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NON-INFECTIOUS FEVER ASSOCIATED WITH MASSIVE UPPER GASTROINTESTINAL BLEEDING

Aoi Kaneko[1], Taku Harada[1,2]

[1] Department of General Medicine, Nerima Hikarigaoka Hospital, Tokyo, Japan
[2] Department of Diagnostic and Generalist Medicine, Dokkyo Medical University Hospital, Tochigi, Japan

Corresponding author's e-mail: aoioa.blue@gmail.com

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ABSTRACT

Introduction: Fever is a common clinical manifestation often attributed to infection, which frequently leads to empirical antibiotic therapy. However, non-infectious causes of fever are easily overlooked. Among patients with gastrointestinal bleeding, a rare but under-recognised phenomenon known as absorption fever has been described. Increasing awareness of this condition is important to prevent unnecessary exposure to antibiotics.

Case description: A 61-year-old man presented with nausea, vomiting, epigastric pain and melaena. On admission, his temperature was 38°C. Laboratory tests revealed leucocytosis, anaemia and mildly elevated C-reactive protein levels. Computed tomography showed periduodenal fat stranding, and upper endoscopy demonstrated Los Angeles Grade D reflux oesophagitis along with multiple duodenal ulcers (Forrest IIa). Two sets of blood cultures were negative. An empirical single dose of cefmetazole was administered but discontinued on day 2 because no infectious source was identified. Supportive care, including transfusions, was provided. Despite persistent fever for four days, the patient's clinical condition remained stable. The fever resolved spontaneously without recurrence and repeat endoscopy on hospital day 12 confirmed mucosal healing. No evidence of infection was observed during hospitalisation.

Discussion: This case illustrates a transient, non-infectious fever associated with massive upper gastrointestinal bleeding, consistent with absorption fever. Clinicians should recognise this underappreciated condition when evaluating febrile patients with gastrointestinal bleeding after carefully excluding infectious or malignant causes such as infectious colitis, inflammatory bowel disease, diverticulitis, enteric fever or gastrointestinal cancer.

Conclusion: Recognising non-infectious fever can prevent unnecessary antibiotic use, reduce adverse drug effects and support antimicrobial stewardship.

KEYWORDS

Gastrointestinal bleeding, non-infectious fever, absorption fever, peptic ulcer, antibiotic stewardship

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LEARNING POINTS

- Fever in the setting of upper gastrointestinal bleeding may represent a non-infectious process, historically termed absorption fever, rather than an occult infection.
- Careful clinical, laboratory and imaging evaluation is crucial to distinguish non-infectious fever from infection and to guide appropriate management.
- Recognising absorption fever helps avoid unnecessary antibiotic use and supports antimicrobial stewardship, but only after serious infectious and inflammatory causes have been carefully excluded.

INTRODUCTION

Fever is one of the most common clinical manifestations and is typically attributed to infection[1]. This often prompts empiric antibiotics even when infection is uncertain[2]. Consequently, non-infectious causes of fever are frequently overlooked, exposing patients to unnecessary antibiotics and adverse outcomes.

Upper gastrointestinal bleeding (UGIB) can occasionally present with transient, non-infectious fever. Although its frequency remains unclear, such fever occurs in peptic ulcer disease and other UGIB aetiologies, and usually resolves as bleeding subsides. This entity was first described as absorption fever by Bang in 1928 in patients with bleeding peptic ulcers[3] and has since been reported sporadically[4–6]. Nevertheless, awareness remains limited in modern clinical practice. The pathophysiology is not fully understood; proposed mechanisms include cytokine release during haematoma absorption and inflammatory responses triggered by mucosal injury[7,8]. Blood degradation products and tissue trauma can activate innate immune pathways and pyrogenic cytokines, producing fever without infection.

Failure to recognise non-infectious fever in UGIB can lead to unnecessary antibiotic use, diagnostic confusion and increased healthcare costs. When fever occurs concurrently with gastrointestinal bleeding but no clinical, laboratory or radiologic evidence of infection is present, clinicians should consider non-infectious aetiologies.

We report a case of massive UGIB with persistent fever that resolved spontaneously without antimicrobial therapy, emphasising the need to distinguish infectious from non-infectious fever to avoid unnecessary antibiotics and promote antimicrobial stewardship.

