Cureus
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Open Access Case Report

Vancomycin-Associated Pancytopenia in Two Children With Methicillin-Resistant Staphylococcus aureus (MRSA) Musculoskeletal Infections: A Report of Two Cases

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Review began 10/24/2026
Review ended 11/07/2026
Published 11/10/2026

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DOI: 10.7759/cureus.119409

Abstract

Vancomycin is widely used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Although hematological adverse effects, particularly neutropenia and thrombocytopenia, have been reported, vancomycin-associated pancytopenia is uncommon, especially in children. We report two previously healthy children who developed pancytopenia during intravenous vancomycin treatment for MRSA musculoskeletal infections. The first patient, a seven-year-old girl treated for distal-radius osteomyelitis with a Brodie's abscess, developed severe pancytopenia by Day 16 of vancomycin therapy, with a white blood cell (WBC) count of 1.4 × 10^3/μL, an absolute neutrophil count of 0.27 × 10^3/μL, hemoglobin of 6.8 g/dL, and a platelet count of 119 × 10^3/μL. The second patient, a 15-year-old boy treated for MRSA septic arthritis of the hip with associated pyomyositis, developed progressive cytopenias, with a WBC count of 1.50 × 10^3/μL, hemoglobin of 6.7 g/dL, and a platelet count of 105 × 10^3/μL on Day 18. In both patients, renal function remained preserved, vancomycin trough concentrations were within the reported range of 10-20 μg/mL, and investigations for viral and autoimmune causes were unrevealing. Vancomycin was discontinued, and antimicrobial treatment was changed to oral linezolid. Neither patient received granulocyte colony-stimulating factor, blood transfusion, or other specific hematological treatment. Both patients subsequently demonstrated hematological recovery during follow-up. These cases highlight vancomycin-associated pancytopenia as a potentially serious adverse event in children receiving treatment for MRSA musculoskeletal infections. Significant cytopenias may develop despite preserved renal function and vancomycin trough concentrations within the reported therapeutic range. Baseline and serial blood counts, prompt investigation of unexplained cytopenias, and reassessment of antimicrobial therapy are important during treatment.

Categories: Hematology, Orthopedics, Infectious Disease
Keywords: children, methicillin-resistant staphylococcus aureus, neutropenia, osteomyelitis, pancytopenia, septic arthritis, vancomycin

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains an important cause of serious musculoskeletal infections in children, including osteomyelitis, septic arthritis, and deep soft-tissue infections. These conditions may require surgical drainage or debridement combined with prolonged antimicrobial therapy. Treatment selection is influenced by infection severity, microbiological susceptibility, local resistance patterns, and the need to achieve adequate antimicrobial activity within infected bone and joint tissues. Vancomycin remains an important treatment option for serious MRSA infections, particularly when resistance patterns or clinical severity limit the use of alternative agents. However, its use requires careful monitoring for treatment-related adverse effects [1,2].

Vancomycin-associated toxicity is most commonly discussed in relation to renal injury, but hematological adverse effects are also recognized. These abnormalities include neutropenia, leukopenia, thrombocytopenia, and, rarely, pancytopenia. Although the reported frequency and clinical significance vary across studies, hematological toxicity may complicate prolonged treatment and create additional challenges when antimicrobial therapy is still required to control a deep-seated infection. Recognition is particularly important in children, in whom treatment decisions must balance infection control, medication safety, and the potential consequences of severe cytopenias [3,4].

Vancomycin-associated neutropenia has been described predominantly after sustained exposure rather than

as a predictable consequence of a particular daily dose or serum concentration. A systematic review of published cases and retrospective studies found that neutropenia was more frequently reported after more than seven days of treatment, with many cases developing after longer courses. The review also emphasized the importance of monitoring the white blood cell (WBC) count and differential, including the absolute neutrophil count (ANC), during extended therapy. Nevertheless, the available evidence is limited by the predominance of retrospective studies and case reports, making it difficult to establish reliable incidence estimates or identify all relevant risk factors [3].

The mechanisms underlying vancomycin-associated hematological toxicity are not fully established. Proposed explanations include immune-mediated peripheral destruction of blood cells and effects on bone marrow production. The clinical presentation may involve an isolated reduction in one cell line or abnormalities affecting multiple lineages. Pancytopenia is particularly concerning because it may reflect simultaneous impairment of erythrocytes, leukocytes, and platelets and requires careful assessment for alternative infectious, inflammatory, autoimmune, nutritional, and medication-related causes. A published case report has described pancytopenia developing during vancomycin treatment and improving after drug withdrawal, supporting the need to recognize this uncommon potential adverse effect [5,6].

