A STUDY ON ANTIMALARIAL PRESCRIPTION PATTERN IN RURAL TERTIARY CARE TEACHING HOSPITAL

By

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation/thesis entitled**"A STUDY ON ANTIMALARIAL PRESCRIPTION PATTERN IN RURAL TERTIARY CARE TEACHING HOSPITAL"** is a bonafide and genuine research work carried out byme under the guidance of **MR. M. KUMARASWAMY**Associate Professor, Dept. of Pharmacy Practice, SAC College of Pharmacy, B.G.Nagara.

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Solely Dedicated To My Son

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Mrs. JAMUNA T. R.

List of Abbreviations Used

Abbreviations	Expansions
WHO	World Health Organization
NVBDCP	National Vector Borne Disease Control Programme
CQ	Chloroquine
PV	*Plasmodium vivax*
PF	*Plasmodium falciparum*
CQR	Chloroquine Resistance
AQ	Amodiaquine
MQ	Mefloquine
PQ	Primaquine
SP	Sulphadoxine + Pyrimethamine
AS	Atemisinin
ACT	Antimalarial Combination Therapy
BD	Twice daily
OD	Once daily
GGT	Gamma Glutamine Transferase
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
ALP	Alkaline Phosphatase
ADR	Adverse Drug Reaction
ADEs	Adverse Drug Event
AH&RC	Adhichunchanagiri Hospital & Research Center

List of Abbreviations Used

CIMS	Current Index of Medical Specialities
G_6PD	Glucose 6 Phosphate Deficiency
AO	Acridine Orange
QBC	Quantitative Buffy Coat
RDT	Rapid Diagnostic Test
RR	Risk Ratio
OBG	Obstetrics And Gynaecology

ABSTRACT

Background

Malaria is one of the deadliest disease affecting world-wide. Prompt and accurate treatment should be provided for the patient. Prescription pattern has a prominent role in antimalarial drug use in malaria infectious patient. Inappropriate and irrational prescribing practices has led emergence of drug resistance with antimalarials.

Objective

To study on prescribing pattern of anti-malarials in in-patients of general medicine department at tertiary care hospital.

Methodology

A prospective and observational study was conducted over a period of 9 months at Adichunchanagiri Hospital and Research Center (AH&RC), B.G.Nagara. Patients who satisfied the inclusion criteria were enrolled after taking their written consent. Their specific demographic details, past medical history, laboratory investigations and other relevant details were collected in a specially designed Data Collection Form and analysed.

Results

Prescribing pattern of antimalarials is studied in the 112 in-patients. Males were more infected by malaria than female; infection was more inpatients of age group between 18-35 years than in older adults and elder patients. The most commonly used antimalarial was found to be Artesunate, followed by Artesunate+Mefloquine and CQ. Total antibiotic used in 112 patients was 182 among them (51.6%) Ceftriaxone was used in 84.7% patients followed by Doxycycline (13.2%) in 21.6% of patients. It was noted that monotherapy 63 (56.2%) was most preferred than

combination therapy 49 (43.8%). WHO guideline was followed to prescribe antimalarial drug. A total of 14(12.5%) patients were identified with ADR, possible was seen in 12(10.7%) and probable in 2(1.8%) nature by NARANGO's causality assessment scale. Most commonly seen ADR is Nausea and vomiting it was found in 9(8%) patients in most of the patients additional treatment was given for management of ADR.

Conclusion

Inappropriate diagnosis and use of antimalarials was high in febrile patients. Adoption of standard guideline should be strengthened for rational use of antimalarial drug in the hospital. Antimalarial should be prescribed only after conformation test.

Key words: Antimalarials, Prescription Pattern, Clinical Malaria, Resistance.

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Chapter-I

Introduction

INTRODUCTION

Malaria is a serious health problem caused by the protozoa transmitted by the bite of infected female anopheles mosquitoes that affects millions every year. Globally, around 3.2 billion people are at risk of being infected with malaria and 1.2 billion are at high risk. 198 million cases of malaria occurred and the disease led to 584000 deaths which has been estimated by World Health Organization (WHO) in 2013. The burden of malaria is more in the African region, in which there is an estimation of 90% deaths due to malaria [1].

As per World Health Organization report 2012, South East Asian Region bears the second largest burden of malaria (13%), next to African (81%) region. Among South-East Asia region, India shares two-thirds of the burden (66%) followed by Myanmar (18%) and Indonesia (10%) [2].

In India, National Vector Borne Disease Control Programme (NVBDCP) has reported that, nearly 1.5 million confirmed cases are reported annually, of which 50% are due to P.vivax. The combinations of *P.falciparum* and *P.vivax*, six primary malaria vectors, several ecotypes including, urban malaria and various transmission intensities ranging from unstable to hyper endemic create a challenging epidemiological scenario in India [3].

In the last two decades, an increasing incidence of *P. falciparum* infection is proving to be resistance of chloroquine in India. In a study conducted by Muddaih et al., in South Canara, Karnataka, reported that the prevalence of *P.vivax* (52.54%), *P.falciparum* (33.75%) and 13.69% were of mixed malarial infection. And one *P.vivax* patient has shown chloroquine resistance inspite of receiving 48 hour of chloroquine (25 mg/kg), fever was persisting and smear was positive [4.]

INTRODUCTION

Prescribing practice can be defined as the ability of health professionals to differentiate and discriminate among the various choices of drugs and to determine the need of therapy which will be most beneficial to their patient. Prescribing practice of antimalarial drugs may influence rational use of medicine. Studies conducted in many developing countries have shown major prescribing problems due to poly pharmacy, over use of antibiotics, selection of wrong drug, unsuitable doses and dosages, improper duration of antimalarial drugs. Most of the medical practitioners in many countries are inclined to adopt their own protocol to treat malaria rather than adhering to standard regimen [5, 6].

Chemotherapy has an important role in treatment and control of malaria. It is very much important to diagnose the type of plasmodium species before the commencement of the treatment, then only specific and effective drug can be chosen and drug resistance can be prevented. Quinoline and 4-aminoquinolines class of drugs have been safer and effective of which chloroquine (CQ) has been used from ancient period which is cheap, effective, safe and commonly available drug in the treatment of *P. vivax* infection which was introduced in year late 1950s. Along with this drug Amodiaquine (AQ), Sulfadoxine/ Pyrimethamine (SP); Sulfaline/ Pyrimethamine, Mefloquine, Halofantrine, Quinine, Atovaquone/ Proguanil, Primaquine artemisinin derivatives like artemether, artesunate and arteetherare the single agent therapy along with this fixed dose combination drugs are also available like Mefloquine + Artesunate , Sulfadoxine + Pyrimethamine + Artesunate, Lumefantrine + Artemether. These drugs have their own mode of action, active against specific parasite and also specific side effects which limit their use in the therapy [7].

INTRODUCTION

The combination therapy can increase effectiveness of available antimalarial drug, gets synergetic or additive potential of two or more drugs [8] and delay the emergence of spread of drug resistance comparatively to monotherapy. Incidence of resistance strains of the parasite can be minimized by using two or more drug with independent mechanism of action, since it is believed that mutation that confer resistance to each drug will co-exist in the same parasite. Therefore ACT combination therapy is expected to improve the treatment cure rate [9].

Combination of antimalarial drug with antibiotics significantly improve the treatment efficacy compared to single antimalarial drug therapy of drug resistant malaria. World health organization (WHO) has recommended combination of artesunate plus tetracycline or doxycycline or clindamycin, and quinine plus tetracycline or doxycycline or clindamycin (either one of these combination given for a total of 7 days) as a second line treatment for the treatment of uncomplicated *P. falciparum* malaria [1]. However, a proper diagnosis for malarial parasite can lead to rational use of antibiotic in febrile patients. Batwala V et al., conducted a study and found that there was an increased rate of antibiotic use in the treatment and in positive malaria test there was a reduction in antibiotic use when compared to negative malaria test which showed increased use of antibiotics [10]. Doxycycline a derivative of tetracycline is a potent drug and when combined with rapidly action schizonticide like quinine. This drug has been used for prophylaxis and also in quinine resistant areas and / to reduce the side effects associated with the quinine by decreasing its duration of treatment [11].

Inappropriate use of antimalarial drugs was high in *P.falciparum*, clinical malaria and non-malarial patients which has shown in various conducted in India on a drug utilization. In a study

conducted in India found that, the percent of incorrect drugs prescribed was high (55.48%) when compared to those from guidelines for diagnosis and treatment of malaria in 2011 [12]. Prescribing practice have been shown to influence the emergence of resistance to antimalarial drug, in order to prevent drug resistance, drug use pattern should be evaluated in terms of prescribing and dispensing practices as well as patients use of the drug [13].

Resistance can be defined as 'either the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal–to or higher than those usually recommended, but with -in the limits to tolerance of the patients' [14]. Resistance to chloroquine was observed in 44.4% isolates in India. High proportion is seen in Orissa, 16.66% of resistance is seen in Karnataka [7]. CQ resistance (CQR) in P. vivax in Papua New Guinea from then it has spread all over the world. In India, CQR was detected in 1973 in Assam, currently northeast and southeastern part are with high CQR rates and morbidity and mortality is increasing but southern part is affected with moderate degree of resistance. Till date artemisinin derivatives resistance has not been reported. So Artemisinin based combination drugs are in line for the CQR malaria [15].

WHO defines an adverse drug reaction as 'any response to a drug which in noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function [16]. One of the study conducted by Ranjita et al. showed that an artesunate administered at a dose of 110 mg/kg body weight for 14 days caused a significant increase in the levels of ALT, ALP, AST, GGT in serum.

This reveals that the drug artesunate has a potential to cause liver injury and should be cautiously used in malaria patients who have previous history of liver disease [17].

Sulphonamide containing antimalarial have been found to causes severe adverse reaction including severe skin rashes and Stevens - Johnson syndrome,liver disorders and bone marrow suppression [18]. Study by Njan et al., revealed that 78% of patients reported experiencing multiple ADR symptoms with 36 hours of SP and/or AS intake. In the Malaysian study, ADR incidence was estimated at 2.4 per 100,000 exposure to SP. In Peru, 8% ADR was reported in SP + Artesunate therapy. Tinnitus, nausea, headache, blurred vision, hemolytic anemia, severe toxic rash, erythematous are ADR associated with quinine use. In one study has reported 69.1% mild and 7.3 % severe cases and 23.6% were serious ADR and were hospitalized with the use of artemisinin combination therapy [13, 19].

Use of Clindamycin has frequent adverse effect including anorexia, nausea, vomiting, and abdominal discomfort. Conflicting results associating overdose of artemisinin containing drugs with unusual and selective patterns of damage to certain brainstem nuclei in animals and humans have also been reported. In one study has reported 69.1% mild and 7.3 % severe cases and 23.6% were serious ADR and were hospitalized with the use of artemisinin combination therapy [20].

