MAJOR ARTICLE

Conflict and Kala-Azar: Determinants of Adverse Outcomes of Kala-Azar among Patients in Southern Sudan

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We analyzed data obtained from 3365 patients with kala-azar (KA) or post-KA dermal leishmaniasis (PKDL) treated by Médecins Sans Frontières–Holland in south Sudan from October 1998–May 2002. Patients were malnourished (median body mass index [BMI], 15.5; median weight for height [WFH], 75.5%) and anemic (median hemoglobin (Hb) level, 8.5 g/dL). The proportion of patients with primary KA who were children <5 years old increased from 2.5%, in 1998, to 19.8%, in 2002 ($P < .0001$). Therapy with sodium stibogluconate cured 91.9% of patients with primary KA, and dosages of >850 mg per day did not decrease the chances of survival. Risk factors for death among adults were age ⩾45 years (odds ratio [OR], 4.6), malnutrition (BMI, <13; OR, 11.0), anemia (Hb level, <8 g/dL; OR, 4.0), and duration of illness (duration, ⩾5 months; OR, 2.3). Risk factors for death among children and adolescents were age <2 years (OR, 5.4,), malnutrition (WFH, <60%; OR, 5.0), anemia (Hb level, <6 g/dL; OR, 3.7), and splenomegaly (OR, 2.9). A higher risk of death was associated with episodes of diarrhea (OR, 1.4), vomiting (OR, 2.7), and bleeding (OR, 2.9). Relapse and PKDL occurred in 3.9% and 10.0% of cases, respectively.

Kala-azar (KA) (also known as visceral leishmaniasis) is a chronic multisystemic disease characterized by fever, hepatosplenomegaly, small-volume lymphadenopathy, pancytopenia, wasting and weakness, and eventual death due to bleeding or secondary infections. In southern Sudan, the infectious agent is *Leishmania donovani*, and the main sandfly vector is *Phlebotomus orientalis* [1]. Anthroponotic transmission is probably the main transmission cycle, especially during epidemics, because no animal species has yet been definitively identified as a reservoir.

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Throughout the 20th century, KA has been reported in southern Sudan, and major outbreaks have followed population movement, flooding, food shortages, and conflict [2]. The worst recorded epidemic probably killed >100,000 people in the western Upper Nile area of southern Sudan from 1984–1994, a loss of one-third of the population of that area [3, 4]. Médecins Sans Frontières–Holland (MSFH) has been running KA treatment centers since 1989, and >20,000 patients were treated by MSFH in southern Sudan between 1989 and February 2002.

A study of adult patients with KA who were admitted to an MSFH treatment center in Duar, western Upper Nile, between August 1990 and July 1991 (during the epidemic) linked young and old age, long duration of illness, anemia, malnutrition, splenomegaly, high parasite density, and vomiting with a higher risk of death [5]. However, the cause of subsequent fluctuations in death rates at MSFH treatment centers by year, month, and location remained unclear and could not be de-

termined from our routine statistics. In addition, new drug treatments and MSFH's desire to provide optimal care for the most severely ill patients required further investigation of risk factors for death.

We used the electronic archive of treatment data maintained by MSFH since 1998 to analyze a large and recent data set in order to compare current outcomes to earlier findings and to provide an evidence base for better treatment. We anticipated that the data set would provide information on the epidemiology of KA and identify risk factors for relapse and post-KA dermal leishmaniasis (PKDL). We also hoped to resolve the lingering controversy over the World Health Organization's (WHO's) recommendation that the sodium stibogluconate (SSG) dosage need not be limited to a maximum of 850 mg per day.

Since 1989, MSFH has documented the impact of violence and insecurity on the health of the population of southern Sudan, and this situation remained prevalent at the time of this study [6]. Despite the difficult conditions, MSFH has a tradition of conducting operational research into KA to gain an understanding of the disease and to improve the treatment of patients in southern Sudan [7, 8].

