EDITORIAL

Redefining Pyrexia of Unknown Origin for South Asia: Why a 65-year-old Definition No Longer Fits Our Wards

Neeraj Singla[1], Navneet Sharma[2], Neharika Saini[3]

Journal of Postgraduate Medicine, Education and Research (2026): 10.5005/jp-journals-10028-1834

The Tyranny of an Inherited Definition

Few diagnostic constructs have proved as durable or as quietly restrictive as the one Petersdorf and Beeson advanced in 1961: fever exceeding 38.3°C on several occasions, persisting for more than 3 weeks, remaining undiagnosed after 1 week of inpatient investigation.[1] It was a definition engineered for a specific purpose, namely to exclude self-limiting viral illness and to concentrate scholarly attention on the genuinely obscure. Durack and Street later loosened the inpatient requirement to 3 days of hospitalization or three outpatient visits, acknowledging that diagnostic tempo had accelerated.[2] Yet the essential architecture—3 weeks, 38.3°C, a fixed evaluative threshold—has passed into textbooks and examination syllabi largely unexamined, and it continues to govern how we frame prolonged undiagnosed fever in settings epidemiologically and structurally remote from mid-century Durham.

In much of South Asia, the patient with 3 weeks of undiagnosed fever is not the typical patient but the survivor of a filtration process. Before reaching a tertiary center, the patient has usually passed through pharmacy-based self-medication, one or more primary practitioners, empirical antimicrobials, and sometimes empirical antitubercular therapy. Fever may have been partially suppressed, cultures rendered sterile, and the syndrome pharmacologically distorted. Meanwhile, patients with clinically important, actively evolving, undiagnosed fevers of 5–14 days—the group in whom timely evaluation would alter outcome most—fall outside the classical rubric entirely and are therefore understudied and underreported.

A Regionally Calibrated Proposal

Against this background, Panda and Dhangar proposed a set of modified definitions for FUO in Indian patients, subsequently operationalized in a tertiary-care evaluation by Dhangar et al.[3–5] Their innovation is structural rather than merely numerical: instead of a single dichotomous threshold, they construct a factorial grid from three clinically meaningful axes—duration of nondiagnosis (3–21 days vs more than 21 days), recorded temperature (99.1–100.9°F vs ≥101°F), and duration of hospitalization (3–7 days vs more than 7 days)—yielding eight strata, labeled A through H. Definition H approximates the classical construct; the remaining seven describe the far larger population of undiagnosed febrile inpatients that classical criteria render invisible.

A rigid 38.3°C threshold is a poor instrument in populations where thermometry is often axillary, where antipyretics are consumed almost reflexively before presentation, and where tuberculosis, brucellosis, visceral leishmaniasis, and indolent connective tissue disease frequently present with sustained low-grade pyrexia. To exclude such patients by definitional fiat is to exclude precisely the diagnoses that most reward persistence.

What the Present Cohort Adds

The study by the AIIMS Rishikesh infectious disease unit is the first to describe the etiological spectrum of patients captured by these modified criteria.[5] Among 228 adults admitted between 2018 and 2022, the distribution across strata was strikingly skewed: definition B (3–21 days undiagnosed, 99.1–100.9°F, hospitalization beyond 7 days) accounted for 40.8% of the cohort, followed by A (21.5%) and D (19.3%). The four strata requiring more than 21 days of undiagnosed fever together comprised under 6%. Put plainly, more than nine in ten patients whom experienced physicians were treating as diagnostic problems would not have qualified as FUO under Petersdorf–Beeson criteria.

The etiological profile that emerges is correspondingly shifted. Infections dominated at 81.1%, with tuberculosis (28.1%), community-acquired pneumonia (17.8%), urinary tract infection (9.7%), and visceral leishmaniasis (7.0%) leading; autoimmune disease accounted for 12.7% and malignancy for 8.7%. The tuberculosis predominance is entirely consonant with earlier Indian classical FUO series from CMC Vellore, Medical College and Hospital, Kolkata, and PGIMER Chandigarh.[6–8] The prominence of pneumonia and urinary sepsis, however, is not, and the authors are right to interpret this as a predictable consequence of a shorter inclusion window rather than as diagnostic laxity. Compress the entry criterion, and the cohort will inevitably include conditions that would have declared themselves by week 3, but whether that is a feature or a defect depends entirely on the purpose to which the definition is put.

[1–3]Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Corresponding Author: Neeraj Singla, Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India, Phone: +91 9646121641, e-mail: neerajsingladr@gmail.com

How to cite this article: Singla N, Sharma N, Saini N. Redefining Pyrexia of Unknown Origin for South Asia: Why a 65-year-old Definition No Longer Fits Our Wards. J Postgrad Med Edu Res 2026;https://doi.org/10.5005/jp-journals-10028-1834.

