Nonmalarial Acute Undifferentiated Fever in a Rural Hospital in Central India: Diagnostic Uncertainty and Overtreatment with Antimalarial Agents

Rajnish Joshi, John M. Colford Jr., Arthur L. Reingold, and Shripaksh K. Kalantri*
Division of Epidemiology, School of Public Health, University of California, Berkeley, California; Department of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India

Abstract. Nonmalarial acute undifferentiated fever (NMAUF) refers to a febrile illness with no indication of an organ-specific disease after diagnosis of malaria has been excluded. In developing countries, the empirical treatment of NMAUFs with antimalarial drugs continues even in the era of highly specific rapid diagnostic tests (RDTs) for malaria. We carried out a retrospective review of patients with fever admitted to a rural teaching hospital in central India. We categorized patients with NMAUF into different clinical syndromes and determined their demographic profile, inhospital course, and the pattern of antimalarial use. The study sample included 1,197 adult patients who were investigated for malaria; 1,053 (88%) of them had NMAUF, and use of further diagnostics in this group was limited. Despite one or more negative tests for malaria, many patients (39.9%, 95% CI 37.0–43.3) received antimalarial drugs. These results suggest a need for guidelines and training to improve empirical treatment of NMAUF.

INTRODUCTION

Nonmalarial acute undifferentiated fever (NMAUF) refers to a febrile illness with no indication of an organ-specific disease after diagnosis of malaria has been excluded. Depending on the local epidemiology, the term “acute undifferentiated fever” has different connotations. Although this term often refers to self-limiting viral diseases in the developed world, in most developing countries malaria and other nonmalarial diseases (such as dengue, leptospirosis, enteric fever, and Japanese encephalitis) present as acute undifferentiated fever and are major public health problems.

Laboratory evaluations for fever in developing countries usually include light microscopy for malaria. According to official estimates in India, although about 100 million individuals are investigated for malaria by microscopy every year, fewer than 2% of them are slide-positive. The annual slide-positivity in malaria-endemic countries is estimated to be about 5% (6 million confirmed cases of 128 million investigated in 43 countries). Individuals who test negative for malaria could either have false-negative microscopy, an organ-specific infection (pneumonia, infectious diarrhea, etc.), or an acute undifferentiated fever due to a cause other than malaria. In expert hands, malaria microscopy is an accurate tool (sensitivity, 99.6%; specificity, 100%), but the accuracy of this test can be much lower if microscopists are not well trained (sensitivity, 69%; specificity, 62%). Newer histidine-rich protein (HRP-2)-based rapid diagnostic tests (RDTs) for falciparum malaria have a high accuracy (sensitivity, 92.7%; specificity, 99.2%) and hence provide an alternative to microscopy. Because the sensitivity of these tests in detecting other malaria species is low, RDTs have not yet replaced microscopy.

Health-care providers in malaria-endemic regions overdiagnose and overtreat most NMAUFs as malaria. It is estimated that between 30% and 90% of all patients with acute undifferentiated fever are treated with antimalarial drugs, although only 7–45% of them have laboratory-confirmed malaria. In regions with chloroquine-resistant falciparum malaria, expensive artemisinin compounds are increasingly being used as first-line antimalarial agents. Use of antimalarial drugs in patients with NMAUF continues even in the era of HRP-2–based RDTs and expensive artemisinin-based compounds. Previous research shows that if diagnosis of malaria is improved and antimalarial drugs are prescribed to only those with a positive diagnostic laboratory test, 60% of the costs of malarial treatment programs can be saved.

Overdiagnosis of malaria leads to overestimates of the incidence of malaria, underestimates of the incidence of NMAUFs, distorts the accuracy of data related to malaria resistance, and leads to misallocation of financial and manpower resources. Over-prescription of antimalarial drugs also has the potential for promoting the development of drug resistance. Such practices were implicated in the emergence of chloroquine resistance and could also lead to resistance to artemisinin derivatives.

A syndromic approach to classification, based on simple and easily elicited clinical signs, can help health workers classify NMAUFs into different categories, such as fever-myalgia, fever–arthralgia, fever–icterus, fever–rash, or acute encephalitic syndrome. Each of these syndromes is a constellation of nonspecific symptoms and represents several diseases that can be prioritized according to public health importance in different areas. Although syndromic definitions are used to track emerging infections or bioterrorism threats in the developed countries, they are increasingly being used to determine burden of diseases in many resource-poor settings where diagnostic facilities for accurate diagnosis of NMAUFs are not available.