METHODS

Diagnosis, treatment, and discharge. The diagnostic, treatment, and discharge procedures used were consistent with WHO guidelines [9] and are described in an MSFH document [10] (updates of which are available from R.N.D.). In brief, patients with KA who had no previous history of treatment were termed "patients with primary KA," and patients with KA who reported a history of previous treatment for KA were termed "patients with relapsed KA." We diagnosed KA by microscopy of splenic or lymph node aspirates; by high titer (>1:6400), as determined by direct agglutination test (DAT; freeze-dried *Leishmania* antigen was provided by the Royal Tropical Institute, Amsterdam); and, on rare occasions when the laboratories were not functioning, by clinical judgement and the patient's response to SSG.

Standard treatment for primary KA comprised 30 daily intramuscular injections of SSG at a dose of 20 mg/kg (minimum dose, 200 mg; no maximum dose). In cases of primary KA, a test-of-cure (TOC) was performed on spleen or lymph node aspirates if the patient did not respond clinically to treatment. If the TOC result was positive, daily SSG injections were continued until the results of 2 consecutive weekly TOCs were negative. Patients whose results remained positive for parasites after 60 SSG injections received SSG plus paromomycin (formerly called aminosidine; supplied by the International Dispensary Association, Amsterdam, and manufactured by Pharmamed Parenterals) or liposomal amphotericin B (AmBisome; Gilead Pharmaceuticals).

Patients with relapsed KA always received a diagnosis based on the results of an aspirate (because a positive DAT result does not distinguish between patients who are cured and those who have experienced relapse), and they were treated with 17 daily injections (dose, 15 mg/kg) of paromomycin plus 30–60 daily injections of SSG. Patients who experienced relapse twice or more were treated with 6 intravenous doses of ~4 mg/kg of liposomal amphotericin B on alternate days.

PKDL, a complication of KA, is a skin condition, sometimes involving mucosae and eyes, that often develops during or after treatment for KA [11]. PKDL is graded according to the distribution and density of lesions [2]. Patients with grade 2 or grade 3 PKDL were treated with SSG or a combination of SSG and paromomycin until the condition improved.

Demographic details, treatment history, and discharge date were recorded on treatment cards, and, on discharge, patients were given a discharge card to be presented at readmission to a treatment center for PKDL or KA relapse. Our study was based on all treatment cards archived at the MSFH administrative center in Lokichoggio, Kenya, from October 1998 (when patient treatment data were first electronically recorded) to May 2002. During this period, MSFH treatment centers operated in Wudier (in eastern Upper Nile), Lankien (in Bieh State), Magang (in Sobat Province), and Nimne and Thonyor (in western Upper Nile).

Data entry. Data were entered into EpiInfo, version 6.04 (Centers for Disease Control and Prevention [CDC]), by an MSFH staff member and by one of the authors (S.C.). Because of time and resource constraints, all data were entered once.

Data cleaning. Data cleaning was performed by identifying anomalous, inconsistent, or missing values and cross-checking data against the treatment cards. Summary statistics for each month were generated and compared with admission and discharge data from monthly reports that were compiled by each MSFH treatment center. All body mass index (BMI) and weight for height (WFH) values were recalculated. WFH values were compared with those on National Center for Health Statistics/CDC/WHO reference charts from 1982 for children and adolescents <16 years old and <164 cm in height (for female subjects) or <175 cm in height (for male subjects). A review of duplicate patient identification numbers in the data set identified a subset of 159 patients whose discharge and readmission (for KA relapse or PKDL) could be verified.

Statistical analysis. All statistical analysis was performed using Stata software, version 7.0 (Stata). Proportions were compared using χ^2 tests or Mantel-Haenzsel χ^2 tests. The Wilcoxon rank sum test was used for ordinal variables and to compare nonnormal distributions of interval variables. Equality of me-

dians was compared by a nonparametric K-sample test. "Multiple regression analysis" refers to ordinary least squares regression of a single predicted variable on multiple predictor variables. "Multiple logistic regression" refers to logistic regression of a single predicted variable on multiple predictive variables.

RESULTS

Treatment center admissions. The aggregate trend in treatment center admissions for primary KA shows a peak in December (figure 1). The seasonal peak in incidence of primary KA is determined by the incubation period for KA in the study area, the peak period of activity of the vector *P. orientalis* (April–June), and the duration of symptoms before treatment. Of 3365 admissions for treatment of KA or PKDL, 87.4% were for primary KA, 3.5% were for relapsed KA, and 9.1% were for PKDL. An increasing trend in the proportion of patients with primary KA who were <5 years old ($P < .0001$) reflects a maturing of the epidemic. In 1998, 3 (2.5%) of 119 patients with primary KA admitted to our treatment centers were <5 years old; in 1999, 41 (6.5%) of 636 patients; in 2000, 26 (7.5%) of 346 patients; in 2001, 290 (19.1%) of 1520 patients; and, in 2002, 52 (19.8%) of 263 patients.

