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High mortality of infant bacteraemia clinically indistinguishable from severe malaria

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Summary

Background: Early recognition of children at highest risk of dying and the targeting of appropriate drug therapy are vital to the improvement of paediatric care in developing countries. This will rely upon the development of simple clinically-based algorithms and treatment guidelines.
Aim: To determine the role of bacteraemia in children presenting with clinical signs and symptoms of severe malaria.
Design: Retrospective analysis of blood culture results following prospective data collection.
Methods: We studied 251 children presenting with symptoms and signs of severe malaria to a tertiary referral centre in Ghana. Blood was taken for malaria blood films, bacterial culture and haemograms.
Results: On the basis of clinical signs alone, malaria-film-positive ($n=182$) and -negative ($n=69$) patients were indistinguishable. Some 40% of film-negative patients were bacteraemic, vs. 12% of film-positive patients. Severe malaria and bacteraemia were not positively associated. Film-negative bacteraemic patients had a mortality of 39%, primarily affecting the age group <30 months.
Discussion: Infants presenting with symptoms and signs of severe malaria but a negative malaria film require immediate antibiotic treatment.

Introduction

One of the challenges facing health-care workers in resource-poor countries is how to recognize children at highest risk of death, and how to target the use of available drugs cost-effectively. It is not always possible to perform a series of investigations on ill children, and to cover them with all medications until results become available.

Several studies have demonstrated an association between invasive bacterial infection and malaria,[1–3] although how relevant this is clinically, remains controversial.[4] The question remains whether all children presenting with signs of severe illness should be treated with both anti-malarial drugs and broad-spectrum antibiotics, or whether it is possible to distinguish those 'at risk'.

We investigated the prevalence of bacteraemia amongst children presenting with symptoms and signs of severe malaria, in a tertiary referral centre in Kumasi, Ghana.

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Methods

Study site and patients

The study was carried out in the three children's wards of the Komfo Anokye Teaching Hospital (KATH), a tertiary referral centre in Ghana's second city. There are >7500 admissions per year and the wards run at well over 150% bed occupancy (KATH statistics 2002).

The study was carried out as part of a pilot exercise in data collection for a future study on genetic factors responsible for resistance and susceptibility to severe malaria. The Ethical Committee of the School of Medical Sciences, Kumasi, granted ethical permission for the study.

Patients were admitted to the study if they had clinical symptoms suggestive of severe malaria according to WHO guidelines,[5] including children with the following symptoms and signs: (i) a Blantyre coma score of 2 or less; (ii) severe anaemia, with a haemoglobin level of <5 g/dl or a haematocrit of <15%; (iii) severe respiratory distress, being the presence of either marked in-drawing of the bony structure of the lower chest wall or deep (acidotic) breathing; (iv) prostration, being the inability to sit upright in a child normally able to do so, or to drink in the case of children too young to sit.

Patients were examined once for malaria; thick and thin blood films were taken, stained with Giemsa and counted for asexual stages of *P. falciparum*. Likewise, a single blood culture was taken from the patients before the result of the malaria blood film was known, and prior to blood transfusion. Following cleaning of the skin, 2 ml of venous blood was taken and inoculated into brain heart infusion and cooked meat broth. The bottles were incubated for 7 days at 37°C, and were examined daily for evidence of bacterial growth, including turbidity or haemolysis. On alternate days, bottles were subcultured to blood and MacKonkey agar. Subsequent colonies were then identified morphologically using Gram stain, and enterobacteria were further identified by the use of a series of biochemical tests. Serological testing to allow the identification of *Salmonella* species was not available.

Haematocrit was estimated at the bedside using a microcentrifuge and a Hawksley haematocrit reader card; haemoglobin estimation was done using a Sysmex KX-21N cell counter.

Patients were weighed on admission, but height was not routinely measured. Weight-for-age z-scores were calculated. (Anthro software, CDC/WHO Nutrition Unit, 1999).

Children were treated according to local hospital guidelines; this includes all children presenting with a history of convulsions receiving antibiotics (penicillin and chloramphenicol) until the results of lumbar puncture become available. Admitting physicians decided on an individual basis which patients should receive treatment for possible bacteraemia, and they were provided with the blood culture results as soon as they became available.

