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Research Article

A TEN YEAR STUDY OF THE MANAGEMENT OF MALARIA AT A TERTIARY HOSPITAL IN SOUTH WEST NIGERIA.

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ABSTRACT

This retrospective study was carried out to investigate drug management pattern of malaria among patients admitted at the University College Hospital Ibadan, Nigeria during the ten year period of 1997 to 2006. A total of three hundred and seventy four (374) case notes consisting of 204 (54.5%) males and 170 (45.5%) females from the medical record that satisfied the inclusion criteria were randomly selected. Each case note was thoroughly studied. Ninety seven (97) (25.9%) were referral cases while 266 (71.1%) were recent cases. The most common symptom fever, accounted for 310 (27.5%) cases. Nausea and vomiting accounted for 149 (13.2%) cases and anemia 162 (14.3%) with convulsion being 83 (7.4%) cases. The drug management indicated chloroquine prescriptions was used in 134 (26.5%) cases, quinine 93 (18.4%) cases, artemeter (ART) 88 (17.4%) cases while amodiaquine was prescribed in 72 (14.3%) cases. Intravenous (I.V) fluids were administered in 134 (18.0%) cases. Between 2003 and 2006, number of cases of chloroquine use dropped from 35 (41.7%) to 4 (8.2%) while the cases of ACTs use increased from 4 (4.8%) to 22 (44.9%). It was observed that patients on chloroquine (CQ) therapy were hospitalized for seven (7) days while patients on artesunate combination therapies (ACTs) were hospitalized for 5 days. The chloroquine therapy was at its peak in 2003 and declined from 2004 to 2006. The study showed that malaria management improved within the 10 years (1997-2006) with a consequent decrease in the chloroquine use and increase in use of artemisinin combination therapy (ACTs).

Keywords: Drug, Malaria, Management, Patients.

INTRODUCTION

Malaria threatens the lives of 56% of the world's population[1]. Annually, malaria is estimated to affect about 300 million and kill more than one million people, the majority of whom are young children. Over ninety (90) % of malaria cases worldwide occur in Sub-Saharan Africa[2]. In Nigeria, malaria is the most prevalent parasitic disease and one of the five most important causes of morbidity and mortality of children under five years old and pregnant women[3,4]. It is estimated that 5% of children die as a result of the direct or indirect effects of malaria before the age of five years[5]. The virulence of both the parasite and the vector has thwarted control efforts that lead to emergence of multi drug resistant malaria[7,8,9]. Parasite strains appear to be exacting an increasing human toll, resulting in pressure on productivity and over burdened health services[6,10]. In Nigeria, *P. falciparum* accounts for about 95% of malaria infection. Others are due to *P. malaria and P. ovale*[11,12]. Diagnosis of severe falciparum malaria constitutes a medical emergency. Coma, seizures, metabolic acidosis, hypoglycemia and severe anaemia are common presenting features of severe falciparum malaria in children[14]. Acidiotic breathing or deep coma defines a child at high risk of dying.

The signs and symptoms of malaria such as fever, chills, headache and anorexia, are non-specific and are common to many disease conditions. Malaria is a common cause of fever and illness in endemic area,[15,16] such that it is not possible to apply any one set of clinical criteria to the diagnosis as malaria manifests itself in different forms among patients. The appropriateness of a particular clinical diagnostic criteria varies from one area to another according to the intensity of transmission, the species of malaria parasite, other prevailing causes of fever and the health service infrastructure[17]. The greatest problems with drug resistance occur with *P. falciparum*[18]. Treatment failure may occur due to adulterated drugs as predominant in Nigeria. It is therefore important for effective management to have the principles of clinical management of *P. falciparum* malaria which include early recognition of infection due to *P. falciparum,* rapid institution of effective anti-malarial chemotherapy by the appropriate route of administration, recognition of and use of appropriate therapy for complications and monitoring of the immediate and long term clinical and parasitological responses to treatment[13]. Effective management of malaria could be defined in three ways, with different contexts. These include clinical remission, indicating clearance of signs and symptoms, clinical cure, indicating clinical remission with prevention of clinical recrudesce such as clearance of signs or symptoms in 14 days following the end of treatment and parasitological cure (or radical cure), indicating elimination of all parasites from the body. In Nigeria, infected adults are often asymptomatic in many area of intense transmission and when symptomatic, can often achieve clinical cure without parasitological cure. In low density transmission, asymptomatic infections are rare and clinical cure can rarely be achieved without parasitological cure. The objective of this study was to assess the management of malaria during the ten year period of between 1997 and 2006 and to determine the improvement in malaria management over those years with the goal of providing and promoting pharmaceutical care.