Many patients with infectious disease like malaria are being affected in the study site so there is a need to evaluate the factors and motivations that underlie problems in prescribing practices in order to treat malaria in a more rational way. Therefore, the present study was to investigate prescribing pattern of antimalarial drugs, pattern of antibiotics used in the infectious patient in

tertiary care teaching hospital at Adichunchanagiri Hospital and Research Center (AH&RC), B.G.Nagara.

Chapter -II

Objectives

OBJECTIVES

Primary Objective:

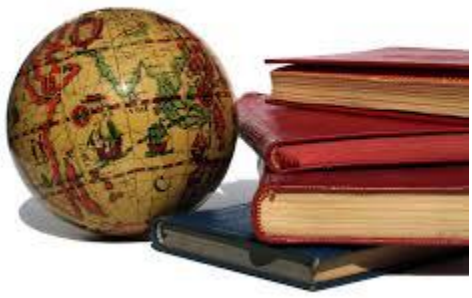
- To study prescribing pattern of anti-malarials.

Secondary Objective:

- To assess the type of malaria.
- To assess the prescribing pattern to accepted standard guidelines.
- To assess antibiotic use in malarial therapy.
- To assess monotherapy and combination therapy.
- To assess the ADRs associated with the treatment, if any.

Chapter –III

Review of Literature



History of malaria [21]:

- ✓ Around 12,000 years ago with rise in temperature & humidity creating new water bodies and pools and the start of agriculture in the Middle East and North East Africa. This led to a favorable climate and area to the mosquito for breeding and transmission of malaria parasites. Malaria has found more than 4000 years ago.
- ✓ The word malaria has derived from the Italian word "Mal'aria" meaning "bad air". The ancient Chinese described the symptoms of malaria in their medical writing. In "Nei Ching"- The Canon of Medicine, the characteristic symptoms of malaria has been described in 2700 BC, later it was edited by Emperor Huang Ti. In the 4th century BCE, malaria was recognized by Grecee and then in the period of Hippocrates and Romans, they also described about the malarial disease. In India, the Susruta, a medical treatise described that malarial fever symptoms & was found that symptoms was after the bite of certain insects.
- ✓ Charles Louis Alphonse Laveran, a French army surgeon stationed in Constantine, Algeria, observed parasites in the blood of a patient suffering from malaria on the 6th of November 1880. Laveran was awarded the Nobel Prize in 1907 for his discovery.
- ✓ Camillo Golgi, an Italian neurophysiologist, established that there were at least two forms of the disease, one with tertian periodicity (fever every other day) and one with quartan periodicity (fever every third day). He also observed that the forms produced differing numbers of merozoites (new parasites) upon maturity and that fever coincided with the

rupture and release of merozoites into the blood stream. He was awarded a Nobel Prize in Medicine for his discoveries in neurophysiology in 1906.

- ✓ Giovanni Batista Grassi and RaimondoFiletti, Italian researchers named Plasmodium vivax, and Plasmodium malariae in 1890, and an American, Welch, named Plasmodium falciparum in 1897.
- ✓ It was Sir Ronald Ross, an officer in the Indian Medical Service who discovered the transmission of malaria by mosquito from bird to bird in 1897 in Calcutta, India, earning the Nobel Prize in 1902.
- ✓ John William Watson Stephens named the last of the four, P. ovale, in 1922.
- ✓ P. knowlesi was first described by Robert Knowles and Biraj Mohan Das Gupta in 1931 in a long-tailed macaque. The first documented human infection with P. knowlesi was in 1965
- ✓ Discovery of the Transmission of the Human Malaria Parasites Plasmodium (1898-1899): Led by Giovanni Batista Grassi, a team of Italian investigators, which included Amico Bignami and Giuseppe Bastianelli, collected Anopheles claviger mosquitoes and fed them on malarial patients. The complete sporogonic cycle of *Plasmodium falciparum*, *P. vivax,* and *P. malariae* was demonstrated. In 1899, mosquitoes infected by feeding on a patient in Rome were sent to London where they fed on two volunteers, both of whom developed malaria.

Some of the Anopheles species have been found 6 out of 58 are the main malaria vectors they are An. culicifacies, An. dirus, An. fluviatilis, An. minimus, An. sundaicus and An.stephensi. An.

philippinensis-nivipes, An. varuna, An. annularis and An. Jeyporiensis are some of the local vectors. Species of Plasmodium which infect the humans are *P.falciparum, P.vivax, P. ovule, P. malariae*, and the fifth species acquired from macaque monkey is *P. Knowlesi* [22].

EPIDIMIOLOGY:

According to latest estimation 104 malaria endemic countries and territories are infected by malaria, 9 countries are in on-going transmission. 219 million cases of malaria and 660000 deaths has been reported. Africa is the most affected continent in the world around 90% of death has occurred due to malaria. Six highest burden countries in Africa region are Nigeria, Democratic Republic of the Congo, United Republic of Tanzania, Uganda, Mozambique and Cote d'Ivoire. These six countries account for an estimated 103 million (or 47%) of malaria cases. In South East Asia, the second most affected region in the world, India has the highest malaria burden (with an estimated 24 million cases per year), followed by Indonesia and Myanmar [1].

Malaria is an epidemic disease in areas, such as northern India, Sri Lanka, Southeast Asia, Ethiopia, Southern Africa, and Madagascar. The principal determinants of the epidemiology of malaria are the number (density), the human-biting habits, and the longevity >1 day of the anopheles mosquito vectors. Mosquito longevity is particularly important, because the portion of the parasite's life cycle that takes place within the mosquito from gametocyte ingestion to subsequent inoculation (sporogony)—lasts for 8 to 30 days, depending on ambient temperature; thus, to transmit malaria, the mosquito must survive for >7 days [23].

In India major Plasmodium species responsible for malaria are *P.falciparum* (53%) and *P.vivax* (48%) & Anopheles species are An. culicifacies, An. fluviatilis, An. stephensi, An. minimus, An. dirus, and An. annularis. In this programme there was a control phase and 881730 confirmed cases, 440 death cases were reported [1].

ETIOLOGY AND PATHOGENESIS [21]:

LIFE CYCLE OF MALARIA PARASITE:

A. EXO-ERYTROCYTIC CYCLE:

i. Female anophelene mosquito inoculates Plasmodial sporozoites from its salivary gland to human during a blood meal and infects a healthy human.
ii. The malarial parasite which are motile and microscopic are carried by the bloodstream which infect liver parenchymal cells. Thus, asexual reproduction begins in the human liver.
iii. This process leads to production of intrahepatic or pre-erythrocytic schizogony or merogony. This process is called 'amplification process '.
iv. The swollen liver cells get bursts to discharge motile merozoites into the blood stream, these have the capability to invade RBC and multiplies 6-20 fold in 2 to 3 days.

B. ERYTROCYTIC CYCLE:

i. When the parasites reaches density of ~50/μL of blood, the symptomatic stage begins, the merozoites invade erythrocytes to form trophozoites.
ii. The small ring forms of the four parasite species appear similar under light microscope. As these get mature species specific characteristics become evident, pigment is visible, and the

parasite take its shape. All these changes takes place in early stage of intra- erythrocytic stage development.

By the end of this stage the parasite consumes nearly all the Hb and grows to occupy most of the RBC. The period taken is 48 hour (72 hr. for P, malariae). Now the parasite is called Schizont. This Schizont undergo multiple nuclear divisions to form schizogony or merogony and RBC ruptures to release 6 to 30 daughter merozoites. Each merozoites are capable of affecting a new RBC and repeat the asexual cycle.

iii. By continuous series of asexual cycles *P. falciparum*, or release from the hepatic rupture (*P.vivax, P. Ovuale, P. malariae*) develop into morphologically distinct, long lived sexual forms i.e., gametocytes which are capable of transmitting malaria. *P.vivax* and *P. Ovuale* parasites, after release from liver donot divide rather remain dormant for a long period up to 3 weeks to a year or longer until they undergo reproduction. These dormant forms are called hypnozoites which causes relapse of fever and is the main characteristic tool for diagnosis of these two species.

When *P.vivax* parasite enter blood to invade erythrocyte the attachment is mediated by a specific erythrocyte surface receptor and is related to the Duffy blood group antigen Fya or Fyb.

iv. During a blood meal mosquito ingest a male and female gametocytes from an infected person and forms a zygote in the insect's midgut. This zygote matures into ookinete, penetrates and encysts in the mosquito's gut wall this results in oocysts. This expands by asexual division bursts to liberate myriad motile sporozoites which travel to salivary gland of the mosquito

along with hemolymph. Again when the mosquito bites healthy human for blood meal it infects and asexual cycle begins.

Clinical Presentation of Malaria:

Initial symptoms: Nonspecific fever, chills, rigors, diaphoresis, malaise, vomiting, Orthostatic-hypotension, Electrolyte abnormalities

Erythrocytic phase

Prodrome: headache, anorexia, malaise, fatigue, myalgia

Nonspecific complaints such as abdominal pain, diarrhea, chest pain, and arthralgia

Paroxysm: high fever, chills, and rigor.

Cold phase: severe pallor, cyanosis of the lips and cutis anserina ("goose-flesh")

Hot phase: fever between 40.5°C (104.9°F) and 41°C (105.8°F).

Sweating phase: Follows hot phase by 2–6 hours; Fever resolves, marked fatigue and drowsiness, warm, dry skin, tachycardia, cough, severe, headache, nausea, vomiting, abdominal pain, diarrhea, and delirium, Lactic acidosis and hypoglycemia (with falciparum malaria)

Anemia

Splenomegaly

P. falciparum infections: Hypoglycemia, acute renal failure, pulmonary edema, severe anemia, thrombocytopenia, high-output heart failure, cerebral congestion, seizures and coma, and adult respiratory syndrome.

