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CASE REPORT

Clinical Pharmacist Involved in the Treatment of *Pneumocystis carinii* Pneumonia: A Case Report

Fangyuan Lai[1,*], Xiuqiong Huang[2,*], Jiao Peng[3], Nannan He[4], Zhongqiang Cao[1], Yuhui Wu[4], Wei Li[5], Zebin Chen[1], Xuejuan Li[1]

[1]Department of Pharmacy, Shenzhen Children's Hospital, Shenzhen, People's Republic of China; [2]Department of Pharmacy, The First People's Hospital of Zhaoqing, Zhaoqing, People's Republic of China; [3]Department of Pharmacy, Peking University Shenzhen Hospital, Shenzhen, People's Republic of China; [4]Department of Pediatric Intensive Care Unit, Shenzhen Children's Hospital, Shenzhen, People's Republic of China; [5]Department of Pharmacy, The Third People's Hospital of Shenzhen, Shenzhen, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xuejuan Li, Department of Pharmacy, Shenzhen Children's Hospital, Shenzhen, People's Republic of China, Email xuejuanli@126.com

Objective: The first-line treatment for severe *Pneumocystis carinii* pneumonia (PCP) is trimethoprim-sulfamethoxazole (TMP/SMZ). Here, we report a case involving 6-month-old child with a PCP infection, highlighting the role of clinical pharmacists in providing individualized pharmaceutical care and guidance through the process of therapeutic drug monitoring (TDM).

Methods: The clinical pharmacist monitored the concentration of TMP/SMZ in the serum, urine and sputum of a 6-month-old child with PCP infection. To improve the serum levels of TMP/SMZ, the dose of TMP/SMZ was increased, while infusions of other medications were reduced to decrease the rate of drug excretion. Additionally, the patient received other supportive medications to enhance clinical therapeutic efficacy.

Results: Clinical pharmacists observed that, despite administration of a sufficient dose of TMP/SMZ, plasma concentration of TMP/SMZ remained below the therapeutic window, while urine concentrations were extremely high. This phenomenon was attributed to Augmented Renal Clearance (ARC), often seen in critically ill patients and associated with increased renal clearance. Throughout treatment, the concentrations of SMZ remained below the minimum effective concentration, while the concentrations of TMP fell within the effective target range. However, sufficient therapeutic effects were ultimately achieved and observed in the patient, likely due to improved drug distribution in lung tissue (sputum) and the patient's recovering immune functions. Finally, thanks to individualized pharmaceutical care from clinical pharmacists and the combined efforts of clinicians, the patient was discharged after 58 days of hospitalization.

Conclusion: Throughout treatment, the clinical pharmacist played a vital role in optimizing the treatment plan based on the serum, urine and sputum concentrations of TMP/SMZ and providing pharmaceutical care to ensure a safe, rational and effective medications in children. Individualized dose adjustments, particularly high-dose TMP/SMZ guided by TDM, can significantly enhance the management of PCP in pediatric patients and support clinical pharmacists in delivering individualized pharmaceutical care.

Keywords: *Pneumocystis carinii* pneumonia, trimethoprim/sulfamethoxazole, therapeutic drug monitoring, plasma drug concentration

Introduction

Pneumocystis carinii is widely distributed in nature, inhabiting the respiratory tracts of humans and a variety of mammals. While most are inapparent infections, this organism can cause opportunistic infections in individuals with immunodeficiency or compromised immune functions, leading to severe *Pneumocystis carinii* pneumonia (PCP).[1] A recent study also estimated that *Pneumocystis carinii* pneumonia (PCP) affects approximately 505,000 people, with 214,000 deaths (42.4%) across more than 120 countries.[2] Some studies indicate that PCP has a high mortality rate regardless of co-infection with human immunodeficiency virus (HIV), with mortality rate in non-HIV patients exceeding 50%.[3–5] The first-line treatment for PCP is trimethoprim-sulfamethoxazole (TMP/SMZ).[6,7] However, high mortality rates and significant incidence of adverse drug reactions (ADRs) amongst other clinical challenges remain common despite

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TMP/SMZ therapy.[8,9] Recent studies showed an increase in TMP/SMZ use in pediatric populations, correlating with a rise in treatment-related ADRs.[10,11] Therefore, achieving precise administration of TMP/SMZ with adequate drug concentration at the site of infection while minimizing the risk of related ADRs remains a key clinical priority.