Source of support: Nil

Conflict of interest: None

The Undiagnosed Fraction is the Real Signal

The most surprising numbers in the published manuscript are easily overlooked. Within the infection category, 27.1% remained etiologically unidentified, and in the autoimmune category, 55.2%. A syndromic label was assigned, but the organism or the disease entity was not identified. This mirrors the persistently high undiagnosed proportion, typically 20–50%, reported in contemporary Western FUO series despite advanced imaging and molecular diagnostics.[9,10] In resource-constrained settings, the same fraction carries additional weight, because it plausibly reflects unavailable rather than merely uninformative tests: limited access to ^{18}F-FDG PET-CT, restricted tissue sampling, and negligible penetration of metagenomic sequencing.

This is where the regional definitions could do their most useful work. Their value is not taxonomic elegance but triage: a graded framework that tells a physician on day six of undiagnosed fever which patients warrant escalation and which can be safely observed. That prescriptive step has not yet been taken.

Conceptual Hazards of Overinclusive Definitions and the Need for Prospective Validation

Several limitations temper enthusiasm, and the authors acknowledge most of them.[5] The study is single-center, with retrospective and prospective ascertainment, and critically, not a validation application. It reported the composition of the strata, not their discriminative performance. It does not compare modified against classical criteria in the same population, does not report diagnostic yield per investigation within each stratum, and does not link stratum membership to outcome. Follow-up was available for only 129 patients, among whom 20.2% had died by 6 months; that mortality is substantial and demands explanation, yet it cannot presently be attributed to stratum, etiology, or delayed diagnosis. Furthermore, no additional diagnoses were established during follow-up among those undiagnosed discharged patients, which raises the possibility of incomplete telephonic ascertainment rather than genuine diagnostic closure.

There is also a conceptual hazard. A definition that admits nearly every febrile inpatient risks dissolving the very entity it seeks to describe. If community-acquired pneumonia diagnosed on day 5 constitutes FUO, the term ceases to identify a distinct clinical problem and becomes a synonym for "fever under evaluation." The modified criteria must therefore justify themselves prospectively by demonstrating that stratification predicts something a clinician cannot already predict without it.

Validation Pathways Ahead

Three studies are needed to validate new criteria in the South Asian subcontinent. First, a prospective multicenter cohort applying the A–H grid concurrently with classical criteria, reporting diagnostic yield, time to diagnosis, cost, and mortality by stratum. Second, derivation of stratum-specific diagnostic algorithms—which strata justify early PET-CT, early bone marrow examination, and early tissue biopsy—with formal cost-effectiveness analysis appropriate to public-sector Indian hospitals. Third, deliberate incorporation of the region's distinctive entities: scrub typhus and the rickettsioses, dengue with hemophagocytic progression, melioidosis in the eastern littoral, and drug-induced fever, including antitubercular hypersensitivity, which is systematically underdiagnosed.

Definitions are instruments, not truths. Petersdorf and Beeson built one exquisitely suited to their era and their ward; we have retained it long past the point at which it describes ours. The modified regional definitions, and the cohort now reported under them, represent a serious and overdue attempt to build an instrument fitted to South Asian practice. They should be tested rigorously, revised without sentiment, and can be adopted if validated.

Orcid

Neeraj Singla https://orcid.org/0000-0002-7983-1637
Navneet Sharma https://orcid.org/0000-0001-5707-9686

References

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 1961;40:1–30. DOI: 10.1097/00005792-196102000-00001
2. Durack DT, Street AC. Fever of unknown origin—reexamined and redefined. Curr Clin Top Infect Dis 1991;11:35–51. PMID: 1651090.
3. Panda PK, Dhangar P. Definition of fever of unknown origin in Indian patients. JASPI 2024;2:1–4. DOI: 10.62541/jaspi028
4. Dhangar P, Panda PK, Kant R, et al. Evaluating fever of unknown origin definitions in a tertiary care setting: implications for diagnostic criteria revision. World J Exp Med 2025;15(2):101388. DOI: 10.5493/wjem.v15.i2.101388
5. Dhangar P, Panda PK, Mohamed S. Etiological spectrum of fever of unknown origin in India using modified diagnostic definitions: a longitudinal cohort study. J Postgrad Med Edu Res 2026.
6. Rupali P, Garg D, Viggweswarupu S, et al. Etiology of classic fever of unknown origin (FUO) among immunocompetent Indian adults. J Assoc Physicians India 2019;67(1):21–26. PMID: 30935167.
7. Bandyopadhyay D, Bandyopadhyay R, Paul R, et al. Etiological study of fever of unknown origin in patients admitted to the medicine ward of a teaching hospital in eastern India. J Glob Infect Dis 2011;3(4):329–333. DOI: 10.4103/0974-777X.91052
8. Pannu AK, Golla R, Kumari S, et al. Aetiology of pyrexia of unknown origin in north India. Trop Doct 2021;51(1):34–40. DOI: 10.1177/0049475520947907
9. Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. J Intern Med 2003;253(3):263–275. DOI: 10.1046/j.1365-2796.2003.01120.x
10. Wright WF, Auwaerter PG. Fever and fever of unknown origin: review, recent advances, and lingering dogma. Open Forum Infect Dis 2020;7(5):ofaa132. DOI: 10.1093/ofid/ofaa132