

Management of severe malaria in children: current practices and development of a paediatric malaria protocol

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Abstract

Introduction Malaria is one of the leading causes of death and morbidity in Uganda. Children are particularly susceptible to severe malaria and account for 70% of total malarial deaths. This audit aimed to analyse the adherence of two Ugandan hospitals to the World Health Organisation (WHO) guidelines for the treatment of severe malaria in children and provide an updated paediatric malaria protocol.

Methods Data was collected from children who were admitted with severe malaria to two hospitals in Masaka, Uganda, over a 6-week period. Each patient's notes were examined to determine whether their clinical management had been in accordance with the eight action points identified in the WHO guidance.

Results Twenty-nine children were included in the study. Artesunate, an anti-malarial drug, was administered correctly in 82.7% of cases. None of the patients had urine output documented and blood sugar was measured in 20.7% of cases. Modal frequency of observations was twice daily (44.8%), with five patients having observations recorded only once during admission. Of the patients who received blood transfusions or paracetamol, 43.8% and 53.8% did not meet the WHO's criteria for either treatment, respectively.

Conclusion The administration of antimalarial medication, the mainstay of treatment, was performed to a very high standard. In contrast, this audit identified large disparities in the provision of supportive treatment and little evidence for effective monitoring of patients during their hospital stay. Therefore, the paediatric malaria protocol used by the hospitals was updated to ensure sufficient monitoring of patients during their time in hospital and clear criteria for supportive treatments.

Introduction

Malaria is one of the leading causes of morbidity and mortality in Uganda.¹ Due to a lack of immunity to the disease, children are a particularly vulnerable group, accounting for 70% of all malarial deaths.¹ Severe malaria is defined as a positive malaria test plus signs of organ failure, including impaired consciousness, renal impairment, pulmonary oedema and shock.² The management of severe malaria in children includes three aspects: antimalarial treatment, supportive management and monitoring.²

This audit set out to observe the management of severe malaria in children admitted to two hospitals in Masaka, Uganda. It also aimed to analyse the adherence of the two hospitals to the World Health Organisation's (WHO's) recommendations for the treatment of severe malaria in children;^{2,3} these are international guidelines collated from reliable evidence.

Methods

Data collection occurred in Kitovu Hospital and Villa Maria Hospital, both in Masaka, Uganda. Records from the 1st June to the 16th July 2019 were examined and all children under the age of 16 years with a diagnosis of severe malaria were selected for inclusion.

The collation of three WHO documents^{2,3,4} resulted in a list of eight actions in the management of severe malaria in children. These include: (1) antimalarial treatment, which consists of three doses of artesunate; (2) a 3-day course of Coartem after antimalarial treatment; (3) monitoring urine output; (4) monitoring blood sugar; (5) 4-hourly observations; (6) supportive management with broad-spectrum antibiotics until bacterial infection is excluded; (7) supportive management with paracetamol for pyrexia >38.5°C; and (8) supportive management with blood transfusion if haemoglobin falls below 5 g/dl.^{2,3,4}

The adherence rate for each action was assessed by examining medical notes and observation and drug charts.

Results

The sample group comprised of 29 children ranging from 8 months old to 11 years, of whom 16 (55.2%) were male and 13 (44.8%) were female.

Antimalarial treatment All patients received artesunate. However, artesunate was started 24 hours late in one case, and four patients received an incorrect dose of the drug ($n=3$ received too small a dose and $n=1$ had a dose that exceeded the recommendation; see **Figure 1**).

Coartem was prescribed correctly in 100% of cases and all patients were discharged with instructions to complete the course at home.

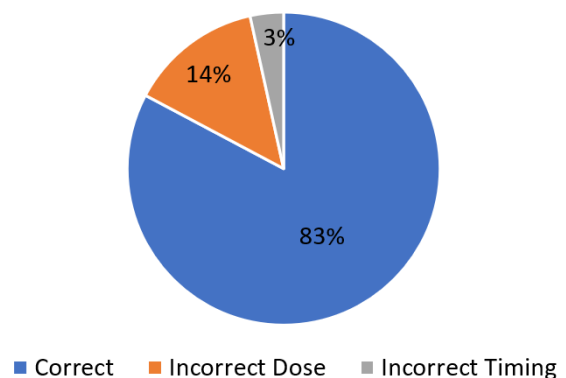


Figure 1. Proportion of correct administration of artesunate and causes of incorrect administration.

Monitoring None of the patients had urine output or fluid balance documented. In contrast, blood sugar was documented for $n=6$ patients (20.7%), of whom $n=3$ were hypoglycaemic and treated accordingly (data not shown). The modal frequency of clinical observations was twice daily (44.8%; **Figure 2**). Observations were done once during admission into hospital in $n=5$ patients.

