

## Antibiotic-induced Fever in a post-operative Patient—A Diagnostic Challenge

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### Abstract

Postoperative fever is a common clinical challenge, and its etiology varies with the timing of onset. While infectious causes dominate the differential diagnosis, non-infectious etiologies such as drug-induced fever must not be overlooked, especially when clinical findings are inconclusive.

We report the case of a 43-year-old male with a prior diagnosis of appendiceal adenocarcinoma, who underwent a completion right hemicolectomy following an open appendectomy. The early postoperative period was uneventful until postoperative day (POD) 5, when the patient developed intermittent fever spikes. Extensive workup—including laboratory investigations, imaging, and clinical examination—failed to identify any infective focus. A temporal correlation was noted between the administration of intravenous cefuroxime and the onset of fever. Discontinuation of the antibiotic on POD-7 led to complete resolution of symptoms, confirming the diagnosis of cefuroxime-induced drug fever.

Drug-induced fever, particularly due to  $\beta$ -lactam antibiotics like cefuroxime, remains an underrecognized yet significant postoperative complication. Characterized by a lack of systemic toxicity and resolution upon drug cessation, it should be considered when infectious causes have been ruled out. Awareness of this phenomenon is crucial to avoid unnecessary investigations and prolonged antibiotic use.

### Introduction

Fever is a common complication in postoperative patients, the etiology of which is strongly influenced by timing. It is defined as a rise in body temperature after a surgical procedure, higher than 38 C (or greater than 100.4 F) on two consecutive postoperative days or higher than 39 C (or greater than 102.2 F) on any postoperative day [1].

Knowledge about the timing and various etiology of fever helps in narrowing down the actual cause. The five W's of postoperative fever – Wind, Water, Walking, Wound and Wonder drugs is a useful mnemonic to remember the etiology [2]:

POD 1-2: Wind: Atelectasis.

POD 3-5: Water: Urinary tract infections (UTIs).

POD 4-6: Walking: Deep venous thrombosis.

POD 5-7: Wound: Wound infections.

Any post day: Wonder drugs: Drug induced fever.

Our focus in this report is on antibiotics as a cause of fever postoperatively after a right hemicolectomy. Discussion about the characteristics of and diagnostic approach to antibiotic-induced fever is important for rapid identification and treatment in postoperative patients.

## Case Report

A 43-year-old male, with no history of any comorbidities, came with a previous history of pain in abdomen, fever and vomiting 2 months ago which was diagnosed as acute appendicitis for which he underwent an open appendicectomy at an outside centre.

The histopathology report of the appendix specimen was noted to be moderately differentiated adenocarcinoma with the tumour involving the cut end of the base and subserosal fat, but mesenteric cut margin and serosa not involved. A PET-CT was done postoperatively which suggested 'post appendicectomy status with mild soft tissue fat stranding with low-grade metabolic activity is seen in the mesenteric fat in the operated bed and omentum, more likely secondary to recent postoperative changes and no abnormal metabolic activity or lesion seen elsewhere in the body'.

Pertaining to these postoperative findings, the patient was referred to our centre for a completion right hemicolectomy. An open right hemicolectomy was performed for this patient wherein an intra-abdominal drain was placed and a Foley catheter was inserted intra-op. The procedure was uneventful.

Patient was started on injectable Cefuroxime 12 hourly and Metronidazole 8 hourly from POD-0. Metronidazole was stopped after 3 days while Cefuroxime was continued. First four postoperative days were uneventful with the intra-abdominal drain around 20ml in quantity and serosanguinous in nature and Foley catheter in-situ with a urine output of around 2800ml on the morning of POD-4. His vitals were within normal range, per-abdominal examination showed minimal operative site tenderness, soft abdomen and he was passing flatus freely had opened bowel by POD-4. With a satisfactory out of bed mobilisation, decision was taken to remove his Foley catheter on POD-4. Patient developed a fever of 101.3F on the morning of POD-5 which subsided with injectable Paracetamol. He developed another fever spike of 102F in the same evening which also subsided with injectable Paracetamol. Over the next two days our diagnostic approach to this newly developed fever included:

1. Laboratory tests- complete blood count, CRP, ESR, Dengue and Malaria antigen, Urine for routine and culture/sensitivity.
2. Examining the operative scars and drain site for surgical site infections.
3. Nature and quantity of drain output.
4. Ultrasonography of the abdomen and pelvis to look for any intra-abdominal collection.