MATERIALS AND METHODS

The study was carried out at the University College Hospital, Ibadan in South West Nigeria. The University College Hospital (U.C.H) is a tertiary healthcare facility which provides referral services to the numerous primary and secondary healthcare facilities in Oyo State and beyond. The work was designed as a retrospective study, involving the thorough study of case notes of in-patients diagnosed, admitted and treated for malaria between March 1997 and February 2006.

The case notes were randomly selected from the available case notes at the time of study. A total number of 374 case notes were studied. Essential information such as sex, age, presenting symptoms, history of prior use of anti-malarial. Other relevant information collected were patients' education, laboratory results before and after treatment, drug management, number of days spent by each patient, and the referrals at the University College Hospital. The data were analyzed using SPSS 11.0 for windows. Descriptive statistics was done using tables showing frequencies and percentages. Relationship between variables was detected using linear correlation method. Comparison of categorical variables was done using the Pearson chi-square while continuous variables were expressed as means and comparison done with student *t*-test. P-values < 0.05 were considered statistically significant. The ethical committee of the University College Hospital (U.C.H.) gave an approval for this study.

Table 1: **Sex and Age Distribution of patients**

Sex	Frequency	%
Male	204	54.5
Female	170	45.5
Total	374	100
Case notes studied		
Referral	97	25.9
Fresh	266	71.1%
Total	374	100
Age		
1 month-5years	162	43.3
>5-60 years	212	56.7
Total	374	100

Table 2: **Symptoms presented at the hospital by the patient**

Clinical presentation	*Frequency	Percentage
Nausea & Vomiting	149	13.2
Fever	310	27.5
Body weakness	98	8.7
Convulsion	83	7.4
Coca cola coloured urine	52	4.6
Anaemia	162	14.3
Poor/loss of appetite	50	4.4
Loss of consciousness	30	2.7
Dehydration	22	1.9
Headache	70	6.2
Dizziness	9	.8
Hypoglyceamia	5	.4
Hepatomegaly	15	1.3
Spleenomegaly	9	.8
Others	64	5.7

* Multiple responses

Table 3: Comparison of degree of parasitaemia and symptoms

Row %	Degree of parasitaemia					Row Total
Column%	+	+ +	+ + +	+ + + +	-ve	
Symptoms						
Nausea vomiting	30	13	7	20	15	85
	35.3% 43.5%	15.3% 33.3%	8.2%	23.5%	17.6% 45.5%	40.7
			31.8%	43.5%		
Fever	59	29	4	41	32	175
	33.7% 85.5%	16.6% 74.4%	8.0	23.4%	18.3% 97.0%	83.7
			63.6	89.1%		
General body weakness	15	10	2	7	12	46
	32.6% 21.7%	21.7% 25.6%	4.3%	15.2%	26.1% 36.4%	22.0
			9.1%	15.2%		
Convulsion	14	12	8	16	3	53
	26.4% 20.3%	22.6% 30.8%	15.1% 36.4%	30.2%	5.7%	25.4
				34.8%	9.1%	
Coca cola coloured	8	9	3	5	6	31
urine	25.8% 11.6%	29.0% 23.1%	9.7%	16.1%	19 .4% 18.2%	14.8
			13.6%	10.9%		
Anaemia	29	15	15	21	14	94
	30.9% 42.0%	16.0% 38.5%	16.0% 68.2%	22.3%	14.9% 42.4%	45.0
				45.7%		

Table 4: List of antimalarials prescribed during the ten year period of 1997-2006

Antimalarials	*Frequency	Percentage
Chloroquine	134	26.5
Amodiaquine	72	14.3
Quinine	93	18.4
SP[a]	42	8.3
ACT[b]	40	7.9
ART[c]	88	17.4
Halofantrine (Halfan®)	10	2.0
Paludrine®	26	5.2

*Multiple responses

[a] SP=Sulfadoxine/Pyrimethamine

[b] ACT=Artemisinin-based combination therapy

[c] ART= Artemeter.