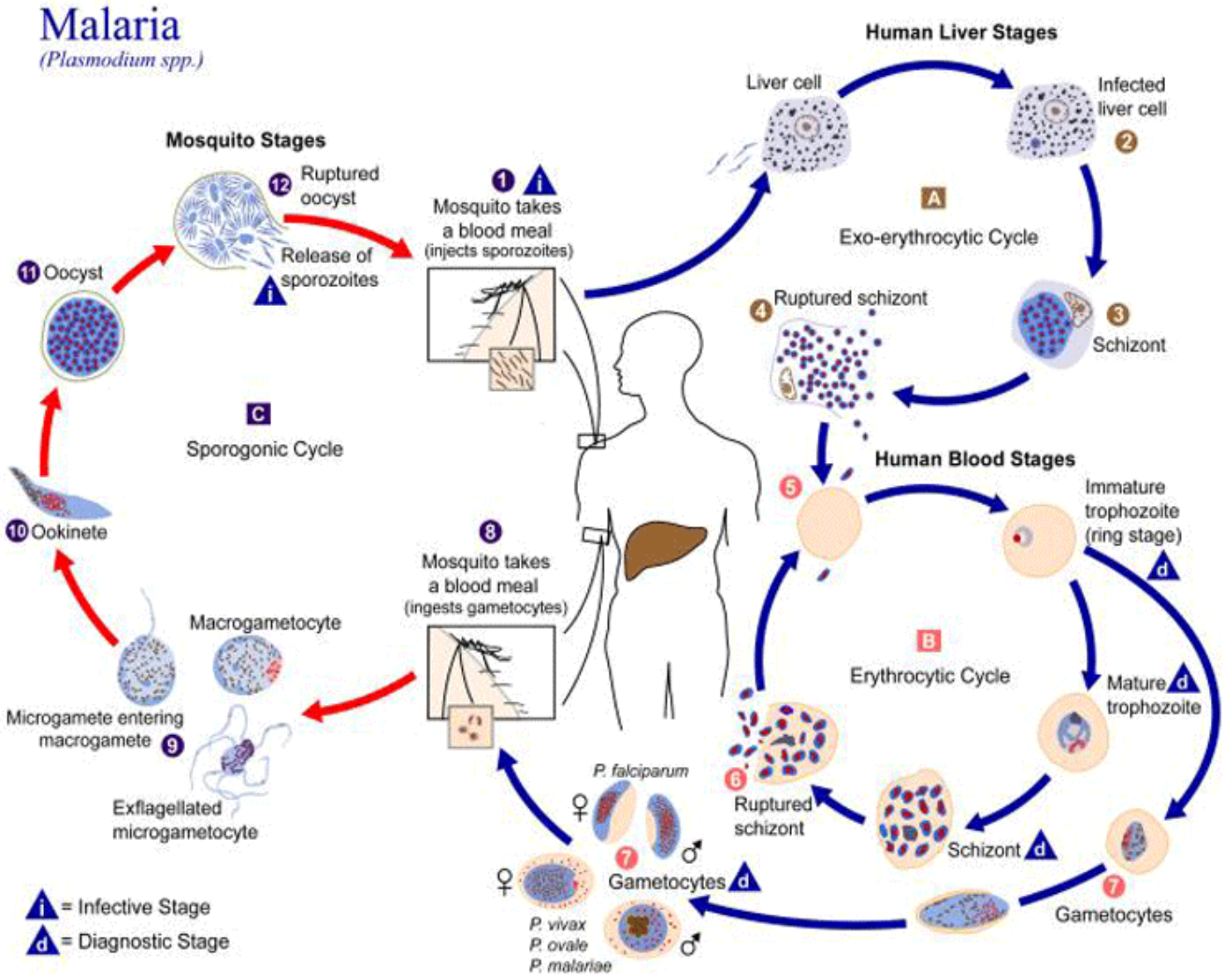


Fig.1: Illustration of life-cycle of parasites of the genus Plasmodium, which are causal agents of malaria (Centers for Disease Control and Prevention).

DIAGNOSIS:

To ensure a positive diagnosis, blood smears should be obtained every 12 to 24 hours for 3 consecutive days. The presence of parasites in the blood 3 to 5 days after initiation of therapy suggests drug resistance. According to WHO, the diagnosis of malarial parasite is tested from one among the following [1].

METHOD	ADVANTAGES	DISADVANTAGES
Rapid diagnostic test	Differentiates PF from non-falciparum infections. Speed and ease of use; minimal training required to perform test.	Cannot differentiate between non-falciparum species. Will not quantify parasitemia.
Rapid diagnostic stick test	Speed and ease of use; minimal training required to perform test. Card format easier to use for individual tests, dipstick test is easier to use for batched testing.	Will not diagnose non-falciparum malaria. Will not quantify parasitemia. Can remain positive after clearance of parasites.
Light microscopy	Species –specific diagnosis. Quantification of parasites aids treatment follow-up.	Sensitivity and specificity dependent on training and supervision, electricity desirable and time consuming.
Fluorescent	Results attainable more quickly	Special equipment and supplies needed.

microscopy : • **Acridine orange [AO] stained thick blood smear;** • **Quantitative Buffy Coat [QBC] (Becton-Dickison)**	than normal microscopy.	Sensitivity of AO poor with low parasite densities. Electricity needed, staining of non-parasitic cells, miss diagnose of unreliable species. QBC will not quantify parasitemia. AO is hazardous material.
Clinical	Speed and ease to use. No electricity, no special equipment needed beyond normal clinical equipment {thermometer, stethoscope, otoscope, timer.}	Can result in misdiagnose and over treatment, requires close supervision and retraining to maximize reliability.

TREATMENT:

Treatment for the malaria should only be initiated after the laboratory investigations have done. But at the extreme circumstances "Presumptive treatment" can be given. Treatment is guided by three main factors they are, primarily infecting plasmodium species; secondly the clinical status of the patient, and finally *P.falciparum* & *P.vivax* species that have acquired resistance to the drug at different stages and different geographic regions and previous use of Antimalarials, for these two species urgent initiation of appropriate therapy is needed. After the initiation of the therapy, the patient's clinical and parasitological state should be monitored. Blood smears should be done to confirm adequate parasitologic response to treatment [14].

CLASSIFICATION OF ANTIMALARIALS:

- Classification of Drugs Acting on Different Stages of Parasites:
- Blood [erythrocytic] schizontocides – for clinical cure and suppressive prophylaxis:
  - Fast acting high efficacy drugs:
    - Chloroquine
    - Amodiaquine
    - Quinine
    - Mefloquine
    - Atovaquone
    - Halofantrine
    - Lumefantrine

- Artemisinin derivatives - artesunate, artemether & arteether.

➢ Slow acting low efficacy drugs:

- Proguanil
- Pyrimethamine + sulfonamides
- Tetracyclines [Doxycycline]

❖ Tissue schizontocides- for radical cure and causal prophylaxis (pre-erythrocytic and exo-erythrocytic stage):

- Primaquine
- Bulaquine

❖ Gametocytocides and sporontocides-for preventing transmission through mosquitoes:

- Primaquine
- Proguanil
- Pyrimethamine
- Chloroquine and
- Quinine

- Structural Classification of Currently Used Antimalarials

A. Aminoquinolines	Eg. Chloroquine, Hydroxychloroquine, Amodiaquine
B. 8- Aminoquinolines,	Eg. Primaquine, Tafenoquine, Bulaquine
C. Aryl amino Alcohols,	Eg. Quinine
D. Methanol's I. 4 Quinoline Methanol Ii. 9- Phenanthrene Methanol	 Eg. Mefloquine Eg. Halofantrine, Lumefantrine
E. Biguanides	Eg. Proguanil
F. Diaminopyrimidines	Eg. Pyrimethamine
G. Antimalarial Endoperoxidases I. First Generation Endoperoxidases (Artemisinin Derivatives) Ii. Second Generation Endoperoxidases A. Trioxanes B. Tetroxanes	Eg. Artesunate, Artemether, Arteether
H. Hydroxynaphthoquinone	Eg. Atovaquone
I. Benzonaphthyridine Deriative	Eg. Pyronaridine
J. Antibiotics	Eg. Sulfonamides, Tetracycline, Doxycycline, Clindamycin, Azithromycin

PROPERTIES OF ANTIMALARIALS:

NAME	MOA	Half life	ADVANTAGE	DISADVANTAGE
Chloroquine	Inhibits plasmodial heme & polymerase forms Toxic drug-heme complex =cell lysis.	41±14 days	Highly potent against sensitive strains, Long half-life, Effective at once a week dose as prophylactic agent	Rapid development of resistance
Quinine	(Same as Chloroquine)	11 hrs.	Rapid development of resistance not yet seen	Higher toxicity
Artesunate / Artemether / Arteether	Activated by heme/ molecular iron to produce carbon centered free radicals, Membrane damage by free radical	<1 hr. 3-11 hrs > 20 hrs.	Broader window period of effectiveness, Little/ no cross resistance, Resistance not yet recorded	High recrudescence rate when used as monotherapy (10-50%) when used for <5 days
Mefloquine	Formation of toxic subs. with heme Damages membrane and other comp. Causes swelling of food vacuole	20 days	Useful as prophylactic agent for non-immune travellers Single dose sufficient Good alt. To quinine in MDR Pf.	Only oral prep. Available. So cannot be used in sev. Pf malaria. High chances of cross-resistance, might lead to quinine resistance as well
Halofantrine	Concentrates and combines with ferriprotoporphyrin IX, leading to memb. Damage.	10-90 hrs.	Good alternative to mefloquine/ quinine in chloroquine/ MDR Pf	Oral absorption erratic High chances of cross resistance with Mefloquine,

				Cardiotoxicity
Atovaquone	Inhibits parasite mitochondrial electron transport chain (complex III)	70 hrs.		Erratic absorption High recrudescence rate when used alone
Pyronaridine	Inhibits vacuolar degradation, leading to impaired Hb degradation	60 hrs.	Good oral absorption Cross resistance not yet documented. Well tolerated	
Sulfadoxine - Pyrimethamine	Acts against the parasite dihydrofolate reductase enzyme	Sulfadoxine – 180 hrs. Pyrimethamine – 95 hrs	Can be used against chloroquine resistant P.falciparum. No cross resistance with the 4 aminoquinolines, mefloquine, quinine, artemisinin derivatives	Risk of severe skin reactions
Primaquine	May get converted to electrophiles that act as redox mediators	6 hrs.	Useful for the terminal prophylaxis and radical cure of PV and PO	Cannot be used in patient with G-6PD deficiency.
Proguanil	Selective inhibition of the bi-functional dihydrofolate reductase-thymidylate synthetase of Pl.	16 hrs.	Good prophylactic agent for Pf or mixed infection, when used with chloroquine	Cannot be used alone in treatment of malaria

TREATMENT SCHEDULE [14]:

TREATMENT OF UNCOMPLICATED PLASMODIUM FALCIPARUM MALARIA

Artemisinin combination therapy (ACT) is the drug of choice for all confirmed cases of uncomplicated PF cases. This should be combined with primaquine (PQ) (0.75 mg/kg body weight or 45 mg) on day-2. One of combination drug is artesunate + sulfadoxine and pyrimethamine (SP).

TREATMENT OF UNCOMPLICATED PLASMODIUM VIVAX MALARIA

Chloroquine is the drug of choice of *Plasmodium vivax* (PV) cases. It is given at a dose of 10 mg/kg (600 mg) on day-1 and day-2 and 300 mg on day-3.

Primaquine at a dose of 0.25 mg/kg (15 mg/day) for 14 days is to be added to prevent relapse. Primaquine is contraindicated in G6PD deficiency cases.

 Treatment of mixed infection (PF + PV): Artemisinin combination therapy to be given with PQ

 Treatment of unconfirmed but suspected uncomplicated PF malaria cases: Chloroquine should be used as advised for treatment of PV malaria.

TREATMENT OF SEVERE *PLASMODIUM FALCIPARUM*

 Parenteral artemisinin derivative or quinine should be promptly given to prevent death. Intravenous (IV) preparations are preferred.

