Ebola virus infection

The right clinical information, right where it's needed

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Summary

- Initial stages of infection are nonspecific, which makes the differential diagnosis broad; therefore, clinical suspicion of the infection with prompt isolation is very important in the context of a history of exposure.

- Management is centered around supportive care and infection control. The lack of any specific antiviral treatment or approved vaccine makes treatment difficult; however, several potential therapeutic agents are undergoing accelerated development, and clinical studies are either planned or ongoing.

- Case fatality rates range from 25% to 90%, but the average rate was approximately 50% in most treatment centers in the 2014 outbreak in West Africa. Survivors often have prolonged ill health with significant disability.

- The risk of sexual transmission from male survivors may persist for at least 12 months.

- As there is the possibility of infected people traveling, all countries should have tested and practiced protocols ready for screening and managing patients.
Definition

A severe, often fatal, zoonotic infection caused by infection by a virus of the Filoviridae family (genus *Ebolavirus*). There are currently 5 known species: *Zaire ebolavirus*, *Sudan ebolavirus*, *Tai Forest ebolavirus*, *Bundibugyo ebolavirus*, and *Reston ebolavirus*. The *Zaire ebolavirus* is responsible for the outbreak that started in West Africa in 2014, the largest outbreak since the virus was first discovered in 1976.

The virus is thought to be initially acquired from infected animals such as bats and nonhuman primates, but has potential for human-to-human transmission. Transmission occurs by close contact with body fluids of infected patients. The incubation period after infection is 2 to 21 days (typically 3-12 days). Incubation periods may be shorter in children. Patients are not considered infectious until they develop symptoms.

Ebola virus infection is part of the group of conditions known as viral hemorrhagic fevers, and was formerly known as Ebola hemorrhagic fever.

[BMJ Best Practice podcast: Ebola - medical guidance and lessons from West Africa with Dr Tom Fletcher]

Epidemiology

The first cases of Ebola virus infection were reported in Zaire (now known as the Democratic Republic of the Congo) in 1976. There were 318 cases and 280 deaths, an 88% case fatality rate. Transmission in this outbreak was traced back to the use of contaminated needles in an outpatient clinic at Yambuku Mission Hospital. Since then, frequent outbreaks have occurred in Central and Western Africa. The most common species of Ebola virus responsible for outbreaks is the *Zaire ebolavirus*, the second most common species being the *Sudan ebolavirus*.

The *Zaire ebolavirus* was responsible for the outbreak that started in West Africa in 2014. It was first reported in March 2014, and was the largest outbreak since the virus was first discovered in 1976. Genetic sequencing has shown that the virus isolated from infected patients in the 2014 outbreak is 97% similar to the virus that first emerged in 1976. Over 28,000 cases (confirmed, probable, and suspected) were reported in this outbreak, with over 11,000 deaths.

A new outbreak was announced in the Democratic Republic of the Congo (DRC) in August 2018. As of 12 February 2019, 823 cases (762 confirmed, 61 probable), including 517 deaths, have been reported in the North Kivu and Ituri provinces of the DRC. This comes soon after a previous outbreak in the Equateur Province of the DRC (Bikoro, Iboko, and Wangata regions), with 54 cases and 33 deaths (a case fatality rate of 61%), was declared over. It has been confirmed that this latest outbreak is not related to the one in the Equateur Province, but is also due to the *Zaire ebolavirus* species. This latest outbreak is the tenth identified in the DRC to date.

The *Zaire ebolavirus* has a reported case fatality rate of up to 90% in previous outbreaks. Direct comparison of case fatality rates between different Ebola treatment centers and outbreaks should be interpreted with caution as many variables can introduce bias and skew even large cohort data. The case fatality rate during the 2014 outbreak was up to 64.3% in hospital admissions, falling to 31.5% in some treatment centers in West Africa, and around 20% in patients managed outside West Africa.
In contrast to this, the *Sudan ebolavirus* has a lower case fatality rate of 53% to 65% in previous outbreaks, with the largest outbreak occurring in 2000 in Uganda (425 cases).[28] There has only been 1 outbreak of *Bundibugyo ebolavirus* in 2007 in western Uganda, and this outbreak had a case fatality rate of 25%.[32]

WHO declares an outbreak over when a country has no new reported cases for 42 days (i.e., twice the maximum incubation period), provided that active surveillance is demonstrably in place and there is good diagnostic capacity.[33]

**Etiology**

The Ebola virus is a member of the Filoviridae family (genus *Ebolavirus*; order: *Mononegavirales*). These viruses are elongated, filamentous structures of variable length. [Fig-1]

The virus is thought to be initially acquired from exposure to body fluids or tissue from infected animals such as bats and nonhuman primates; however, the natural reservoir and mode of transmission to humans has not been confirmed.[34] Laboratory testing of reservoir competence shows that successful infection is possible in bats and rodents, but not in plants or arthropods.[35] [36] [37] Animal-to-human transmission may occur during hunting and consumption of the reservoir species or infected nonhuman primates. The local practice of eating bush meat or food contaminated with bat feces (3 species of tree-roosting bats have been implicated as a reservoir) is also thought to contribute.
Ebola virus infection

**Basics**

Ebolavirus ecology showing enzootic and epizootic cycles

Centers for Disease Control and Prevention

Human-to-human transmission occurs via contact with body fluids from infected patients.[38] In the early epidemics, the reuse of nonsterile injections was responsible for many healthcare-associated transmissions.[39] However, while this still remains a risk, most cases result from close physical contact or contact with body fluids (e.g., sweat, blood, feces, vomit, saliva, genital secretions [including semen], and breast milk) of infected patients.

The level of virus in the blood increases during the course of illness and patients are most infectious in the later stages of the disease (i.e., during diarrhea, vomiting, and hemorrhage).[40] Large amounts of virus can be found in the skin and, as sweat may also contain the virus, touching an infected patient may result in transmission.[41] Super-spreading events in the community are also increasingly recognized as a contributing factor: a funeral of a traditional healer in Sierra Leone in 2015 was linked to 300 cases.[42] In one study, it was found that super-spreaders were responsible for approximately 61% of infections in the 2014 outbreak.[43]

In a study to identify the rate of viral shedding in various body fluids, Ebola virus was isolated from saliva, breast milk, stool, tears, and semen up to 40 days after the onset of illness.[44] [45] [46] The virus can still be detected in semen more than 12 months after recovery from infection, possibly due to testicular tissue being an immunologically-protected site.[47] This means that sexual transmission may be possible long after the infection has resolved.[44] [45] [46] [48] [49] and such cases were confirmed during and following the 2014 outbreak.[50] [51] [52] Ebola virus has also been detected in vaginal fluid.[53] Viral shedding may continue...
from urine and sweat. In one recovered patient in Germany, virus was detected in urine 14 days after it was not detected in serum, and in sweat for up to 19 days after it was not detected in serum.\[41\]

Infection via the inhalation route has been shown to be possible in nonhuman primates; however, there is no evidence for airborne transmission in humans.\[14\] \[54\] The possibility of opportunistic airborne transmission of the virus during forceful vomiting (similar to that seen with norovirus infection), and during aerosol-generating procedures associated with critical care interventions, should still be considered.

Outside the endemic areas, Ebola virus infection is rare and is usually an imported infection.\[55\] Travelers arriving from affected areas, as well as laboratory scientists and others working with potentially infected materials and animals, are at high risk.

[Centers for Disease Control and Prevention (CDC): Ebola transmission]

Pathophysiology

There have been major advances in elucidating the pathogenesis of Ebola virus infection; however, most of the studies have been performed in nonhuman primate and rodent models.\[10\] This is because of the difficulties in conducting human studies in poorly-resourced settings where these infections naturally occur.

The virus genome consists of a single 19 kb strand of negative-sense RNA with 7 viral genes that are transcribed by the viral RNA-dependent RNA polymerase present in the virion. The single strand of RNA is covered by helically-arranged viral nucleoproteins NP and VP30 that are linked by matrix proteins VP24 and VP4 to the lipid bilayer that coats the virion.\[14\] There was rapid mutation of the virus in the 2014 outbreak, raising concerns about its ability to evade host immune responses and evolve under pressure of novel therapies.\[56\] \[57\]

The incubation period after infection is 2 to 21 days (typically 3-12 days).\[2\] Tissue invasion occurs via infected fluid coming into contact with breaks in the mucosa or skin. This can occur with animal-to-human or human-to-human transmission. Monocytes, macrophages, and dendritic cells are the preferred replication sites for filoviruses on initial infection. Infected cells migrate to the regional lymph nodes, liver, and spleen, thereby disseminating the infection. Ebola virus has a wide cell tropism and is able to infect a variety of different cell types, but extensive viral replication occurs in lymphoid tissue, liver, and the spleen.\[10\] \[14\] \[58\] It also has the remarkable ability to modulate the expression of genes involved in the host immune response, causing lymphocyte apoptosis and attenuation of the protective effects of interferon.\[59\] \[60\] \[61\] \[62\] \[63\]

The host immune response is crucial and dictates the outcome of infection. Progression to the severe end of the disease spectrum occurs when the virus triggers expression of a host of pro-inflammatory cytokines, including: interferons; interleukins (IL) such as IL-2, IL- 6, IL-8, and IL-10; interferon inducible protein; and tumor necrosis factor (TNF)-alpha.\[10\] \[14\] \[64\] This, in turn, causes endothelial activation and reduced vascular integrity, release of tissue factor (with associated onset of coagulopathy), and increased nitric oxide levels (with associated hypotension).\[65\] Infection leads to lymphocyte depletion through indirect apoptosis (since the virus does not replicate in lymphocytes), and neutrophil suppression via glycoprotein GP.\[66\] The most common cause of thrombocytopenia is platelet disappearance from damaged tissue or more generalized virus-induced disseminated intravascular coagulation, where coagulation factors are depleted.\[67\] Disseminated intravascular coagulation, along with acute hepatic impairment, predisposes the patient to bleeding complications. Other complications of severe disease include acute kidney injury, hepatitis, and pancreatitis.\[14\] Early antibody response, along with reduced lymphocyte depletion, is associated with effective viral clearance and survival.\[68\] Flow cytometry, which was used in a treatment
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BASICS

The development of shock is still not well understood. Multiple factors may contribute, including: bacterial sepsis, possibly through gut translocation of bacteria; a direct effect of the virus; disseminated intravascular coagulation; or hemorrhage.[64]

Classification

Virus taxonomy

The virus is a member of the Filoviridae family (genus *Ebolavirus*). Five distinct species of Ebola virus have been isolated from various epidemics, mainly in African countries, with the exception of the Reston virus that originated in the Philippines.[1] The latter is remarkable in that it has never caused symptomatic human disease. The other 4 species cause slightly different clinical syndromes of varying severity, and have a reported case fatality rate of 25% to 90% across different outbreaks (the average rate was approximately 50% in most treatment centers in the 2014 outbreak in West Africa).[2] *Zaire ebolavirus* and *Sudan ebolavirus* are especially known for their virulence; the other species are considered to be less virulent. The taxonomy of the virus continues to evolve, with new names emerging for variants of the virus.[4]

**Zaire ebolavirus**:

- First isolated in 1976 during an outbreak in northern Zaire (now known as the Democratic Republic of the Congo, or DRC).[5] Seems to be the most virulent of the 5 species and has the highest case fatality rate out of all species.[6] It is responsible for the outbreak that started in West Africa in 2014. A separate, limited outbreak in the DRC in 2014 was caused by a strain of *Zaire ebolavirus* distinct from the one that was circulating in West Africa.[7]

**Sudan ebolavirus**:

- First isolated in 1976 during an outbreak in southern Sudan. Causes an identical syndrome to *Zaire ebolavirus*; however, the case fatality rate is less.[6]

**Tai Forest ebolavirus** (formerly known as *Cote d'Ivoire ebolavirus*):

- Only 1 case has been documented in 1994 in a Swiss researcher who performed an autopsy on a dead chimpanzee in Tai National Park in Cote d'Ivoire.[8] She recovered from the febrile phase of the illness with no hemorrhagic complications.