Early clinical trial data indicated that higher exposure levels (mean C_{max} of 13.6 μg/mL for TMP and 372 μg/mL for SMZ) are associated with intolerable incidences of drug toxicity in treating *Pneumocystis carinii* infections.[12–14] Research by Brown suggests a target C_{max} levels of 5–8 μg/mL for TMP and 100–200 μg/mL for SMZ.[15] In addition, TMP/SMZ exhibits significant interindividual pharmacokinetic variability.[16] Notably, the half-life of TMP/SMZ increases with age and correlates directly with serum creatinine levels.[17] A recent study reported that using the recommended dose adjusted for renal function resulted in sub-therapeutic plasma concentrations of TMP/SMZ during continuous veno-venous hemofiltration (CVVH) in a patient with COVID-19 and pulmonary *Pneumocystis carinii* co-infection.[18] Therefore, monitoring TMP/SMZ concentrations during treatment is essential for evaluating the efficacy and safety of drug therapy, helping to optimize clinical therapeutic effects and reduce adverse reactions. Further studies are needed to determine the optimal dosage of TMP/SMZ that balances efficacy with tolerable side effects, thereby achieving an optimal antimicrobial therapy for PCP.[19] This paper presents a systematic analysis of a case in which clinical pharmacists monitored the plasma, urine and sputum concentrations of TMP/SMZ in a child with PCP. They adjusted the treatment plan based on the results to manage the child's deteriorating condition, ultimately achieving a successful cure. This study offers significant insights for the clinical prevention and management of PCP.

Case Presentations

A six-month-old male patient was admitted to our hospital's pediatric intensive care unit on September 21, 2023, due to a persistent cough for over 20 days, accompanied by wheezing and shortness of breath for one day. The patient's medical history included recurrent eczema; however, there were no known food or drug allergies. Family history revealed allergic rhinitis in the father and an allergy to yams and penicillins in the mother.

Upon admission, physical examination stated the following vital signs: temperature (T), 36.8 °C; pulse rate (P), 118 beats per minute; respiratory rate (RR), 50 breaths per minute; blood pressure (BP), 99/55 mmHg; pulse oxygen saturation (SpO2), 90%; and body weight, 6.6 kg (Figure 1).

Upon hospitalization on September 24, the patient was empirically treated with TMP/SMZ tablets (0.12 g, q6h) via nasal feeding. On September 25, a chest CT scan revealed severe pneumonia (Figure 2). Further diagnostic test was carried out on September 28, large amounts of *Pneumocystis carinii* cysts were identified in the bronchoalveolar lavage fluid (BALF) upon silver hexamine staining. Subsequently, on September 29, treatment regimen was adjusted from TMP/SMZ tablets to TMP/SMZ injections (0.24 g, q8h), in conjunction with caspofungin (17.5 mg, qd) for intravenous administration against *Pneumocystis carinii* infection (Figure 3). On October 2, Next-Generation Sequencing (NGS) of

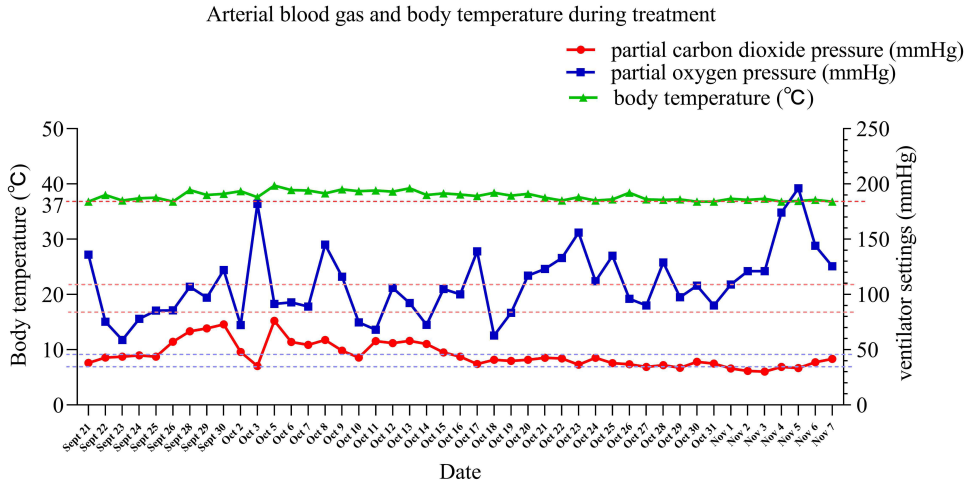

Figure 1 Ventilator settings and body temperature in this patient during treatment.

