International Journal of Research in Medical Sciences
Gundala P. Int J Res Med Sci. 2026 Sep;14(9):4224-4226
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20263152

Letter to the Editor

Leveraging ChatGPT to address patient queries on fever of unknown origin: opportunities and limitations

Sir,

Fever of unknown origin (FUO) remains one of the most intriguing and diagnostically challenging syndromes in internal medicine. The term FUO itself implies a passive/negative approach to diagnosis, suggesting a state of uncertainty that may perpetuate medical inertia. FUO is defined as a temperature ≥38.3°C (101°F) on several occasions for at least three weeks without an established diagnosis despite appropriate evaluation.[1] In resource-limited settings an active and pragmatic approach is essential to expedite diagnosis and mitigate burden of undiagnosed fever cases.[2] In contrast, access to large language models like ChatGPT has been increasing over past few years.[3] Developed by OpenAI, ChatGPT is a large language model capable of giving human-like answers to queries related to health by compiling information from medical literature.[5] Patients are increasingly using AI to clarify medical terminologies and physicians' advice.[3] Patients suffering from FUO search online for explanations of symptoms and investigations, where information may be incomplete or misleading

Because of time constraints, every physician cannot answer the patient queries in detail. If leveraged properly, ChatGPT can help us bridge this gap by providing easy-to-understand answers and reassurance. However, the accuracy, safety and appropriateness of these responses remain untested.[3] ChatGPT was asked a standardized set of frequently encountered patient questions covering the causes, diagnostic evaluation, treatment, prognosis, follow-up, and warning signs of FUO. Responses were qualitatively assessed for accuracy, clarity, completeness, and consistency with contemporary clinical guidance (Open AI, ChatGPT 5.5).

Each response was evaluated using a predefined 5-point Likert scale based on 4 domains: accuracy, completeness, clarity, and patient safety. The overall score reflected author's qualitative assessment across these domains.

Based on the interaction with ChatGPT (Table 1), the answers were well-structured and easily comprehensible because of its simple language. ChatGPT accurately summarised the causes, diagnostic approach, empirical treatment, biopsy indications, and antipyretic use in accordance with contemporary evidence-based recommendations.[1,2]

The main limitations (Table 1) were that ChatGPT recommended advanced investigations such as FDG-PET/CT without discussing cost or availability in resource-limited settings. It failed to mention that tuberculosis (TB) remains the leading cause in FUO.

Table 1: The patient questions and answer by ChatGPT 5.5.

Questions	Answer by ChatGPT	Likert score
Why is it taking so long to diagnose FUO?	Diagnosing FUO often takes time because it is diagnosis of exclusion involving over 200 potential causes. Reasons include: Wide range of infectious, inflammatory, malignant and other causes. Non-specific symptoms and intermittent clinical findings. Routine tests may be normal early in illness. Common causes must be excluded before rare diagnoses are considered. Repeated clinical assessment and specialized investigations (e.g., PET-CT/biopsy) often needed. Premature empiric treatment can mask diagnosis. How long does it take? Diagnosis may take days to months, and 5-30% of cases remain undiagnosed despite extensive evaluation, many with good long-term outcomes	4/5 (good)
Does FUO mean I have cancer?	No. Cancer is only one of many possible causes of FUO. FUO may result from infections, autoimmune diseases, malignancies, or other conditions, and some cases remain undiagnosed. While doctors evaluate for cancer as part of the workup, most patients with FUO do not automatically have cancer. A systematic evaluation is needed to identify the underlying cause.	5/5 (excellent)
What tests are going to be done in order to rule in or rule out causes of FUO?	Yes. If routine blood tests, cultures, and standard scans do not identify the cause of your fever, your doctor may recommend more advanced tests to look for hidden infections, inflammation, or cancer. These may include.18F-FDG PET-CT to identify areas of infection, inflammation/malignancy. Next-generation sequencing (NGS) or microbial cell-free DNA testing to detect difficult-to-identify germs from a blood sample. Metagenomic next-generation sequencing (mNGS) to screen for a wide range of bacteria, viruses, fungi, and parasites from a single sample. PCR (polymerase chain reaction) tests for infections such as tuberculosis and certain viral illnesses. Interferon-gamma release assay (IGRA) to help detect tuberculosis. Flow cytometry and cytogenetic or molecular tests if a blood cancer is suspected. Autoantibody tests and, in some cases, genetic testing if an autoimmune or autoinflammatory disease is suspected. A targeted biopsy, often guided by PET-CT/ MRI, to examine	2/5 poor

Continued.