In this study, we carried out a retrospective review of electronic-discharge summaries (EDSs) of hospitalized patients (age > 12 years) with fever. We used a syndromic classification to categorize all NMAUFs and determined specific laboratory tests done and the pattern of empirical antimalarial use in patients with each clinical syndrome.

MATERIALS AND METHODS

Setting. The Mahatma Gandhi Institute of Medical Sciences, Sevagram, is a rural medical school and hospital located in a small town in central India. It is a 648-bed teaching hospital.
institution with more than 400,000 patient visits and about 8,000 patient admissions to the internal medicine wards each year. Last year, one-third of all internal medicine discharges carried an infectious disease diagnosis, and one-fourth of all deaths in the hospital were attributed to an infectious disease (unpublished hospital records). The most common infectious causes of mortality were septicemia (31%), meningitis (18%), tuberculosis (16%), and malaria (15%). In the past, about 90% of all malaria cases have been caused by *Plasmodium falciparum* and the remaining, by *Plasmodium vivax*.25

Residents, who are supervised by the internal medicine faculty, evaluate all fever patients in the outpatient and emergency departments and admit those with severe symptoms to the hospital. All seriously ill patients with fever and older than age 12 years are admitted to the internal medicine wards of the hospital. Three-fourths of all fever-related admissions occur in the hot and humid months of June to November (unpublished hospital data), when vector-borne and enteric infections are common. During the study period, the health care providers at the MGIMS hospital cared for an exceptionally large number of patients presumably suffering from chikungunya, a mosquito-transmitted viral disease presenting as an epidemic of fever and severe arthralgia, in several states in India.26

After admission, internal medicine consultants review the patient’s history, perform focused physical examination, and order complete blood counts, light microscopy (thin smears), and/or RDTs for malaria for patients with an acute undifferentiated fever. Physicians often begin their patients on anti-malarial medications without waiting for, or regardless of, the results of malaria microscopy. Additional diagnostic tests (chest radiograph, liver and renal function tests, appropriate bacterial cultures, and cerebrospinal fluid examination, etc.) are ordered based on the clinical picture, in-hospital events, and response to initial therapy. The IgM ELISA for dengue, hepatitis E, and leptospirosis are sometimes done, depending on the ability of patients to pay for the tests or as determined by the treating physicians. Diagnostic tests for chikungunya, Japanese encephalitis, hepatitis A, or rickettsiosis are never performed because their commercial costs are prohibitive.

**Sources of data.** In 2005, a hospital information system (HIS) was established in the hospital. The system collects and stores patient-related data and supplies that information to health workers on request. A 12-digit unique patient identifier (case record number) is used to track all transactions of a patient admitted to the hospital. This identifier is linked to demographic data, medical history and physical findings, results of all in-hospital investigations, and in-hospital and discharge medications. The treating physicians assign a discharge diagnosis to each patient and use the electronic system to prepare an electronic discharge summary (EDS) for all hospitalized patients.

**Study design.** We used the HIS to electronically retrieve an EDS for all inpatients, aged 12 and above, who underwent light microscopy or a HRP-2–based RDT for malaria from June to November 2006. We blackened the names and addresses of the patients from the EDSs before abstracting the data. A study investigator (R.J.) abstracted the data on demographic variables, discharge diagnoses, symptoms and signs, laboratory test results, medication use, length of hospital stay, and in-hospital outcomes and recorded them on standardized forms. We excluded patients who had fever of 14 days or more before hospitalization and those with missing clinical data. We also excluded patients with a definite source of infection identified, such as pneumonia (air-space consolidation on chest radiograph), acute infectious diarrhea (presence of loose stools as a presenting symptom), urinary tract infection (positive urine cultures), smear-positive pulmonary tuberculosis, and skin or soft-tissue infection. The study design was approved by the institutional review boards at MGIMS and University of California, Berkeley, and a request for waiver of consent from the individual patients was granted.

