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Treatment of Severe Sepsis with Artemether-Lumefantrine Is Associated with Decreased Mortality in Ugandan Patients without Malaria

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Abstract. We enrolled 382 patients at two hospitals in Uganda in a prospective observational study of severe sepsis. Because artemisinins improve survival in murine sepsis models, we performed a *post hoc* analysis of the association between the use of artemether-lumefantrine (A-L) and mortality in patients with or without malaria. In patients with negative malaria smears (N = 328 of 379), Kaplan–Meier curves revealed decreased combined inpatient and 30-day mortality among patients receiving A-L versus those who did not (20.6%, SE = 10.6 versus 48.8%, SE = 3.2; Log rank $\chi^2 = 3.93$, $P = 0.048$). The decrease in mortality associated with A-L was maintained in the most clinically ill patients determined by Karnofsky Performance Scores ≤ 50 (16.7%, SE = 15.2 versus 58.3%, SE = 3.7; Log rank χ^2 3.94, $P = 0.041$). Research into the properties of A-L is needed to improve treatment of sepsis without compromising malarial susceptibility.

INTRODUCTION

Sepsis is defined by the presence of infection and the systemic inflammatory response syndrome (SIRS), which requires disarray of two or more of the following clinical parameters: heart rate, respiratory rate, temperature, or peripheral white blood cell concentration.[1] As sepsis escalates to severe sepsis and septic shock, defined by end-organ damage and refractory hypotension, respectively, mortality can be as high as 40–70%.[2] In regions endemic for malaria, initial treatment of septic patients is often targeted to both bacteremia, which is often a result of non-typhoidal *Salmonella*, *Streptococcus pneumoniae*, or *Mycobacteria tuberculosis* infection, and malaria.[3] Both sepsis and malaria can manifest with indistinguishable clinical findings and may occur together.[4–9]

In malaria endemic regions, the World Health Organization (WHO) recommends treatment of febrile illnesses with anti-malarial agents.[10] Use of artemisinin-based combination chemotherapy is suggested in areas such as sub-Saharan Africa where chloroquine resistance is a concern. Artemisinin was initially isolated in China and is the active ingredient of sweet wormwood also known as *qinghao*. Artemisinin and its derivatives, including dihydroartemisinin, artesunate, artemether, and arteether, are proven as anti-malarial compounds.[11–14] The fixed dose combination of artemether-lumefantrine (A-L) is currently the preferred anti-malarial agent prescribed in Uganda.[15]

Beyond their direct anti-parasitic effect, artemisinins suppress tumor necrosis factor (TNF)-α and interleukin (IL)-6 in a murine model of sepsis and in human rheumatoid arthritis fibroblast-like synoviocytes.[16,17] Because of these promising experimental anti-inflammatory findings and the decreased mortality attributable to artemisinins in murine sepsis models, we performed a *post hoc* analysis of the association between A-L use and mortality of patients enrolled in a prospective observational study of the management and outcomes of severe sepsis in Uganda.

MATERIALS AND METHODS

Patient recruitment. To study the management and outcomes of patients with severe sepsis in Uganda, we enrolled 382 patients in a prospective observational study at the Mulago National Referral Hospital in Kampala and Masaka Regional Referral Hospital. Consent was obtained from each patient or their guardian. Inclusion criteria were age ≥ 18 years and admission to a medical ward, along with 1) ≥ 2 of the following: body temperature > 37.5°C or < 35.5°C, heart rate > 90 beats/minute, or respiratory rate > 20 breaths/minute, or thermodysregulation alone; 2) a systolic blood pressure (SBP) ≤ 100 mm of Hg; and 3) a suspected infection. White blood cell concentration was not part of the inclusion criteria because of inconsistent availability of laboratory testing. Exclusion criteria included acute cerebrovascular events, gastrointestinal hemorrhage, or admission to a non-medical ward.

