Basic Clinical and Laboratory Features of Filoviral Hemorrhagic Fever

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The filoviruses Marburg and Ebola cause severe hemorrhagic fever (HF) in humans. Beginning with the 1967 Marburg outbreak, 30 epidemics, isolated cases, and accidental laboratory infections have been described in the medical literature. We reviewed those reports to determine the basic clinical and laboratory features of filoviral HF. The most detailed information was found in descriptions of patients treated in industrialized countries; except for the 2000 outbreak of Ebola Sudan HF in Uganda, reports of epidemics in central Africa provided little controlled or objective clinical data. Other than the case fatality rate, there were no clear differences in the features of the various filovirus infections. This compilation will be of value to medical workers responding to epidemics and to investigators attempting to develop animal models of filoviral HF. By identifying key unanswered questions and gaps in clinical data, it will help guide clinical research in future outbreaks.

The filoviruses Marburg and Ebola cause fulminant hemorrhagic fever (HF) in humans, with high case fatality rates. Beginning with the first recognized outbreaks in Germany and Yugoslavia in 1967, a total of 30 epidemics, individual cases, and accidental laboratory infections, totaling nearly 2500 confirmed cases, have been reported in the medical literature (Table 1). To date, however, no article has attempted to summarize the essential clinical and laboratory features of filoviral infections based on those published reports. Because such a study would clearly be of value to medical workers responding to outbreaks and to researchers attempting to develop and validate models of these diseases in laboratory animals, we reviewed the medical literature to establish the basic characteristics of Marburg and Ebola HF.

In this article, we summarize the information we found in more than 40 journal articles cited in PubMed, in 2 books published after the 1967 outbreak of Marburg HF in Germany and Yugoslavia and the 1976 epidemics of Ebola HF in Zaire and Sudan, and in a recently published compendium of the filovirus literature [42–44]. We focus on the objective physical features of the disease caused by Marburg virus and by species of Ebola virus. We do not discuss Ebola Reston virus, which is not known to have caused disease in humans. Because it has only been reported once, we also do not describe the phenomenon of "asymptomatic" infection in close contacts of Ebola HF patients [45]. Two Russian case reports not available in English were translated by 1 of the authors [12, 32]. Interested readers can obtain copies by contacting the corresponding author.

In addition to providing a concise summary of information useful to clinicians and researchers, this review can also serve as a guide to the filovirus clinical literature, which varies greatly in the quantity and quality of data in the various case reports and descriptions of outbreaks. In general, articles published before the mid-1980s provide more detailed clinical information on

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Table 1. Epidemics and Confirmed Cases of Filoviral Hemorrhagic Fever Since the Disease Was First Recognized in 1967 [1, 2]

Virus	Date	Location	Source of infection	No. of cases	CFR (%)	References[a]
Marburg						
	1967	Germany	Contact with NHPs	29	23	[3–8]
	1967	Yugoslavia	Contact with NHPs	2	0	[9]
	1975	S. Africa	Unknown	3	33	[10]
	1980	Kenya	Unknown	2	50	[11]
	1987	Kenya	Unknown	1	100	
	1990	Russia	Lab accident	1	0	[12]
	1998	DRC	Contact with bats	154	83	[13, 14]
	2000	Angola	Unknown	252	90	
	2007	Uganda	Contact with bats	4	25	
	2007	Uganda	Contact with bats	1	100	[15]
	2008	Uganda	Contact with bats	1	0	[16]
Ebola						
Zaire	1976	Zaire[b]	Unknown	318	88	[17–21]
	1977	Zaire	Unknown	1	100	[22]
	1994	Gabon	Contact with NHPs	49	65	
	1995	DRC	Unknown	315	88	[23–27]
	1996	Gabon	Contact with NHPs	37	57	[28–30]
	1996	Gabon	Contact with NHPs	60	75	[31]
	2001	Gabon/RC	Contact with NHPs	123	79	
	2003	RC	Contact with NHPs	143	90	
	2003	RC	Contact with NHPs	35	83	
	2004	Russia	Lab accident	1	100	[32]
	2005	RC	Unknown	12	75	
	2007	DRC	Contact with bats	264	71	[1]
	2008	DRC	Unknown	32	47	
Sudan	1976	Sudan	Unknown	284	53	[33, 34]
	1976	England	Lab accident	1	0	[35]
	1979	Sudan	Unknown	34	65	
	2000	Uganda	Unknown	425	53	[36–38]
	2004	Sudan	Unknown	17	42	
Côte d'Ivoire	1994	Côte d'Ivoire	Necropsy of chimp	1	0	[39]
Bundi-bugyo	2007	Uganda	Unknown	102	42	[40, 41]

NOTE. CFR = case fatality rate; NHPs = nonhuman primates; DRC = Democratic Republic of the Congo; RC = Republic of the Congo.