**Bundibugyo ebolavirus**:

- Discovered in 2007 during a single outbreak in the Bundibugyo district of western Uganda. The isolated virus was identified as a distinct species, distantly related to *Tai Forest ebolavirus*.[9]

**Reston ebolavirus**:

- First isolated in Reston, Virginia, US in 1989 where it was found in Cynomolgus monkeys imported from the Philippines. Several workers exposed to infected animals were found to have positive
serology, but no clinical symptoms. Since then, the virus has also been isolated from swine in the Philippines.[10][11]

Other filoviral infections

The Filoviridae family of viruses includes: Ebola virus, Marburg virus, and Cuevavirus. Marburg virus is the only other member of this group known to cause human infection. It has been isolated from bats and causes a similar syndrome to Ebola virus infection. Several outbreaks have been reported, often related to animal exposure in mines or caves.[12]
Primary prevention

The Centers for Disease Control and Prevention (CDC) recommends the following preventive measures for people in an area affected by an outbreak:

- Practice careful hygiene (e.g., wash hands with soap and water, alcohol-based hand sanitizer, or chlorine solution)
- Avoid contact with body fluids
- Do not handle items that have come into contact with an infected person’s body fluids (e.g., clothes, medical equipment, needles)
- Avoid funeral or burial rituals that require handling of the body of someone who has died from confirmed or suspected Ebola virus infection
- Avoid contact with nonhuman primates and bats, including body fluids or raw meat prepared from these animals
- Avoid hospitals in West Africa in which infected patients are being treated (unless going there to work)
- Returning travelers (including healthcare workers) should follow local policies for surveillance and monitor their health for 21 days and seek medical attention if symptoms develop, especially fever.

Healthcare workers who may be exposed to infected patients should follow these steps:

- Wear protective clothing
- Practice proper infection control and sterilization measures [Centers for Disease Control and Prevention (CDC): infection control for viral haemorrhagic fevers in the African health care setting]
- Isolate suspected patients from each other if possible, and confirmed patients from suspected patients
- Avoid direct contact with bodies of people who have died from confirmed or suspected infection. During epidemics, direct contact with any dead body should be avoided
- Notify health officials if you have direct contact with the body fluids of an infected patient.

[Centers for Disease Control and Prevention (CDC): infection control for viral haemorrhagic fevers in the African health care setting]

[World Health Organization (WHO): aide-memoire for infection prevention and control in a health care facility]

If infection is suspected based on initial screening, immediate isolation is warranted before any further workup is carried out. This is crucial to reduce contact with other patients and healthcare workers while the patient is being investigated. Isolation measures should be continued until the patient has tested negative.[73]

The highest risk facing healthcare workers when looking after infected patients is inadvertently touching their own faces or neck under the face shield during patient care, and removing (doffing) personal protective equipment (PPE). Healthcare workers should understand the following basic principles of using PPE:[73]

- Donning: PPE must be donned correctly in proper order before entry into the patient care area. Since PPE cannot be modified while in the patient care area, caution should be taken to ensure it is as comfortable as possible before entering the area. No skin should be exposed. Donning activities must be directly observed by a trained observer, and a final check performed before entering the patient care area
- During patient care: PPE must remain in place and be worn correctly for the duration of exposure to potentially contaminated areas. PPE should not be adjusted during patient care. Healthcare workers should perform frequent disinfection of gloved hands using an alcohol-based hand rub or chlorine solution, particularly after handling body fluids. If there is a partial or total breach in PPE (e.g., gloves separate from sleeves leaving exposed skin, a tear develops in an outer glove, a needlestick) during patient care, the healthcare worker must move immediately to the doffing area to assess the exposure and implement the facility exposure plan, if indicated. The immediate action drills to take in the event
of a high-risk exposure (needle stick injury and mucous membrane splash) should be clear to all healthcare workers. After safe doffing, a rapid risk assessment and consideration of post-exposure prophylaxis (PEP) should be undertaken.[74]

- Doffing: removal of used PPE is a high-risk process that requires a structured procedure, a trained observer, and a designated area for removal to ensure protection. PPE must be removed slowly and deliberately in the correct sequence to reduce the possibility of self-contamination or other exposure. A stepwise process should be developed and used during training and daily practice.

[Fig-3]

The importance of a "buddy" when inside the patient care area and during donning and doffing, to ensure safe practice cannot be overstated, together with guidance from independent monitors if available. [Centers for Disease Control and Prevention (CDC): the buddy system]

The CDC and World Health Organization (WHO) produce detailed guidance on PPE:

- [Centers for Disease Control and Prevention (CDC): guidance on personal protective equipment (PPE) to be used by healthcare workers during management of patients with confirmed Ebola or persons under investigation (PUIs) for Ebola]
- [World Health Organization (WHO): personal protective equipment for use in a filovirus disease outbreak - rapid advice guideline]
- [World Health Organization (WHO): steps to put on personal protective equipment (PPE)]
- [World Health Organization (WHO): steps to remove personal protective equipment (PPE)]

Vaccines:

- No vaccines have been licensed for use in humans.[75] See Emerging section for detail on vaccines in development.

[Centers for Disease Control and Prevention (CDC): Ebola prevention]

[World Health Organization (WHO): Ebola: infection prevention and control]

Screening

Ebola virus infection is communicable mainly through close physical contact with infected patients. There is no evidence of a risk of infection before patients are symptomatic, but late diagnosis delays effective patient isolation, allowing for potential transmission of the infection among contacts. Screening and active case finding is, therefore, an essential management strategy to avoid or stop an epidemic.

Early diagnosis hinges on identifying patients who are at risk. Case definitions developed by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) are based on the presence of a history of exposure, as well as clinical evidence of illness (e.g., fever, headache, myalgia). Within epidemic areas, history of exposure is less useful. Links to the case definitions by the CDC and WHO are below:

- [Centers for Disease Control and Prevention (CDC): case definition for Ebola virus disease (EVD)]
- [World Health Organization (WHO): case definition recommendations for Ebola or Marburg virus diseases]

Screening for these patients ensures the quick identification of potential cases that need immediate isolation and investigation. People who are asymptomatic and have epidemiological risk factors may need to be monitored (e.g., twice-daily temperature readings) for the duration of the incubation period depending on their risk of exposure. This is to ensure rapid recognition of symptoms followed by immediate isolation.
Secondary prevention

Ebola virus infection is a notifiable disease.

If infection is suspected, the patient should be put in isolation and all healthcare workers in contact with the patient should wear personal protective equipment. The Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) produce detailed guidance on PPE:

- [Centers for Disease Control and Prevention (CDC): guidance on personal protective equipment (PPE) to be used by healthcare workers during management of patients with confirmed Ebola or persons under investigation (PUIs) for Ebola]
- [World Health Organization (WHO): personal protective equipment for use in a filovirus disease outbreak - rapid advice guideline]

Contact tracing (e.g., family, friends, work colleagues) is essential. People who have been exposed to the Ebola virus within the last 21 days and who are asymptomatic need to be monitored for the duration of the incubation period in order to ensure rapid recognition of symptoms followed by immediate isolation. The WHO has produced guidance on contact tracing:

- [World Health Organization (WHO): implementation and management of contact tracing for Ebola virus disease]

Healthcare workers suspected of being infected should be isolated and treated the same as any other patient until a negative diagnosis is confirmed.[175] If exposure to body fluids from a patient with suspected infection has occurred, the person should immediately wash affected skin surfaces with soap and water and irrigate mucous membranes with copious amounts of water.

Safe burial practices are essential but are not always culturally accepted, and this continues to be a challenge.[70]

[World Health Organization (WHO): how to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola virus disease]

Post-exposure prophylaxis (PEP):

- This is a rapidly changing field.[265] A useful framework that takes a stratified approach to exposure risk has been proposed.
- PEP is recommended in high-risk patients (e.g., people with broken skin or mucous membrane contact with an infected patient (alive or deceased) or their body fluids, a penetrating sharps injury, or contact with contaminated gloves or clothing). It may also be considered in patients with intact skin-only contact with an infected patient (alive or deceased) or their body fluids. Options to consider include passive immunotherapy with monoclonal antibodies (e.g., ZMapp, MIL77), antiviral agents (e.g., favipiravir, remdesivir, BCX4430), or vaccination (e.g., rVSV-ZEBOV) depending on specific patient circumstances.[266]
- In addition to these interventions, psychological support is needed for healthcare workers exposed to dangerous pathogens.[267]
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Prevention

[Centers for Disease Control and Prevention (CDC): Ebola prevention]

[World Health Organization (WHO): Ebola: infection prevention and control]
Case history

Case history #1

A 35-year-old man is brought to the Ebola screening center in Liberia with a 3-day history of diarrhea, vomiting, and fever. He reports that he attended the funeral of a nurse who died from Ebola virus infection 2 weeks ago. He developed dysphagia and hiccups 24 hours ago, but had been eating normally until then. He has no symptoms of bleeding. On exam, he is found to have mild conjunctival injection, a faint maculopapular rash over his trunk, mild epigastric tenderness, and hepatomegaly. His vital signs on admission are a temperature of 101.5°F (38.3°C), heart rate 100 bpm, blood pressure 115/62 mmHg, respiratory rate 25 breaths per minute, and oxygen saturation 99%.

Case history #2

A 37-year-old doctor who worked in an Ebola treatment center in Sierra Leone returned to the US 3 days ago. She presents with a fever of approximately 12 hours duration, headache, and myalgia. She reports sustaining a cut while opening a vial at the Ebola treatment center 10 days ago. During her stay, she reports taking atovaquone/proguanil for malaria prophylaxis. There are no abnormal findings on exam except for several mosquito bites. Her vital signs are a temperature of 102.2°F (39.0°C), heart rate 110 bpm, blood pressure 120/75 mmHg, respiratory rate 25 breaths per minute, and oxygen saturation 99%.

Other presentations

People who eventually die from Ebola virus infection tend to develop clinical signs early on in the infection, with death (due to shock and multi-organ failure) typically occurring between days 6 and 16 of infection.[6] [13] [14] [15]

Bleeding manifestations (e.g., epistaxis, bleeding gums, hemoptysis, easy bruising, conjunctival bleeding, hematuria, oozing from injection or venipuncture sites) were present in 30% to 36% of infected patients in previous outbreaks;[11] [16] [17] however, they were only reported in 5% to 18% of patients in the 2014 outbreak.[18] [19] Massive bleeding is usually only observed in fatal cases, and typically occurs in the gastrointestinal tract (e.g., bloody diarrhea, melena).[16] [20] [21] [22] Internal bleeding may be missed if there are no external signs.

Other signs that indicate severe or advanced infection include hiccups, hypotension, tachycardia, hepatomegaly, splenomegaly, confusion, and seizures.

Up to half of patients develop a maculopapular rash, which may become purpuric or petechial in patients with coagulopathy.[16] [23]

Step-by-step diagnostic approach

Ebola virus infection is a notifiable disease. The case definition for Ebola virus infection is very broad and includes a long list of possible differential diagnoses.

The initial assessment of a patient with suspected Ebola virus infection hinges on 2 main factors:
• Epidemiological risk (e.g., living or working in, or travel to, endemic area in previous 21 days); and
• Presence or history of a fever in the past 24 hours.