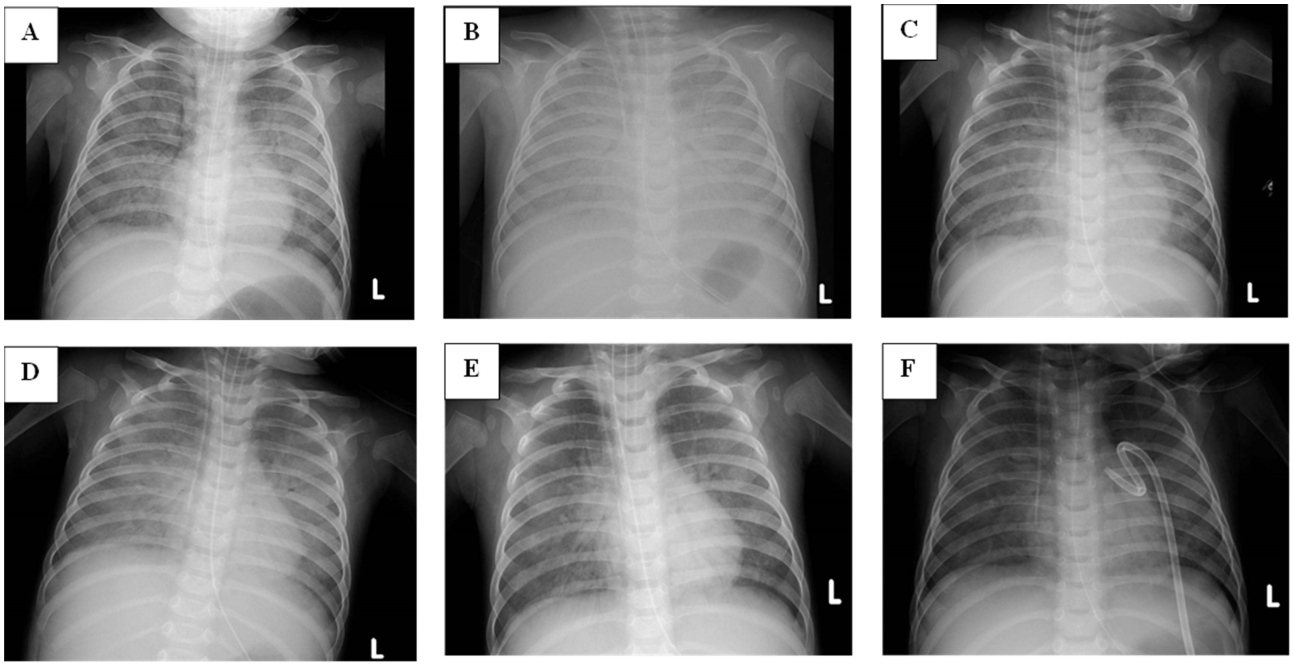

Figure 2 Posteroanterior Chest Digital Radiography (DR) of patient at different time-points during treatment (**A**: September 25), (**B**: September 28), (**C**: October 7), (**D**: October 19), (**E**: October 29) and (**F**: November 6).

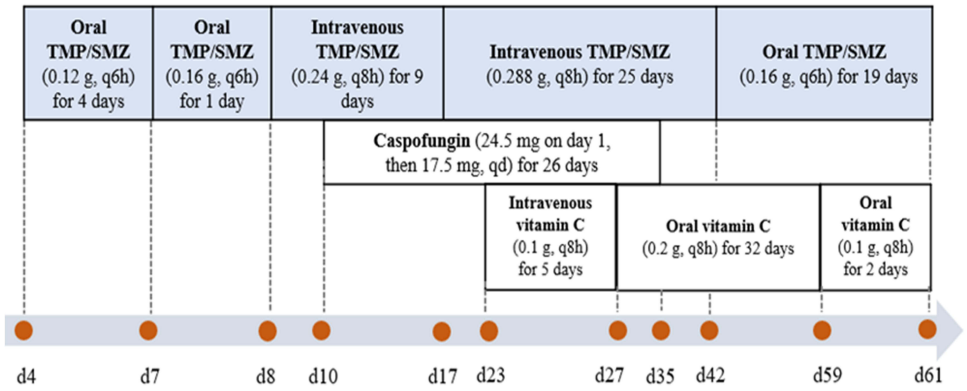

Figure 3 Course of medication during the patient's treatment.

pathogenic microorganisms in the blood confirmed the presence of *Pneumocystis carinii* with sequence number 196. On October 7, a Posteroanterior Chest Digital Radiography (DR) showed that pneumonia was combined with pulmonary oedema, which had persisted and exacerbated compared to previous assessments. At this time, the plasma concentrations were measured as 67.7 μg/mL for SMZ, and 3.9 μg/mL for TMP (Figure 4A). According to concentration results, the dose of TMP/SMZ was increased to 0.288 g, q8h, and administered via intravenous infusions. On October 9, silver hexamine staining of the BALF revealed and increased number of *Pneumocystis* trophozoites, indicating an ongoing infection. NGS of the BALF confirmed the presence of *Pneumocystis carinii* with sequence number 10013; To acidify the urine, Vitamin C injections (0.1 g, q8h) were administered. Clinical response has been seen and marked by gradual improvements. On October 18, the patient's body temperature gradually returned to normal, and symptoms of shortness of breath and wheezing had ameliorated, allowing for the gradual weaning of ventilator parameters. On November 2, the patient was successfully extubated and transitioned to high-flow oxygen therapy, signifying a critical step in the recovery process. Treatment regimen was adjusted and the route of TMP/SMZ administration transitioned from intravenously back to via nasal feeding (0.16g, q6h). On November 7, the patient was transferred to the ward of infectious disease for