[a] Reports that include clinical data used as sources of information for this article are cited.

[b] Zaire: the present Democratic Republic of the Congo.

patients with Marburg and Ebola HF than papers which have appeared since that time. The best sources of data on the clinical and laboratory features of filoviral HF are the numerous publications describing the 1967 Marburg HF outbreaks in Germany and Yugoslavia and reports of individual cases of Marburg and Ebola Zaire virus infection treated in hospitals in Kenya and South Africa, a case of Ebola Côte d'Ivoire virus infection treated in Switzerland, and 3 accidental laboratory infections (Table 1) [3–5, 9, 11, 12, 17, 28, 32, 35, 39]. A considerable amount of patient data were also obtained during the 2000 outbreak of Ebola Sudan HF in Uganda [36–38]. In contrast, most reports of epidemics in central Africa have provided either general descriptions of patients, summaries of signs and symptoms, or no clinical information at all.

In our review of the literature, we found that certain observations, such as fever, rash and thrombocytopenia, appeared repeatedly in descriptions of patients with filoviral HF, and we have therefore accepted them as standard features of illness. In contrast, some other physical or laboratory findings were described in only 1 or a few reports, and we consider them to be in need of further study. Although health workers responding to African epidemics have certainly monitored the pulse rate, blood pressure, and other physiological parameters of their patients, those data have unfortunately not been compiled and published [13]. By identifying gaps in our knowledge of filoviral HF, this paper will help medical workers plan basic clinical studies in future outbreaks, devise efficient record-keeping mechanisms, and prepare their findings for publication.

CLINICAL AND LABORATORY FEATURES OF FILOVIRAL HF

Because our review of the literature indicated that Marburg and Ebola HF cannot be distinguished by physical examination or standard clinical laboratory tests, these diseases are discussed together in the following sections.

Incubation Period

The most reliable information on the incubation period of Ebola and Marburg HF has been obtained from situations in which a single well-defined event, such as a laboratory accident, contact with an infected animal, or exposure in a hospital, has occurred. For example, the incubation period after a needlestick injury with Ebola Sudan virus was 6 days [35], and it was 7 days for a similar exposure to Ebola Zaire virus [32]. An ethologist who performed a necropsy on a dead chimp in Côte D'Ivoire became ill 8 days later [39], and 2 tourists who were exposed to bats while visiting the same cave in Uganda developed Marburg HF 10 days and 13 days later [15, 16], respectively. During the first Marburg outbreak, incubation periods for infections resulting from well-defined exposures ranged from 5–9 days, while for outbreaks of Ebola Zaire HF they have varied from 3–12 days [3, 5, 6, 9, 11, 22–24, 28]. Overall, these reports indicate a range of 3–13 days for the incubation period.

Initial Signs and Symptoms

All reports agree that Marburg and Ebola HF patients become ill abruptly with a variety of nonspecific signs and symptoms, including fever, chills, fatigue, headache, myalgia, nausea, vomiting, and diarrhea. Because of the nonspecific nature of these findings, physicians in sub–Saharan Africa generally assume that a febrile patient is suffering from malaria, typhoid fever, or other illness common to the region. Filoviral HF is usually not suspected until a rash or hemorrhage is noted or person-to-person transmission, especially to doctors and nurses, has occurred.

Physical Examination

Body temperature. As its name implies, elevated body temperature is a characteristic feature of filoviral HF [5, 9, 10, 12, 14, 15, 17–19, 23–25, 32, 33, 35]. Temperatures of 39°C–40°C early in the disease course are frequently observed. The progression of fever over time is displayed graphically in several articles [3, 5, 9, 10, 12, 18, 32, 35, 39]. Wide swings in body temperature during the course of illness, with drops to below normal, have been described [5, 10, 35, 39].

