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Drug Utilization Study of Anti-Malarial Drugs in a Tertiary Care Hospital

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ABSTRACT

To evaluate the prescribing pattern of anti-malarial drug and to assess the adherence of anti-malarial drugs prescribing according to Guidelines for diagnosis and treatment of malaria in India 2011 and to explore the possibility of development of resistance with anti-malarial drugs.A retrospective, Single-centric study with cases of anti-malarial drugs prescribed in duration of 1 year from Jan-2011 to Dec-2011 at Lions General hospital, Mehsana, Gujarat, India. Data were analyzed with different evaluations. A total of 474 cases were collected including 282 (59.49%) male and 192 (40.51%) female. Out of these 283 (59.70%) were uncomplicated, 115(24.26%) were complicated and 76 (16.04%) were seen of non-malaria prescribed with anti-malarial drugs. Artemisinin Combination Therapy (ACT) was prescribed in 44(7.96%) patients. Artesunate monotherapy were prescribed in 230 (41.59%) patients. Adherence to National Guideline in cases with *P. vivax* malaria is 71.53% and for pregnant women and with mixed infection is 100%, while non adherence is more than 80% seen in *P. falciparum* malaria (87.39%) and clinical malaria (84%) cases. Artesunate and Chloroquine were also prescribed in non-malarial patients. Among all the cases IV injection of anti-malarial drugs prescribed were 48.82%. Average drug cost/prescription is INR 123.28 Rs and % drug cost on injection is 87.50%.This study shows the prescribing pattern of anti-malarial drug adherence to National Guideline therapy is low. Inappropriate use of anti-malarial drugs among the patients is very high. So possibility of development of resistance with anti-malarial drugs in the population will rapidly spread and cost of the prescription will burden on the patients.

Key Words: Malaria, Anti-malarial drugs, Artesunate, Chloroquine, Drug resistance

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INTRODUCTION

Malaria is a tropical disease transmitted by the female Anopheles mosquito of which Anopheles gambiae is the most efficient vector [1]. It is caused by infection by the protozoan parasite of the genus plasmodium, is a disease of global importance [2]. Malaria is a major cause of morbidity and mortality in the developing world [3]. It is a public health problem in more than 90 countries. Each year, between 300 and 500 million new cases are reported worldwide [4].

India has the largest population in the world at risk of malaria, with 85% living in malarious zones. The combination of *Plasmodium falciparum* and *Plasmodium vivax*, six primary malaria vectors, several ecotypes including urban malaria, and various transmission intensities ranging from unstable to hyperendemic create a challenging epidemiological scenario in India [5]. Around 1.5 million confirmed cases are reported annually by the National Vector Borne Disease Control Programme (NVBDCP), of which about 50% are due to *P. falciparum* [6]. As a component of the Million Death Study, Neeraj Dhingra and colleagues estimate by verbal autopsy that about 2, 00,000 people die of malaria in India each year [7].

In the past, chloroquine was effective or treating nearly all cases of malaria [6]. Artemisinin-based combination therapies are now recommended by the World Health Organization (WHO) as first-line treatment of uncomplicated *P. falciparum* malaria in all areas in which malaria is endemic [8]. To expand knowledge of safety profiles of ACT, pharmacovigilance activities are included in the implementation process of therapy changes [9]. In 2010 artesunate plus sulfadoxine–pyrimethamine treatment became the first-line treatment throughout India [5].

For decades, effort to eradicate malaria has been met with the emergence of resistance to most of anti-malarial drugs such as chlloroquine, sulfadoxine-pyrimethamine, amodiaquine and mefloquine [3]. In recent studies, chloroquine-resistant *P. falciparum* malaria has been observed with increasing frequency across the country [6]. A revised National Drug Policy on Malaria has been adopted by the Ministry of Health and Family Welfare, Govt. of India in 2010 and the National guidelines have been prepared for healthcare personnel including clinicians involved in the treatment of malaria [6].