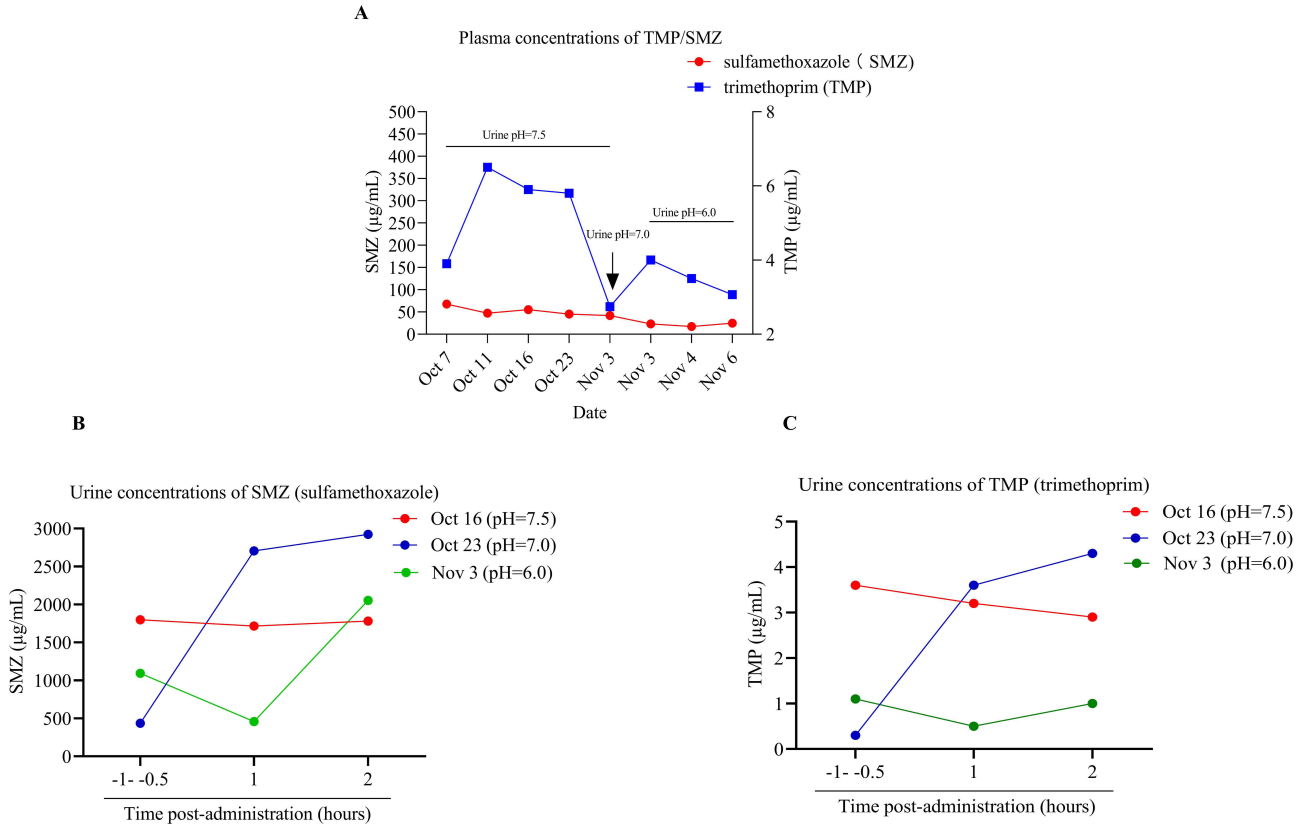

Figure 4 Plasma concentration–time curves of TMP/SMZ during 8-hour (iv, between September 29 and November 1) or 6-hour (po, between November 2 and November 18) dosing period in this patient (**A**). Plasma drug concentrations were measured 0.5 hour after last administration on October 7, 11, 16 and 23; 1.5 hours and 4 hours afterwards on November 3; and 2 hours afterwards on November 4 and 6. Urine concentration-time curves of TMP/SMZ (**B** and **C**) in this patient.

continued treatment. Throughout this period, the patient's breathing rate and temperature remained stable, and her general condition was deemed satisfactory. She was discharged on November 20 with a prescription of TMP/SMZ tablets to be taken orally (0.16 g, bid) for a 14-day course post-discharge. A comprehensive overview of the course of medication and significant clinical events during hospitalization is depicted in Figures 3 and 5.

