ORIGINAL ARTICLE

Selective ambulatory management of *Plasmodium falciparum* malaria in paediatric refugees

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Background: *Plasmodium falciparum* (*Pf*) malaria is a leading cause of childhood mortality and morbidity. In developed countries, it is widely recommended that even patients with uncomplicated *Pf* malaria are hospitalised for at least 24 h, whereas ambulatory treatment is usual for uncomplicated infections in developing countries. This observational study assessed the safety of selective admission of paediatric refugees with *Pf* malaria in Australia.

Methods: Data were collected on African humanitarian refugee children (<16 years of age) presenting with malaria between February 2005 and April 2006. Children were treated as outpatients if they fulfilled specific criteria devised to maximise the safety of outpatient management of this potentially life-threatening condition.

Results: Ninety paediatric refugees were infected with *P falciparum*, of whom 56 were treated as outpatients. Of the 34 children admitted to hospital, four had parasite loads ⩾4%. Most children were treated with oral atovaquone-proguanil. Eighty eight patients attended follow-up; all were compliant and none reported side-effects. One infant failed treatment and was subsequently readmitted; he did not meet criteria for severe malaria on either occasion and had been initially treated as an inpatient.

Conclusions: Using this protocol, outpatient management of refugee children with *Pf* malaria appears safe, with minimal complication and treatment failure rates. This approach has rationalised management of paediatric malaria in this carefully selected population and substantially reduced utilisation of hospital resources.

Malaria is responsible for considerable global mortality and morbidity and accounts for up to 20% of childhood deaths in Africa.[1] *Plasmodium falciparum* (*Pf*) malaria has a significant case-fatality rate even when managed appropriately.[2] Prompt recognition and treatment is essential in the non-immune patient and in young children, who are at increased risk of rapid deterioration and death.[3] In Australia, as in the US[4] and Canada,[5] there has been a increase in the incidence of malaria in recently resettled African refugees.[6–8]

Current guidelines generally advocate mandatory admission to hospital of all children with *Pf* malaria in developed countries,[9–11] but there is little evidence to support this recommendation. This study evaluated the safety of selective ambulatory management of African refugee children with *Pf* malaria in Australia.

METHODS

Most refugees resettled in Western Australia (WA) undergo routine health screening, including testing for malaria with a single thick and thin malaria smear and immunochromatography (ICT), irrespective of symptoms. We performed an audit of refugees (0–16 years of age) presenting with malaria to two centres (Princess Margaret Hospital for Children (PMH) and Fremantle Hospital, WA). Referral sources included the refugee screening clinic, general practitioners or self-presentation to the emergency department. Exclusion criteria were non-*Pf* cases, children who had received pre-departure anti-malarial therapy with negative blood smears on arrival and non-refugee children with malaria.

We commenced ambulatory management of *Pf* malaria in February 2005 using a locally devised protocol that defined criteria for ambulatory management (box 1). The protocol also assessed generic refugee issues including language and literacy, financial constraints, availability of transport and likely ability to access local health services.[12] We employed a modification of the WHO criteria for severe malaria, in an attempt to maximise the safety of selective non-admission.[13 14] Children were followed for 2 months after treatment.

Data collection and statistical analyses

Details of initial presentation, demographics, clinical and laboratory parameters, treatment and follow-up were obtained from medical records. Re-presentations were confirmed by chart review and from hospital databases. Malaria was diagnosed by microscopy of thick and thin blood smear and by ICT (Binax NOW, Portland, ME, USA). Children were diagnosed with malaria if peripheral blood smear was positive and/or if the initial ICT was positive and there was a high clinical suspicion (presence of symptoms or absence of a history of pre-departure anti-malarial treatment). Children were considered to be clinically unwell at presentation if they had symptoms likely to be attributable to malaria (including fever, cough, headache, abdominal pain, anorexia or vomiting).

Data were analysed using SPSS (Version 12.0 for Windows). Continuous numerical data were compared using independent samples t tests or Mann Whitney U tests where appropriate. Categorical variables were analysed using χ^2 or Fisher exact test. Statistical significance was recorded at the level of $p<0.05$ (two-tailed). The study was approved by the PMH Scientific Advisory and Ethics Committees.