Trials of artemisinin combination treatments in India have consistently shown treatment success above 95%. Only a few case reports from Mumbai, Uttar Pradesh, and Bihar of chloroquine resistant *P. vivax* malaria exist. Contrary to these reports, systematic trials from across the country have reported 100% efficacy of standard dose chloroquine (25 mg/kg over 3 days). Furthermore, drug resistance studies have been done by various institutions, but a complete

analysis of Indian data across institutions is absent [5]. The World Health Organization (WHO) has recommended that an anti-malarial agent may not be used as first line when the level of resistance is above 25% in an area [10].

Drug utilization studies are powerful tools to ascertain the role of drugs in a society. They provide a sound sociomedical and health economic basis for health care decision making [11]. Despite one or more negative tests for malaria, many patients received anti-malarial drugs. These suggest a need for guidelines and training to improve empirical treatment of Non-malarial acute undifferentiated fever (NMAUF) [12]. Thereby this study will show an intention to bring to notice our clinical experience which, we think, deserves attention for management of malaria cases with accordance of National Guidelines. The study can also suggest that new drug targets are required for the in front of the resistance of anti-malarial drugs. There are more than 20 new drug targets, mostly active small molecule inhibitors that are currently under investigation [3].

MATERIALS AND METHOD:

Study Site:

Lions General Hospital, Mehsana, Gujarat, India.

Study Design:

Retrospective, Single-centric study

Study Procedure:

Case report of all the patients admitted in General medicine, ICU, Gynecology ward in tertiary care hospital during duration of Jan 2011 to Dec 2011 were been reviewed. Patient specific data such as demographic detail, laboratory parameter (diagnostic test for malaria), clinical history, diagnosis, drug therapy given and discharge prescription were noted in case report form. Further data were analyzed for the anti-malarial drugs usage according to Guidelines for diagnosis and treatment of malaria in India 2011 and explore the possibility of development of resistance with anti-malarial drugs.

Target population and sample

Case files of these patients were retrieved from the medical record office for random selection and information extraction. It covers both the peak malaria season and the period of low occurrence. Prescriptions of all patients admitted to the Lions General hospital, Mehsana with a diagnosis/suspected diagnosis of malaria and given anti-malarial drugs were targeted for inclusion in the study. The sample included 474 patients. Data were collected consecutively on

every case of malaria diagnosed either clinically and/or parasitological or given anti-malarial drugs.

Information extraction:

Information extracted from the case files were: demographic data (age, gender, presenting complaints) and diagnosis of malaria (provisional or confirmatory and *P. vivax* or *P. falciparum*), anti-malarial prescribed and prescription of the anti-malarial by generic/proprietary names or acronym/abbreviation.

Ethical Approval:

Ethical Approval was taken from SSPC IRB.

RESULTS AND DISCUSSION:

A total of 474 cases were collected with 282 (59.49%) male and 192 (40.51%) female. The Guidelines for diagnosis and treatment of malaria in India 2011 was available. The outcomes were measured in three ways. One is evaluating individual drugs; another is evaluation of drug prescribed according to national guideline and last is evaluation of prescribing indications.

EVALUATION OF INDIVIDUAL DRUGS PRESCRIBED

- **Monotherapy or combination therapy**

The patients were prescribed different drugs which are listed in **Table 1**. Among them Artemisinin Combination Therapy (ACT) was prescribed in 44 (7.96% of the Total) patients. Artesunate plus sulfadoxine and pyrimethamine (A+SP) was most frequently prescribed among antimalarial agents (in 16 cases, 36.36% of all ACT). Artesunate monotherapy were prescribed in 230 (41.59%) patients. Other prescribing behavior was Artesunate monotherapy followed by Chloroquine (50.63%, n=28), Primaquine (3.07%, n=17), Mefloquine (1.06%, n=3) and Quinine (3.25%, n=18). The least anti-malarial combination recorded was Chloroquine plus primaquine (n=8, 1.45% out of Total cases). Graphical illustration is described in **Figure 1**.