The interpretation of suspected drug-associated cytopenia requires consideration of the temporal relationship between medication exposure and laboratory abnormalities, the severity and pattern of cytopenia, competing clinical explanations, and the subsequent course after treatment modification. Recovery following withdrawal of a suspected medication may strengthen the clinical suspicion of an association, but it does not independently establish causality, particularly when another antimicrobial agent is introduced simultaneously. In patients being treated for MRSA musculoskeletal infections, these considerations are especially relevant because an effective alternative antimicrobial regimen must be maintained while the hematological abnormality is evaluated [7].

This report describes two children treated for MRSA musculoskeletal infections who developed pancytopenia of differing severity during intravenous vancomycin therapy. Both underwent clinical and laboratory evaluation that did not identify an alternative explanation, and both demonstrated subsequent hematological recovery following modification of antimicrobial treatment. By presenting the clinical courses, serial blood counts, investigations, and follow-up findings, this report aims to highlight a potential but uncommon complication of vancomycin treatment and emphasize the importance of recognizing unexplained hematological abnormalities during prolonged antimicrobial therapy.

Case Presentation

Case 1: vancomycin-associated pancytopenia in a child with MRSA osteomyelitis

A previously healthy seven-year-old girl presented with osteomyelitis of the left distal radius associated with a Brodie's abscess to the clinic as a referred case from the pediatric infectious disease consultant. She underwent surgical incision and drainage with bone biopsy on the same day of admission. Microbiological examination identified MRSA, and intravenous vancomycin was initiated at a weight-based dose of 20 mg/kg per dose on the fourth day of admission. The patient was subsequently monitored clinically and through serial laboratory investigations during antimicrobial treatment.

The first hematological abnormalities were observed on Day 9 of vancomycin therapy, when a decline in the WBC and neutrophil counts became apparent. The abnormalities progressed during the following week. By Day 16 of vancomycin therapy, the patient had developed severe pancytopenia, with a WBC count of 1.4 × 10^3/µL (reference range: approximately 4.5-13.5 × 10^3/µL), an ANC of 0.27 × 10^3/µL (reference range: approximately 1.5-8.0 × 10^3/µL), a hemoglobin concentration of 6.8 g/dL (reference range: approximately 11.5-15.5 g/dL), and a platelet count of 119 × 10^3/µL (reference range: approximately 150-450 × 10^3/µL). These findings confirmed pancytopenia characterized by severe neutropenia and marked anemia, accompanied by mild thrombocytopenia.

Given the progressive and clinically significant cytopenias, vancomycin was discontinued on Day 17, and antimicrobial treatment was changed to oral linezolid at a dose of 300 mg every eight hours for a total duration of four weeks. Nevertheless, the cytopenias remained severe on Day 18. Laboratory investigations at that time showed a WBC count of 1.6 × 10^3/µL, a hemoglobin concentration of 5.4 g/dL, and a platelet count of 112 × 10^3/µL. The continued deterioration in hemoglobin after vancomycin discontinuation highlighted that hematological recovery was not immediate.

A comprehensive evaluation was undertaken with hematology and immunology input to investigate alternative causes of pancytopenia. Viral testing was negative, and the reported immunological investigations, including antinuclear antibody, rheumatoid factor, and anti-cyclic citrullinated peptide testing, did not identify an alternative explanation. Renal function remained preserved throughout treatment, and the documented vancomycin trough concentrations were within the reported therapeutic

range of 10-20 μg/mL. No granulocyte colony-stimulating factor (G-CSF), blood transfusion, or other specific hematological treatment was administered.

Serial follow-up investigations subsequently demonstrated improvement in the blood counts. At early follow-up, the WBC count had increased to 2.6 × 10^3/μL, with a calculated ANC of approximately 0.55 × 10^3/μL, a hemoglobin concentration of 8.0 g/dL, and a platelet count of 126 × 10^3/μL. At a subsequent assessment, the WBC count had recovered to 8.3 × 10^3/μL, the calculated ANC was approximately 1.90 × 10^3/μL, hemoglobin had increased to 12.4 g/dL, and the platelet count was 258 × 10^3/μL.

At the latest outpatient follow-up on Day 62, the patient remained under clinical follow-up, with a hemoglobin concentration of 13.4 g/dL, a WBC count of 7.5 × 10^3/μL, and a platelet count of 260 × 10^3/μL. These findings indicated recovery of the reported hematological parameters. Overall, the development of progressive pancytopenia during vancomycin therapy, the absence of an alternative cause identified through the documented investigations, and subsequent recovery following drug discontinuation supported a suspected association between vancomycin exposure and pancytopenia.

