NONMALARIAL ACUTE UNDIFFERENTIATED FEVER- DIAGNOSTIC UNCERTAINTY AND OVERTREATMENT WITH ANTIMALARIALS
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ABSTRACT

BACKGROUND
Nonmalarial Acute Undifferentiated Fever (NMAUF) means a febrile illness with no indication of an organ-specific disease after exclusion of diagnosis of malaria. Empirical treatment of NMAUFs with antimalarial drugs continues despite the availability of highly specific Rapid Diagnostic Tests (RDTs) for malaria.

MATERIALS AND METHODS
This retrospective study was conducted in patients with fever admitted to Jhalawar Medical College Hospital, Jhalawar, Rajasthan. We categorised patients with NMAUF into different clinical syndromes and determined the pattern of antimalarial use. 1523 adult patients were investigated for malaria, 1355 (88.97%) of them had NMAUF.

RESULTS
Having negative tests for malaria, many patients (38.16%, 95% CI (31.0-39.5)) received antimalarial drugs. These results suggest a need to improve empiric treatment for NMAUF.

CONCLUSION
Most of the hospitalised patients with acute febrile illness do not have malaria, but received antimalarial therapy. There is a need to develop rapid antigen based tests, detection of pathogens responsible for NMAUFs, so that definitive causative organisms can be identified.

KEYWORDS
Malaria, Nonmalarial Acute Undifferentiated Fever (NMAUF), RDT (Rapid Diagnostic Test), Anti-Malarial Drugs.


BACKGROUND
The outcome of treatment in malaria depends on the correct diagnosis, appropriate drug and its effectiveness and compliance of the patient.1 Overdiagnosis of malaria overestimates the malarial cases, underestimates NMAUFs and leads to misuse of financial and manpower resources.2 It is estimated that between 30 and 90% of all patients with fever are treated with antimalarial drugs, although only a small proportion of them have laboratory confirmed malaria.2-4 In chloroquine-resistant areas with falciparum malaria, highly-effective and expensive artemisinin derivatives are being used as the first line antimalarial agents.5 If diagnosis of malaria is made and antimalarial drugs are prescribed to those only with a positive diagnosis, 60% of the costs of malarial treatment can be reduced.6 Overdiagnosis and treatment of malaria can lead to resistance to artemisinin derivatives.7

Syndromic approach can help to classify NMAUFs in different categories such as fever-myalgia,8 fever-arthralgia.8 Healthcare providers in malaria endemic regions overdiagnose and overtreat most NMAUFs as malaria,9 fever-icterus,9,10 fever-rash10 or acute encephalitic syndrome.8,11 Each of these syndrome groups nonspecific symptoms and represents several diseases and can be given importance according to public health importance in different areas. While syndromic definitions are used to detect emerging infections or bioterrorism threats in the developing countries,11,12,13 they are also helpful to find out diseases in many resource-poor places where facilities to diagnose NMAUFs are not available.9,10

One should avoid irrational use of antimalarial drugs in those patients most of whom do not have malaria with an acute febrile illness.14 In areas of low transmission such as, in India, treatments based on identification of species can help initiate species-specific treatments for P. vivax and P. falciparum malaria,15 this policy that can also reduce the development of drug-resistance.16

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In this study, we tried to determine the pattern of empirical antimalarial use in each patient presented with acute undifferentiated fever.

MATERIALS AND METHODS
This study has been done in Jhalawar Medical College Hospital. All seriously ill patients with fever and of more than 14 years of age were admitted to the medical wards of the hospital. Three-fourths of all fever-related admissions occur in the hot and humid months of June to September when vector-borne and enteric infections are common.

Patient’s History
Physical examination and complete blood counts, light microscopy or rapid diagnostic tests for malaria for patients with an acute undifferentiated fever were done. Physicians gave antimalarial medications without waiting for or regardless of the results of malaria microscopy. Additional diagnostic tests (such as chest radiograph, liver and renal function tests, appropriate bacterial cultures, cerebrospinal fluid examination, etc.) were done based on the clinical picture, in-hospital events and response to initial therapy.

RESULTS
1751 inpatients were investigated for malaria by (RDT) rapid diagnostic test and by light microscopy (thin peripheral smear examinations for malarial parasite; n=1523). After excluding 228 (13%) patients (Figure 1), 1523 patients (938 men, 61.59%) between 13 and 84 years of age (mean (SD) age 36.5 (16.9) years) who fulfilled the criteria for acute undifferentiated fever. These patients attended the hospital after 1 to 14 days (mean (SD) duration 5.4 (4.5) days) of the first symptoms. Malaria was diagnosed in 168 (11.03%) patients.

Of 168 patients with malaria, 124 (79%) were positive for Plasmodium falciparum by RDT, and except four, all positives were confirmed by light microscopy; the remaining 40 were slide positive for Plasmodium vivax. Compared to patients with NMAUF, patients with malaria had longer febrile periods, lower haemoglobin and platelet counts, longer in-hospital stay, but lower mortality. A total of 186/1523 (12.21%) patients were tested for dengue infection; 63 (4.14%) of all patients were positive for IgM antibodies (Table 1).

Antimalarial drugs were prescribed to 468 (34.53%; 95% CI 33.7-42.9) patients with NMAUF; antimalarial drug use was high in the dengue and fever-arthralgia group. Of the antimalarial recipients in NMAUF group, 161 (34.40%) received chloroquine and 247 (52.77%) received an artemisinin derivative. Of the 168 patients with malaria, 82 (48.41%) received artemisinin derivatives, 23 (13.69%) received quinine and 19 (11.31%) received chloroquine either alone or in combination (Table 1).