**Data analysis.** We used abstracted data to classify patients who tested negative for malaria into fever syndromes (fever–myalgia, fever–arthralgia, fever–jaundice, and acute encephalitic syndromes) using standardized definitions (see Box 1). Patients with positive anti-dengue IgM antibodies by a rapid test were classified separately in NMAUF group as having

### Box 1

**Study definitions**

**Acute undifferentiated fever (AUF):** Fever, without any localized source of infection, of 14 days or less in duration. Myalgia, arthralgia, headache, altered sensorium, and jaundice were considered not to have localizing values.

**Localized fever:** Fever, with a symptom, sign, or an investigation that localized the source of infection to skin or soft tissue, respiratory, gastrointestinal, or genitourinary systems was defined as a localized fever. Patients detected to have a malignancy or autoimmune disorder were also classified in this group.

**Malaria:** Malaria was defined as either a positive peripheral smear by microscopy for *Plasmodium* species or a positive malarial RDT for *P. falciparum* in presence of a history and clinical features of AUF.

**Nonmalarial acute undifferentiated fever (NMAUF):** All patients with AUF, but negative for malaria, were defined as having nonmalarial acute undifferentiated fever. This entity was further divided in the following syndromic subtypes:

**Fever–arthralgia syndrome:** Presence of fever and tenderness over three or more joint areas.

**Fever–myalgia syndrome:** Presence of fever, with body ache or headache. Individuals with signs suggestive of raised intracranial tension or meningitis were excluded from this definition.

**Acute encephalitic syndrome:** Presence of fever and development of altered behavior, with or without seizures or neurologic deficit. Patients with meningoencephalitis were included in this group.

**Fever–icterus syndrome:** Presence of fever and jaundice as demonstrated by presence of icterus or biochemical hyperbilirubinemia. This definition is irrespective of a rise in liver enzymes.

**Others:** Patients with fever and associated symptoms not indicated above (including but not limited to vomiting, abdominal pain, skin rash, and/or conjunctival congestion) are classified in this group.
dengue (including dengue fever, dengue shock syndrome, and dengue hemorrhagic fever). We analyzed the pattern of antimalarial use across different syndromic categories. We used bivariate analysis to compare age, sex, symptom duration, hematological (hemoglobin, white cell and platelet counts) and in-hospital variables in patients with malaria and NMAUFs. We used the t test for continuous, normally distributed variables and χ² or Fisher’s exact test as appropriate for categorical variables. All tests were two sided, with a P value of 0.05 or less considered statistically significant. All statistical analyses was done using Stata statistical software (version 9.0, Stata Corp., College Station, TX).

RESULTS

A total of 1671 inpatients were investigated for malaria by commercially available RDT (Parachek-Pf, to detect the HRP2 of P. falciparum, Orchid Biomedical Laboratories, India; N = 1652) and by light microscopy (thin peripheral smear examinations for presence of malarial parasite; N = 1314). A total of 1309 patients received both these tests. After 474 (28%) patients who did not meet inclusive criteria from the study were excluded (Figure 1), our analytical sample consisted of 1,197 patients (738 men, 61.6%) between 13 and 84 years of age [mean (SD) age, 36.6 (17.4) years] who fulfilled the criteria for acute undifferentiated fever. These patients were seen in the hospital from 1 to 14 days [mean (SD) duration, 4.7 (3.5) days] after onset of the first symptoms. Malaria was diagnosed in 144 (12%) patients based on light microscopy or RDT; of these patients with malaria, 124 (86%) had P. falciparum infection, and the remaining were infected with P. vivax. The remaining 1,053 (88%) patients were negative for malaria and classified as having NMAUF. A total of 565 (33.8%) patients received antimalarial drugs. These included all 144 patients with malaria, and 421 of 1,053 patients (39.9%; 95% CI 37.0–43.0) with NMAUF. Of the antimalarial recipients in the NMAUF group, 274 (65%) received chloroquine and 144 (34%) received an artemesinin derivative. Of the 144 patients with malaria, 92 (63.8%) received artemesinin derivatives, 44 (30.5%) received quinine, and 40 (29.1%) received chloroquine either alone or in combination (Table 1). Compared with patients with NMAUF, patients with malaria were twice as likely to receive an artemesinin derivative (RR 2.46; 95% CI 1.83–3.31). Compared with patients with NMAUF, patients with malaria had longer febrile periods, lower hemoglobin and platelet counts, longer in-hospital stays, but lower mortality rates (Table 1).