Table 5: Other prescribed drugs

Class of Drugs	*Frequency	Percentage %
Heamatinics	154	20.4
Antibiotics	147	19.5
Analgesics	132	17.5
Anticonvulsant	39	5.2
Antihypertensive	7	0.9
Sedative	16	2.1
Antihistamine	40	5.3
Steroids	2	0.3
I.V fluid	134	17.8
Oral fluid	10	1.3
Neoplastic	9	1.2
Antiemetics	26	3.4
Others	38	5.0

* Multiple response

Table 6: Drugs used for the treatment of patients from 1997 to 2006

	Drugs									
Year	**CQ**	**AQ**	**Oral fluid**	**IV fluid (%)**	**Quinine**	**SP**	**ACT**	**ART**	**Halofantrine Halfan**	**Paludrine**
	(%)	**(%)**	**(%)**		**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
1997-2004										
1997	19(14.1)	-0	1(10)	11(8.2)	1(1.0)	4(9.5)	-0	1(1.1)	1(10.0)	1(3.8)
1998	5(3.7)	-0	-0	4(3.0)	-0	2(4.7)	-0	1(1.1)	1(10.0)	1(3.8)
1999	23(17.2)	1(1.4)	-0	7(5.2)	6(6.5)	2(4.7)	-0	-0	2(20.0)	3(11.5)
2000	7(5.2)	4(5.6)	-0	6(4.5)	11(11.8)	1(2.4)	-0	4(4.5)	-0	-0
2001	7(5.2)	-0	-0	11(8.2)	3(3.2)	2(4.7)	-0	-0	4(40.0)	4(15.4)
2002	11(8.2)	3(4.2)	-0	13(9.7)	9(9.7)	2(4.7)	-0	5(5.7)	-0	3(11.5)
2003	35(26.1)	26(36.1)	3(20.0)	31(23.1)	28(3.0)	10(23.9)	4(10.0)	22(25.0)	2(20.0)	8(30.7)
2004	20(14.9)	23(31.9)	3(3.0)	24(17.9)	25(26.9)	4(9.5)	6(15.0)	10(10.9)	-0	2(7.7)
2005- 2006										
2005	3(2.2)	6(8.34)	3(30.0)	12(9.0)	3(3.2)	4(9.5)	8(20.0)	24(27.3)	-0	1(3.8)
2006	4(3.0)	9(12.5)	-0	15(11.2)	7(7.5)	11(26.2)	22(55.0)	21(23.9)	-0	3(11.5)
Total	134(100)	72(100)	10(100)	134(100)	93(100)	42(100)	40(100)	88(100)	10(100)	26(100)

Table 7: Comparing different antimalarials and the length of stay of patients on admission.

Drug	Mean ± S.D	Range
Q	7.54 ± 2.89	2.0-15.0
CQ	6.42 ± 3.31	1.0-15.0
SP	6.80 ± 2.86	2.0-11.0
*ACT	5.28 ± 3.10	2.0-13.0
αART	6.60 ± 2.77	2.0-12.0

*ACT= Artemisinin- based combination therapy

α ART= Artemeter.

Table 8: Anova Table Comparing Length of days stayed by years

Year	Mean	Std. Dev	Std. error	Min	Max
1997	6,3810	3.12212	0.68130	2.00	11.00
1998	5.7500	1.83225	0.64780	2.00	8.00
1999	6.5000	3.95132	0.69850	1.00	15.00
2000	8.3333	3.18082	0.74973	3.00	15.00
2001	6.0000	3.05505	0.84732	2.00	11.00
2002	8.0435	3.48344	0.72635	2.00	14.00
2003	6.9241	2.96463	0.33355	2.00	13.00
2004	5.9605	3.22259	0.36966	1.00	14.00
2005	6.0000	3,01279	0.47636	2.00	15.00
2006	6.4375	3.37643	0.48735	1.00	15.00

	Sum of	Df	Mean squares	F	Sig
Between groups	168.375	9	18.708	1.605	.066
Within groups	3607.647	348	10.367		
Total	3776.022	357			

RESULTS

A total of 374 case notes consisting of 204 (54.5%) males and 170 (45.5%) females were studied. The majority of the patients were children below the age of five 162 (43.3%) followed by the patients aged between 5 and 60 years accounting for 212 (56.7%). (Table 1). Fever was the most common presented symptom by the patients and it accounted for 310 (27.5%) cases. This was followed by other major signs and symptoms such as anemia 162 (14.3%) nausea and vomiting, 149 (13.2%), body weakness 98 (8.7%) convulsion 83 (7.4%), headache 70 (6.2%) and loss of appetite 50 (4.4%) (Table 2).The degree of parasitaemia was highest in fever 175 (83.7%) followed by anemia 94 (45.0%) with nausea, convulsion, general body weakness and coca cola coloured urine accounting for 94 (45.0%), 53 (25.4%), 46 (22.0%) and 31 (14.8%) respectively (Table 3).

