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Case Series

Fever of Unknown Origin: A Case Series of Five Diagnostically Challenging Presentations in a Tertiary Care Teaching Institute

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Abstract

Fever of unknown origin (FUO) remains a major diagnostic challenge because its causes span infections, inflammatory disorders, malignancy and miscellaneous conditions. This case series describes five patients with diagnostically difficult febrile illnesses and highlights the clinical clues, targeted investigations, treatment and outcomes. We retrospectively reviewed five patients presenting with prolonged or otherwise unexplained fever admitted to Yashwantrao Chavan Memorial Hospital, Pimpri, Pune over a period of April 2024 to June 2025. Clinical assessment, laboratory testing, imaging and advanced diagnostic procedures were performed according to clinical suspicion. Final diagnoses included disseminated tuberculosis, scrub typhus without eschar, enteric fever with delayed culture positivity, adult-onset Still's disease and culture-negative infective endocarditis. All patients improved with targeted treatment.

Keywords: Fever of unknown origin, Tuberculosis, Scrub typhus, Enteric fever, Adult-onset Still's disease, Infective endocarditis.

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Introduction

Fever of unknown origin (FUO) was classically defined by Petersdorf and Beeson in 1961 as a temperature greater than 38.3°C on several occasions, persisting for more than three weeks, with no diagnosis despite one week of inpatient evaluation [1].

This definition has evolved over time, with modern criteria accounting for advances in diagnostic capabilities and the shift toward outpatient evaluation [2].

The contemporary approach recognizes FUO as fever persisting beyond three weeks with no clear diagnosis after appropriate initial investigations, including basic laboratory tests, imaging, and focused clinical assessment [3].

The differential diagnosis of FUO is extensive and traditionally categorized into four major groups: infections (30-40%), malignancies (20-30%), inflammatory and autoimmune conditions (10-20%), and miscellaneous causes (10-20%), with approximately 10-15% remaining undiagnosed despite exhaustive evaluation [4]. The distribution varies significantly based on geographic location, patient demographics, and local disease epidemiology. In resource-limited settings and tropical regions, infectious etiologies, particularly tuberculosis and rickettsial infections, account for a higher proportion of FUO cases [5].

The diagnostic approach to FUO requires a systematic and stepwise strategy [6]. Initial evaluation includes detailed history-taking with particular attention to travel, occupational exposures, animal contacts, medication use, and family history.

Physical examination should be thorough and repeated, as new findings may emerge with disease progression. First-line investigations typically include complete blood count, inflammatory markers (ESR, CRP), blood cultures, urinalysis and urine culture, chest radiography, and abdominal ultrasonography [7].

Advanced investigations such as bone marrow examination, serological testing for specific pathogens, cross-sectional imaging (CT or PET-CT), and tissue biopsy are guided by clinical suspicion and initial findings [8]. This case series

illustrates five distinct etiologies of FUO, highlighting diagnostic challenges and emphasizing the importance of maintaining broad differential diagnosis while pursuing targeted investigations.

Criteria for Inclusion of Patients for the Study: Patients presenting to the Department of Internal Medicine between January 2024 and December 2025 with-

- Documented fever ≥38.3°C on multiple occasions
- Fever duration exceeding three weeks
- No diagnosis after initial comprehensive evaluation were considered for inclusion.

Case Presentation

Case 1 – Disseminated tuberculosis: A 30-year-old previously healthy male presented with intermittent evening-predominant fever for five weeks, fatigue, and anorexia and 5-kg weight loss. Examination showed mild hepatosplenomegaly. Hemoglobin was 9.2 g/dL, ESR 85 mm/hour and CRP 68 mg/L; chest radiography was normal. Bone marrow biopsy showed epithelioid granulomas with central caseous necrosis and GeneXpert on marrow aspirate detected Mycobacterium tuberculosis without rifampicin resistance. He received standard four-drug antitubercular therapy followed by continuation therapy and achieved complete clinical recovery.

Case 2 – Scrub typhus without eschar: A 22-year-old female from a rural area presented during monsoon with 23 days of high-grade fever, severe headache, myalgia and weakness. No eschar was found despite repeated skin examination. Platelet count was 92,000/µL with AST 156 U/L and ALT 142 U/L; malaria and dengue tests were negative.

Empirical doxycycline 100 mg twice daily was started because of strong epidemiological suspicion. She became afebrile within 36 hours and scrub typhus IgM ELISA subsequently returned positive. Platelet count and liver enzymes normalized on follow-up.

