CASE REPORT

Severe Cefazolin-Associated Coagulopathy Corrected with Vitamin K Supplementation: A Case Report

R. Vincent Smith, MD,[1] Nathan Brott, MD,[1] Brittany N. White, PharmD, BCPS, CACP,[1] Haden S. Hall[1]

[1]University of Tennessee Health Science Center Chattanooga, Department of Internal Medicine, Chattanooga, TN, United States

Corresponding author: R. Vincent Smith, MD, Assistant Professor, Internal Medicine, Erlanger Health System, 979 E. 3rd St, Chattanooga, TN 37403, United States (vince.smith@erlanger.org)

Received: 12/11/2023 Revised: 02/06/2024 Accepted: 03/17/2024 Published: 03/31/2024

Am j Hosp Med Jan;8(1): 2024. DOI: https://doi.org/10.24150/ajhm/2024.009

Keywords: Antibiotics, Coagulation Disorder, Drug-Related Side Effects and Adverse Reactions, Hematologic Diseases, Hemorrhagic Complication

ABSTRACT

Cefazolin, a commonly used antibiotic in clinical practice, has been associated with coagulation disorders, including hypoprothrombinemia and elevated international normalized ratio (INR) in the absence of vitamin K antagonist administration. However, these cases often involve patients with renal dysfunction or malnutrition. We present a unique case of a 66-year-old male with severe cefazolin-associated coagulopathy despite normal kidney function. The patient had a complex medical history, including heart failure with preserved ejection fraction and rheumatoid arthritis on immunosuppression therapy. He was initially admitted to the hospital with COVID-19, acute pulmonary embolism, and non-ST-segment elevation myocardial infarction. Subsequently, he developed methicillin-sensitive Staphylococcus aureus bacteremia and epidural abscesses, for which high-dose cefazolin was initiated. The patient presented with gross hematuria and hematochezia, along with an elevated INR and prolonged prothrombin time. Despite holding rivaroxaban, his coagulation profile remained abnormal. After vitamin K administration and discontinuation of cefazolin, the INR quickly corrected. This case highlights the need for monitoring cefazolin therapy in patients with hemorrhagic complications to assess for coagulopathy.

INTRODUCTION

Cefazolin is a first-generation cephalosporin antibiotic used widely in clinical practice. It is commonly used for surgical antimicrobial prophylaxis, to treat non-purulent cellulitis and considered a first-line agent to treat blood stream infections caused by methicillin-susceptible Staphylococcus aureus (MSSA) based on meta-analyses demonstrating a mortality benefit compared to anti-staphylococcal penicillins.[1, 2] Although rare, cefazolin has been associated with abnormal coagulation parameters, specifically elevation of PT/INR.

The exact mechanism of anticoagulation exerted by cefazolin is unclear. There are two proposed mechanisms: (1) second- and third-generation cephalosporins containing a N-methyl-thiotetrazole (NMTT) side chain or cephalosporins containing a methyl-thiadiazole (MTD) side chain (specific to cefazolin) inhibit vitamin K epoxide reductase. Similarly, warfarin produces an anticoagulant effect by inhibiting vitamin K epoxide reductase and vitamin K reductase, leading to decreased levels of vitamin K, an essential cofactor for production of coagulation factors II, VII, IX, and X as well as protein C and protein S. (2) Antibiotic induced alterations in gut microbiota, which serve as a major source of vitamin K.

There have been at least 12 documented cases of suspected cefazolin-associated coagulopathy.[3-11] Nearly all have been associated with a concurrent acute kidney injury or end stage renal disease. This case (along with a case presented by Smith et al.) is unique, as a coagulopathy developed in the setting of preserved kidney function.