CASE DESCRIPTION

A 61-year-old man with a history of hypertension, type 2 diabetes mellitus, obstructive sleep apnoea and duodenal ulcers presented to the emergency department with nausea, vomiting, epigastric pain and melena. He had first noticed black stools approximately three weeks before admission and subsequently experienced recurrent episodes of epigastric discomfort and vomiting over the following two weeks. Twelve days before admission, he was evaluated in the emergency department and diagnosed with acute gastroenteritis and had been discharged after receiving intravenous fluids and oral medications. His symptoms improved transiently but recurred two days before current admission, prompting consultation with his primary physician and eventual referral to our hospital.

On arrival, his temperature was 38°C, respiratory rate 16 breaths/min, heart rate 92 beats/min and blood pressure 133/66 mmHg. Physical examination revealed epigastric tenderness without rebound tenderness or guarding. Bowel sounds were normal, and cardiopulmonary findings were unremarkable.

Laboratory evaluation showed leucocytosis (15,490/µl), anaemia (haemoglobin 7.5 g/dl; haematocrit 23.9%) and mildly elevated C-reactive protein (3.64 mg/dl). Biochemical testing revealed elevated blood urea nitrogen (28.5 mg/dl) with preserved creatinine (0.68 mg/dl), yielding an increased blood urea nitrogen/creatinine ratio consistent with UGIB. The platelet count was 50.8 $\times 10^4$/µl, and liver enzyme levels were within normal limits. Urinalysis demonstrated glucosuria and ketonuria, consistent with diabetes, but no evidence of infection. Reference ranges for key laboratory parameters are provided in *Table 1*.

Chest and abdominal computed tomography performed on admission showed fat stranding around the descending and horizontal portions of the duodenum, without evidence of perforation, abscess or other intra-abdominal infectious

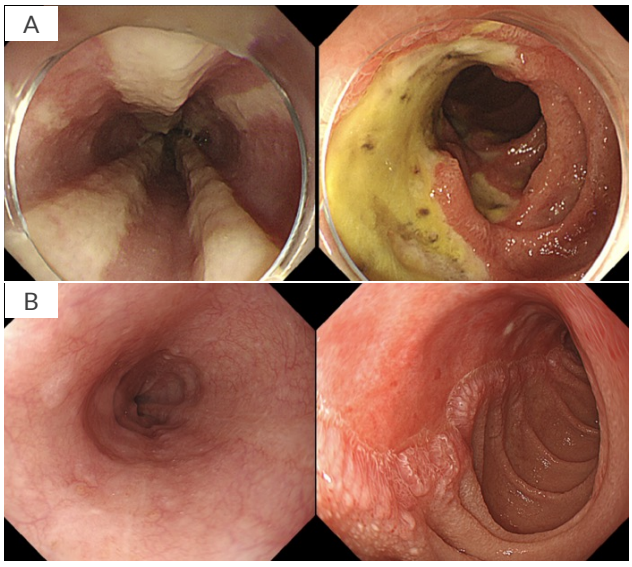


Figure 1. Endoscopic findings. A) Endoscopy on day 2 of hospitalization showing Los Angeles Grade D reflux oesophagitis and multiple duodenal ulcers (Forrest IIa); B) Endoscopy on day 12 of hospitalization showing mucosal healing and no evidence of rebleeding.

foci. The lungs were clear, with no consolidation or pleural effusion, further lowering the likelihood of an infectious aetiology. Two sets of blood cultures obtained prior to antibiotic administration were negative. Given the presence of fever, leucocytosis and elevated C-reactive protein levels, a single intravenous dose of cefmetazole (2 g) was administered empirically in the emergency department. Both peripheral blood culture sets were obtained before cefmetazole administration; no growth was detected during standard incubation.

