SUPPLEMENT ARTICLE

Marburg Hemorrhagic Fever in Durba and Watsa, Democratic Republic of the Congo: Clinical Documentation, Features of Illness, and Treatment

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The objective of the present study was to describe day of onset and duration of symptoms of Marburg hemorrhagic fever (MHF), to summarize the treatments applied, and to assess the quality of clinical documentation. Surveillance and clinical records of 77 patients with MHF cases were reviewed. Initial symptoms included fever, headache, general pain, nausea, vomiting, and anorexia (median day of onset, day 1–2), followed by hemorrhagic manifestations (day 5–8+), and terminal symptoms included confusion, agitation, coma, anuria, and shock. Treatment in isolation wards was acceptable, but the quality of clinical documentation was unsatisfactory. Improved clinical documentation is necessary for a basic evaluation of supportive treatment.

In Durba and Watsa, both situated in Watsa Health Zone, northeastern Democratic Republic of the Congo (DRC), a Marburg hemorrhagic fever (MHF) outbreak occurred between October 1998 and September 2000. A detailed description of the Marburg hemorrhagic fever outbreaks in the Durba area has been published elsewhere [1]. In summary, primary cases were found among gold miners, and secondary cases were found among family members and health workers. The total number of cases was 154, with a case fatality rate of 83%. In May 1999, an international team, coordinated by the World Health Organization (WHO), arrived in Durba to investigate and respond to the epidemic [1, 2].

Before the Durba outbreak, the knowledge of clinical manifestations of and treatment options for Marburg virus infection was based on observations of 39 patients in Europe only [3–8]. The primary objective of the present article is to extend the knowledge base by reporting clinical information on patients with Marburg virus infection in the 1998–2000 outbreaks in Durba and Watsa, DRC. A secondary objective is to assess the quality of the clinical documentation of these patients.

METHODS

In this article, we report on 51 patients with confirmed cases of MHF (including 3 cases identified retrospectively) and 26 patients with probable MHF. Probable cases were patients with suspected MHF who were epidemiologically linked (had been in close contact) with

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We dedicate this article to Dr. Bonzali Katenga and all the other health workers who gave their lives caring for patients with Marburg hemorrhagic fever in Durba and Watsa, Democratic Republic of the Congo.

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a confirmed case. A patient with confirmed MHF was defined as someone who fulfilled the definition of having a probable case and had at least 1 laboratory test result positive for Marburg virus (ELISA antigen detection, ELISA IgM antibody detection, virus culture, reverse-transcription polymerase chain reaction, and/or immunohistochemical analysis). Patients with suspected MHF who were not epidemiologically linked were not included in our analysis because of the relative uncertainty of the diagnoses.

We extracted data from surveillance records on symptom onset and duration. For patients who had sought health care, we extracted data from clinical records on symptom onset, duration, and patterns, as well as on treatment received.

To assess the quality of the clinical documentation, we defined the assessment of the following clinical parameters to be essential: body temperature (measured at least twice daily), pulse rate, respiratory rate, vomiting, diarrhea, dehydration, bleeding signs (including petechiae), level of consciousness, and pain (assessed at least daily). We considered the assessment of the following parameters as nonessential but relevant: blood pressure and urine output. Normally, these parameters also would have been considered to be essential, but the decontamination of the cuffs is difficult, and the manipulation of potentially contaminated urine is hazardous; therefore, it may be acceptable not to assess these parameters.

We extracted all data on treatment regimens that were documented in the clinical records. We defined essential systematic treatment as treatment with antimalarials and antibiotics, under the assumption that neither malaria nor bacterial infection could be ruled out under the given circumstances; in addition, treatment with analgesics, antipyretics, or antiemetics was classified as "essential if indicated." We considered the following to be not essential but relevant: nasogastric feeding, antiulcer drugs, and intravenous fluids; for this analysis, intravenous fluids were not considered to be essential, because they should be expected to be given only if it can be done safely. We classified the following as contraindicated: acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, and intramuscular injections. Note that it would, in our view, be a sensible policy to give the "essential if indicated" drugs systematically.

RESULTS

In the set of patients we analyzed, 45 (58%) were male, 68 (88%) were adult (≥15 years of age), 35 (45%) were gold miners, and 22 (29%) were housewives. The case fatality rate was 78%, with a median interval of 8 days (range, 2–16 days) between the onset of symptoms and death.

Completeness and quality of documentation. Surveillance forms and clinical records were available for 64 and 13 patients, respectively. It was not uncommon to find inconsistencies between the surveillance and clinical records. In such situations, we gave preference to the information contained in the clinical records. Of the 13 clinical records, 2 came close to being case notes and were too unsystematic for further analysis, and 2 referred to patients who died so shortly after admission that the clinical record was just about to be started. Thus, only 9 clinical records were available for further analysis, all relating to hospitalized patients with confirmed MHF.