 Artesunate: It is the drug of choice. It should be given in a dose of 2.4 mg/kg IV on admission (0 hour), then at 12 hours and 24 hours and then once daily till the patient takes orally or for 7 days. Then, they should get full course of ACT for 3 days. However,

ACT containing MQ should be avoided in cerebral malaria due to possibility of development of neuropsychiatric complication.

 Quinine: It is an acceptable alternative to AS. It should be given at a dose of 20 mg quinine salt/kg of body weight in 5% dextrose/ dextrose saline, over 4 hours, on admission.

 It is followed by 10 mg/kg of body weight 8 hourly infusions which should be started 8 hours after the 1st loading dose.

 The infusion rate should not exceed 5 mg/kg of body weight/hour.

 If, quinine therapy is used beyond 48 hours, the dose should be reduced to 7 mg/kg of body weight 8 hourly till patient takes orally.

 Then, he should be given oral quinine in a dose of 10 mg/kg of body weight 8 hourly to complete 7 days of therapy. Quinine injection must not be given as bolus injection. It is always given in IV infusion.

 Doxycycline in a dose of 3 mg/kg of body weight per day for 7 days is to be added when the patient starts taking orally.

 Artemether: It should be given in the dose of 3.2 mg/kg of body weight intramuscularly on admission and 1.6 mg/kg of body weight intramuscularly once per day for 4 more days. Then, ACT is to be given for 3 days

 Alpha-beta artemether: It should be given in a dose of 150 mg/day for 3 days intramuscularly. It should be followed by ACT for 3 days.

CHEMOPROPHYLAXIS

Short-term Prophylaxis (< 6 Weeks)

Doxycycline: 100 mg/day (1.5 mg/kg of body weight per day) to be started 2 days before and continued 4 weeks after leaving a malarias area.

Long-term Prophylaxis (> 6 Weeks)

Mefloquine: 250 mg weekly (5 mg/kg of body weight/week) to be started 2 weeks before going to the affected area and continued for 4 weeks after leaving the affected area. It is contraindicated in cases with history of convulsions, neuropsychiatric problems and cardiac conditions.

- **Malik M et al.,** carried out a qualitative study to explore the perceptions of medical practitioners regarding antimalarial prescribing practices. Semi-structured interviews were conducted using in-depth interview guides to collect data. The interviews focused on three major components, i.e., treatment practices in malaria and influencing factors, role of Malaria Control Program, and suggestions for improvements. Thematic content analysis of these components yielded further themes: (1) Prevalence of malaria, (2) Common trends of treatment, (3) Current scenario of rational drug use, (4) Major contributing factors to irrational drug use, (5) Use of antibiotics, (6) Role of healthcare system, (7) Role of Malaria Control Program, (8) Role of hospital pharmacist, (9) Collaborative efforts of doctors and pharmacists in promoting rational treatment practices, and (10) Strategies to improve current treatment practices. The current study showed that all the respondents in the two cities agreed that irrational prescribing

practices, unavailability of drugs, lack of awareness and adherence of prescribers to standard treatment guidelines, were the major factors contributes to irrational drug use in malaria in Pakistan [2].

- **Olurishe T O et al.,** conducted a retrospective study to evaluate the prescription pattern of antimalarials. The study indicated that the monotherapy with artemisinin was a more favored prescription practice over the ACT prescription advocated by the new national malaria policy. This study revealed that chloroquine was the most frequently prescribed followed by Sulphodoxine / Pyrimethamine combination. Artesunate was also largely prescribed as a monotherapy with the Artesunate/ amodiaquine combination as the highest ACT prescribed [5].
- **Mannan A. A. et al.,** carried out a facility based, cross sectional descriptive study to assess the antimalarial drug prescribing and dispensing practices of health care providers in health centers. A total of 720 patients and their prescriptions in 24 health centers were included. Prescribers adhered to national treatment guidelines for only 278 (38.6%) of patients. Although all were treated for malaria, only 64.6% had fever and positive blood films. More than 90% of prescriptions prescribed antimalarial drugs by generic names but dosage forms were correctly written in only 23.5%. There was a high rate of prescribing antimalarial injections [6].
- **Anvikar A. R. et al.,** conducted a study which was aimed at determiningthe in vitro sensitivity of P. falciparum isolates to antimalarials, in vitro activity of 108 P. falciparum

isolates obtained from five States of India was evaluatedusing WHO micro test (Mark III) to chloroquine, monodesethylamodiaquine, dihydroartesunate and mefloquine. In addition, representative samples from differentStates of India cryopreserved and culture adapted in the Malaria Parasite Bank of National Institute ofMalaria Research, New Delhi, were also evaluated and concluded that the Indian P. falciparum isolates showed a high degree of resistance to Chloroquine (44.4%) followed by Monodesethylamodiaquine (25%). No resistance was recorded to mefloquine and dihydroartesunate [7].

- **Meremikwu M M et al,.** an open-label, non-comparative therapeutic efficacy clinical trial carried out to assess the therapeutic efficacy, safety and tolerability of three dosage schedules of fixed-dose combination of artemisinin (125 mg) and naphthoquine (50 mg) for treating uncomplicated *Plasmodium falciparum* malaria among adolescents and adults in Calabar, South-east Nigeria. A total of 121 patients with uncomplicated *P. falciparum* malaria were enrolled and randomly assigned to three dosage schedules. A total of 108 patients completed the study. The overall 28-day cure rate was 88.9%. Day 28-cure rates of the three dosage schedules were 85.3%, 93.1% and 88.9% for Group A, B and C respectively. Adverse events were few and mild, the commonest being weakness and headache; there was no serious adverse event [9].

- **Batwala V et al,.** carried out a randomized feasibility trial to see the antibiotic use among patients with febrile illness in a low malaria endemicity. The proportion of patients who were prescribed antibiotics was calculated among those not tested for malaria, those who

tested positive and in those who tested negative. This study resulted seven thousand and forty (41.5%) patients in the presumptive arm were prescribed antibiotics. Of the patients not tested for malaria, 1,537 (23.9%) in microscopy arm and 810 (56.2%) in RDT arm were prescribed antibiotics. Among patients who tested positive for malaria, 845 (25.8%) were prescribed antibiotics in the RDT and 273(17.6%) in the microscopy arm. Among patients who tested negative for malaria, 7809 (61.4%) were prescribed antibiotics in the RDT and 3749 (39.3%) in the microscopy arm. Prescription of antibiotics in patients with febrile illness is high. Testing positive for malaria reduces antibiotic treatment but testing negative for malaria increases use of antibiotics [10].

- **Limbachia D M et al.,** conducted a retrospective, single –centric study to evaluate the prescribing pattern of antimalarial drug and to assess the adherence of antimalarial drugs and to explore the possibility of development of resistance with anti-malarial drugs. A total of 474 cases were collected 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%. This study showed that inappropriate use of antimalarials was high among patients with *P. falciparum*, clinical malaria and non-malarial patients. The percentage of incorrect drug prescribed is high when compared to those from guidelines for diagnosis and treatment of malaria in India 2011 [12].

- **Halchar S et al.,** a prospective and observational study was conducted to analyse the prescription pattern and cost of antimalarials in malaria. Out of 148 patients, a total number of 230 antimalarials were prescribed. Among 230 antimalarials the maximum number of prescriptions were with artesunate followed by primaquine, chloroquine, artemether+lumefantrine, quinine, Pyrimethamine+sulfadoxime and artesunate+pyrimethamine+sulfadoxime. The most preferred therapy was monotherapy followed by combination therapy. Out of 230 antimalarials prescribed, 224(97.40%) were prescribed with their brand name and 06(2.60%) were with generic name. In majority of the patients monotherapy was preferred over the combination therapy [13].
- **Ranjita et al.,** conducted a research to study the hepatotoxic effect of artesunate, an antimalarial drug on liver in wistar albino rats**.** Artesunate was administered at a dose of 36, 72 and 110mg/kg body weight intraperitonially respectively for 14 days in Wistar albino rats. The effect of artesunate on liver was assessed based on biochemical and histopathological analysis. There was a significant increase ($p<0.001$) in the levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyltransferase in serum. Histopathological analysis showed a pattern of

hepatocellular necrosis. The levels of superoxide dismutase and catalase in liver homogenate were also decreased significantly ($p<0.01$) in artesunate administered animals. The present study proved that artesunate has a potential to cause hepatic damage [17].

- **Thiam S et al,.** conducted a retrospective analysis of ADEs cases related to ACT as self-reported by patients at the health facilities. It was based on spontaneous reports of ADEs in public health facilities. Data on patient demographic characteristics, dispensing facility, adverse signs and symptoms and causality were collected from a total of 123 patients. Of the reported symptoms, 46.7% were related to the abdomen and the digestive system. Symptoms related to the nervous system, skin and subcutaneous tissue, circulatory and respiratory systems and general symptoms and signs were 7%, 9.7%, 3.5% and 31.3%, respectively. Causality results linked 14.3% of symptoms to FalcimonW (Artesunate-Amodiaquine) with certainty. Effects were classified as mild and severe in 69.1% and 7.3 % of cases respectively and 23.6% were serious and were hospitalized. One death was reported in patient who had taken 24 pills at once. This study demonstrates the feasibility and the need to set up a safety monitoring system for anti-malarial drugs within a national pharmacovigilance system [18].
- **Njau J D et al.,** carried out an active and passive surveillance to identify ADR from Sulphodoxine –Pyrimethamine (SP) and artemisinin use. Patients were classified as having ‘possible’ or ‘probable’ ADR by a physician. A total of 95 suspected ADR were identified, of which 79 were traced and 67 reported use of SP and /or AS prior to ADR

onset. 34 cases were classified as probable and possible ADRs. Most cases were associated with SP monotherapy, 13 with the AS/SP combination and one with AS monotherapy. Both passive and active surveillance methods proved to be feasible for carrying out SP and/or AS related ADR surveillance. Active surveillance provided an important complement to the health facility-based passive surveillance, given the widespread practice of self-medication in Tanzania [19].

- **Obonyo C O et al.,** conducted a randomized controlled trials to assess the efficacy of clindamycin plus quinine versus other anti-malarial drugs in the treatment of uncomplicated *falciparum* malaria. Two authors independently assessed study eligibility, extracted data and assessed methodological quality. The primary outcome measure was treatment failure by day 28. Dichotomous data was compared using risk ratio (RR), in a fixed effects model. Seven trials with 929 participants were included. Clindamycin plus quinine significantly reduced the risk of day 28 treatment failure compared with quinine, quinine plus sulphadoxine- pyrimethamine, amodiaquine, or chloroquine, but had similar efficacy compared with quinine plus tetracycline, quinine plus doxycycline, artesunate plus clindamycin, or chloroquine plus clindamycin. Adverse events were similar across treatment groups but were poorly reported [20].
- **Builders M I et al.,** carried out a descriptive cross sectional survey to assess the pattern of antimalarial drug use among the patients attending the teaching hospital in Jos North local Government of Nigeria. Sample size of 441 male and female patients was selected Four hundred and forty one (441) patients completed the questionnaire. Almost all the

patients were able to describe the causes and symptoms of malaria. One hundred and sixty nine (38.3%) frequently treated their malaria with Sulphadoxine-Pyrimethamine (SP) combination, Three hundred and eighty two (86.6%) reported to have used oral preparation, almost half of the respondents (47.6%) obtained these medications from many sources apart from hospitals, only two hundred and forty eight reported to comply to treatment. And concluded that **c**oncerted effort should be made to educate the population on malaria as-well as the importance of drug adherence [23].