Discussion

TMP/SMZ is the first-line therapy for PCP.[4] However, alternative therapeutic agents such as pentamidine, dapsone, atovaquone and primaquine are not produced domestically in some regions and may not be readily available. *Pneumocystis carinii* primarily exists in two structural forms: trophozoites and cysts. TMP/SMZ is effective primarily against the trophozoite form of *Pneumocystis carinii*, while caspofungin acts on the spore cysts by inhibiting the synthesis of β-(1,3)-D-glucan.[20] However, despite the potential of echinocandins in the treatment or prevention of PCP, the current lack of randomized controlled clinical trial data in humans leaves the use of this agent controversial.[21] In particular, the efficacy of caspofungin, an echinocandin, cannot be conclusively determined from existing literature; Therefore, this article focuses on the optimization of the first-line treatment, TMP/SMZ, in the clinical management of PCP.

Justification for the Use of High Dose TMP/SMZ in Pediatric Patients with Severe PCP Infection

Therapeutic drug monitoring (TDM) of TMP/SMZ is a critical component in the management of patients with severe infections to ensure therapeutic efficacy while minimizing the risk of ADRs. In this reported case, TDM for this patient was conducted throughout the entire course of treatment, and the treatment plan adjusted according to the plasma

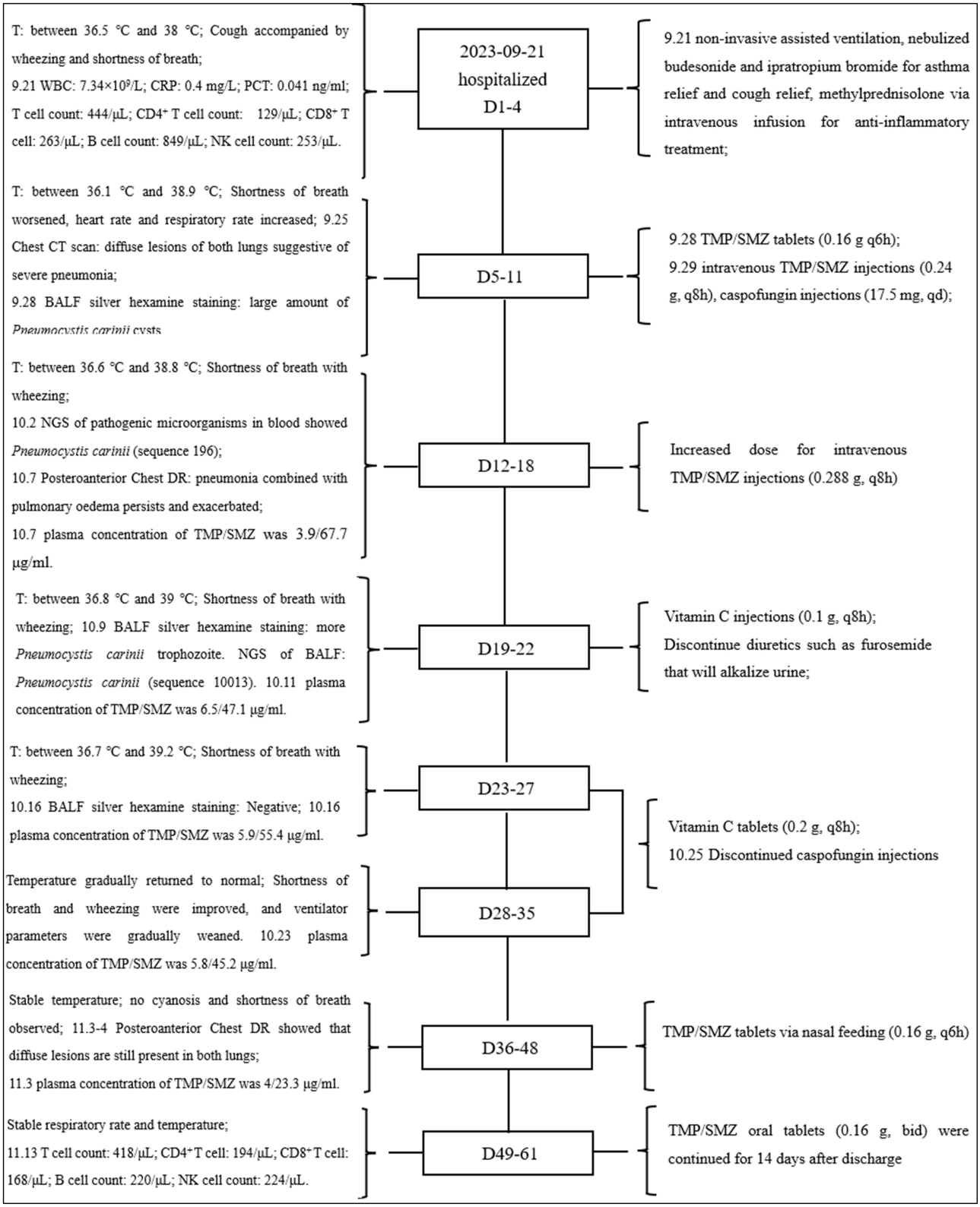

Figure 5 Important clinical information and treatment timeline of patient during hospitalization.
Abbreviations: T, temperature; WBC, white blood cell; CRP, C-reaction protein; PCT, procalcitonin; BALF, bronchoalveolar lavage fluid; NGS, Next-Generation Sequencing; DR, Digital Radiography.

concentration of TMP/SMZ in conjunction with the patient's clinical response. To ascertain the peak concentration (C_{max}), blood samples were collected 3 hours following oral administration and between 0.5 and 1 hour following intravenous administration of TMP/SMZ.

In alignment with the treatment guidelines for PCP as recommended by UpToDate (with a therapeutic dosage of 90–120 mg/kg/d, in 3 to 4 divided doses), the route of administration for TMP/SMZ was changed from orally to intravenously (at a dose of 0.24 g, q8h) on September 28. This change was prompted when BALF silver hexamine staining revealed large amount of *Pneumocystis carinii* cysts. On October 7, the serum concentrations of SMZ and TMP were measured as 67.7 μg/mL and 3.9 μg/mL, respectively. According to Brown et al, the optimal target range of C_{max} of TMP/SMZ for PCP is 100–200 μg/mL for SMZ and 5–8 μg/mL for TMP.