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CASE REPORT

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# Ceftriaxone-induced neutropenia successfully overcome by a switch to penicillin G in *Cardiobacterium hominis* endocarditis

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**Abstract**

Leukopenia, including agranulocytosis, is a severe complication of treatment with all β-lactam antibiotics. Its incidence increases with age. *Cardiobacterium hominis* endocarditis after implantation of an aortic valve bio-prosthesis in a 77-year-old woman was treated with ceftriaxone 2 g/day plus gentamicin 160 mg/day intravenously. On Day 25 of treatment, blood leukocytes had decreased to 1800/μl (neutrophils 370/μl). Antibiotic therapy was switched to penicillin G 20 million international units (IU)/day. Thereafter, blood leukocytes including neutrophils normalized suggesting that penicillin G was less bone marrow-toxic than ceftriaxone. High-dose ciprofloxacin, the alternative to penicillin G, was avoided because of the risk of cognitive and behavioral side effects. The present case suggests that with close laboratory monitoring a β-lactam with differing side chains should not be considered contraindicated after β-lactam antibiotic-induced neutropenia.

**KEYWORDS**

*Cardiobacterium hominis*, ceftriaxone, endocarditis – leukopenia, penicillin G

**JEL CLASSIFICATION**

Geriatrics, Infectious Diseases

## 1 | INTRODUCTION

*Cardiobacterium hominis* is a Gram-negative rod-shaped bacterium colonizing the mouth and the upper respiratory tract. It can cause endocarditis, predominantly prosthetic valve endocarditis.[1,2] It is a member of the HACEK group (*Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*) consisting of Gram-negative bacteria which are part of the normal flora of the oral cavity and upper respiratory tract in humans and can cause endocarditis typically in patients with heart diseases or artificial valves.[3] The clinical course of *C. hominis* endocarditis often is indolent with a long duration of symptoms prior to the establishment of the diagnosis.[4] A review of *C. hominis* endocarditis cases from 2006 found a duration

of preceding symptoms of 138 ± 128 days. The symptoms most frequently reported were fever (74%), fatigue and malaise (53%), weight loss (40%), night sweats (24%), and joint and muscle pain (21%). Confusion was noted in only one of 61 patients.[5] Standard therapy of *C. hominis* endocarditis consists of ceftriaxone for 6 weeks in combination with gentamicin for 4 weeks.[2]

Drug-induced neutropenia is defined by a decrease of the blood neutrophil count below 500/μl. Neutropenia or agranulocytosis associated with exposure to non-chemotherapy drugs ranges from approximately 2.4 to 15.4 cases per million population per year.[6] Non-chemotherapy drugs most often associated with neutropenia or agranulocytosis include clozapine, other neuroleptic and antidepressant drugs, dipyrone, ticlopidine, thyreostatic drugs, carbamazepine, β-lactams, and other antibiotics including sulfamethoxazole-trimethoprim, sulfasalazine, fluoroquinolones, clindamycin, linezolid, glycopeptides, and valganciclovir.[6] Drug-induced neutropenia probably can occur with all β-lactam antibiotics. Both direct toxic and immune-mediated mechanisms have been implicated.[7]

## 2 | CASE REPORT

A 77-year-old woman (body weight 52 kg) with no known allergies to antibiotics or other drugs had received aortic valve replacement (Carpentier-Edwards Perimount Magna Ease bio-prosthesis) for aortic regurgitation. 11 years later, her general state of health declined, she became forgetful and disoriented at night. 2 months later, she developed fever up to 38°C, elevated C-reactive protein (up to 57 mg/L), and was encountered disoriented in