Data collection. Background information, including age and gender, was recorded. At enrollment, temperature, heart rate, respiratory rate, and blood pressure were obtained and Karnofsky performance scores (KPS) were documented. Human immunodeficiency virus (HIV) status was acquired by antibody testing with Determine (Abbott Laboratories, Tokyo, Japan) and Statpak (Chembio Diagnostic Systems, Inc, Medford, NY). If results of the initial antibody tests were equivocal, Unigold (Trinity Biotech plc, Bray, Ireland) was used for a tie breaker. The CD4 T lymphocyte concentration (Mulago hospital: FACSCount System, BD Biosciences, San Jose, CA; Masaka hospital: Guava Technologies, Hayward, CA), portable whole blood lactate concentration (Accutrend portable lactate analyzer; Sports Resource Group, Inc., NY), and serum bicarbonate concentration (Diagnostic Systems International, Holzheim, Germany) were also analyzed. A malaria smear was obtained via Field's staining and parasitemia was graded as 1+, 2+, 3+, or 4 + based on the presence of 1–9 parasites/100 high-power fields (hpf), 10–100 parasites/100 hpf,

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1–9 parasites/single hpf, or 10–100 parasites/single hpf, respectively. As in other areas of sub-Saharan Africa, capacity for further quality control of malaria diagnosis was not available.[4] The study team followed patients throughout their hospitalization, but the admitting medical team was responsible for clinical management. Use of anti-bacterial and anti-malarial agents was recorded. To determine outpatient survival, an attempt was made to telephone patients at 30 days after their discharge.

Statistical analysis. Data were entered into an Epi-Info database (version 6.04d, Centers for Disease Control and Prevention, Atlanta, GA) and analyzed using SPSS software (version 15.0, SPSS Inc., Chicago, IL). Baseline characteristics were assessed for statistical significance using the 2-sample Student *t* test for continuous variables and χ^2 test for categoric variables. Kaplan Meier (KM) survival curves were used to assess univariate differences in survival and the log-rank test was used to assess significance. Cox proportional hazards regression was used to model simultaneous and interaction effects of A-L with baseline characteristics. Baseline characteristics were included in Cox models when they were associated with mortality and A-L at $P < 0.10$. Overall, statistical significance was defined as 2-tailed at $P < 0.05$.

Ethical considerations. Approval was obtained from the University of Virginia Institutional Review Board, Mulago Hospital Office of Director, Makerere University Faculty of Medicine Research Ethics Committee and Infectious Disease Institute Scientific Research Committee, and Uganda National Council of Science and Technology.

RESULTS

Patient characteristics. The 17 patients with negative malaria smears that received A-L were similar to those that did not in age, HIV-1 prevalence, mean CD4 lymphocyte count, mean systolic and diastolic blood pressure, mean whole blood lactate concentration, mean bicarbonate concentration, amount of intravenous fluid administration at 6 and 24 hours after admission, and empiric anti-bacterial administration. Admission KPS and the proportion of women were higher in the A-L treated group (Table 1). Demographic parameters were similar between patients with positive malaria smears compared with those with negative malaria smears (data not shown).

Malaria prevalence and associated mortality. Only 13.5% (51 of 379) patients had a positive malaria smear. The majority (86.3%, *N* = 44 of 51) with positive malaria smears had low grade 1 + parasitemia. Few patients with positive malaria smears had grade 2+ (7.8%, *N* = 4 of 51), 3+ (2.0%, 1 of 51), or 4+ (3.9%, *N* = 2 of 51) parasitemia (Figure 1). Thirty-day follow-up was completed for 337 patients. For patients with follow-up information at 30 days, the combined in- and outpatient mortality at different grades of malaria parasitemia was 40.5% (*N* = 17 of 42) for 1 + parasitemia, 50.0% (*N* = 2 of 4) for 2 + parasitemia, 100% (*N* = 1 of 1) for 3 + parasitemia, and 0% (*N* = 0 of 2) for 4 + parasitemia.

There were 286 patients with negative malaria smears who were followed to 30 days. Combined inpatient and 30-day mortality for patients with negative malaria smears was 43.4% (*N* = 124 of 286). The majority (*N* = 76) of these deaths occurred while patients were still in the hospital. Another 48 patients died after discharge from the hospital. The KM estimated combined mortality was 52.7% (SE = 3.1%). There was no significant difference between mortality in patients with a positive malaria smear of any grade parasitemia versus those with negative malaria smears (relative risk [RR] = 1.05, 95% confidence interval [CI] 0.81–1.35, $P = 0.74$]. There was also no difference in rate of death using KM estimates (Log rank $\chi^2 = 0.37$, $P = 0.848$).

A total of 72 out of 328 (22.0%) patients with negative malaria smears received an anti-malarial agent. A majority (62.5%, *N* = 45 of 72) received quinine. Other anti-malarial agents prescribed included A-L (23.6%, *N* = 17 of 72), chloroquine (6.9%, *N* = 5 of 72), sulfadoxine and pyrimethamine (1.4%, *N* = 1 of 72), or other anti-malarial agents (5.6%, *N* = 4 of 72).

