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Inpatient Mortality in Children With Clinically Diagnosed Malaria As Compared With Microscopically Confirmed Malaria

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Abstract

Background—Inpatient treatment for malaria without microscopic confirmation of the diagnosis occurs commonly in sub-Saharan Africa. Differences in mortality in children who are tested by microscopy for *Plasmodium falciparum* infection as compared with those not tested are not well characterized.

Methods—A retrospective chart review was conducted of all children up to 15 years of age admitted to Mulago Hospital, Kampala, Uganda from January 2002 to July 2005, with a diagnosis of malaria and analyzed according to microscopy testing for *P. falciparum*.

Results—A total of 23,342 children were treated for malaria during the study period, 991 (4.2%) of whom died. Severe malarial anemia in 7827 (33.5%) and cerebral malaria in 1912 (8.2%) were the 2 common causes of malaria-related admissions. Children who did not receive microscopy testing had a higher case fatality rate than those with a positive blood smear (7.5% versus 3.2%, $P < 0.001$). After adjustment for age, malaria complications, and comorbid conditions, children who did not have microscopy performed or had a negative blood smear had a higher risk of death than those with a positive blood smear [odds ratio (OR): 3.49, 95% confidence interval (CI): 2.88–4.22, $P < 0.001$; and OR: 1.59, 95% CI: 1.29–1.96, $P < 0.001$, respectively].

Conclusions—Diagnosis of malaria in the absence of microscopic confirmation is associated with significantly increased mortality in hospitalized Ugandan children. Inpatient diagnosis of malaria should be supported by microscopic or rapid diagnostic test confirmation.

Keywords

malaria; microscopy; *Plasmodium falciparum*; mortality; children

The diagnosis of malaria in children attending a tertiary unit in an endemic area is not straightforward. Clinical manifestations of malaria overlap with those of other common infections, making definitive diagnosis difficult.[1-5] A history of fever and positive blood smear on light microscopy is the standard for malaria diagnosis and basis of treatment, but in practice this is not often adhered to. Microscopy is often not used even when it is available[6] and has

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varying sensitivity and specificity according to the expertise of the personnel at the site of testing.[7-9] As a result it is not uncommon for malaria to be diagnosed and treated without microscopic confirmation or despite a negative blood smear.

The practice of diagnosis and treating children presumptively for malaria can result in excessive reporting of malaria cases,[7] under-reporting of diseases that mimic malaria symptoms,[10] increased true or perceived antimalaria drug resistance, treatment of smear negative cases as malaria[6] and misallocation of resources, including overuse of artemisinin-based combination therapy.[11] Few studies have examined the effect on inpatient mortality of diagnosing and treating malaria without microscopic confirmation.

To assess how mortality differs in children with a diagnosis of malaria according to status of microscopy testing for *P. falciparum*, we analyzed by retrospective chart review the differences in inpatient mortality between clinically and microscopically diagnosed malaria in all malaria-related admissions in children in the national referral hospital in Uganda during a 3½ year period.

MATERIALS AND METHODS

Study Type

A retrospective chart review was conducted of all malaria-related pediatric admissions aged 0–15 years to Mulago Hospital, Kampala, Uganda between January 2002 and July 2005.

Study Site

Mulago hospital is a 1500 bed national referral hospital in Uganda and a teaching hospital for Makerere University Medical School. It serves Kampala, the capital city, and surrounding districts in the central region of Uganda, which is an area of seasonal malaria transmission.[12] Approximately 20,000 children are admitted to Mulago Hospital annually, of whom about 30% are treated for malaria.[13]