- **Olasehinde G I et al.,** carried out a research work on In vitro studies on the sensitivity pattern of *Plasmodium falciparum* to anti-malarial drugs and local herbal extracts, in which Sensitivity pattern of 100 *Plasmodium falciparum* isolates were resistance to chloroquine (51%), amodiaquine (13%), sulphadoxine/Pyrimethamine (5%) was determined using the in vitro microtest (Mark III) technique to determine the IC50 of the drugs. All the isolates tested were sensitive to quinine, mefloquine and artesunate. A positive correlation was observed between the responses to artemisinin and mefloquine ($P<0.05$), artemisinin and quinine ($P<0.05$) and quinine and mefloquine ($P<0.05$). A negative correlation was observed between the responses to chloroquine and mefloquine ($P>0.05$). Highest anti-plasmodial activity of natural herbs was obtained with the ethanolic extract of D. monbuttensis (IC50 = 3.2nM) while the lowest was obtained from M. lucida (IC50 =25nM).this study concludes that natural products isolated from plants used in traditional medicine, which have potent anti-plasmodial action in vitro, represent potential sources of new anti-malarial drugs [24].

- **Muddaiah M et al.,** A retrospective study on clinical profile of malaria a total of 314 patients were diagnosed and treated for malaria, of them 124 were treated as outpatients and 190 cases were managed as inpatients. Males (81%) out numbered females (19%) and many were within the age group of 21–30 yr. The incidence of malaria increased from the month of June onwards coinciding the monsoon season. *Plasmodium vivax* was the major parasite type (52.54%), followed by *P. falciparum* (33.75%), mixed malarial infection (13.69%) and most of them received combination therapy. Hepatopathy was the most common complication and all the deaths were due to cerebral malaria. *P. vivax* was the major parasite type causing malaria and most of the complications were due to *P. falciparum* [25].
- **Builders M I et al.,** A retrospective quantitative study was designed to examine Prescription Pattern of Antimalarial Drugs, in which case record files of 130 patients were selected, 80.7% of the patients were prescribed antimalarial drugs. 55.2% of patients admitted for malaria were males, 44.8% were between 21-50 years of age. Fever (35.2%) was the most common presenting symptom, 71.4% of the patients had diagnostic blood slides. Antimalarial drugs were prescribed for malaria and malaria associated with other disease conditions, artemisinin and lumefantrine was the most prescribed antimalarial agent. 44.0% of these drugs were prescribed by trade names, 29.0% were administered orally, all the practitioners followed current WHO guidelines , half of the clinicians would prescribe parenteral antimalarial drugs for severe and cerebral malaria,

laboratory and clinical assessment were used for malaria diagnosis, 71.4% of the physicians adhered to hospital guidelines[26].

- **Meremikwu M et al.,**a descriptive study was conducted to assess prescribing for uncomplicated malaria in government and private health facilities. Malaria blood slides were only performed in 45% of patients, with no difference between private and public sector. Almost all who were screened for parasites were positive, probably because positive parasitaemia was a criterion for case definition of malaria in this study. Most cases were with a low parasitaemia. Overall, 45% of patients had a diagnostic blood slides; 77% were prescribed monotherapy, either chloroquine (30.2%), sulphadoxine-pyrimethamine (22.7%) or artemisinin derivatives alone (15.8%). Some 20.8% were prescribed combination therapy; the commonest was chloroquine with sulphadoxine-pyrimethamine. A few patients (3.5%) were prescribed sulphadoxine-pyrimethamine-mefloquine in the private sector, and only 3.0% patients were prescribed artemisinin combination treatments. The study concluded that malaria treatments were varied, but there were not large differences between the public and private sector. Very few are following current WHO guidelines. Use of monotherapy with artemisinin derivatives was relatively common [27].
- **Mubeen F et al.,** conducted a retrospective case record, to analyze the use of antimalarial agents in treatment of Malaria diagnosed patients. A total sample size was 478 and pattern of Uncomplicated and complicated Malarial Parasite Infection was evaluated. Study suggested that First line therapy for falciparum malaria may need reconsideration.

There is increased use of artemisinin as first line drugs, irrespective of the causative agent for malaria. The use of primaquine for all types of malaria is also on the increase and this practice must be curbed too [28].

Chapter- IV

Methodology

METHODOLOGY

STUDY SITE

This study was conducted at Adichunchanagiri Hospital and Research Center (AH&RC), B.G.Nagara. It is a 1050 bedded tertiary care teaching hospital having emergency department, ICCU, ICU, PICU and different specialties like medicine, surgery, orthopedics, obstetrics and gynecology. Approximately from all departments 200-250 patients are being treated every day. This hospital provides specialized health care services to the rural population in and around B.G.Nagara.

STUDY DESIGN

This was a prospective and observational study.

STUDY PERIOD

The study was conducted over a period of 9 months.

STUDY CRITERIA

Inclusion Criteria:

- All in-patients of general medicine who have prescribed with antimalarials and willing to participate in the study.
- Patients of above 18 years and of either sex admitted in the general medicine department.

Exclusion Criteria:

- Pregnant/lactating women.

METHODOLOGY

MATERIALS USED:

- Patient profile form
- Specially designed data collection form
- Patient consent form

SOURCE OF DATA

Demographic details of the patient was obtained from the patient case records, medication charts and laboratory data reports and other relevant source.

STUDY PROCEDURE

Patients who satisfied the inclusion criteria were enrolled after taking their written consent (ANNEXURE IV). The drug therapy of enrolled patients were routinely monitored, interviewed whenever necessary and discussed with the physician regarding therapy. Their specific demographic details (name, age, gender, and address), past medical history, laboratory investigations and other relevant details were collected in a specially designed 'Data Collection Form' (ANNEXURE II) and analysed.

The analysis of prescribed antimalarials, antibiotics used were carried out by using standard sources like articles, journals, Micromedex, CIMS and other relevant sources. Severity of ADRs were assessed using NARANJO's causality assessment scale.

RESEARCH AND ETHICAL COMMITTEE APROVAL

The Study was approved by the Institutional research and ethical committee of AH &RC, B.G.Nagara.

STATISTICAL METHODS

Data was analysed for frequency and percentage by descriptive statistical analysis using IBM SPSS 20 software.

Chapter -V

Results

RESULTS

A total of 112 patients were enrolled into the study in which 68(60.7%) were male patients and 44(39.3%) were female patients.

TABLE 4: GENDER AND AGE WISE DISTRIBUTION

DEMOGRAPHICS	CATEGORY	NO. OF PATIENTS (%)
Gender	Male	68(60.7)
	Female	44(39.3)
Age	18-35	51(45.5)
	36-55	37(33.0)
	>55	24(21.4)

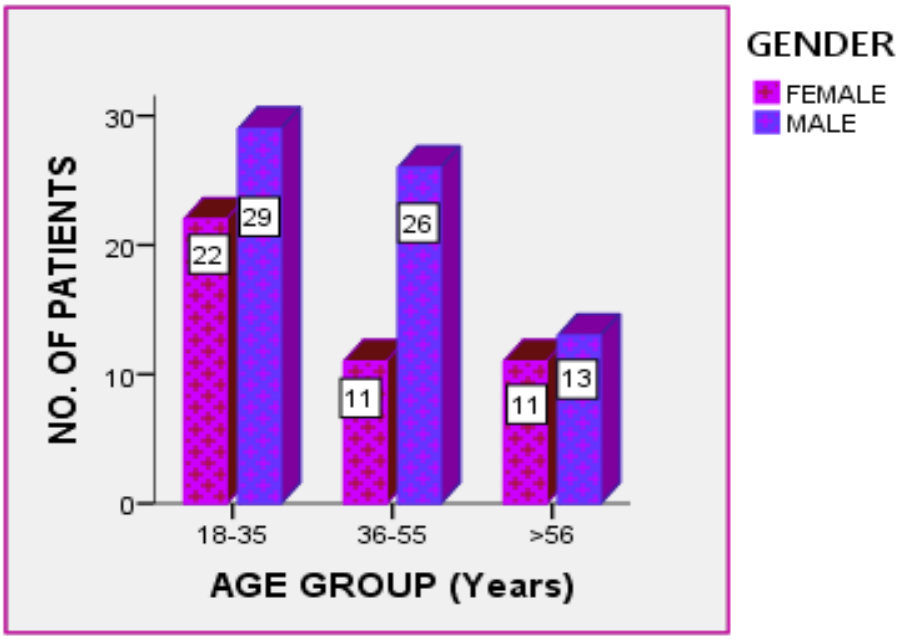


FIGURE 2: Gender and age wise distribution in the study population

TABLE 5: DISTRIBUTION OF TYPE OF MALARIAL CASES

TYPE OF MALARIA	NO. OF PATIENTS (%)
Clinical malaria	85(75.9)
P.vivax	25(22.3)
P.falciparum	2(1.8)
Total	112(100.0)

Clinical malaria cases were 85(75.9%), *P.vivax* cases were 25(22.3%) and 2(1.8%) were *P.falciparum* malaria.

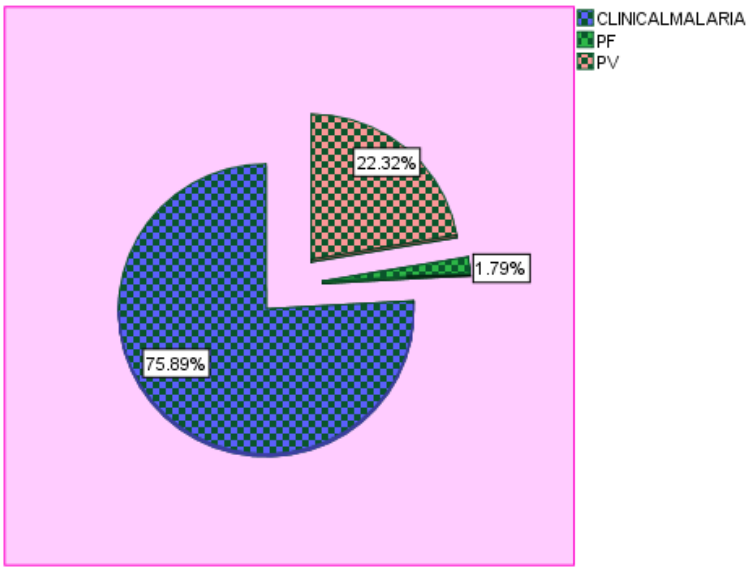


FIGURE 3: Types of malaria in the study population.