There were no interventional groups, *per se*, but we performed analyses by dividing patients into those that did or did not have positive malaria smears (Figure 2). These groups were then divided into groups that did or did not receive an anti-malarial agent. There was a statistically significant reduced mortality between combined in- and outpatient mortality among patients with negative malaria smears who received A-L (20.0%, *N* = 3 of 15) compared with those who did not (44.6%, *N* = 121 of 271, RR = 1.45 [95% CI 1.10–1.90], $P < 0.05$). The KM estimated rate of mortality was 20.6% (SE = 10.6) for patients who received A-L and 48.8% (SE = 3.2) for those who did not (Log rank $\chi^2 = 3.93$, $P = 0.048$; Figure 3). Specifically, only 2 of 17 patients who received A-L (11.8%) died in the hospital compared with 74 of 311 (23.8%) patients who did not receive A-L. We had information for 13 of the 15 discharged A-L treated patients at 30 days. Of these 13, only 1 patient (7.7%) died after discharge in comparison to the 47 out of 198 (23.7%) patients who died after discharge in the group who did not receive A-L.

Cox Regression was used to test A-L as a predictor of overall mortality. The KPS and HIV status were included as covariates to account for differences in initial illness before treatment with A-L. Interaction terms were also included to assess the combined effect of A-L and KPS, as well as A-L and HIV status. The use of A-L remained significantly and independently related to mortality ($P = 0.026$), whereas KPS and HIV status became non-significant. The interaction term with A-L and HIV was also non-significant. A significant interaction effect of A-L and KPS was significant ($P = 0.022$).

Exploration of this interaction revealed a larger effect of A-L among the sickest patients KPS ≤ 50 (i.e., disabled, requiring special care and help, or worse) compared with the effect of A-L among less ill patients (KPS > 50). Among patients with KPS ≤ 50, none of the 8 patients treated with A-L died compared with 68 of 235 (29.1%) patients who died in the hospital who did not receive A-L (RR = 1.4 [95% CI 1.30–1.53], $P = 0.068$). We had follow-up information at 30 days for 7 of the 8 A-L treated patients, of whom only 1 patient died (14.3%) compared with 96 of 207 (30.7%) discharged patients who had not received A-L (RR = 1.85 [95% CI 1.32–2.59], $P = 0.032$). The KM estimated rate of death to 30 days reached 16.7% (SE = 15.2) compared with 58.3% (SE = 3.7) (Log rank χ^2 3.94, $P = 0.041$; see Figure 4). There was no significant difference in total mortality between A-L treated and non-treated patients whose KPS score at admission was > 50 (RR = 0.89 [95%

TABLE 1
A comparison of the demographic characteristics of patients with severe sepsis and negative malaria smears who did or did not receive A-L*

Characteristic or outcome	Received A-L	Did not receive A-L	*P* value
Age, mean years ± SD *N* = 327	34.82 ± 13.9 *N* = 17	34.4 ± 10.5 *N* = 310	0.871
Female, % *N* = 325 (133 male, 195 female)	88.2 *N* = 15	57.9 *N* = 180	0.007
HIV-1 prevalence, % *N* = 325 (*x* = HIV-1 infected)	70.6 *N* = 12	87.0 *N* = 268	0.086
CD4 lymphocyte count, mean lymphocytes/mm^3 ± SD *N* = 278	149.3 ± 139.7 *N* = 12	95.5 ± 130.9 *N* = 266	0.143
Blood pressure at hospital admission, mean mm Hg ± SD *N* = 328			
Systolic	85.2 ± 9.3 *N* = 17	81.7 ± 16.5 *N* = 311	0.388
Diastolic	52.7 ± 11.7 *N* = 17	48.0 ± 19.0 *N* = 307	0.317
Whole blood lactate, mean mmol/L ± SD *N* = 161	2.89 ± 1.57 *N* = 15	3.91 ± 2.56 *N* = 146	0.135
Bicarbonate, mean mmol/L ± SD *N* = 221	21.1 ± 1.53 *N* = 5	21.1 ± 2.92 *N* = 216	0.991
Admission KPS ± SD *N* = 328	58.8 ± 16.2 *N* = 17	45.9 ± 15.9 *N* = 311	0.001
Discharge KPS ± SD *N* = 220	71.5 ± 16.8 *N* = 13	71.1 ± 14.8 *N* = 207	0.912
Received greater than 2 L of intravenous fluid resuscitation, %			
At 6 hours *N* = 328	0.0 *N* = 17	4.2 *N* = 311	0.235
At 24 hours *N* = 220	5.9 *N* = 17	15.4 *N* = 293	0.239
Received empiric antibacterial therapy, % *N* = 311	94.1 *N* = 17	86.5 *N* = 294	0.234
> 2 SIRS criteria *N* = 328	70.6% *N* = 17	83.0% *N* = 311	0.223
Heart rate > 90 bpm, % *N* = 328	94.1% *N* = 17	94.5% *N* = 311	0.942
Respiratory rate > 20 bpm, % *N* = 326	82.4% *N* = 17	94.5% *N* = 309	0.089
Temperature < 36°C or > 38°C, % *N* = 324	62.5% *N* = 16	60.1% *N* = 308	0.846
WBC < 4,000 or > 12,000, % *N* = 318	58.8% *N* = 17	47.8% *N* = 301	0.378
Blood pressure < 90 mm of Hg, % *N* = 328	47.1% *N* = 17	53.4% *N* = 311	0.612
Mean Glasgow Coma Score *N* = 328	15 ± 0 *N* = 17	14.79 ± 1.024 *N* = 311	0.408