Blood pressure. Despite the utility of the blood pressure as a basic measure of cardiovascular status, actual values are mentioned in only a handful of reports, typically when a patient is first examined and the hemodynamic parameters are normal [9, 10, 23, 32]. Fatally infected patients are known to proceed through hypotension and shock to death, but blood pressure data during the course of illness have rarely been reported [17, 23–25, 28, 32]. Only in the case of a nurse in South Africa who became fatally infected with Ebola Zaire virus during patient care have data obtained through Swann-Ganz catheterization been reported [28]. However, the published findings cover only day 18 of illness (5 days before death) when the pulmonary artery occlusion pressure was 22 mm Hg and the left ventricular stroke work index and systemic vascular resistance were low.

Pulse. Although heart rates have rarely been included in case reports, some authors have noted that a pulse–temperature dissociation (relative bradycardia) is a common finding early in the course of filoviral HF [3, 9, 10, 12, 17, 18, 23, 32, 35]. As the illness progresses, patients may become tachycardic, with rates as high as 120–140 beats/min, especially late in the disease course. Regarding the first Marburg outbreak, Martini commented that ''tachycardia corresponding to the height of temperature was only found in fatal cases'' [3]. Three articles contain excellent graphs of daily pulse and temperature [3, 9, 18].

Respiratory rate. The respiratory rate is the vital sign least frequently documented in clinical reports [9, 10, 24, 32]. In 2 cases, patients had rates of 24 and 20 breaths/min, respectively, on days 4 and 5 of illness [9, 10]. Both were febrile, and the first had an elevated pulse of 100 beats/min. Another individual whose condition was described as ''extremely grave'' on day 13 of illness had respiratory rates of 32–36/min supine and 40/min standing, with a pulse of 108 beats/min and blood pressure 90/60 mm Hg [9]. Accounts of the 1995 Ebola Zaire outbreak noted that tachypnea was present in 31 of 84 nonsurvivors, but none of the 19 survivors [24, 25].

Rash. Most descriptions of Marburg or Ebola HF note the development of a rash early in the course of illness. In a number of outbreak reports, a rash was seen in 25%–52% of individuals [3, 5, 9, 10, 12, 13, 15–19, 23–25, 28, 32–35, 39–41]. It is frequently described as being nonpruritic, erythematous, and maculopapular, sometimes beginning focally, then becoming diffuse, generalized, and confluent. Others have described it as morbilliform (measles-like) [18, 34] or scarletinoid [5]. The rash may be difficult to discern in dark-skinned individuals. Martini provides an excellent description in a report on the 1967 Marburg HF outbreak: ''The most reliable diagnostic sign was a characteristic rash. It began between the fifth and seventh day at the buttocks, trunk, and outside of both upper arms as a distinctly marked, pin-sized red papula around the hair roots. This stage lasted up to 24 hours and developed into a macular, papular, sharply delineated lesion which later coalesced into a more diffuse rash.'' [3] Desquamation of the same areas may occur during convalescence [10, 17, 34].

Hemorrhage. Patients with filoviral HF often develop multiple foci of mucosal hemorrhage, most evident in the conjunctiva, together with easy bruising and persistent bleeding from injection or venipuncture sites [3–5, 9, 10, 13, 19, 20, 22,

24, 25, 28, 34]. However, hemorrhage is not seen in all patients, and massive bleeding is usually observed only in fatal cases when it is typically localized to the gastrointestinal tract. Intracranial hemorrhage has been described [28].

Other findings. Other abnormalities on physical examination of patients with filoviral HF that have been mentioned frequently in case descriptions or outbreak reports include pharyngeal erythema with a complaint of sore throat, enlarged lymph nodes, tender hepatomegaly with the edge of the liver palpable below the ribcage, and abdominal pain and tenderness to palpation [3, 5, 9, 10, 13, 20, 24, 25, 32, 34, 35]. Jaundice, as manifested by icteric sclera, is rarely mentioned [11, 17, 18, 32]. Hiccups have been described as part of the terminal syndrome in fatal cases [24, 25, 40].