CASE PRESENTATION

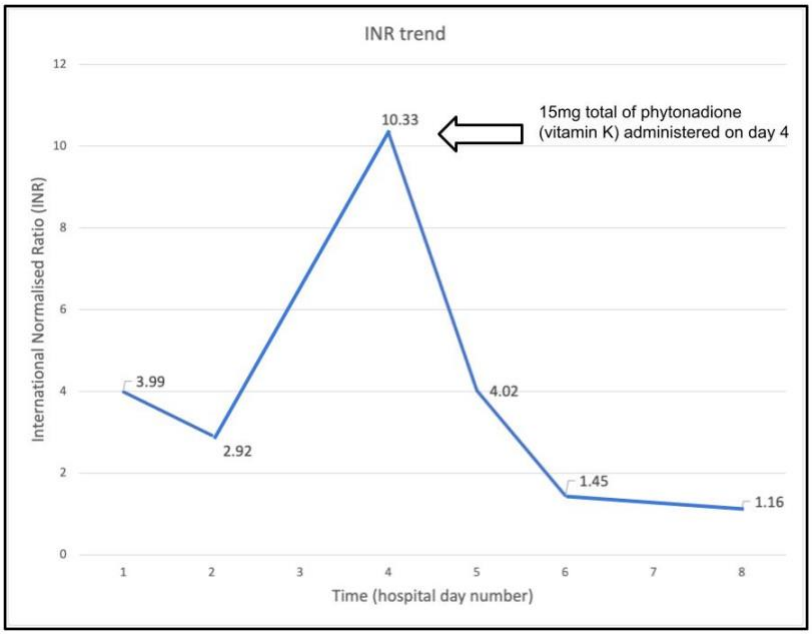
This case is a 66-year-old male with a past medical history of heart failure with preserved ejection fraction (LVEF 50-55%), hypertension, gout, rheumatoid arthritis on immunosuppression, and peripheral artery disease, who had two recent complex hospitalizations prior to presenting with gross hematuria and hematochezia. Six weeks prior to this admission, he was treated at an outside hospital for COVID-19, deep vein thrombosis (DVT) of the right popliteal and peroneal veins, acute pulmonary embolism (PE), and non-ST-segment elevation myocardial infarction. He received anticoagulation therapy with an unfractionated heparin infusion and underwent cardiac catheterization with placement of a drug-eluting stent for a 99% stenosis of the left anterior descending artery. He was started on dual antiplatelet therapy with ticagrelor and aspirin 81 mg daily (for 15 days followed by ticagrelor alone for the intended duration of one year) in addition to the recommended 21-day rivaroxaban loading dose regimen for his acute DVT and PE. Additionally, he received remdesivir and dexamethasone for COVID-19 treatment. Two days after discharge, he presented with septic shock due to methicillin-sensitive Staphylococcus aureus bacteremia and epidural abscesses that resulted in lower extremity hemiparesis and neurogenic bladder, for which he received high-dose intravenous cefazolin (3 gm intravenous every 8 hours) with a planned therapy duration of six weeks. He was discharged to an inpatient rehab facility but presented again two days later with gross hematuria and hematochezia.

Laboratory studies upon admission were notable for hemoglobin 8.8 gm/dL (from 11.2 gm/dL on recent discharge), an elevated INR of 5.26, and prolonged prothrombin time (PT) of 59.8 seconds (baseline INR at the outside hospital three weeks prior was 0.95). A serum creatinine at the time of admission was 1.1 mg/dL and remained normal (range 0.8 - 1.1 mg/dL) throughout his entire stay with hemorrhagic complications.

Just before admission, he was receiving rivaroxaban and ticagrelor (aspirin had been stopped as directed 2 weeks after coronary drug-eluting stent placement). Rivaroxaban and ticagrelor were initially held, and a cangrelor infusion was initiated due to the high risk of in-stent thrombosis while holding oral antiplatelet therapy. An inferior vena cava filter was placed given recent diagnosis of DVT/PE and contraindication to anticoagulation with active bleeding.

Urology was consulted for evaluation of hematuria, and continuous bladder irrigation was initiated. Despite discontinuing rivaroxaban, a repeat INR level continued to increase daily. Gross hematuria persisted, and by hospitalization day four, more than four days since the last rivaroxaban administration, the INR peaked beyond limits of detection (>10). Hematology was consulted. To evaluate for delayed clearance of rivaroxaban as a potential cause of coagulopathy, a non-specific anti-Xa level assay was performed, which was undetectable (<4 IU/mL; reference range 0.30-0.70) and strongly argued against delayed drug clearance. A partial thromboplastin time (PTT) mixing study resulted as 46 seconds (reference range 25.1 - 36.5 seconds), which is prolonged and is consistent with the presence of a coagulation inhibitor, given the correction after mixing with normal pooled plasma to 31 seconds.

