


# Pediatric pharmaceutical care with anti-infective medication in a patient with acute hematogenous osteomyelitis caused by methicillin-resistant *Staphylococcus aureus*

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## Abstract

The infection of the bone marrow system caused by methicillin-resistant *Staphylococcus aureus* (MRSA) leads to a variety of common diseases which usually occur in children under the age of 12. Vancomycin (VCM) is the first-line therapy for MRSA-caused serious infections such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe skin and soft-tissue infection (e.g. necrotizing fasciitis) with a recommended dosage of 15–20 µg/mL. In this study, we first report a case of a child with MRSA-caused osteomyelitis who was successfully cured by VCM at a concentration of 4.86 µg/mL. VCM's clinical daily dose of more than 4g was of concern in light of recent evidence suggesting the increased risks of nephrotoxicity and red man syndrome when  $C_{\min} \geq 15 \mu\text{g/mL}$  and doses  $\geq 10 \text{mg/kg}$  in children. As far as we know, this is the first report on the lower dose of VCM in children with MRSA osteomyelitis.

## Keywords

acute hematogenous osteomyelitis (AHO), methicillin-resistant *Staphylococcus aureus* (MRSA), pharmaceutical care, vancomycin serum concentrations

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## Introduction

Osteomyelitis is a skeletal inflammation caused by microorganisms (mainly bacteria) entering the bone from blood, which usually occurs in children under 12 years of age.

*Staphylococcus aureus* is the main pathogen causing pediatric osteomyelitis.<sup>1</sup> Surgical debridement and drainage of associated soft-tissue abscesses is the mainstay of therapy and should be performed whenever feasible. Meanwhile, the selection of appropriate antibacterial drugs to control infection at early stage is key to prevent the formation of dead bones and progressing to chronic osteomyelitis.<sup>1</sup> This article reports the treatment

process with the participation of clinical pharmacists in the diagnosis and treatment of a pediatric patient with acute hematogenous osteomyelitis

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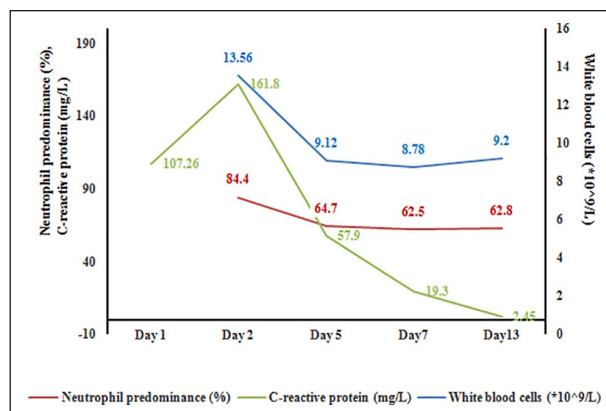
(AHO) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and explores the role of clinical pharmacists in the treatment of patients with osteomyelitis. There is no universal standard concentration of vancomycin (VCM) administration in children, the experience of which we share in this article.

## Case presentation

A 69-kg, 11-year-old girl was admitted to Shandong Provincial Hospital, because of “pain in the left knee joint 3 days ago and fever for 1 day.” The patient had fever without obvious cause 1 day before hospitalization and her temperature was 38.7°C. Her physical examination was normal except for the musculoskeletal component and she was sent to Jinan Central Hospital on the morning of that day. Direct digital radiography of her left knee joint showed no obvious abnormalities, and some laboratory results included erythrocyte sedimentation rate (ESR) of 62 mm/h, C-reactive protein (CRP) value of 48.7 mg/dL, and total white blood cell (WBC) count of  $14.9 \times 10^9$  cells/L. For further treatment, they came to Shandong Provincial Hospital. On admission, her blood pressure was 104/70 mmHg with heart rate of 100 beats/min, respiratory rate of 24 beats/min, and temperature of 37.2°C. From the disease onset, the child did not feel any specific discomfort. Magnetic resonance imaging (MRI) of the left knee joint showed that there were abnormal signals in the upper medullary cavity of left tibia, the epiphysis, and surrounding soft tissue, which were consistent with MRI diagnosis of osteomyelitis with surrounding soft-tissue infection. Orthopedic examination indicated that the patient’s left knee joint was slightly swollen, and her left tibia was painful which was harmed at the proximal end. This limited the activity of her left leg. The temperature of her local skin was normal, and there was no abnormal blood supply to the left toe. Therefore, the initial diagnosis was AHO of the left tibia.