Use of diagnostic tests to detect other infectious causes of the febrile illness in patients with NMAUF was limited (Table 2). Of the 176 (16.7%) patients with NMAUF tested for anti-dengue IgM antibodies by a qualitative rapid test, 47 (26.7%) were positive, consistent with dengue as the cause of their illness. Blood cultures were obtained in 240 (22.8%) patients, but none grew Salmonella species. Growth of likely contaminant organisms (coagulase-negative Staphylococci or Micrococci species) was reported in 8% of all blood cultures. Cerebrospinal fluid (CSF) examination was performed in 90 (46%) of 192 patients with acute encephalitic syndrome; based on CSF cytology, chemistry, and negative bacterial cultures, 71 (78.8%) were classified as presumptive viral encephalitis. No specific viral diagnostic tests were performed in these patients. Of the remaining 19 patients, 12 (13%) were diagnosed to have tubercular meningitis (CSF lymphocytosis; CSF proteins > 100 mg/dL), 7 (6%) were diagnosed to have pyogenic meningitis (CSF polymorphonuclear cytology; CSF sugar/blood glucose ratio < 0.25, or positive cultures). Very few patients were tested for leptospira, hepatitis E, or hepatitis B. Although an ongoing chikungunya outbreak suggested

![Figure 1. Study flow chart.](image-url)
Table 1

Clinical presentation and anti-malarial medication use among patients with malaria and nonmalarial acute undifferentiated fever syndrome subtypes (*N* = 1197)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Malaria</th>
<th>Nonmalarial acute undifferentiated fever syndrome (NMAUF) syndrome (<em>N</em> = 1053)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Dengue</td>
</tr>
<tr>
<td>N</td>
<td>144</td>
<td>1,053</td>
</tr>
<tr>
<td>Percent distribution (95% CI)</td>
<td>12 (10.2–14.0)</td>
<td>87.7 (85.9–88.7)</td>
</tr>
<tr>
<td>Age [mean, years (SD)]</td>
<td>36.9 (16.4)</td>
<td>36.6 (17.5)</td>
</tr>
<tr>
<td>Fever duration† [mean, days (SD)]</td>
<td>5.8 (3.6)</td>
<td>4.6 (3.5)</td>
</tr>
<tr>
<td>Male sex, N (%)</td>
<td>98 (68.1)</td>
<td>640 (60.7)</td>
</tr>
<tr>
<td>Hb† [mean, g/dL (SD)]</td>
<td>10.9 (2.9)</td>
<td>12.1 (2.2)</td>
</tr>
<tr>
<td>White cell count [mean, ×10^3/mm^3 (SD)]</td>
<td>7.0 (4.7)</td>
<td>7.5 (3.5)</td>
</tr>
<tr>
<td>Platelets† [mean, ×10^3/mm^3 (SD)]</td>
<td>164 (123.2)</td>
<td>200 (95.4)</td>
</tr>
<tr>
<td>Hospital stay† [mean, days (SD)]</td>
<td>5.1 (2.8)</td>
<td>43 (3.5)</td>
</tr>
<tr>
<td>Mortality†</td>
<td>7 (4.8)</td>
<td>55 (5.2)</td>
</tr>
<tr>
<td>Any antimalarial†</td>
<td>144</td>
<td>421</td>
</tr>
<tr>
<td>Percent use of antimalarial in each category (95% CI)</td>
<td>100 (97–100)</td>
<td>39.9 (37.0–43.0)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>106 (73.6)</td>
<td>406 (38.5)</td>
</tr>
<tr>
<td>Chloroquine (CQ)</td>
<td>19 (13.2)</td>
<td>249 (23.6)</td>
</tr>
<tr>
<td>Quinine (Q)</td>
<td>25 (17.4)</td>
<td>20 (1.9)</td>
</tr>
<tr>
<td>Artemether (Ar)</td>
<td>62 (43)</td>
<td>137 (13.1)</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>38 (26.4)</td>
<td>15 (1.4)</td>
</tr>
<tr>
<td>CQ + Q</td>
<td>4 (2.8)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>CQ + sulfonamide</td>
<td>4 (2.8)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Ar + CQ</td>
<td>15 (10.4)</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>Ar + Q</td>
<td>15 (10.4)</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

* All figures indicate number (%), unless indicated otherwise.
† For these variables, there was a statistical significant difference between the patients with malaria and those with nonmalarial acute undifferentiated fever (NMAUF).
that patients with fever–arthralgia were most likely to have chikungunya, we could not confirm the diagnosis by appropriate laboratory tests.

