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Acetaminophen and Ibuprofen in Pediatric Central Nervous System Malaria
A Randomized Clinical Trial

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IMPORTANCE A third of children who survive malaria with neurological involvement (central nervous system [CNS] malaria) develop sequelae. A higher maximum temperature (Tmax) and seizures are risk factors for sequelae.

OBJECTIVE To compare aggressive antipyretic therapy using scheduled acetaminophen and ibuprofen vs usual care with acetaminophen alone given only for a temperature of 38.5 °C or higher.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial was conducted at inpatient pediatric services of 1 tertiary care and 1 district hospital in Zambia and a tertiary care center in Malawi. Included were children aged 2 to 11 years with CNS malaria (excluding those with creatinine >1.2 mg/dL), who were enrolled from 2019 to 2022. Data analysis took place from December 2022 to April 2023.

INTERVENTION The aggressive antipyretic group received acetaminophen (30 mg/kg load, then 15 mg/kg) plus ibuprofen, 10 mg/kg, every 6 hours, regardless of clinical temperature for 72 hours. The usual care group received 15 mg/kg of acetaminophen as needed every 6 hours for a temperature of 38.5 °C or higher.

MAIN OUTCOMES AND MEASURES The primary outcome variable was Tmax over 72 hours, the total duration of follow-up. Secondary outcomes included seizures and parasite clearance.

RESULTS Five hundred fifty-three patients were screened, 226 (40.9%) were ineligible, and 57 (10.3%) declined. A total 256 participants (n = 128/group) had a mean (SD) age of 4.3 (2.1) years; 115 (45%) were female, and 141 (55%) were male. The aggressive antipyretic group had a lower Tmax, 38.6 vs 39.2 °C (difference, −0.62 °C; 95% CI, −0.82 to −0.42; $P < .001$) and lower odds of experiencing multiple or prolonged seizures, 10 (8%) vs 34 children (27%) in the usual care group (odds ratio [OR], 0.26; 95% CI, 0.12 to 0.56). No group difference in parasite clearance time was detected. Severe adverse events occurred in 40 children (15%), 25 (20%) in the usual care group and 15 (12%) in the aggressive antipyretic group, including 13 deaths (10 [8%] and 3 [2%], respectively). Increased creatinine resulted in study drug discontinuation in 8 children (6%) in the usual care group and 13 children (10%) in the aggressive antipyretic group (OR, 1.74; 95% CI, 0.63 to 5.07).

CONCLUSIONS AND RELEVANCE This study found that aggressive antipyretic therapy reduced mean Tmax to temperature levels comparable with the Tmax among children without neurological impairments in prior observational studies and improved acute seizure outcomes with no prolongation of parasitemia.

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Supplemental content

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In 2021, there were 619 000 malaria deaths worldwide with most occurring in African children.[1] Severe malaria mortality remains high despite widespread availability of antimalarials providing rapid parasite clearance[2,3] and is highest (about 18%) among children with central nervous system (CNS) involvement.[4] Malaria-associated brain injuries with subsequent neurologic sequelae occur in approximately 135 000 African children each year, resulting in developmental impairments, neurocognitive deficits, behavioral disorders, and epilepsy.[5-8] Prospective studies have determined that deeper coma and focal neurological deficits at presentation, acute symptomatic seizures, male sex, and a higher maximum temperature (Tmax) during the acute infection are associated with subsequent neurological impairments.[5,6,9]

Substantial evidence has established that after brain injury, hyperthermia during the peri-injury period worsens neurological outcomes.[10] This has been shown in trauma,[11] ischemic stroke,[12] subarachnoid hemorrhage,[13] intracranial hemorrhage, and hypoxic-ischemic encephalopathy.[14] Aggressive strategies for temperature control have been shown to improve outcomes and are the standard of care in high-income settings.[15-17] During acute malaria infection, fevers may increase excitotoxicity, worsen vasogenic edema, increase metabolic demand beyond compensatory capacity, and worsen increased intracranial pressure.[18] In vitro models have shown that febrile temperatures enhance the process of rosette formation that is key to parasite sequestration.[19] Children younger than 5 years are particularly vulnerable to severe malaria and are of an age to be susceptible to febrile seizures.[20] Because acute symptomatic seizures are a well-established risk factor for postmalaria neurologic sequelae, avoidance of seizures during malaria infection may be particularly important.

