antigens is partially suppressed. Immunosuppression occurs in part by massive lymphoid depletion in lymph nodes, spleen, and thymus in the absence of reactive inflammatory cellular responses. Results from animal studies suggest that depletion is a direct consequence of considerable bystander apoptosis of lymphocytes; this explanation would also account for the severe lymphopenia that develops in patients. The consequence of these events is not only florid filovirus dissemination but also a proclivity of the patient for secondary bacterial and fungal infections.

Other pathogenetic hallmarks of filovirus infections are a severe disturbance of the clotting system and the impairment of vascular integrity. Disseminated intravascular coagulation is the cause of the severe imbalance in the clotting system of filovirus-infected patients. Thrombocytopenia, increased concentrations of tissue factor, consumption of clotting factors, increased concentrations of fibrin degradation products (D-dimers), and declining concentrations of protein C are typical features of infection. Consequently, the occlusion of small vessels by widely distributed microthrombi leads to extensive necroses/hypoxic infarcts in target tissues (particularly the gonads, kidneys, liver, and spleen) in the absence of marked inflammatory responses. In addition, petechiae, ecchymoses, extensive visceral effusions, and other hemorrhagic signs are observed in internal organs, mucous membranes, and skin. Actual severe blood loss, however, is a rare event. Aberrance in cytokines or other factors such as nitric oxide and direct infection and activation of endothelial cells most likely are responsible for upregulated permeability of the endothelia of blood vessels. This upregulation leads to fluid redistribution (*third spacing*); interstitial and myocardial edema and hypovolemic shock are common developments. Clinical improvement is rare and is usually characterized by falling viral titers during the development of a virus-specific immune response.

CLINICAL MANIFESTATIONS

MVD and EVD cannot be differentiated by mere observation of clinical manifestations. The incidence of clinical signs does not differ significantly among infections caused by disparate filoviruses (Table 234-2). The incubation period ranges from 3 to 25 days, after which infected people develop a biphasic syndrome with a 1- to 2-day

TABLE 234-2 DISTRIBUTION OF CLINICAL SIGNS/SYMPTOMS OF FILOVIRUS-INFECTED PATIENTS IN THREE REPRESENTATIVE OUTBREAKS

	Frequency (%) Among Survivors			Frequency (%) Among Fatal Cases		
Sign/Symptom	**BDBV**	**EBOV**	**MARV**	**BDBV**	**EBOV**	**MARV**
Abdominal pain	88	68	59	93	62	57
Abortion	NR	5	NR	NR	2	NR
Anorexia	83	47	77	80	43	72
Anuria	NR	0	NR	NR	7	NR
Arthralgia or myalgia	83	79	55	86	50	55
Asthenia	NR	95	NR	NR	85	NR
Bleeding from puncture sites	NR	5	0	NR	8	7
Bleeding from the gums	NR	0	23	NR	15	36
Bleeding from any site	NR	NR	59	NR	NR	71
Bloody stools	NR	5	NR	NR	7	NR
Chest pain	NR	5	18	NR	10	4
Conjunctival injection	NR	47	14	NR	42	42
Convulsions	NR	0	NR	NR	2	NR
Cough	NR	26	9	NR	7	5
Diarrhea	92	84	59	87	86	56
Difficulty breathing	26	NR	36	57	NR	58
Dysesthesia	NR	5	NR	NR	0	NR
Epistaxis	NR	0	18	NR	2	34
Fever	100	95	100	100	93	92
Headaches	84	74	73	93	52	79
Hearing loss	NR	11	NR	NR	5	NR
Hematemesis	NR	0	68	NR	13	76
Hematoma	NR	0	0	NR	2	3
Hematuria	NR	16	NR	NR	7	NR
Hemoptysis	NR	11	9	NR	0	4
Hepatomegaly (without jaundice)	NR	5	NR	NR	2	NR
Hiccups	17	5	18	40	17	44
Lumbar pain	NR	26	5	NR	12	8
Maculopapular rash	35	16	NR	33	14	NR
Malaise or fatigue	96	NR	86	100	NR	83
Melena	NR	16	41	NR	8	58
Nausea and vomiting	92	68	77	87	73	76
Petechiae	NR	0	9	NR	8	7
Sore throat, odynophagia, or dysphagia	43	58	43	60	56	43
Splenomegaly	NR	5	NR	NR	2	NR
Tachypnea	NR	0	NR	NR	31	NR
Tinnitus	NR	11	NR	NR	1	NR

Abbreviations: BDBV, Bundibugyo virus; EBOV, Ebola virus; MARV, Marburg virus; NR, not reported.