RESULTS

Ninety eight children with possible malaria presented between 1 February 2005 and 30 April 2006. Eight children were excluded: three had non-*Pf* malaria and five had received pre-departure anti-malarial treatment and were asymptomatic with

Abbreviations: ICT, immunochromatographic testing; *Pf*, *Plasmodium falciparum*; PMH, Princess Margaret Hospital for Children

Box 1: Selective non-admission policy for paediatric refugees with *Plasmodium falciparum* malaria

In general, all children with falciparum malaria should be admitted to hospital unless the following criteria are met:

1. >5 Years of age
2. Clinically well and has been reviewed by a senior and experienced clinician
3. No clinical or laboratory features of severe malaria
4. Has previously had proven malaria (and has anti-disease immunity)
5. Has resided in an endemic area for most of the previous year
6. Tolerates first dose of oral medication (observed post-administration for 4–6 h)
7. Family has sufficient understanding to ensure compliance
8. Family has sufficient understanding to ensure follow-up
9. Family has sufficient understanding to know to return to hospital immediately if the child becomes more unwell
10. Family have a discharge letter stating that child has falciparum malaria
11. Child has no other co-morbidity necessitating admission

If there is any doubt whether to discharge a child with *Plasmodium falciparum* malaria, hospital admission is advised for at least the first 24 h.

negative repeat blood smears. Ninety children (42 males) with *Pf* malaria were therefore included in the analysis.

Demographic, clinical and laboratory characteristics

The median age at presentation was 100.5 months (interquartile range 65.0–151.0 months). Those treated as inpatients were significantly younger, more likely to be anaemic and presented sooner to hospital. Most children (68.0%) were afebrile and asymptomatic at presentation. Clinical and laboratory characteristics are shown in table 1.

The main ethnic groups were Liberian (31.1%), Sudanese (24.4%) and Congolese (22.2%). The main countries of transit were Guinea (34.3%), Tanzania (27.8%) and Uganda (26.7%), where most refugees had spent >5 years in refugee camps. Most families were not fluent in English and a quarter of families spoke no English. The majority of families (90%) did not have a primary care physician and less than 10% had independent transportation.

Diagnostic features

Eighty four (93.3%) children had *Pf* malaria and six (6.7%) had mixed infections. Blood smears were positive in 79 children, and ICT was positive in 85 of 88 children in whom it was performed. Nine children had positive ICT with a negative single blood smear; none had received recent anti-malarials. Four children had >4% parasitaemia (range 4.2–14%), all of whom had reportedly received pre-departure anti-malarial treatment.[8]

Inpatient treatment

Thirty four children were managed as inpatients and 17 of these (50%) were >5 years of age (table 2). No child required admission to intensive care. Twenty children (22.2%) with positive blood smears had received pre-departure anti-malarial treatment, of whom 15 were subsequently hospitalised (table 1). Thirty two children were treated with atovaquone-proguanil, one received mefloquine and one received intravenous quinine for 48 h followed by atovaquone-proguanil.

Ambulatory treatment

Fifty six children (62.2%) received ambulatory care (box 1). Fifty three (94.6%) received atovaquone-proguanil and the remainder mefloquine. A senior clinician reviewed ~90% of children prior to discharge; those not reviewed presented after hours and spoke fluent English.

All families received information on the need for compliance, potential side effects and need for immediate re-presentation to hospital if the child deteriorated. Discharge letters, given to families, stated diagnosis, therapy and emergency hospital contacts.

Follow-up

Eighty eight children (97.7%) attended day 28 follow-up. All had been compliant with no significant side-effects. Follow-up malaria blood smears were performed in 85 of 88 children with one positive result. This 8-month-old infant had completed supervised therapy with atovaquone-proguanil as an inpatient. He did not have severe malaria on presentation. Parasite clearance on blood smear had occurred at 2 weeks, with positive blood smear and ICT at day 28 follow-up. He underwent retreatment with a supervised inpatient regimen (artemether-lumefantrine) with parasitological cure.

DISCUSSION

P falciparum is a potentially life-threatening infection and deterioration may occur rapidly despite appropriate anti-malarial treatment.[15 16] In developed countries, it is generally recommended that all patients with *Pf* malaria are treated as inpatients for at least the first 24 h to ensure tolerance of

Table 1 Demographic, clinical and laboratory characteristics of inpatients versus ambulatory management

Variable	Inpatients (n = 34)	Ambulatory care (n = 56)	p Value
Median age (months) (IQR)	58.0 (28.8–119.2)	129.0 (95.0–162.5)	<0.001
Gender (M:F)	18:16	24:32	NS
Mean time to hospital presentation after arrival (weeks) (SD)	3.1 (1.7)	6.1 (3.8)	<0.001
Pre-departure anti-malarial treatment (%)	15/34 (44.1)	5/56 (8.9)	<0.001
Positive initial blood smear (%)	31/34 (91.2)	48/56 (85.7)	NS
Positive ICT (%)	32/34 (94.1)	53/56 (94.6)	NS
Median percentage parasitised red blood cells (IQR)	0.4 (0.1–1.15)	0.1 (0.1–0.35)	0.014
Febrile at presentation (%)	6/34 (17.6)	0/50 (0)	0.003
Symptoms at presentation (%)	24/34 (70.6)	9/47 (19.1)	<0.001
Splenomegaly (%)	14/34 (41.2)	21/54 (38.9)	NS
Mean haemoglobin at presentation (g/dl) (SD)	10.3 (2.0)	11.6 (1.4)	0.001
Haemoglobinopathy present* (%)	19/34 (55.9)	29/56 (51.8)	NS

*No child was homozygous for thalassaemia and/or sickle cell disease.
ICT, immunochromatographic testing; IQR, interquartile range; F, female; M, male; NS, not significant; SD, standard deviation.

