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MAJOR ARTICLE

High Frequency of Clinically Significant Bacteremia in Adults Hospitalized With Falciparum Malaria

Phyo Pyae Nyein,[1] Ne Myo Aung,[1] Tint Tint Kyi,[1] Zaw Win Htet,[1] Nicholas M. Anstey,[2] Mar Mar Kyi,[1] and Josh Hanson[2]

[1]Insein General Hospital, Yangon, Myanmar; [2]Menzies School of Health Research, Charles Darwin University, Darwin, Australia

Background. African children with severe falciparum malaria commonly have concomitant Gram-negative bacteremia, but co-infection has been thought to be relatively rare in adult malaria.

Methods. Adults with a diagnosis of falciparum malaria hospitalized at 4 tertiary referral hospitals in Myanmar had blood cultures collected at admission. The frequency of concomitant bacteremia and the clinical characteristics of the patients, with and without bacteremia, were explored.

Results. Of 67 adults hospitalized with falciparum malaria, 9 (13% [95% confidence interval, 5.3%–21.6%]) were also bacteremic on admission, 7 (78%) with Gram-negative enteric organisms (*Escherichia coli* [n = 3], typhoidal *Salmonella* species [n = 3], nontyphoidal *Salmonella* [n = 1]). Bacteremic adults had more severe disease (median Respiratory Coma Acidosis Malaria [RCAM] score 3; interquartile range [IQR], 1–4) than those without bacteremia (median RCAM score 1; IQR, 1–2) and had a higher frequency of acute kidney injury (50% vs 16%, $P = .03$). Although 35 (52%) were at high risk of death (RCAM score ≥2), all 67 patients in the study survived, 51 (76%) of whom received empirical antibiotics on admission.

Conclusions. Bacteremia was relatively frequent in adults hospitalized with falciparum malaria in Myanmar. Like children in high transmission settings, bacteremic adults in this low transmission setting were sicker than nonbacteremic adults, and were often difficult to identify at presentation. Empirical antibiotics may also be appropriate in adults hospitalized with falciparum malaria in low transmission settings, until bacterial infection is excluded.

Keywords. antibiotics; bacteremia; clinical management; falciparum malaria; salmonella.

More than 6% of African children with severe falciparum malaria (SFM) have concurrent bacteremia when admitted to hospital; these children have a case-fatality rate that is more than two fold greater than those with SFM alone [1]. There is no reliable way to identify these bacteremic children either clinically or with basic laboratory tests, and so World Health Organization (WHO) guidelines recommend that all children hospitalized with SFM in areas of intermediate and high malaria transmission receive immediate broad-spectrum antibiotics in addition to their antimalarial therapy [2].

In contrast, there are fewer data in adults with SFM. Only 1 case of bacteremia was identified in an Indian series of 67 adults hospitalized with malaria [3]. None of 38 Tanzanian adults with hospitalized with Plasmodium *falciparum* parasitemia and severe febrile illness were bacteremic [4], whereas unpublished Vietnamese data from the 1990s suggested that concomitant bacteremia occurred in only 0.2% of adults [2]. As a result, when compared with the strong recommendation for immediate antibacterial therapy in all children with SFM in moderate and high transmission areas, WHO guidelines for the management of adults are less prescriptive. Although a low threshold for initiation is generally advised, the guidelines do not clearly recommend empirical antibacterial therapy in adults unless they are hypotensive or have a clinical syndrome compatible with serious bacterial infection [2].

However, clinicians in resource-limited settings commonly start antibacterial therapy in any patient hospitalized with malaria. Although not necessarily conforming to WHO guidelines, the practice is understandable. Falciparum malaria can be rapidly fatal, and antibiotics are one of the few affordable adjunctive treatments that is widely available in these settings [2]. However this strategy has potential shortcomings: indiscriminate use of antibiotics increases health care costs and the risk of drug side effects, while driving antibiotic resistance, which is already at concerning levels in malaria endemic areas [5].

Given the paucity of published data to guide practice, this study was performed to better define the frequency of concomitant bacteremia in adults hospitalized with falciparum malaria and the clinical characteristics of such patients.

MATERIALS AND METHODS

The study enrolled adults admitted with a diagnosis of falciparum malaria to 4 tertiary referral hospitals in Yangon and Mandalay, Myanmar, between January 1, 2014 and September 30,

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Correspondence: J. Hanson, Cairns Base Hospital, The Esplanade, Cairns, Queensland 4870, Australia (drjoshhanson@gmail.com).