Laboratory Tests

Hemoglobin and hematocrit. These indices are rarely mentioned and have been recorded over the course of illness for only 2 patients. In the first case, no hemorrhage was described, and only a minor, transient decrease in hemoglobin and hematocrit was seen [39]. The other patient bled from injection sites, developed a hemorrhagic rash, and had a progressive decline in hemoglobin [32].

White blood cells. Patients with filoviral HF typically are leukopenic at the time of clinical presentation, with an abnormally low number of lymphocytes and an increased percentage of granulocytes [3, 5, 9, 10, 28, 39]. As the disease progresses, the total leukocyte count rises above normal, with an increase in immature granulocytes and the appearance of numerous atypical lymphocytes. In fatal cases, leukocytosis persists through death.

Platelets. Thrombocytopenia is a constant feature of filoviral HF; it is present either at the time of clinical presentation or develops early in the course of illness [3, 5, 7, 10, 28, 39]. In severely ill patients, the platelet count continues to decline, and in fatal cases it remains low until death.

Liver-associated enzymes. Elevated serum levels of alanine and aspartate aminotransferase (ALT, AST) are a common feature of Marburg and Ebola HF [3, 5, 9–12, 16, 18, 28, 32, 38, 39]. However, peak serum concentrations of these enzymes are usually much lower than those seen in infections by viruses such as hepatitis A or B or yellow fever. In all but 1 report, the AST is higher than the ALT [9]. A study of 123 patients in the 2000 outbreak of Ebola Sudan HF in Uganda found that mean AST values over the course of illness were significantly higher in fatal cases than in survivors, and that the mean AST concentration was 7–12 times higher than the ALT in fatal cases and 2–4 times higher in nonfatal cases [38]. The serum alkaline phosphatase level, when reported, has been either normal or elevated, while the lactate dehydrogenase and gamma-glutamyl transferase concentrations were elevated in the few instances when they were measured [3, 11, 28, 32, 39].

Bilirubin. The serum total bilirubin level was mentioned in only 4 reports in which it was either normal or elevated [3, 10, 38, 39]. As noted above, jaundice is not a common feature of filoviral HF.

Other serum chemistry values. Serum electrolyte and glucose measurements have rarely been reported. In the 1967 Marburg HF outbreak, hypokalemia was seen in 50% of patients, typically coinciding with vomiting and diarrhea [3]. Patients in the 2000 Ebola Sudan HF outbreak showed a decline in glucose levels on days 3–5 of illness that persisted beyond day 8; no difference was noted between fatal and nonfatal cases [38]. In contrast, a decrease in the serum calcium level to <6 mg/dL was associated with fatal illness.

Renal function. Renal function is generally normal at the time of presentation or in the early phase of illness, but by the end of the first week, patients may show a progressive decline in urine output and a rise in BUN and creatinine [9, 11, 17, 24, 28, 32, 38, 39]. Two papers describe oliguria that did not improve despite the administration of intravenous fluids [23, 35]. Renal failure is more common in fatal cases [24, 38]. Hematuria and proteinuria have also been noted [5, 35, 39]. In 2 cases in which patients were tested frequently for proteinuria, its presence appeared to correspond with fever [5, 35]. The need for renal dialysis is mentioned in 2 reports [11, 28].

Pancreatic enzymes. A handful of articles mention pancreatitis without specifying its time course; when serum amylase concentrations are stated, they range from normal to elevated [3, 10, 16, 17, 32, 38, 39]. Lipase levels have not been reported.

Coagulation parameters. Several reports have described prolongation of the prothrombin time (PT), partial thromboplastin time (PTT), or bleeding time and other coagulation defects [3, 4, 10, 18, 28, 39]. Patients with filoviral HF frequently meet the criteria for disseminated intravascular coagulation (DIC). In the 2000 outbreak of Ebola Sudan HF in Uganda, patients had elevated plasma levels of D-dimers, with markedly higher levels in fatal cases [38].

Terminal Course

Reports generally state that patients dying of filoviral HF progress from prostration and obtundation to severe hypotension and shock, ending in coma [3, 5, 20, 24, 34]. As noted above, few data have been published on the pulse, blood pressure, respiratory rate, and other physiological parameters during the final phase of illness.