All parents and guardians were asked whether they had pre-treated the child for malaria, self-medication with a variety of drugs obtained from local pharmacies being common in this area.

Statistical analysis used Statview 5.0. Proportions were compared on contingency tables using χ^2 statistics, and continuous variables using the Mann-Whitney U test for non-parametric data. Multivariate analysis was carried out using STATA 8.2 (StataCorp).

Results

Based on initial clinical assessment, 297 patients were admitted to the study, but 46 were excluded, because a diagnosis other than severe malaria quickly became apparent. Of the 251 remaining, 182 had a blood film positive for *P. falciparum*, and 69 had a negative blood film. A significantly higher proportion of the film-negative group were bacteraemic, compared with the film-positive group ($p < 0.0001$) (Figure 1).

Comparison of presenting clinical features

Blood-culture-positive patients were significantly younger than negative ones ($p < 0.0001$) (Table 1). There was no difference in the proportion of male and female children when comparing the four groups. Nutritional status, as expressed by weight-for-age z scores were comparable between the four groups of patients. There was also no difference in weight-for-age z scores in patients who survived vs. those who died.

The spectrum of presenting symptoms was similar when comparing film-positive and film-negative patients, and also those with and without bacteraemia (Table 2). The film-negative group had somewhat higher reported pre-treatment with antimalarial drugs than the film-positive group, but not significantly so. Subsequent studies on similar groups of patients showed no difference in plasma chloroquine levels when comparing film-positive and film-negative patients (manuscript in preparation).

In the group of film-positive children, white blood cell counts were slightly higher in blood-culture-positive vs. blood-culture-negative patients ($p = 0.05$), but no such difference was seen in the film-negative children (Table 1). There was also

