

## Case Report

# Vancomycin-Induced Neutropenia with Fever

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## Abstract

Vancomycin is a glycopeptide antibiotics acts by inhibiting cell wall and is used for the treatment of resistant Gram-positive bacteria. Vancomycin-induced fever with neutropenia is not commonly encountered in our clinical practice, it can lead to diagnostic dilemmas during the course of management. We report the case of a 43-year-old female with infective endocarditis of the aortic valve, who was started empirically on vancomycin and ceftriaxone. She later developed fever with neutropenia following 2 weeks of intravenous antibiotics. This was attributed to the rare adverse effect of vancomycin, after further investigating and ruling out all other possible etiologies. After discontinuing vancomycin, the symptoms resolved rapidly. Although the exact mechanism of the fever and neutropenia is not known, many researchers believe it to be immune mediated.

**Keywords:** Fever, neutropenia, vancomycin

## INTRODUCTION

Vancomycin is a glycopeptide antibiotics acts by inhibiting cell wall and is used for the treatment of resistant Gram-positive bacteria. Vancomycin has been used in clinical for a long time, adverse effects such as nephrotoxicity, red man syndrome, hypersensitivity rash, and ototoxicity are common and have been well described in literature. Agranulocytosis and neutropenia have also been described in case reports and case series, but drug fever accompanying neutropenia is a rare entity. Vancomycin-induced fever with neutropenia is a rarely reported adverse event of the drug and not more than four to five reported cases in literature, to the best of our knowledge. Although the exact mechanism is unknown, multiple mechanisms have been described for the same. Here in this report, we have described such a case and how it was managed subsequently.

## CASE REPORT

A 43-year-old female, resident of Gwalior, housemaker by profession and with no prior comorbidities presented with high-grade fever (102°F) with chills for 14 days and multiple joint pain involving the left shoulder, left elbow, and left hip for 10 days. Initially, she was admitted in a local hospital for the same and had received intravenous (IV) antibiotics for 2 days before she was referred to our hospital. On presentation,

she was febrile, with a heart rate of 104/min, blood pressure of 118/74 mmHg, respiratory rate of 20/min, and room air saturation of 99%. There was mild pallor, no icterus, cyanosis, clubbing, pedal edema, lymphadenopathy nor raised jugular venous pressure. On further examination, there were few nontender, small erythematous macular lesions on both palms. On cardiovascular examination, S1 and S2 were normal, an early diastolic murmur was heard over the aortic area. Both lung fields were clear on auscultation. The abdomen was soft, nontender with the tip of the spleen just being palpable. An echocardiography was done which revealed a vegetation of size 8 mm × 10 mm on the aortic valve with moderate aortic regurgitation. A diagnosis of native valve infective endocarditis (IE) was made on modified Dukes criteria (1 major and 3 minor).<sup>[1]</sup> Two paired cultures were sent and the patient was started on empirical IV antibiotic therapy comprising vancomycin and ceftriaxone. The patient was afebrile from the 3<sup>rd</sup> day following antibiotic therapy and the same was continued as blood cultures were sterile following 7 days of incubation.

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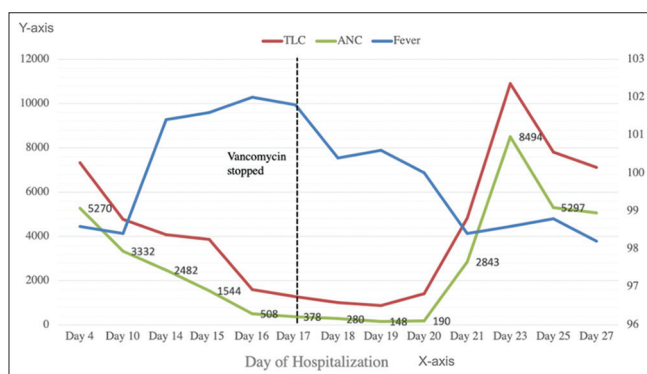
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**Table 1: Routine investigation (date wise) during the in-hospital stay and follow-up**

| Date                        | Vancomycin day 1 | Vancomycin day 16 | Vancomycin day 17 | Teicoplanin day 2 | Teicoplanin day 4 | Teicoplanin day 7 | On follow up visit (after 1 month) |
|-----------------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------------------------------|
| <b>Haemogram</b>            |                  |                   |                   |                   |                   |                   |                                    |
| Hb (g/dl)                   | 7.1              | 7.6               | 8.0               | 7.4               | 7.1               | 7.4               | 9.1                                |
| PLT (/μL)                   | 222,000          | 161,000           | 176,000           | 166,000           |                   | 185,000           | 219,000                            |
| TLC (/mm <sup>3</sup> )     | 7230             | 1590              | 1260              | 870               | 4820              | 6740              | 7200                               |
| Neutrophil (%)              | 72.1             | 32.7              | 30.0              | 17.4              | 59.1              | 68.3              | 69                                 |
| Eosinophil (%)              | 0.6              | 1.9               | -                 | 1.1               | 0.4               | 0.3               | 04                                 |
| Lymphocytes (%)             | 15.3             | 40.9              | -                 | 49.4              | 18.3              | 17.7              | 27                                 |
| Monocyte (%)                | 11.5             | 24.5              | -                 | 31.0              | 22.2              | 13.6              | 00                                 |
| Basophil (%)                | 0.7              | 0.0               | -                 | 1.1               | 0.0               | 0.1               | 00                                 |
| <b>Renal function</b>       |                  |                   |                   |                   |                   |                   |                                    |
| Urea (mg/dl)                | 33.9             | 20                | 26                | 18                | 16                | 22                | 20                                 |
| Creatinine (mg/dl)          | 0.7              | 0.9               | 1.2               | 0.9               | 0.9               | 0.9               | 0.8                                |
| <b>Liver function test</b>  |                  |                   |                   |                   |                   |                   |                                    |
| Bilirubin (total) (mg/dL)   | 0.6              | 0.6               | 0.6               | 0.5               | 0.9               | 1.0               | 0.8                                |
| Protein (total) (g/dL)      | 7.5              | 7.5               | 7.3               | 6.5               | 6.7               | 7.0               | 7.1                                |
| SGOT (IU/L)                 | 20               | 50                | 75                | 29                | 29                | 28                | 30                                 |
| SGPT (IU/L)                 | 11               | 10                | 14                | 9                 | 12                | 11                | 16                                 |
| ALP (IU/L)                  | 300              | 249               | 244               | 292               | 323               | 328               | 280                                |
| <b>Inflammatory markers</b> |                  |                   |                   |                   |                   |                   |                                    |
| CRP (mg/dL)                 | 18.72            | 12.6              | -                 | 7.818             | -                 | -                 | <1.0                               |
| Procalcitonin (ng/mL)       | 1.2              | 0.4               | -                 | 0.02              | -                 | -                 | -                                  |