Duration of Illness in Fatal Cases

In 25 well-documented fatal cases of Marburg and Ebola HF, the majority of deaths occurred during the second week of illness, with a median survival of 9 days from onset of illness to death (Figure 1) [3, 5, 10, 13, 15, 18, 19, 22, 23, 28, 32]. The only patient who died after day 16 suffered a terminal intracerebral hemorrhage while being treated in an intensive care unit [28]. The observation that persons who live through the second week of illness are likely to recover is consistent with a report from the 1995 Ebola Zaire HF outbreak that

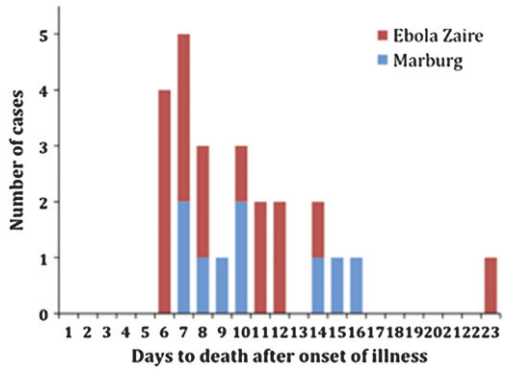

Figure 1. Time from onset of illness to death in 25 well-documented fatal cases of Marburg and Ebola HF [3, 5, 10, 13, 15, 18, 19, 22, 23, 28, 32]. The median survival is 9 days.

showed that patients who were still alive on day 14 had a >75% chance of survival [46].

Convalescence

All descriptions of survivors of filoviral HF agree that recovery is prolonged, lasting weeks to months. Sequelae of the acute illness include asthenia, weight loss, headache, dysesthesias, migratory arthralgias, sloughing of skin, loss of scalp hair, and persistent anemia [5, 9–12, 16, 19, 24, 26, 33, 35, 39]. In a number of instances, acute orchitis or uveitis has developed weeks after the resolution of acute illness, and virus was detected in samples of semen or aqueous humor [3, 10, 26, 35]. During the 1967 Marburg HF outbreak, a convalescent male patient transmitted the virus to his wife, apparently through sexual intercourse [3].

FINDINGS AT AUTOPSY

Pathologic changes in fatal cases of filoviral HF are known from a few autopsies performed during the 1967 Marburg HF outbreak and in single cases and epidemics in Africa; they have been summarized by Zaki and Goldsmith [6, 8, 21, 34, 47]. In both Marburg and Ebola HF, the principal gross abnormality is the presence of multiple foci of hemorrhage. The most characteristic histopathologic finding is extensive hepatocellular necrosis, with eosinophilic inclusion bodies corresponding to aggregates of nucleocapsids seen by electron microscopy. The spleen and lymph nodes show a marked decrease in lymphocytes, variously described as follicular "necrosis" or "atrophy," leaving residual cellular debris. Evidence of acute tubular necrosis, consistent with hypovolemic shock, is seen in the kidneys. Other organs show scattered foci of necrosis, edema, and other nonspecific changes.

DIAGNOSIS

Because the clinical and laboratory features of filoviral HF are nonspecific, confirmation of the diagnosis requires detection of virus in a blood sample or the demonstration of a virus-specific antibody response.

Viremia

There is no evidence that persons infected with Ebola or Marburg virus are viremic during the incubation period, but virus has been detected in blood samples on the day of illness onset [37]. Serum levels of viral genomes, as detected by reverse transcription–polymerase chain reaction (RT-PCR), and of viral antigen, as detected by enzyme-linked immunosorbent assay (ELISA), increase during the first week of illness, and in fatal cases remain elevated until death [26, 27, 29, 31, 32, 35–37]. Studies performed during outbreaks in Gabon and Uganda found that titers of circulating viral genomes were significantly higher in fatal than in nonfatal cases [29, 31, 36, 37]. In patients who survive infection, viremia usually becomes undetectable by the end of the second week of illness [26, 27, 29, 31, 37]. However, infectious virus may persist in certain anatomic sites, such as the testes or the anterior chamber of the eye (see above).