In contrast to the proactive, preventive approach to fever management for patients with brain injury in Western settings, standard of care for malarial fevers is entirely reactive. World Health Organization (WHO) Malaria Care Guidelines recommend the administration of acetaminophen, 15 mg/kg, for a temperature of 38.5 °C or greater.[21] Withholding antipyretics until this fever threshold is met often results in children with malaria experiencing very high temperatures. Furthermore, treatment with acetaminophen alone has been shown to have limited antipyretic effects in malaria. An outpatient malaria fever study of acetaminophen vs placebo found no differences in mean temperature.[22] Antipyretic efficacy has been shown in some studies; acetaminophen is more effective in malaria fever reduction than tepid sponging.[23] But in general, very limited fever reduction benefits have been shown from any single antipyretic agents in malaria.[24] No malaria studies to date have evaluated the effect of prophylactic antipyretics or using 2 antipyretics with different mechanisms of action.

One reason for the WHO's constrained recommendations for malaria fever management may be concerns regarding the impact of antipyretics on parasite clearance. In in vitro studies, febrile temperatures inhibit parasite growth, leading some to conclude that "long, high fevers during malaria may be beneficial for parasite clearance."[25] This supposition was bolstered by a malaria clinical trial showing that treatment with acetaminophen increased peripheral parasite clearance time.[26] Peripheral parasitemia is an imperfect measure of parasite burden that does not quantify the burden of the sequestered parasites responsible for the pathological effects of severe malaria. Parasitized erythrocytes lose their flexibility at temperatures higher than 37.0 °C, which likely exacerbates sequestration.[27] Increases in temperature from 37.0 to 40.0 °C accelerate rosette formation,[19] doubling red blood cell cytoadherence, and thus may explain why antipyretic use appears to slow parasite clearance.[26] So the clinical effects of lowering temperature may be a transient increase in peripheral parasitemia as cytoadherence is attenuated and sequestered parasites are liberated into the bloodstream. This may actually be a desirable effect if antipyretics reduced sequestration at the capillary level and thus improved cerebral blood flow. Histidine rich protein 2 (HRP2), a *Plasmodium*-specific protein, facilitates quantification of whole-body parasite burden[28] and can facilitate evaluation of the impact of antipyretics on parasite clearance.

To better inform fever management policies for children with CNS malaria, we conducted a clinical trial comparing usual care with 15 mg/kg of acetaminophen for temperatures at least 38.5 °C to aggressive antipyretic therapy with scheduled, 6-hourly acetaminophen plus ibuprofen for 72 hours. The primary outcome was Tmax, and secondary outcomes were seizures after enrollment and parasite clearance using serial HRP2 levels. We hypothesized that children receiving aggressive antipyretics would have a lower Tmax, fewer and less severe postenrollment seizures, and more rapid parasite clearance.

Key Points

Question In central nervous system (CNS) malaria, can aggressive antipyretic therapy with scheduled, preemptive oral acetaminophen plus ibuprofen reduce maximum temperature (Tmax) and/or acute symptomatic seizures, the primary risk factors for neurological sequelae?

Findings This randomized clinical trial found that compared with usual care, which is giving acetaminophen alone for a temperature of 38.5 °C or higher, aggressive antipyretic therapy reduced Tmax to levels comparable with those of children who had good neurological outcomes in prior observational studies and resulted in better acute seizure outcomes.

Meaning Preemptive treatment using combined therapy with 2 readily available, affordable, oral antipyretics (acetaminophen plus ibuprofen) reduces the burden of both fever and acute symptomatic seizures in CNS malaria.

Methods

This was a randomized, double-blind, placebo-controlled trial comparing usual care with aggressive antipyretics in children with CNS malaria.[29] The trial was conducted at Queen Elizabeth Central Hospital in Blantyre, Malawi, and in Zambia at the University Teaching Hospital, Lusaka, and Chipata Central Hospital, Eastern Province. This work was approved by the appropriate ethics review boards. We vouch for the completeness

and accuracy of the data and for the fidelity of the trial to the protocol (Supplement 1).

