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Risk factors for death in hospitalized dysentery patients in Rwanda

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Summary To evaluate the management of severe dysentery cases in in-patient facilities during an epidemic of *Shigella dysenteriae* type 1 (Sd1), and to identify the factors associated with the risk of death, we conducted a prospective cohort study in 10 Rwandese hospitals between September and December 1994. Data were obtained from 849 cases admitted to hospitals with diarrhoea and visible blood in stools. The proportion of patients with persistent bloody diarrhoea was 51.0% at treatment day 3 and 27.9% at treatment day 5. At discharge, 79.9% had improved or were cured. The case fatality ratio was 13.2%, higher for patients treated with nalidixic acid than for those treated with ciprofloxacin (12.2% *vs*. 2.2%, RR = 5.80, 95% CI = 0.83–40.72). In a logistic regression model three risk factors were significantly associated with an increased risk of death during hospitalization: severe dehydration on admission (adjusted OR = 2.79, 95% CI = 1.46–5.33), age over 50 (adjusted OR *vs*. 5–49 age group = 3.22, 95% CI = 1.70–6.11) and prescription of nalidixic acid (adjusted OR *vs*. ciprofloxacin = 8.66, 95% CI = 1.08–69.67). Those results were consistent with reported high levels of resistance of Sd1 to the commonest antibiotics, including nalidixic acid. Patients belonging to groups with a higher risk of dying should be given special medical attention and supportive care. In areas of high resistance to nalidixic acid, severe cases of dysentery should be treated with fluoroquinolones in order to reduce the mortality associated with these epidemics.

keywords dysentery, *Shigella dysenteriae* type 1, antibiotic treatment, nalidixic acid, fluoroquinolone, Rwanda

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Introduction

For more than 10 years, epidemics of dysentery caused by *Shigella dysenteriae* type 1 (Sd1) have been regularly affecting Central African countries. Because of the increasing number of cases reported each year, the high case fatality ratio (CFR) associated with the disease, and the increasing cost of effective antibiotic treatment, dysentery has become a major public health problem in these countries (WHO 1995).

The civil war that occurred in Rwanda in 1994, and the population movements it induced, facilitated the transmission of Sd1 (Paquet *et al*. 1995). A large outbreak of bloody diarrhoea started in July 1994 and spread all over the country. The control of this outbreak has been further complicated by the rapid progression of Sd1 resistance to the recommended antibiotic treatment, nalidixic acid (Ries *et al*. 1994; Ndihokubwayo *et al*. 1996).

In August 1994, Médecins Sans Frontières (MSF) started assisting the newly appointed Ministry of Health in Rwanda and, among other programmes, provided assistance to 10 district hospitals covering 8 of the 9 *préfectures* of the country. Between August and December 1994, dysentery was the first cause of admission and mortality in these hospitals. In order to evaluate the management of severe dysentery cases in Rwandan in-patient facilities, and to identify the factors associated with the risk of death, we conducted a prospective cohort study in the 10 district hospitals supported by MSF between September and December 1994.

Methods

Study population

All patients admitted for dysentery in the 10 district hospitals supported by MSF from September 15th to December 2nd

1994, were included in the study. Participating hospitals were located in Kibuye, Gisenyi, Ruhengeri, Kigali, Gitarama, Butare, Gikongoro and Cyangugu *préfectures*. Dysentery was defined as 3 or more liquid stools per day and the presence of visible blood in stools, checked by medical personnel. Only severe cases were treated in hospitals.

Data collection

A standardized data collection form was completed for each patient admitted for dysentery, recording age, sex, history of the disease, delay and self-medication before admission as well as clinical presentation. Nutritional status, anaemia and dehydration were assessed clinically by physicians in charge. A follow-up clinical examination was performed daily between day 1 and day 5 and at discharge. There was no follow-up after hospital discharge.

Outcome was recorded for each study patient on the day of discharge. Outcome definitions were: 'cured', normal stools or less than 3 liquid stools per day, and no visible blood in stools; 'improved', 3 or more liquid stools per day, and no visible blood in stools; 'treatment failure': persistence of visible blood in stools. Deaths of hospitalized dysentery patients were also recorded.

Data analysis

Data were entered and analysed with Epi-Info 6.0. The relative risk (RR) with 95% confidence interval was used to measure the association between risk factors and the outcome of the disease. A multivariate analysis (logistic regression) was performed using EGRET software (Epidemiological Graphics, Estimation and Testing package, SERC). All variables included in the questionnaire, except those with more than 10% missing values, were forced into regression models (clinical signs, age group, delay on admission, self-medication before admission and type of treatment). Adjusted odds ratios (OR) were computed, and variables not associated with the outcome and not identified as confounders were excluded from the final model.