Table 2 Criteria necessitating admission with malaria

Reason for admission	Number (%) (n = 34)
Less than 5 years old and well	11 (33)
More than 5 years old and unwell*	8 (24)
Less than 5 years old and unwell	6 (18)
Compliance concerns	5 (15)
Anti-malarial immunity considered unlikely	2 (6)
Social concerns	2 (6)

*Unwell indicates febrile and/or malaria-attributable symptoms.

anti-malarials and to detect early treatment failure leading to clinical deterioration.[9–11 13 17] There are reports of successful ambulatory treatment of adults with *Pf* malaria in developed countries using combination therapy;[10 18] this is the first analogous paediatric study.

Children infected with *P falciparum* are at the highest risk of complications or death compared with other age groups.[19] Severe infection with *P falciparum* requires prompt recognition, immediate hospitalisation and aggressive management.[19] In hyper-endemic regions, low level parasitaemia is prevalent, with children often having a degree of anti-disease immunity and clinically mild malaria that may mimic other childhood illnesses.[3] African refugee children are often asymptomatic or mildly unwell despite moderate parasitaemia, which may have been present for weeks prior to presentation.[4]

Assessment of previous malaria exposure (a proxy of anti-disease immunity) is important.[9] Additionally, the patient's social context may necessitate inpatient management in case of subsequent deterioration, even if clinically not indicated at presentation.[10] Education regarding medication compliance, side-effects (particularly vomiting), and the necessity and practicalities for immediate re-presentation in the event of clinical deterioration are integral to the safety of ambulatory management. Discharge documentation aims to minimise incorrect diagnosis if non-English speaking families re-present to health care facilities.

Generally the diagnosis of malaria is made on repeat microscopic examination of Geimsa stained thick and thin peripheral blood smear.[19] However, in our population, only a single blood smear was obtained at initial screening, with rapid diagnostic methods used as an adjunct. This approach is in keeping with the results of a recent meta-analysis of malaria diagnosis in the absence of a gold standard.[20] The ICT may remain positive for up to 4 weeks after treatment,[21] which has implications for diagnosis in refugees who received pre-departure anti-malarial therapy. PCR testing is sensitive but costly and time-consuming and is generally not used in routine diagnosis.[3]

Ambulatory treatment is common in Africa where hospitalisation is reserved for severe disease or complications and children are often treated empirically in the community.[22] Most resettled African refugees are from hyper-endemic malaria regions.[23] With the rise in multi-drug resistant *Pf* and side-effects of therapy, combination therapy is now advocated as first line treatment and can be administered in the outpatient setting.[9 24]

Atovaquone-proguanil is well tolerated, with a short and simple treatment regimen (once daily for 3 days) and high efficacy (day 28 parasitological cure).[25] Alternative oral anti-malarials include artemether-lumefantrine combination therapy. Although there are limited comparative data between atovaquone-proguanil and artemether-lumefantrine in children, the WHO recommends artemisinin-based combination therapies in developing countries, especially for life-threatening malaria.[13 26] In refugees significant language barriers and other factors may reduce understanding, and complex dosing regimens may therefore affect compliance. Thus our current practice in uncomplicated malaria is to reserve artemether-lumefantrine for those who fail initial therapy with atovaquone-proguanil.

What is already known on this topic

- *Plasmodium falciparum* malaria is responsible for considerable global morbidity and mortality, particularly in Africa.
- Prompt recognition and treatment is essential in the non-immune patient and in young children.
- Refugee children from malaria-endemic regions often have a degree of anti-disease immunity, which may alter the clinical course of the disease.

What this study adds

- Selective outpatient management of refugee children is safe with minimal complication or treatment failure rates.
- Combination oral therapy is the treatment of choice in this population (atovaquone-proguanil or artemether-lumefantrine).
- Safeguards are necessary to ensure refugee families understand treatment and are able to access hospital services in the event of deterioration.

CONCLUSION

Selected ambulatory treatment appears effective and safe in children with *Pf* malaria who have been previously resident in endemic regions, with minimal complication and treatment failure rates. Social factors, such as language barriers and lack of transportation, must be considered when determining suitability for ambulatory management, even if other criteria are met. It is essential that the family have both an understanding and the capability to re-present urgently if deterioration occurs. This approach has substantially reduced the use of hospital resources and should be relevant to developed countries that resettle humanitarian refugee children from malaria endemic regions. Centres with limited experience of *Pf* malaria may need to continue mandatory admission, which is also essential for non-immune patients such as returned travellers. Further studies are required to confirm the safety of ambulatory management in refugee children <5 years of age and to assess more complex dosing regimens in ambulatory care.

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