Case 3 – Enteric fever with delayed culture positivity: A 19-year-old male presented with two weeks of step-ladder fever, abdominal discomfort, anorexia and constipation. Initial blood culture and Widal testing were negative and he had received fluoroquinolones. In the third week he had relative bradycardia, leukopenia and mild transaminitis. Repeat blood cultures grew Salmonella typhi with intermediate fluoroquinolone susceptibility. He was treated with intravenous ceftriaxone followed by oral azithromycin and recovered without complications.

Case 4 – Adult-onset Still's disease: A 27-year-old male presented with four weeks of quotidian high-spiking fever, recurrent sore throat, evanescent salmon-pink rash and wrist/MCP joint symptoms. Leukocyte count was 18,200/µL with 85% neutrophils, ESR 96 mm/hour, CRP 142 mg/L and ferritin 8,460 ng/mL. Infectious work-up, ANA and rheumatoid factor were negative. After exclusion of infection and malignancy, the clinical pattern fulfilled Yamaguchi criteria. Prednisolone 0.75 mg/kg/day with naproxen produced rapid resolution of fever, rash and arthritis.

Case 5 – Culture-negative infective endocarditis: A 45-year-old male with rheumatic mitral regurgitation presented with six weeks of low-grade fever, fatigue and 7-kg weight loss. Examination revealed a pansystolic murmur, splinter hemorrhages, Osler nodes and mild splenomegaly. Hemoglobin was 9.8 g/dL, ESR 88 mm/hour and CRP 96 mg/L; urinalysis showed microscopic hematuria.

Transthoracic echocardiography demonstrated severe mitral regurgitation with two vegetations measuring about 8 mm and 6 mm. Repeated blood cultures remained negative. He was treated empirically with ceftriaxone and gentamicin, with clinical improvement and reduction in vegetation size on follow-up echocardiography.

Observations

Table 1:

Patient No	Age	Sex	Duration	Key findings	Etiology	Management	Diagnostic modality	Outcome
1	30	M	5 weeks	Anemia, ESR 85, CRP 68, hepatosplenomegaly	Disseminated tuberculosis	HRZE + pyridoxine; continuation HRE	Bone marrow biopsy + GeneXpert	Complete recovery
2	22	F	23 days	Thrombocytopenia, transaminitis, no eschar	Scrub typhus	Doxycycline 100 mg BD × 7 days	Scrub typhus IgM ELISA	Complete recovery
3	19	M	~3 weeks	Step-ladder fever, relative bradycardia, leukopenia	Enteric fever	IV ceftriaxone then azithromycin	Repeat blood culture: S. typhi	Complete recovery
4	27	M	4 weeks	Quotidian fever,	Adult-onset	Prednisolone	Yamaguchi	Rapid

				salmon rash, arthritis, ferritin 8460	Still's disease	+ naproxen	criteria after exclusion	clinical response
5	45	M	6 weeks	MR murmur, splinter hemorrhages, Osler nodes, hematuria	Culture-negative infective endocarditis	Ceftriaxone + gentamicin	Echocardiography + Duke criteria	Improved; vegetation reduced

Discussion

This case series demonstrates the diagnostic complexity of fever of unknown origin and highlights several key principles in approaching such patients. The five cases presented represent different categories of FUO etiology: infectious (Cases 1, 2, 3, and 5) and inflammatory/autoimmune (Case 4), collectively illustrating the broad differential diagnosis that must be considered.

Diagnostic Challenges and Strategic Approach: The evaluation of FUO requires a systematic, stepwise approach that balances thoroughness with resource utilization. Our experience reinforces the importance of repeated, careful clinical evaluation. Physical examination findings may evolve with time, as demonstrated in Case 2 where conjunctival injection was present but eschar was absent, and in Case 5 where peripheral stigmata of endocarditis (splinter hemorrhages and Osler nodes) became apparent only on detailed examination.

The timing and selection of diagnostic tests is critical. In Case 1, bone marrow examination proved diagnostic when other investigations were unrevealing, demonstrating its continued value in disseminated tuberculosis particularly in the absence of pulmonary involvement [9]. The yield of bone marrow examination for mycobacteria has been reported to range from 30-60% in disseminated disease [10]. In Case 3, repeat blood cultures drawn in the third week after initial negative cultures established the diagnosis, emphasizing that negative initial cultures do not exclude bacteremic infections, particularly when drawn after antibiotic exposure or during the later phases of enteric fever [11].