TABLE 6: PATTERN OF ANTIMALARIALS USED IN MALARIA

ANTIMALARIAL USED	TYPE OF MALARIA			TOTAL NO. OF PATIENTS (%)
	P.vivax	*P.falciparum*	Clinical Malaria	
Artesunate	11	1	29	41 (36.6)
Artesunate+Mefloquine	6	1	27	34 (30.4)
Artesunate+SP	2	0	9	11 (9.8)
Chloroquine	2	0	16	18 (16.1)
Artesunate & Primaquine	2	0	1	3 (2.7)
Artesunate+SP&Primaquine	1	0	1	2 (1.8)
Artesunate+Mefloquine &Chloroquine	0	0	1	1 (0.9)
Artesunate&Chloroquine	1	0	1	2 (1.8)
Total	25	2	85	112 (100)

Table 3 shows used of antimalarials in malaria. Most commonly used antimalarial was artesunate 41(36.6%) in 112 study population. In which 29 cases were clinical malaria, 11 were *P. vivax*, and one was with *P.falciparum* malaria. Fixed dose combination of Artesunate+Mefloquine was used in 34(30.4%) of the cases where, 27 were clinical malaria, 6 were *P. vivax*, one was with *P.falciparum* malaria. And 18 (16.1%) cases were treated with CQ among them, 16 were clinical malaria patients followed by two *P. vivax* patients.

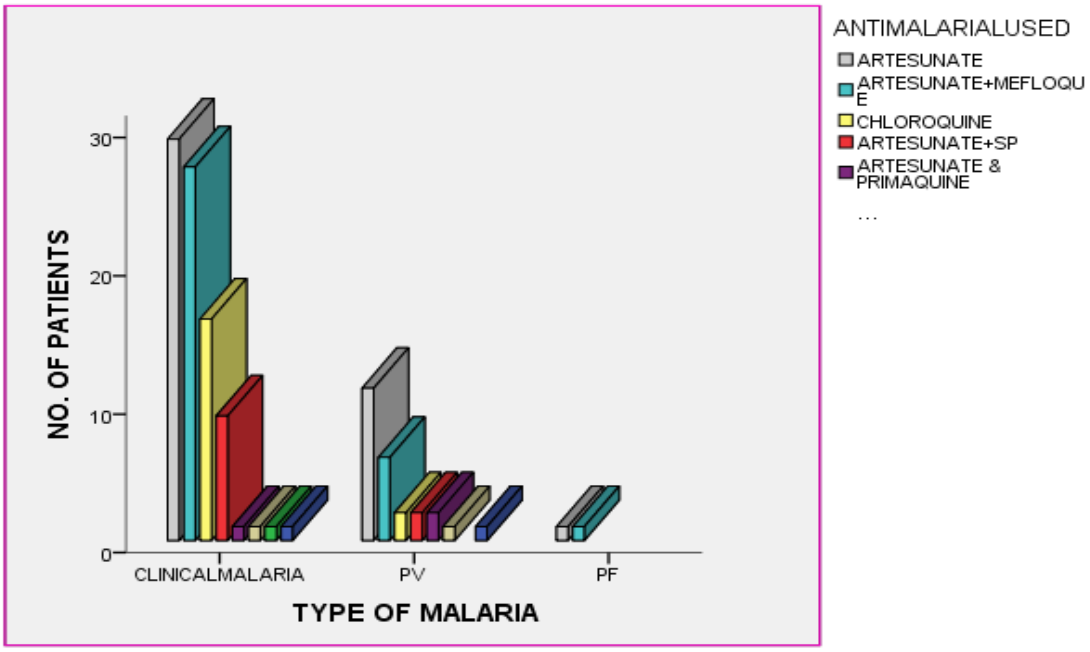


FIGURE 4: Represents commonly used antimalarials in malaria.

TABLE 7: FREQUENCY OF ANTIBIOTICS USED IN MALARIA.

Antibiotic	Clinical malaria	*P. vivax*	*P. falciparum*
Ceftriaxone	74	18	2
Cefoperazone+Salbactum	2	0	0
Nitrofurantoin	5	1	0
Cefixime	2	0	0
Levofloxacin	4	1	0
Cefpodoxime	1	0	0
Piperacillint+Azobactum	17	3	0
Amikacin	3	3	0
Doxycycline	18	6	0
Ceftriaxone+Salbactum	6	3	0

Azitromycin	3	1	0
Norfloxacin	2	0	0
Ofloxacin+Ornidazole	2	0	0
Ciprofloxacin	2	1	0
Ampicillin	1	0	0
Meropenum	1	0	0
Cefotaxime	1	1	0

TABLE 8: DETAILS OF TYPES OF THERAPY

THERAPY	CLINICAL MALARIA	*P. vivax*	*P. falciparum*	TOTAL NO.OF PATIENTS
MONOTHERAPY	46	16	1	63 (56.2%)
COMBINATIONTHERAPY	39	9	1	49 (43.8%)
TOTAL % WITH IN TYPE OF MALARIA	75.9%	22.3%	1.8%	112 (100%)

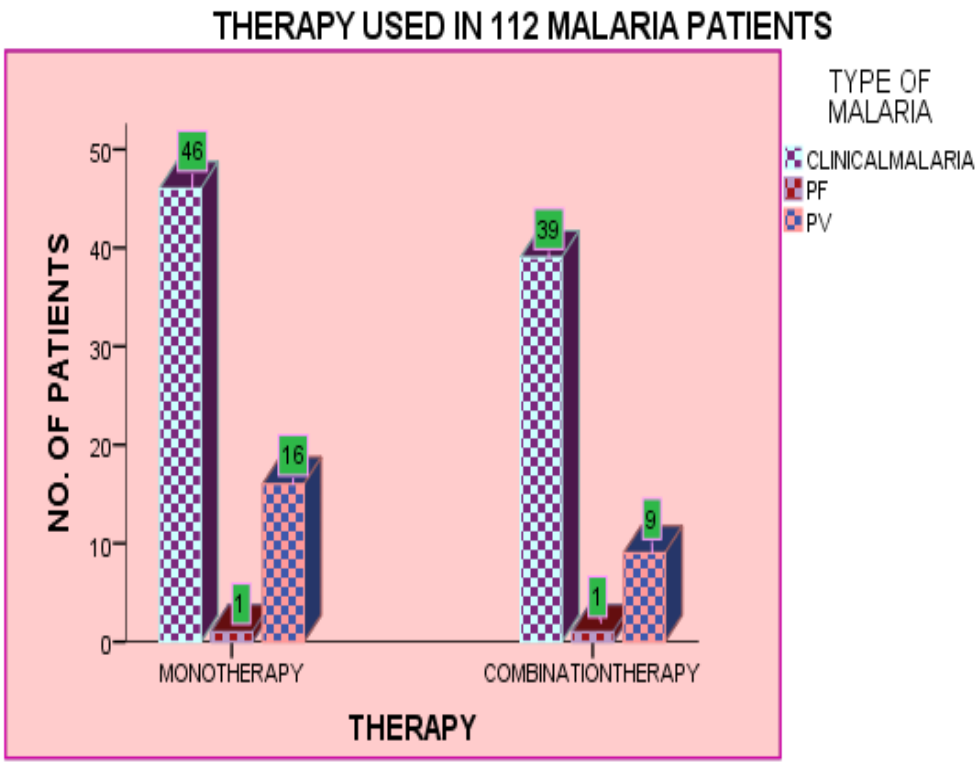


FIGURE 5: Represents details of types of therapy.

TABLE 9: DETAILS OF TREATMENT IN ENROLLED POPULATIONS

TREATMENT	NO. OF PATIENTS (%)
Empirical	85(75.9)
Specific	27(24.1)

Out of 112 patients only 27 (24.11%) of patients received specific treatment for fever diagnosed as malaria rest of all are treated empirically 85(75.9%) which has been diagnosed as clinical malaria.

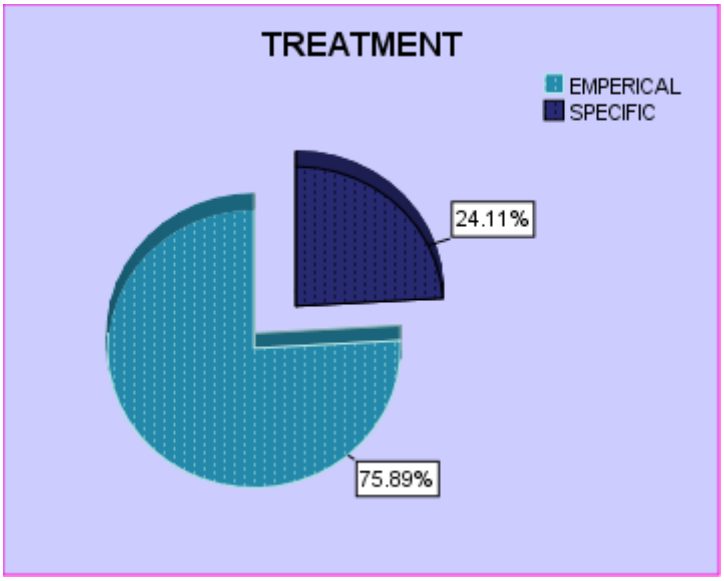


Figure 6: Chart representing type of treatment received by study populations.

TABLE 10: PATIENTS DISTRIBUTION ON ADR

ADR	NO. OF PATIENTS (%)
No	98(87.5)
Yes	14(12.5)
Total	112(100.0)

Adverse drug reaction documented in this study population YES 14(12.5%) and NO 98(87.5%).

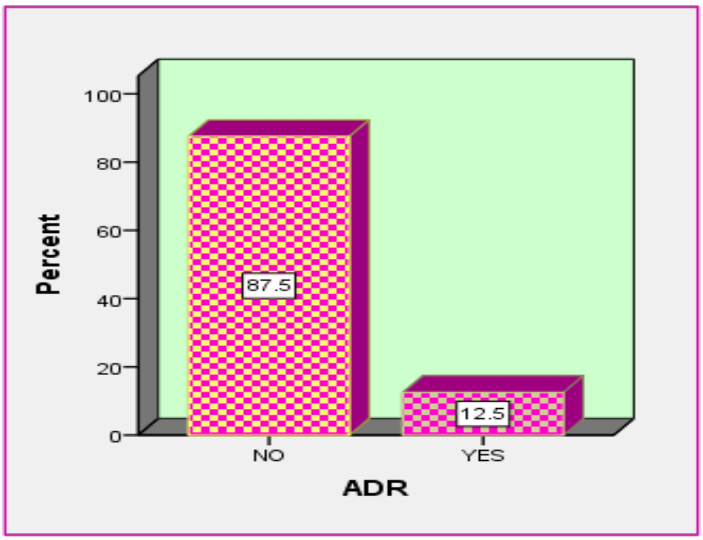


Figure7: Figure showing percentage of ADR incidences in the study population

Table 11: SEVERITY OF ADR

SEVERITY OF ADR	NO. OF PATIENTS [%]
Probable	2(14.2%)
Possible	12(85.7%)
Total no. of ADR	14(100%)

Out of 112 patients 14 ADR's categorized on severity- possible 12(85.7%) and probable 2(14.2%) identified and documented.