Trial Population

Parents or guardians of potentially eligible children were approached by local health care workers, who initiated an informed consent discussion. Written consent was required. Eligible children were aged 24 to 132 months with evidence of *Plasmodium falciparum* infection, based on a thick peripheral blood smear or rapid diagnostic test, and symptoms of CNS malaria, including complicated seizures (multiple seizures, focal seizures, or prolonged seizures lasting more than 15 minutes) or impaired consciousness. Consciousness was quantified using the Blantyre coma scale (BCS) or the Glasgow coma scale (GCS), with the GCS score converted to a BCS score for analytic purposes. Children with a BCS score of 2 or less or GCS score of 10 or less were categorized as having cerebral malaria, the most severe form of CNS malaria. Exclusion criteria included vomiting within 2 hours prior to enrollment assessment, having any contraindication for nasogastric tube placement, clinical evidence of circulatory failure, a creatinine value higher than 1.2 mg/dL, jaundice or total bilirubin higher than 3.0 mg/dL, active bleeding, having a history of liver disease, gastric ulcers, or other gastrointestinal bleeding, or having a known allergy to the study drugs or any nonsteroidal anti-inflammatory drug.

Randomization

Children were assigned with 1:1 allocation to receive either usual care or aggressive antipyretics. Permuted block randomization was stratified by country. A programmer in Rochester, New York (A.W.), generated the randomized list of assignments by sequential identification numbers (participant IDs) and provided this to pharmacists preparing treatment packs off-site that were subsequently transferred to the study sites. Only the programmer and pharmacy teams had access to treatment assignments. After informed consent, the next sequential study drug pack based on participant ID was selected for immediate use.

Interventions and Usual Care

Children in the usual care group received 15 mg/kg of acetaminophen as needed every 6 hours for a temperature of 38.5 °C or higher based on axillary temperatures obtained every 2 hours in Malawi and every 6 hours in Zambia. Children in the aggressive antipyretic group received a loading dose of acetaminophen (30 mg/kg) followed by 15 mg/kg every 6 hours plus ibuprofen, 10 mg/kg, every 6 hours regardless of clinical temperature for 72 hours. No loading dose was given if an antipyretic had been administered in the previous 24 hours. A cooling fan was added for persistent fevers. To maintain double blinding, an initial loading dose of placebo and placebos for acetaminophen and ibuprofen were used in the usual care group. Placebos were formulated by a compounding pharmacist to have identical color, taste, and consistency to the active treatments. When a temperature of 38.5 °C or higher was detected, 15 mg/kg of placebo was given in the aggressive antipyretic group.

Outcomes and Measures

As detailed previously,[29] baseline demographic and clinical information was collected by research staff before study drug administration. All outcomes were assessed for 72 hours after enrollment. The primary outcome was Tmax based on axillary temperatures measured by TempTraq patches (Blue Spark Technologies) that captured temperatures every 2 to 4 minutes and sent data via Bluetooth to a mobile device for storage and transmission. The mobile device was stored in a locked cupboard not accessible to nursing staff responsible for clinical temperature assessments and the administration of medications. Secondary efficacy outcomes included fever exposure, defined as the area under the temperature × time curve (AUC) for temperatures of at least 38.5 °C (computed using the trapezoidal rule), seizure activity, and parasite clearance. Seizures were captured by bedside convulsion charts and a 30-minute electroencephalogram obtained daily until the child regained consciousness. Seizures were categorized as none, single and brief, or multiple or prolonged, yielding a 3-category outcome. Parasite clearance was based on AUC for $\log_{10}$-transformed plasma HRP2 concentration every 6 hours. Parasite clearance time was determined as the hours from enrollment to the first of 2 consecutive negative thick blood smears taken every 6 hours.

Harms

Adverse events captured included vomiting, aspiration, nasogastric tube–related injury, recurrent hypoglycemia, lactic acidosis, hyperbilirubinemia, acute kidney injury (AKI), anemia requiring transfusion, occult blood loss, clinical evidence of thrombocytopenia or bleeding, and prolonged parasitemia. Definitions, severity grading, and prespecified procedures were in place to clinically manage these potential adverse events. Study drug was discontinued if creatinine increased by 0.5 mg/dL or doubled compared with the baseline value (AKI criterion 1). A second criterion for AKI (AKI criterion 2) was specified as an increase of 0.3 mg/dL or 150% increase from baseline. Study drug was also permanently discontinued for recurrent vomiting, aspiration, a nasogastric tube–related injury, total bilirubin greater than 5 mg/dL, or clinically significant bleeding. If lactic acidosis persisted more than 24 hours after enrollment, a local study monitor review determined if the study drug should be discontinued.

