Outpatient treatment of malaria in recently arrived African migrants

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ABSTRACT

Objective: To describe the clinical features and management of African migrants recently arrived in Western Australia and subsequently diagnosed with malaria.

Design, participants and setting: Retrospective case record analysis of African migrants aged ⩾ 16 years with malaria referred to Royal Perth Hospital (RPH) from the WA Migrant Health Unit (MHU) between 1 March 2003 and 30 September 2005.

Main outcome measures: Demographic variables; clinical and laboratory variables; *Plasmodium* species; antimalarial medications used and their efficacy.

Results: 57 (3.5%) of 1609 adult African migrants screened at the MHU were diagnosed with malaria and referred for treatment. 52 were infected with *P. falciparum*, two with *P. ovale*, one with *P. malariae*, and one with both *P. falciparum* and *P. malariae*; the malaria parasite could not be identified in one individual. No patients had severe malaria by World Health Organization criteria. Most patients (53/57) were treated as outpatients with oral antimalarial therapy; four patients without severe malaria were admitted to hospital for treatment and observation. Atovaquone–proguanil was the antimalarial medication most commonly used (in 52/57), and treatment was well tolerated in most patients. Post-treatment follow-up was possible in 50 patients; all 27 of those who were followed for 4 weeks or longer were cured. Cure could not be concluded in patients with shorter follow-up periods. All follow-up blood films were negative for malarial parasites.

Conclusions: Outpatient treatment of malaria in recently arrived adult African migrants appeared to be safe and efficacious in our cohort.

MJA 2006; 185: 598–601

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Australia was declared malaria-free in 1981,[1] however, 600–900 cases of imported malaria are reported each year, mostly in returning travellers or people previously living in endemic areas. The region of northern Australia above 19° S is still a receptive zone for re-introduction of malaria because of the presence of *Anopheles* mosquitoes.[1,2]

In recent years, Australia has increased its intake of migrants under the Refugee and Special Humanitarian Program. The number of entry visas granted increased from 7113 in 2000–01 to 12 096 in 2004–05,[3] and priority was given to people from Africa, the Middle East, and south-west Asia. In 2003–04, 71% of the offshore humanitarian visa grants were allocated to African refugees.[4] The resultant changes in migration patterns to Australia are likely to be at least partly responsible for increasing numbers of notified cases of malaria, particularly those caused by *Plasmodium falciparum*.[5]

People infected with species of *Plasmodium* and who live in malaria-endemic regions often demonstrate few or no symptoms or signs of infection because they have acquired partial immunity. In these regions, people with all forms of non-severe malaria are routinely managed as outpatients, and recent reports from developed countries suggest that outpatient therapy for falciparum malaria may be appropriate in certain circumstances.[6,7] In Australia, experts advocate that all patients diagnosed with *P. falciparum* infection receive initial treatment in hospital.[8]

Because of the significant number of recently arrived African migrants from malaria-endemic regions with asymptomatic or minimally symptomatic malaria being referred to Royal Perth Hospital (RPH), a management program was instituted whereby selected patients could receive antimalarial th1erapy as outpatients. Here, we report a retrospective observational study of adult African migrants referred from the Western Australian Migrant Health Unit (MHU) to RPH for the management of malaria. Our findings were presented, in part, in poster form at the 2005 Annual Scientific Meeting of the Australasian Society for Infectious Diseases.[9]

METHODS

Refugees and humanitarian entrants arriving in WA are offered free health assessment at the MHU; attendance is voluntary. The health assessment comprises a clinical assessment, including laboratory tests, catch-up vaccination, health education and referral for ongoing health care. Individuals arriving from malaria-endemic regions are routinely screened for malaria. A blood specimen is examined for malarial parasites by thick and thin film microscopy and a rapid antigen test (NOW Malaria; Binax Inc, Scarborough, Me, USA) that detects a specific histidine-rich protein II antigen of *P. falciparum*.

Patients with malaria aged 16 years or more who were referred from the MHU to RPH for assessment and treatment between 1 March 2003 and 30 September 2005 were included in the study. Clinical data collected from RPH medical records included country of birth, country of refuge before migration, relevant history and examination findings, investigation results, treatment efficacy, and adverse events.

Patients with fever (⩾ 37.5° C), hypotension, parasitaemia of 2% or greater at presentation, or other clinical and laboratory features of severe malaria according to World Health Organization criteria,[10] or who were pregnant were offered admission; otherwise, patients received outpatient treatment. All antimalarial medications were administered as per product information, and possible side effects were carefully explained. Antimalarial medications were chosen according to national guidelines[8] and at the discretion of the treating clinician. Those treated as outpatients had their first dose of antimalarial medication under supervision, were observed for 1 hour, and were offered admission only if therapy was not tolerated. Subsequent doses were given to the patients and the course was completed unsupervised at home. All patients were instructed to seek review if they became ill or could not tolerate subsequent doses after leaving RPH. Subsequent outpatient review was arranged for all patients. Patients were considered cured at subsequent review if they were asymptomatic and the thick and thin blood films were negative for malarial parasites at 4 weeks or more after completion of therapy. As this was a retrospective clinical audit, ethical approval was not necessary.