Role of Empirical Therapy: The decision to initiate empirical therapy in FUO is complex and must be individualized. In our series, empirical doxycycline for suspected scrub typhus (Case 2) was justified by the strong epidemiological and clinical context, the potential for serious complications if untreated, and the excellent safety profile of doxycycline. The dramatic clinical response within 36 hours served as a therapeutic trial, with subsequent serological confirmation. This approach is supported by current recommendations that advocate for empirical rickettsial therapy in appropriate clinical scenarios even before laboratory confirmation, given the time-sensitive nature of the disease [12].

In contrast, Cases 1, 3, and 5 benefited from pursuing diagnostic confirmation before definitive therapy, as the clinical presentations allowed time for diagnostic workup without immediate life-threatening deterioration. However, Case 5 illustrates the need for empirical broad-spectrum therapy in culture-negative endocarditis once the diagnosis is established by other means, as delay in treatment can result in valvular destruction and systemic complications [13].

Geographic and Epidemiological Considerations: The spectrum of FUO etiologies varies significantly based on geographic location and local disease prevalence. In tropical and subtropical regions, including India, infectious causes predominate, with tuberculosis being the leading diagnosis in many series, accounting for 20-40% of FUO cases14. Rickettsial infections, particularly scrub typhus, have emerged as important causes of acute undifferentiated febrile illness and FUO in endemic areas during monsoon and post-monsoon seasons [15]. The absence of eschar, as in our Case 2, is well-documented and should not exclude the diagnosis when other features are compatible.

Enteric fever remains an important cause of FUO in regions with poor sanitation and limited access to safe water. The emergence of antimicrobial resistance, particularly fluoroquinolone resistance as documented in Case 3, has important therapeutic implications and affects empirical treatment choices [16]. Third-generation cephalosporins and azithromycin have become preferred agents in areas with high rates of fluoroquinolone resistance.

Non-Infectious Causes and Diagnosis of Exclusion: While infections dominate the FUO landscape in tropical regions, non-infectious etiologies must be systematically considered and excluded. Adult-onset Still's disease (Case 4) exemplifies a diagnosis of exclusion that can only be made after comprehensive evaluation rules out infectious and malignant causes. The Yamaguchi criteria provide a useful diagnostic framework, but their limited specificity mandates rigorous exclusion of alternative diagnoses [17]. Extremely elevated ferritin levels (>5 times upper limit of normal), particularly with low glycosylated ferritin

fraction, support the diagnosis but are not pathognomonic [18].

The recognition of characteristic clinical patterns—quotidian fever with evanescent salmon-pink rash appearing during fever spikes, arthralgia or arthritis, pharyngitis, and marked neutrophilic leukocytosis—should raise suspicion for adult-onset Still's disease. However, these features may develop sequentially rather than simultaneously, requiring longitudinal observation. The dramatic response to corticosteroid therapy, while supportive, is not specific and can be seen in other inflammatory conditions.

Culture-Negative Infections: Culture-negative infective endocarditis (Case 5) represents a specific diagnostic challenge within the broader category of FUO. Prior antibiotic exposure is the most common cause of negative blood cultures in endocarditis, but fastidious organisms requiring specialized culture conditions or serological diagnosis account for a significant proportion of cases [19]. The modified Duke criteria remain the diagnostic standard, with echocardiography playing a central role [20]. Transthoracic echocardiography has a sensitivity of 60-70% for vegetations, while transesophageal echocardiography increases sensitivity to 90-95% and should be performed when clinical suspicion is high despite negative transthoracic findings [21].

In our case, the presence of predisposing valvular disease (rheumatic heart disease with mitral regurgitation), classic peripheral manifestations (splinter hemorrhages, Osler nodes), and echocardiographic evidence of vegetations established the diagnosis despite negative cultures.

The empirical antibiotic regimen chosen (ceftriaxone plus gentamicin) provided broad coverage for the most likely causative organisms in culture-negative native valve endocarditis, including viridans group streptococci, nutritionally variant streptococci, HACEK organisms, and enterococci [22].

Limitations

This case series has several limitations. As a retrospective review from a single center, the findings may not be generalizable to other geographic regions or healthcare settings. The small sample size of five cases limits statistical analysis and the ability to draw broad conclusions about the relative frequency of different FUO etiologies. Selection bias is inherent in case series, as these represent successfully diagnosed cases; patients with prolonged undiagnosed fever may have had different characteristics. The absence of standardized diagnostic protocols across all cases reflects the individualized nature of FUO evaluation but may limit reproducibility.