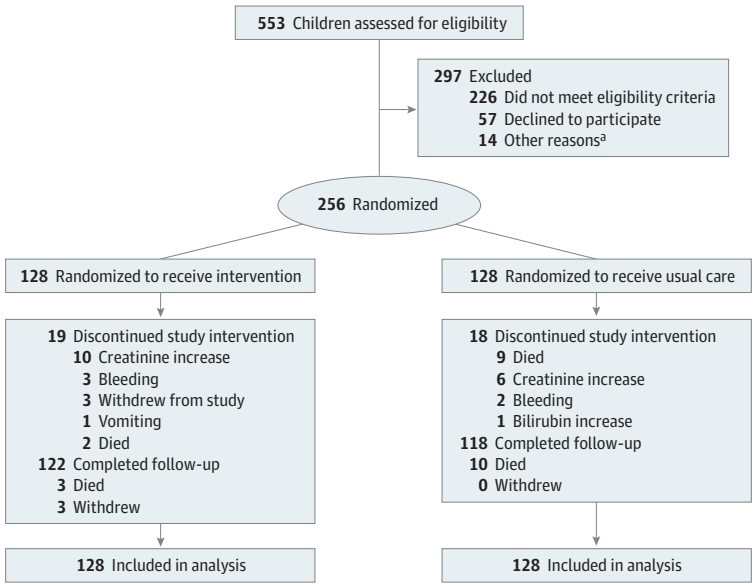
Sample Size Determination

Assuming a Tmax standard deviation of 1.1 °C,[5] 142 children per group was determined to provide 90% power to detect a mean group Tmax difference of 0.425 °C, using a 2-sample *t* test and a 5% significance level (2-tailed). Further details are provided in the statistical analysis plan (Supplement 1).

Interim Analyses

Annual data and safety monitoring board evaluations included review of accrual, safety outcomes, and data quality. A formal interim efficacy analysis of Tmax was performed after approximately 70% of the anticipated participants had completed follow-up using a 1-sided O'Brien-Fleming stopping boundary.

Figure 1. Participant Flow



[a]Five participants died during screening, 8 had no research bed available, and 1 needed an isolation unit for a comorbid infection.

Statistical Analyses

The analysis of the primary outcome, Tmax, involved fitting an analysis-of-covariance model with treatment group as the factor of interest, country and disease severity (cerebral malaria, yes or no) as stratification factors, and admission temperature as a covariate. The estimated treatment effect and associated 95% CI, as well as a *t* test for significance of the treatment effect, were derived from this model. For participants who did not complete the 72-hour follow-up period, Tmax during their shortened assessment was used. Subgroup analyses for Tmax were performed by country, disease severity, age group, and sex by adding the appropriate main effect and interaction terms to the analysis-of-covariance model.

A secondary efficacy measure included fever exposure as measured by the AUC for temperatures of 38.5 °C or higher during the 72-hour follow-up period, categorized as 0 degree-hours, greater than 0 and less than 2 degree-hours, and 2 or more degree-hours. An ordinal logistic regression model assuming proportional odds with terms for treatment group, country, and disease severity as covariates was used to derive the estimated adjusted treatment group odds ratio (OR) and associated 95% CI. Sensitivity analyses with best-case and worst-case imputation were performed to accommodate missing data for the 12 participants with insufficient temperature data to determine the proper outcome.

Seizure occurrence, defined as a 3-level ordinal variable, was analyzed using a multinomial logistic regression model because there was evidence that the proportional odds assumption did not hold. This model included treatment group as the factor of interest and country and disease severity as stratification factors. The adjusted treatment group ORs, and associated 95% CIs were derived from this model. Relative risks (RRs) were also estimated from this model using methods proposed by Austin.[30]

Parasite clearance measured by $\log_{10}$(HRP2 level) was analyzed with a repeated measures analysis-of-covariance model (mixed model repeated measures)[31] with terms for treatment group, country, disease severity, $\log_{10}$(HRP2 level) at admission, time (treated as a categorical variable), and interaction terms for admission $\log_{10}$(HRP2 level) and time, and for treatment group and time. The covariance matrix for the within-participant observations was modeled using an unstructured pattern. The adjusted treatment group difference in mean area under the $\log_{10}$(HRP2 level) × time curve was estimated using appropriate contrasts among the treatment group means over time that quantify this comparison. Time to parasite clearance was evaluated using a discrete-time proportional hazards model with a complementary log-log link. The model included terms for treatment group, country, and disease severity.