[15] Given that the patient's plasma concentrations of TMP/SMZ were outside the target range, the dose was increased (at a dose of 0.288 g, q8h; equating to 130 mg/kg/d). Subsequent plasma concentrations were measured on October 11, as 47.1 μg/mL for SMZ and 6.5 μg/mL for TMP (Figure 4A). Considering the dose of TMP/SMZ had exceeded 120 mg/kg/d and the observed clinical improvement in patient, no further increase in dosage was made, nor were any additional medications introduced, to avoid ADRs such as neutropenia.

It has been well documented that pediatric patients with severe infection can exhibit Augmented Renal Clearance (ARC), which is associated with accelerated drug excretion. In some studies, ARC is characterized by a creatinine clearance (CrCl) of ≥ 130 mL/min.[22] This was also supported by studies such as those by Hirai, where the child's estimated Glomerular Filtration Rate (eGFR) of ≥ 160 mL/min/1.73m^2 was used to define ARC.[23] According to Practice of Pediatrics by Zhu Futang, normal urine output for children under one year of age should be 400–500 mL/day. The urine output of this patient exceeding 500 mL/d, and a CrCl ranging 180–230 mL/min/1.73m^2 for the majority of treatment period (Figure 6A and B). The plasma and urine concentrations of TMP/SMZ were closely monitored during this period. The results showed that the urine concentration of SMZ was approximately 40–60 times higher than that of the plasma in the same period, consistent with the distribution tendency described in the product literature for SMZ. Meanwhile, the concentration of TMP in urine was 0.6–1 times that of plasma in the same period (Figure 4B and C), further supporting the influence of ARC on drug excretion, resulting in the observed suboptimal SMZ concentrations.

Therefore, when treating pediatric patients with severe PCP infection, high doses of TMP/SMZ can rapidly distribute to the lung tissue, achieving a relatively high level that is sufficient for therapeutic effects in the tissue. The metabolic rate of TMP/SMZ in lung tissue is relatively slow, which contributes to maintaining a sustained local concentration for therapeutic efficacy. Consequently, it is recommended that drug concentrations of TMP/SMZ to be measured in plasma, urine and sputum simultaneously to guide individualized treatment strategies. Individualized treatment can be optimized by combining a comprehensive evaluation of drug efficacy and safety assessments. This approach carries significant clinical implications, ensuring both the effectiveness of the treatment and ensuring the safety of the patient by avoiding ADRs.