Clinical Implications and Future Directions: This series reinforces several practical principles for approaching FUO in clinical practice. First, repeated clinical evaluation is essential, as physical findings may evolve and new clues emerge with disease progression. Second, a thorough understanding of local disease epidemiology guides appropriate test selection and empirical therapy decisions. Third, negative initial investigations do not exclude a diagnosis; repeat testing at appropriate intervals may be revealing.

Fourth, advanced diagnostic procedures including bone marrow examination, echocardiography, and cross-sectional imaging should be pursued based on clinical suspicion rather than reflexively ordering all available tests. Finally, the judicious use of empirical therapy is appropriate in specific clinical contexts while maintaining diagnostic vigilance.

Conclusion

Fever of unknown origin continues to challenge clinicians despite advances in diagnostic technology. Success requires a systematic approach combining careful history-taking, thorough and repeated physical examination, thoughtful test selection guided by clinical suspicion and local epidemiology, and recognition of the diverse etiologies encompassing infectious, inflammatory, malignant, and miscellaneous causes.

This case series illustrates representative examples from different FUO categories, highlighting the diagnostic process and management strategies. Tuberculosis, scrub typhus, and enteric fever remain important infectious causes in tropical regions, while conditions such as adult-onset Still's disease and culture-negative endocarditis require high clinical suspicion and systematic exclusion of alternative diagnoses.

The judicious use of empirical therapy guided by epidemiological context and clinical presentation, balanced with continued diagnostic pursuit, can lead to favorable outcomes in the majority of cases. Ongoing vigilance for emerging infections and changing antimicrobial resistance patterns is essential for optimizing FUO diagnosis and management.

References

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore). 1961;40:1-30.
2. Durack DT, Street AC. Fever of unknown origin—re-examined and redefined. Curr Clin Top Infect Dis. 1991;11:35-51.
3. Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. Arch Intern Med. 2003;163(5):545-51.

4. Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. J Intern Med. 2003;253(3):263-75.
5. Prasad R, Singh A, Gupta N. Fever of unknown origin: a clinical study. J Assoc Physicians India. 2018;66(2):56-60.
6. Wright WF, Auwaerter PG. Fever and fever of unknown origin: review, recent advances, and lingering dogma. Open Forum Infect Dis. 2020;7(5):ofaa132.
7. Cunha BA, Lortholary O, Cunha CB. Fever of unknown origin: a clinical approach. Am J Med. 2015;128(10):1138.e1-15.
8. Bleeker-Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. Medicine (Baltimore). 2007;86(1):26-38.
9. Thakur R, Goyal R, Sarma S. Bone marrow involvement in disseminated tuberculosis. J Assoc Physicians India. 2018;66(12):53-6.
10. Sharma SK, Mohan A, Sharma A. Challenges in the diagnosis and treatment of miliary tuberculosis. Indian J Med Res. 2012;135(5):703-30.
11. Mogasale V, Ramani E, Mogasale VV, Park J. What proportion of Salmonella Typhi cases are detected by blood culture? A systematic literature review. Ann Clin Microbiol Antimicrob. 2016;15:32.
12. Kim DM, Won KJ, Park CY, et al. Distribution of eschars on the body of scrub typhus patients: a prospective study. Am J Trop Med Hyg. 2007;76(5):806-9.
13. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. Circulation. 2015;132(15):14 35-86.
14. Joshi N, Rajeshwari K, Dubey AP, et al. Clinical spectrum of fever of unknown origin among Indian children. Ann Trop Paediatr. 2008;28(4):261-6.
15. Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Elsevier Saunders; 2015.
16. Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive Salmonella infections. Clin Microbiol Rev. 2015;28(4):901-37.
17. Ruscitti P, Cipriani P, Masedu F, et al. Adult-onset Still's disease: evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. BMC Med. 2016;14:194.
18. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult-onset Still's disease. J Autoimmun. 2018;93:24-36.
19. Fournier PE, Gouriet F, Casalta JP, et al. Blood culture-negative endocarditis: improving the diagnostic yield using new diagnostic tools. Medicine (Baltimore). 2017;96(47):e8392.
20. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30(4):633-8.
21. Mugge A, Daniel WG, Frank G, Lichtlen PR. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. J Am Coll Cardiol. 1989;14(3):631-8.
22. Morpeth S, Murdoch D, Cabell CH, et al. Non-HACEK gram-negative bacillus endocarditis. Ann Intern Med. 2007;147(12):829-35.