Chloroquine was the most prescribed antimalaria drug and it accounted for 134 (26.5%) cases. Quinine was prescribed in 93 (18.4%) cases, artemeter (ART) 88 (17.4%) cases amodiaquine 72 (14.3%) cases, sulfadoxine/pyrimethamine (SP) 42 (8.3%) cases, ACT 40 (7.9%) cases with halofantrine (Halfan^{R}) in 10 (2.0%) cases and paludrine in 26 (5.2%) cases (Table 4). The most prescribed among other drugs beside antimalaria was heamatinics and it was prescribed in 154 (20.4%) cases.

This was followed by other drugs such as antibiotics, intravenous fluid and analgesic accounting for 147 (19.5%), 134 (17.8%) and 132 (17.5%) cases respectively. Other drugs prescribed were antihistamine, anticonvulsant, steriods, sedative, oral fluid, neoplastic and antihypertensive accounting for 40 (5.3%), 39(5.2%), 2 (0.3%), 16 (2.1%), 10 (1.3%), 9 (1.2%) and 7 (0.9%) cases respectively. Other prescribed drugs accounted for 38 (5.0%) (Table 5). Comparing the years of the use of antimalaria drugs, the use of chloroquine was at the highest peak in 2003 with 35 (26.1%) patients receiving chloroquine among the total number of 134 patients who were on chloroquine during the ten years covered in the study.

The use of chloroquine declined to 3 (2.2%) patients in 2005 and 4 (3.0%) patients in 2006 respectively (Table 6). The use of ACTs was as its peak in 2006 with 22 (55%) patients on ACT prescriptions out of the total number of 40 patients on ACTs during the ten years covered in this study (Table 6). Patients on ACTs were on it on the average of 5.3 days while the patients on artemether (ART) and quinine were on them on 6.6 and 7.5 days respectively (Table 7).The average days spent on admission by the patients was 6.5 days in 2001 and 2002 while the average days spent by the patients admitted for malaria in 2004 and 2005 were 5.9 and 5.4 days respectively (Table 8).

DISCUSSION

Studies have shown that children below the age of five years are at the greatest risk of been diagnosed and admitted for malaria infection than any other age group[14]. This may be attributed to low immunity reported in children less than five years living in endemic areas such as Nigeria[18]. Few studies focus specifically on this age range due to ethical dilemmas and technical difficulties with sampling[19].

In this study, majority of the patients were children under age five totaling 162 (43.3%) (Table 1) Majority of these children could not report symptoms thereby relying on their parents and health professionals for the detection of symptoms and adverse drug effect[20]. There are potential and important pharmacokinetic differences in infants compared to older children and adult[21]. In this study, the most common clinical feature of malaria was fever which was observered in 310 (27.5%) cases (Table2). This is in line with the WHO report on malaria symptom and diagnosis[22].

Anaemia results from the haemolysis of parasitized red blood cells (RBC) as well as non parasitized RBC due to oponizaion, dyserythropoiesis, hypersplenism and folate deficiency[23,24]. In this study, aneamia accounted for 162 (14.3%) cases (Table 2). Loss of consciousness (Table 2) accounted for the highest number of referrals both from the private clinics and other secondary health care services. Among the anaemic patients, the degree of parasitaemia was high in malaria infection.

This study showed that 21 (22.3%) of the anaemic patients had 4+ (Table 3). This is supported by Almeida et al, who reported that anaemia correlates with the severity of the infection and it is an important parameter in assessing these patients (Table 3). The world health organization (WHO) in its recent guidelines[23] for the management of malaria infection recommends parasitological diagnosis of malaria in areas of high stable transmission. It states that for children under age 5, treatment should be based on clinical diagnosis. In older children and adults, a parasitological diagnosis is recommended before treatment.

In the absence of or a delay in obtaining parasitological diagnosis, patients should be treated for severe malaria on clinical grounds. In this study many patients were treated without a parasitological confirmation. Only 260 (76.2%) had a diagnostic tests results in their case files. In some cases, treatment had commenced before the results arrived. Many patients got to the hospital when the home management had failed. The symptoms were therefore more severe and treatment had to commence immediately. The new guideline also stresses the importance of repeating the diagnostic test to establish cure rate[24].