Figure 1. INR Trend During Patient's Hospital Admission



Cefazolin-associated coagulopathy was suspected; cefazolin was discontinued, and linezolid was initiated for treatment for MSSA infection. The patient was given oral phytonadione (Vitamin K) 15 mg divided in two doses on day four of hospitalization. His INR subsequently declined to 4.0 on day five, 1.4 on day six, and 1.2 on day seven (Figure 1). The hematuria and hematochezia improved. However, he did have recurrence of gross hematuria while receiving continuous intravenous cangrelor infusion. Given his previous history of prostate cancer with radiation, he was suspected to have radiation cystitis. The patient was offered hyperbaric treatment but declined due to claustrophobia. Additional efforts to treat the gross hematuria, including continuous bladder irrigation, cystoscopy with fulguration, and local aminocaproic acid, were unsuccessful. Given his intractable gross hematuria requiring frequent blood transfusions and significant quality of life impairment from recent lower extremity hemiparesis that left him bedbound, the patient elected to pursue comfort measures only and was discharged home with hospice services.

DISCUSSION

Cefazolin-induced coagulopathy has been previously reported, but most cases involve patients with renal dysfunction or malnutrition. Our case is unique as the patient developed severe coagulopathy despite preserved kidney function throughout the hospitalization. Given the protracted course of illness in this patient and prolonged nothing-by-mouth status, there may have been a component of protein-calorie malnutrition that contributed to inadequate coagulation factor synthesis.

In contrast to previous case reports, this patient also received a higher dose of cefazolin (3 gm IV every 8 hours) due to obesity, with a documented actual body weight of 159 kilograms. This may suggest there is a dose-response relationship with cefazolin-induced coagulopathy, but there is a lack of evidence to support or refute this hypothesis. A large multi-center, retrospective analysis of high dose cefazolin for treatment of bacteremia in obese patients demonstrated a similar safety profile to a standard dosing regimen of 1 gm IV every 8 hours.[13]

The International Normalized Ratio (INR) provides a standard of prothrombin times (PT) across laboratories testing therapeutic efficacy of vitamin K antagonists. Interpreting an abnormal INR outside the context of vitamin K antagonism is challenging. For example, an elevated INR has not proven clinically reliable in predicting hemorrhagic complications in conditions like chronic liver disease or congenital coagulation protein deficiencies.[14, 15] Interpreting elevated PT/INR values is also difficult in relation to direct oral anticoagulant (DOAC) use. Prompt resolution of a severely elevated INR with administration of vitamin K is commonly reported in suspected cefazolin-induced coagulopathy and provides indirect evidence that cefazolin may mimic the mechanism of action of vitamin K antagonist. In this case, the concomitant use of antiplatelet and anticoagulant medications very likely contributed to hemorrhagic complications irrespective of abnormal coagulation parameters.

This case highlights the importance of considering cefazolin-associated coagulopathy in patients treated with cefazolin therapy who have active hemorrhage, even in the absence of renal dysfunction. Further, it is important to recognize that cefazolin can cause a significantly elevated PT/INR, irrespective of presence of active hemorrhage. Clinicians should be aware of the potential for severe cefazolin-associated coagulopathy and consider close monitoring and appropriate interventions, such as early vitamin K supplementation to prevent complications.

Notes
Conflicts of Interest: None declared
Funding: None declared
Acknowledgements: None

REFERENCES

1. Bidell MR, Patel N, O'Donnell JN. Optimal treatment of MSSA bacteraemias: a meta-analysis of cefazolin versus antistaphylococcal penicillins. J Antimicrob Chemother. 2018 Oct 1;73(10):2643-2651. doi: 10.1093/jac/dky259. PMID: 30085140.
2. Shi C, Xiao Y, Zhang Q, Li Q, Wang F, Wu J, Lin N. Efficacy and safety of cefazolin versus antistaphylococcal penicillins for the treatment of methicillin-susceptible Staphylococcus aureus bacteremia: a systematic review and meta-analysis. BMC Infect Dis. 2018 Oct 11;18(1):508. doi: 10.1186/s12879-018-3418-9. PMID: 30305037; PMCID: PMC6180622.