Table 1: List of Anti-malarial drugs prescribed

Anti-malarial Drugs	Numbers Prescribed	%(Drug)
Artesunate	339	61.3
Chloroquine	154	27.85
Sulfadoxine + Pyrimethamine	16	2.89
Primaquine	22	3.97
Quinine	16	2.89
Mefloquine	3	0.55
Artemether + Lumifentrine	3	0.55
Total	553	100

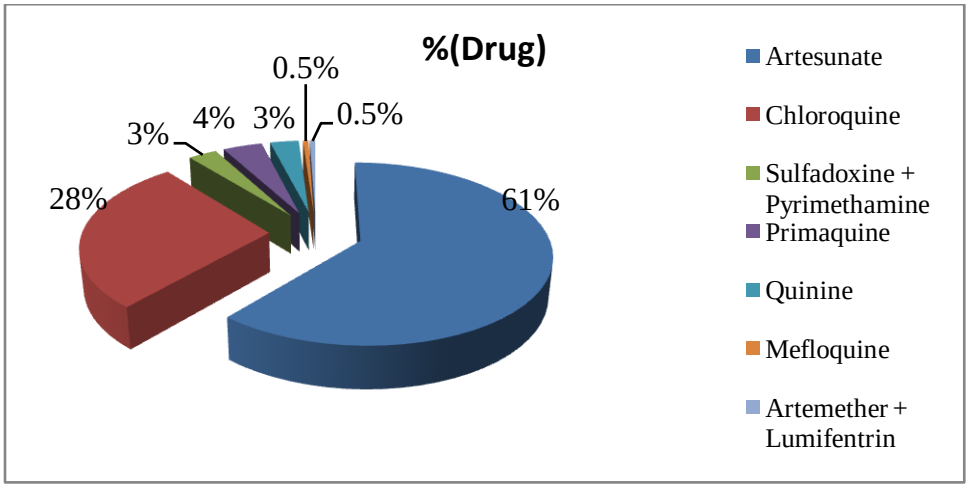

Figure 1: Anti-malarial drugs prescribed.

The fact that anti-malarial were prescribed for all the patients showed that malaria is the most common illness affecting to population.

The improvement is needed in anti-malarial drug prescription. As in the whole article we can see that Artemisinin is prescribed in 339 (61.3%) cases. It is weather in monotherapy or in combination. According to National Guideline oral artemisinin monotherapy is banned in India and Dodoo et al also suggest that artemisinin monotherapy, a regimen which has not been recommended by WHO since January 2006 due to the potential for drug resistance in the class of drug due to its shot half-life. Our study shows that artemisinin monotherapy is mostly in injection form and none of the cases prescribed oral artemisinin monotherapy.

CORRELATION OF ANTI-MALARIAL TREATMENT ACCORDING TO NATIONAL GUIDELINE

Out of the 474 case files selected, in confirmed malaria cases, the uncomplicated malaria cases were 283 (59.70%). The complicated malaria cases were 115 (24.26%). And the 76 (16.04%) other cases were seen of non-malaria prescribed with anti-malarial drugs.

Treatment of uncomplicated malaria

Out of 474 patients 283 (59.70%) patients were identified as uncomplicated malaria. There were 5 different conditions recorded in **Table 2**. Out of that the causative parasite species were *P. falciparum* in 111 cases (39.22%), *P. vivax* in 137 cases (48.41%). There were 5 (1.77%) pregnant women were diagnosed with *P. vivax* malaria. 5 patients (1.77%) were diagnosed with mixed infection. The patients with clinical malaria were 25 (8.83%). In order to assess the anti-malarial drug utilization according to Guidelines for diagnosis and treatment of malaria in India 2011in tertiary care hospital, Lions General Hospital, Mehsana; the appropriateness of drug prescribed was evaluated. **Table 3** presents data on the pattern of anti-malarial drugs used.

Table 2: Number of uncomplicated malaria cases.