## Surgical treatment

At 23:30 on day 1, under general anesthesia, the patient was taken to the operating room for an incision and drainage of the identified left femoral subperiosteal abscess. During the operation, incision and drainage abscess were performed. Around



**Figure 1.** Changes in main inflammation indicators throughout the treatment.

5 mL of yellow pus was found in the periosteum and sent for bacterial culture. A drainage tube and an irrigation tube were indwelled in the infection site; meanwhile, aseptic dressing was applied.

## Anti-infective treatment

Empirical therapy with cefoperazone/sulbactam 1.5 g and flucloxacillin sodium 1 g twice daily was started after postoperation at 1:00 on day 2. But the patient had not improved after 3 days (WBC,  $13.56 \times 10^9$  cells/L $\uparrow$ ; neutrophil predominance (N%), 84.4% $\uparrow$ ; CRP, 161.80 mg/L $\uparrow$ ). For the patient, MRSA was isolated from both the blood and subperiosteal abscess cultures on day 4. Antimicrobial susceptibility test (AST) showed the isolated MRSA is highly sensitive to erythromycin, gentamicin, ciprofloxacin, trimethoprim (TMP)/sulfamethoxazole (SMX), rifampin, and VCM with a minimum inhibitory concentration (MIC) of  $<0.5 \mu\text{g/mL}$ , but it is resistant to other antibiotics. Flucloxacillin sodium was discontinued according to AST results. In view of the toxicity of VCM and economic reasons, we decided that the starting dose was 0.5 g q6h. Finally, VCM 0.5 g q6h was thus applied as a replacement, while cefoperazone/sulbactam 1.5 g bid was continued. Changes in main inflammation indicators throughout the treatment are shown in Figure 1.

The WBC count declined to  $9.20 \times 10^9$  cells/L, N% declined to 62.8%, procalcitonin was 0.03 ng/mL, CRP declined to 3.50 mg/L, and human serum amyloid A was  $<4.80 \text{ mg/L}$  after VCM treatment for 8 days. However, an initial trough concentration of 4.38  $\mu\text{g/mL}$  was found to be less than 10  $\mu\text{g/mL}$ .

VCM treatment was changed to 1 g (15 mg/kg/dose) q8h according to the instructions. The serum trough concentration of VCM was 4.86  $\mu\text{g/mL}$  when the steady state was reached at 30 min prior to the fifth dose. The clinical pharmacist recommended continuing with the current treatment considering the patient's good response. So far, there has been a reduction in swelling and relief from pain in the left leg and the wound has healed well. The dressing was dry and fixed, no oozing was observed, and the peripheral circulation and toe activity were recovered at 24 days after admission. Based on the review of the literature and guidelines regarding the possible adverse reactions of VCM related to osteomyelitis (such as high ototoxicity and nephrotoxicity), clinical pharmacists decided to discontinue VCM and cefoperazone/sulbactam, which were replaced by oral administration of rifampin 0.6 g daily and TMP/SMX two tablets (160 mg/800 mg) q12h based on the AST. The patient was discharged on day 25 with a medication of rifampin and TMP/SMX. No adverse effects were noted during 3 months after the diagnosis of osteomyelitis.