Results

Sample description

A total of 849 cases of dysentery, admitted to MSF hospitals between September 15th and December 2nd 1994, were included in the study. The sex ratio (M/F) was 0.73 (339/463); the median age on admission, 20. Three hundred and sixty-one patients (42.5%) were less than 15 years old, 182 (21.4%) were under 5, and 90 patients age 50 or older (10.6%) (Table 1).

Table 1 Antibiotic treatment given on admission of 849 in-patients dysentery cases, Rwanda 1994

Antibiotic treatment	Number of cases	(%)
Nalidixic acid	633	74.6
Ciprofloxacin	47	5.5
Chloramphenicol	37	4.4
Metronidazol	15	1.8
Ampicillin	14	1.6
Cotrimoxazol	13	1.5
Other	7	0.8
No antibiotic	29	3.4
Unknown	54	6.4
Total	849	100

Past history and clinical presentation at admission

The median time lag between onset of symptoms and admission was 4 days, ranging from less than 24 h to 60 days. Of 819 documented patients, 190 (23.2%) had taken some kind of antibiotic treatment before admission (Table 1). Most of the 160 patients with documented information had taken nalidixic acid (68/160; 42.5%) and cotrimoxazol (50/160; 31.3%). None of the patients took ciprofloxacin before admission.

Abdominal pain, tenesmus and fever (38.0 °C) were the signs most commonly associated with bloody diarrhoea on admission (Figure 1). Among admitted patients, 12.7% (101/797) were recorded as severely dehydrated and 6.0% (30/497) as severely malnourished.

Evolution and outcome

The median length of stay in hospital was 6 days, ranging from less than 24 h to 41 days. The majority of the patients were treated with nalidixic acid 4 g/day for 5 days (Table 1). Nalidixic acid was the treatment recommended for dysentery by the Rwandan Ministry of Health. However, two hospitals (Gisenyi and Ruhengeri) had been allowed to use ciprofloxacin because of their location close to the Zairian border, where this drug was the first-line treatment for the refugee population. Thus 47 patients (5.5%) were treated with ciprofloxacin.

At treatment day 3, 51.0% of the surviving patients (413/810) had persisting bloody diarrhoea. This proportion fell to 27.9% (219/785) at treatment day 5. At treatment day 3, the proportion of patients with persisting bloody diarrhoea was higher among those receiving nalidixic acid than among those receiving ciprofloxacin (56.9% *vs*. 30.4%, RR = 1.87, 95% CI 1.20–2.91). Similarly at treatment day 5, bloody diarrhoea was more prevalent among patients treated

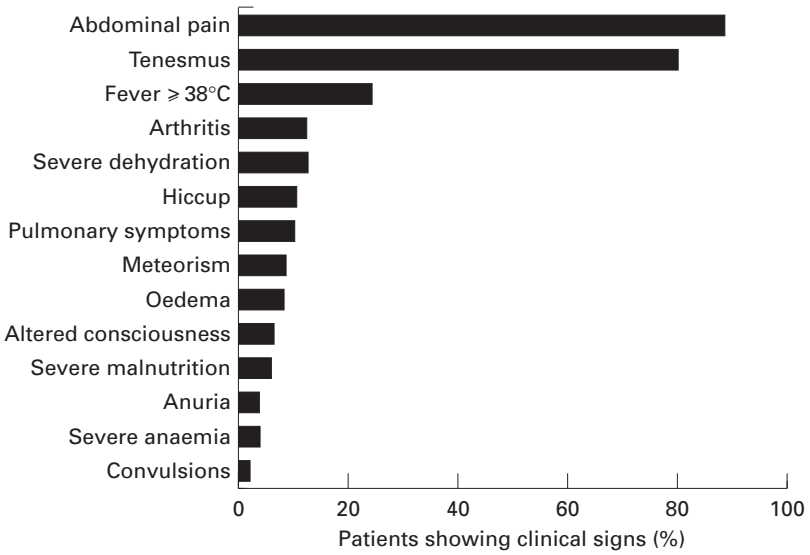

Figure 1 Clinical signs on admission in 849 in-patient dysentery cases, Rwanda 1994.

with nalidixic acid (31.6% *vs*. 17.4%, RR = 1.82, 95% CI 0.96–3.45) (Figure 2).