Isolation and personal protective equipment (PPE)

Infection control risk should be assessed. Having determined that a patient may be infected, the physician needs to determine how infectious the patient is currently. For example, the absence of vomiting/diarrhea reduces the risk; however, uncontrolled diarrhea greatly increases the risk of transmission.

Identifying that a symptomatic patient may be at risk of infection mandates precautionary isolation procedures and use of PPE until the infection is either confirmed or excluded. It is extremely important to minimize the risk of transmission while working up the patient.\[76\] [77]

The CDC and World Health Organization (WHO) produce detailed guidance on PPE:

- [Centers for Disease Control and Prevention (CDC): guidance on personal protective equipment (PPE) to be used by healthcare workers during management of patients with confirmed Ebola or persons under investigation (PUIs) for Ebola]
- [World Health Organization (WHO): personal protective equipment for use in a filovirus disease outbreak - rapid advice guideline]
- [World Health Organization (WHO): steps to put on personal protective equipment (PPE)]
- [World Health Organization (WHO): steps to remove personal protective equipment (PPE)]

The CDC and WHO also produce detailed guidance on infection control for healthcare workers in West Africa:

- [Centers for Disease Control and Prevention (CDC): international infection control for healthcare workers (non-US healthcare settings)]
- [World Health Organization (WHO): infection prevention and control (IPC) guidance summary]

History

A detailed history helps to clarify the level of risk for Ebola virus infection, as well as assess the possibility of other causes of an acute febrile syndrome.

People living or working in endemic areas (e.g., West Africa, Democratic Republic of the Congo) are at high risk of infection. However, recent arrival from endemic areas is also an important risk factor.

Most patients with suspected infection in developed countries will be returning travelers and healthcare workers who have cared for patients during outbreaks. Therefore, a comprehensive travel history is extremely important. History of recent arrival from an endemic area is significant. Up-to-date knowledge of the geographical locations of active epidemics helps to clarify the patient's epidemiologic risk.

Apart from healthcare workers, other high-risk occupations include those where people work with primates or bats from endemic areas, or high-risk clinical samples.

As malaria is still the most common cause of febrile illness in returning travelers from West Africa, the presence of risk factors for acquiring malaria should be assessed (e.g., living/working in, or traveling to, endemic area; inadequate or absent chemoprophylaxis; not using insecticides or bed nets).[78] However, coinfection with malaria was seen in up to 5% of patients in West Africa during the 2014 outbreak, so the possibility of dual infection should be considered in all patients.[79]
### Exposure risk

Contacts of infected patients (including healthcare workers and household contacts) are at risk of infection if the person was exposed to body fluids of the infected patient without appropriate protective equipment. The incubation period after infection is 2 to 21 days (typically 3-12 days).[2] Incubation periods may be shorter in children.[3] Brief interactions, such as walking by a person or moving through a hospital, do not constitute close contact.

Contact is defined by the World Health Organization (WHO) as someone who has:[80]

- Slept in the same household as a patient
- Had direct physical contact with the patient during the illness or at the funeral
- Touched the patient’s body fluids or clothes/bed linens during the illness
- Been breastfed by the patient (babies).

### Case definitions

Case definitions are updated frequently and differ depending on the organization. Links to the case definitions by the CDC and WHO are below:

- [Centers for Disease Control and Prevention (CDC): case definition for Ebola virus disease (EVD)]
- [World Health Organization (WHO): case definition recommendations for Ebola or Marburg virus diseases]

### Symptoms

Patients are not considered infectious until they develop symptoms. The initial presentation is nonspecific, which makes early clinical diagnosis difficult; however, typical symptoms include:[5]

- Fever
- Fatigue
- Nausea/vomiting
- Diarrhea
- Headache
- Abdominal pain
- Myalgia
- Prostration
- Sore throat
- Unexplained bruising or bleeding.

The most common symptoms reported between the onset of symptoms and case detection in the 2014 outbreak included: fever (87.1% to 89%), fatigue (76.4%), loss of appetite (64.5%), vomiting (67.6%), diarrhea (65.6%), headache (53.4%), abdominal pain (44.3%), and unexplained bleeding (18%).[18] [22] Chest pain (10%), cough (7%), and sore throat (9%) have also been reported,[19] but direct involvement of the lungs has only rarely been reported.[81] Myalgia has also been reported (22%) and, in facilities that could measure this, raised creatine kinase was common (36% to 83%).[19] [79] [82] [83]

Three phases of illness are typically recognized, starting with a few days of nonspecific fever, headache, and myalgia, and followed by a gastrointestinal phase where diarrhea, vomiting, abdominal symptoms, and dehydration are prominent.[58] In the second week, the patient may either recover, or deteriorate with
Ebola virus infection

Diagnosis

a third phase of illness, which includes collapse, neurological manifestations, and bleeding. This phase is often fatal.[18]

Data from the 2014 outbreak indicate that children are relatively spared; however, this may be confounded by a high fatality rate before being registered as a case, or the bias of high rates in healthcare workers.[84] Children present with similar symptoms to adults; however, in previous outbreaks, younger children are reported to have more respiratory (e.g., cough, dyspnea) and gastrointestinal symptoms, but less bleeding and neurological signs compared with adults.[85] Data were sparse for this patient group in the 2014 outbreak.[85] A pediatric cohort study in Sierra Leone described symptoms in 282 patients and found vomiting (60%), abdominal pain (59%), diarrhea (45%), and conjunctivitis (38%) were common, while hiccups (5%) and bleeding (2%) were rare.[87] Another study in Sierra Leone found that weakness, fever, and distress were each present in more than 63% of children, and loss of appetite, diarrhea, and cough were present in more than 50%. Approximately 25% of these children did not have fever at the time of admission.[88]

Anecdotally, children under 4 years of age initially present with more subtle symptoms before developing a fever, and are often diagnosed later in the course of illness.

Physical exam

A full physical exam should be undertaken with the aim of excluding a focus for sepsis while looking for signs of viral hemorrhagic fever (e.g., conjunctival injection, purpuric rash, or other signs of bleeding).

Vital signs should be taken:

- Fever: the presenting symptom in approximately 90% of patients,[18] [22] [89] its presence is enough to raise concern for infection in the appropriate epidemiological context. Although fever is a major presenting symptom, a normal temperature at presentation is common. Wide variations in body temperature can be observed during the course of illness, especially in children.[88] [90] with normothermia or hypothermia occurring in the later stages of fatal infection.[16] [17] [85] Some patients may initially have a low-grade fever with no other symptoms, or alternatively the temperature may be near normal at first evaluation.[91] The temperature threshold for fever differs among countries and guidelines, and using a lower temperature threshold (e.g., ≥99.5°F [37.5°C]) increases the sensitivity of finding cases.[89] [92] The World Health Organization use a threshold of >100.4°F (38°C).[93] However, in a large cohort in Sierra Leone, <30% had a fever of ≥100.4°F (38°C) at presentation, although a history of fever was reported by 89% of patients.[22]
- Blood pressure: hypotension is a feature of preterminal disease and shock. It is under-documented in field studies, owing to a lack of measuring equipment in endemic areas.[16] However, septic shock with vascular leakage and microcirculatory failure does not appear to be a dominant feature.
- Pulse rate: bradycardia may be present in the initial stages of illness; however, tachycardia may be seen in the later stages of fatal infections.[16]
- Respiratory rate: tachypnea, along with tachycardia, correlates with a more severe or advanced infection, and is more likely to be respiratory compensation of a metabolic acidosis rather than respiratory involvement.[16] However, respiratory involvement has been described.[81]

Other findings may include:[16]

- Maculopapular rash: develops early in the course of illness in approximately 25% to 52% of patients,[16] although was much lower (1% to 5%) in the 2014 outbreak.[18] [19] [83] It is frequently described as nonpruritic, erythematous, and maculopapular. It may begin focally, then become
diffuse, generalized, and confluent. Some have described it as morbilliform. It may become purpuric or petechial later on in the infection in patients with coagulopathy.[23] May be difficult to discern in dark-skinned patients.

- **Bleeding:** bleeding manifestations (e.g., epistaxis, bleeding gums, hemoptysis, easy bruising, conjunctival bleeding, hematuria, ooze from injection or venipuncture sites) were present in 30% to 36% of infected patients in previous outbreaks.[11] [16] [17] however, they were reported in only 5% to 18% of patients in the 2014 outbreak.[18] [19] [20] [21] [22] It is less common in children.[87]
- **Hiccups:** a sign of advanced infection, typically seen in the last 2 to 3 days of fatal infections. They are less common in children.[87] [88]
- **Hepatomegaly:** tender hepatomegaly with the edge of the liver palpable below the ribcage has been reported, but is uncommon.
- **Lymphadenopathy:** enlarged lymph nodes have been reported, but are uncommon.
- **Neurologic signs:** depressed consciousness, encephalopathy, and seizures are rare but their presence indicates advanced infection. Confusion was more common in the 2014 outbreak.[83] Confusion may be multifactorial in children and is associated with a poor prognosis.[88] [90]

**Initial investigations**

All specimens should be collected according to strict protocols. The CDC and WHO have published guidance on this:

- [Centers for Disease Control and Prevention (CDC): guidance for collection, transport and submission of specimens for Ebola virus testing]
- [World Health Organization (WHO): how to safely collect blood samples from persons suspected to be infected with highly infectious blood-borne pathogens]
- [Centers for Disease Control and Prevention (CDC): guidance for US laboratories for managing and testing routine clinical specimens when there is a concern about Ebola virus disease]

The main confirmatory test for Ebola virus infection is a positive reverse transcriptase-polymerase chain reaction (RT-PCR) for Ebola virus.[94] This test should be ordered in all patients with suspected Ebola infection while the patient is in isolation. It has the advantage of returning a result 24 to 48 hours before ELISA testing. Several different commercial PCR kits are available with varying sensitivity, specificity, and limits of detection.[95] In Western settings, the test may only be available in regional or national laboratories that have category 4 facilities.[10] In epidemic settings and some countries, category 4 laboratories are set up locally and results are available 4 hours after the sample has arrived. Viral RNA can be detected in the patient’s blood by RT-PCR from day 3 up to days 6 to 17 of symptom onset. A positive PCR result implies that the patient is potentially infective, particularly if he or she has active diarrhea, vomiting, or bleeding. If negative, the test should be repeated within 48 hours since viral load is low and can be undetectable early in the course of the illness. Negative tests should be repeated to rule out a diagnosis if it is strongly suspected (or confirm resolution of infection).[94] Higher viral load correlates with adverse outcome and increased mortality.[20] [21] [22] [65] [79] [94] [96]

The choice of whether to test for Ebola virus infection depends on the patient’s history and their risk of infection according to the algorithm below.
Malaria is still the most common cause of fever in people who live/work in, or travelers who have returned from, an endemic area and should be ruled out. Coinfection with malaria was seen in up to 5% of patients in West Africa during the 2014 outbreak, so the possibility of dual infection should be considered in all patients. In the case of a positive rapid diagnostic test result for malaria, the infection should be treated while keeping in mind the patient’s risk for Ebola virus infection and the possibility of a dual infection. Ebola virus infection should be considered in a patient who does not respond to antimalarial therapy.

It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests for other suspected conditions if Ebola virus infection is suspected.

**Other investigations**

Traditionally, no other investigations outside of a malaria screen and RT-PCR were recommended due to the fear of putting laboratory workers at risk. However, it is now recognized that other investigations can be done safely according to recommended guidelines, as long as the laboratory is informed of the sample in advance, and the bloods are correctly packaged and retained at the end in case the RT-PCR is positive. Local protocols should be clear about safe transport of samples to the local and referral laboratories, and safe handling on receipt in the local laboratory.