Condition	No. of cases	%
P. vivax	137	48.41
P. falciparum	111	39.22
Pregnant women with *P. vivax*	5	1.77
Mixed infection	5	1.77
Clinical malaria	25	8.83
Total	283	100

Table 3: Anti-malarial treatment according to guideline for uncomplicated malaria

Condition	Treatment			
	Correct		Incorrect	
	Total	%	Total	%
P. vivax	98	71.53	39	28.47
P. falciparum	14	12.61	97	87.39
Pregnancy	5	100	0	0
Mixed infection	5	100	0	0
Clinical Malaria	4	16	21	84
Total	126	44.52	157	55.48

Prescription pattern of artemisinin monotherapy (87.39%, n=97) is high among the *P. falciparum* patients, indicating widespread acceptance of artemisinin therapies. According to National Guideline Artemisinin Combination Therapy (ACT) should be given to all confirmed *P. falciparum* cases found positive by microscopy. This is to be accompanied by single dose primaquine (0.75 mg/kg body weight) on Day 2. ACT consists of artemisinin derivative combined with mefloquine, Sulfadoxine + Pyrimethamine. In our study data, ACT were prescribed in less than 25% of patients (12.61%, n=14).

In *P. falciparum* malaria, chloroquine was resistant widely. Our study has interesting observation showed that none of the patients having *P. falciparum* malaria were prescribed with chloroquine. According to National Guideline *P. vivax* patients should be treated with chloroquine in full therapeutic dose of 25 mg/kg divided over three days. For relapse (A form of *P. vivax* or *P. ovale* parasites called as hypnozoites remains dormant in the liver cells. These hypnozoites can later cause a relapse) prevention, primaquine should be given at a dose of 0.25 mg/kg body weight daily for 14 days under supervision. Our study data shows, most of *P. vivax* patients were prescribed Chloroquine (69.34%). Only 3 patients (2.19%) were given anti relapse therapy of Primaquine after treatment with Chloroquine. Correct treatment was prescribed in 71.53% (n=98) cases. However, it should be 100% as we know that *P. vivax* is known to produce relapse. All effort should be made to diagnose malaria either by microscopy or Rapid Diagnostic Test (RDT). National Guideline says that special circumstances if RDT for only *P. falciparum* is used, negative cases showing signs and symptoms of malaria without any other obvious cause

for fever should be considered as 'clinical malaria' and treated with chloroquine in full therapeutic dose of 25 mg/kg body weight over three days. If a slide result is obtained later, the treatment should be completed according to species. Present work shows that use of artesunate alone in clinically not confirmed patients (84%, n=21) may lead to resistance against artemisinin. This evaluation showed that nearly one year following the national anti-malarial guideline, the first-line therapy was adhered to in less than 50% of cases.

100% treatment adherence to National Guideline was seen in pregnant women with uncomplicated malaria and patients suffering with mixed infection malaria.

Treatment of complicated malaria

Out total 474malaria cases there were 115(24.26%) cases of complicated malaria. Their different clinical features with malaria and their anti-malarial treatment were given in the **Table4**.

Table 4: List of complicated malaria cases with treatment

Clinical Features	No. of Cases	Death	Anti-malarial treatment	
			Artesunate	Quinine
Repeated generalized convulsions	7	-	6	6
Renal Failure	37	8	36	15
Jaundice	13	2	11	4
Severe Anaemia	16	-	16	3
COPD	14	3	14	-
Hypoglycemia	6	-	6	-
High grade fever	6	-	6	-
Cerebral malaria	6	3	6	4
Complicated malaria				
P. vivax	7	1	7	
P. falciparum	3	-	3	-
Total	115	17 (14.78%)	111	32

It is important to eradicate complicated malaria also with clinical feature with which malaria is diagnosed. In our study total 115 (24.26%) complicated cases were collected. Out of that 17 (14.78%) patients died after treatment. They were having malaria with complication of renal failure, Jaundice, COPD and Cerebral malaria. For management of complicated malaria National Guideline suggest that health facilities should be equipped with parenteral anti-malarial, intravenous infusion facilities special nursing for patients in coma, blood transfusion, well equipped laboratory, oxygen and other appropriate treatment of their clinical features. If these facilities are not available, the patients must be referred without delay to a facility, where they are available.