## Discussion

For children with acute hematogenous MRSA osteomyelitis and septic arthritis caused by MRSA, VCM is still the primary treatment. The half-life time of drug elimination may be prolonged and the duration of high drug concentration may be longer in growing children, so it is important to monitor the concentration of VCM and maintain it within a safe and effective range.<sup>2</sup> The trough concentration of VCM is the most accurate and practical parameter to guide VCM dosing. Initially, the patient was treated with VCM 0.5 g q6h by intravenous drip, and the initial trough concentration of VCM was 4.38  $\mu\text{g/mL}$ , which was less than 10  $\mu\text{g/mL}$ . At the consultation, 0.75 g q6h dosing was recommended, but the clinician considered that the specification of VCM in our hospital was 0.5 g/piece. The economic condition of our patient was not good. If 0.75 g/time was given, half of VCM would be wasted. After discussion, we tried to use the dosing of 1 g q8h. Then, dosage of VCM treatment was changed to 1 g q8h with serum trough concentrations of VCM increasing to 4.86  $\mu\text{g/mL}$ . Taking comprehensive consideration of the patient's condition into account, the clinical pharmacist did not continue to increase the dosage to avoid increase in

adverse reactions (e.g. ototoxicity and nephrotoxicity). Although the concentration was not within the recommended range, which may increase the risk of treatment failure, the disease symptoms of the child were significantly reduced. Her body temperature indexes and blood routine examination results returned to normal level, the wounds healed well, and a good anti-infective effect was observed.

At present, there is still controversy about the proper dose and trough concentration of VCM that should be applied to pediatric patients. For serious infections, such as osteomyelitis caused by MRSA, VCM trough concentrations of 15–20  $\mu\text{g/mL}$  are recommended to be used in adults.<sup>3</sup> However, whether the efficacy and safety of trough concentrations of 15–20  $\mu\text{g/mL}$  are also applicable to children requires further exploration since so far there is no relevant study about the trough concentration range of VCM in Chinese children. Apart from that, nephrotoxicity is associated with high doses of VCM,<sup>3,4</sup> so blood concentration should be carefully examined. After reviewing relevant literature and guidelines, clinical pharmacists speculated some reasons why this patient could achieve a good outcome with a much lower VCM concentration than the recommended concentration of guidelines:

1. Differences in ethnic factors can lead to difference in the safety and efficacy of the same drug. The physiology, pathology, genetics, eating habits, living environment, medical measures, or bacterial resistance rate could be different between Chinese and Westerners. Apart from this, a study also revealed that compared to low trough concentration of VCM, high trough concentration of VCM did not reduce mortality and clinical failure rate, but it increased the incidence of nephrotoxicity.<sup>5</sup> The pharmacokinetic variation in pediatric and adult VCM clearance is significantly different and likely one of the major reasons for potential differences in clinical outcomes. Pediatric patients often clear VCM much faster than adults.<sup>6</sup>
2. Systemic inflammatory reactions are usually caused by severe infections which severely damage endothelial cells and increase the vascular permeability.<sup>7</sup> As a result, liquid permeation increases the amount of extracellular

fluid. In addition, a large daily intake of fluid causes the accumulation of extracellular interstitial fluid which also influences the volume of distribution ( $V_d$ ).<sup>8</sup> VCM is a hydrophilic antibacterial antibiotic with low  $V_d$ . Extracellular increase in fluid leads to a subsequent increase in  $V_d$  of VCM with a subsequent drop in plasma and tissue concentrations.<sup>9</sup> There was an animal model experiment in which the concentrations of VCM in the bone and serum of rabbits with *S. aureus* osteomyelitis were assessed after each rabbit was given a single dose of VCM 300 mg/kg. The result was that the mean concentration of VCM at infected bone was twice as much as non-infected.<sup>10</sup> Although the concentration of VCM is unknown in the infected bone, we infer that the mean concentration of VCM at the infected bone may be higher than the non-infected ones.