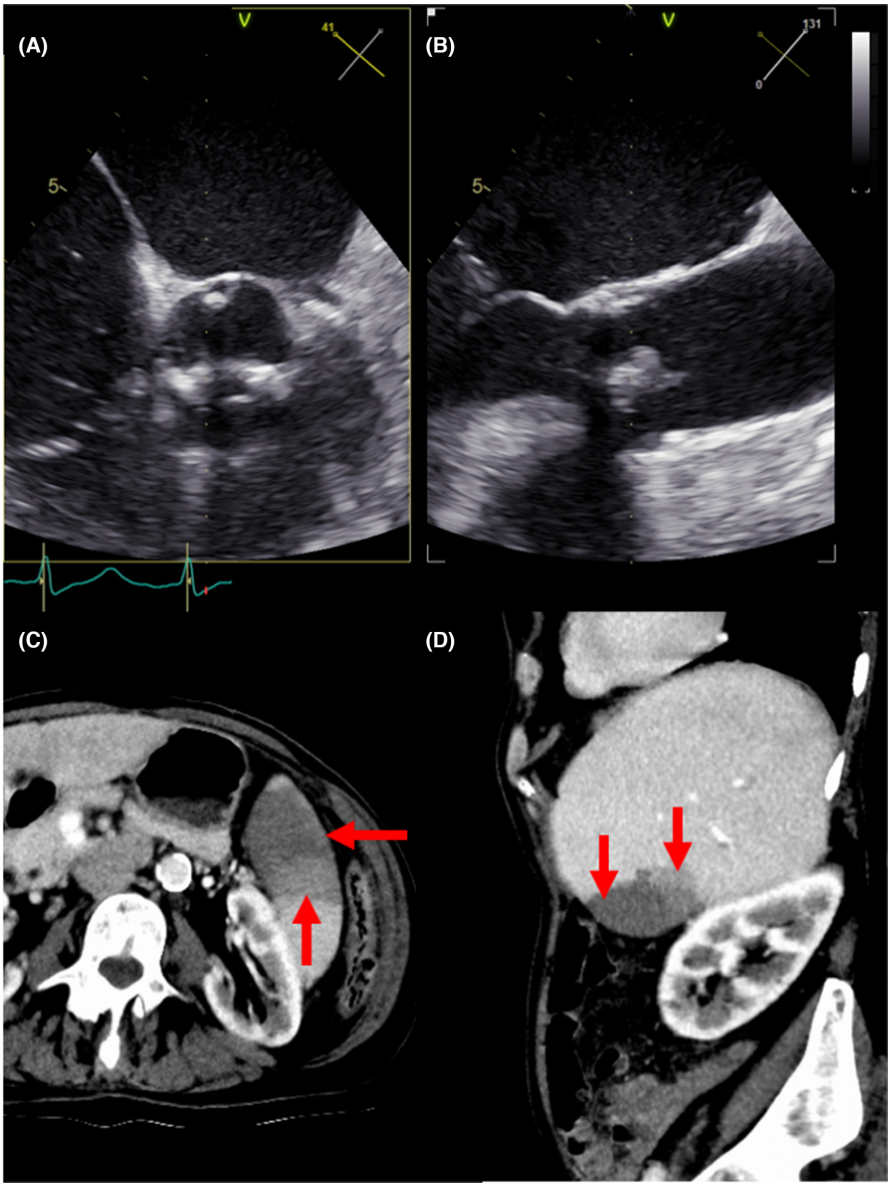


**FIGURE 1** Transesophageal echocardiography (A, B) and abdominal computer tomography (C, D) prior to the initiation of antibiotic treatment in *Cardiobacterium hominis* endocarditis. Strongly degenerated aortic valve bio-prosthesis suggesting infective endocarditis, (A) short axis, (B) long axis. Splenomegaly and splenic infarction (arrows), contrast-enhanced sagittal computer tomography, (C) transversal image, (D) sagittal image.

a shop, which led to a short hospital admission without definite diagnosis. In the next 2 months, the episodes of elevated temperature persisted, the cognitive decline worsened (decline of the Montreal Cognitive Assessment from 24 to 16 of 30 points), and the patient developed gait disturbances and sleep apnea. She did not complain of abdominal pain, and physical exam of the abdomen was normal except for a small inguinal hernia. Auscultation did not reveal a systolic or diastolic cardiac murmur. Three blood cultures drawn after admission at our institution (i.e., 4 months after the start of cognitive abnormalities and 2 months after the onset of fever) on consecutive days grew *Cardiobacterium hominis* within 72 h. The bacterium was identified by matrix-assisted laser desorption/ionization-time of flight mass spectroscopy (MALDI-TOF MS) and cultured on Mueller-Hinton agar supplemented with 5% horse blood and 20 mg/L nicotinamide adenine dinucleotide (NAD) for the determination of antibiotic susceptibility. No pathogens were isolated from other sites. A throat swab grew physiological flora. Transesophageal echocardiography showed strong degeneration of the aortic valve with high-grade aortic stenosis (area of valve opening 1 $cm^2$) suggesting endocarditis (Figure 1) and a large patent foramen ovale with continuous left-to-right atrial shunting. Abdominal computer tomography revealed splenomegaly and fresh splenic infarction. Magnetic resonance imaging of the brain excluded acute or subacute septic-embolic encephalitis, but showed cerebral microangiopathy and a small left-sided infratentorial meningioma. The diagnosis of endocarditis was made because of the typical pathogen, the history of cardiac valve replacement, suspicious findings in echocardiography, and the splenic infarction.