Case 2: vancomycin-associated pancytopenia in an adolescent with MRSA septic arthritis

A previously healthy 15-year-old boy was admitted with a three-day history of progressive left hip pain and limping, associated with fever reaching 38.3°C, through our emergency department (ED) in January 2026. Clinical assessment and radiological investigations revealed septic arthritis of the left hip accompanied by extensive pyomyositis involving the iliopsoas, vastus intermedius, and adductor magnus muscles. Magnetic resonance imaging and computed tomography were performed to characterize the extent of the musculoskeletal infection and identify the involved anatomical structures. Given the severity and distribution of the infection, the patient underwent surgical incision and drainage on the second day of admission. Microbiological examination of the operative specimens identified MRSA. The isolate was reported to be susceptible to vancomycin, linezolid, teicoplanin, and levofloxacin.

The patient's admission hemoglobin concentration was 14.3 g/dL. Surgical incision and drainage was associated with minimal estimated intraoperative blood loss of approximately 10-20 mL. Subsequent blood sampling was performed intermittently on separate days, with no substantial cumulative blood loss from phlebotomy documented in the clinical records.

The patient underwent surgical incision and drainage on the second day of admission. Following the procedure, cefazolin was administered in accordance with our institutional postoperative antibiotic protocol. After microbiological identification of MRSA and confirmation of its susceptibility profile, intravenous vancomycin was initiated on the fifth day of admission (designated Day 1 of vancomycin therapy) at a weight-based dose of 20 mg/kg per dose. No concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors (PPIs) were administered during the treatment course. In our institution, these medications are not routinely prescribed unless specifically recommended by the treating immunology or infectious diseases consultant; neither recommendation was made in this case.

The patient underwent clinical and laboratory monitoring during treatment. Although the infection required effective antimicrobial therapy, progressive hematological abnormalities subsequently emerged. By Day 16 of vancomycin therapy, the WBC count had decreased to 1.90 × 10^3/μL (reference range: approximately 4.5-13.0 × 10^3/μL), with an ANC of 0.29 × 10^3/μL, indicating severe neutropenia. At the same assessment, the hemoglobin concentration was 7.6 g/dL (reference range: approximately 12.0-16.0 g/dL for a 15-year-old male), and the platelet count was 113 × 10^3/μL (reference range: approximately 150-450 × 10^3/μL). These findings demonstrated pancytopenia, characterized particularly by severe neutropenia and marked anemia.

In view of the progressive cytopenias, vancomycin was discontinued on Day 17, and antimicrobial treatment was changed to oral linezolid (600 mg every 12 hours) for a total duration of four weeks. Complete blood counts (CBCs) were monitored serially during and after linezolid treatment. Following the switch, the WBC count increased to 2.20 × 10^3/μL on Day 20 and 4.20 × 10^3/μL on Day 23. By Day 33, the WBC count had recovered to 4.80 × 10^3/μL, with a hemoglobin concentration of 13.1 g/dL and a platelet count of 355 × 10^3/μL. At the latest follow-up on Day 58, the WBC count was 6.90 × 10^3/μL, hemoglobin was 12.8 g/dL, and the platelet count was 254 × 10^3/μL. These serial results demonstrated progressive hematological recovery during and after the alternative antimicrobial treatment, without documented worsening of cytopenias during linezolid administration. However, the hematological abnormalities persisted after discontinuation. On the 18th day, the WBC count reached 1.50 × 10^3/μL, while the hemoglobin concentration was 6.7 g/dL and the platelet count was 105 × 10^3/μL. The hemoglobin and platelet count subsequently declined further, indicating that the hematological disturbance continued beyond the initial withdrawal of vancomycin. The available laboratory findings therefore demonstrated progressive involvement of the leukocyte, erythrocyte, and platelet lineages rather than isolated leukopenia.

A comprehensive investigation was undertaken with hematology and immunology input to evaluate potential alternative causes of pancytopenia. Viral testing was negative. The reported immunological investigations, including antinuclear antibody, rheumatoid factor, and anti-cyclic citrullinated peptide testing, did not identify an alternative explanation for the hematological abnormalities. Renal function remained preserved throughout treatment, and the documented vancomycin trough concentrations were within the reported therapeutic range of 10-20 μg/mL. No G-CSF, blood transfusion, or other specific hematological treatment was administered. Accordingly, management of the suspected drug-associated hematological adverse event consisted principally of discontinuing vancomycin, changing the antimicrobial regimen, and monitoring subsequent blood counts.