The following investigations add valuable information to the workup and help guide further management, and should be ordered if possible. If investigations are limited due to the geographical location or facilities...
available, the most important tests to order are renal function, serum electrolytes, and blood lactate (if available).

Renal function and serum electrolytes:

- Elevated serum creatinine or BUN and abnormal electrolytes may indicate acute kidney injury. This may be seen at the end of the first week of infection.[98] Hypokalemia or hyperkalemia, due to vomiting and diarrhea or acute kidney injury, was seen in approximately 33% of cases in the 2014 outbreak.[79] Hypocalcemia has been associated with fatal infection. Hematuria and proteinuria may also be seen in severe disease. Oliguria that does not respond to fluid resuscitation is a poor prognostic sign.[16]

Blood lactate:

- Elevated lactate is a marker of tissue hypoperfusion and is an indicator of shock. It is useful in acutely ill patients with signs of sepsis to identify the degree of systemic hypoperfusion and to guide fluid resuscitation.[99] Elevated lactate was one indicator of gram-negative sepsis at day 15 in a patient treated in Germany.[41]

ABG:

- Arterial or venous pH and bicarbonate are useful in acutely ill patients with signs of sepsis to identify the degree of systemic hypoperfusion and guide fluid resuscitation.[99]

CBC:

- Decreasing platelet count and marked lymphopenia can be seen in the initial stages of infection; however, this is not diagnostic. This is often followed by neutrophil leukocytosis in the later stages of patients who eventually recover, along with normalization of thrombocytopenia. Leukocytosis may persist and show immature forms. Patients with severe disease may show a progressive decline in platelet count as a manifestation of disseminated intravascular coagulation (DIC). Decreased hemoglobin levels were reported in 24% of patients in the 2014 outbreak,[79] and have been associated with bleeding in previous outbreaks.[16]

Coagulation studies:

- Prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT) is associated with more severe infection and bleeding manifestations such as DIC. Also, patients with fatal infections have been found to have D-dimer levels four-fold higher on days 6 to 8 of infection compared with patients who survive.[100]

LFTs:

- Both ALT and AST are usually elevated; however, most studies show that AST rises out of proportion to ALT, and this is more suggestive of systemic tissue damage rather than hepatocellular injury.[79] The AST:ALT ratio peaked at 15:1 on days 6 to 8 of infection in fatal cases when compared with nonfatal cases, which had a peak of 5:1.[8] [16] [100] Bilirubin, GGT, and ALP are often slightly elevated. Highly elevated ALT with severe jaundice suggests an alternative diagnosis (e.g., viral hepatitis).

Serum amylase:
Ebola virus infection

Diagnosis

- Elevated levels have been reported in several studies and indicate the presence of pancreatitis, an indicator of severe infection.[16]

Serum blood glucose:

- Hypoglycemia may be present in adults, but it is not commonly reported.[22] However, it is common in children and may be severe. It is a potentially reversible cause of confusion.[87] [88]

Blood cultures:

- Negative blood cultures are helpful as they rule out other nonviral infectious causes (e.g., sepsis, enteric fever). Gram-negative bacteremia, presumably from gut translocation, has been identified as a complication of the disease course in two patients.[101] [41] However, a study in Sierra Leone where blood cultures were taken from patients on admission to an Ebola treatment center found that only one of the 22 cultures was positive with a presumed contaminant.[102] Therefore, blood should be collected for culture at baseline and/or at the time of the onset of gastrointestinal symptoms or other clinical deterioration.

Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing:

- A useful diagnostic test with high specificity; however, it is not universally available. It is most likely to give a positive result from day 3 until day 6 of infection, and can give widely variable results from days 7 to 16.[46] Can be used to confirm the diagnosis along with a positive RT-PCR result.

IgM and IgG antibodies:

- Useful in later stages of infection. IgM antibodies can appear in serum as early as day 2 post infection, but can give variable results up to day 9. They become negative between 30 and 168 days after symptom onset. An IgG response develops between day 6 and 18 and can persist for several years. A positive IgM or a rising IgG titer is strong evidence for recent Ebola virus infection.[46]

CXR:

- Useful in patients with respiratory symptoms. Pulmonary infiltrates are not typical of infection and suggest an alternative (or comorbid) diagnosis. May be difficult to arrange in an isolation unit and should only be ordered judiciously to avoid contamination.[103]

Rapid diagnostic tests

Rapid PCR testing for Ebola virus infection remains a major hurdle for effective, targeted isolation of affected patients. Current tests take an average of 4 hours to perform with a fully equipped level 3 or 4 biosafety laboratory close at hand, but results may take several days to arrive in remote areas. This means that, until they are confirmed negative, patients with febrile illnesses other than Ebola virus infection are confined to isolation and often unwittingly exposed to the virus. Rapid bedside tests can therefore make a very significant contribution to infection control in treatment centers.

[World Health Organization (WHO): interim guidance on the use of rapid Ebola antigen detection tests]

Several different technologies are being evaluated by WHO for use in field conditions. These include numerous RT-PCR-based assays that have been made simpler to use with a shorter turnaround time of <1 hour. The WHO has listed ReEBOV™ Antigen Rapid Test Kit for potential use; however, it currently
only recommends its use in special situations. The alternatives are ELISA-based antigen-detection assays that could be quicker and simpler with the possible advantage of only needing a drop of blood. Their major disadvantage is a reduced sensitivity, particularly in the initial stages of illness.\cite{104} \cite{105} Nanopore technology may allow rapid detection and sequencing in the presence of very low levels of virus, and can potentially be deployed using a pocket-sized detection kit.\cite{106} \cite{107} Rapid sequencing of Ebola virus using these new technologies during an outbreak could allow real-time understanding of viral dynamics.\cite{108}

A GeneXpert® diagnostic tool has been developed and trialled in the field. The Xpert® Ebola is an automated cartridge-based system that requires minimal laboratory skill. An inactivated sample is placed into a single-use cartridge, which is then entered into the enclosed machine. Sample preparation, nucleic acid amplification and detection, and production of a result are automated processes minimizing staff training requirements, risk of infection, and cross contamination.\cite{109} This test was used in the field during the 2018 outbreak in the Democratic Republic of the Congo.

This is a rapidly evolving field and different kits are approved according to the country and settings in which they are to be deployed. Food and Drug Administration (FDA) and WHO recommendations are available:

- Food and Drug Administration (FDA): 2014 Ebola virus emergency use authorizations
- World Health Organization (WHO): Ebola vaccines, therapies, and diagnostics
- Centers for Disease Control and Prevention (CDC): Ebola diagnosis
- World Health Organization (WHO): clinical management of patients with viral haemorrhagic fever: a pocket guide for the front-line health worker

### Risk factors

#### Strong

**living or working in, or arrival from, endemic area in previous 21 days**

- People living or working in endemic areas (e.g., West Africa, Democratic Republic of the Congo) are at high risk of infection. However, recent arrival from endemic areas is also a significant risk factor. Most patients with suspected infection in developed countries will be returning travelers and healthcare workers who have cared for patients during outbreaks.
- Up-to-date knowledge of the geographical locations of active epidemics helps to clarify the patient’s epidemiological risk.

**contact with infected body fluids**

- Human-to-human transmission occurs via contact with body fluids (e.g., sweat, blood, feces, vomit, saliva, genital secretions [including semen], and breast milk) from infected patients.\cite{38} \cite{44} Virus levels in these fluids are particularly high in more severe or advanced infection. The incubation period after infection is 2 to 21 days (typically 3-12 days).\cite{2} Incubation periods may be shorter in children.\cite{3}
- Contacts of infected patients (including healthcare workers and household contacts) are at risk of infection if the person was exposed to body fluids of the infected patient without appropriate protective equipment. Household contacts of infected patients are at a higher risk of infection if there is active diarrhea, vomiting, or bleeding.\cite{38}
**Ebola virus infection**

**Diagnosis**

- Body fluids remain infectious even after death. As a consequence, many infections have occurred at traditional funeral services in Africa where mourners touch the bodies of the deceased.[70] Super-spreading events in the community are also increasingly recognized as a contributing factor: a funeral of a traditional healer in Sierra Leone in 2015 was linked to 300 cases.[42] In one study, it was found that super-spreaders were responsible for approximately 61% of infections in the 2014 outbreak.[43]
- Sexual transmission has been documented during active infection. The virus can still be detected in semen more than 12 months after recovery from infection, possibly due to testicular tissue being an immunologically-protected site.[47] This means that sexual transmission may be possible long after the infection has resolved.[44] [45] [46] [48] [49] and such cases were confirmed during the 2014 outbreak.[50] [51] [52]

**occupational exposure**

- Healthcare workers in contact with infected patients are at high risk, and most epidemics have resulted in numerous infections in healthcare professionals.
- Needlestick injuries from an infected donor are a very high-risk exposure depending on the inoculum and nature of the injury. Use of nonsterile needles was responsible for the nosocomial spread of the first epidemic in 1976.[39] Accidental needle exposure has occurred in research laboratories in the UK, Russia, and Germany. The incubation periods in such cases may be considerably shorter compared with human-to-human transmission.[10] [17] [45]
- Other high-risk occupations include those where people work with primates or bats from endemic areas, or high-risk clinical samples.

**butchering or consumption of meat from infected (or potentially infected) animals**

- This route of transmission is likely to be a cause of animal-to-human transmission in sporadic epidemics.[71]

**Weak bioterrorism**

- Ebola virus has long been considered a potential bioterrorism weapon due to its high case fatality rate and the ease of human-to-human transmission. However, despite its potential, there is no evidence that the Ebola virus has been used as a weapon.[72]

**History & examination factors**

**Key diagnostic factors**

**exposure to Ebola virus in previous 21 days (common)**

- Human-to-human transmission occurs via contact with body fluids (e.g., sweat, blood, feces, vomit, saliva, genital secretions [including semen], and breast milk) from infected patients.[38] [44] Virus levels in these fluids are particularly high in more severe or advanced infection. The incubation period after infection is 2 to 21 days (typically 3-12 days).[2] Incubation periods may be shorter in children.[3]
- Contacts of infected patients (including healthcare workers and household contacts) are at risk of infection if the person was exposed to body fluids of the infected patient without appropriate protective equipment. Household contacts of infected patients are at a higher risk of infection if there is active diarrhea, vomiting, or bleeding.[38]
Body fluids remain infectious even after death. As a consequence, many infections have occurred at traditional funeral services in Africa where mourners touch the bodies of the deceased. Super-spreading events in the community are also increasingly recognized as a contributing factor: a funeral of a traditional healer in Sierra Leone in 2015 was linked to 300 cases.[42] In one study, it was found that super-spreaders were responsible for approximately 61% of infections in the 2014 outbreak.[43]

People who have traveled to endemic areas are considered to be at high risk of infection. Up-to-date knowledge of the geographical locations of active epidemics helps to clarify the patient’s epidemiological risk.

**fever (common)**

- Presenting symptom in approximately 90% of patients, and is often >102.2°F (39.0°C) with a remitting pattern.[18] [89] Some patients may initially have a low-grade fever with no other symptoms, or alternatively the temperature may be near normal at first evaluation.[91]
- The temperature threshold for fever differs among countries and guidelines, and using a lower temperature threshold (e.g., ≥99.5°F [37.5°C]) increases the sensitivity of finding cases.[89] [92] The World Health Organization use a threshold of >100.4°F (38°C).[93] However, in a large cohort in Sierra Leone, <30% had a fever of ≥100.4°F (38°C) at presentation, although a history of fever was reported by 89% of patients.[22] Another study in Sierra Leone found that 25% of children did not have a history of fever, or a temperature ≥100.4°F (38°C) at the time of admission.[88]
- Reported in 87% to 89% of patients in the 2014 outbreak.[18] [22]
- Presence is enough to raise concern for infection in the appropriate epidemiological context.
- Wide variations in body temperature can be observed, especially in children.[88] [90] Patients are often normothermic or hypothermic in the later stages of fatal infection.[16] [17] [85]

**myalgia (common)**

- Common feature of infection, present in up to 80% of patients in previous outbreaks.[9] [17]
- Reported in 22% to 38% of patients in the 2014 outbreak. Raised creatine kinase was common (36% to 83%).[18] [19] [79] [82] [83]
- May be associated with arthralgia and persist through convalescence.