Antibiotic therapy with ceftriaxone 2 g/day plus gentamicin 160 mg/day i.v. administered as single daily doses was started immediately. Other drugs administered included oral bisoprolol, candesartan, torasemide, rivaroxaban, levothyroxine, melatonin, and inhaled beclometasone. These drugs carry a very low risk of inducing leukopenia. No surgical interventions were performed. The patient's general and cognitive status improved rapidly, and fever and C-reactive protein declined. When on Day 25 of treatment, blood leukocytes had decreased to 1800/µl (neutrophils 370/µl) (Figure 2), ceftriaxone and gentamicin were discontinued. Antibiotic therapy was switched to penicillin G 5 million international units (IU) every 6 h (20 million IU/day = 12 g/day; 1 million IU penicillin G equivalent to 0.6 g penicillin G). Thereafter, blood leukocytes including neutrophils gradually increased to 5910/µl and 3420/µl, respectively, on Day 160. The patient made an uneventful recovery and was discharged home after 6 weeks of antibiotic treatment. A blood culture drawn 2 days after termination of penicillin G treatment was sterile. At 6 months intervals, the degree of aortic valve stenosis is monitored by echocardiography in order not to miss the slot for an intervention at the aortic valve.

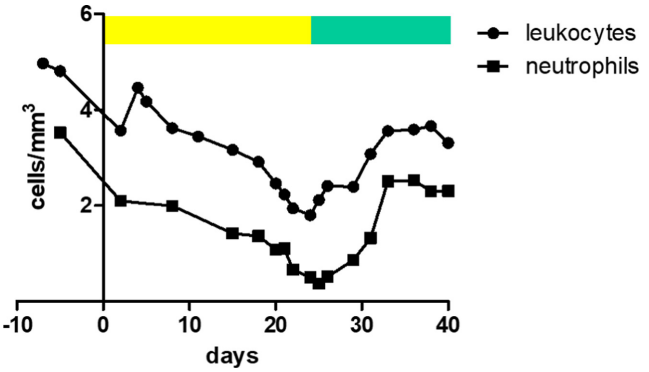


**FIGURE 2** Time course of total leukocyte (filled circles) and neutrophilic granulocyte counts (filled squares) in a 77-year-old woman receiving ceftriaxone 2 g/day plus gentamicin 160 mg/day (yellow bar)* and penicillin G 4 × 5 million international units/day (green bar)# for endocarditis of an aortic valve bio-prosthesis by *Cardiobacterium hominis*. Please note the drop of neutrophilic granulocytes on Day 25 of treatment, which led to the switch of antibacterial therapy. *Black and white: light gray. #Black and white: dark gray.

## 3 | DISCUSSION

Leukopenia, including agranulocytosis, is a severe, usually reversible, complication of treatment with all β-lactam antibiotics. The pathogenesis of neutropenia and agranulocytosis induced by β-lactam antibiotics remains controversial. Either an immunological mechanism or direct bone marrow toxicity have been implicated.[8] Often—as in the present case—bone marrow histology and the search for antibodies directed against the β-lactam antibiotic administered are not performed.[6] Fortunately, the outcome often is favorable: according to our PUBMED search, only one fatal case caused by ceftriaxone in a pregnant woman eventually dying of *Aspergillus* sp. necrotizing bronchopneumonia after repeated treatment with ceftriaxone prior and after caesarean section was reported (case #15).[8,9] In a review of 26 patients from the first 50 years of penicillin use (18 of the 26 patients suffered from endocarditis), all patients with penicillin G-induced leukopenia or agranulocytosis survived.[10] In a more recent retrospective systematic study on prolonged high-dose intravenous penicillin G for the treatment of neurosyphilis (n = 1367, total cumulative dose from 240 to 324 million IU), neutropenia and severe neutropenia occurred in 2.4% and 0.35% of the cases. No fatal cases were reported.[11] Gentamicin has not been reported to cause leukopenia in an extensive narrative review on non-chemotherapy