On hospital day 2 his general condition remained stable, with no clinical, laboratory or radiologic evidence of infection. Accordingly, antimicrobial therapy was discontinued. Follow-up laboratory testing revealed a further decline in haemoglobin to 6.4 g/dl, and the patient received a transfusion of four units of red blood cells. Upper gastrointestinal endoscopy on hospital day 2 demonstrated Los Angeles Grade D reflux oesophagitis and multiple duodenal ulcers with stigmata of recent haemorrhage (Forrest IIa) *(Fig. 1A)*. High-dose proton pump inhibitor therapy was initiated with intravenous omeprazole (20 mg twice daily) from hospital day 1 to day 5, followed by oral lansoprazole (30 mg daily) from day 6 to day 12. He was discharged on hospital day 12 in stable condition and continued oral vonoprazan (20 mg daily) from day 13 to day 42 as maintenance therapy. The initial endoscopy on hospital day 2 was performed for diagnostic observation only; no endoscopic haemostatic intervention was required. Throughout hospitalisation, no antipyretic agents were administered, as the patient's fever remained haemodynamically stable and self-limiting. Oral intake was resumed on hospital day 5, and the fever resolved spontaneously on day 4 without recurrence (Fig. 2). Follow-up visits were conducted on day 19 and day 42, confirming continued clinical stability and absence of recurrent bleeding. Repeat endoscopy on hospital day 12 demonstrated mucosal healing without rebleeding *(Fig. 1B)*. He had no history of non-steroidal anti-inflammatory drug use, did not drink alcohol and was not on any antithrombotic therapy; *Helicobacter pylori* antibody test results were negative.

DISCUSSION

This massive UGIB case with persistent fever supports a non-infectious mechanism, given the negative work-up and spontaneous defervescence without further antimicrobial therapy. Although a single empirical dose of cefmetazole was administered at admission, the persistence of fever for four days after antibiotic discontinuation, followed by spontaneous defervescence with supportive care alone, is more consistent with a self-limiting, non-infectious process than with occult infection.

Non-infectious fever in the setting of gastrointestinal bleeding was first described by Bang in 1928, who introduced the term absorption fever to characterise fever in patients with bleeding peptic ulcers despite the absence of infection[3]. Subsequent reports have described

Haematology	Result	Reference range
WBC (×10³/μl)	15.49	3.3–8.6
RBC (×10⁶/μl)	2.6	4.27–5.7
Hb (g/dl)	7.5	13.7–16.8
Ht (%)	23.9	40.7–50.1
MCV (fl)	91.9	83–99
PLT (×10⁴/μl)	50.8	15.8–34.8
Biochemistry		
AST (U/l)	13	13–30
ALT (U/l)	15	10–42
LDH (U/l)	212	124–222
T-Bil (mg/dl)	0.8	0.4–1.5
ALP (U/l)	74	106–322
GGT (U/l)	12	13–64
Alb (g/dl)	3.1	3.7–5.3
UN (mg/dl)	28.5	8–20
Cr (mg/dl)	0.68	0.65–1.07
eGFR (ml/min/1.73 m²)	90.9	≥60
Na (mmol/)	141	138–145
K (mmol/)	4.6	3.6–4.8
Cl (mmol/)	103	101–108
CRP (mg/)	36.4	<14
Urinalysis		
Specific gravity	1.037	1.005–1.030
pH	5	5.0–7.5
Glucose	4+	–
Ketone	4+	–
Protein	–	–
Occult blood	–	–
Urobilinogen	±	±
Bilirubin	–	–
Nitrite	–	–
WBC	–	–

Table 1. Laboratory results on admission.

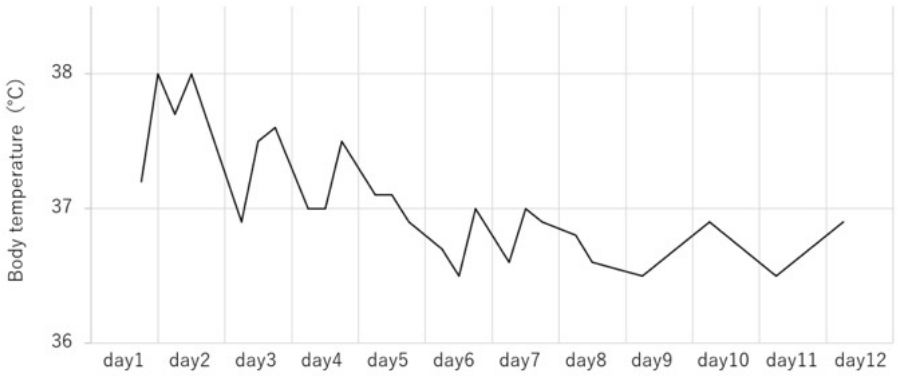


Figure 2. Clinical course of body temperature. Fever persisted from day 1 to day 4 despite a single dose of cefmetazole and resolved spontaneously after providing supportive care, including blood transfusion on day 2, without recurrence following resumption of oral intake on day 5.