Clinical features. Patients had signs of advanced disease. The median BMI for male patients ⩾16 years old or with a height ⩾175 cm was 15.6. The median BMI for female patients ⩾16 years old or with a height ⩾164 cm was 15.2. The median WFH of patients <16 years old was 75.5% of the predicted value. The median hemoglobin (Hb) level was 8.5 g/dL. Marked splenomegaly (i.e., a spleen size of Hackett grade 2 or above [12]) was recorded for 2164 (68.0%) of 3183 patients. The median duration of illness before treatment center admission was 2 months.

Treatments. Table 1 shows the drug regimens used, by diagnosis. The median number of SSG injections is derived from cases in which the patient completed a course of therapy; 66.8% of patients with primary KA received the median number of injections (i.e., they received 30 injections). The numbers of patients treated with a combination of SSG and paromomycin or with a combination of SSG and liposomal amphotericin B were too small to support analysis of the impact of these regimens on patient outcomes.

Effect of body weight and SSG dose. Multiple logistic regression (controlling for admission characteristics of age, sex, duration of illness, Hb level, and spleen size) indicated that the odds of survival of patients treated with SSG increased by 1.39 (95% CI, 1.18–1.63; $P < .001$) for each additional kilogram of body weight. Table 2 shows Mantel-Haenzsel ORs for survival of adult patients treated with SSG according to patient weight and with adjustment for age. These results show that doses of SSG of >850 mg are not associated with a higher risk of death

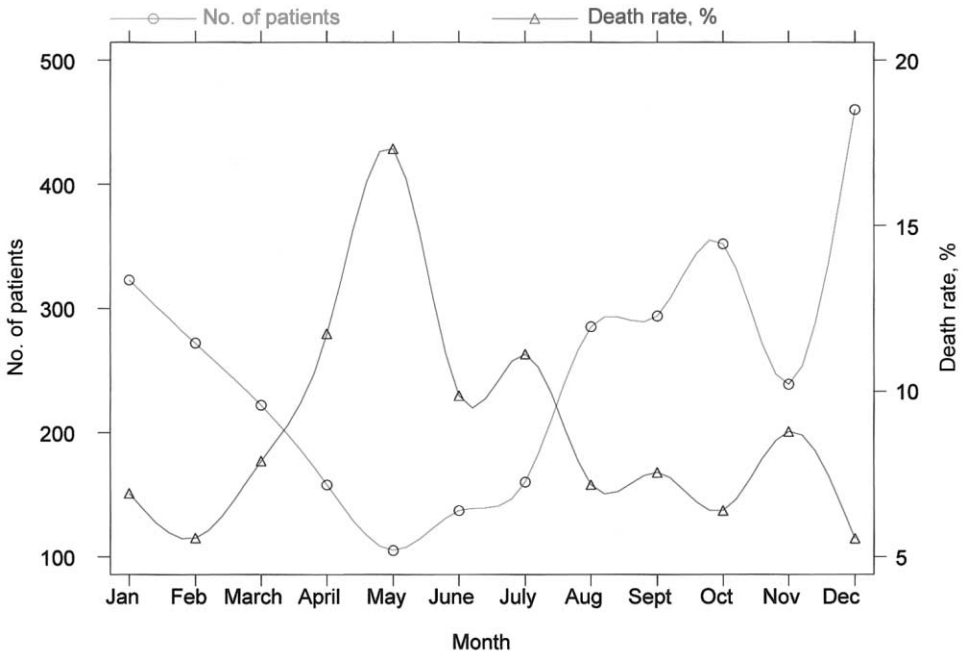

Figure 1. Aggregate monthly admissions of patients with primary kala-azar and aggregate monthly death rate among those patients. Data are for October 1998 through May 2002; therefore, 4 years of data are aggregated for the months January through May and October through December, and 3 years of data are aggregated for the months June through September.