For these 9 patients, 3 different models of clinical records were used:

1. A sheet ("tick list") with 36 clinical parameters, which were supposed to be assessed on a daily basis. These parameters included all parameters we considered to be essential and many more, but they did not include the relevant parameters dehydration and respiratory rate. Not only the presence but also the absence of symptoms was documented ("zero reporting"). However, there was no room allotted for the documentation of treatment.

2. A chart on which temperature, pulse rate, respiratory rate, and blood pressure were supposed to be graphically represented. There was some empty space at the bottom of the form, which was used to document the presence of the essential parameters vomiting and diarrhea but not dehydration, consciousness, pain, bleeding signs, or the relevant parameter urine output. Most of the empty space was used to document treatment.

3. A combination of the chart described above plus a short list of essential symptoms. However, because no space was provided to document treatment, these symptoms—for example, dehydration—were stroked through and replaced by drug names, effectively turning model 3 into model 2. Only the presence of vomiting and diarrhea was documented rather reliably; none of the other symptoms were. The absence of symptoms was not documented when this model or model 2 was used.

The documentation of temperature and pulse rate was good, and that of respiratory rate and blood pressure was satisfactory. The documentation of symptoms was poor, with the exception of diarrhea and vomiting. There was no documentation of dehydration, despite this symptom being crucial for triggering and monitoring oral or intravenous rehydration therapy. Documentation of the absence of key symptoms was the exception. The duration of symptoms was reported in <10% of the clinical records.

Frequency and succession of symptoms. The frequency of symptoms at any stage of disease is presented in table 1. The most frequently seen general symptoms included fever (86%), fatigue (82%), loss of appetite (77%), severe headache (74%), nausea/vomiting (73%), and generalized pain (65%); the most frequently observed hemorrhagic signs were hematemesis (56%), melena or bloody diarrhea (55%), and bleeding gums (32%). Restricting the analysis to confirmed cases would have

Table 1. Symptoms in patients with confirmed or probable Marburg hemorrhagic fever (MHF).

Symptom (sorted by frequency)	Total ($N = 77$)	Patients with confirmed MHF ($n = 51$)	Patients with probable MHF ($n = 26$)	Patients who survived ($n = 17$)	Patients who died ($n = 60$)	P[a]
Fever	66 (86)	44 (86)	22 (85)	13 (76)	53 (88)	.22
General						
Fatigue	63 (82)	47 (92)	16 (62)	16 (94)	47 (78)	.14
Loss of appetite	59 (77)	44 (86)	15 (58)	15 (88)	44 (73)	.20
Severe headache	57 (74)	41 (80)	16 (62)	12 (71)	45 (75)	.71
Nausea/vomiting	56 (73)	42 (82)	14 (54)	13 (76)	43 (72)	.69
Generalized pain	50 (65)	37 (73)	13 (50)	11 (65)	39 (65)	.98
Diarrhea	46 (60)	33 (65)	13 (50)	7 (41)	39 (65)	.08
Dyspnea	43 (56)	28 (55)	15 (58)	10 (59)	33 (55)	.78
Abdominal pain	41 (53)	29 (57)	12 (46)	6 (35)	35 (58)	.09
Sore throat/dysphagia	40 (52)	30 (59)	10 (38)	8 (47)	32 (53)	.65
Hiccups	30 (39)	23 (45)	7 (27)	5 (29)	25 (42)	.36
Conjunctivitis	28 (36)	21 (41)	7 (27)	3 (18)	25 (42)	.07
Chest pain	18 (23)	15 (29)	3 (12)	12 (71)	6 (10)	<.01
Lumbar pain	13 (17)	11 (22)	2 (8)	5 (29)	8 (13)	.12
Coughing	12 (16)	9 (18)	3 (12)	3 (18)	9 (15)	.79
Coma >24 h	1 (1)	1 (2)	0 (0)	0 (0)	1 (2)	.59
Hemorrhagic						
Any	64 (83)	42 (82)	22 (100)	11 (65)	53 (88)	.03
Hematemesis	43 (56)	32 (63)	11 (42)	8 (47)	35 (58)	.41
Melena, bloody diarrhea	42 (55)	28 (55)	14 (54)	6 (35)	36 (60)	.07
Bleeding gums	25 (32)	16 (31)	9 (35)	3 (18)	22 (37)	.14
Epistaxis	15 (19)	8 (16)	7 (27)	2 (12)	13 (22)	.36
Bleeding at injection site	11 (14)	8 (16)	3 (12)	0 (0)	11 (18)	.06
Hemoptysis	7 (9)	4 (8)	3 (12)	3 (18)	4 (7)	.16
Petechiae	4 (5)	3 (6)	1 (4)	1 (6)	3 (5)	.89
Vaginal bleeding[b]	3 (9)	1 (6)	2 (14)	0 (0)	3 (12)	.47
Hematuria	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Combinations						
Fever plus at least 3 general symptoms	63 (82)	45 (88)	18 (69)	14 (82)	49 (82)	1.0
Fever plus hemorrhage	57 (74)	38 (74)	18 (69)	11 (65)	48 (80)	.21

NOTE. Data are no. (%) of patients with a given symptom, unless otherwise indicated.