His total leukocyte count, CRP, ESR were within normal range, negative for Dengue and Malaria antigen, indicating a lack of infection or inflammation as a cause of his fever. The possibility of a transient bacteraemia following removal of Foley catheter as a cause of fever prompted a urinalysis to be done which showed pus cells within the normal range and no growth in culture by the 2nd day. Operative scars and drain site were healthy and showed no signs of infection or inflammation. The drain output was maintained at around 20-25ml, serosanguinous in nature and ultrasonography of the abdomen showed no obvious collection intra-abdominally. The drain was removed on POD-6, eliminating it as a cause of fever [3].

A careful study of fever characteristics indicated a 12 hourly rise in temperature which subsides with injectable Paracetamol. On correlating his fever chart with the drug chart showed a rise in temperature following the 12 hourly dose of Injection Cefuroxime which was the only injectable drug going on at that point. With the lack of evidence for any ongoing infectious process, decision was taken to stop Cefuroxime on POD-7. No fever spikes were noted following the discontinuation of Cefuroxime, strongly indicating it as the cause

of fever. Patient recovery was uneventful and smooth following this and he was discharged on POD-9.

## Discussion

Normal thermoregulatory control of our body is neuronally mediated but fever occurs because of circulating pyrogens. These pyrogens are triggered by infectious or non-infectious causes, which may be seen in patients undergoing surgery [4].

A fever following surgery may raise concerns about a potential infection affecting the patient's recovery. However, fever alone is not a dependable sign of infection, and its absence does not ensure that the patient is free from infection. It is important to acknowledge that infections related to surgery can significantly increase healthcare costs [5].

Among non-infectious causes, drug-induced fever remains our focus of attention in this report. In a systematic review of case reports on drug-fever by Afra F et al., propofol, morphine, and cephalosporins were the medications most commonly associated with adverse reactions. The onset of fever varied, occurring either immediately after surgery or several days later, and presented in diverse forms such as intermittent, remittent, or continuous patterns. In most cases, cessation of the suspected drug led to patient recovery [6].

Confirmation of drug-induced fever relies primarily on the withdrawal of the suspected medication. Management typically begins with discontinuing the most likely causative agent, followed by the stepwise cessation of other potential drugs if the fever persists [7].

The etiology of drug-induced fever is multifactorial and, in many cases, remains insufficiently investigated or poorly understood. Experts generally categorize the underlying mechanisms into six primary types [8-10]:

1. *Administration-related reactions*, where the act of delivering the medication itself triggers a febrile response.
2. *Contamination or intrinsic drug properties*, whereby fever arises from contaminants or inherent pharmacologic features.
3. *Hypersensitivity responses*, particularly humoral immune reactions, are believed to be the most frequent cause.
4. *Thermoregulatory disruption*, where medications interfere with body temperature control by either increasing heat production or reducing heat loss.
5. *Pharmacologic effects*, where the fever is a direct result of the drug's action—for instance, the Jarisch–Herxheimer reaction seen during antibiotic therapy for spirochetal infections like syphilis and leptospirosis.
6. *Idiosyncratic responses*, often involving genetic predispositions, leading to febrile reactions in select individuals.