1 Country of origin and country of refuge of 57 recently arrived adult migrants treated for malaria at Royal Perth Hospital, 1 March 2003 to 30 September 2005

Country	Number
Country of origin	
Sudan	33
Liberia	13
Congo	4
Sierra Leone	4
Burundi	2
Kenya	1
Country of refuge	
Uganda	31
Guinea	16
Kenya	5
Tanzania	3
Ghana	1
Malawi	1

RESULTS

In the 31-month review period, 1609 African migrants aged 16 years and older were assessed at the MHU, of whom 57 were diagnosed with malaria. The most common country of origin was Sudan, and Uganda was the most common country of refuge before resettlement in Australia (Box 1).

Clinical and laboratory characteristics of the patients are shown in Box 2. Box 3 shows that most (52) were infected with *P. falciparum*. The species of malarial parasite could not be identified in one patient. No patients had severe malaria by WHO criteria. Eighteen patients with *P. falciparum* malaria were symptomatic; common symptoms included chills (in 16), headaches (10) and myalgias (2). Two patients were febrile; both had *P. falciparum* infection. The time after arrival in WA before treatment ranged from 7–67 days (median, 28 days). Sixteen patients had a haemoglobinopathy.

Fifty-three patients were treated entirely as outpatients. Although five patients satisfied criteria for hospital admission (two were febrile, three were pregnant), only one agreed to be admitted. The four patients who met admission criteria but refused admission were all successfully treated as outpatients. Three other patients who did not fulfil the criteria for admission were admitted because of significant constitutional symptoms. None of the patients (inpatients or outpatients) developed complications of malaria while on treatment.

Drugs used to treat malaria are outlined in Box 3. Atovaquone–proguanil was given to 52 patients and was well tolerated in 49. All patients tolerated their first dose of antimalarial medications. Two patients reported nausea and one reported dizziness while on atovaquone–proguanil, and one patient who received mefloquine reported nausea and dizziness during therapy; all of these patients completed their therapy.

Follow-up blood films were performed between 1 to 20 weeks after treatment (median, 4 weeks) in 50 patients. Forty-one

2 Clinical and laboratory characteristics of 57 recently arrived adult migrants treated for malaria at Royal Perth Hospital, 1 March 2003 to 30 September 2005

Characteristic	Value
Number of men	37
Number of women	20
Mean age	24.6 years (16–47 years)
Parasitaemia (7 migrants only*)	
Range	3130–29 000 parasites/μL
Geometric mean	6965 parasites/μL
% Red blood cells parasitised	0.05%–0.8%
Haemoglobinopathy	
Number with α-thalassaemia trait	10
Number with Hb-S heterozygosity	5
Number with raised Hb-F level	1
Number with splenomegaly	10
Mean haemoglobin level (range)	
Women	124 g/L (96–147)
Men	144 g/L (98–167)
Mean platelet count (range)	
Women	224×10^9/L ($92–349 \times 10^9$/L)
Men	218×10^9/L ($74–373 \times 10^9$/L)
Number with symptoms	18
Time in Australia before diagnosis	
Mean	32 days (range, 7–67 days)
Median	28 days

* Quantification was not possible in 50/57 patients because of very low parasite counts. ◆

3 *Plasmodium* species causing malaria in the 57 recently arrived adult migrants, and antimalarial medications used in treatment

Type of infection	No. infected	Medication
P. falciparum	49	Atovaquone + proguanil*
P. falciparum	2	Mefloquine†
P. falciparum	1	Quinine + doxycycline‡
P. falciparum and *P. malariae*	1	Atovaquone + proguanil*
P. malariae	1	Chloroquine§
P. ovale	1	Chloroquine§
P. ovale	1	Atovaquone + proguanil*
Unidentified *Plasmodium* species	1	Atovaquone + proguanil*

* 250 mg/100 mg, four tablets daily for 3 days. † 750 mg followed by 500 mg 6 hours thereafter. ‡ 600 mg quinine sulfate 8-hourly and 100 mg doxycycline 12-hourly, orally for 7 days. § 620 mg initially, 310 mg 6 hours later and 310 mg on Days 2 and 3. ◆

of these patients had blood films performed at 2 weeks or more, and 27 had films performed at 4 weeks or more after completion of treatment. All follow-up films were negative for malarial parasites.

DISCUSSION

The initial clinical assessment of an individual with *P. falciparum* infection can be misleading. The condition of otherwise fit patients can deteriorate rapidly, even after prompt initiation of appropriate therapy. The risk of severe malaria is greater in the non-immune, the young, pregnant women, the immunosuppressed, and patients with significant parasitaemia (≥ 2%). Moreover, patients with *P. falciparum* infection often have associated nausea, vomiting and dehydration requiring intravenous fluids and possibly intravenous antimalarial therapy. Therefore, many specialists in developed countries advocate management of *P. falciparum* malaria in a hospital setting. Until recently, most *P. falciparum* infections at our institution have occurred in non-immune returned travellers; all such patients are routinely admitted for at least the initial part of therapy. More recently, we have seen a change in the pattern of referrals for treatment of malaria, with a significant increase in cases of *P. falciparum* infection in minimally symptomatic or asymptomatic semi-immune African migrants, raising the possibility that ambulatory treatment may be appropriate in this patient group.