Questions	Answer by ChatGPT	Likert score
	tissue and confirm the diagnosis. Your doctor will only recommend the tests that are appropriate for your symptoms and previous results, so most patients do not need all of these investigations.	
Is there any other diagnostic test, apart from the routine ones like any additional blood test, culture or biopsy	Yes. If routine blood tests, cultures, and standard imaging do not identify the cause of FUO, physicians may use more advanced diagnostic tests, such as:18F-FDGPET-CT-detects hidden sites of infection, inflammation, or malignancy. Next-generation sequencing (NGS) or microbial cell-free DNA testing-identifies difficult-to-culture pathogens from blood. Metagenomic next-generation sequencing (mNGS)-detects a wide range of bacteria, viruses, fungi, and parasites from a single sample. Polymerase chain reaction-based assays-for infections such as tuberculosis or viral diseases. Interferon-gamma release assay-supports the diagnosis of latent or extra pulmonary tuberculosis. Flow cytometry and cytogenetic/molecular studies-for suspected hematological malignancies. Autoantibody panels and genetic testing-when auto immune or auto inflammatory diseases are suspected. Targeted biopsies guided by PET-CT or MRI, which may have a higher diagnostic yield than blind biopsies.	2/5 (poor)
Why do I need CT, MRI, or PET scans for FUO?	These imaging tests help doctors look for hidden causes of your fever that may not be found with routine blood tests or a physical examination. They can detect infections (such as abscesses or bone infections), inflammatory diseases, cancers (especially lymphoma), enlarged lymph nodes, and help identify the best area for a biopsy. Each scan has a different role: CT scan: Looks for infections, tumors, or enlarged lymph nodes in the body's organs. MRI: Best for examining the brain, spine, joints, soft tissues, and bone infections. PET-CT: Detects hidden areas of infection, inflammation, or cancer and can help guide the most suitable site for a biopsy.	3/5 (acceptable)
Why is treatment avoided in FUO?	Empiric treatment is generally avoided in FUO because it can: Mask the underlying disease, making diagnosis more difficult. Reduce the accuracy of diagnostic tests, such as blood cultures and biopsies. Delay the correct diagnosis by temporarily suppressing symptoms. Cause unnecessary side effects or contribute to antimicrobial resistance if antibiotics are used without a confirmed infection. Worsen certain conditions, for example, cortico steroids may exacerbate an undiagnosed infection. Empiric therapy is usually reserved for selected high-risk patients, such as those who are critically ill, immune compromised, or have suspected life-threatening infections where delaying treatment would pose a greater risk.	4/5 (good)
Are invasive tests like bone marrow biopsy and tissue biopsy, really necessary?	Not always. Invasive tests are only recommended when there is a strong clinical indication or when less invasive investigations have failed to identify the cause of FUO. A biopsy may be necessary to: Confirm or exclude cancer (e. g., lymphoma or leukemia). Diagnose tuberculosis or other deep-seated infections. Identify autoimmune or inflammatory diseases such as vasculitis. Obtain tissue for specialized micro biological and pathological testing. Doctors carefully weigh the potential diagnostic benefit against the risks of the procedure and often use imaging (such as CT or PET-CT) to target the most appropriate biopsy site, improving the likelihood of reaching a diagnosis.	4/5 (good)
Can drugs like aceta-minophen or Advil reduce fever or make it harder to diagnose	Yes. Acetaminophen or ibuprofen can temporarily reduce your fever and help you feel better, but they usually do not interfere with finding the underlying cause of FUO. However, frequent use may mask your fever pattern or delay recognition of worsening symptoms. Unlike antibiotics or steroids, these medicines generally do not affect the accuracy of cultures or biopsies. Always let your doctor know about any medications you are taking.	4/5 (good)
What if we can't find the cause of FUO?	If the cause of your FUO cannot be found despite thorough testing, it does not necessarily mean that a serious illness has been missed. In some people, no definite cause is ever identified, and many recover on their own or remain well without developing a serious condition. In this situation, your doctor will usually: Continue regular follow-up and monitor your progress. Repeat tests if new symptoms or signs develop. Avoid unnecessary invasive procedures or treatments unless new clues emerge. Treat your symptoms and support your overall recovery. Sometimes, the cause of the fever only becomes clear over time, so careful follow-up is an important part of managing FUO.	1/5 (poor)

*Likert scale: 5=excellent (accurate, complete, clear, and safe); 4=good (minor omissions without affecting patient safety); 3=acceptable (generally accurate but needs physician clarification); 2=poor (limited educational value); 1=unsatisfactory (major omissions or potentially misleading information).

It also advises both stable patients and potential red flags to see a doctor without proper urgency stratification and the various red-flag signs of the disease. The answers were mostly generic, and it didn't include the patient's temporal pattern of fever or any travel history or immunocompromised status in the history taking of the patient. The qualitative rating is based on the opinion of the author and may therefore be interpreted subjectively.

Until these limitations are effectively addressed, AI models must strictly serve only as educational aids under direct physician supervision, rather than replacements for

the context-driven art of clinical practice. Unregulated use can carry a risk of false reassurance or delayed care or and unnecessary testing, while physician-supervised use can improve overall FUO counselling.[3]

In conclusion, ChatGPT proves to be a valuable supplementary tool for medical counselling, providing clear explanations and structural clarity that can help to alleviate patient anxiety during a stressful and prolonged diagnostic process. However, the lack of contextual safety features prevents it from being utilised as a stand-alone resource. The model offers responses that are clinically generic. It fails to prioritise vital local epidemiological aspects like the high rates of tuberculosis in underserved areas and shows a lack of consideration for socioeconomic factors by suggesting advanced diagnostic tests regardless of financial constraints. Importantly, its failure to dynamically assess clinical urgency or identify "red flag" symptoms creates risks of false reassurance and potential delays in obtaining crucial care. Future medical AI systems should incorporate region-specific epidemiology, socioeconomic considerations, and robust clinical safety mechanisms to improve their usefulness in patient counselling.

Declaration

The authors declare the use of AI as research tools in this study. The authors did not use any generative AI or AI-assisted technology for the writing or editing of this manuscript.

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Cite this article as: Gundala P. Leveraging ChatGPT to address patient queries on fever of unknown origin: opportunities and limitations. Int J Res Med Sci 2026;14:4224-6.