DISCUSSION
Our study showed that 88.97% of all hospitalised adults with acute undifferentiated fever do not have malaria. An indiscriminate use of antimalarial drugs has been done among patients with NMAUFs. Despite the availability of rapid diagnostic test for malaria in the hospital, presumptive treatment of malaria was common. In 40% patients, physicians requested a malaria test and treated patients for malaria even though the rapid diagnostic test was negative.

Physicians continue to diagnose malaria on clinical grounds and treat it without obtaining a blood test despite the lack of accuracy of perception and touch for detecting fever and a lack of accuracy of symptoms and signs to diagnose malaria in adults. An overemphasis on malaria results in underdiagnosis of NMAUFs.

In a study from Tanzania by Reyburn and colleagues showed that overtreatment of malaria is not reduced by RDTs. RDTs done in 1193 patients, only 52% had a correct prescription in this study. Antimalarials were given to most of the patients who had negative tests.

According to Reyburn and colleagues this practice of giving antimalarial drugs is due to perception of increased risk of malaria in fever patients and due to overemphasis by national guidelines on malaria treatment. Physicians have big apprehension of missing malaria as it has high prevalence, morbidity and mortality. Physicians justify overuse of antimalarials by saying it is better to treat the nonmalarial febrile illnesses by giving antimalarial rather than to miss one true case. A study from Uganda showed that risk is negligible of missing a true case of malaria when diagnostic test is negative. In this study of 2359 febrile cases, only 2 malarial cases were missed when antimalarial was not given when microscopy test was negative. Our study also shows that our hospital physicians not prescribed antimalarial when RDT was negative. In hospital settings, the use of RDT for other diseases, influenza for example has been shown to result in substantial reduction in antibiotic use. As more sensitive, rapid and simple malaria diagnostics become available, it is important to reserve antimalarial drugs for those who actually need them. Because of increasing use of artemisinin-based therapy for malaria, there is need to limit the unnecessary use of antimalarial drugs in patients having negative test for malaria. Rational use of artemisinin therapy saves the cost of treatment and thereby help to improve availability of rapid malaria diagnostics.

Our study shows syndromic approach can be used to classify patients with NMAUF. This approach could help to use cost-effective diagnostic tests for fever of different types. Because of a wide clinical spectrum diseases could be classified in different categories.

CONCLUSION
Most of the patients with acute febrile illnesses admitted in hospital do not have malaria, they receive antimalarial therapy. Overemphasis on malaria in the national guidelines, attitudes of treating doctors and a lack of good quality diagnostics for NMAUFs are the main reasons for this practice. The improvement in diagnostic tests for NMAUFs would lead to identify specific aetiologies in different clinical syndromes, so that meaningful diagnostic algorithms are devised.
Patients presenting with an undifferentiated fever, investigated for malaria (n=1471)

Excluded (n=228)
Insufficient clinical information (n=189)
Fever > 14 days duration (n=39)

Patients with acute undifferentiated fever (n=1523)

Malaria (n=158)

Non-malarial acute undifferentiated fever (n=1365)

Dengue (n=63)
Fever arthralgia (n=286)
Fever myalgia (n=445)
Acute encephalitis syndrome (n=82)
Fever–icterus (n=271)
Others (n=206)

### Table 1. Clinical Presentation and Antimalarial Medication Use Among Patients with Malaria and Nonmalarial Acute Undifferentiated Fever Syndrome Subtypes (n=1523)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Malaria</th>
<th>Nonmalarial Acute Undifferentiated Fever Syndrome (NMAUF) (n=1355)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Dengue</td>
</tr>
<tr>
<td>N</td>
<td>168</td>
<td>1355</td>
</tr>
<tr>
<td>Percent distribution (95%CI)</td>
<td>11.03</td>
<td>(9.2-13.1)</td>
</tr>
<tr>
<td>Age (mean, years (SD))</td>
<td>36.4</td>
<td>(15.4)</td>
</tr>
<tr>
<td>Fever duration* (mean, days (SD))</td>
<td>5.9</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Male Sex N (%)</td>
<td>115</td>
<td>(68.4)</td>
</tr>
<tr>
<td>Hb* (mean, g/dL (SD))</td>
<td>10.7</td>
<td>(2.9)</td>
</tr>
<tr>
<td>White cell count (mean, x 10^3 /mm^3 (SD))</td>
<td>7.1</td>
<td>(4.6)</td>
</tr>
<tr>
<td>Platelets* (mean x 10^3 /mm^3 (SD))</td>
<td>167</td>
<td>(124.3)</td>
</tr>
<tr>
<td>Hospital stay* (mean, days (SD))</td>
<td>5.3</td>
<td>(2.7)</td>
</tr>
<tr>
<td>Mortality*</td>
<td>8</td>
<td>(4.76)</td>
</tr>
<tr>
<td>Any Antimalarial</td>
<td>168</td>
<td>517</td>
</tr>
<tr>
<td>Percent use of antimalarial in each category (95% CI)</td>
<td>100</td>
<td>(97-100)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>124</td>
<td>468</td>
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<tr>
<td>Chloroquine (CQ)</td>
<td>19</td>
<td>161</td>
</tr>
<tr>
<td>Quinine (Q)</td>
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<td>60</td>
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<td>Artemether (Ar)</td>
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<td>247</td>
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<tr>
<td>Combination therapy</td>
<td>44</td>
<td>49</td>
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<tr>
<td>CQ+Q</td>
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<td>17</td>
</tr>
<tr>
<td>CQ + Sulphonamide</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Ar+CQ</td>
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<td>17</td>
</tr>
<tr>
<td>Ar+Q</td>
<td>15</td>
<td>6</td>
</tr>
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REFERENCES
1. NIMR and NVBDCP 2013.