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2015. The 4 hospitals serve socioeconomically disadvantaged, predominantly urban populations exposed to low, seasonal transmission of malaria [6].

Patients with symptoms of malaria were screened with immunochromatographic rapid diagnostic tests (SD Bioline Malaria Ag P.f/P.v; Standard Diagnostics). Experienced hospital laboratory technicians confirmed the diagnosis of falciparum malaria using blood films. Patients who had received 1 dose of parenteral, or more than 24 hours of oral, antibacterial therapy were excluded from the study. The remaining patients had 10 ml of blood inoculated into a BACTEC-Plus Aerobic blood culture bottle (Becton Dickinson) and incubated for 5 days. Positive cultures were subcultured, and the isolates' identity and antibiotic sensitivity were determined using the Vitek system (Biomérieux). Patients were managed according to WHO guidelines [2], receiving artesunate, although any prescription of antibacterial therapy was left to the discretion of treating clinicians. Logistical issues frequently precluded the prompt availability of blood culture results, and so they did not always influence the type or duration of the antibiotics that were prescribed. The study enrolled all patients hospitalized with a diagnosis of falciparum malaria, and disease severity was measured using the Respiratory Coma Acidosis Malaria (RCAM) score. In previous series, adults with RCAM scores of 2, 3, and 4 who were able to receive artesunate had case-fatality rates of 14%, 28%, and 57%, respectively [7]. The Ethical Review Committees of the University of Medicine 2, Yangon and the Menzies School of Health Research, Darwin approved the study. Groups were analyzed using the Kruskal–Wallis, χ^2 and Fisher's exact tests using Stata 10.0 software (StataCorp).

RESULTS

After 23 patients had been excluded on the basis of prior antibiotic exposure, 67 adults with falciparum malaria were enrolled. All 67 survived to discharge despite the fact that 35 (52%) were at high risk of death: 19 (28%), 10 (15%), and 6 (9%) with RCAM scores of 2, 3, and 4, respectively. Attending clinicians prescribed empirical parenteral antibacterial therapy in 51 (76%) patients; 41 (80%) received third-generation cephalosporins. Only 1 of 62 (2%) patients tested for human immunodeficiency virus was seropositive. The other characteristics of the patients are presented in Table 1.

Of the 67 adults with falciparum malaria, 13 had positive blood cultures. Nine (13.4%; 95% confidence interval, 5.3%–21.6%) had significant isolates (3 *Escherichia coli*, 2 *Salmonella* Paratyphi A, 2 *Staphylococcus aureus* [1 methicillin sensitive and 1 methicillin resistant], 1 *Salmonella typhi*, and 1 *Salmonella typhimurium*), whereas 4 isolates were considered contaminants (2 coagulase-negative staphylococci, 1 *Sphingomonas paucimobilis* and 1 *Microbacterium aerolatum*). The 9 patients with significant bacteremia all received antibacterial therapy on admission to hospital (Table 2), although 4 (44%) had isolates with in vitro resistance against the initially selected therapy.

Bacteremic patients were sicker than the other patients in the study: they had higher RCAM scores—4 of 6 (66%) of the patients with the highest RCAM score of 4 were concurrently bacteremic—and a greater incidence of acute kidney injury (Tables 1 and 2). However, the minority (33%) of the bacteremic patients had bacterial co-infection suspected by clinicians. Bacteremic patients were usually not hypotensive; only 2 (22%) had an admission mean arterial pressure <65 mmHg (60 and 63 mmHg, respectively). No patient required vasopressor support during the study, and none had gastrointestinal bleeding or suspected splenic rupture. Although bacteremic patients had a higher median neutrophil count, 4 of 9 (44%) of these patients had a neutrophil count within the normal range.

DISCUSSION

This series identified a higher rate of concurrent bacteremia than has been previously identified—or thought to be present—in adults hospitalized with falciparum malaria. Patients in this series were enrolled consecutively and had less severe disease than in previously published large cohorts [7] excluding active case finding as an explanation. Human immunodeficiency virus seropositivity is a risk factor for bacteremia [1], but this was rare in this series and so would not explain our results. Even if all of the patients excluded from the study for prior antibacterial therapy had returned negative blood cultures, clinically significant bacteremia would still have been present in 10%, comparable to the rate seen in African children with SFM.