**conjunctival injection (common)**

- Early sign of infection in approximately 40% of laboratory-confirmed cases in some outbreaks.[17] [85] [110]

**Other diagnostic factors**

**fatigue (common)**

- Severe tiredness and lethargy is a common feature in up to 90% of cases in previous outbreaks.[17] [85]
- Reported in 76% of patients in the 2014 outbreak.[18]

**diarrhea (common)**

- Common feature of infection, present in 88% of patients in a previous outbreak.[17]
- Reported in 65% of patients in the 2014 outbreak.[18]
- May be bloody.
- Cholera beds may be used for cases of profuse diarrhea in undeveloped countries.
**nausea/vomiting (common)**
- Common feature of infection, present in 65% to 70% of patients in previous outbreaks.[9] [17]
- Vomiting reported in 67% of patients in the 2014 outbreak.[18]
- Vomit may contain blood.

**severe headache (common)**
- Nonspecific feature of early infection, present in 10% to 70% of patients in previous outbreaks.[17] [85]
- Reported in 53% of patients in the 2014 outbreak.[18]
- Meningism has been observed rarely.

**abdominal pain or heartburn (common)**
- Reported in 44% of patients in the 2014 outbreak.[18]
- It may be difficult to distinguish heartburn from lower anterior chest pain or dysphagia. Dysphagia and heartburn are likely due to esophagitis.

**cough, dyspnea, chest pain (common)**
- Chest pain and cough reported in 10% and 7% of patients respectively in the 2014 outbreak;[19] however, direct involvement of the lungs has only rarely been reported.[81]
- Difficulty breathing reported in 20% to 23% of patients in the 2014 outbreak.[18] [19]
- Respiratory symptoms tend to be more common in children compared with adults; however, data are limited.[85] [86] Difficulty breathing was reported in 14% of children in the 2014 outbreak.[88]

**sore throat (common)**
- Pharyngitis is a nonspecific feature, present in 10% to 58% of patients in previous outbreaks.[17] [85]
- Reported in 9% of patients in the 2014 outbreak.[19]
- May cause dysphagia, which was reported in 26% to 32% of patients in the 2014 outbreak.[18] [19]

**prostration (common)**
- Profound prostration is a typical finding reported in 73% of patients in the 2014 outbreak.[83]

**tachypnea (common)**
- Present in 31% of fatal infections in a previous outbreak and not seen in any survivors.[16] [17]
- Reported in 5% of patients in the 2014 outbreak.[83]
- May reflect metabolic acidosis due to uremia and hypoperfusion.

**maculopapular rash (uncommon)**
- Developed early in the course of illness in approximately 25% to 52% of patients in previous outbreaks.[16]
- Reported in 1% to 5% of patients in the 2014 outbreak.[18] [19] [83]
- Frequently described as nonpruritic, erythematous, and maculopapular. It may begin focally, then become diffuse, generalized, and confluent. Some have described it as morbilliform. May become purpuric or petechial later on in the infection in patients with coagulopathy.[23]
- May be difficult to discern in dark-skinned patients.

**bleeding (uncommon)**
- Presence suggests advanced infection and presence of disseminated intravascular coagulation.
• Bleeding manifestations (e.g., epistaxis, bleeding gums, hemoptysis, easy bruising, conjunctival bleeding, hematuria, oozing from injection or venipuncture sites) were present in 30% to 36% of infected patients in previous outbreaks,[11] [16] [17] however, they were reported in only 5% to 18% of patients in the 2014 outbreak.[18] [19] [20] [21] [22]

• Massive bleeding is usually only observed in fatal cases, and typically occurs in the gastrointestinal tract (e.g., melena, bloody diarrhea).[16] In a previous outbreak, melena was present in 8% of fatal infections and 16% of survivors.[17]

• Internal bleeding may be missed if there are no external signs.

• Bleeding manifestations are less common in children.[87]

hepatomegaly (uncommon)

• In a previous outbreak, tender hepatomegaly with the edge of the liver palpable below the ribcage was present in 2% of fatal infections and 8% of survivors.[17]

lymphadenopathy (uncommon)

• Enlarged lymph nodes have been reported.[16]

hiccups (uncommon)

• Sign of advanced infection and poor prognosis, typically seen in the last 2 to 3 days of fatal infections.[16]

• May be due to uremia, hypokalemia, hyponatremia, hypocalcemia, or hypocarbia due to respiratory compensation of metabolic acidosis.

• In a previous outbreak, hiccups were present in 17% of fatal infections and 5% of survivors.[17]

• Reported in 11% of patients in the 2014 outbreak.[18] [83]

• Less common in children.[87] [88]

tachycardia (uncommon)

• May be seen in the later stages of fatal infections.[16]

hypotension (uncommon)

• Feature of preterminal disease and shock. It is under-documented in field studies owing to a lack of measuring equipment in endemic areas.[16]

• However, septic shock with vascular leakage and microcirculatory failure does not appear to be a dominant feature.

neurological signs (uncommon)

• Confusion was reported in 19% of patients in the 2014 outbreak. It appeared to be more common compared with previous outbreaks, and is a predictor of death.[88] [90] [83] Confusion may be multifactorial in children and is associated with a poor prognosis.[88] [90]

• Often coexist with bleeding and hypotension making fluid resuscitation hazardous.

• Encephalopathy is possibly related to electrolyte disturbances, uremia, and cerebral hypoperfusion in terminal infection.

• Seizures occurred in 2% of fatal infections in a previous outbreak.[17]
## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>reverse transcriptase-polymerase chain reaction (RT-PCR)</td>
<td>positive for Ebola virus RNA</td>
</tr>
<tr>
<td>• Should be ordered in all patients with suspected Ebola</td>
<td></td>
</tr>
<tr>
<td>infection while the patient is in isolation.[94]</td>
<td></td>
</tr>
<tr>
<td>• Returns result 24 to 48 hours before ELISA testing.</td>
<td></td>
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<tr>
<td>• Several different commercial PCR kits are available</td>
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<tr>
<td>with varying sensitivity, specificity, and limits of</td>
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<td>detection.[95]</td>
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<td>• In Western settings, the test may only be available in</td>
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<td>regional or national laboratories that have category 4</td>
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<td>facilities.[10]</td>
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<td>• Viral RNA can be detected in the patient’s blood by</td>
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<td>RT-PCR from day 3 up to days 6 to 17 of symptom onset.</td>
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<tr>
<td>A positive PCR result implies that the patient is</td>
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<tr>
<td>potentially infective, particularly if he or she has</td>
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<tr>
<td>active diarrhea, vomiting, or bleeding.</td>
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<tr>
<td>• If negative, the test should be repeated within 48</td>
<td></td>
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<tr>
<td>hours since viral load is low and can be undetectable</td>
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<tr>
<td>early in the course of the illness. Negative tests</td>
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<tr>
<td>should be repeated to rule out a diagnosis if it is</td>
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<td>increased mortality.[20] [21] [22] [65] [79] [94] [96]</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>malaria investigations</th>
<th>negative (may be positive if dual infection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Giemsa-stained thick and thin blood smears and rapid</td>
<td></td>
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<tr>
<td>diagnostic tests are the tests of choice for malaria</td>
<td></td>
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<tr>
<td>screening.</td>
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<tr>
<td>• A negative result makes Ebola virus infection more</td>
<td></td>
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<tr>
<td>likely in the appropriate epidemiological context;</td>
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<tr>
<td>however, coinfection with malaria was seen in up to 5%</td>
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<tr>
<td>of patients in West Africa during the 2014 outbreak, so</td>
<td></td>
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<tr>
<td>the possibility of dual infection should be considered</td>
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<tr>
<td>in all patients.[79]</td>
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</tbody>
</table>

### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>serum electrolyte levels</td>
<td>may be abnormal</td>
</tr>
<tr>
<td>• Important test to order (if available) in areas where other investigations are limited.</td>
<td></td>
</tr>
<tr>
<td>• May indicate acute kidney injury.[98]</td>
<td></td>
</tr>
<tr>
<td>• Especially useful in patients with diarrhea and vomiting.</td>
<td></td>
</tr>
<tr>
<td>• Hypokalemia or hyperkalemia, due to vomiting and diarrhea or acute kidney injury, was seen in approximately 33% of cases in the 2014 outbreak.[79]</td>
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<tr>
<td>• Hypocalcemia has been associated with fatal infection.[16]</td>
<td></td>
</tr>
<tr>
<td>• Useful to guide correction of electrolytes and fluid replacement.</td>
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</tr>
<tr>
<td>Test</td>
<td>Result</td>
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<tr>
<td>-----------------------------</td>
<td>---------------------------------------------</td>
</tr>
</tbody>
</table>
| **BUN/serum creatinine**    | • Important test to order (if available) in areas where other investigations are limited.  
                            | • May indicate acute kidney injury, which was common in the 2014 outbreak,[22] [98] and was associated with death.[79]  
                            | • Especially useful in patients with diarrhea and vomiting. may be elevated |
| **blood lactate**           | • Important test to order (if available) in areas where other investigations are limited.  
                            | • Elevated lactate is a marker of tissue hypoperfusion and is an indicator of shock. It is useful in acutely ill patients with signs of sepsis to identify the degree of systemic hypoperfusion and to guide fluid resuscitation.[99]  
                            | • Elevated lactate was one indicator of gram-negative sepsis at day 15 in a patient treated in Germany.[41] variable |
| **ABG**                    | • Arterial or venous blood pH and bicarbonate are useful in acutely ill patients with signs of sepsis to identify the degree of systemic hypoperfusion and guide fluid resuscitation.[99] variable |
| **CBC**                    | • Decrease in platelet count and marked lymphopenia can be seen in the initial stages of infection; however, this is not diagnostic. Often followed by neutrophil leukocytosis in the later stages of patients who eventually recover, along with normalization of thrombocytopenia. Leukocytosis may persist and show immature forms.[16]  
                            | • Patients with severe disease may show a progressive decline in platelet count as a manifestation of disseminated intravascular coagulation (DIC).  
                            | • Decreased hemoglobin levels were reported in 24% of patients in the 2014 outbreak,[79] and have been associated with bleeding in previous outbreaks.[16] thrombocytopenia, marked lymphopenia; decreased hemoglobin (if bleeding manifestations) |
| **coagulation studies**     | • Prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT) is associated with more severe infection and bleeding manifestations such as DIC.  
                            | • Patients with fatal infection have been found to have D-dimer levels four-fold higher on days 6 to 8 of infection compared with patients who survive.[100] prolonged PT or aPTT, elevated D-dimer level (if bleeding manifestations) |
| **urinalysis**             | • Hematuria or proteinuria may be seen in severe disease.[16]  
<pre><code>                        | • Oliguria that does not respond to fluid resuscitation is a poor prognostic sign. may show hematuria or proteinuria |
</code></pre>
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LFTs</strong></td>
<td>high AST:ALT ratio; bilirubin, GGT, and ALP may be slightly elevated</td>
</tr>
<tr>
<td>• Both ALT and AST are usually elevated;</td>
<td></td>
</tr>
<tr>
<td>however, most studies show that AST</td>
<td></td>
</tr>
<tr>
<td>rises out of proportion to ALT, and this</td>
<td></td>
</tr>
<tr>
<td>is more suggestive of systemic tissue</td>
<td></td>
</tr>
<tr>
<td>damage rather than hepatocellular injury.</td>
<td></td>
</tr>
<tr>
<td>• AST:ALT ratio peaked at 15:1 on days 6</td>
<td></td>
</tr>
<tr>
<td>to 8 of infection in fatal cases when</td>
<td></td>
</tr>
<tr>
<td>compared with nonfatal cases, which had</td>
<td></td>
</tr>
<tr>
<td>a peak of 5:1.</td>
<td></td>
</tr>
<tr>
<td>• Bilirubin, GGT, and ALP are often slightly elevated. Highly elevated ALT and severe jaundice suggests an alternative diagnosis (e.g., viral hepatitis).</td>
<td></td>
</tr>
<tr>
<td><strong>serum amylase level</strong></td>
<td>may be elevated</td>
</tr>
<tr>
<td>• Elevated levels have been reported in</td>
<td></td>
</tr>
<tr>
<td>several studies and indicates the</td>
<td></td>
</tr>
<tr>
<td>presence of pancreatitis, an indicator</td>
<td></td>
</tr>
<tr>
<td>of severe infection.</td>
<td></td>
</tr>
<tr>
<td><strong>serum blood glucose</strong></td>
<td>may be low</td>
</tr>
<tr>
<td>• Hypoglycemia may be present in adults,</td>
<td></td>
</tr>
<tr>
<td>but it is not commonly reported.</td>
<td></td>
</tr>
<tr>
<td>• However, it is common in children and</td>
<td></td>
</tr>
<tr>
<td>may be severe.</td>
<td></td>
</tr>
<tr>
<td>• It is a potentially reversible cause of</td>
<td></td>
</tr>
<tr>
<td>confusion.</td>
<td></td>
</tr>
<tr>
<td><strong>blood cultures</strong></td>
<td>negative</td>
</tr>
<tr>
<td>• Negative blood cultures are helpful as</td>
<td></td>
</tr>
<tr>
<td>they rule out other nonviral infectious</td>
<td></td>
</tr>
<tr>
<td>causes (e.g., sepsis, enteric fever).</td>
<td></td>
</tr>
<tr>
<td>• Gram-negative bacteremia, presumably</td>
<td></td>
</tr>
<tr>
<td>from gut translocation, has been</td>
<td></td>
</tr>
<tr>
<td>identified as a complication of the</td>
<td></td>
</tr>
<tr>
<td>disease course in two patients.</td>
<td></td>
</tr>
<tr>
<td>• However, a study in Sierra Leone where</td>
<td></td>
</tr>
<tr>
<td>blood cultures were taken from patients</td>
<td></td>
</tr>
<tr>
<td>on admission to an Ebola treatment</td>
<td></td>
</tr>
<tr>
<td>center found that only one of the 22</td>
<td></td>
</tr>
<tr>
<td>cultures was positive with a presumed</td>
<td></td>
</tr>
<tr>
<td>contaminant.</td>
<td></td>
</tr>
<tr>
<td>• Therefore, blood should be collected for</td>
<td></td>
</tr>
<tr>
<td>culture at baseline and/or at the time</td>
<td></td>
</tr>
<tr>
<td>of the onset of gastrointestinal symptoms</td>
<td></td>
</tr>
<tr>
<td>or other clinical deterioration.</td>
<td></td>
</tr>
<tr>
<td>**antigen-capture enzyme-linked</td>
<td>positive for Ebola virus antibodies</td>
</tr>
<tr>
<td>immunosorbent assay (ELISA)**</td>
<td></td>
</tr>
<tr>
<td>• Useful diagnostic test with high</td>
<td></td>
</tr>
<tr>
<td>specificity; however, it is not</td>
<td></td>
</tr>
<tr>
<td>universally available. Can be used to</td>
<td></td>
</tr>
<tr>
<td>confirm the diagnosis along with a</td>
<td></td>
</tr>
<tr>
<td>positive RT-PCR result.</td>
<td></td>
</tr>
<tr>
<td>• Most likely to give a positive result</td>
<td></td>
</tr>
<tr>
<td>from day 3 until day 6 of infection,</td>
<td></td>
</tr>
<tr>
<td>and can give widely variable results</td>
<td></td>
</tr>
<tr>
<td>from days 7 to 16.</td>
<td></td>
</tr>
<tr>
<td><strong>IgM and IgG antibodies</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• Useful in later stages of the infection.</td>
<td></td>
</tr>
<tr>
<td>• IgM antibodies can appear in serum as</td>
<td></td>
</tr>
<tr>
<td>early as day 2 post infection, but can</td>
<td></td>
</tr>
<tr>
<td>give variable results up to day 9. They</td>
<td></td>
</tr>
<tr>
<td>become negative between 30 and 168 days</td>
<td></td>
</tr>
<tr>
<td>after symptom onset. IgG response</td>
<td></td>
</tr>
<tr>
<td>develops between day 6 and 18 and can</td>
<td></td>
</tr>
<tr>
<td>persist for several years.</td>
<td></td>
</tr>
<tr>
<td>• A positive IgM or a rising IgG titer is</td>
<td></td>
</tr>
<tr>
<td>strong evidence for recent Ebola virus</td>
<td></td>
</tr>
<tr>
<td>infection.</td>
<td></td>
</tr>
<tr>
<td><strong>CXR</strong></td>
<td>negative</td>
</tr>
<tr>
<td>• Useful in patients with respiratory</td>
<td></td>
</tr>
<tr>
<td>symptoms.</td>
<td></td>
</tr>
<tr>
<td>• Pulmonary infiltrates are not typical of</td>
<td></td>
</tr>
<tr>
<td>infection and suggest an alternative</td>
<td></td>
</tr>
<tr>
<td>(or comorbid) diagnosis.</td>
<td></td>
</tr>
<tr>
<td>• May be difficult to arrange in an</td>
<td></td>
</tr>
<tr>
<td>isolation unit and should only be ordered</td>
<td></td>
</tr>
<tr>
<td>judiciously to avoid contamination.</td>
<td></td>
</tr>
</tbody>
</table>
### Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>rapid bedside tests</strong></td>
<td>positive for Ebola virus</td>
</tr>
</tbody>
</table>
| • Rapid PCR testing for Ebola virus infection remains a major hurdle for effective, targeted isolation of affected patients. Current tests take an average of 4 hours to perform with a fully equipped laboratory close at hand, but results may take several days to arrive in remote areas. This means that, until they are confirmed negative, patients with febrile illnesses other than Ebola virus infection are confined to isolation and often unwittingly exposed to the virus.  
• Rapid bedside tests can therefore make a very significant contribution to infection control in treatment centers.  
• Several different technologies are being evaluated by WHO for use in field conditions. These include numerous RT-PCR-based assays that have been made simpler to use with a shorter turnaround time of <1 hour. The WHO has listed ReEBOV™ Antigen Rapid Test Kit for potential use; however, it currently only recommends its use in special situations.  
• The alternatives are ELISA-based antigen-detection assays that could be quicker and simpler with the possible advantage of only needing a drop of blood. Their major disadvantage is a reduced sensitivity, particularly in the initial stages of illness.[104]  
• Nanopore technology may allow rapid detection and sequencing in the presence of very low levels of virus, and can potentially be deployed using a pocket-sized detection kit.[106]  
• A GeneXpert® diagnostic tool (Xpert® Ebola) has been trialled in the field, and is an automated cartridge-based system that requires minimal laboratory skill. An inactivated sample is placed into a single-use cartridge, which is then entered into the enclosed machine. Sample preparation, nucleic acid amplification and detection, and production of a result are automated processes minimizing staff training requirements, risk of infection, and cross contamination.[109]  
• The Food and Drug Administration has approved a rapid, single-use test for the detection of *Zaire ebolavirus*. It is the second rapid antigen fingerstick test available under an emergency use authorization, but is the first that uses a portable battery-operated reader which can provide results outside of laboratories.[111]  
• This is a rapidly evolving field and different kits are approved according to the country and settings in which they are to be deployed. Food and Drug Administration (FDA) and WHO recommendations are available: [Food and Drug Administration (FDA): 2014 Ebola virus emergency use authorizations]   [World Health Organization (WHO): Ebola vaccines, therapies, and diagnostics] |
# Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria infection</td>
<td>• Most common cause of nonspecific febrile illness in returning travelers.[97]</td>
<td>• Giemsa-stained thick and thin blood smears: positive for Plasmodium species.</td>
</tr>
<tr>
<td></td>
<td>• Inadequate or no malaria chemoprophylaxis.</td>
<td>• Rapid diagnostic tests: positive for Plasmodium species (note: <em>P. ovale</em> is not always detected by some rapid diagnostic tests).</td>
</tr>
<tr>
<td></td>
<td>• There are no differentiating signs and symptoms.</td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola virus infection is suspected.</td>
</tr>
<tr>
<td></td>
<td>• Coinfection with malaria was seen in up to 5% of patients in West Africa during the 2014 outbreak, so the possibility of dual infection should be considered in all patients.[79]</td>
<td></td>
</tr>
<tr>
<td>Marburg virus infection</td>
<td>• There are no differentiating signs and symptoms.</td>
<td>• Reverse transcriptase-polymerase chain reaction (RT-PCR): positive for Marburg virus RNA.</td>
</tr>
<tr>
<td></td>
<td>• Epidemiologic features can help differentiate between the viral hemorrhagic fevers (i.e., exposure to bats, caves, or mining).[112]</td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola virus infection is suspected.</td>
</tr>
<tr>
<td>Crimean-Congo hemorrhagic fever (CCHF)</td>
<td>• There are no differentiating signs and symptoms.</td>
<td>• RT-PCR: positive for CCHF virus RNA.</td>
</tr>
<tr>
<td></td>
<td>• Epidemiologic features can help differentiate between the viral hemorrhagic fevers (i.e., animal butchering, tick bite, or exposure to animals).[113]</td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola virus infection is suspected.</td>
</tr>
<tr>
<td>Lassa fever</td>
<td>• There are no differentiating signs and symptoms.</td>
<td>• RT-PCR: positive for Lassa virus RNA.</td>
</tr>
<tr>
<td></td>
<td>• Epidemiologic features can help differentiate between the viral hemorrhagic fevers (i.e., exposure to rats in endemic areas).[114]</td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola virus infection is suspected.</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Rift Valley fever</strong></td>
<td>• There are no differentiating signs and symptoms.</td>
<td>• RT-PCR: positive for Rift Valley fever virus RNA.</td>
</tr>
<tr>
<td></td>
<td>• Epidemiologic features can help differentiate between the viral hemorrhagic fevers (i.e.,</td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if</td>
</tr>
<tr>
<td></td>
<td>mosquito exposure, livestock handling, consuming raw animal fluids/tissues).</td>
<td>Ebola virus infection is suspected.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yellow fever</strong></td>
<td>• There are no differentiating signs and symptoms.</td>
<td>• RT-PCR: positive for yellow fever virus RNA.</td>
</tr>
<tr>
<td></td>
<td>• Epidemiologic features can help differentiate between the viral hemorrhagic fevers (i.e.,</td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if</td>
</tr>
<tr>
<td></td>
<td>mosquito exposure, lack of immunization).</td>
<td>Ebola virus infection is suspected.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Typhoid infection</strong></td>
<td>• There are no differentiating signs and symptoms.</td>
<td>Blood or stool culture: positive for <em>Salmonella enterica</em>.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola</td>
</tr>
<tr>
<td></td>
<td></td>
<td>virus infection is suspected.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rickettsial infections</strong></td>
<td>• Includes murine typhus, African tick-bite fever, and epidemic typhus.[115]</td>
<td>Serology: positive for <em>Rickettsia</em> species.</td>
</tr>
<tr>
<td></td>
<td>• Eschar is typical.</td>
<td>• Eschar PCR: positive for <em>Rickettsia</em> species.</td>
</tr>
<tr>
<td></td>
<td>• Lymphadenopathy may be present.</td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola</td>
</tr>
<tr>
<td></td>
<td>• Discrete rash.</td>
<td>virus infection is suspected.</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dengue fever</td>
<td>• There are no differentiating signs and symptoms.</td>
<td>• Serology: positive IgM or IgG.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nonstructural protein (NS1) detection: positive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reverse transcriptase-polymerase chain reaction (RT-PCR): positive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola virus infection is suspected.</td>
</tr>
<tr>
<td>Measles infection</td>
<td>• Unvaccinated.</td>
<td>• Serology: positive for measles virus.</td>
</tr>
<tr>
<td></td>
<td>• There are no differentiating signs and symptoms in prodromal phase.</td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola virus infection is suspected.</td>
</tr>
<tr>
<td></td>
<td>• Koplik spots (red spots with bluish-white central dot) on buccal mucosa.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rash typically starts on face and spreads craniocaudally.</td>
<td></td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>• There are no differentiating signs and symptoms; however, a history of exposure may be helpful.</td>
<td>• PCR: positive.</td>
</tr>
<tr>
<td></td>
<td>• Exposure to contaminated water or soil contaminated by infected rodents.[116]</td>
<td>• Serology: positive.</td>
</tr>
<tr>
<td></td>
<td>• More common in tropical climates.</td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola virus infection is suspected.</td>
</tr>
<tr>
<td>Seasonal influenza</td>
<td>• Respiratory signs and symptoms (e.g., cough, nasal congestion) are more common.</td>
<td>• Viral culture or PCR: detection of seasonal influenza virus or viral RNA.</td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td>• CBC: normal.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola virus infection is suspected.</td>
</tr>
</tbody>
</table>
## Diagnosis