Data Collection

All inpatient charts of children up to 15 years of age with a diagnosis of malaria were retrieved using the International Classification of Diseases (ICD 9) record codes and reviewed. The diagnoses recorded on the files are the final diagnoses for which the patient was treated during hospitalization. Information was collected from the patient's charts on the child's age, whether diagnostic microscopy for malaria had been performed (and if so, the results of microscopy), type of malaria complication, if any, other listed diagnoses, and outcome of hospitalization. Clinical diagnoses were recorded as listed in the chart (eg, cerebral malaria, severe malarial anemia, pneumonia), with or without supporting laboratory data. Accordingly, for these clinical data, WHO criteria might not be met (eg, cerebral malaria might be recorded in children with impaired consciousness rather than coma, and severe malarial anemia might be recorded without laboratory measurement of hemoglobin level). Although this means that not all clinical diagnoses are supported by strict inclusion criteria, our data do reflect the practice and diagnostic categorization in many hospitals in sub-Saharan Africa, where lack of resources and other factors often translate into diagnoses based purely on clinical criteria. Microscopy results were recorded as either not done, or negative or positive for *Plasmodium* species. The side-laboratory where all the malaria microscopy is done uses Field's Method.[14] To allow for detection of even scanty parasitemia, thick films are routinely used. Although the specific *Plasmodium* parasite cannot be identified on thick films, malaria causing admission in this area is overwhelmingly caused by *P. falciparum*, so all cases are reported and treated as cases of *P. falciparum* malaria. The laboratory is open from 7 AM to 10 PM, during which period the majority of patients are admitted. Patients admitted after 10 PM have malaria blood smears done

the next morning. In addition to the side-laboratory the hospital has a main laboratory that is capable of doing other diagnostic tests like blood counts, urinalysis, blood cultures and analysis of cerebral spinal fluid.

This study was approved by the Institutional Review Boards for Human Studies at Makerere University Faculty of Medicine, Case Western Reserve University and the University of Minnesota.

Data Analysis

Data entry was done in Filemaker Pro 7. Analysis was done with STATA 9.2 (Stata Corporation, Austin, TX). Frequencies were compared using the χ^2 test or the χ^2 test for trend, as appropriate. Multivariate logistic regression was used to assess the risk of mortality for specific malaria complications, comorbid diagnoses, and microscopy testing status. *P* values of <0.05 were considered significant.

RESULTS

Malaria Admissions and Microscopy Testing

A total of 23,342 children 15 years of age and under were admitted with a diagnosis of malaria. A peripheral blood smear for malarial parasites was done in 18,536 of these children (79%), of whom 12,256 (66%) had a positive result. Mean age did not differ between children who were microscopy positive [mean age, 2.6 years; standard deviation (SD), 2.7], and those who were microscopy negative (mean age, 2.6 years; SD, 2.8), but children who were not tested by microscopy were older (mean age, 3.1 years; SD, 3.6; $P < 0.001$ as compared with microscopy positive children). Gender frequencies were similar in the 3 groups, with a slight preponderance of males in all the groups (54%, 53%, and 52% male for children who were microscopy positive, microscopy negative, and did not have microscopy testing for *P. falciparum*, respectively). Children who did not have a smear done on average died earlier after admission than those that had a smear done (1.9 days versus 2.6 days, $P = 0.01$).

Malaria Seasonality and Overall Malaria-Attributed Morbidity and Mortality

From January 2002 to July 2005, malaria-related admissions accounted for 30.4% of hospital admissions in children 15 years of age and younger and malaria-related deaths accounted for 18.1% of total inpatient pediatric deaths. There was a significant increase in the proportion of admissions with a diagnosis of malaria from 2002–2004, but there was no significant increase in the proportion of inpatient deaths attributed to malaria during that period (Table 1).

Case Fatality Rates for Malaria Complications and Comorbid Conditions

The 3 most common complications of malaria were severe malaria anemia (SMA), cerebral malaria (CM), and malaria associated with convulsions (Table 2). Pneumonia and acute diarrhea were the 2 most common comorbid diagnoses in children with malaria-related admissions (Table 2). Other comorbid conditions occurring in >1% of children included upper respiratory tract infection (1.3%), urinary tract infection (1.1%), and sickle cell disease (1.1%). The overall case fatality rate of malaria-related admissions during the study period was 4.2%. SMA and CM accounted for 72% of all malaria-related deaths.

Malaria-Associated Mortality According to Microscopic Confirmation of Diagnosis

Case fatality rate (CFR) was assessed according to microscopy testing: blood smear for *P. falciparum* positive, negative, or not performed. The CFR for children with no microscopy performed was more than twice that of children who were smear positive (7.5% versus 3.2%, respectively; $P < 0.001$), and children with no microscopy performed had higher CFR for each

malaria complication and comorbid diagnosis than children who were smear positive (Table 3). Similarly, among children in whom microscopy was performed, the CFR overall was higher in children who were microscopy negative than microscopy positive (3.8% versus 3.2%; $P = 0.03$). This was largely because of a greater CFR for CM in microscopy negative as compared with microscopy positive children (17.7% versus 12.1%; $P = 0.01$; Table 3).