*A-L = artemether-lumefantrine; HIV = human immunodeficiency virus; KPS = Karnofsky performance scores; SIRS = systemic inflammatory response syndrome; WBC = white blood cell.

CI 0.59–1.34], $P = 0.53$). Among patients with KPS > 50, there was also a non-significant difference in rate of mortality when comparing A-L treated with non A-L treated patients (Log rank $\chi^2 = 0.29$, $P = 0.59$).

We extended our analysis to include those patients with detectable parasitemia and A-L use was again associated with improved survival. No patient receiving A-L had greater than 1 + parasitemia. A total of 23 patients with a negative or 1 + smear received A-L. Only 2 of these 23 patients died in-hospital compared with 86 of 348 who did not receive A-L (RR = 1.21 [95% CI 1.06–1.36], $P = 0.05$). This difference did not quite reach statistical significance. There was significant decreased mortality at 30 days after discharge of the patients who received A-L (4 of 21, 19%) compared with patients who did not receive A-L (137 of 307, 44.6%) (RR = 1.46 [95% CI 1.61–1.84] $P = 0.02$). The KM estimates were significantly different with 20.7% (SE = 9.3%) mortality among A-L treated patients and 49.1% (SE = 3.1%) among non-A-L treated patients, (Log rank χ^2 4.92, $P = 0.027$).

DISCUSSION

For the first time we have shown that administration of an artemisinin-based combination treatment, specifically A-L, is associated with decreased mortality in patients with severe sepsis in the absence of detectable malaria. This is an important finding given that there are currently few effective adjunctive therapies available for the treatment of sepsis. The improvement in outcomes in patients who received A-L cannot be attributed to differences in age, severity of presentation (as determined by whole blood lactate or blood pressure), degree of immunosuppression, amount of fluids received, or antibacterial therapy as these parameters were similar between groups (Table 1). Furthermore, the positive association

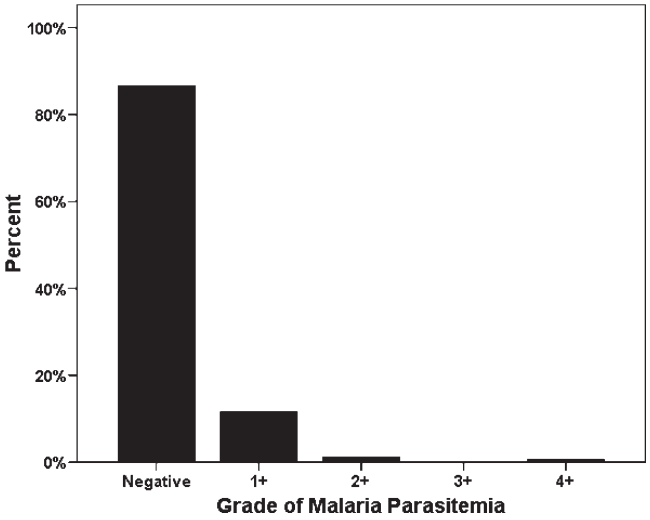

FIGURE 1. Bar graph comparing proportions of different grades of malaria parasitemia in patients with severe sepsis.

between A-L and survival was maintained even in the most clinically ill patients whose KPS was less than 50. In fact, based on the analysis of the interaction between A-L and KPS, these patients were the *most* likely to benefit from the administration of A-L.