Safety Evaluation of High Dose TMP/SMZ in Pediatric Patients with Severe PCP Infection

It has been reported that TMP is weakly alkaline, while SMZ is weakly acidic. When urine is alkaline (pH 7–8), 30–40% of SMZ is excreted in its original form.[24] Moreover, product literature for TMP/SMZ mentioned that the concurrent use of urinary alkalizing agents can increase the solubility of TMP/SMZ in urine, and thereby enhancing excretion. This suggests that the suboptimal SMZ concentrations observed in the early stages of treatment for this patient may be related to the alkalinity of their urine. Despite attempts to adjust the urine pH from 7.5 to 6 in the follow-up treatment, the plasma concentration of SMZ remained suboptimal, while that of TMP was within the normal range. In this case, the changes in urine pH did not significantly influence the excretion of TMP/SMZ. In addition, even with an increased dosage of TMP/SMZ to 130 mg/kg/d, the concentration of SMZ in urine was found to be 40–60 times higher than that in the plasma during the same period. The absence of TMP/SMZ crystals in the urine indicates a high solubility of TMP/SMZ in urine. Further research is needed in the future to determine the specific levels of TMP/SMZ that could lead to crystallization and consequent renal impairment. Notably, even with a large dose of TMP/SMZ administered, no

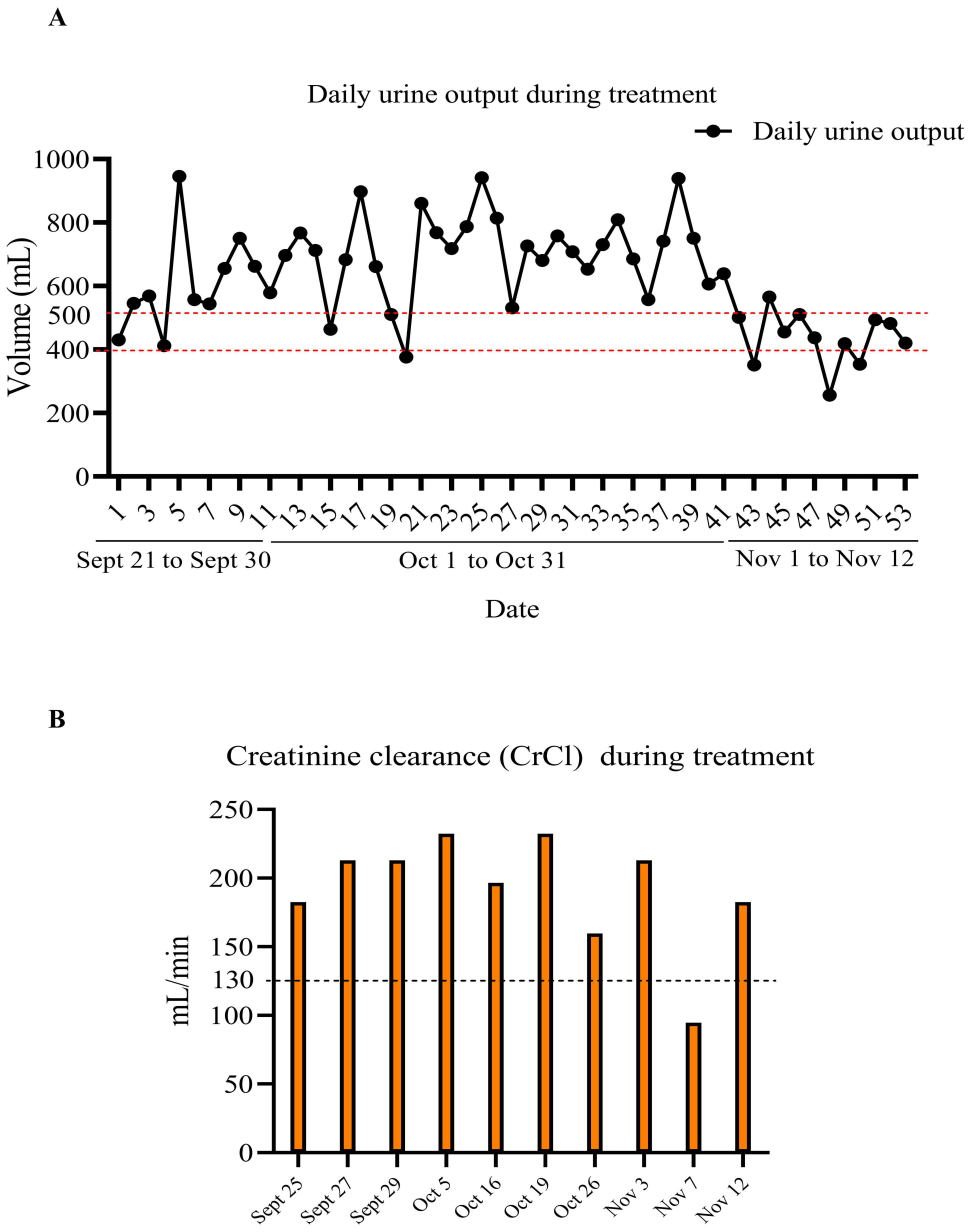

Figure 6 Daily urine output (**A**) and CrCl (**B**) in this patient during treatment.

crystallization was observed when the urine concentration of TMP/SMZ reached a maximum of 2924.8/4.3 μg/mL, suggesting a high solubility in the urine and indicating that the dose is relatively safe.