In the past, clinical and parasitological cure were considered separately. Recognising the adverse effects of treatment failure, the two are now considered together. Persistence of parasitaemia without fever represents a treatment failure. The reappearance of parasite indicates reduction of parasite sensitivity to the drug treatment. As a significant proportion of treatment failure does not appear until after day 14, shorter observation periods lead to a considerable overestimation of the efficacy of the tested drug. The recommended duration of follow up should be from 28 days after treatment. Patients should therefore be advised to repeat the malaria parasite (MP) test 28 days following treatment. Since most patients did not repeat their laboratory results, success of treatment was measured mostly by clinical symptoms.

Different treatment protocols have emerged due to numerous reports on resistance in the management of severe falciparum infection. The first report of chloroquine resistance was in the 1950s, which was 12 years after the drug was introduced. In Africa, chloroquine resistance emerged in 1978 from the east and gradually spread west wards in the 1980s. Chloroquine was the most prescribed antimalaria drug during the ten year period covered by this study. It was prescribed in 134 (26.5%) cases (Table 4) Oral preparations such as amodiaquine were also used to manage patients. This was based on earlier report that oral therapy may be given safely to hyper-parasitaemic patients in Africa provided the parasites are fully sensitive to the drugs.[24] In this study amodiaquine was prescribed in 72 (14.3%) cases (Table 4).

Another common practice in the management of malaria was to start treatment with I.V quinine and continue with either oral chloroquine and amodiaquine once the patient was stable. This is supported by WHO recommendations[26,27]. This is being fast replaced with IV artemether (Paluther^{R}) start, especially since many authors have reported that there is no difference between IV quinine and IM artemether[26]. The uses of rectal dosage forms are not common for quinine and artemether. The use of the rectal dosage form is however supported by Elsenhut[29] who reported no difference between intra rectal artemisinin and IV/IM quinine. This is very beneficial in paediatrics. In the case of rectal arthemisinin[29], when compared with I.V. quinine, there was a lower mortiality with artemisinin and quicker coma recovery time though the difference was not significant ($P>0.05$), fever clearance times were not significant either ($P>0.05$) (Table 4). Antiemetic were used to treat nausea and vomiting while phenobarbitone which is the most common anticonvulsant used by the physician were used to manage children with severe malaria in this study (Table 5).

The use of phenobarbitone was supported by Cochrane review of 2004 where three trials were conducted with placebo or no treatment. In the three trials, Phenobarbital was associated with fewer convulsion than placebo or no treatment. In this study, the use

of chloroquine started to decline from late 1990s to early 2000, while the use of amodiaquine rose gradually during this period. Amodiaquine use however started to decline afterwards. The use of quinine also started to decline with the emergence of ART since the latter had fewer side effects (Table 6). This is supported by the recent findings by artemether-quinine meta-analysis[28]. In this study, the shortest 5.3 days was for ACT while ART had a mean of 6.6 days. There was need to continue using ACT and discontinue quinine which gave a mean of 7.5 days (Table 7).

This is supported by the WHO technical consultation team who listed the advantage of ACT as rapid substantial reduction of the parasite biomass, rapid resolution of clinical symptoms, effective action against multi-drug resistant *P. falciparum,* reduction of gametocyte carriage which may reduce transmission of resistant alleles in areas with low or moderate malaria transmission with no parasite resistance documented with artemisinin and its derivatives and fewer reported adverse clinical effects. The mean number of days spent by the patients was 6.5 days in 2001 and 2002. The mean number of days in 2004 was 5.9 days. In 2005 it was 6.0 days and in 2006 it was 5.4 days (Table 8).

Patients that were anaemic on admission were immediately transfused. This is supported by Merenikwu[29] who compared initial blood transfusion with conservative treatments and iron supplements. The trial excluded children who were unstable with respiratory distress or signs of cardiac failure. The trial established fewer deaths in the transfused children. The review however established coma and convulsion after transfusion. Thus, care must be taken in the management of severe falciparum infection in children.

The current practice for patients with hyper-parasitaemia found in 0.20% patients is to give parenteral artesunate. These patients might have evidence of vital organ dysfunction but there is a subgroup of individuals in whom there is no manifestations of severe disease.

CONCLUSION

Based on the data from this study, there has been an improvement in overall care given to malaria patients admitted at the University College Hospital, Ibadan during the 10 year period of 1997 and 2006. However, improvement in treatment has to be an ongoing process with the continuous used of arteminsinin combination therapy (ACTs) which was discovered during the ten years and whose use has contributed significantly to the improvement of malaria treatment during the ten years studied.

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