Twenty-nine patients were lost to follow-up and outcome was documented for the remaining 820 patients (96.6%). On the day of discharge, 655 of 820 patients (79.9%) had improved or were cured. This proportion was higher among patients treated with ciprofloxacin (44/45 documented = 97.8%) than among those who received nalidixic acid (488/613 documented = 79.6%) (RR = 1.23, 95% CI 1.16–1.30). Fifty-seven (6.9%) treatment failures and 108 deaths (CFR 13.2%) were reported. The median duration of stay in hospital for patients deceased was 4 days (range 0–35 days). Twenty-one of 108 deaths (20.0%) occurred during the first 48 h following admission.

Risk factors for death

Children under 5 (RR = 1.5, 95% CI 1.0–2.3) and adults over 50 (RR = 3.0, 95% CI 2.0–4.5) were at higher risk of dying with reference to the 5–49 age group (Table 2). Seventy-nine deaths (CFR 12.9%) were recorded among patients treated with nalidixic acid and 1 (CFR 2.2%) among those who received ciprofloxacin (RR = 5.8, 95% CI 0.8–40.7) (Table 2). The clinical symptoms recorded on admission significantly associated with an increased risk of death during hospitalization were severe dehydration, altered consciousness and oedema of the legs (Table 2). The results of the final logistic regression model are shown in Table 3. Severe dehydration on admission, oedema of the legs, age over 50 and age below 5

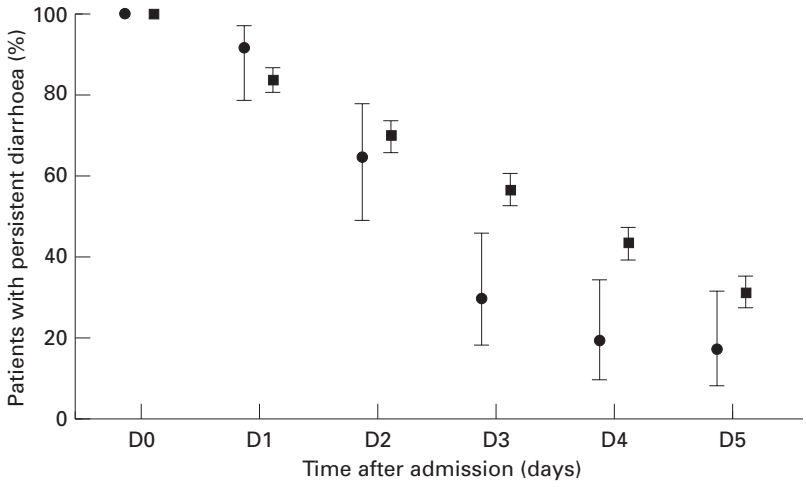

Figure 2 Proportion of in-patient dysentery cases with persistent bloody diarrhoea from admission to treatment day 5 according to antibiotic treatment, Rwanda 1994. ● Ciprofloxacin; ■ Nalidixic acid; bars show 95% confidence interval. At D0 $n = 633$ for nalidixic acid and $n = 47$ for ciprofloxacin.

Table 2 Factors associated with an increased risk of death during hospitalization of 849 in-patient dysentery cases (univariate analysis), Rwanda 1994

Risk factors	Proportion of deaths among exposed	Proportion of deaths among nonexposed	Relative risk	95% C I
Severe dehydration (clinical)	30/99	70/672	2.9	2.0–4.2
Altered consciousness	16/53	87/740	2.6	1.6–4.1
Oedema of the legs	18/67	84/732	2.3	1.5–3.7
Anuria	7/31	93/770	1.9	1.0–3.7
Severe anaemia (clinical)	6/28	87/719	1.8	0.9–3.7
Abdominal pain	89/685	9/85	1.2	0.6–2.3
Age group 0–4*	27/177	55/547	1.5	1.0–2.3
Age group ⩾ 50*	25/184	55/547	3.0	2.0–4.5
Self-medication §	23/182	81/608	1.0	0.6–1.5
Nalidixic acid †	79/613	1/45	5.8	0.8–40.7
Other antibiotics †,‡	8/83	1/45	4.3	0.6–33.6

*: the nonexposed age group is 5–49; § history of self medication before admission (the nonexposed group did not take antibiotic); † the non-exposed group received ciprofloxacin; ‡ ampicillin, chloramphenicol, cotrimoxazol, metronidazol.

Table 3 Factors associated with an increased risk of death during hospitalization of 849 in-patient dysentery cases (logistic regression model), Rwanda 1994

Risk factors	Adjusted OR*	95% C I
Severe dehydration (clinical)	2.8	1.5–5.3
Severe anaemia (clinical)	2.6	0.8–8.5
Oedema of the legs	2.2	1.0–4.6
Age group 0–4§	1.6	0.9–3.0
Age group _79 50§	3.2	1.7–6.1
Nalidixic acid †	8.7	1.1–69.7
Other antibiotics†,‡	5.8	0.6–53.5

* Odds ratios adjusted for: dehydration, age group, oedema of the legs, antibiotic treatment, anaemia; § the reference age group is 5–49; † the reference treatment group received ciprofloxacin; ‡ ampicillin, chloramphenicol, cotrimoxazol, metronidazol.