Indeed, this study's findings closely resemble those in the pediatric population: there was a similarly high frequency of concomitant bacteremia, a similar preponderance of enteric Gram-negative pathogens, and a similar association with more severe disease [1]. This may not be surprising because the mechanisms that have been proposed to explain the pathogenesis of bacteremia in SFM in children are also present in adults. Sequestration of parasitized erythrocytes in the microcirculation is central to the pathogenesis of falciparum malaria in both adults and children [2] and leads to impaired blood flow and endothelial dysfunction [8]. The resulting tissue ischemia is hypothesized to impair mucosal barrier function, increasing bacterial translocation from the gastrointestinal tract [9, 10]. Infection with *P falciparum* also impairs the host's immune response to bacterial infection [10]. Rapid phagocytosis by neutrophils of the parasite's digestive vacuoles drives neutrophils into a state of functional exhaustion, blunting their response to challenge with bacterial pathogens [11]. Meanwhile, hemolysis inhibits the neutrophil oxidative burst by inducing heme oxygenase [10] and quenching nitric oxide [12]. Macrophage and humoral immune dysfunction have also been hypothesized to increase susceptibility to concomitant bacterial infection [10].

However, although the pathophysiology of falciparum malaria is similar in adults and children, adults with SFM have a

Table 1. Comparison of the Clinical and Laboratory Features of the 67 Patients Who Were Hospitalized With Falciparum Malaria With and Without Pathogens in Admission Blood Cultures[a]

Variable	Pathogen in Blood Culture n = 9	No Pathogen in Blood Culture n = 58	*P* Value
Age (years)	32 (22–46)	34 (25–44)	.91
Sex (number and % male)	7 of 9 (78%)	47 of 58 (81%)	.82
Fever duration before admission (days)	5 (5–8)	5 (3–7)	.17
Temperature on admission (°C)	39.8 (39.2–40)	38.9 (38.3–39.6)	.05
Suspected bacterial co-infection[b] (number and %)	3 of 9 (33%)	8 of 54 (15%)	.18
HIV positive[c] (number and %)	1 of 9 (11%)	0 of 53	.15
Glasgow Coma Scale	11 (9–15)	15 (12–15)	.08
Coma[d]	4 of 9 (44%)	10 of 58 (17%)	.06
Respiratory rate[e] (breaths/minute)	40 (33–46)	32 (24–36)	.01
Heart rate[e] (beats/minute)	112 (100–118)	100 (88–112)	.03
Mean arterial blood pressure[e] (mmHg)	87 (67–98)	80 (70–87)	.43
Mean arterial pressure <65 mmHg[e]	2 of 9 (22%)	8 of 55 (15%)	.56
Systolic blood pressure[e] (mmHg)	110 (90–125)	100 (90–120)	.90
Hemoglobin (g/dL)	8.8 (5.3–10.4)	10.1 (8.0–12.6)	.09
White blood cell count ($\times 10^9$/L)	8.6 (7.0–11.8)	6.5 (4.9–8.5)	.01
Neutrophil count[f] ($\times 10^9$/L)	7.9 (5.7–8.7)	3.9 (2.9–6.3)	.004
Neutrophilia[f] (number and %)	5 of 9 (56%)	9 of 56 (16%)	.007
Lymphocyte count[f] ($\times 10^9$/L)	1.3 (0.8–2.2)	1.5 (1.1–2.1)	.39
Neutrophil/lymphocyte ratio[f]	4.5 (3.5–9.2)	2.7 (1.5–5.2)	.02
Platelet count ($\times 10^9$/L)	72 (55–140)	96 (40–150)	.99
Creatinine[g] (mg/dL)	1.9 (1.2–2.9)	1.2 (1.0–1.6)	.08
Acute kidney injury[g]	4 of 8 (50%)	9 of 56 (16%)	.03
RCAM score[h]	3 (1–4)	1 (1–2)	.04
Clinical jaundice	5 of 9 (56%)	26 of 58 (45%)	.55
Abnormal bleeding	0 of 9	3 of 58 (5%)	.49
Diarrhea	2 of 9 (22%)	4 of 58 (7%)	.13
Acute respiratory distress syndrome[i]	0 of 9	1 of 58 (1%)	.69
Significant comorbidities[j]	2 of 9 (22%)	9 of 58 (16%)	.61

Abbreviations: HIV, human immunodeficiency virus; RCAM, Respiratory Coma Acidosis Malaria.

[a] All numbers are the median and interquartile range unless otherwise stated.

[b] In 4 patients, there were insufficient clinical data to determine whether bacterial co-infection was suspected.

[c] Five patients did not have their HIV status tested.

[d] Glasgow Coma Scale score <11.

[e] Four nonbacteremic patients did not have their admission blood pressure, heart rate, or respiratory rate recorded.