Creatinine increases meeting either of the 2 AKI criteria were analyzed using a stratified Cochran-Mantel-Haenszel procedure with country as the stratification factor. The treatment group differences in mean log (creatinine level) at each hour (24, 48, and 72 hours) were estimated using a repeated measures analysis-of-covariance model similar to that used for $\log_{10}$(HRP2 level) adjusting for country and creatinine on admission. Creatinine levels obtained after children stopped study medication were omitted from this analysis.

All data analyses were performed using SAS, version 9.4 (SAS Institute). Study data were analyzed from December 2022 to April 2023.

Results

From January 7, 2019, to June 17, 2022, 553 children were screened; 226 were ineligible, 26 because their creatinine value was greater than 1.2 mg/dL. Details regarding ineligibility are provided in eTable 1 in Supplement 2. Two hundred fifty-six

Table 1. Demographic and Clinical Characteristics of Children at Baseline

Characteristic	No. (%)	
	Usual care (n = 128)	Aggressive antipyretics (n = 128)
Age, median (IQR), y	3.8 (2.8-5.1)	4.4 (2.9-6.6)
Country of enrollment		
Malawi	72 (56)	74 (58)
Zambia	56 (44)	54 (42)
Sex		
Female	56 (44)	59 (46)
Male	72 (56)	69 (54)
Weight, mean (SD), kg	14.0 (3.2)	15.1 (4.4)
Admission temperature, mean (SD), °C	38.1 (1.3)	38.1 (1.3)
Cerebral malaria	83 (65)	72 (56)
Blantyre coma scale score		
0	6 (5)	2 (2)
1	27 (21)	22 (17)
2	50 (39)	48 (38)
3	16 (13)	21 (16)
4	11 (9)	12 (9)
5	18 (14)	23 (18)
Seizures[a]		
None	20 (16)	23 (18)
Single and brief	10 (8)	16 (13)
Multiple or prolonged	98 (77)	88 (69)
Received antipyretics	110 (86)	115 (91)
Received anticonvulsant	69 (54)	64 (50)
Quantitative parasite count among positive smears		
Parasites/μL	89	92
No. (range)	640 (8 to 1 213 250)	1240 (40 to 903 500)
Mean (IQR)	1890 (160-45 000)	3281 (280-93 075)
HRP2, ng/mL		
No. (range)	110 (0.20-2012)	108 (0.20-3305)
Median (IQR)	86 (5-376)	123 (9-424)
Packed cell volume, mean (SD), %	29 (7)	28 (7)
Creatinine, mean (SD), mg/dL	0.63 (0.20)	0.64 (0.23)
Bilirubin, median (IQR) [range], mg/dL	0.60 (0.05-1.20) [0-2.90]	0.50 (0.10-1.10) [0-2.60]
Lactate, median (IQR) [range], mmol/L[b]	3.20 (1.90-5.90) [1.00-25.00]	3.30 (2.10-5.80) [1.00-25.00]
HIV positive	4 (3)	3 (2)

Abbreviation: HRP2, histidine rich protein 2.

SI conversion factor: To convert bilirubin to μmol/L, multiply by 17.104; creatinine to μmol/L, multiply by 88.4.

[a] One file for a child in the aggressive antipyretic group was lost, and these data were not otherwise recoverable.

[b] The maximum value the point-of-care equipment can register is 25.

children were enrolled and randomized, 128 each in the usual care and aggressive antipyretic groups (**Figure 1**). Baseline demographic and clinical characteristics are presented in **Table 1**. The mean (SD) age overall was 4.3 (2.1) years; 115 (45%) were female, and 141 (55%) were male. Median (SD) ages for the usual care and aggressive antipyretic groups were 3.8 (1.9) and 4.4 (2.3) years, respectively; slightly more than half of the children were male in Zambia (54% and 56%, respectively) and in Malawi (56% and 58%, respectively). The mean (SD) admission temperature in both groups was 38.1 (1.3) °C. The study drug was discontinued in 18 children (14%) in the usual care group and 19 (15%) in the aggressive antipyretic group. The commonest reasons for discontinuation were death and AKI. Three children, all in the aggressive antipyretic group, withdrew from the study.