Serial laboratory assessments subsequently demonstrated progressive recovery. On the 20th day, the WBC count had increased to 2.20 × 10^3/μL. A further assessment on the 23rd day showed an increase to 4.20 × 10^3/μL, indicating improvement in the leukocyte count over the ensuing days. By the 33rd day, the WBC count had reached 4.80 × 10^3/μL, the hemoglobin concentration was 13.1 g/dL, and the platelet count was 355 × 10^3/μL, according to the available follow-up record. These findings demonstrated substantial recovery of the reported blood cell parameters following vancomycin discontinuation. The interval between drug withdrawal and the documented improvement also provides a clinically relevant temporal sequence for evaluating the suspected association.

At the latest outpatient follow-up on Day 58, the patient's hemoglobin concentration was 12.8 g/dL, the WBC count was 6.9 × 10^3/μL, and the platelet count was 254 × 10^3/μL. These results demonstrated sustained recovery of the reported hematological parameters at the latest assessment. The case was notable for the development of progressive pancytopenia during vancomycin treatment for a confirmed MRSA musculoskeletal infection, continued hematological deterioration after treatment discontinuation, and subsequent recovery without G-CSF, transfusion, or other specific hematological therapy. Although the temporal relationship, negative investigations for alternative causes, and subsequent recovery support a suspected association with vancomycin exposure, the observational nature of a single case does not establish definitive drug causality.

The clinical timelines and hematological courses of the two patients are summarized in Table *1*. Both patients developed progressive hematological abnormalities during intravenous vancomycin treatment for confirmed MRSA musculoskeletal infections, with clinically significant cytopenias emerging after approximately two weeks of therapy. Vancomycin was discontinued in both cases, and antimicrobial treatment was changed to oral linezolid. Subsequent laboratory assessments demonstrated hematological recovery, with the latest outpatient follow-up showing recovery of the reported WBC and platelet counts in both patients. Although the severity and pattern of cytopenias differed between the cases, the temporal relationship between vancomycin exposure and the development of pancytopenia, together with improvement after drug discontinuation, suggests a suspected association.

Time point	Case 1: Seven-year-old girl	Case 2: 15-year-old boy
Presentation	Osteomyelitis with a Brodie's abscess of the left distal radius.	Left hip septic arthritis with pyomyositis involving the iliopsoas, vastus intermedius, and adductor magnus muscles.
Day 1	Surgical incision and drainage with bone biopsy; MRSA identified and intravenous vancomycin initiated.	Intravenous vancomycin initiated following surgical drainage for MRSA septic arthritis and associated pyomyositis.
Day 9	Initial decline in WBC and neutrophil counts observed.	No specific hematological event documented at this time point.
Day 16	Severe pancytopenia: WBC 1.4 × 10^3/μL, ANC 0.27 × 10^3/μL, Hb 6.8 g/dL, and platelets 119 × 10^3/μL.	WBC 1.90 × 10^3/μL, ANC 0.29 × 10^3/μL, Hb 7.6 g/dL, and platelets 113 × 10^3/μL.
Day 17	Vancomycin discontinued; treatment changed to oral linezolid.	Vancomycin discontinued; treatment changed to oral linezolid.
Day 18	WBC 1.6 × 10^3/μL, Hb 5.4 g/dL, platelets 112 × 10^3/μL.	WBC 1.50 × 10^3/μL, Hb 6.7 g/dL, platelets 105 × 10^3/μL.
Early follow-up	WBC 2.6 × 10^3/μL, calculated ANC 0.55 × 10^3/μL, Hb 8.0 g/dL, and platelets 126 × 10^3/μL.	WBC increased to 2.20 × 10^3/μL, followed by 4.20 × 10^3/μL at the next reported assessment.
Subsequent follow-up	WBC 8.3 × 10^3/μL, calculated ANC 1.90 × 10^3/μL, Hb 12.4 g/dL, and platelets 258 × 10^3/μL.	WBC 4.80 × 10^3/μL, Hb 13.1 g/dL, and platelets 355 × 10^3/μL, according to the original follow-up record.
On the latest outpatient follow-up	Hb 13.4 g/dL, WBC 7.5 × 10^3/μL, and platelets 260 × 10^3/μL.	Hb 12.8 g/dL, WBC 6.9 × 10^3/μL, and platelets 254 × 10^3/μL.