[f] Neutrophil reference range (2.5–7.5 $\times 10^9$/L); 2 patients did not have a white cell differential count available.

[g] Acute kidney injury (defined as serum creatinine >2 mg/dL); 3 patients did not have a serum creatinine recorded.

[h] Calculated by combining respiratory rate and Glasgow Coma Score [7].

[i] Bilateral alveolar changes on chest x-ray and oxygen saturation <90%.

[j] Comorbidities were HIV infection and diabetes mellitus, respectively, in the 2 patients with pathogens in blood culture. The 9 patients with significant comorbidities, without pathogens in blood culture, included 2 patients with hazardous alcohol intake, 1 patient with diabetes mellitus, 1 patient with pulmonary tuberculosis, 1 patient with chronic airways limitation, 1 patient with chronic hepatitis B infection, 1 patient with chronic hepatitis C infection, 1 patient with chronic renal impairment, and 1 patient with radiological and clinical evidence of pneumonia.

higher case-fatality rate [2]. The majority of deaths occur within 48 hours of hospitalization [13], emphasizing the importance of optimal early supportive care. Although the patients in this study were generally not as sick as in some other series [13], more than half had RCAM scores of 2 or greater; scores that have been historically associated with case-fatality rates of 14%–57% [7]. It is therefore notable that in a study in which most of the patients received empirical antibiotics on admission to hospital, the overall survival was 100%.

Malaria is prevalent in locations where microbiological and other laboratory services are usually limited. This lack of diagnostic support—and an inability to identify children with concomitant bacterial infection reliably with clinical assessment—led the WHO to recommend that all children with SFM in areas of intermediate and high transmission should also receive immediate broad-spectrum antibiotics. However, clinicians caring for adults with malaria in low transmission settings face similar challenges. Diagnostic support is very limited at the 4 Myanmar referral hospitals where this study was performed, with the financial cost of blood cultures and many other laboratory investigations precluding their collection outside of the research setting. Furthermore, in this series, just as in children, clinical evaluation frequently failed to identify those adults with concurrent bacterial infection. If there is a similar

Table 2. Characteristics of the 9 Patients With Pathogens in Blood Culture on Admission to Hospital

Age, Sex	Organism	RCAM Score	Blood Pressure on Admission (MAP) (mmHg)	Bacterial Infection Suspected Clinically	White Cell Count (Neutrophil Count) ($\times 10^9$/L)	Plasma Creatinine (mg/dL)	Antibiotics Prescribed on Admission	Sensitive in Vitro to Antibiotics Prescribed on Admission	Outcome
42, M	*Salmonella typhimurium*	4	80/50 (60)	No	10.8 (8)	3	Ceftriaxone	No[a]	Survived
52, M	*Salmonella* Paratyphi A	4	130/90 (103)	No	8.6 (7.9)	7.9	Ceftriaxone	Yes	Survived
26, M	*Staphylococcus aureus* (CA-MRSA)	4	120/80 (93)	No	12.8 (9.4)	2.5	Ceftriaxone	No[b]	Survived
32, M	*Salmonella typhimurium*	4	100/80 (87)	Yes	6.6 (4.9)	2.5	Ciprofloxacin and cotrimoxazole	Yes	Survived
36, F	*Escherichia coli*	3	90/50 (63)	No	6.5 (4.2)	Not recorded	Ceftriaxone	Intermediate	Survived
20, M	*Escherichia coli*	2	90/60 (70)	No	8.4 (6.5)	1.4	Ceftriaxone	No[c]	Survived
23, M	*Salmonella* Paratyphi A	1	110/80 (90)	No	7.3 (6.5)	1.1	Ceftriaxone	Yes	Survived
19, F	*S aureus* (MSSA)	1	110/70 (83)	Yes	12.8 (9.8)	0.9	Ceftriaxone and levofloxacin	Yes	Survived
50, M	*Escherichia coli*	1	140/100 (113)	Yes	10.4 (8)	1.3	Levofloxacin	No[d]	Survived

Abbreviations: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; MAP, mean arterial blood pressure; MSSA, methicillin-sensitive *Staphylococcus aureus*; RCAM score, Respiratory Coma Acidosis Malaria score.

[a] Antibiotic therapy changed to cefepime, to which the organism was sensitive, at 48 hours.

[b] Levofloxacin, to which the organism was sensitive, was added at 48 hours.

[c] Patient received only 5 days of ceftriaxone to which the organism was resistant in vitro but the patient improved steadily, was afebrile after 3 days, and was discharged after 6 days.