### Condition | Differentiating signs / symptoms | Differentiating tests
---|---|---
Gastroenteritis | • In the correct epidemiological context, this can present in a similar way to Ebola virus infection. However, features such as rash, conjunctival injection, and prostration are very rare in gastroenteritis. | • Stool culture, PCR, or rapid antigen testing: positive. • It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola virus infection is suspected.

Sepsis | • Bacterial sepsis with an unclear origin is a common presentation in developing countries. Often turns out to be deep abdominal infection, upper urinary tract infection, endocarditis, or discitis. • Diarrhea is often absent. | • Blood cultures: positive. • It is recommended that appropriate confirmatory tests for Ebola virus infection are performed before, or in tandem with, differentiating tests if Ebola virus infection is suspected.

### Diagnostic criteria

**Centers for Disease Control and Prevention (CDC): case definition for Ebola virus disease (EVD)**[@77]

**Person under investigation (PUI):**

- A person who has both consistent signs or symptoms and risk factors as follows:
  - Elevated body temperature or subjective fever or symptoms, including severe headache, fatigue, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained hemorrhage; AND
  - An epidemiological risk factor within the 21 days before the onset of symptoms.
  - Guidelines of when to discharge a PUI are available: [Centers for Disease Control and Prevention (CDC): considerations for discharging people under investigation (PUIs) for Ebola virus disease (EVD)]

**Confirmed case:**

- Laboratory-confirmed diagnostic evidence of Ebola virus infection.
  - [Centers for Disease Control and Prevention (CDC): case definition for Ebola virus disease (EVD)]

**World Health Organization: case definition for Ebola or Marburg virus disease**[@80]

The World Health Organization (WHO) has also produced a case definition:

[World Health Organization (WHO): case definition recommendations for Ebola or Marburg virus diseases]
Step-by-step treatment approach

The mainstay of treatment is early recognition of infection coupled with effective isolation and best available supportive care in a hospital setting.

High case fatality rates may be related to the supportive care available in resource-poor, rural settings where outbreaks have occurred, and reflect the difficulties patients in these settings have in accessing basic medical care in a healthcare structure that is overwhelmed.[126] [127]

Cases imported to developed countries such as Spain, Germany, France, Italy, Switzerland, Norway, the UK, and the US present a different scenario with comprehensive supportive care available in these settings, including organ support in intensive care units.[128] [129] Despite this, the lack of specific, proven therapies means that fatalities occur even in developed countries where best supportive care is available.[130] [131] [132]

There was previously an active debate about the suitability of moving patients with advanced disease and a poor prognosis to intensive care where the risk for nosocomial infection may be high. It was thought that failure to provide full supportive care to those who are suspected (but not confirmed) of being infected may result in substandard care for these patients, who may subsequently be shown to have a treatable disease such as malaria. It is now clear that full supportive care can reduce mortality, with a reported survival rate of 81.5% in patients managed outside the West African setting, and that it should be provided whenever possible.[133] [134] [135] Local hospital protocols should consider how this situation would be handled for patients with suspected infection before possible transfer to the intensive care unit, and for those who have already been transferred there.[136] [132] [134] [137] [138]

Children should be managed by teams of health care workers with pediatric expertise. Planning for the care of children in nonendemic settings is complex and early involvement of intensivists has been advocated whenever feasible.[139] [140] [141]

Increased clinician-to-patient ratios are likely to reduce mortality. A staffing ratio of at least one clinician (defined as nurses, clinical officers, or physicians) to four patients is recommended to allow patient assessment three times daily.[142]

Ebola virus infection is a notifiable disease.

[Centers for Disease Control and Prevention (CDC): current Ebola treatment centers]
[Fig-6]

[Fig-7]

[Fig-8]

Isolation and infection control

Patients who are identified as being at risk of infection as per the Centers for Disease Control and Prevention (CDC) or World Health Organization (WHO) case definitions should immediately be isolated in a room with private bathroom facilities:

- [Centers for Disease Control and Prevention (CDC): case definition for Ebola virus disease (EVD)]
Ebola virus infection

**TREATMENT**

- [World Health Organization (WHO): case definition recommendations for Ebola or Marburg virus diseases]

All healthcare personnel attending to the patient must wear appropriate personal protective equipment (PPE) that conforms to published protocols. All contaminated materials (e.g., clothes, bed linens) should be treated as potentially infectious. The CDC and WHO produce detailed guidance on PPE:

- [Centers for Disease Control and Prevention (CDC): guidance on personal protective equipment (PPE) to be used by healthcare workers during management of patients with confirmed Ebola or persons under investigation (PUIs) for Ebola]
- [World Health Organization (WHO): personal protective equipment for use in a filovirus disease outbreak - rapid advice guideline]
- [World Health Organization (WHO): steps to put on personal protective equipment (PPE)]
- [World Health Organization (WHO): steps to remove personal protective equipment (PPE)]

The CDC and WHO produce detailed guidance on infection control for healthcare workers in West Africa:

- [Centers for Disease Control and Prevention (CDC): international infection control for healthcare workers (non-US healthcare settings)]
- [World Health Organization (WHO): infection prevention and control (IPC) guidance summary]

Specimens for laboratory investigations (e.g., Ebola RT-PCR, CBC, serum creatinine/BUN, LFTs, ABG, coagulation studies, blood cultures, and investigations for other conditions such as malaria) should be collected and sent off according to local and national protocols. Judicious selection of investigations is important in order to reduce risk of transmission to laboratory workers and other healthcare personnel. Placement of a central line early in the patient stay (if possible) allows bloods to be taken and fluids to be given while minimizing the risk of needlestick injuries.[143] The CDC and WHO produce detailed guidance on specimen collection:

- [Centers for Disease Control and Prevention (CDC): guidance for collection, transport and submission of specimens for Ebola virus testing]
- [World Health Organization (WHO): how to safely collect blood samples from persons suspected to be infected with highly infectious blood-borne pathogens] [Fig-9]

**Fluid and electrolyte management**

The high frequency of vomiting and diarrhea means that patients are often dehydrated and hypovolemic, particularly if they present late. This is probably responsible for the high case fatality rates in outbreaks as basic clinical monitoring (i.e., temperature, respiratory rate, pulse rate, blood pressure, and fluid input/output) is essential, but often difficult in resource-poor settings.

Oral rehydration solutions can be used for patients who can tolerate oral administration and who are not severely dehydrated, but the majority of patients require intravenous fluid replacement with either normal saline or lactated Ringer solution.[127] [144] [Fig-10]

[Fig-11]
Markers of poor perfusion may indicate poor or inadequate oral intake and patients should be promptly switched to intravenous administration. Options include the peripheral or central intravenous route, or the intraosseous route.[142]

The volume of intravenous fluids required should be assessed based on clinical exam (i.e., level of dehydration, signs of shock) and fluid losses (i.e., volume of diarrhea and/or vomitus). Large volumes of fluid replacement (up to 10 L/day) may be required in febrile patients with diarrhea.[128] [145] [146] Large amounts of potassium replacement (e.g., 5-10 mmol potassium chloride per hour) may also be required.[147] [129] [148]

Close supervision and frequent monitoring are required as it is important to assess response and prevent fluid overload. Patients should be checked frequently for signs of shock, dehydration, or overhydration, and the fluid rate adjusted accordingly. Systematic monitoring of vital signs (e.g., heart rate, blood pressure, urine output, gastrointestinal fluid loss) and volume status at least three times daily is required to detect hypovolemia.[142]

Oral loperamide may help reduce profuse diarrhea, but further evidence is required to determine its role and it is not currently recommended by the WHO.[149] [150] [151] [152]

The availability of point-of-care tests within the isolation facility makes monitoring the patient's biochemical status more efficient and reduces the risks associated with specimen transport.[136] Electrolyte monitoring should be performed daily, and repletion given as necessary.[127] More frequent monitoring can be considered if large volumes of intravenous fluids are being administered or if there are severe biochemical abnormalities present. High blood lactate levels can be a reliable measure of hypoperfusion and can help guide fluid resuscitation.[136]

WHO guidelines should be consulted for specific recommendations on fluid and electrolyte management as well as on maintaining adequate nutrition during acute illness and the convalescent phase.

[World Health Organization (WHO): manual for the care and management of patients in Ebola care units/ community care centres - interim emergency guidance]

[World Health Organization (WHO): clinical management of patients with viral haemorrhagic fever: a pocket guide for the front-line health worker]

**Symptomatic management**

**Fever and pain:**

- Should be treated with acetaminophen first line. Opioid analgesics (e.g., morphine) are preferable for more severe pain. Nonsteroidal anti-inflammatory drugs (including aspirin) should be avoided due to their associated increased risk of bleeding and potential for nephrotoxicity.[152]

**Gastrointestinal symptoms:**

- Fluid replacement is required for vomiting and diarrhea as per the recommendations above.
- Oral or intravenous antiemetics (e.g., ondansetron, metoclopramide) are recommended for nausea/vomiting.[152]
- Zinc is recommended in children with diarrhea.[152]
Treatment

- Patients should be evaluated for gastrointestinal infections and managed accordingly.[152]
- Fecal management systems were used successfully in the 2014 outbreak in West Africa in patients with severe diarrhea. They were well tolerated and provided infection prevention and control benefits for healthcare workers.[153]

Heartburn/dysphagia/abdominal pain:

- Patients may benefit from administration of a suitable antacid or a proton-pump inhibitor (e.g., omeprazole).[152]

Seizures:

- Although uncommon, seizures are a feature of advanced disease and pose a risk to healthcare workers because they increase the risk of contact with the patient's body fluids. Recognition and correction of contributing factors (e.g., high temperature, hypoperfusion, electrolyte disturbances, hypoglycemia) is essential. A benzodiazepine can be used to abort the seizure while an anticonvulsant (e.g., phenobarbital) can be given for repeated seizures.[152] If there is no intravenous access, it can be given intramuscularly or rectally.