TABLE 1: Clinical timeline and hematological course of two pediatric patients with vancomycin-associated pancytopenia

Reference ranges for pediatric laboratory parameters were as follows: white blood cell (WBC) count, 4.5-13.5 × 10^3/μL; absolute neutrophil count (ANC), 1.5-8.0 × 10^3/μL; Hb, 11.5-15.5 g/dL for the seven-year-old girl and 12.0-16.0 g/dL for the 15-year-old boy; and platelet count, 150-450 × 10^3/μL.

Hb: hemoglobin; MRSA: methicillin-resistant *Staphylococcus aureus*

Discussion

Vancomycin-associated pancytopenia is an uncommon but potentially serious hematological adverse event that may complicate the treatment of severe bacterial infections. Although vancomycin is widely used to treat infections caused by MRSA, its hematological adverse effects are more commonly described as isolated neutropenia or thrombocytopenia than as simultaneous reductions in all three major blood cell lineages. Published evidence regarding vancomycin-associated pancytopenia remains limited, particularly in children, and consists predominantly of individual case reports and small observational studies [4,8]. The present report describes two pediatric patients who developed progressive pancytopenia during vancomycin treatment for microbiologically confirmed MRSA musculoskeletal infections. Both patients demonstrated substantial hematological recovery following vancomycin discontinuation and a change in antimicrobial therapy, supporting a suspected association between vancomycin exposure and the observed cytopenias.

Although vancomycin-associated pancytopenia has been rarely reported, previous case reports have described reversible hematological toxicity in both adult and pediatric patients. Leng et al. reported pancytopenia in a 16-month-old child receiving vancomycin for MRSA osteomyelitis, while Gupta et al. described pancytopenia in an adult patient receiving intravenous vancomycin. The present cases add to this limited literature by describing two children with MRSA musculoskeletal infections who developed substantial hematological abnormalities during treatment. A comparison of the published cases and the present cases is provided in Table *2*.

Study	Patient	Infection/indication	Onset and hematological findings	Management and outcome
Gupta et al., 2016 [4]	56-year-old man	Chronic paraspinal abscess	Pancytopenia identified on readmission approximately two weeks after vancomycin initiation; detailed nadir values not available in the abstract.	Vancomycin discontinued; blood counts improved.
Leng et al., 2020 [8]	16-month-old boy	MRSA osteomyelitis	Reversible pancytopenia accompanied by pulmonary infection and skin rash during vancomycin treatment; exact onset and nadir values require full-text verification.	Vancomycin withdrawn; reported clinical and hematological abnormalities resolved.
Present case 1	Seven-year-old girl	MRSA osteomyelitis of the distal radius with Brodie's abscess	Initial decline in WBC and neutrophils on Day 9; severe pancytopenia by Day 16. Day 18: WBC 1.6 × 10^3/μL, Hb 5.4 g/dL, platelets 112 × 10^3/μL.	Vancomycin discontinued on Day 17; changed to linezolid. Subsequent hematological recovery documented.
Present case 2	15-year-old boy	MRSA septic arthritis of the hip with extensive pyomyositis	Progressive cytopenias by Day 16. On the recorded Day 18 assessment: WBC 1.50 × 10^3/μL, Hb 6.7 g/dL, platelets 105 × 10^3/μL; further declines in Hb and platelets were reported.	Vancomycin discontinued on Day 17; changed to linezolid. Subsequent hematological recovery documented.

TABLE 2: Comparison of published cases of vancomycin-associated pancytopenia with the present cases

Day numbers refer to vancomycin treatment in the present cases.

Hb: hemoglobin; MRSA: methicillin-resistant *Staphylococcus aureus*; WBC: white blood cell count

Clinical presentation and comparison with previous reports

The two cases illustrate the importance of recognizing hematological abnormalities during antimicrobial treatment for serious musculoskeletal infections. The first patient was a seven-year-old girl treated for osteomyelitis of the distal radius associated with a Brodie's abscess, whereas the second was a 15-year-old boy with septic arthritis of the hip and extensive adjacent pyomyositis. Despite differences in age, anatomical site, and infection extent, both patients developed progressive reductions in circulating blood cell counts during vancomycin therapy. The occurrence of this pattern in two patients with different MRSA musculoskeletal infections suggests that clinicians should remain alert to hematological adverse effects even when vancomycin is being administered for a clear microbiological indication.