An increased risk of death was seen in children with CM in all 3 groups, and an increased risk of death for SMA was seen in children who were microscopy positive compared with children without these diagnoses. In addition, increased mortality was seen in children with a diagnosis of pneumonia in all 3 groups and with a diagnosis of acute diarrhea in children who were smear negative or who did not have microscopy testing performed (Table 4). After adjustment for age, malaria complications and comorbid conditions, lack of microscopy testing and negative microscopy testing remained highly significant independent risk factors for death in children admitted with a diagnosis of malaria (OR for no microscopy testing: 3.49, 95% CI: 2.88–4.23, $P < 0.001$; OR for microscopy negative: 1.59, 95% CI: 1.29 –1.96, $P < 0.001$; both as compared with children who were microscopy positive).

DISCUSSION

In malaria endemic regions, there is a tendency to treat all fevers as malaria, particularly in high risk groups such as young children. The World Health Organization (WHO) guidelines for diagnosis and management of severe falciparum malaria,[15] which have been adopted for use here in Uganda, encourage the use of peripheral blood smear to confirm the diagnosis of malaria whenever possible. In routine clinical practice diagnosis and treatment of severe falciparum malaria without blood smear confirmation (presumptive diagnosis and treatment) is not uncommon even where facilities for microscopy do exist. For example, in the present study a blood smear was not done in 21% of the malaria-related admissions. The most striking finding of the present study was the more than 3-fold increase in the risk of death in children who were given a diagnosis of malaria without microscopy testing for *P. falciparum* compared with children who were microscopy positive for *P. falciparum*. Furthermore, when microscopy was performed on children suspected for malaria, more than a third of children were microscopy negative but were still diagnosed and treated for malaria, and these children also had a 1.5-fold increased risk of mortality as compared with microscopy-positive children.

Our study findings on mortality in microscopy negative as compared with positive children are similar to those of a prospective study conducted in Tanzania,[8] which also documented a higher case fatality rate in microscopy negative than in microscopy positive patients. The Tanzanian study was a prospective study with specific criteria for the malaria complications assessed, and so was able to define diagnoses with a degree of precision not possible in the present retrospective study. However, the design of the present study allowed us to answer a question of significant clinical importance in sub-Saharan Africa: how is lack of microscopy testing associated with outcome in patients admitted with a clinical diagnosis of malaria?

The higher mortality in children diagnosed and treated for malaria without microscopic confirmation is likely due at least in part to misdiagnosis and a lack of treatment for conditions other than malaria. We were not able to record complete treatment details on the patients in this study, so we do not know how many of the children with a diagnosis of malaria received antibiotics in addition to antimalarials. At Mulago Hospital, antibiotics are usually given only to those with a listed diagnosis of a bacterial illness (eg, pneumonia or sepsis), so we suspect that most of the children with a clinical diagnosis of malaria were not treated with antibiotics. Other causes of febrile illnesses in children, like bacteremia, meningitis, encephalitis or other diagnoses, may be obscured by the focus on malaria. A recent study in post neonatal infants (1–12 months) in Nigeria reported that 38.2% of children presenting with febrile illness had

bacteremia[16] and in another study 40% of children with febrile illness who were smear negative had bacteremia compared with 12% in smear positives.[17] Consideration should be given to the possibility of both antimalarial therapy and empiric antibiotic therapy in the management of severely ill children with febrile illnesses in malarial areas.

The risk of severe disease or death from malaria in children in malaria endemic areas supports the approach of presumptive treatment of febrile children in facilities where microscopy is not available.[18,19] However, in this tertiary referral center, microscopy was readily available and is free of charge, yet it was frequently not performed, or when performed, not used in assignment of a diagnosis. Among children who had no microscopy testing performed, mortality was particularly increased in children with cerebral malaria, with a case fatality rate of 33.6% and an almost 7-fold increase in the risk of death in this group as compared with a case fatality rate of 12.1% and a 6-fold risk of death in children with cerebral malaria confirmed by blood smear. A case fatality rate this high strongly suggests the possibility of misdiagnosis, and underscores the critical need for microscopy testing in children thought to have severe malaria.