Antibody Response

Because immunofluorescence assays have a high positive background rate, the detection of antifilovirus antibodies has been based on ELISA since the 1995 Kikwit outbreak [26, 27]. Experience during several large epidemics has shown that most fatally infected patients fail to develop an antibody response; the detection of virus-specific immunoglobin M (IgM) or G (IgG) in a serum specimen is therefore a favorable prognostic sign [27, 29]. When an IgM response occurs, it is generally detectable during the first week of illness, and peaks during the second week [26, 27, 39]. Virus-specific IgG appears soon after the IgM. Limited reports indicate that IgG can be detected by ELISA in disease survivors for as long as 11 years [26, 27, 39, 48].

SUMMARY: DESCRIPTION OF A "TYPICAL CASE"

A "typical" case of filoviral HF begins after an incubation period of about 1 week with the abrupt onset of fever, chills, and a variety of nonspecific signs and symptoms. At the time of presentation, the pulse and blood pressure may be within normal limits. Virus is detectable in the blood at the onset of illness, and persists at high levels in fatal cases. An erythematous, maculopapular rash may be seen during the first week, more commonly in light-skinned individuals. A variety of minor hemorrhagic manifestations, such as petechiae, ecchymoses, and persistent bleeding from needle punctures, are also seen. Laboratory abnormalities include leukopenia and lymphocytopenia, with an increased percentage of neutrophils; thrombocytopenia; and increased serum AST and ALT levels, with AST > ALT. Leukocytosis with a left shift and the appearance of atypical lymphocytes are seen as the disease progresses. Worsening illness is characterized by the development of hypotension, renal

insufficiency, and shock, and in many cases by major bleeding from the gastrointestinal tract. Fatally infected patients usually die during the second week of illness, without developing a detectable antibody response. Extensive hemorrhage, hepatocellular necrosis, and a diffuse loss of lymphocytes are the principal findings at autopsy. Survivors undergo a prolonged convalescence, with persistent asthenia, weight loss, and sloughing of skin and hair. Infectious virus may persist for weeks to months in the anterior chamber of the eye or the testes, with the potential for sexual transmission.

CONCLUSION

Our review of the published literature has shown that, although a number of features of filoviral HF are well defined, many aspects remain poorly characterized or incompletely documented. From the point of view of modern critical care medicine, the most significant gap in knowledge is the almost complete absence of the types of data that physicians have come to rely on in managing severely ill patients: basic parameters of cardiovascular function such as pulse, blood pressure, and urine output, and markers of physiologic status such as the serum electrolytes, glucose, lactate, and pH. Impediments to collecting these data during past outbreaks have included their frequently remote location and limited resources and the traditional focus on outbreak control rather than patient care [49]. The hazard, real or perceived, of accidental exposure to the virus has also been a concern; in recent years, however, improved understanding of the specific modes of virus transmission and the standardization of personal protective equipment have lessened the risk to healthcare workers [50].

Lacking information on changes in cardiovascular function and other data for patients with filoviral HF, it is difficult to recommend appropriate therapies or assess their impact. For example, although outbreak reports indicate that severely ill patients develop hypotension and renal insufficiency, it is not clear if this is the result of intravascular volume depletion, a decline in systemic vascular resistance, a fall in cardiac output, or some combination of the 3. Safety concerns and limited resources at outbreak sites may make it impossible to carry out advanced interventions such as intravenous pressure monitoring, but simpler and less invasive measures, such as the regular recording of pulse, blood pressure, fluid intake, and urine output, together with careful record keeping, would go a long way toward improving our understanding of the clinical course of filoviral HF [13]. Such data will be essential to evaluate the benefit of such approaches as the provision of intravenous fluids or blood products or treatment with pharmacologic agents to maintain adequate organ perfusion.

Another approach to understanding the pathophysiology of filoviral HF is to study the disease in laboratory animals, especially in nonhuman primates, which appear to closely replicate the fatal disease seen in humans [51–53]. As described in another article in this issue, implanted telemetry devices are now being used to monitor body temperature, pulse, systolic and diastolic blood pressure, and other parameters in macaques infected with Ebola Zaire virus [54]. Accompanied by rapid, point-of-care laboratory tests, such studies should make it possible to identify critical physiological factors associated with recovery or death, and to assess the impact of intravenous fluid administration, treatment with inotropic agents and other therapeutic measures. Combined with the knowledge that has been acquired by medical investigators since the 1967 Marburg HF epidemic, such data will help guide outbreak response teams to reduce the burden of severe illness and death from filoviral HF.

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