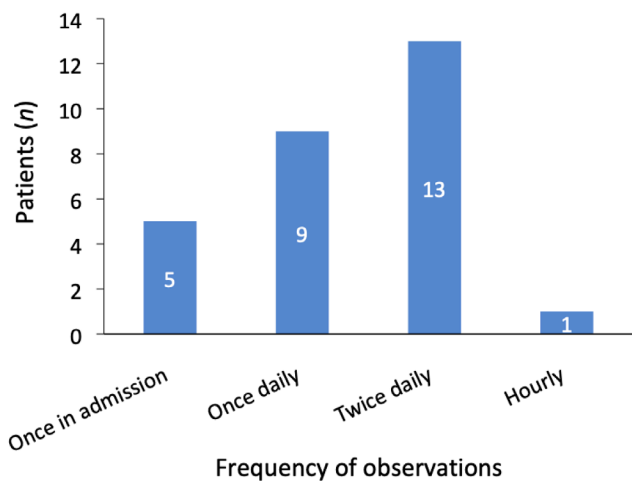


Figure 2. Frequency of clinical observations on the paediatric ward.

Supportive treatment Broad-spectrum antibiotics were started in 19 of 29 patients (65.5%), of which none were stopped upon exclusion of bacterial infection (data not shown).

Of the patients who received paracetamol (89.7%), 53.8% had a temperature $<38.5^{\circ}\text{C}$ (**Figure 3**). Of the 16 patients who received blood transfusions, $n=9$ had a haemoglobin concentration <5 g/dl (data not shown). Of the patients who received blood transfusions or paracetamol, 43.8% and 53.8% did not meet the WHO's criteria for either treatment, respectively.

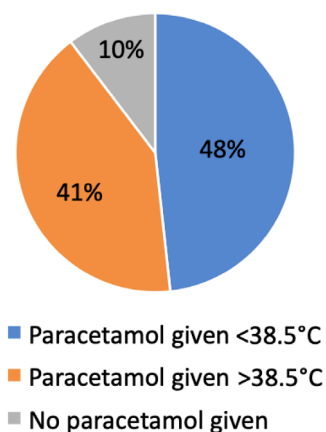


Figure 3. Proportion of patients who received paracetamol, based on whether their temperature was over 38.5°C or not.

Discussion

The hospitals that this audit was conducted in used the Republic of Kenya Ministry of Health's protocol for management of severe malaria in children.⁵ The doctors treating the patients in this study had extensive experience in managing children with severe malaria, yet the results of this audit reflect incomplete adherence to the WHO guidelines. Based on the findings of this audit, the paediatric malaria protocol used was updated (**Figure 4**). The evidence behind each addition to the adapted Ugandan protocol, as well as challenges to adherence are discussed below.

Antimalarial treatment Prompt artesunate administration has the largest effect on survival, reducing the mortality rate of severe malaria from 100% to 20%.¹ The provision of antimalarial treatment was shown to be well-executed by this audit: 96.6% of patients received artesunate immediately on diagnosis and all patients were started on a 3-day course of Coartem.

The wrong dose of artesunate was given to four patients (14%). Whilst records show none of these patients experienced adverse effects whilst in hospital, low dosing could result in treatment failure and malaria recurrence.² Furthermore, Xie et al⁶ describe that side effects, such as anaemia and reticulocytopenia, can result from a high dose of antimalarial drugs. The dosing measurements were, therefore, added to the Ugandan protocol and efforts for two health professionals to check the drug dose should be considered.

Monitoring The WHO recommend that clinical observations and blood sugar concentration are recorded 4-hourly in children administered with severe malaria, as well as daily fluid balances.^{2,3,4} In this study, however, no children had urine output measured, despite four patients developing renal impairment (data not shown). Furthermore, only 20.7% of children had their blood sugar measured on admission and the recommended 4-hourly observation was not carried out in 96% of patients (**Figure 2**). Monitoring is essential to ensure early diagnosis and management of common complications of malaria, such as shock, hypoglycaemia and acute kidney injury (AKI).⁷ One study showed the prevalence of hypoglycaemia in children with severe malaria to be as high as 46.9%⁸ and another found 45.5% of children with malaria developed AKI.⁷ There are practical implications to increasing monitoring and there were concerns amongst staff in Kitovu Hospital about the cost and time repercussions. However, many children urinated into buckets making urine output an easy and reliable, albeit crude, marker of renal function. Furthermore, the effect that these complications have on mortality rate is so severe^{8,9} that it is essential to measure blood sugar concentration and perform clinical observations at least daily.

Supportive treatment Only some of the rationale behind the WHO's recommendations regarding antibiotics, paracetamol and blood transfusions is explained by the literature. Bacterial infection is an important differential diagnosis in a febrile child and co-morbidity of bacterial infection with malaria can be fatal.⁹ There is not, however, clear criteria for excluding bacterial infection nor supporting evidence for the use of antibiotics in malaria. This is needed to provide a uniform approach to antibiotic prescription, as only 65.5% of patients received antibiotics in this study, and the reasoning for who did and who did not was not apparent.