Hb=Hemoglobin, TLC=Total leukocyte count, PLT=Platelets, SGOT= serum glutamic-oxaloacetic transaminase, SGPT= Serum Glutamic Pyruvic Transaminase, ALP=Alkaline phosphatase, CRP=C-reactive protein



**Figure 1:** Graphical representation showing the impact of vancomycin on total leukocyte count, absolute neutrophilic count and body temperature. Days of hospitalization is on x-axis. Total leukocyte count (in per cubic millimeter) is represented on left side on y-axis, depicted in red line in the graph. Fever (in degree Fahrenheit) is represented on right side on y-axis, depicted in blue line in graph. Absolute neutrophilic count (in cubic millimeter) is depicted in green line. Dotted black line represent day of stopping vancomycin

On day 14 of hospitalization, the patient had new-onset fever (101F). All routine workups for in-hospital fever were negative along with repeat echocardiography with did not show any local complication of IE. On day 16<sup>th</sup> of hospitalization, there was a leukocytopenia (1590/μL) with neutropenia (absolute neutrophilic count [ANC] =1544) noted along with mild transaminitis. Keeping a possibility of vancomycin-induced neutropenia and drug fever, vancomycin

was replaced by high dose teicoplanin on day 17<sup>th</sup> of hospitalization, following which the fever subsided after 72 h and neutropenia normalized by 4<sup>th</sup> day after stopping the offending agent. The trend of routine investigation on vancomycin and teicoplanin has been shown in Table 1 and relationship of fever with neutropenia is shown in Figure 1.

## DISCUSSION

Vancomycin is an important antibiotic against Gram-positive organisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), but it infrequently causes neutropenia which can limit its use in conditions such as IE and acute osteomyelitis. Vancomycin-induced neutropenia is likely to be associated with therapy longer than 7 days, with the highest number of incidents occurring past 20 days of therapy.<sup>[2]</sup> There has been no association between cumulative dosage or serum concentrations of vancomycin with the development of neutropenia.<sup>[3]</sup> Neutropenia is completely reversible by stopping vancomycin, normalizing within 1 week after discontinuation.<sup>[4]</sup> Drug fever accompanying neutropenia by vancomycin is rare in literature, limited to handful of case reports.<sup>[5-7]</sup> Smith and Taylor in their review described vancomycin drug fever typically occurs after 7 days or more of therapy and resolves within 48–72 h after discontinuation of drug, running all almost similar course to that of vancomycin-induced neutropenia.<sup>[6]</sup> Our patient developed new-onset fever on day 14<sup>th</sup> of illness on vancomycin, followed by neutropenia on day 16<sup>th</sup>, which

was consistent with other case reports. Before making a diagnosis of drug fever, other etiologies such as worsening of primary disease or hospital-acquired infection must be ruled out by detailed clinical examination and appropriate investigations. Although the exact mechanism of neutropenia and fever is not known, few researchers have attributed it to immune mediated and very rarely due to bone marrow suppression.<sup>[8]</sup> The incidence of vancomycin-induced neutropenia is around 2%.<sup>[4]</sup> Therapeutic alternative for this adverse effect of vancomycin includes changing to alternative antibiotic of related class such as teicoplanin and linezolid. In a retrospective review done by Hung *et al.*, 4 out of 8 patients with vancomycin-induced neutropenia ( $n = 117$ ) subsequently again developed neutropenia after switching to teicoplanin with a mean nadir leukocyte count being 2300 (ANC 900/mm).<sup>[9]</sup> Lai *et al.* used granulocyte colony-stimulating factor along with vancomycin to maintain absolute neutrophil count above normal threshold in two patients to prevent further neutropenia.<sup>[10]</sup> Desensitization of vancomycin has never been tried in the context of neutropenia. Although rare owing to this serious adverse event of vancomycin, it is advisable to frequently monitor the complete blood count at least twice weekly after 1 week of therapy.<sup>[11]</sup> In our patient, the diagnosis of vancomycin-induced neutropenia and fever was clinically confirmed owing to the rapid defervesce of fever and recovery of neutrophilia following discontinuation of vancomycin.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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