Anti-malarial drugs prescribe in infectious disease other than malaria

A total of 76 (16.04%) patients which were negative for malaria and given anti-malarial drugs,

were classified as Non-malarial fever. In this group mostly Chloroquine and Artemesinin derivative were prescribed. Prescription pattern is described in **Table 5**.

Table 5: Anti-malarial treatment which they used in other than malaria patients

Condition	Patients	Artesunate	Chloroquine
Fever	14	10	4
Viral fever	54	42	12
Dengue	8	3	5
Total	76	55	21

Study also shows that artemisinin prescribing pattern is high among the patient who were not confirmed with malaria and also not having as clinical malaria, but diagnosed as fever, viral fever or other condition like dengue. A recent study from Uganda, where malaria is common, suggests 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 and all patients were given anti-malarial drugs[13]. In our data there were 76(16.04%) patients having Fever, Viral fever and Dengue and all were prescribed Artesunate and Chloroquine. The need to educate health care workers to stop recommending artemisinin monotherapy is obvious and urgent.

EVALUATION OF PRESCRIBING INDICATOR

Average no. of anti-malarial drugs per case will calculate by dividing the total number of anti-malarial drug products prescribed by number of cases surveyed and Percentage of cases with an injection prescribed will calculated by dividing the number of patients encounters during which an injection was prescribed by the total number of cases surveyed, multiplied by 100. This is described in **Table 6**.

Table 6: List of prescribing indicator

Sr. No	Indicator	Data
1.	Average number of drugs	1.17
2.	IV injection	48.82 %

After evaluation of this study it shows that average number of anti-malarial drug prescribed per case is 1.17. IV fluids were prescribed in 48.82% cases. This will increase the cost of the prescription as injections were costlier than oral therapy.

Table 7: Cost of Anti-malarial drugs prescribed

Sr. No.	Indicator	Data
1.	Average drug cost/Prescription	INR 123.28 Rs.
2.	% Drug cost on injection	87.50 %

EVALUATION OF COST FOR THE TREATMENT

Table 7 showed the cost parameter like Average drug cost per case is determined by dividing the total cost of all drugs prescribed by the number of cases surveyed and % of drugs costs spent on

injection

is determined by dividing the cost of injections prescribed by the total drug cost.

Not only quantity but also the quality and the cost of anti-malarial prescribing are important component of drug utilization studies. Artemisinin derivatives are much more expensive than conventional anti-malarial drugs. As in our study average drug cost/prescription is INR 123.28 Rs. Drug cost on injection is 87.50% out of the total cost. As the use of injection in 73.42 % case with arsesunate derivative and quinine will increase the cost of the treatment.

CONCLUSION:

This study showed that inappropriate use of anti-malarial drugs was high among patients with *P. falciparum*, clinical malaria and non-malarial patients. The percentage of incorrect drug prescribed is high (55.48%) when compared to those from Guidelines for diagnosis and treatment of malaria in India 2011. While treatment of pregnant women with malaria and patients with mixed infection of malaria were adhering 100% to National Guideline. Cost of the therapy was very high. As Artesunate resistance is spreading widely in the world, drug-resistance monitoring has to be done in India and a complete analysis of countrywide data across institution is required. This study also illustrated some practical realities of the day-today diagnosis and treatment of uncomplicated malaria. Firstly, the high level of presumptive diagnosis of malaria, based on country-specific guidelines, seems to be a limiting factor for prescribing the new first-line therapy. Apart from all for instance, the Roll-Back Malaria initiative is working to improve prevention efforts in affected countries, through insecticide-treated nets (ITNs), indoor residual spraying (IRS) of pesticides and intermittent preventive treatment (IPT) for pregnant women [14]. Continued education of government and private providers on the new national anti-malarial guidelines is also recommended.

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