From the literature, it is not clear why the temperature threshold for paracetamol prescription in children with severe malaria is so high (38.5°C). Of the children who were given paracetamol, 53.8% had a temperature $<38.5^{\circ}\text{C}$. However, considering temperatures can peak rapidly in children with malaria⁴ and paracetamol is cheap and well-tolerated,¹⁰ there are limited negative consequences to this apparent over-prescription.

As with the guidance surrounding paracetamol use, there is also limited evidence for the haemoglobin threshold used to indicate when a blood transfusion is required.¹¹ WHO guidelines state that the threshold chosen reduces the overuse of blood products and transfusion-related complications.¹² Maitland et al, conducted a randomised controlled trial to determine the appropriate haemoglobin threshold for transfusion, as they proposed that the conservative threshold set by WHO may increase mortality risk.^{11,13} However, their study concluded that, although it resulted in longer hospital stays, a transfusion threshold of 4 g/dl did not increase 28-day mortality in comparison to a threshold of 6 g/dl, and it resulted in lower blood use.¹³

In line with the audit findings, prompts for supportive treatment was added to the Ugandan protocol. However, evidence to support the

If high quality BS is negative with signs of **SEVERE** malaria, start presumptive treatment **BUT REPEAT** testing and **STOP** treatment if test is negative

SEVERE MALARIA
Fever **plus** any of:

- AVPU = 'V' 'P', 'U'; or
- Unable to drink; or
- Respiratory distress with severe anaemia or acidotic breathing; or
- Hypoglycaemia (glucose ≤ 2.5 mmol/l); or
- >2 convulsions

Treat with artesunate
(or quinine if artesunate is not available)
< 20 kg – give 3 mg/kg
> 20 kg – give 2.4 mg/kg
Give dose at 0, 12 and 24 hours

1. Measure **blood sugars**. If < 3 mmol/l, treat with 5% or 10% dextrose
2. Measure **temperature**. If $> 38.5^{\circ}\text{C}$, treat with 15 mg/kg paracetamol every 4 hours
3. **Maintenance of fluids**: do NOT give bolus fluids unless diarrhoea with signs of shock
4. Start **broad spectrum antibiotics** until invasive bacterial infection is excluded (UTI, pneumonia, meningitis)
5. Measure **Hb**. If Hb < 5 g/dl or signs of severe anaemia, transfuse 10 ml/kg of packed blood **urgently**

Monitor

1. Clinical **observations** every 4 hours
2. **Blood sugar** every 4 hours
3. Fluid balance including **urine output**

No

Severe anaemia, Hb < 5 g/dl, alert (AVPU = 'A'), able to drink and breathing comfortably.

Treatment:

- AL (or oral second line if not available)
- Iron and
- If Hb < 4 g/dl; transfuse 10 ml/kg packed cells or 20 ml/kg whole blood **over 4 hours**

Yes

No

Conduct reliable malaria test (BS or RDT)

Treat with AL (or oral second line if 1st line is not available)

Test positive

Test negative

Antimalarial **NOT** required, look for another cause of illness. **Repeat test** if concerns remain.

If Hb < 9 g/dl, treat with oral iron for 14 days initially. If respiratory distress develops, and Hb < 5 g/dl, transfuse urgently

Treatment failure:

1. Consider other causes of illness/co-morbidity
2. A child on oral antimalarials who develops signs of severe malaria (unable to sit or drink, AVPU=V, U or P and/or respiratory distress) at any stage should be changed to iv artesunate (or quinine if not available)
3. If a child on oral antimalarials has fever and a positive BS after 3 days (72 hours) then check compliance with therapy and if treatment failure proceed to second line treatment

Figure 4. Adaptation to the Ugandan protocol for management of severe malaria in children to include the necessary improvements identified by this audit. AL, artemether-lumefantrine; AVPU, Alert, responds to Voice, responds to Pain and Unresponsive; BS, blood slide; Hb, haemoglobin; RDT, rapid diagnostic test. Figure adapted from the Republic of Kenya Ministry of Health's Basic Paediatric Protocols.⁵

provision of this treatment and guidance on its implementation is still required.

Limitations and conclusions An audit of the management of severe malaria in 29 children in two hospitals in Uganda revealed that, whilst overall management was sufficient, there was incomplete adherence to the WHO guidelines. The small number of patients included in this study limits the significance of these findings as they cannot be generalised to every child admitted with severe malaria in these two hospitals or the wider population. Furthermore, the study was conducted over a short time period of 2 weeks and longer duration studies are required. The lack of complete documentation was also a major limitation of the study as it made it hard to comment on whether actions had been carried out or not. Despite these limitations, this audit identified similar trends across all patients. The administration of antimalarial drugs, the mainstay of treatment, was performed to a high standard. There was, however, limited monitoring of patients and variable provision of supportive care. The findings of this audit have been converted into recommendations, which have been incorporated into a potential protocol to provide the best care for children with severe malaria.

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