3. The renal clearance rate of patients with severe infections may increase, as well as the renal clearance of the drug. Four independent risk factors that contribute to the occurrence of augmented renal clearance are summarized as follows: age  $\leq 65$  years, brain injury, febrile neutropenia, and a mean volume of infusion fluid  $\geq 1500$  mL/day.<sup>11</sup> In this case, the child was 11 years old, the infusion volume was greater than 1500 mL/day, and her creatinine clearance (CrCl) was calculated to be about 280.3 mL/min. These risk factors may have led to the lower trough concentration of VCM in this patient.
4. According to the section of drug pharmacokinetics (PK)/pharmacodynamics (PD) and administration plan designed in the "Guide of Clinical Experts in Clinical Application of VCM (2011 Edition)," VCM is a time-dependent antibacterial drug with post-antibiotic effect (PAE). The PAE for *S. aureus* is about 1–2 h. In a certain concentration range, the antibacterial effect is related to the time when concentration is greater than MIC ( $T > MIC$ ) and the optimal bactericidal concentration is four to five times MIC. After exceeding this concentration, the peak concentration will not improve the anti-bactericidal effect and the sterilization mode is non-concentration-dependent. For this patient, the trough VCM was 4.86  $\mu\text{g/mL}$  with an

MIC of  $< 0.5 \mu\text{g/mL}$ , so the trough concentration was much greater than four to five times MIC.<sup>12</sup>

5. Some studies have confirmed that the value of  $AUC_{0-24h}/MIC \geq 400$  was associated with a successful outcome of VCM. A very interesting and clinically significant finding by Le et al.<sup>6</sup> suggested that  $AUC_{0-24h}/MIC \sim 400$  corresponded to  $C_{min} \sim 8-9 \text{ mg/L}$ . Another study conducted by Frymoyer et al.<sup>13</sup> found that with a dose of 40 mg/kg/day, the target of  $AUC_{0-24h}/MIC > 400$  was achieved only when the MICs of MRSA isolates were 0.5  $\mu\text{g/mL}$ . Studies had shown that in adult patients, VCM  $AUC_{0-24h}/MIC > 400$  corresponded to a trough concentration of 15–20  $\mu\text{g/mL}$ , but this correlation could not be directly extrapolated to children.<sup>14</sup> The 24-h VCM AUC was calculated using the formula  $AUC_{0-24h} = \text{VCM Daily Dose}/\text{VCM Clearance}$ , where  $\text{VCM Clearance} = (\text{CLcr} \times 0.79 + 15.4) \times 0.06$  and  $\text{CLcr} = \{[(140 - \text{age in years}) \times \text{weight in kg}] / (\text{CR in } \mu\text{mol/L} \times 0.814)\} \times 0.85$  if female. The  $AUC_{0-24h}/MIC$  of the patient in this case was more than 282 when the dosage of VCM was 0.5 g q6h, while the  $AUC_{0-24h}/MIC$  was more than 422 with a dosage of VCM of 1 g q8h. Therefore, the child may reach  $AUC_{0-24h}/MIC > 400$  at a lower trough concentration and achieve the effect of anti-MRSA infection osteomyelitis.

Our institution's daily recommendation in terms of dose (mg/kg) and frequency for children and infants is intravenous injection of 40–60 mg/kg three to four times. In order to prevent adverse reaction such as red man syndrome, clinical pharmacists recommend an infusion rate of 1 g over 60 min for VCM. Because of the ototoxicity and nephrotoxicity of VCM, it was recommended that physicians should closely monitor the renal function and hearing status of the child during treatment. No adverse effects or limitations were noted in our case.

With the emergence of community-associated MRSA (CA-MRSA) in some countries, early diagnosis, identification of the pathogen, and appropriate antibiotic use are crucial to achieve favorable outcomes and avoid complications. Clinical pharmacists played an important role in the selection of antimicrobial agents for the treatment of

osteomyelitis. Considering the pathophysiological characteristics of patients, the clinical pharmacist should design individual medication scheme by comprehensively considering the selection of anti-infective drugs, drug type and dosage, route of administration, and adverse reactions, and the concentration of VCM was monitored. Through cooperation with clinical pharmacists, doctors and nurses could ensure medication safety and efficacy.

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### Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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### Informed consent

The patient's parents provided written informed consent to publish this case. Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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