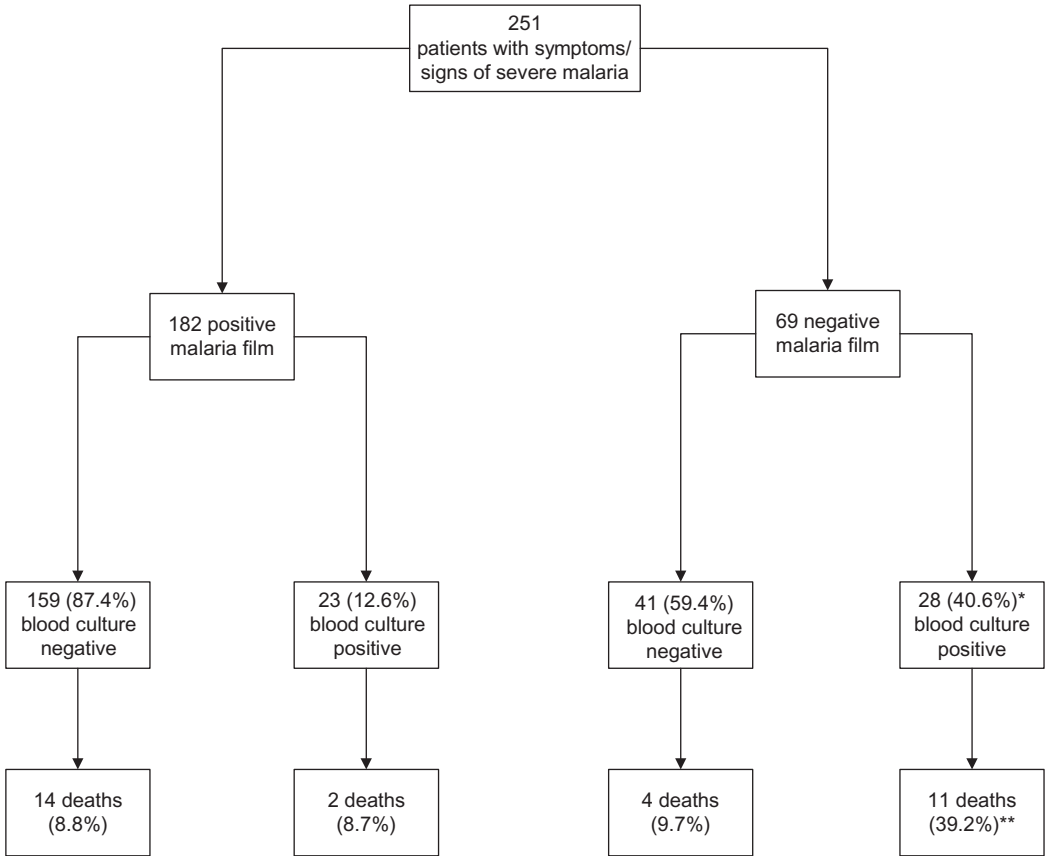

Figure 1. Children presenting with symptoms and signs of severe malaria: results of malaria blood films, blood cultures and mortality. *p < 0.0001; **$p < 0.0001$.

Table 1 Clinical and laboratory characteristics of patients

	Malaria film +ve, blood culture −ve ($n = 159$)	Malaria film +ve, blood culture +ve ($n = 23$)	Malaria film −ve, blood culture −ve ($n = 41$)	Malaria film −ve, blood culture +ve ($n = 28$)
Age in months (median)[1]	4–120 (24)	7–74 (12)	5–132 (24)	5–42 (12)
Sex[2] (F:M)	78:81	11:12	24:17	11:17
Parasite count (/μl)[3]	58 220 (40–1 064 586)	144 319 (110–2 044 100)	–	–
White cell count ($\times 10^9$/l)[4,5] (mean)	1.2–21.0 (7.8)	4.4–27.9 (9.7)	1.6–30.8 (9.9)	3.6–19.7 (9.5)
Median (range) weight-for-age z-score[6]	−1.51 (−5.0 to 2.99)	−1.64 (−4.18 to 0.25)	−1.64 (−4.55 to 0.43)	−1.54 (−2.87 to 0.29)

[1]Blood-culture-positive patients were significantly younger then negative ones ($p < 0.0001$). [2]No significant difference. [3]No significant difference. [4]WCC slightly higher in parasite-positive, blood-culture-positive patients when compared to parasite-positive blood-culture-negative ones ($p = 0.04$). [5]No difference in WCC between parasite-negative, blood-culture-positive and -negative children. [6]No difference in weight-for-age z-scores between groups.

Table 2 Patients presenting with symptoms and signs of severe malaria

	Malaria film +ve, blood culture −ve ($n=159$)	Malaria film +ve, blood culture +ve ($n=23$)	Malaria film −ve, blood culture −ve ($n=41$)	Malaria film −ve, blood culture +ve ($n=28$)
Prostration	31%[1]	35%[1]	35%[1]	32%[1]
Coma	19%	9%	12%	14%
Severe anaemia	15%	4%	19%	17%
Prostration + severe anaemia	22%	35%	20%	25%
Prostration + RDS[2]	2%	4%	1%	0%
Coma + severe anaemia	6%	9%	6%	4%
Coma + RDS	2%	0%	3%	4%
Severe anaemia + RDS	1%	4%	1%	0%
Prostration + severe anaemia + RDS	1%	0%	3%	4%
Coma + severe anaemia + RDS	1%	0%	0%	0%
Pre-treated with antimalarial drugs[3]	69%	78%	75%	82%

[1]Although inappropriate for the small sample size, percentages are presented for intelligibility. [2]Respiratory distress syndrome. [3]No significant difference was found between film-positive and film-negative patients ($p=0.18$).

no significant difference between the parasite counts of the blood-culture-positive and -negative children in the film-positive group.

Risk factors for mortality

In this setting, mortality risk was higher in children with bacteraemia than in those without (crude OR 3.5, 95%CI 1.4–8.2) and lower in children with parasitaemia than in those without (crude OR 0.4, 95%CI 0.2–0.8). These effects were predominantly seen in younger children: children aged <18 months with bacteraemia had an almost 5-fold greater risk of dying (OR 4.7, 95%CI 1.4–17.3). In children aged >18 months, this effect was not significant in a bivariate χ^2 test.