Among children with a negative blood smear, there was only a minor increase in the case fatality rate compared with children with a positive smear (3.8% versus 3.2%, $P = 0.03$), but after controlling for other potential confounding factors such as age, type of malaria complication and comorbid diagnosis, the increased risk of death was highly significant (OR: 1.59, 95% CI: 1.29–1.96, $P < 0.001$). The increased risk of death in children with negative blood smears is also most likely the result of misdiagnosis and lack of treatment for the real cause of illness in these children. However, it is possible that true infection was undetected in some children because of prior antimalarial treatment. In Uganda antimalarials are often purchased from drug shops or pharmacies: a study conducted at 7 sites around the country found chloroquine metabolites in 32–80% of the general population.[20] Much of this informal use of antimalarial medications is associated with inappropriate dosing,[21,22] which can lead to delayed parasite clearance and presentation to the hospital. This could lead to a more severely ill population on presentation and increased mortality in children who were smear negative. In addition, use of ineffective medications, even at the correct dose, may lead to persistent symptoms despite low level parasitemia. There is also a need for public health policy makers to enforce the dispensing and proper use of antimalarials by the public.[21]

The reliance on microscopy to make a diagnosis of malaria has been subject of much debate.[11,23,24] Accurate microscopy requires considerable experience and expertise and low level parasitemias are sometimes not detected.[25] Clinicians' confidence in the accuracy of microscopy may vary, depending on the area of testing and the expertise of microscopists in this area. A lack of confidence in microscopy results may lead clinicians to prescribe antimalarial drugs even when the blood smear is negative to cover for potential missed cases of malaria. For example, a recent Kenyan study documented that although the results of the routine negative blood slides were correct 92.7% of the time, 78.5% of patients with negative blood slides were prescribed antimalarial medications.[26] An alternative to microscopy is the use of rapid diagnostic tests, or newer technologies like polymerase chain reaction methods several of which have been shown to be sensitive, specific and stable under operational conditions.[27,28] Rapid diagnostic tests in particular, are generally easier to perform than microscopy, requiring significantly less expertise, and may detect parasitemia in individuals who have taken antimalarial medications.[29] Clinician education will be critical in any effort to improve accurate treatment of malaria, as recent studies from Tanzania and Zambia document that patients with negative rapid diagnostic tests were treated for malaria just as frequently as patients with negative microscopy results.[11,30]

Pneumonia and acute diarrhea were the most common comorbid conditions associated with malaria and were both strong predictors of mortality, as has been documented in previous studies.[31,32] The diagnosis of pneumonia in a child with malaria might be a coexisting bacterial or viral respiratory illness, but the diagnosis might also be given to a child with malaria-related respiratory distress, which is associated with a high mortality rate.[31] Likewise, acute diarrhea might be a feature of clinical malaria,[4] or the result of concurrent diarrheal disease from an enteric pathogen.[33] The increased mortality associated with these conditions emphasizes the importance of prompt evaluation as to the cause of the condition, and appropriate cause-specific treatment after evaluation.

Drug resistance to the first-line drugs recommended for malaria at the time of this study (chloroquine and sulfadoxine-pyrimethamine) is the most likely cause of the increased frequency of malaria-related admissions in children from 2001–2004.[34-36] The national drug policy for treatment of uncomplicated malaria in Uganda has since been changed to artemisinin-based combination therapy.[37] This change was implemented widely in 2006, and it remains to be seen if this will result in a decrease in the proportion of admissions with a diagnosis of malaria.

The present study used the diagnoses assigned by the many different inpatient clinicians admitting these children. These diagnoses were not necessarily validated by rigorous or uniform criteria. For this reason, we cannot definitively conclude that all children with a diagnosis of cerebral malaria, for example, actually had cerebral malaria. Indeed, it is likely that a significant proportion assigned this diagnosis without blood smear confirmation had another cause of their coma. But the latter case points out the practical relevance of chart review study such as the present study: clinical diagnosis of malaria, often without microscopy confirmation, is not infrequent in hospitals and clinics throughout sub-Saharan Africa. Our study results provide evidence that lack of testing in children with a diagnosis of malaria is associated with significantly increased rates of death, and argue for microscopy or rapid diagnostic testing of all children admitted with a diagnosis of malaria and evaluation of other causes of disease in children with negative results. Based on the findings of previous studies, however, it is likely that reductions in mortality will only be accomplished with clinician education on the utility of these tests, the risks of specific malaria complications and the importance of evaluation for alternative diagnoses.