[d] Patient changed to cefepime, to which the organism was also resistant in vitro, after 48 hours, but the patient improved steadily, was afebrile after 3 days, and made a complete recovery after 7 total days of antibiotic therapy.

prevalence of bacterial co-infection in adults and children with SFM in malaria-endemic areas and similar obstacles to its diagnosis, it is reasonable to suggest that empirical antibacterial therapy may potentially have a role in adults as well.

Evolving antimicrobial resistance in malaria-endemic areas [5, 14] makes the selection of empirical regimens challenging. Indeed, in this series, almost half of the isolates displayed in vitro resistance to the initial antibiotic regimen; the relative youth of the patients, their limited comorbidities, and their presentation before septic shock had supervened may all have mitigated the anticipated increased risk of death [15]. However, based on the findings in this study and in the African pediatric literature, perhaps some general recommendations are possible: it would appear prudent to select an initial broad-spectrum regimen that covers Gram-negative enteric organisms and that takes into account local resistance patterns. Prompt de-escalation would minimize further antimicrobial selection pressure.

The improved diagnostic yield in this study might be explained by its use of modern microbiological techniques. Community-acquired bacterial infections are not uncommonly identified in studies of imported severe malaria where there is access to better laboratory support. In one such series, 30 of 400 (8%) cases had microbiologically proven bacterial infections, including 10 (2.5%) with bacteremia, the majority of which were enteric organisms [16]. Collecting a greater volume of blood and excluding patients with significant prior antibiotic exposure may also have contributed to our results, as may have geographical differences in the prevalence of *Salmonella* infection. It is notable that the majority of invasive *Salmonella* isolates in this low malaria transmission area were typhoidal *Salmonella* species. This is consistent with previous studies of co-infection epidemiology in Africa, where nontyphoidal *Salmonella* species predominate in high malaria transmission areas but typhoidal *Salmonella* species predominate in regions of low, unstable malaria transmission [17, 18]. A 1929 report from British Guiana, where *Salmonella* Paratyphi C was endemic at the time, noted an increased incidence and virulence of paratyphoid in adults and children during malaria epidemics [19]; in one such epidemic, 29% of patients presenting with paratyphoid also had malaria, with the case-fatality rate for paratyphoid—in the pre-antibacterial era—rising to 38%.

The study's findings generate other hypotheses. Hypotension in patients with malaria—previously termed "algid malaria"—is incompletely understood, but it was present in 12% of patients enrolled in the largest study of adults with SFM [13], and it is more common with increasing age [2]. Although a number of pathophysiological mechanisms have been proposed to explain this hypotension—including hypovolemia, gastrointestinal bleeding, splenic rupture, and cardiovascular collapse from metabolic acidosis—the relative frequency of bacteremia seen in this series suggests that concomitant bacterial infection may be underdiagnosed. Indeed, given that blood cultures are commonly negative in patients with bacterial sepsis [20], the 13% prevalence of bacteremia in this study may even represent

an underestimate of the true frequency of significant bacterial co-infection. The association between leukocytosis and bacteremia in this study could explain, at least in part, the longstanding recognition that adults with SFM and leukocytosis have a worse prognosis [2].

With the epidemiology of bacterial co-infections varying with malaria transmission intensity [17], our findings in this region of low, seasonal transmission may not necessarily be generalizable to adults in high transmission areas. Indeed, in regions of high malaria transmission, positive blood films in adults—who have developed at least partial immunity to the parasite—may be incidental to their clinical presentation. A positive malaria film in adults in these locations, by itself, would not be an indication for antibacterial therapy. However, studies of very sick febrile patients in these high malaria transmission settings have demonstrated a high incidence of severe bacterial infection, and the importance of early antibacterial therapy in patients with and without parasitemia has been emphasized [4].

CONCLUSIONS

Our data require replication in larger series; however, they demonstrate that adults hospitalized with falciparum malaria may have concomitant bacteremia in the absence of hypotension or a clinical suspicion of bacterial co-infection. This suggests that the present WHO guidelines for antibacterial therapy in adults with severe malaria may be too conservative. Limited diagnostic services preclude targeted antibacterial therapy in most malaria-endemic areas, and, for this reason, empirical antibacterial therapy is recommended in all children with SFM in high and intermediate transmission settings. Although more supporting data are required before this recommendation can necessarily be expanded to adults in low transmission settings, the high rates of bacteremia seen in this series suggest that particularly in sicker patients, such a strategy may be appropriate.

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