The pathophysiology of both sepsis and malaria is thought to involve dysregulation of the innate immune system leading to elevated serum cytokines including IL-1β, IL-6, and TNF-α, among others.[18,19] Unfortunately, trials of anti-cytokine antibodies for the treatment of both illnesses have not met with clinical success despite promising results in animal models.[20,21] This may be because antibodies neutralize specific cytokines rather than exert a pluripotent effect on the course of systemic inflammation.

However, the anti-inflammatory effect of artemisinins is thought to occur via inhibition of inducible nitric oxide synthase and the transcription factor nuclear factor κB.[17,22] There is also evidence that the anti-inflammatory effect is mediated through a decrease in phosphorylation of the Akt serine-threonine protein kinase signal pathway, which leads to decreased production of TNF-α induced IL-1β, IL-6, and IL-8.[17] Given the limited benefit of cytokine antibody therapy for sepsis, the multifocal impact of artemisinins on inflammation may be more clinically beneficial. Moreover, because a murine sepsis model revealed that artemisinin has no anti-bacterial effect, the beneficial effect of A-L in the treatment of sepsis is likely derived from its anti-inflammatory properties.[16]

Lumefantrine belongs to the aryl aminoalcohol group of anti-malarials, which also includes quinine, mefloquine, and halofantrine.[10] It has a similar mechanism of action to these agents, which involves inhibition of parasite heme detoxification, but we are unaware of any associated anti-inflammatory properties. Thus, we ascribe the beneficial effects of A-L in sepsis to artemether, but it is possible that lumefantrine contributes to improved sepsis survival by an as of yet unknown mechanism.

We also showed that adult patients who present with severe sepsis in the two study hospitals are unlikely to have significant malaria parasitemia. Only 13.3% (51 of 379) of patients in our study had detectable parasitemia at the time of

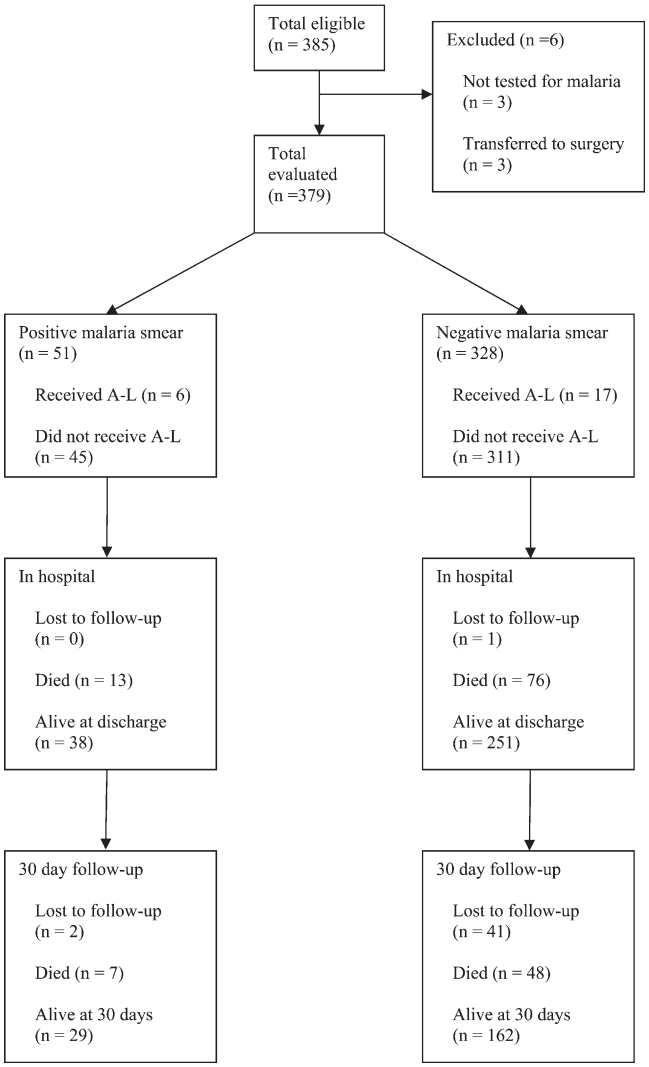

FIGURE 2. Flow chart describing enrollment and follow-up of patients with regard to malaria status.

enrollment and of these only 15.7% (N = 7 of 51) of patients had greater than grade 1 + parasitemia. The 6 patients with positive malaria smears that received A-L all had grade 1 + parasitemia, and they also had improved survival compared with patients that did not receive A-L. Although some of the benefit in survival in these patients may have been because of treatment of malaria, this low level of parasitemia is not usually associated with critical illness in endemic adult populations.[23] Furthermore, microscopy in resource-limited settings is more likely to over-diagnose rather than under-diagnose malaria, which suggests that some of these 1 + malaria smears could have been false-positive results.[24] Therefore, the improvement in survival was likely an extension of the anti-inflammatory effect of A-L rather than a direct anti-parasitic effect. Importantly, our study was limited to adults 18 years of age or older, so we cannot comment on the etiology of severe sepsis in the local pediatric population where malaria is a common cause of critical illness.