Table 1. Drug regimens administered to patients with kala-azar (KA) or post-KA dermal leishmaniasis (PKDL) treated by Médecins Sans Frontières–Holland in southern Sudan from October 1998–May 2002, by diagnosis.

	KA		PKDL	
Variable	Primary (n = 2942)	Relapsed (n = 118)	Grade 1 or grade 2 (n = 223)	Grade 3 (n = 82)
Duration of treatment, median days	35	41	46	45
No. of drug injections per patient				
SSG				
Median	30	35	39	40
Maximum	99	95	82	88
Paromomycin				
Median	17	21	17	20
Maximum	21	22	22	34
Drugs received, no. (%) of patients				
SSG only	2886 (98.1)	61 (51.7)	130 (58.3)	26 (31.7)
SSG and paromomycin	27 (0.9)	53 (44.9)	93 (41.7)	56 (68.3)
SSG and liposomal AmB	25 (0.9)	1 (0.8)	…	…
SSG, paromomycin, and liposomal AmB	1 (0.0)	3 (2.5)	…	…

NOTE. AmB, amphotericin B; SSG, sodium stibogluconate.

and, therefore, provide the first direct evidence in support of the WHO (and CDC) recommendation [10] that there should be no upper limit on the daily SSG dose.

Effects of treatment on clinical condition. All patients received daily food rations, with supplementary and therapeutic feeding for the most malnourished patients. Between admission to and discharge from the treatment center, the median BMI for adults increased from 15.6 to 16.4 for men and from 15.2 to 15.6 for women. Median WFH of children at discharge from the treatment center was 79.9%, compared with 75.5% at admission. The mean percentage increases in BMI and WFH during treatment were greatest for the most malnourished patients (figure 2). All patients received iron and folate supplements; the median Hb level increased from 8.5 g/dL at admission to 11.0 g/dL at discharge. A normal spleen size was recorded for 1750 (78.0%) of 2244 patients at discharge from the treatment center.

Outcomes. Patients were categorized as either having been cured and discharged (active follow-up was not possible), having died during treatment, or having discontinued therapy during treatment. The cure rate and death rate do not include those patients who discontinued therapy. The overall cure rate for patients with primary KA was 91.9% (2620 of 2851 pa-

Table 2. Sodium stibogluconate (SSG) dose, outcome, and OR for survival for patients with kala-azar (KA) or post-KA dermal leishmaniasis treated by Médecins Sans Frontières–Holland in southern Sudan from October 1998 through May 2002, by sex and weight.

Patient group, by sex and weight in kg	SSG dose, mg	Outcome, no. of patients		OR (95% CI)
		Death	Survival	
Male				
<42.5	<850	88	1016	1.00
42.5– 49.9	850–999	31	243	2.36 (1.17–4.77)
⩾50	⩾1000	19	420	4.35 (2.21–8.57)
Female				
<30	<600	55	666	1.00
30– 39.9	600–799	30	256	3.55 (1.31–9.61)
⩾40	⩾800	31	406	16.44 (3.68–73.52)

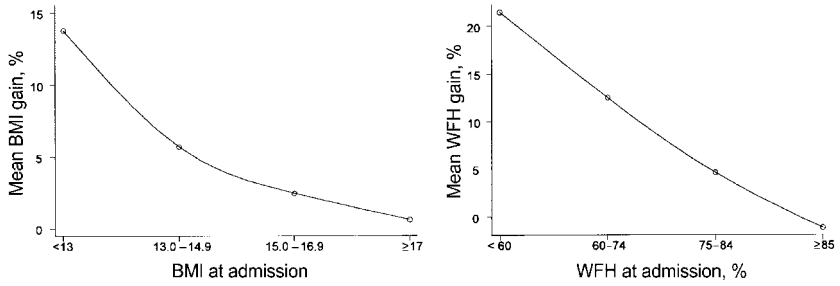

Figure 2. Percentage increase in body mass index (BMI) and weight for height (WFH) during treatment among patients with kala-azar (KA) or post-KA dermal leishmaniasis (PKDL) treated by Médecins Sans Frontières–Holland in southern Sudan from October 1998 through May 2002, as a function of BMI and WFH at admission to treatment. BMI data were recorded for 613 patients, and WFH data were recorded for 571 patients.