**DISCUSSION**

Our study in a rural teaching hospital in central India shows that 88% of all hospitalized adults with acute undifferentiated fever tested for malaria did not have evidence of malaria by light microscopy or by RDT. Despite the availability of the rapid diagnostic test for malaria in the hospital, overtreatment of malaria was common. Forty percent of the patients with a negative test for HRP-2-based RDT received treatment of malaria despite the negative RDT.

Our study has a few limitations. We may have misclassified patients across different categories of NMAUF because we did not collect data prospectively. Because of our focus on hospitalized adults (i.e., the most severely ill patients), our study findings should not be generalized to the acute febrile illness subtypes seen in outpatients or in the community. Our results cannot be applied to infants and children. In our study, malaria was diagnosed by laboratory testing in 12% of patients, which is higher than the national slide-positivity estimates (2%), probably due to a referral bias, better microscopy facilities, and use of RDTs.

Our study demonstrates that the syndromic approach to classifying patients is simple and cost-effective and can be used to classify patients with NMAUF. Such an approach could help health workers select cost-effective diagnostic tests for different fever subtypes. A drawback of syndromic classification is that diseases often have a wide clinical spectrum, and they can often be classified in more than one category.

The availability of point-of-care diagnostics for malaria (such as microscopy or rapid antigen-based tests) is limited, particularly in rural areas. The lack of diagnostic facilities and low cost of treatment have led to national guidelines that overemphasize inappropriate treatment of malaria. In addition, because of the high prevalence and the morbidity and mortality malaria causes, physicians dread failing to treat malaria correctly. Physicians are known to recall their most recent or dramatic clinical experiences and often let these events color their judgment. In our hospital, too, physicians used the "just in case" defense to justify overuse of antimalarials: "it is better to treat several cases of non-malarial febrile illnesses with an antimalarial drug than to miss one true case." A recent study from Uganda, where malaria is common, suggests that that the risk of missing a true case of malaria in the event of a negative diagnostic test is almost negligible: only 2 malaria cases out of 2,359 febrile episodes were missed when febrile children were not given antimalarial treatment when the results of microscopy were negative. Our data also show that, had our hospital physicians not prescribed an antimalarial when the RDT was negative (N = 421), they would have deprived < 1% of malaria cases the benefits of antimalarial treatment (estimated malaria prevalence, 12%; estimated sensitivity and specificity of the RDT, 90% and 96.6%, respectively).
Clearly, if overdiagnosis of malaria and indiscriminate antimalarial use among hospitalized adults with fever are to be curtailed, physicians need not only avoid these cognitive traps and affective errors but also to believe in the diagnostic accuracy of rapid tests (where available) for confirming or ruling out malaria. Such a change could come by having fever treatment algorithms for malaria-negative patients, thus recognizing the importance of nonmalarial diagnosis in medical education and practice. National guidelines also need modifications to accommodate different causes of acute undifferentiated fever.

We acknowledge that, in resource-restrained settings, neither malaria microscopy nor RDTs for malaria are available or affordable for a vast majority of people suffering from acute undifferentiated fevers, and our arguments do not generalize to these settings. Health workers in such settings argue that insisting on an accurate diagnosis is an ivory tower approach and use this argument to justify empirical treatment of most fevers with antimalarial medications. To change this practice, we believe that the availability of RDTs for falciparum malaria should be increased, and more sensitive and specific rapid tests for other malaria species need to be developed. The results of these tests should be acted upon rationally. Such an investment could have substantial benefits for patient care, including reduced ancillary diagnostic testing and shorter hospital stays. In hospital settings, the use of RDTs for other diseases (e.g., influenza) has been shown to result in substantial reductions in antibiotic use.38 As more sensitive, rapid, and simple point-of-care malaria diagnostic tests become available,39 it is equally important for the health-care provider to reserve antimalarial drugs for those who have malaria. The commercially available RDT for malaria and parenteral artemesinin therapy currently cost $2 and $10, respectively, in our hospital; these costs could be substantially lower with their more widespread use.15 Given the increasing use of artemesinin-based therapy for malaria, there is need to limit the unnecessary use of antimalarial drugs in patients testing negative for malaria. The cost savings associated with rational use of artemesinin-based therapy could help improve availability of rapid malaria diagnostics.15