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TABLE 1

Malaria-Related Admissions and Mortality in Children 15 Years of Age and Younger in Mulago Hospital, Kampala, Uganda, January 2002–July 2005

Cases	2002	2003	2004	2005*	Overall	P† 2002–2004
Malaria admissions	6040	6440	6396	4466	23,342	
Total pediatric admissions	25,939	20,638	19,216	10,996	76,789	
Proportional morbidity (%)	23.3	31.3	33.3	40.6	30.4	<0.001
Malaria deaths	248	273	305	165	991	
Total pediatric deaths	1437	1598	1654	774	5463	
Proportional mortality (%)	17.3	17.1	18.4	21.3	18.1	0.55

* From January to July 2005, not included in the analysis for trend.

† χ^2 test for trend.

TABLE 2

Malaria-Related Complications and Associated Comorbid Conditions as Ascertained From Discharge Diagnoses, and Corresponding Case Fatality, 2002–2005

Diagnosis*	N (%)	Deaths (N)	Case Fatality Rate (%)
Malaria			
All malaria-related admissions	23,342 (100)	991	4.2
Severe malaria anemia	7827 (33.5)	389	5.0
Cerebral malaria	1912 (8.2)	326	17.1
Malaria with convulsions	8154 (34.9)	412	5.1
Comorbid diagnoses			
Pneumonia	3441 (14.7)	232	6.7
Acute diarrhea	2330 (10.0)	122	5.2

* Nonmutually exclusive disease categories, hence sub categories may be >100%.

N indicates number of cases.

TABLE 3

Case Fatality Rates for Malaria-Related Complications and Comorbid Conditions, According to Microscopy Testing for *Plasmodium falciparum*

Cases	Smear Positive N = 12,295		Smear Negative N = 6305			Smear Not Done N = 4822		
	Cases N	Deaths N (%)	Cases N	Deaths N (%)	P^*	Cases N	Deaths N (%)	$P^\dagger$
All malaria admissions	12,255	390 (3.2)	6280	239 (3.8)	0.03	4798	361 (7.5)	<0.001
SMA	4504	178 (4.0)	2041	89 (4.4)	0.44	1278	122 (9.5)	<0.001
CM	1194	145 (12.1)	378	67 (17.7)	0.01	336	113 (33.6)	<0.001
Malaria with convulsions	4637	177 (3.8)	1968	87 (4.4)	0.25	1545	148 (9.6)	<0.001
Comorbid conditions								
Pneumonia	1301	77 (5.9)	1265	59 (4.7)	0.16	874	96 (11.0)	<0.001
Acute diarrhea	673	32 (4.8)	907	40 (4.4)	0.75	749	49 (6.5)	0.12

*χ^2 test for frequency of death, smear negative vs. smear positive.

†χ^2 test for frequency of death, smear not done vs. smear positive.

N indicates number of cases; SMA, severe malarial anemia; CM, cerebral malaria.

TABLE 4

Risk of Mortality Associated With Age, Malaria Complications, and Comorbid Conditions, According to Microscopy Testing for *Plasmodium falciparum*

Risk Factor	Smear Positive N = 12,256		Smear Negative N = 6,280		Smear Not Done N = 4,799	
	OR (95% CI)*	*P**	OR (95% CI)*	*P**	OR (95% CI)*	*P**
Age (yr)	1.01 (0.96–1.06)	0.69	0.93 (0.87–1.00)	0.05	0.96 (0.91–1.02)	0.18
Malaria complications						
SMA	1.44 (1.12–1.85)	0.005	0.87 (0.48–1.57)	0.64	1.05 (0.65–1.69)	0.84
CM	6.01 (4.64–7.78)	<0.001	6.41 (3.47–11.85)	<0.001	7.74 (4.54–12.30)	<0.001
Malaria with convulsions	1.17 (0.90–1.51)	0.25	0.76 (0.49–1.19)	0.23	0.85 (0.58–1.23)	0.38
Comorbid conditions						
Pneumonia	2.75 (1.92–3.94)	<0.001	2.38 (1.46–3.88)	0.001	2.44 (1.43–3.89)	<0.001
Acute diarrhea	1.14 (0.49–2.65)	0.75	3.15 (1.36–7.31)	0.01	3.10 (1.64–5.85)	0.001

*Multivariate logistic regression analysis, each factor adjusted for all other risk factors.

N indicates number of cases; OR, odds ratio; 95% CI, 95% confidence interval; SMA, severe malarial anemia; CM, cerebral malaria.