drug-induced neutropenia.[6] Leukopenia and agranulocytosis during antibiotic treatment are less frequent and often less dramatic than agranulocytosis caused by cancer chemotherapy. Here, in-hospital mortality rates range from 0.4% to 3.0% in children with cancer, 2.6% to 7.0% in adults with solid tumors, and 7.4% in adults with hematologic malignancies.[12] Cytostatic regimens most commonly associated with leukopenia/agranulocytosis often include doxorubicin, cyclophosphamide, platinum, etoposide, or gemcitabine. These regimens frequently require granulocyte colony-stimulating factor (G-CSF).[12,13] The patient reported here did not require G-CSF.

The alternative to continuing treatment of the present patient with a β-lactam antibiotic would have been high-dose ciprofloxacin.[1,14] Fluoroquinolones carry a substantial risk of cognitive and behavioral side effects especially in the elderly and therefore were avoided in this patient with cognitive abnormalities.

Because of the low minimum inhibitory concentration of penicillin G for the bacterium isolated (0.008 mg/L) and the structural dissimilarities of ceftriaxone and penicillin G, treatment was continued with the latter drug. The daily penicillin G dose necessary to achieve therapeutic plasma concentrations for 24 hours was higher than the daily ceftriaxone dose: 5 million IU four times a day (=4×3 g/day) of penicillin G versus 2 g ceftriaxone/day. The mean area under the concentration-time curve (AUC) of a penicillin dose of 1 million IU in healthy young volunteers (mean age 34 years) with a mean weight of 70 kg was reported to be 22.3 mg x h/l.[15] By assuming approximately linear pharmacokinetics, 20 million IU penicillin G would result in an AUC of 446 mg×h/l. Based on the population pharmacokinetics in 25 patients with infective endocarditis (age 21–83 years, mean age 54 years, mean creatinine clearance 82.5 mL/min), a daily dose of 20 million IU penicillin G resulted in an AUC of approximately 692 mg×h/l.[16] A single dose of 2 g of ceftriaxone produced a mean AUC of 1703 mg×h/l in young healthy volunteers (mean age 36 years)[17] and of 1774 mg×h/l in intensive care patients (age 49–76 years, mean age 60 years) with respiratory tract infections.[18] These data indicate a lower AUC of 20 million IU penicillin G/day than of 2 g ceftriaxone/day. However, when differences in protein binding are considered,[19] the estimated AUCs of the free fraction of 20 million IU penicillin G/day and of 2 g ceftriaxone/day are similar both in healthy volunteers and in critically ill patients. Since the free fraction probably is responsible for toxicity, it appears unlikely that the differences in AUCs account for the reduced toxicity of penicillin G.

In vitro, the cephalosporin group is 3–25 times more potent than penicillins in inhibiting granulopoiesis.[20] Moreover, ceftriaxone possesses a R2 side chain with a triazinedione group, which is more reactive than the side chains of other β-lactam antibiotics including the otherwise very similar cefepime.[8] The cornerstone of management of β-lactam antibiotic-induced neutropenia is the cessation of the causative agent. Direct substitution or future use of an alternative β-lactam antibiotic is controversially discussed.[7] Because of the superiority of β-lactam antibiotics compared to alternative therapeutic options for several infections including endocarditis, the present case suggests that the use of a β-lactam with differing side chains should not be considered contraindicated after β-lactam antibiotic-induced neutropenia.[7] Close laboratory monitoring, however, is indispensable.

## AUTHOR CONTRIBUTIONS

**Roland Nau:** Conceptualization; investigation; writing – original draft; writing – review and editing. **Stefan Schmidt-Schweda:** Investigation; writing – review and editing. **Tobias Frank:** Investigation; writing – review and editing. **Johannes Gossner:** Investigation; writing – review and editing. **Marija Djukic:** Investigation; writing – review and editing. **Helmut Eiffert:** Conceptualization; investigation; writing – review and editing.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

## DATA AVAILABILITY STATEMENT

The personal data of the patient are not publicly available.

## ETHICAL APPROVAL

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval is not required for this study in accordance with national guidelines. The patient has given her written informed consent to publish this case (including publication of the images).

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