[a] χ^2 test comparing proportions in survivors and fatalities.

[b] Denominator contains female patients only.

resulted in exactly the same ranking of symptoms. Virtually all symptoms were documented more frequently in confirmed than in probable cases. The most significant predictors of a fatal outcome ($P < .1$, χ^2 test) were diarrhea, abdominal pain, conjunctivitis, absence of chest pain, melena/bloody diarrhea, and bleeding at the injection site.

For each symptom, table 2 presents the median day of onset and the median duration, as well as whether symptoms, which lasted longer than 2 days, occurred on consecutive days. The description of 2 typical cases of MHF can be found in the Appendix, which appears only in the online edition of the *Journal*.

Disease usually started with fever and severe headache on day 1, followed by fatigue, generalized pain, and loss of appetite on day 2. Nausea, vomiting, and diarrhea were lead symptoms for day 3, and dysphasia, dyspnea, and conjunctivitis typically marked day 4. Minor hemorrhage (e.g., epistaxis) typically started on day 3–4, and major hemorrhage (melena, bloody diarrhea, and hematemesis) started on day 5–7. Coma lasting >24 h occurred in only 1 patient, starting on day 6. The patient did not regain consciousness and died on day 10.

Treatment. A total of 8 records included data on treatment. These data were sometimes documented in specific forms but were often scribbled in the margins of temperature sheets. All of these records belonged to patients whose MHF had been diagnosed on clinical grounds before laboratory confirmation

Table 2. Date of onset, duration, and continuity of symptoms in 77 patients with confirmed and probable Marburg hemorrhagic fever (MHF).

Symptom (sorted by day of onset)	Patients, no.		Day of onset		Duration of symptom		Pattern
	Had symptom	Received health care	No. of records with data	Day of onset, median	No. of records with data	Duration of symptom, median, days	
Fever	66	54	49	1	8	2	Intermittent
General symptoms							
Severe headache	57	48	44	1	2	3	Intermittent
Fatigue	63	50	50	2	3	2	Intermittent
Chest pain	18	15	11	2	4	2.5	Unknown
Generalized pain	50	42	40	2	0	…	…
Loss of appetite	59	49	49	2	5	1	Intermittent
Nausea/vomiting	56	48	44	2.5	8	3	Intermittent
Coughing	12	11	10	2.5	4	2.5	Unknown
Diarrhea	46	36	38	3	5	3	Continuous[a]
Abdominal pain	41	33	37	3	1	1	…
Lumbar pain	13	9	7	4	3	2	Continuous
Sore throat/dysphagia	40	30	32	4	5	1	Continuous
Dyspnea	43	32	32	4	1	1	…
Conjunctivitis	28	21	22	4	0	…	…
Hiccups	30	24	23	6	0	…	…
Coma >24 h	1	1	1	6	0	…	…
Hemorrhagic symptoms							
Any	64	59	64	5.5	6	3	…
Epistaxis	15	14	11	3	0	…	…
Bleeding gums	25	20	21	4	0	…	…
Melena	42	32	33	5	1	6	…
Hematemesis	43	37	37	5	5	2	Continuous
Vaginal bleeding[b]	3	3	2	6	0	…	…
Hemoptysis	7	6	3	7	0	…	…
Petechiae	4	3	2	9	0	…	…
Death	60	45	59	8	…	…	…

[a] In 4 of 5 patients.
[b] Denominator contains female subjects only.

was available. All patients systematically received antimalarial and antibiotic treatment, the latter often in combination therapy and sometimes in polypharmacy (e.g., the combination of tetracycline, cotrimoxazole, chloramphenicol, and metronidazol).

The only analgesic administered was acetaminophen, rather generously, possibly also for its antipyretic characteristics. It is impossible to judge from the records whether stronger analgesia was indicated occasionally or whether all patients had adequate pain relief. Antiemetics (chlorpromazine or metoclopramide) were given rather frequently, as was aluminium hydroxide as an antacid. Almost all patients received intravenous fluids. Because no data on dehydration were collected, we do not know whether this was done to prevent or to treat dehydration. Nasogastric feeding was not practiced. No contraindicated drugs or types of applications were used in the treatment of these 8 patients.