3. Smith M, Doyle J, Crane C, Bussell C. Cefazolin-induced hypoprothrombinemia. Proc (Bayl Univ Med Cent). 2022 Jul 13;35(6):868-870. doi: 10.1080/08998280.2022.2095859. PMID: 36304595; PMCID: PMC9586601.
4. Barnes JL, Pabian IE, Bonjour AK, Mosbacher KA, Mortrude GC, Beasley KA. Cefazolin-Associated INR Elevation: A Case Report. J Pharm Pract. 2022 Oct 7:8971900221132680. doi: 10.1177/08971900221132680. Epub ahead of print. PMID: 36206055.
5. Ngiam JN, Liong TS, Tham SM, Pramotedham T, AlAgha R, Yong J, Tambyah PA, Lum LHW. Deranged Coagulation Profile Secondary to Cefazolin Use: Case Report. Infect Dis Rep. 2021 Mar 1;13(1):187-190. doi: 10.3390/idr13010021. PMID: 33804372; PMCID: PMC7931061.
6. Shaikh, N.; Al Khowtair, J.; Al Sulaiti, G.; Nasser, A.; Ummunnisa, F.; Ahmed, Z.; Hassens, Y. Cefazolin and Coagulation Disorder: A case report and review literature.Qatar.Med.J.2013,21,54–55.
7. Chung AH, Watson K. Cefazolin-induced hypoprothrombinemia. Am J Health Syst Pharm. 2008 May 1;65(9):823-6. doi: 10.2146/ajhp070243. PMID: 18436729.
8. Kuypers DR, Claes K. Intracerebral haemorrhage caused by cefazoline-induced hypoprothrombinaemia in a renal transplant recipient. Nephrol Dial Transplant. 2002 Mar;17(3):532-3. doi: 10.1093/ndt/17.3.532. PMID: 11865120.
9. Kurz RW, Wallner M, Graninger W, Tragl RH. Hypoprothrombinaemia and bleeding associated with cefazolin. J Antimicrob Chemother. 1986 Dec;18(6):772-3. doi: 10.1093/jac/18.6.772. PMID: 3818501.
10. Shimada K, Matsuda T, Inamatsu T, Urayama K. Bleeding secondary to vitamin K deficiency in patients receiving parenteral cephem antibiotics. J Antimicrob Chemother. 1984 Sep;14 Suppl B:325-30. doi: 10.1093/jac/14.suppl_b.325. PMID: 6389475.
11. Yan H, Chen Y, Zhu H, Huang WH, Cai XH, Li D, Lv YJ, Si-Zhao, Zhou HH, Luo FY, Zhang W, Li X. The Relationship Among Intestinal Bacteria, Vitamin K and Response of Vitamin K Antagonist: A Review of Evidence and Potential Mechanism. Front Med (Lausanne). 2022 Apr 18;9:829304. doi: 10.3389/fmed.2022.829304. PMID: 35510250; PMCID: PMC9058076.
12. Ryu HY, Mohayya S, Hong T, et al. Safety and Effectiveness of High-Dose Cefazolin in Patients with High Body Weight: A Retrospective Cohort Study. Open Forum Infect Dis. 2022. Feb 28;9(4):ofac105. doi: 10.1093/ofid/ofac105. eCollection 2022 Apr.
13. Afzal A, Gage BF, Suhong L, Schoen MW, Korenblat K, Sanfilippo KM. Different risks of hemorrhage in patients with elevated international normalized ratio from chronic liver disease versus warfarin therapy, a population-based retrospective cohort study. J Thromb Haemost. 2022 Jul;20(7):1610-1617. doi: 10.1111/jth.15743. Epub 2022 May 26. PMID: 35491428; PMCID: PMC9247029.
14. Julia M. Cunningham, Craig M. Kessler, 2 - A Systematic Approach to the Bleeding Patient: Correlation of Clinical Symptoms and Signs With Laboratory Testing, Editor(s): Craig S. Kitchens, Craig M. Kessler, Barbara A. Konkle, Michael B. Streiff, David A. Garcia, Consultative Hemostasis and Thrombosis

(Fourth Edition), Elsevier, 2019, Pages 17-37, ISBN 9780323462020