similar phenomena, with temperatures reaching as high as 40°C[4,5]. More recently, studies in critical care settings have recognised gastrointestinal bleeding as a potential cause of non-infectious fever[9,10]. Moon et al. defined this entity as fever associated with massive gastrointestinal bleeding in the absence of another identifiable source, emphasising that the diagnosis is one of exclusion[10]. Despite nearly a century of observations, awareness remains limited, contributing to diagnostic uncertainty and unnecessary antibiotic use.

The underlying pathophysiology of non-infectious fever in gastrointestinal bleeding is not fully understood. Early studies proposed cytokine release during haematoma absorption as a mechanism[6,7], whereas later investigations have implicated mucosal injury and inflammatory responses to tissue trauma[8]. Lai et al. demonstrated that intraoperative bleeding is an independent risk factor for non-infectious fever after gastric endoscopic submucosal dissection, suggesting that exposure to blood and tissue injury may trigger systemic inflammatory cascades independent of infection[8]. Similarly, Hu et al. observed that fever following percutaneous renal biopsy-related haematoma, termed absorption fever, had a median duration of four days, comparable to our case[6]. Together, these findings support that haemorrhage and blood resorption can provoke transient inflammation leading to non-infectious fever.

In the present case, fever >37.5°C persisted for four days before resolving spontaneously, consistent with previous reports of absorption fever lasting several days and resolving without antimicrobial therapy[6]. The absence of other systemic signs of infection, the patient's clinical stability and spontaneous improvement with supportive care further reinforce a non-infectious mechanism.

Alternative causes were carefully evaluated. Pulmonary, urinary and biliary infections were unlikely given the absence of localising symptoms, negative urinalysis and no consolidation on computed tomography. Drug fever was also improbable, as no new sustained medications were introduced other than a single empirical dose of cefmetazole, and there were no cutaneous eruptions, eosinophilia or other signs of hypersensitivity. A febrile non-haemolytic transfusion reaction was excluded because fever preceded transfusion and there was no evidence of haemolysis or subsequent deterioration. Collectively, these considerations argue against other aetiologies and support the interpretation of non-infectious fever secondary to UGIB.

This study has limitations. Culture-negative infection cannot be entirely excluded. Biomarkers such as procalcitonin or interleukin-6, which may aid in distinguishing infectious from non-infectious fever, were not measured. Additionally, the precise mechanism underlying the fever could not be determined. Nevertheless, the absence of recurrent fever, negative blood cultures and spontaneous resolution strongly support a non-infectious aetiology.

Although absorption fever is generally benign and self-limiting, it should be diagnosed only after excluding other causes of fever with gastrointestinal bleeding. Infectious colitis due to Shigella, Salmonella or Campylobacter, inflammatory bowel disease, diverticulitis, enteric fever, oesophagitis and gastrointestinal malignancies can all present with fever and bleeding. Systematic evaluation to exclude these entities is essential before attributing fever to a non-infectious mechanism.

Clinically, this case underscores the importance of recognising non-infectious fever in UGIB. Reflexive antibiotic use in such settings may lead to unnecessary exposure, adverse effects and increased costs. Awareness of this entity, which has been described for nearly a century yet remains under-recognised, is essential to avoid diagnostic errors and support antimicrobial stewardship by preventing inappropriate antibiotic administration.

CONCLUSION

This case illustrates that fever in the setting of UGIB can represent a non-infectious, self-limiting response rather than an occult infection. Careful evaluation of clinical, laboratory and imaging findings is essential to avoid reflexive antibiotic administration when no infectious focus is identified. Recognition of non-infectious fever, historically described as absorption fever, remains limited despite nearly a century of observations.

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