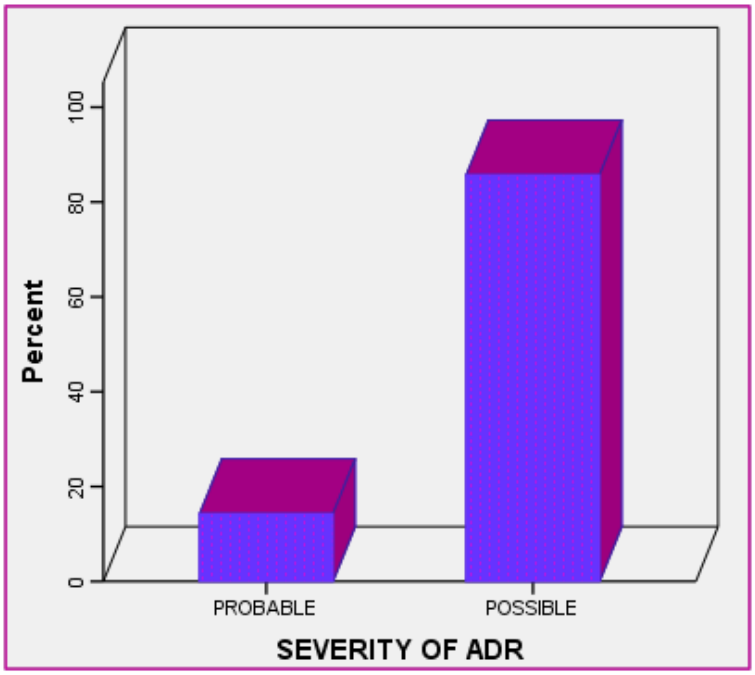


Figure 8: Illustration of severity of ADR in the patients.

TABLE 12: ADVERSE DRUG REACTIONS

ADVERSE DRUG REACTION	NO. OF PATIENTS	PERCENTAGE (%)
Nausea & Vomiting	9	8.0
Reversible Increase In Serum Transaminases	3	2.7
Bad Taste, Rash, Vomiting	2	1.8
Total ADR	14	12.5
Total Patients	112	100.0

According to the study, 14 ADRs were identified among 112 patients in which nausea and vomiting was in 9(8%) patients, reversible increase in Serum transaminases and bad taste, rash, vomiting was observed in 3 and 2 patients respectively.

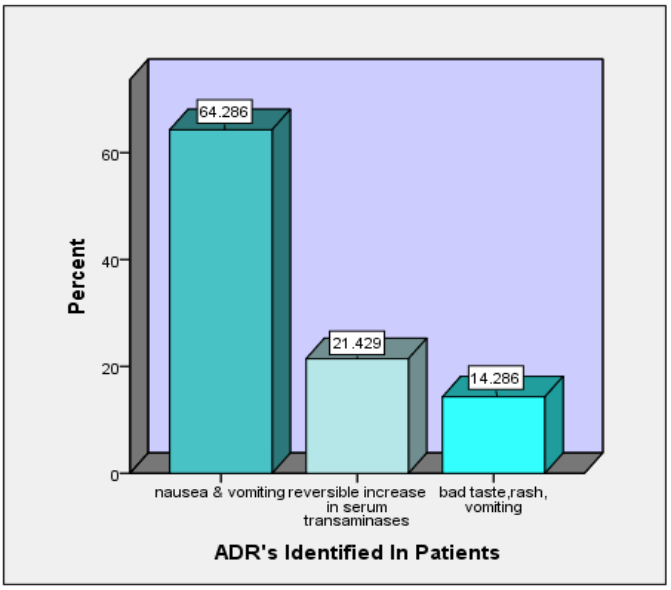


FIGURE 9: Graph showing percentage of ADRs identified in study populations.

TABLE 13: ADRS ACCEPTED BY PHYSICIANS

Physician Acceptance	ADRs (n=14) [%]
Yes	10[71.4]
No	04[28.5]

TABLE 14: ACTION TAKEN BY PHYSICIAN

Action Taken	Accepted ADRs (n=6) [%]
Additional treatment given	5(83.3%)
Drug stopped	0
Dosage altered	0
Monitor functional test	1(1.6%)

TABLE 15: DETAILS OF DRUGS CAUSING ADR AND ITS MANAGEMENT

Drug	ADR	Naranjo's scale	Management
Artesunate	Nausea and vomiting	Possible	Inj. Ondansetron, 4mg, IV, BD
Artesunate	Reversible Increase In Serum Transaminases	Probable	Monitored liver enzymes
CQ	Bad taste, rash on hands, vomiting	Possible	Cap.Pantoprazole + Domperidone
Artesunate + SP	Nausea and vomiting	Possible	Cap. Pantoprazole+Domperidone

Chapter-VI

Discussion

DISCUSSION

Malaria is a complex disease that vary in epidemiology, clinical signs and symptoms in different parts of the world this is the result of factors such as the species of malaria parasite, commonly used antimalarials, nature of mosquito vectors to the environment level and immunity acquired by the exposed human population. Prescribing pattern of the physicians has influence the emergence of drug resistance to antimalarials. This study which seeks evaluation, monitoring of the prescribing practice to achieve rational use of antimalarials and to prevent emergence of drug resistance to newer antimalarials.

Malaria is clinically suspected mostly on the basis of fever or a history of fever. Diagnosis based on clinical features alone has very low specificity and results in over-treatment. Other possible causes of fever and the need for alternative or additional treatment must always be carefully considered. The WHO recommendations for clinical diagnosis/suspicion of uncomplicated malaria in different epidemiological settings are as follows: in settings where the risk of malaria is low, clinical diagnosis of uncomplicated malaria should be based on the possibility of exposure to malaria and a history of fever in the previous three days with no features of other severe diseases; in settings where the risk of malaria is high, clinical diagnosis should be based on a history of fever in the previous 24 h and/or the presence of anaemia, for which pallor of the palms appears [1].

In all settings, clinical suspicion of malaria should be confirmed with a parasitological diagnosis. However, in settings where parasitological diagnosis is not possible, the decision to provide antimalarial treatment must be based on the prior probability of the illness being malaria. Other possible causes of fever and need for alternative treatment must always be carefully considered [14].

DISCUSSION

Demographic details:

Prescribing pattern of antimalarials is studied in the 112 in-patients in the study site. The demographic study [Table 4] shows that, 68(60.7%) were male and 44(39.3%) were female patients. The findings were similar to the study conducted in Nigeria reports male (55.2%) than female(44.8%) that malaria is not associated with the gender but it merely reflects the sex distribution in the study population or an indication of a less immunity developed by the male patients [26]. The incidence rate is high in 51(45.5%) age group of younger adults between 18-35 age group followed by, 37(33.0%) were of older adults in 36-55 age group and 24(21.4%) patients were elderly above 55 of age. Similar findings was observed in Gulbarga, study conducted by Halchar S et al., which shows 65 patients were in the 18-30 age group who were diagnosed with malaria. This shows that the prevalence of malaria is more commonly seen in males than female patients and in the younger adult group [13]. Factors like socio-economic differences, exposure to infectious environment influence prevalence of malaria in the study population.

In this study, the cases are categorized as clinical malaria 85(75.9%), followed by *P.vivax* 25(22.3%) and *P.falciparum* 2(1.8%) malaria. Clinical malaria is non-specific in nature and reliable diagnosis cannot be made on the basis of signs and symptoms but, where malaria is prevalent, clinical malaria diagnosis results in all fever cases and in endemic areas presumptive clinical diagnosis is the only realistic option [12] and this relays on presumptive treatment for malaria.

DISCUSSION

A study conducted in Nigeria, shows that the one-fifth (28.6%) out of 105 study population are treated on the basis of clinical signs and symptoms. This type of diagnosis and treatment leads to miss-classify patients who may not require the treatment and leads to over use of the drug & drug resistance [26].

Pattern of antimalarials used in malaria:

Current study shows that the most commonly prescribed antimalarial was artesunate 41(36.6%) in 112 study population. In which 29 cases were clinical malaria, 11 were *P. vivax*, and one was with *P.falciparum* malaria. Fixed dose combination of Artesunate+Mefloquine was used in 34(30.4%) of patients where, 27 were clinical malaria, 6 were *P. vivax*, one was with *P.falciparum* malaria. 18 (16.1%) cases were treated with Chloroquine among them, 16 were clinical malaria patients followed by *P. vivax* two patients.

In our study we observed that, Chloroquine was prescribed after artesunate therapy in a *P. vivax* and a clinical malarial patients and also after Artesunate+Mefloquine therapy in one of the clinical malarial patient. Artesunate & Primaquine was given in 3 (2.7%) patient. Artesunate+SP & Primaquine 2 (1.8%) was given in*P. vivax* and clinical malaria patients.

WHO recommends that uncomplicated *P. falciparum* malaria should be treated with an ACT. In areas where chloroquine is still effective, *P. vivax* malaria should be treated with this drug. Where resistance to chloroquine has been documented, *P. vivax* malaria should be treated with an appropriate ACT. To prevent relapses, both chloroquine and ACT should be combined with a 14-day course of primaquine, subject to consideration of the risk of haemolysis in patients with

glucose-6-phosphate dehydrogenase (G6PD) deficiency [1]. In our study 2.7% are treated accordingly to prevent relapse of fever.

In this study, 75.9%of the patients are diagnosed as clinical malaria and treated empirically, whose test for malarial parasite was negative and 24.1% patients were diagnosed with specific parasite and treated. Details of types of treatment given is shown in Table 8.

Antibiotics used in malaria:

In this study out of 112 patients antibiotics were prescribed in all patients. In that most frequently prescribed antibiotic was Ceftriaxone, it was used in 74 clinical malaria, 18 *P.vivax* and *P.falciparum* in two malaria cases. Doxycycline which is a derivative of tetracycline is used commonly next to Ceftriaxone, in 18 clinical malaria and in 6 *P.vivax*. Piperacillint+Azobactum was given in 17 patients with clinical malaria and in 3 *P.vivax* malaria. And other antibiotics prescribed (43%) in all cases of malaria were quinolones, macrolides, other cephalosporin's, penicillin's, aminoglycosides.

The findings were similar to the study conducted by Batwala et al.,showed that the rate of antibiotic treatment was high in negative malarial cases, reduction of use of antibiotics positive malarial cases [10]. Drugs with different mechanism of action, different therapeutic efficacy and half- life combined with antimalarials significantly improve the therapeutic efficacy of the treatment. Over prescription of antibiotics with antimalarials can lead to drug-drug interaction, adverse drug reaction and may cause drug resistance.