The concept of ambulatory treatment of *P. falciparum* malaria is not new. Outpatient treatment of uncomplicated *P. falciparum* malaria is accepted practice in malaria-endemic areas,[6,11,12] and in returned travellers in Switzerland.[7,13] As a result of a combination of factors, including pre-existing immunity, coexisting protective haemoglobinopathy, initial low parasitaemia and/or partial treatment by refugee resettlement agencies before entering Australia, recently arrived African migrants are probably less likely to develop complications of malaria than non-immune returned travellers, and are therefore potentially suitable for outpatient therapy. Outpatient antimalarial therapy is also less resource-demanding and is significantly less disruptive to migrant families.

Atovaquone–proguanil was selected at our institution as the preferred therapy for uncomplicated malaria in this cohort because of its short treatment course, favourable side-effect profile and the previous favourable response to this therapy in non-immune patients. Furthermore, the once-daily dosing (with food) is easily understood by non-English-speaking people, which may minimise the likelihood of incorrect dosing in an unsupervised setting. Atovaquone and proguanil act synergistically against blood-stage malarial parasites, interfering with plasmodial respiration, and the combination is effective in the treatment of *P. falciparum* infection.[14] It is also efficacious against non-falciparum malaria.[15]

There are reports of clinical failures of atovaquone–proguanil in the treatment of *P. falciparum* infections in travellers returning from Africa.[16,17] However, atovaquone–proguanil resistance in Africa is not a widespread concern at present,[17] and we did not see any treatment failures in our cohort, although follow-up was incomplete.

Efficacious alternative agents include mefloquine and artemether–lumefantrine; artemether–lumefantrine has the additional benefit of activity against early-stage gametocytes, thereby potentially preventing malaria transmission. Acquisition costs for one course of atovaquone–proguanil, mefloquine, and artemether–lumefantrine at our institution are $56, $21 and $80, respectively. Outpatient-based treatment of recently arrived African migrants with uncomplicated malaria with any antimalarial is thus likely to be cost-effective relative to the expense of "bed-costs" of a hospital admission ($450 per day in 2005 at RPH).

We believe that screening and treatment for malaria in people migrating to Australia from malaria-endemic regions is an essential part of the initial health assessment, and should be performed as soon as possible after arrival. Individuals with untreated *P. falciparum* malaria, including those with minimally symptomatic or asymptomatic infection, can: (i) progress to developing severe malaria, even after prompt initiation of appropriate treatment; (ii) potentially reintroduce malaria into Australia if they settle or travel to a malaria-receptive zone; (iii) have persistent symptomatic anaemia; and/or (iv) present months or even years later with symptomatic disease.[18]

Our study has several limitations. It was a retrospective uncontrolled study, and therefore subject to bias. As attendance at the MHU for screening is voluntary, the real prevalence of malaria in African migrants cannot be known. However, given that most refugee and humanitarian entrants arriving in WA do attend for screening (Dr Jennifer Martin, Resident Medical Officer, MHU, personal communication), the reported prevalence of 3.5% in this cohort is likely to be close to the true prevalence.

Our study did not include children, a group that bears a significant burden of *P. falciparum* infection in Africa. Over half of all *P. falciparum* cases diagnosed at the MHU between 2003 and 2004 occurred in children aged 15 years or less (Dr Jennifer Martin, Resident Medical Officer, MHU, personal communication). Children with malaria are also more likely to vomit oral therapy. Ambulatory treatment of malaria in this group warrants further study. In addition, we would stress that the implications of our data cannot be extrapolated to the treatment of malaria in returned travellers, in whom there is unlikely to be any pre-existing protective immunity.

Follow-up was incomplete, with seven of our patients not returning for outpatient review. For those who did attend at least once for review, only 27 were seen at 4 weeks or more after treatment. It has been shown in prior malaria treatment studies in endemic areas that treatment success is best predicted with assessments at 4 weeks or more after treatment is completed.[19,20] Although unlikely, treatment failures cannot be completely excluded in those patients assessed after shorter follow-up times.

Our study suggests that outpatient treatment of asymptomatic or minimally symptomatic malaria (including *P. falciparum* infection) in recently arrived adult African migrants is a potentially efficacious and safe strategy in carefully selected patients. A large, prospective, randomised clinical trial would be required to validate our findings.

ACKNOWLEDGEMENTS

We acknowledge the assistance of Dr Aesen Thambiran, Ms Anita Clayton, Ms Evelyn Craig and Ms Joanna Fagan from the Western Australian Migrant Health Unit, who facilitated data extraction from the MHU electronic database; Dr William Beresford (former Director of Clinical Services, Royal Perth Hospital) who authorised the provision of all outpatient antimalarial therapy for the patients free of charge; and the ward medical and nursing staff who assisted in the assessment and management of the patients.

COMPETING INTERESTS

Dr Murray has received speakers fees from GlaxoSmithKline.

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(Received 5 May 2006, accepted 19 Oct 2006) ❑