The first of the 2 planned interim analyses scheduled to take place after the second recruiting season was deferred because of lagging enrollment, so only 1 interim analysis was performed in December 2021 based on a sample size of 198 participants. A significant benefit of aggressive antipyretics on the primary outcome, Tmax, was detected, but the data and safety monitoring board had concerns that there were inconclusive findings regarding the risk of AKI from aggressive antipyretics at this juncture. Despite evidence for efficacy in terms of mean Tmax reduction, without more safety data, aggressive antipyretics would not be appropriate for use in malaria endemic regions where kidney function tests are not routinely or rapidly available. After consultation with a bioethicist, enrollment was continued until the initial scheduled time for study completion to obtain further safety data. The data and safety monitoring board shared no further information beyond noting (qualitatively) the significant benefit of aggressive antipyretics and the double blind was maintained.

Findings for the prespecified outcomes are detailed in **Table 2**; additional information on miscellaneous outcomes is provided in eTable 2 in Supplement 2. The adjusted mean Tmax was 38.57 °C in the aggressive antipyretics vs 39.19 °C in the usual care group (absolute difference, −0.62 °C; 95% CI, −0.82

Table 2. Treatment Group Comparisons of Primary and Secondary Outcomes

Outcome	No. (%)		Effect (95% CI)
	Usual care (n = 128)	Aggressive antipyretics (n = 128)	
Tmax, mean (95% CI), °C	39.2 (39.1 to 39.3)[a]	38.6 (38.4 to 38.7)[a]	−0.6 (−0.8 to −0.4)[b]; $P < .001$
Worst-case AUC temperature ≥38.5 °C[c]			
0 degree-hours	34 (27)	65 (51)	0.32 (0.20 to 0.52)[d]
>0 and <2 degree-hours	50 (39)	47 (37)	
≥2 degree-hours	44 (34)	16 (13)	
Best-case AUC temperature ≥38.5 °C[e]			
0 degree-hours	37 (29)	67 (52)	0.36 (0.22 to 0.58)[d]
>0 and <2 degree-hours	54 (42)	47 (37)	
≥2 degree-hours	37 (29)	14 (11)	
Seizures (n = 255)[f]			
None	88 (69)	107 (84)	NA
Single and brief	6 (5)	10 (8)	1.51 (0.51 to 4.46)[g]
Multiple or prolonged	34 (27)	10 (8)	0.26 (0.12 to 0.56)[h]
Log_{10}(HRP2) AUC (95% CI)[i]	80.0 (71.5 to 88.4)[a]	86.3 (78.2 to 94.4)[a]	6.3 (−5.1 to 17.7)[b]

Abbreviations: AUC, area under the curve; HRP2, histidine rich protein 2; NA, not applicable.

[a] The values are means adjusted for country of enrollment, disease severity (cerebral malaria, yes or no), and the baseline value of the outcome.

[b] The effect is the difference in adjusted group means.

[c] Area under the temperature × time curve with worst-case imputation for the 12 participants with insufficient temperature data to determine the proper outcome category.

[d] The effect is an odds ratio assuming proportional odds, ie, the same odds ratio for the 0 vs >0 and the <2 vs ≥2 categorizations of outcome; it is adjusted for country of enrollment and disease severity.

[e] Area under the temperature × time curve with best-case imputation for the 12 participants with insufficient temperature data to determine the proper outcome category.

[f] One file for a child in the aggressive antipyretic group was lost, and these data were not otherwise recoverable.

[g] The effect is an odds ratio for the single/brief seizures vs no seizures categorization of outcome; it is adjusted for country of enrollment and diagnosis.

[h] The effect is an odds ratio for the multiple or prolonged seizures vs no seizures categorization of outcome; it is adjusted for country of enrollment and disease severity.

[i] Area under the log_{10}(HRP2) × time curve; n = 182 participants.