tients), and, for patients with relapsed KA, the overall cure rate was 87.3% (97 of 110 patients). The difference between these rates is not statistically significant. The cure rate for patients with PKDL was 98.1% (263 of 268 patients). The therapy discontinuation rate among patients with primary KA was 1.7% (50 of 2903 patients); this was significantly lower ($P < .001$) than the therapy discontinuation rate among patients with relapsed KA (8 [6.8%] of 118 patients). Of 305 patients with PKDL, 37 (12.1%) discontinued therapy. Mantel-Haenzsel ORs generated by univariate analysis of arbitrarily categorized risk factors for death (adjusted for sex and age group) are shown in table 3.

One or more episodes of bleeding (usually epistaxis) occurred in 195 (6.4%) of 3065 patients with either primary KA or relapsed KA and carried a higher risk of death (OR, 2.9; 95% CI, 1.9–4.5; $P < .0001$). The odds of experiencing ⩾1 episode of bleeding were inversely associated with the Hb level at admission to the treatment center (OR, 1.14 per unitary decrease in Hb level, controlling for age and sex; 95% CI, 1.02–1.27; $P < .02$).

The odds of death increased by 1.4 (95% CI, 1.0–1.8; $P < .03$) if ⩾1 episode of diarrhea occurred (which was the case in 51% of all patients) and by 2.7 (95% CI, 2.1–3.5; $P < .0001$) if ⩾1 episode of vomiting occurred (which was the case in 34% of all patients). One-fifth of all patients experienced both diarrhea and vomiting. This was associated with a 3.1-fold increase in the odds of death (95% CI, 2.2–4.5; $P < .0001$). Children <5 years old were particularly susceptible, with 59% developing diarrhea, 49% experiencing vomiting, and 35% experiencing both. Female subjects were more frequently affected by vomiting than were male subjects. Among patients aged 16–24 years, female subjects were almost twice as likely as male subjects to experience vomiting (OR, 1.8; 95% CI, 1.3–2.6; $P = .001$). Among patients aged 25–34 years, women were almost 3 times more likely than men to experience vomiting (OR, 2.6; 95% CI, 1.8–3.9; $P < .0001$).

The aggregate monthly death rate peaked during May (death rate, 17.3%; 95% CI, 11.1%–25.0%), corresponding to a high proportion of patients ill for >5 months before admission and to a high proportion of patients with malnutrition. The incidence of diarrhea also peaked between March and May.

PKDL. Mild PKDL is extremely common and does not require treatment. Our data refer only to PKDL of sufficient severity to require treatment. The overall PKDL admission rate was 9% (305 of 3365 admissions to the treatment centers). Figure 3 shows the odds of developing PKDL. The rate of PKDL among children aged 0–4 years (17.7%) was twice that of children aged 5–9 years (9.9%) and 20 times that of adults aged ⩾45 years (0.9%). Of children who developed PKDL, children aged 0–4 years were twice as likely to develop grade 3 (rather than grade 1 or grade 2) PKDL than were children aged 5–9 years (OR, 2.1; 95% CI, 1.0–4.5; $P < .05$).

Previous treatment was documented for 217 (71%) of 305 patients with PKDL. Previous-treatment cards could be found for 107 of these patients; 99 had been previously treated for primary KA, 1 for relapsed KA, and 7 for PKDL. Apart from age, we could determine no predictors for developing PKDL. The median interval between end of treatment for KA and admission for PKDL was 84 days (range, 12–382 days). Patients reported that PKDL symptoms had begun a median of 26 days after the end of their treatment for KA (the data from which this median was derived included negative values for patients whose self-reported duration of PKDL symptoms was longer than the interval between their discharge from and readmission to the treatment center). For patients who experienced the onset of PKDL during treatment for primary KA (14 patients) or relapsed KA (4 patients), the median interval between the start of treatment and the appearance of PKDL was 33 days (range, 1–81 days). Treatment with ⩾17 doses of paromomycin combined with SSG reduced the median length of treatment of patients with PKDL from 47 days to 39 days ($P = .004$).