DISCUSSION

We analyzed the clinical and surveillance records of 77 patients, 51 of whom had confirmed MHF and 26 of whom had probable MHF. The type of clinical manifestations and the course of disease in patients with Marburg virus infection in DRC were similar to those previously reported in other patients with Marburg virus and Ebola virus infection [3–9]. The illness generally starts with fever, malaise, muscle pain, and headache. Two to 4 days after onset, gastrointestinal symptoms (nausea, vomiting, and diarrhea), as well as conjunctival injection and rash, can be observed. Sore throat/dysphagia was noted to occur generally at around day 4, but 2 of us (R.C. and B.J.) felt that a sore throat might already have been present on days 2–4. Death typically occurred after 8–10 days; diarrhea, bloody diarrhea, and abdominal pain, as well as conjunctivitis and bleeding from

The figure is available in its entirety in the online edition of the *Journal of Infectious Diseases*.

Figure 1. Proposed case report form for future Marburg/Ebola hemorrhagic fever outbreaks, based on a model created by Médicins Sans Frontières for the 2005 outbreak in Uige, Angola. The figure is available in its entirety in the online edition of the *Journal of Infectious Diseases*.

injection sites, were associated with a fatal outcome. The clinical picture we found in Durba and Watsa corresponds to what was seen in Uige, Angola, in 2005 (Paul Roddy, MSF Spain, personal communication).

The most striking difference between the patients in our study and those in Europe is the significantly higher frequency of hemorrhagic manifestations (83% vs. 34%; $P < .001$, Fisher's exact test) and fatal outcomes (78% vs 22%; $P < .001$) in DRC [3, 4]. Possible explanations for this finding include, among others, differences in virus pathogenicity, infectious dose, and inoculation route and in the availability and quality of supportive care.

The patients systematically received antimalarials and antibiotics, which is appropriate when malaria and bacterial infection cannot be ruled out because of the absence of high-level biosafety laboratory facilities. Antipyretics, antiemetics, and antacids were used generously, which is probably appropriate; the question of whether more powerful analgesia might occasionally have been indicated remains unanswered. Intravenous fluids were given frequently, despite the fact that their unproven effectiveness and the biohazard they impose have caused some to question their use. In Watsa, no occupational transmission occurred on the isolation wards, except in 1 incident, when an auxiliary midwife caring for an ill relative refused to use protective gear [10].

Case-fatality rates did not differ significantly between patients who received or did not receive health care (45 [75%] of 60 vs. 11 [65%] of 17; $P = .5$, Fisher's exact test). This crude comparison should not be interpreted as evidence for the ineffectiveness of supportive and symptomatic treatment, because there is hardly any information about disease severity in both groups.

We found the clinical documentation of patients with MHF to be missing, incomplete, and of low quality. It was apparent that those health workers who used clinical records had undertaken considerable efforts to document the clinical course, but they lacked guidance on what information is relevant and the proper forms to achieve decent documentation. Sadly, this outbreak is no exception in this respect: since the Ebola hemorrhagic fever outbreak in Kikwit in 1995, 11 filoviral hemorrhagic fever outbreaks with >1200 patients have been registered, and no clinical data have been published since Kikwit. Of course, only a minority of patients have been treated in isolation wards—but >100 have been treated in such wards, and study of these patients could have provided valuable information. Even when specific diagnostic laboratories have been put in place during an outbreak, laboratory facilities for chemistry and hematology have never been available. The consequence is that we do not know which components of supportive and symptomatic care are given in which situation and how effective they are. Although there is discussion about the feasibility of trials under outbreak conditions to evaluate innovative treatments, we lack basic information about the clinical manifestations of the disease (e.g., the number of patients who survive coma while their fluid and electrolyte balance has been maintained by standard intravenous liquids).

RECOMMENDATION

Setting standards is the mandate of WHO, and standard surveillance and record forms for clinical documentation are urgently needed. Given that only a few organizations are involved in providing clinical care to patients with filoviral hemorrhagic fever, it should be possible to agree on what data need to be collected and which tools to use. Figure 1 shows a case report form that we propose for use in future Marburg/Ebola hemorrhagic fever outbreaks. This form is based on a model that was created by MSF for the 2005 outbreak in Uiga, Angola. Analysis and publication must follow if the collection of data is to be a useful exercise. Given the limited number of patients per outbreak, pooling of data will possibly allow more statistical power and insight to be gained. The recent severe acute respiratory syndrome outbreak has demonstrated how powerful international collaboration can be if short-term institutional interests are put aside.

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