Previous reports have documented vancomycin-associated pancytopenia in both adult and pediatric populations. Gupta et al. described a 56-year-old man who developed pancytopenia approximately two weeks after starting intravenous vancomycin for an MRSA-associated paraspinal infection. His blood counts improved after vancomycin was discontinued [4]. More directly relevant to the pediatric population, Leng et al. reported reversible pancytopenia accompanied by a rash in a 16-month-old boy receiving vancomycin for MRSA osteomyelitis. The hematological abnormalities resolved after withdrawal of the drug [8]. These reports provide clinical precedent for the presentation observed in our patients and support the possibility that pancytopenia may occur during vancomycin treatment in children with osteoarticular infections.

Nevertheless, the evidence base remains limited, and isolated reports cannot establish the frequency of this adverse event or identify reliable patient-level predictors. The present cases therefore add to the limited pediatric literature by describing pancytopenia in two children with distinct MRSA musculoskeletal presentations and documenting the subsequent hematological course. The severe reduction in hemoglobin in both patients also highlights that vancomycin-associated hematological abnormalities may extend beyond the neutrophil-predominant pattern more commonly emphasized in the literature.

Timing of onset and possible mechanisms

The timing of hematological deterioration is an important feature of both cases. In the first patient, an initial decline in WBC and neutrophil counts was identified on Day 9, followed by severe pancytopenia by Day 16. In the second patient, progressive cytopenias were documented by Day 16, with further deterioration after vancomycin discontinuation. This sequence demonstrates that clinically significant hematological abnormalities may emerge during the second week of therapy and may continue to worsen for a period after the suspected drug has been withdrawn.

The timing is consistent with the broader literature on antibiotic-associated hematological adverse effects, although the onset of vancomycin-associated neutropenia varies considerably between patients. In their systematic review, Black et al. found that vancomycin-associated neutropenia was more frequently reported after prolonged treatment, with many cases occurring beyond 20 days. Their review also concluded that the reaction was not consistently associated with daily dosage, cumulative dose, or supratherapeutic serum concentrations [9]. A subsequent systematic review of antibiotic-induced neutropenia in pediatric patients similarly demonstrated considerable variation in time to onset across different antibiotics and clinical settings [10]. The relatively early onset in our patients therefore broadens the clinical time frame in which hematological monitoring may be important; it should not be interpreted as evidence that the timing in these cases is typical of all vancomycin-associated cytopenias.

The mechanisms underlying vancomycin-associated pancytopenia remain incompletely understood. Proposed explanations include immune-mediated peripheral destruction of blood cells, direct or indirect effects on hematopoiesis, and other mechanisms affecting blood cell production or survival. Evidence supporting an immune-mediated mechanism includes reports of vancomycin-dependent platelet-reactive antibodies in patients with thrombocytopenia and reports of antineutrophil antibodies in selected cases of neutropenia [11]. However, the mechanisms responsible for isolated immune thrombocytopenia or neutropenia cannot necessarily be extrapolated to every case of pancytopenia.

In the present patients, the simultaneous involvement of leukocytes, erythrocytes, and platelets is compatible with a broader hematological adverse reaction, but the available clinical findings do not establish a specific mechanism. No definitive mechanistic conclusion can be drawn without additional evidence, such as drug-dependent antibody testing or bone marrow evaluation when clinically indicated [12]. Accordingly, immune-mediated cytopenia and altered hematopoiesis should be considered potential explanations rather than confirmed mechanisms in these cases.

Therapeutic concentrations and the importance of monitoring

Both patients had preserved renal function, and their documented vancomycin trough concentrations were within the reported therapeutic range of 10-20 μg/mL. This observation is clinically relevant because it demonstrates that severe hematological abnormalities may develop despite concentrations that are not reported as supratherapeutic. Previous reviews have similarly found no consistent relationship between vancomycin-associated neutropenia and measured serum concentrations [3,11]. Therapeutic drug monitoring remains important for optimizing antimicrobial exposure and assessing toxicity, but a therapeutic vancomycin concentration should not be interpreted as excluding a possible hematological adverse reaction.

The present cases highlight the importance of regular hematological monitoring during prolonged vancomycin therapy. Based on the available literature, we recommend obtaining a baseline CBC with differential before initiating treatment, followed by at least weekly monitoring in children receiving vancomycin for more than seven days. Monitoring should include the total WBC count, differential count, ANC, hemoglobin, and platelet count. More frequent assessment may be warranted if a declining trend or new hematological abnormality is detected. Furthermore, blood-count monitoring should continue after vancomycin discontinuation in patients who develop cytopenias until hematological recovery is documented. Although the optimal monitoring frequency has not been established specifically in pediatric patients, this pragmatic approach may facilitate early recognition of hematological toxicity and timely reassessment of antimicrobial therapy [3].