Implication of Sputum TMP/SMZ Concentration Monitoring in Pediatric Patients with Severe PCP Infection

TMP is known to distribute more rapidly into tissues than SMZ,[25] with both drugs achieving higher concentrations in most body fluids and secretions compared to plasma. On November 3, the sputum concentration of SMZ 4 hours after administration (117.8 μg/mL) was found to be higher than the plasma concentration (23.3 μg/mL); Conversely, for TMP, the sputum concentration (0.3 μg/mL) was lower than the plasma concentration (4 μg/mL). It is well established that TMP/SMZ are widely distributed in tissue and body fluids, including sputum. In this case, the ratio of TMP to SMZ in the sputum of the patient was 1:393, this contrasts with the findings of Reeves,[24] who reported a ratio of approximately 2:0.25 in sputum, and the concentration of SMZ in sputum was about 20% of that in plasma. The discrepancy between

the analyzed results and those of previous research findings may be attributed to several factors: First, the sputum itself is rather viscous, making it difficult to mix it fully in practice, potentially resulting in inconsistencies with test results;[26] Secondly, the patient, in this case, was a 6-month-old child, whose physiological and pathological characteristics differ significantly from adults. In addition, the severely impaired pulmonary function of this patient could impact the distribution, metabolism and excretion of drugs in the respiratory system. Thirdly, the sputum concentration may not fully represent the concentrations in lung tissues. Therefore, it was speculated that the improvement of the patient's condition, regardless of suboptimal plasma concentrations, was related to the high concentration of drug resulting from high tissue distribution.

While the plasma drug concentration of this patient did not fall within the target range, the final therapeutic outcome achieved was still satisfactory. Consequently, it is recommended that drug concentrations of TMP/SMZ be measured in plasma, urine and sputum simultaneously to guide individualized treatment strategies. Individualized treatment can be optimized by combining a comprehensive evaluation of drug efficacy and safety assessments. This approach carries significant clinical implications, ensuring both the effectiveness of the treatment and ensuring the safety of the patient by avoiding ADRs. For pediatric patients, particularly neonates and infants, the pharmacokinetic properties of TMP/SMZ in vivo differ from those of adults.

Although the synergistic effect is maximized at a concentration ratio of TMP:SMZ is 1:20 on most susceptible bacteria,[27] the plasma concentration ratio of TMP:SMZ in this patient never reached this optimal ratio during treatment. Therefore, this raises questions about the suitability of TMP/SMZ formulations at a ratio of 1:5 for pediatric patients, highlighting the need for further research to optimize dosing regimens in this population.

Conclusion

Pneumocystis carinii is an opportunistic pulmonary pathogen. Early diagnosis, timely treatment and individualized medication regimens significantly influence the prognosis of patients with PCP. In this case, clinical pharmacists played a pivotal role by monitoring the plasma concentration of TMP/SMZ, analyzing the potential causes of suboptimal plasma concentrations by considering the medical history, pathological and physiological characteristics of the paediatric patient, to guide dose adjustments. By monitoring TMP/SMZ concentrations in urine and sputum, to better aid individualized treatment, which contributed to the best clinical outcome for the patient.

TDM in this case study revealed several pertinent findings regarding the treatment of paediatric patients with severe PCP infection. Firstly, it underscored the necessity of administering high doses of TMP/SMZ to critically ill pediatric patients with PCP (with a final dose of 130 mg/kg/d of TMP/SMZ used) to ensure adequate drug concentration in the tissues. Secondly, the absence of drug crystals in the urine at this dosage, indicating that the current treatment dose was relatively safe. Thirdly, due to the distinct pharmacokinetic properties of TMP and SMZ, cast doubt on the suitability of the 1:5 ratio currently used in clinical practice for pediatric patients, especially for the treatment of PCP; this ratio remains controversial and thus warrants further investigation to guide the development of evidence-based dosing strategies.

Data Sharing Statement

Data will be provided by the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Shenzhen Children's Hospital (202214203) and has been performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient's immediate family members for the publication of any potentially identifiable images or data included in this case report prior to inclusion.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

None of the authors have any conflicts of interest.

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