In our literature review, we could not find studies on acute undifferentiated fever epidemiology from India, but a number of recent studies have focused on specific etiologies of NMAUFs. The proportion of dengue fever among all fever cases has been estimated to be 14% in a population-based study in rural South India40 and 48% in a hospital based study in urban North India.41 Leptospirosis and Salmonella infections have been implicated in causation of one-third42 and one-tenth43 of all fever cases in 2 different studies. Despite NMAUF being common, the studies on its epidemiology remain limited. Recently, the public health system in India has initiated a more systematic integrated disease surveillance program (IDSP), which aims to compute the burden of infectious diseases, including NMAUFs, in a more comprehensive manner.44

In conclusion, our study shows that, although most hospitalized adults with acute febrile illnesses in our region do not have malaria, they continue to receive antimalarial therapy. We believe that overemphasis on malaria in the national guidelines, the attitudes of treating doctors, and lack of good-quality diagnostic tests for NMAUFs are the main reasons for this practice. The first step in improving diagnostic tests for NMAUFs would be to identify specific etiologies in different clinical syndromes, so that meaningful diagnostic algorithms could be devised. Next, we should develop and deploy rapid antigen-based tests for detection of pathogens responsible for NMAUFs, so that the causative organisms can be identified. The diagnosis of NMAUFs is also influenced by antigenic cross-reactivity and possible past or current co-infections with multiple organisms.3 Because most of these agents are evaluated by serology-based tests, evaluating for multiple organisms in a single battery of tests has limitations.45 Panmicrobial microarrays are currently being investigated to facilitate identification of the causative organism when multiple etiological possibilities exist.46 Multiple pathogen detection by nucleic acid amplification techniques are promising and could provide better solutions in the future. The evidence base, when translated into clinical practice, could change the approach to the diagnosis and management of NMAUFs. We suggest that epidemiologists, physicians, microbiologists, and funding agencies must come together to establish the validity of syndromic classification of NMAUFs and conduct studies that will yield useful answers to the challenges posed by acute febrile illnesses.

Received September 12, 2007. Accepted for publication December 17, 2007.

Acknowledgments: The authors thank Santosh Chavhan, B.S.W., Prashant Raut, B.A., and Vinod Kulkarni, M.S.W., for helping with data collection and entry.

R.J. is a recipient of a training fellowship from the Fogarty AIDS International Training Program (AITRP), USA (grant 1-D43TW00003-17).

Fogarty AITRP had no role in the design, conduct, or review of this manuscript.

Authors’ addresses: Rajnish Joshi, Division of Epidemiology, 101 Haviland Hall, University of California, Berkeley, CA 94720, and Department of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sevagram Distt. Wardha, Maharashtra, India 442102, Telephone: +91-988-101-8559, Fax: +91-7152-284967, E-mails: rjoshi@berkeley.edu and rjoshimgims@gmail.com. John M. Colford Jr., Division of Epidemiology, 113A Haviland Hall, University of California, Berkeley, CA 94720, Telephone: +1 (510) 642-0327, Fax: +1 (510) 642-0327, E-mail: reingold@berkeley.edu. Arthur L. Reingold, Division of Epidemiology, 104 Haviland Hall, University of California, Berkeley, CA 94720, Telephone: +1 (510) 642-0327, Fax: +1 (510) 643-5163, E-mail: reingold@berkeley.edu. Shirprakash Kalantri, Department of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sevagram Distt. Wardha, Maharashtra, India 442102, Telephone: +91-7152-284341, ext. 327, Fax: +91-7152-284967, E-mail: sp.kalantri@gmail.com.

Reprint requests: Shirprakash Kalantri, Department of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sevagram Distt, Wardha, Maharashtra, India 442102, Telephone: +91-7152-284341, ext. 327, Fax: +91-7152-284967, E-mail: sp.kalantri@gmail.com.

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