Different logistic multivariate models with death as the outcome were tested. These incorporated the following exposure variables: presence of parasitaemia, presence of bacteraemia, age under 18 months, sex, and white cell count. Likelihood ratio tests were performed to measure how well a model accounted for the outcome, and whether the exclusion of single variables affected the quality of the model. In the multivariate analysis, presence of bacteraemia was confirmed as the major risk factor for death among children presenting with clinical symptoms of severe malaria, after adjusting for age, sex, and white blood cell counts. The best model was based on a simple interaction between parasitaemia and bacteraemia (LR –86.0, df 3, $p<0.002$). Influence of the other exposure variables on the quality of the model was marginal. Children without parasitaemia but with detectable bacteraemia were at the highest risk (adjusted OR 6.0, 95%CI 1.7–23.5).

Bacteriology results

The commonest organisms isolated from both groups were non-typhoid *Salmonella* (NTS) species and *Staphylococcus aureus* (Table 3). Isolates of *Staphylococcus epidermidis*, micrococcus, *Streptococcus* viridans and *Bacillus* species were considered to be contaminants and were excluded from the analysis.

There was an increased proportion of NTS in the film-negative group, accounting for 9/11 deaths (82%) in that group. In the film-positive group, one death occurred in a patient with NTS and the other in a patient with *Staphylococcus aureus*.

Association between severe malaria and bacteraemia

Twenty-three of the film-positive patients (12%) were bacteraemic. With frequencies in our study group of 0.73 for parasitaemia and 0.20 for bacteraemia, the expected frequency of both incidentally occurring together would be 0.15, or 37 cases. That we found 23 such cases only suggests that in this setting severe malaria and bacteraemia were not positively associated.

Discussion

In this study, patients presenting with WHO-defined clinical signs and symptoms of severe malaria, but with a negative malaria blood film, had a high risk of bacterial sepsis, which carried with it a very high mortality.

This observation was true for all clinical subtypes of severe malaria, including 14 patients

Table 3 Bacterial isolates from patients presenting with symptoms and signs of severe malaria

	Whole patient group ($n=51$)	Malaria-film positive ($n=23$)	Malaria-film negative ($n=28$)
Non-typhoid *Salmonella* species (NTS)	29 (57%)	10 (43%)[1]	19 (68%)[2]
Staphylococcus aureus	15 (29%)	9 (39%)[3]	6 (21%)[4]
Escherichia coli	2 (4%)	1 (4%)	1 (4%)
Proteus	1 (2%)	0	1 (4%)
Providencia	1 (2%)	1 (4%)	0
Other coliforms	2 (4%)	1 (4%)	1 (4%)
Streptococcus pneumoniae	1 (2%)	1 (4%)	0

[1]Clinical findings of film-positive patients with NTS: severe anaemia ($n=8$), coma ($n=1$), prostration ($n=1$). [2]Clinical findings of film-negative patients with NTS: severe anaemia ($n=9$), coma ($n=2$), prostration and respiratory distress syndrome ($n=1$), prostration ($n=7$). [3]Clinical findings of film-positive patients with *S. aureus*: severe anaemia ($n=2$), coma ($n=1$), prostration and respiratory distress syndrome ($n=1$), prostration ($n=5$). [4]Clinical findings of film-negative patients with *S. aureus*: severe anaemia ($n=2$), coma ($n=2$), severe anaemia and coma ($n=1$), prostration ($n=1$).

who presented with severe anaemia. It has long been recognized that children presenting with fever, no focus of infection and a negative malaria film should be treated for bacteraemia,[6] but this clinically-based study goes further in describing a group of patients, clinically indistinguishable from those with any type of severe malaria, who require urgent treatment with broad spectrum antibiotics.

It was impossible to distinguish patients found to be malaria-film-positive from those with a positive blood culture on the basis of clinical signs or white blood cell counts. It may be possible that a more detailed clinical examination of the children would reveal distinguishing clinical features. For example, pulse rate and blood pressure were not measured in these patients, and it remains possible that the bacteraemic patients showed more signs of circulatory shock (tachycardia, hypotension and poor peripheral perfusion) compared to those without bacteraemia. There are, however, clearly many similarities between severe malaria and the sepsis syndrome,[7] as shown by this study. It is probable that the bacteraemic children in this study were shocked, and they may have benefited from bolus intravenous fluids, as may children with severe malaria.[8]