In Uganda, patients will often receive A-L along with an anti-bacterial agent as part of their sepsis therapy. The benefits of this strategy include treatment of both potential bacterial

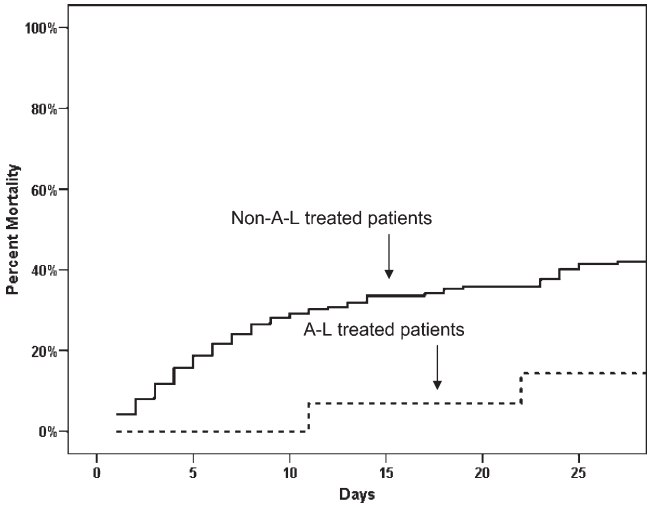

FIGURE 3. Kaplan–Meier survival curves of patients with severe sepsis and negative malaria smears who did or did not receive artemether-lumefantrine (A-L).

and malarial infections, and possibly the anti-inflammatory effects of A-L, but the cost may be manifested in resistance to these agents in the targeted pathogens, unnecessary side effects, and financial burden.[25] Like others, we believe that the most important strategy to improve survival in patients with severe sepsis in this region will come from universal access to adequate initial resuscitation through use of intravenous fluids, and timely and appropriate antibiotics.[26] We also agree with others that resources should be devoted to diagnostic capability, particularly clinical microbiology, along with improved treatment modalities.[27]

More research into the mechanism of action of artemisinins in the therapy of severe sepsis is needed. Identification of the biologic pathways altered by A-L may lead to the development of new drugs, including small molecules that may improve sepsis outcomes. Ideally, such agents would have no anti-malarial activity thereby eliminating the risk of malaria resistance to artemisinins. In the interim, clinical studies should be performed in malaria non-endemic settings to verify the beneficial effects of A-L in the treatment of severe sepsis.

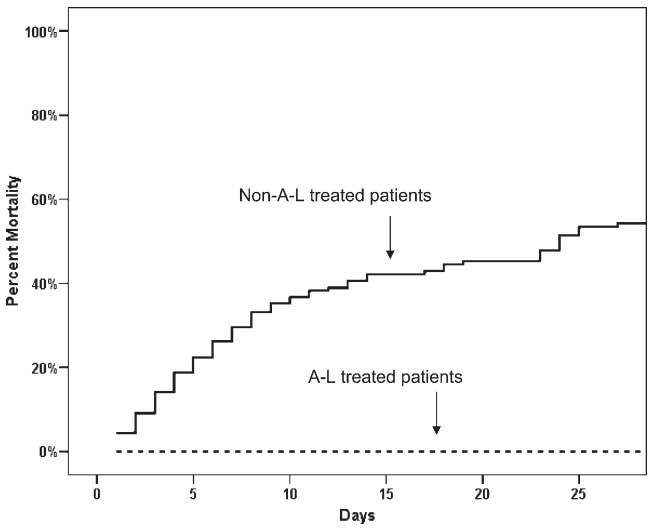

FIGURE 4. Kaplan–Meier survival curves comparing combined inpatient and 30 day mortality (means and 95% confidence intervals) of patients with severe sepsis, a negative malaria smear, and a Karnofsky Performance Score ≤ 50 who did or did not receive artemether-lumefantrine (A-L).

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