Diagnostic assessment and attribution

Establishing a suspected drug-associated hematological adverse event requires consideration of alternative explanations. Severe bacterial infection can itself be associated with changes in circulating blood cell counts, while viral illnesses, immune-mediated disorders, other medications, nutritional deficiencies, and bone marrow disorders may also contribute to cytopenias. In patients with musculoskeletal infections, the underlying inflammatory process and concurrent treatments complicate causal assessment.

In both cases, hematology and immunology evaluations were undertaken. Viral testing was negative, and the reported immunological investigations, including antinuclear antibody, rheumatoid factor, and anti-cyclic citrullinated peptide testing, did not identify an alternative explanation. Renal function remained preserved. These findings reduce support for some alternative explanations but do not exclude every possible cause of pancytopenia. In particular, negative autoimmune serology does not rule out all immune-mediated hematological reactions, and the absence of a clear alternative diagnosis is not, by itself, proof of drug causality.

The marked decline in hemoglobin in the second patient also warrants consideration of potential contributing factors, including perioperative blood loss, repeated phlebotomy, and anemia associated with the underlying inflammatory process. The admission hemoglobin concentration was 14.3 g/dL, and the estimated intraoperative blood loss during surgical drainage was minimal (approximately 10-20 mL). Although repeated phlebotomy and the underlying inflammatory process may have contributed to the

decline, these factors are unlikely to fully explain its magnitude. The subsequent recovery of hemoglobin to 13.1 g/dL without blood transfusion or specific hematological treatment, following vancomycin discontinuation, further supports a suspected drug association. Nevertheless, the contribution of vancomycin cannot be isolated from concurrent clinical factors, and definitive causality cannot be established.

The temporal sequence provides additional support for a suspected association: cytopenias developed during vancomycin exposure, progressed sufficiently to prompt discontinuation, and subsequently improved. Nevertheless, the interpretation should remain cautious because both patients were switched to linezolid at the time vancomycin was stopped, and other clinical factors may have influenced the subsequent course. Linezolid itself is associated with hematological adverse effects, particularly during prolonged treatment, and therefore represents a relevant consideration when interpreting subsequent blood counts. The improvement observed during follow-up is reassuring, but it does not independently establish that vancomycin was the sole cause of the cytopenias [13].

Rechallenge with vancomycin solely to establish causality would not be justified in the setting of severe suspected hematological toxicity. A structured adverse drug reaction assessment may help document the timing, competing explanations, response to withdrawal, and degree of causal certainty. However, the available evidence in these cases supports the descriptive term vancomycin-associated pancytopenia rather than a definitive claim of proven drug-induced marrow toxicity.

To further evaluate the likelihood of a drug-associated adverse reaction, the Naranjo Adverse Drug Reaction Probability Scale was applied separately to both patients. The assessment considered the temporal relationship between vancomycin exposure and the development of pancytopenia, the subsequent hematological improvement following drug discontinuation, objective laboratory findings, and the presence of potential alternative explanations. The resulting scores were interpreted according to the Naranjo classification criteria. Given the probability of contributing clinical factors and the absence of rechallenge, the findings were interpreted cautiously and did not establish definitive causality [14].

The Naranjo Adverse Drug Reaction Probability Scale was applied separately to both patients. Both cases received a score of 5, corresponding to a probable adverse drug reaction. The individual scoring criteria and results are presented in Table *3*. These findings support a probable association between vancomycin exposure and pancytopenia, although definitive causality cannot be established.

Naranjo criterion	Case 1	Case 2
Previous reports (+1)	1	1
Event after drug exposure (+2)	2	2
Improvement after withdrawal (+1)	1	1
Rechallenge	0	0
Alternative causes (-1)	-1	-1
Placebo challenge	0	0
Toxic drug levels (not detected)	0	0
Dose-response relationship	1	1
Previous similar reaction	0	0
Objective evidence (+1)	1	1
Total score	5	5
Classification	Probable	Probable

TABLE 3: Naranjo Adverse Drug Reaction Probability assessment

Scores are calculated using the Naranjo Adverse Drug Reaction Probability Scale (possible: 1-4; probable: 5-8; definite: ≥9)[14].

Management and hematological recovery

The principal management decision in both cases was discontinuation of vancomycin and substitution with oral linezolid for continued antimicrobial treatment. This approach addressed the suspected adverse

reaction while maintaining therapy for the confirmed MRSA infection. Both patients subsequently demonstrated recovery of their reported blood cell parameters, with near-normal or normal WBC and platelet counts at the latest outpatient assessments.

