for pathogens with MIC values of 1 and 2 µg/mL with 4-hour infusion of 40 mg/kg/dose every 8 hours was 87.5% and 68.6%, respectively. It was stated that administration of meropenem at a dosage of 110 mg/kg/day and continuous infusion may be more effective for bacteria with high MIC values (2-8 µg/mL) [12].

In a prospective study conducted by Maimongkol et al. in 2022, meropenem was administered as 20-40 mg/kg/dose every 8 hours, either via intermittent infusion (0.5-1 hour) or prolonged infusion (3 hours) in 72 pediatric patients aged 1 month-18 years. The study emphasized that intermittent infusion of meropenem should not be used in critically ill children, even if central nervous system infection is not suspected. A %fT>MIC ratio of 50% and %fT>MIC ratio of 100% were more frequently achieved in patients receiving extended meropenem infusion at a dosage of 40 mg/kg/dose every eight hours. It was suggested that extended meropenem infusion may be effective for pathogens with MIC values <8 mg/L [13].

Considering the literature data, in this case, the administration of meropenem via a 3-hour infusion at a dose of 20-40 mg/kg/dose every 8 hours led to a significant decrease in CRP and PCT levels, and an improvement was observed in the patient's clinical condition. It can be concluded that meropenem given with prolonged infusion was effective in our patient.

Although meropenem is known as an agent that is primarily excreted by the kidney, several sources have reported that its hepatic metabolism is not completely negligible. In particular, as reported by Craig et al., meropenem is converted to an inactive form in the liver by hydrolysis of the β-lactam ring, suggesting that the drug is also metabolized by the hepatic pathway [14]. This metabolic pathway suggests that the liver fulfills a detoxification role and contributes to meropenem elimination, albeit to a limited extent. However, this conversion by hepatic hydrolysis may contribute to pharmacokinetic variability,

especially in patients with impaired liver function or transplantation.

Meropenem is eliminated unchanged, primarily via the kidneys, by glomerular filtration, with more than 70% of elimination occurring renally. For meropenem, which is eliminated by renal elimination, decreases in glomerular filtration rate may lead to drug accumulation in serum and the development of associated toxic effects [15]. This requires close monitoring of renal function, especially in high-dose and prolonged infusion regimens. Despite the high dose and prolonged infusion, the patient's serum creatinine levels remained stable (range 0.30–0.45 mg/dL) during the pre- and post-treatment periods, indicating that renal functions were preserved and meropenem treatment did not cause nephrotoxicity.

There is an increasing number of studies in the literature suggesting that the combination of meropenem and colistin may reduce the development of resistance compared to colistin monotherapy. In addition, in vitro studies have shown that this combination therapy may suppress the emergence of colistin-resistant subpopulations [16,17]. In the presented case, meropenem was administered as combination therapy with colistin in the treatment of MDR Klebsiella pneumoniae infection, despite the fact that it was reported as resistant in the antibiogram, and a significant clinical and laboratory response was obtained. This approach is thought to not only improve treatment efficacy but also to prevent the development of secondary resistance to colistin. Such synergistic combinations are considered to be an important strategy for antimicrobial resistance management, especially in patient groups with intense immunosuppression such as transplantation.

However, it's important to note that the lack of meropenem blood level measurements in our hospital for this case report constitutes a limitation. The quantitative measurement of meropenem blood levels during the treatment regimens applied would enhance the strength of evidence regarding the infusion method's efficacy.

4 CONCLUSIONS

The prevalence of multidrug-resistant (MDR) organisms is rising among pediatric transplant patients. Considering the regeneration process after liver transplantation and patient-related factors, there is a need for additional data from pediatric liver transplant patients to elucidate the pharmacokinetic and pharmacodynamic characteristics of meropenem.

Based on this case, prolonged meropenem infusion may represent a valuable therapeutic option for the treatment of MDR Gram-negative infections in pediatric liver transplant recipients, due to its potential to improve clinical outcomes while preserving liver function.

5 AUTHOR CONTRIBUTIONS

Hypothesis: K.G.S., D.M., Ö.A.N.; Design: K.G.S., D.M., Ö.A.N.; Literature review: K.G.S., D.M., Ö.A.N.; Data Collection: K.G.S., D.M., Ö.A.N., G.Ş., V.İ.F.,; Analysis and/or interpretation: K.G.S.,D.M., Ö.A.N..G.Ş., V.İ.F.F.,; Manuscript writing: K.G.S., D.M., Ö.A.N., G.Ş., V.İ.F.

6 CONFLICTS OF INTEREST

Authors declare that there is no conflict of interest.

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