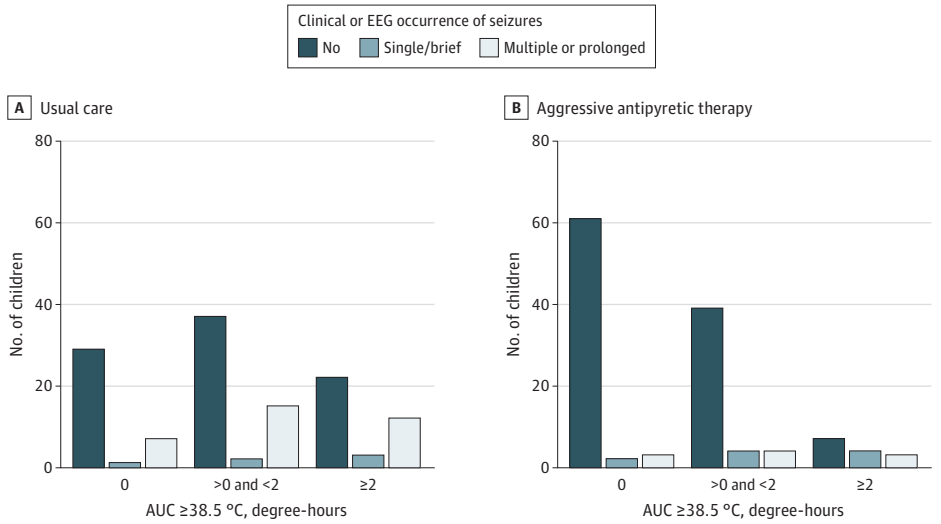
to −0.42; $P < .001$) (eFigure 1 in Supplement 2). This finding was consistent across multiple subgroups (eTable 3 in Supplement 2). Exposure to fever, as measured by the AUC for temperatures of 38.5 °C or higher, was also lower for the aggressive antipyretic group (eTable 2 in Supplement 2). Multiple or prolonged seizures were less frequent in children treated with aggressive antipyretics (10 [8%]) than in the usual care group (34 children [27%]; OR, 0.26; 95% CI, 0.12 to 0.56; RR, 0.34; 95% CI, 0.15 to 0.61). **Figure 2** shows the joint distribution of seizure burden and fever outcome by treatment group. The analysis of HRP2 data was limited by the exclusion of 74 children with missing baseline data (n = 19), no follow-up data (n = 36), or both (n = 19), and no group difference in mean log_{10} (HRP2 level) trajectory was detected (eFigure 2 in Supplement 2). No treatment group difference in the distribution of parasite clearance time was detected (hazard ratio, 0.94; 95% CI, 0.69 to 1.26). Fourteen children (9 in the usual care group and 5 in the aggressive antipyretic group) did not achieve parasite clearance prior to discharge.

Harms are detailed in **Table 3**. Severe adverse events occurred in 15% of participants overall and included death, neurological impairments at discharge, AKI, and clinical bleeding. Thirteen children died, 10 in usual care and 3 in the aggressive antipyretic group (OR, 0.28; 95% CI, 0.07-1.05). Overall, 21 children (8%) met AKI criterion 1, 8 (6%) in the usual care group and 13 (10%) in the aggressive antipyretic group (OR, 1.74; 95% CI, 0.63-5.07); for AKI criterion 2, there were 20 (16%) and 28 (22%), respectively (OR, 1.57; 95% CI, 0.82-3.01). Mean creatinine levels were higher at 24 and 48 hours but not at 72 hours in the aggressive antipyretic group (eFigure 3 in Supplement 2). One child required peritoneal dialysis. Clinically evident bleeding, usually epistaxis, occurred in 3 children (2%) in the usual care and 5 children (4%) in the aggressive antipyretic group. Only 1 bleeding event was a serious adverse event, and this occurred in a child who received usual care.

Discussion

This study found that aggressive antipyretics resulted in a lower Tmax, reduced time with exposure to fever, and better acute symptomatic seizure outcomes without evidence of slowed parasite clearance. Higher Tmax is an established predictor of brain injury and neurological sequelae in this population[5]; hence, aggressive antipyretic therapy may offer long-term neuroprotective benefits. There is also strong biological plausibility for neuroprotection from temperature reduction.[10-14] Mean Tmax reduction by 0.62 °C and the overall decreased exposure to time with fever likely contributed to improved acute seizure outcomes in children this age, but the general anti-inflammatory effects of the aggressive antipyretic agents might have also contributed. Given the role that inflammation plays in epileptogenesis[32] and the high risk of epilepsy following cerebral malaria,[5] further studies are needed to assess long-

Figure 2. Joint Distributions of Seizure Burden and Fever Outcomes by Treatment Group