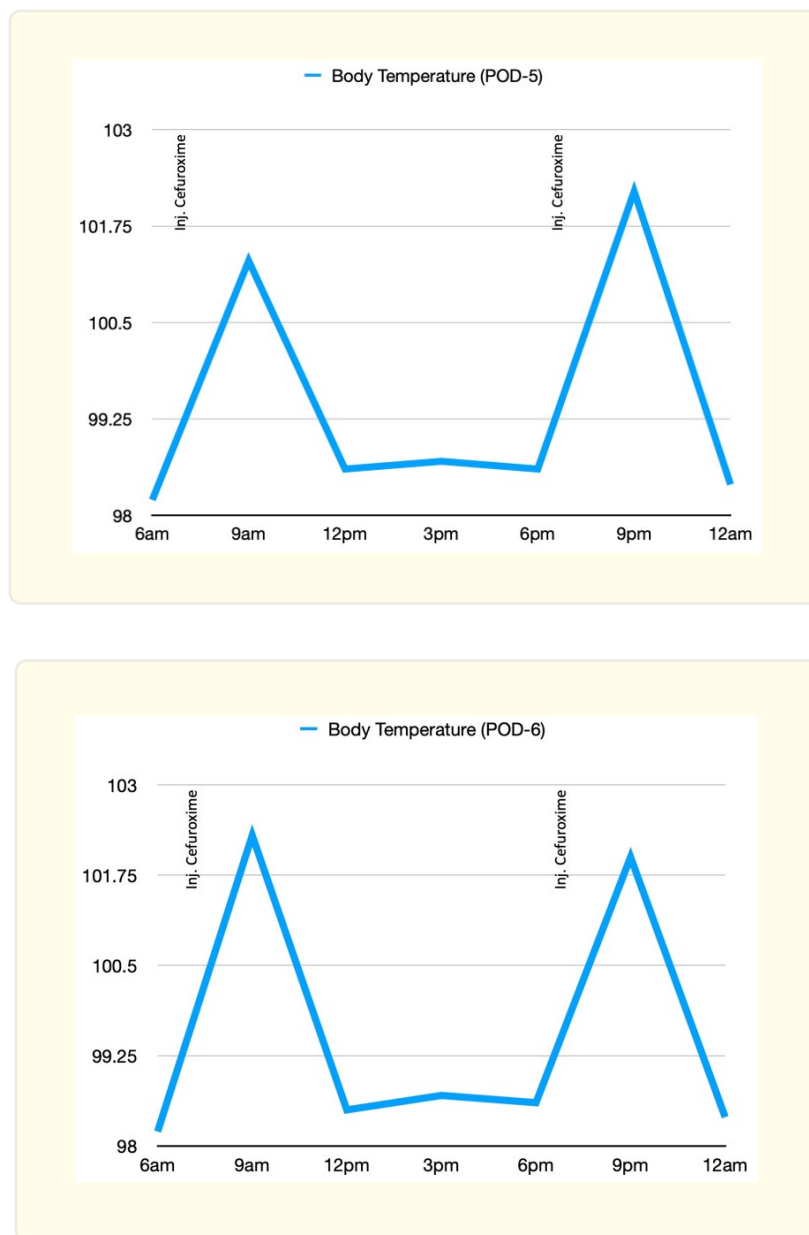
Hypersensitivity reactions are the most frequently implicated cause of drug-induced fever, often presenting with clinical features similar to those of allergic responses. Typically, the fever manifests 7 to 10 days after initiating the offending agent, persists during continued administration, resolves promptly upon withdrawal, and may recur rapidly if the drug is reintroduced. Common culprits include penicillins, cephalosporins, anti-tubercular drugs, quinidine, procainamide, methyldopa, and phenytoin [11].

Antibiotics, especially those within the  $\beta$ -lactam class, have been increasingly implicated in the development of drug-induced fever. In the present case, the patient exhibited febrile reactions following administration of cefuroxime and piperacillin/tazobactam. Consequently, we advised the patient to minimize future exposure to  $\beta$ -lactam antibiotics where clinically feasible [12].

Laboratory evaluations typically provide limited utility in definitively identifying the cause of fever or establishing a clear link between the febrile response and drug exposure. While some patients with drug-induced fever may exhibit leukocytosis, elevated erythrocyte sedimentation rate (ESR), or eosinophilia, these abnormalities are observed in fewer than 20% of cases [13-14].

Relative bradycardia has been proposed as a potential clinical indicator of drug-induced fever. However, its occurrence appears to be relatively uncommon, reported in only approximately 11% of cases [8]. Additionally, cutaneous manifestations such as diffuse rashes are observed in fewer than 30% of patients [15].

Below line graphs represent fever spikes in our patient following administration of Inj. Cefuroxime on POD-5 and POD-6 respectively. Twice a day dosage of Inj. Cefuroxime was given at 7am and 7pm and the fever spikes were noted to occur approximately an hour following the injection. As discussed above, drug fever can start several days after starting the offending drug- in our case 5 days after and occurred intermittently at a 12hr interval.



## Conclusion

In patients who present with a persistent fever—particularly when it arises several days following surgical procedures—it is crucial to conduct a comprehensive infectious evaluation and consider alternative causes. Nonetheless, if clinical assessments and laboratory tests return unremarkable findings, yet the fever persists, further investigation remains warranted. Considering drug-induced fever as

a potential etiology is both important and necessary in the diagnostic process.

In patients undergoing antimicrobial therapy, antibiotics should be considered as a potential cause of fever, particularly when there are no clinical indications of a new or ongoing infection. A key clue pointing toward antibiotic-induced fever is the presence of a high temperature despite the patient's generally well-preserved clinical condition.

Prompt resolution of fever typically occurs following discontinuation of the suspected agent or substitution with an alternative drug, thereby avoiding unnecessary diagnostic investigations and inappropriate continuation of antibiotic therapy.

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