Therapy

In 112 patients monotherapy was seen in 63 (56.2%) patients, among them 46 were clinical malaria cases, 16 were P. vivax and one was *P. falciparum*. Combination therapy was observed in 49 (43.8%) patients where, 39 clinical malaria cases, 9 were *P. vivax* & one *P.falciparum* malarial patients.

Artemisinin derivatives used in combination of other antimalarials (Mefloquine, SP, Amodiaquine) which have long acting action can reduce the parasite densities to lower level with the minimum time and also artemisinin drugs reduces gametogenesis by 8-18 fold. This reduces the gametocytes carrying resistance genes capacity and potentially decreases the malaria transmission rates [1].

Adverse drug reactions

Adverse drug reaction was observed in 14(12.5%) patients out of 112 cases with antimalarial treatment. Out of 14 ADR's possible ADR was seen in 12(10.7%) and probable in 2(1.8%) nature which has been assessed by NARANGO's causality assessment scale. Nausea and vomiting was found in 9(8%) patients, reversible increase in Serum transaminases and bad taste, rash, vomiting was observed in 3(2.7%) and 2(1.8%) patients respectively. ADRs occurred during the hospital stay were managed by giving additional treatment and drug was not withdrawn, dose was not altered and functional test was monitored.

All the ADRs were reported to the physicians among 14 ADRs 10[71.4%] were accepted and took necessary action for the management after clinical pharmacist recommendation, in which

additional treatment was given in 6(60%) out of 10. Inj. Ondansetron (4mg, IV, BD) and cap. Pantoprazole+Domperidone (40+10 mg, OD) were used in the additional treatment for management of ADR.

Chapter -VII

Conclusion

CONCLUSION

- The medical and social burden of malaria is enormous due to irrational prescribing practices, increased drug resistance.
- For appropriate selection of antimalarial and antibiotic treatment proper diagnosis and standard guideline is required.
- Specific hospital guideline should be developed so that selection of antimalarials in specific malarial species can be done rationally.

Chapter-VIII

Summary

SUMMARY

The study concludes that males were more infected by malaria than female patients. The incidence was more in the age group between 18-35 years than in older adults and elder patients. All the cases with negative parasite test are considered as 'clinical malaria', they were treated empirically and positive cases were given specific treatment.

There is no hospital guideline for the treatment of malaria, physicians followed their own protocol to treat malaria. Most of them followed WHO guideline than National guidelines. The most commonly used antimalarial was found to be Artesunate, followed by Artesunate+Mefloquine and CQ. Total antibiotic used in 112 patients was 182 among them (51.6%) Ceftriaxone was used in 84.7% patients followed by Doxycycline (13.2%) in 21.6% of patients. It was noted that monotherapy was most preferred than combination therapy.

The incidence of ADR in our study was found to be less. Out of 14 ADRs physician accepted in 10 ADRs and necessary action for the management was taken after clinical pharmacist recommendation. In our study we found that, there was no proper diagnosis of malaria parasite which leads to improper use of antimalarials. This can cause miss-use of antimalarials and antibiotics which will be the main cause of ADRs and emergence of drug resistance.

Chapter- IX

Limitations

LIMITATIONS

- The sample size of the malaria patient admitted to the hospital during the study period was less.
- By conducting the study at different hospital setting and increase the sample size results can be interpreted more accurately.
- Blood sample for smear for malaria parasite test was not collected when there is relapse of fever in the patient. Accurate diagnosis of the parasite species results in rational drug use. But, this was the major limitation in the study.
- The study was conducted in adult patients only, paediatric and pregnancy/lactating patients were not included.

Chapter- X

Future Directions

FUTURE DIRECTIONS

- Similar study can be conducted in paediatrics, OBG, and orthopaedics departments of the hospital and in community settings.
- Pharmacoeconomics and drug resistance pattern can be studied with antimalarials.
- The study can be extended for longer study period for accurate results.

Chapter- XI

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Chapter- XII

Annexure

Annexure - II

II Jai Sri Gurudev II

Sri Adichunchanagiri College of Pharmacy

Department of Clinical Pharmacy

Adichunchanagiri Hospital and Research Centre, B.G.Nagara-571488

PATIENT DATA COLLECTION FORM

RESEARCH TITLE: "A Study on Antimalarial Prescription Pattern in Rural Tertiary Care Teaching Hospital"

PATIENT DETAILS:

Name: Age: yrs. Gender: M / F Weight: kgs.

IP. No: OP No. Unit: DOA: DOD:

REASON FOR ADMISSION:

PAST MEDICAL AND MEDICATION HISTORY:

ANY ALLERGIC REACTION:

LAB INVESTIGATIONS:

Annexure - II

Malaria type:

DIAGNOSIS:

DETAILS OF DRUG THERAPY

Drugs	Dose	Route	Freq	Started Date	End Date

Class of Drugs Prescribed **Indication of each drug**

Annexure - II

TREATMENT

EMPIRICAL THERAPY _____ SPECIFIC THERAPY_____

SUSPECTED PATHOGENS.....

Guideline Followed:

Monotherapy or Combination Therapy:

ADVERSE DRUG REACTION IF ANY:

- Is there any adverse drug reaction identified? Yes ____ No ____
- Documentation: Mild/ Moderate/ Severe
- ADR assessment scale: WHO Scale Narnjo scale

Associated Drug Description of ADR

Name and Signature of the student Signature of the Guide

Annexure - III

PATIENT CONSENT FORM

I, …… have been explained by the investigators Mr. M. Kumaraswamy / Mrs. Jamuna T. R. about the "A Study on Antimalarial Prescription Pattern in Rural Tertiary Care Teaching Hospital"

I am above 18 years of age and hereby give my consent to be included as a participant in this study.

1. I have been explained about the nature of the study.
2. I have informed the investigator of all the treatments I am taking or have taken in the past……. months including any alternative treatments.
3. I have the option to withdraw from the trial at any stage.
4. I have been answered to my questions by the investigator about the study.
5. I have decided to be in the research study.

I am aware, that if I have any questions during this study, I should contact at any of the above investigators.

Place:- Name:_____

Thumb impression/Signature

Date:-

Witness:-

1)

2)

Annexure - IV

|| ಜೈ ಶ್ರೀ ಗುರುದೇವ್ ||

ಶ್ರೀ ಆದಿಚುಂಚನಗಿರಿ ಫಾರ್ಮಸಿ ಕಾಲೇಜು, ಕ್ಲಿನಿಕಲ್ ಫಾರ್ಮಸಿ ಇಲಾಖೆ
ಶ್ರೀ ಆದಿಚುಂಚನಗಿರಿ ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ
ಬಿ.ಜಿ ನಗರ–571448

ರೋಗಿಯ ಒಪ್ಪಿಗೆ ಪತ್ರ

ನಾನು.....

..... "ಗ್ರಾಮೀಣ ತೃತೀಯ ಆರೈಕೆ ಭೋಧನ ಆಸ್ಪತ್ರೆಯಲ್ಲಿ ಮಲೇರಿಯಾ ನಿರೋಧಕ ಶೀಫಾರಸು ಮಾದರಿಯಲ್ಲಿ ಒಂದು ಆಧ್ಯಯನ" ದ ಬಗ್ಗೆ ಸಂಶೋಧಕರಾದ ಶ್ರೀ ಎಂ. ಕುಮಾರಸ್ವಾಮಿ/ ಶ್ರೀಮತಿ ಜಮುನ ಟಿ.ಆರ್ ನನಗೆ ವಿವರಿಸಿರುತ್ತಾರೆ.

1.ನಾನು 18 ವರ್ಷ ಮೇಲ್ಪಟ್ಟಿದ್ದು, ನನ್ನ ಸ್ವ ಇಚ್ಛೆಯಿಂದ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಗೆ ನೀಡಿರುತ್ತೇನೆ.

2. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆಯು ನನಗೆ ಲಾಭವಾಗಬಹುದು ಅಥವಾ ಲಾಭವಾಗಿರಬಹುದು ಎಂಬುದನ್ನು ತಿಳಿದುಕೊಂಡಿರುತ್ತೇನೆ.

3. ಇದರ ಸಾಮಾನ್ಯ ಉದ್ದೇಶ, ಸಂಭವನೀಯ ಪ್ರಯೋಜನಗಳು, ಅಪಾಯಗಳು ಮತ್ತು ಅನಾನುಕೂಲಗಳ ಬಗ್ಗೆ ನನಗೆ ಸಂತೃಪ್ತಿ ಆಗುವ ಮಟ್ಟಿಗೆ ವಿವರಿಸಲಾಗಿದೆ .

4. ನಾನು ಯಾವುದೇ ಹಂತದಲ್ಲಿ ಈ ಅಧ್ಯಯನದಿಂದ ನಿರ್ಗಮಿಸುವ ಹಕ್ಕು ನನಗಿದೆ ಎಂಬುದನ್ನು ಅರಿತಿದ್ದೇನೆ.

5. ಈ ಮೂಲಕ ನಾನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಸಮ್ಮತಿ ನೀಡಿರುತ್ತೇನೆ.

ನಾನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಯಾವುದೇ ಪ್ರಶ್ನೆಗಳನ್ನು ಹೊಂದಿದ್ದರೆ ನಾನು ಮೇಲಿನ ತನಿಕೆಗಾರರನ್ನು ಸಂಪರ್ಕಿಸ ಬೇಕು ಎಂಬ ಅರಿವಿದೆ.

ರೋಗಿಯ ಹೆಸರು: ಸಹಿ/ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು ;

ಸಾಕ್ಷಿದಾರರು ಅಥವಾ ರೋಗಿಯ ಸಂಬಂಧಿಕರ ಹೆಸರು: ಸಹಿ / ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು:

ಸ್ಥಳ:

ದಿನಾಂಕ:

|| Jai Sri Gurudev ||
Sri Adichunchanagiri Shikshana Trust (R)
Adichunchanagiri Institute of Medical Sciences
(Recognised by Medical Council of India, New Delhi, General Medical Council, London (U.K.) &Affiliated to Rajiv Gandhi University of Health Sciences, Karnataka)

No. AIMS/IEC/ 1040 /2014-15 Date: 16-07-2014

CERTIFICATE

This is to certify that the M. Pharm. research project titled **"A study on antimalarial prescribing pattern in rural tertiary care teaching hospital"** to be submitted to the Rajiv Gandhi University of Health Sciences, Bengaluru, and to be conducted by the research scholar Ms. Jamuna T R, under the guidance of Mr. M Kumaraswamy, Associate Professor, Department of Pharmacy practice, SAC College of Pharmacy, BG Nagara, Mandya, Karnataka - 571448 has been discussed and approved by the Institutional Ethical Committee, Adichunchanagiri Institute of Medical Sciences, BG Nagara, Mandya, Karnataka - 571448 on 14th July 2014.

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