Relapse. Because we could not actively follow-up patients after discharge from the treatment centers, patients were counselled before discharge that they should return for treatment if

Table 3. Outcome and OR for death for patients with kala-azar (KA) or post-KA dermal leishmaniasis treated by Médecins Sans Frontières–Holland in southern Sudan from October 1998 through May 2002,

Variable	Outcome, no. of patients		OR (95% CI)	*P*
	Death	Survival		
Patients ⩾16 years old				
Age, years[a]				
16–24	44	523	1.00	…
25–34	29	458	0.80 (0.49–1.31)	NS
35–44	34	185	2.26 (1.39–3.68)	<.001
⩾45	31	79	4.55 (2.70–7.67)	<.0001
Duration of illness, months				
<2	68	802	1.00	…
2–4	46	306	1.67 (1.09–2.54)	<.02
⩾5	20	99	2.25 (1.26–4.00)	<.005
Hemoglobin level, g/dL				
⩾11	7	89	1.00	…
8.0–10.9	28	209	1.74 (0.96–3.13)	NS
<8	29	130	3.98 (1.39–11.37)	.005
Body mass index				
⩾17	7	265	1.00	…
15.0–16.9	25	358	1.81 (1.00–3.30)	<.05
13.0–14.9	42	283	3.62 (1.84–7.13)	.0001
<13	24	102	11.03 (3.58–33.96)	<.0001
Patients <16 years old				
Age, years[a]				
10–15	22	595	1.00	…
5–9	27	675	3.40 (1.83–6.30)	<.0001
2–4	38	348	4.76 (2.64–8.56)	<.0001
<2	30	82	5.35 (2.89–9.90)	<.0001
Hemoglobin level, g/dL				
⩾6	28	308	1.00	…
<6	8	18	3.65 (1.34–10.00)	.007
Spleen size, by Hackett grade				
0	5	139	1.00	…
1–2	67	1026	1.88 (0.75–4.72)	NS
3–5	37	439	2.85 (1.11–7.32)	.02
Weight for height, %				
⩾80	18	400	1.00	…
70.0–79.9	18	463	1.27 (0.63–2.54)	NS
60.0–69.9	20	282	1.98 (0.90–4.34)	NS
<60	14	82	4.97 (2.18–11.30)	<.0001

NOTE. N/S, not significant.

[a] Adjusted only for sex.

symptoms of KA recurred. The overall relapse rate was 3.9% (118 of 3060 patients). Previous treatment was documented for 90 (76%) of 118 patients who experienced relapse. Previous treatment data were located for 41 of these patients; 36 had been previously treated for primary KA, and 5 had been treated for relapsed KA. No predictors of relapse could be determined from these data. The baseline characteristics of patients with primary KA and those with relapsed KA were similar, except that patients who experienced relapse were less malnourished (median BMI, 16.2) than patients with primary KA (15.3; $P < .01$). Patients who were readmitted for relapse were readmitted to a treatment center a median of 108 days (range, 13– 250 days) after the end of treatment for primary KA; patients reported that symptoms of relapse had begun a median

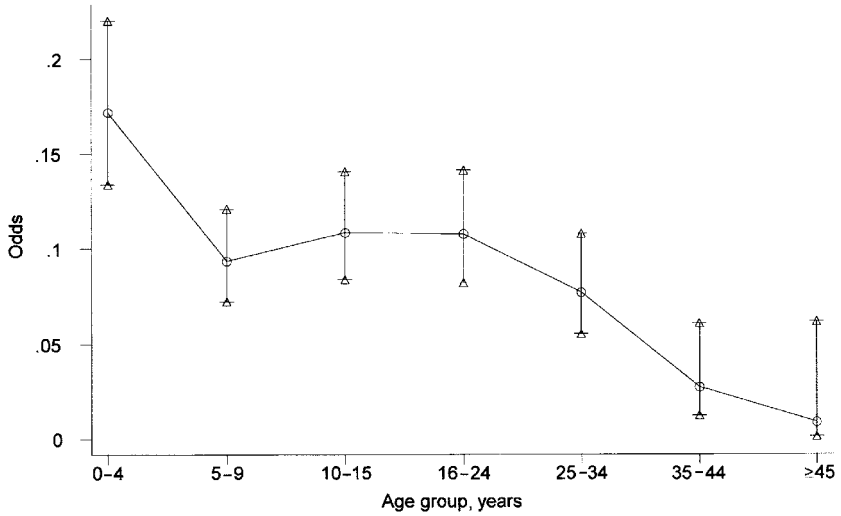

Figure 3. Odds of developing post–kala-azar dermal leishmaniasis (PKDL), by age group, among 3365 patients with kala-azar or PKDL treated by Médecins Sans Frontières–Holland in southern Sudan from October 1998 through May 2002. The total number of patients who developed PKDL was 305. *Bars* indicate 95% CIs.