This study looked at only one group of patients presenting in a specific way and therefore no comment can be made about the presentation of all patients with bacteraemia in this setting. Invasive bacterial disease did occur in the younger patients, as has been shown in other studies.[1] In both malaria-positive and -negative groups, there was a greater proportion of bacteraemic patients in children aged <2 years and, importantly, 12 of the 13 deaths in bacteraemic patients occurred in children aged <2 years. The predominant organisms found in all patients were non-typhoid *Salmonellae* (NTS), responsible in the developed world for gastroenteritis, where they only rarely become invasive. It has been postulated that perhaps young children are more vulnerable due to factors such as decreased gastric acidity or immaturity of gut lymphoid tissue.[9] NTS have been reported in other studies from Africa to be the predominant cause of bacteraemia in children,[10,11] and to be associated with both the presence of malaria parasites and malarial anaemia.[2,12] Fifty percent of the patients in the malaria-negative group who were bacteraemic also had severe anaemia, supporting this association. The study was carried out during the peak malaria season, and should be repeated during the low season to investigate whether the range of responsible organisms changes through the year.

One may argue that some film-negative cases could become positive on repeated examinations, or were malaria infections that had been treated. It was not possible to consistently include in the study repeat malaria films or blood smear examinations for malaria pigment, to provide more sensitive assessments of ongoing parasitaemia and recent parasitaemia, respectively. This particularly applies to the 41 cases with negative malaria films and negative blood cultures (Table 1). Although clinical malaria may persist beyond the period of parasitaemia, cases of film-negative severe malaria are considered to be rare. It appears more likely to us that cases with bacteraemia were missed because they remained undetected in our setting of examining only a single culture of a small blood volume. Therefore, we strongly believe that firstly, the vast majority of our film-negative children have conditions other than malaria, and secondly, that the numbers of cases of bacteraemia we report are still underestimates.

This is a highly selected group of patients, presenting to a tertiary referral centre. A subsequent study showed that 64% of children presenting to the hospital had already attended another health care facility and a total of 95% had either been to another facility or had taken self-medication. In the present study, 72% of patients were said to have previously taken chloroquine, a figure supported by measuring plasma chloroquine levels in the subsequent study. The widespread use of anti-malarials in these patients (Table 2) may simply reflect the general attitude in sub-Saharan Africa to give any child with fever an anti-malarial as a first-line treatment. At present, chloroquine is the drug of choice for the treatment of malaria in the community in Ghana, although in the face of increasing evidence of resistance,[13] this is soon to change. Children admitted to a subsequent study in the months after the one described here were shown to carry *P. falciparum* isolates, 88% of which carried genetic markers of chloroquine resistance.

It is surprising that there are so few cases of pneumococcal disease, but experience in the laboratory in this hospital has shown that *S. pneumoniae* was difficult to culture. Very few carers gave a specific history of having given their child antibiotics prior to admission but, in view of the high proportion of self-medication and health facility visits, it is likely that many children had received antibiotics in some form. This may have contributed to the surprisingly low isolation rate of pneumococcal isolates.

This study cannot answer the question as to which patients presenting with film-positive severe malaria require additional treatment with antibiotics, and the relatively low number of film-positive, bacteraemic cases suggests that severe malaria and bacteraemia in our setting were not positively associated. In contrast to other studies,[1] there was no increase in mortality in patients with both infections. However in common with other studies the children who had bacteraemia were younger, indicating that in children aged <2 years, treatment with additional antibiotics should be considered. Several questions remain, however, including how successful antibiotic treatment of invasive bacterial infection can be achieved in this setting.

This study did not set out to address the question of antibiotic sensitivity. The limited sensitivity testing done indicated that >50% of the NTS isolates were chloramphenicol-resistant, a problem that is of increasing concern throughout Africa.[14] There is an urgent need to review the true prevalence and emergence of resistant strains, and to evaluate methods of rapid detection. This should be carried out alongside studies of the minimal safe period of antibiotic treatment that is necessary in these patients, combining such a study with thorough long-term follow-up. Only then can recommendations for antibiotic regimes be made and their use evaluated.

Many patients admitted to hospital in the developing world die within 24 h of admission, and the need for improvement in triage and the delivery of emergency care is well recognized.[15,16] Simple algorithms enabling decisions regarding drug therapy to be made are useful in these situations and this study emphasizes one such scenario.

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