Importantly, the hematological course was not characterized by immediate improvement after vancomycin withdrawal. In both patients, laboratory abnormalities persisted or worsened after discontinuation, including a further marked decline in hemoglobin in the first patient and continued reductions in hemoglobin and platelet counts in the second. This observation is compatible with a delayed recovery phase, although the available data cannot determine the precise mechanism or establish whether all cytopenias shared the same pathophysiology. It reinforces the importance of continued laboratory monitoring after the suspected agent has been discontinued, particularly when abnormalities are severe or progressive.

Neither patient received G-CSF, blood transfusion, or other specific hematological treatment, according to the documented clinical course. The observed recovery therefore occurred without these interventions. This should not be interpreted as evidence that supportive treatment is unnecessary in other patients. Decisions about transfusion, growth-factor support, infection precautions, and further hematological investigation must depend on the severity of the cytopenias, symptoms, clinical stability, and the patient's overall condition. In particular, profound anemia or severe neutropenia warrants individualized assessment and appropriate specialist input.

The decision to substitute linezolid also requires careful consideration of the patient's infection, susceptibility results, clinical response, treatment duration, and potential adverse effects. The present cases demonstrate that an alternative antimicrobial regimen was used successfully alongside subsequent hematological recovery, but two observations cannot establish the comparative safety or efficacy of linezolid versus other agents in this setting. Antimicrobial selection should remain individualized and informed by microbiology and infectious diseases expertise.

Clinical implications

These cases have several practical implications. First, clinicians should recognize that vancomycin-associated hematological toxicity may involve more than one blood cell lineage. A progressive decline in WBC and neutrophil counts accompanied by falling hemoglobin and platelet counts should prompt evaluation for pancytopenia and potential drug-related causes. Second, therapeutic vancomycin trough concentrations and preserved renal function do not exclude a suspected hematological adverse event. Third, blood-count monitoring should continue after discontinuation when cytopenias are severe, because the nadir may occur after the suspected drug has been stopped. Finally, when a drug-associated reaction is suspected, treatment decisions should balance the urgency of controlling the infection against the risks of continued exposure, while ensuring that an appropriate alternative antimicrobial regimen is maintained.

The relevance of these observations extends beyond pediatric osteomyelitis and septic arthritis. Vancomycin is used for a range of serious Gram-positive infections, and clinicians in orthopedic, pediatric, infectious diseases, and general inpatient settings may encounter patients receiving prolonged courses. Awareness of rare but potentially serious hematological adverse effects can support timely recognition, appropriate investigation, and safer antimicrobial management.

Limitations

This report has several limitations. First, it describes only two patients, and the observations cannot establish the incidence, risk factors, or predictive features of vancomycin-associated pancytopenia. Second, although the temporal relationship, negative investigations for alternative causes, and subsequent recovery support a suspected association, definitive causality cannot be established. Third, no specific immunological or bone marrow findings are available to determine the underlying mechanism. Fourth, both patients were switched to linezolid after vancomycin discontinuation, and the contribution of concurrent clinical factors to the subsequent recovery cannot be completely separated from the effect of vancomycin withdrawal. Finally, the findings may not be generalizable to all children receiving vancomycin, particularly those with different underlying conditions, concurrent medications, or treatment durations.

Despite these limitations, the detailed clinical and laboratory trajectories provide useful observations about the recognition and management of suspected vancomycin-associated pancytopenia in children treated for serious MRSA musculoskeletal infections.

Conclusions

Vancomycin-associated pancytopenia should be considered when progressive abnormalities involving multiple blood cell lineages develop during treatment, even when renal function is preserved and measured vancomycin concentrations remain within the reported therapeutic range. These two pediatric cases suggest that severe cytopenias may emerge during the second week of treatment, persist or worsen after vancomycin discontinuation, and subsequently recover during follow-up. In the second patient, recovery of all three blood cell lines was documented by Day 33, approximately 16 days after vancomycin discontinuation. In the

first patient, substantial hematological recovery was documented by Day 62, approximately 45 days after discontinuation. However, the simultaneous initiation of linezolid, which can also cause hematological toxicity, limits the ability to attribute subsequent recovery exclusively to vancomycin withdrawal. These observations highlight the importance of baseline and serial blood-count monitoring, continued laboratory surveillance after drug withdrawal, timely investigation of alternative causes, and prompt reassessment of antimicrobial therapy when significant hematological abnormalities arise. Further studies and pharmacovigilance reports are needed to clarify the frequency, mechanisms, and optimal management of this uncommon adverse event.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. The Jordanian Royal Medical Services Institutional Ethics Committee issued approval 16/2026. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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