of 38 days after the end of treatment. The 49 patients with relapsed KA for whom previous treatment data could not be located included 34 patients for whom the reported interval between previous treatment and readmission exceeded 1 year (range, 2–11 years).

DISCUSSION

This study evaluated the clinical characteristics and outcomes of 3365 patients admitted to KA treatment centers run by MSFH in southern Sudan. Patient characteristics at treatment center admission matched those reported by a study of >3000 patients admitted to an MSFH treatment center in Duar, western Upper Nile, from August 1990 through July 1991 (during the KA epidemic) [5]. Patients in the present study (who became ill during the period of endemic KA) and patients who became ill during the epidemic showed similarly advanced states of illness. During the epidemic, patients ⩾18 years old had a median BMI of 15.2 (compared with 15.5 in the present study) and had a median Hb level of 7.7 g/dL (compared with 8.5 g/dL in the present study). Severe malnutrition has been no less of a problem since the epidemic ended: in the period of 1990–1991, 10% of patients had a BMI <13 (compared with 11% in the present study). The demographic characteristics of patients had changed: we found that the proportion of patients <5 years old was 14.8% (compared with 9.5% during the epidemic) and the proportion of patients aged ⩾45 years was 3.5% (compared with 6.4% during the epidemic). This indicates a shift to an endemic pattern of leishmaniasis, in which a greater proportion of adults than before are immune.

The overall cure rate of patients in our study (92%) is an improvement on the cure rate found 10 years earlier (86% of patients were cured in 1990–1991). It is reassuring that SSG therapy retains good efficacy in Sudan, compared with the Indian subcontinent. In the Indian state of Bihar, ~60% of patients with KA are unresponsive to SSG therapy [13]. In southern Sudan, we have repeatedly found that <1% of patients with KA are coinfected with HIV (MSFH, unpublished data). Risk factors for death calculated in the present study closely match risk ratios (for old age, Hb level, BMI, duration of illness, and vomiting) reported in southern Sudan during the KA epidemic [5] and match ORs (for old age, vomiting, diarrhea, and bleeding) reported by MSFH in 2000 from Tigray, Ethiopia [14].

The increased odds of survival among patients who received >850 mg of SSG is a key finding of this study. Such patients obviously weigh >42.5 kg, and this might, in turn, imply better nutrition or less-advanced disease; but the absence of a negative impact on their chances of survival that could be attributable to toxicity of SSG at higher doses serves to confirm the WHO recommendations that SSG dosage does not require an upper limit of 850 mg per day. The WHO recommendations are also followed by the CDC and MSFH.

The link between death rate, long duration of illness, and malnutrition is another key finding. This association would appear to explain the seasonal peak in the death rate and would explain the high death rates reported from a treatment center in Lankien during a period of insecurity in which medical personnel were evacuated. Long duration of symptomatic illness and poor nutritional status are both exacerbated by war, which prevents access to treatment and disrupts food supplies. Our policy of incorporating supplementary feeding into the KA treatment program is supported by the strong evidence of a

link between mortality among patients with KA and malnutrition and is supported by the evidence of significant gains in BMI and/or WFH during treatment. Another key finding is that the greatest gains in nutrition were made among those with the most-severe malnutrition at admission to treatment.

Risk factors determined by this study have been used to define criteria for severe and complicated KA on the basis of age, BMI and/or WFH, and Hb level. This system is being used by staff at MSFH treatment centers to identify those patients most at risk of death; these patients are currently being treated with parenteral ceftriaxone and liposomal amphotericin B until their clinical condition improves, at which point SSG therapy is started.

Despite difficult conditions, large numbers of patients with KA have been (and continue to be) successfully treated. The success of MSFH's program is a testament to the efforts of the national and international staff of MSFH over the past 15 years and, above all, to the courage, resilience, and dignity of the patients.

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