(*vs*. 5–49), and prescription of nalidixic acid (*vs*. ciprofloxacin) were associated with an increased risk of death during hospitalization.

Discussion

Our study was conducted during a large Sd1 outbreak in Rwanda which lasted from July to December 1994. From September on, we included almost all patients admitted with bloody diarrhoea from 10 different hospitals throughout the country. Since none of the hospitals was equipped to perform bacteriological examinations, we used a clinical case definition as inclusion criteria. However, various surveys, conducted not only in Rwanda, but also in the refugee populations in the neighbouring countries of Zaire and Tanzania, identified Sd1 as the causative agent of the dysentery outbreak that hit this part of Africa during the second half of 1994 (The Goma Epidemiology group 1995; Steering Committee of the Joint Evaluation of Emergency Assistance to Rwanda 1996). We thus believe that our sample was representative of the severe Sd1 dysentery cases hospitalized in Rwanda during the 1994 outbreak. However, this work was performed in the context of an emergency rehabilitation programme involving multiple centres, where successive expatriate teams were in charge of collecting the data. As a consequence, data collection may have suffered from lack of homogeneity, and missing information might have biased our results.

Overall, more than 13% of patients admitted for dysentery in Rwanda died in hospital. Similar CFR were reported from Bangladesh (Bennish & Wojtyniak 1991; Dutta *et al*. 1992) and this confirms the heavy human toll claimed by large Sd1 outbreaks in developing countries. In our cohort, as in Bangladesh (Bennish & Wojtyniak 1991), the younger patients as well as the elderly were at higher risk of dying. The clinical presentation of severe dysentery cases in Rwanda was similar to what had been reported from India (Mathan & Mathan 1991). In our study severe dehydration was the main clinical predictor of lethal outcome. This finding had already been reported from Burundi (Huskins *et al*. 1994). Our data also suggest that severe anaemia and oedema in the legs on admission increased the risk of death in dysentery patients. Although we did not have the means to diagnose haemolytic uremic syndrome, this finding suggested that some deaths could have been due to this complication.

In Rwanda, patients treated with ciprofloxacin seemed to have a much better cure rate than those treated with nalidixic acid or other antibiotics. At treatment day 3, the proportion of patients with persisting bloody diarrhoea was much lower in the ciprofloxacin group, suggesting that this drug also shortened the duration of the disease. However, only two hospitals used ciprofloxacin and comparability of the different groups of patients cannot be ensured. Differences in supportive care or aetiologies of dysentery might have explained these findings. The clinical condition of the patients admitted might also have differed from one hospital to the other, but multivariate analysis probably controlled for most of the potential confounding effects of the clinical variables.

The progression of Sd1 resistance to the commonest antibiotics had already been reported from Burundi during the 1992 outbreak (Ries *et al*. 1994). A survey on *in vitro* Sd1 resistance was conducted at the time of the study period in Rwanda. Thirty-nine (97.5%) of the 40 Sd1 strains isolated were resistant to nalidixic acid, and 100% (40/40) to ampicillin, chloramphenicol and cotrimoxazol (MSF & EPICENTRE unpublished data). Should these results be representative of the Sd1 strains that circulated in Rwanda in 1994, this would obviously explain the differences in outcomes we observed among the antibiotic groups.

Our study, together with *in vitro* resistance surveys from Rwanda and Burundi, suggests that in some parts of Africa fluoroquinolones such as ciprofloxacin might be the only antibiotics still effective today against Sd1. In these areas, introducing ciprofloxacin as first-line treatment for serious dysentery cases, under strict supervision, would probably strongly reduce the high CFR of the disease. Fluoroquinolones are not recommended for children under 15 because of articular side-effects observed in growing animals, but recent studies suggest that in humans this risk is actually much lower than previously feared (Fontaine 1989; Schaad 1993). Moreover, the risk of complication due to treatment must be balanced with the high CFR associated with Sd1 infection in the younger age groups.

The main factor that prevents recommending fluoroquinolone as the treatment for serious dysentery cases in African hospitals is current cost of the drug, given the potential number of patients to be treated in the course of a single outbreak. Short-course fluoroquinolone might represent a less costly alternative to current 5 day treatment, but the efficacy of these therapeutic schemes against Sd1 remains to be confirmed (Bennish *et al*. 1992).

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