Each bar represents the number of participants in the usual care group (A) and aggressive antipyretics group (B) who had a particular seizure outcome (no seizures, single or brief seizures, multiple or prolonged seizures). Fever exposure was measured by the area under the temperature × time curve (AUC) for temperatures of 38.5 °C or higher, categorized as 0 degree-hours, greater than 0 and less than 2 degree-hours, and 2 or more degree-hours. Best-case imputation was used for the 12 participants with insufficient temperature data to determine the proper fever outcome category. Aggressive antipyretic treatment exhibited beneficial effects on seizures (multiple or prolonged vs no seizures: relative risk [RR], 0.34; 95% CI, 0.10-0.56) and on fever outcome (≥2 vs 0 degree-hours: RR, 0.40, 95% CI, 0.20-0.57; >0 and <2 degree-hours vs 0 degree-hours: RR, 0.68; 95% CI, 0.55-0.81). EEG indicates electroencephalogram.

Table 3. Adverse Events

Adverse event	No. (%)		
	Overall (n = 256)	Usual care (n = 128)	Aggressive antipyretics (n = 128)
Any severe adverse event	40 (15.6)	25 (20)	15 (12)
Bilirubin increase	130 (50.8)	66 (52)	64 (50)
Creatinine increase	112 (43.8)	48 (38)	64 (50)
Lactate >5.0 mmol/L after 24 h	31 (12.1)	19 (15)	12 (9)
Bleeding			
Any	27 (10.5)	10 (8)	17 (13)
Clinical	8 (3.1)	3 (2)	5 (4)
Occult[a]	19 (7.4)	7 (5)	12 (9)
Vomiting	19 (7.4)	9 (7)	10 (8)
Neurologic impairments	19 (7.4)	10 (8)	9 (7)
Death	13 (5.1)	10 (8)	3 (2)
Fell out of bed	4 (1.6)	2 (2)	2 (2)
Diarrhea	3 (1.2)	2 (2)	1 (1)
Hypoglycemia[b]	3 (1.2)	3 (2)	0
Nasogastric tube injury	1 (0.4)	0	1 (1)
Decline in BCS score (from 5 to 4)	1 (0.4)	0	1 (1)
Prolonged hospitalization	1 (0.4)	1 (1)	0
Shock	1 (0.4)	1 (1)	0
Necrotic digits	1 (0.4)	1 (1)	0
Status epilepticus with apnea requiring resuscitation	1 (0.4)	1 (1)	0
Systemic allergic reaction	1 (0.4)	0	1 (1)
Urticaria	1 (0.4)	1 (1)	0

Abbreviation: BCS, Blantyre coma scale.

[a] Included blood detection in urine or stool samples assessed daily.

[b] Glucose <2.2 mmol/L. There were no recurrent events.

term neurological outcomes after aggressive antipyretic therapy. There were fewer deaths in the aggressive antipyretic group compared with usual care, suggesting that aggressive antipyretics may reduce mortality.

This oral, readily available, affordable antipyretic combination provided much-needed acute antiseizure benefits. Malaria-associated seizures often devolve into status epilepticus and are an independent risk factor for neurologic sequelae. Furthermore, acute seizure management in malaria endemic regions is largely limited to benzodiazepines and phenobarbital without an option for ventilatory support, thus making the risk of iatrogenic death from respiratory failure a major challenge in malaria seizure management in Africa.[33]

Strengths and Limitations

This clinical trial used a randomized design with blinded outcomes to evaluate the efficacy of a combination of 2 antipyretics (acetaminophen and ibuprofen) that are affordable and already broadly available in malaria endemic regions for fever reduction and acute seizure outcomes in children with CNS malaria from a multinational population, including both tertiary care centers and a district-level hospital. The usual care comparison group received fever treatment based on WHO guidelines. Given the potential nephrotoxic effects of ibuprofen, children with an admission creatinine level higher than 1.2 mg/dL were ineligible for enrollment, resulting in 12% exclusion. Creatinine assessments, especially point-of-care or rapid results, are not routinely available in many malaria endemic regions.

Conclusions

This study found that aggressive antipyretic therapy reduced mean Tmax to temperature levels comparable with the Tmax among children without neurological impairments in prior observational studies and improved acute seizure outcomes with no prolongation of parasitemia. Additional studies are needed to assess long-term neurological outcomes after aggressive antipyretic therapy.

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