Agitation:

- Although uncommon, agitation may be associated with encephalopathy, or possibly a direct effect of the virus on the brain, and can occur in advanced disease. Judicious use of a sedative (e.g., haloperidol or a benzodiazepine) is imperative for keeping the patient calm and preventing needlestick injuries in healthcare workers.[152]

Respiratory distress:

- Oxygen should be titrated to maintain SpO2 ≥90%. It should also be given if SpO2 <94%. Patients should be evaluated for pneumonia, fluid overload, wheezing, and congestive heart failure and managed accordingly.[152]

Intraosseous access may be required in some patients.

Sepsis/septic shock

Identification of sepsis or septic shock should be done rapidly using established criteria.

Management follows the same principles as for bacterial sepsis. Local guidance should be followed, but should include:[154]

- Broad-spectrum antibiotics in the first hour after sending blood cultures
- Rapid intravenous fluid resuscitation with assessment of response (within 30 minutes or faster if possible)
- Appropriate airway management and oxygen administration
- Monitoring of urine output preferably by urethral catheterization, as well as vital signs and clinical features.

Broad-spectrum antibiotics are used in patients with infection to target the presumed translocation of gut organisms. This is not backed by any evidence, and blood cultures are difficult to do safely in infected
Ebola virus infection

Treatment

Patients. In some settings, especially in endemic areas where there is poor access to diagnostic tests, patients are routinely given broad-spectrum antibiotics as part of the management protocol.

Blood lactate levels are a useful tool to help assess perfusion and response to resuscitation.

In the absence of a response to initial management, inotropic support should be considered, preferably via a central venous catheter in an intensive care unit where invasive monitoring enables more aggressive fluid, electrolyte, and acid-base balance correction.[136] [138]

The possibility of hemorrhage should be considered, particularly in patients with skin or mucosal bleeding.

WHO guidelines should be consulted for specific recommendations on the management of sepsis/septic shock.

[World Health Organization (WHO): manual for the care and management of patients in Ebola care units/community care centres - interim emergency guidance]

[World Health Organization (WHO): clinical management of patients with viral haemorrhagic fever: a pocket guide for the front-line health worker]

Significant bleeding/hemorrhage

Major bleeding occurs infrequently, but is a manifestation of advanced infection that is usually, but not always, fatal.

When available, fresh whole blood or platelet and plasma transfusions should be given according to local protocols and guided by clinical and laboratory (if available) indicators (e.g., hemoglobin, hematocrit, INR).[152] [155]

Vitamin K and tranexamic acid are reasonable treatment options in patients who are bleeding.[152]

Organ dysfunction

Multi-organ dysfunction is a common feature of advanced infection and includes acute kidney injury, pancreatitis, adrenal failure, and liver damage. Liver damage (e.g., hepatitis) is common; however, jaundice is not a common feature.[156] Renal dysfunction is common, but can be reversed with adequate fluid resuscitation in the initial stages.[156] In patients with anuria who do not respond to fluid resuscitation, renal replacement therapy has been used, although there are no trial data to support the efficacy of this intervention. Of the 5 critically ill patients in Europe and North America with multi-organ failure who were managed with both invasive mechanical ventilation and renal replacement therapy, 3 died.[128] [130] [129] [132] [157]

Convalescent whole blood or plasma

There is limited evidence from past outbreaks that transfusion of blood from convalescent patients could be beneficial in the acute phase of infection, and may reduce mortality.[158] [159] Use of convalescent plasma is likely to be more achievable and effective than use of whole blood.[160] [161] The WHO has issued interim guidelines on the use of convalescent blood/plasma. Trials carried out in Guinea failed to show a survival benefit in patients treated with convalescent plasma, although the treatment appeared to be safe with no severe complications documented.[162] [163]

[World Health Organization (WHO): use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks]
Ebola virus infection

Malaria coinfection
Malaria should be tested for and treated with appropriate antimalarial therapy if present while keeping in mind the patient's risk for Ebola virus infection and the possibility of a dual infection. In endemic settings, malaria treatment is usually given as part of the routine management protocol, with or without confirmation of the infection.

Pregnant women
The reported case fatality rate has been higher (up to 96%) in pregnant women compared with nonpregnant women in previous outbreaks.[164]

The general medical management of pregnant women is the same as for any other person who is infected. Intrapartum hemorrhage and spontaneous abortion appear to be common in infected women; therefore, obstetric management should focus on monitoring for, and early treatment of, hemorrhagic complications.[165] [164] [166] [167] [168] Experience during the 2014 outbreak suggests that good outcomes can occasionally be achieved.[169]

Amniotic fluid has been shown to contain the virus, including when the level was found to be undetectable in blood. Therefore recommendations for delivery include avoiding the induction of labor, particularly rupturing of membranes.[169]

Recommendations for PPE use by healthcare workers caring for pregnant women are the same as for healthcare workers caring for nonpregnant adults. There are no data available to recommend one delivery method over another. Infected women or women with suspected infection are advised not to breastfeed unless breast milk has been shown to be PCR negative for Ebola virus. The CDC and WHO have produced specific guidance for caring for pregnant women and neonates.

Communication with family
Isolation in hospital affects the psychological wellbeing of patients, including increased rates of depression, anxiety, anger, fear, and loneliness. Healthcare workers should facilitate communication with family and friends (e.g., use of cell phones or the internet) in order to reduce psychological distress without increasing the risk of infection.[142]

Experimental therapies
An ethics committee convened by WHO approved the use of five investigational therapies under the framework of compassionate use/expanded access during the 2018 outbreaks in the Democratic Republic of the Congo: ZMapp, remdesivir, REGN3470-3471-3479 (a monoclonal antibody cocktail), favipirvir,
and mAb114.\[170\] The rVSV-ZEBOV vaccine was also used. See Emerging section for more detail on experimental therapies.

[Centers for Disease Control and Prevention (CDC): Ebola treatment]

## Treatment details overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

<table>
<thead>
<tr>
<th>Acute</th>
<th>( summary )</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients</td>
<td>1st isolation and infection control</td>
</tr>
<tr>
<td></td>
<td>plus fluid and electrolyte management</td>
</tr>
<tr>
<td></td>
<td>plus analgesia/antipyretic</td>
</tr>
<tr>
<td></td>
<td>plus antiemetic</td>
</tr>
<tr>
<td></td>
<td>plus consider administration of broad-spectrum antibiotics</td>
</tr>
<tr>
<td></td>
<td>plus consider administration of convalescent whole blood or plasma</td>
</tr>
<tr>
<td>with heartburn/ dysphagia/ abdominal pain</td>
<td>plus antacid or proton-pump inhibitor</td>
</tr>
<tr>
<td>with diarrhea</td>
<td>plus supportive therapies</td>
</tr>
<tr>
<td>with seizures</td>
<td>plus benzodiazepine or anticonvulsant</td>
</tr>
<tr>
<td>with agitation</td>
<td>plus sedative</td>
</tr>
<tr>
<td>with respiratory distress</td>
<td>plus oxygen</td>
</tr>
<tr>
<td>with sepsis/septic shock</td>
<td>plus empiric antibiotic therapy + fluid resuscitation + inotropic support + airway management</td>
</tr>
<tr>
<td>with organ dysfunction</td>
<td>plus supportive care</td>
</tr>
<tr>
<td>with significant bleeding/ hemorrhage</td>
<td>plus transfusion, vitamin K, and/or tranexamic acid</td>
</tr>
<tr>
<td>with malaria</td>
<td>plus antimalarial therapy</td>
</tr>
<tr>
<td>pregnant</td>
<td>plus monitoring and early treatment of complications</td>
</tr>
</tbody>
</table>
# Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

<table>
<thead>
<tr>
<th>Acute</th>
<th>1st isolation and infection control</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients</td>
<td>Patients who are identified as being at risk of infection as per the Centers for Disease Control and Prevention (CDC) or World Health Organization (WHO) case definitions should immediately be isolated in a room with private bathroom facilities.[77][80]</td>
</tr>
<tr>
<td></td>
<td>All healthcare personnel attending to the patient must wear appropriate personal protective equipment (PPE) that conforms to published protocols. [Centers for Disease Control and Prevention (CDC): guidance on personal protective equipment (PPE) to be used by healthcare workers during management of patients with confirmed Ebola or persons under investigation (PUIs) for Ebola] [World Health Organization (WHO): personal protective equipment for use in a filovirus disease outbreak - rapid advice guideline]</td>
</tr>
<tr>
<td></td>
<td>All contaminated materials (e.g., clothes, bed linens) should be treated as potentially infectious.</td>
</tr>
<tr>
<td></td>
<td>Specimens for laboratory investigations (e.g., Ebola RT-PCR, CBC, serum creatinine/BUN, LFTs, ABG, coagulation studies, blood cultures, and investigations for other conditions such as malaria) should be collected and sent off according to local and national protocols. Judicious selection of investigations is important in order to reduce risk of transmission to laboratory workers and other healthcare personnel. [Centers for Disease Control and Prevention (CDC): guidance for collection, transport and submission of specimens for Ebola virus testing] [World Health Organization (WHO): how to safely collect blood samples from persons suspected to be infected with highly infectious blood-borne pathogens]</td>
</tr>
<tr>
<td></td>
<td>Placement of a central line early in the patient stay (if possible) allows bloods to be taken and fluids to be given while minimizing the risk of needlestick injuries.[171]</td>
</tr>
</tbody>
</table>
|  | A staffing ratio of at least one clinician (defined as nurses, clinical officers, or physicians) to
Ebola virus infection

TREATMENT

### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommended for ALL patients in selected patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluid and electrolyte management</td>
<td>Oral rehydration solutions can be used for patients who can tolerate oral administration and who are not severely dehydrated, but the majority of patients require intravenous fluid replacement with either normal saline or lactated Ringer solution. Options include the peripheral or central intravenous route, or the intraosseous route.</td>
</tr>
</tbody>
</table>

- The volume of intravenous fluids required should be assessed based on clinical exam (i.e., level of dehydration, signs of shock) and fluid losses (i.e., volume of diarrhea and/or vomitus). Large volumes of fluid replacement (up to 10 L/day) may be required in febrile patients with diarrhea.

- Close supervision and frequent monitoring are required as it is important to assess response and prevent fluid overload. Patients should be checked frequently for signs of shock, dehydration, or overhydration, and the fluid rate adjusted accordingly. Systematic monitoring of vital signs (e.g., heart rate, blood pressure, urine output, gastrointestinal fluid loss) and volume status at least three times daily is required to detect hypovolemia.

- The availability of point-of-care tests within the isolation facility makes monitoring the patient's biochemical status more efficient and reduces the risks associated with specimen transport. Electrolyte monitoring should be performed daily, and repletion given as necessary. More frequent monitoring can be considered if large volumes of intravenous fluids are being administered or if there are severe biochemical abnormalities present.

- Large amounts of potassium replacement (e.g., 5-10 mmol potassium chloride per hour) may be required.

- Healthcare workers should facilitate communication with family and friends (e.g., use of cell phones or the internet) in order to reduce psychological distress without increasing the risk of infection.

- Ebola virus infection is a notifiable disease.
Acute

» High blood lactate levels can be a reliable measure of hypoperfusion and can help guide fluid resuscitation.[99]

» WHO guidelines should be consulted for specific recommendations on fluid and electrolyte management as well as on maintaining adequate nutrition during acute illness and the convalescent phase.

» [World Health Organization (WHO): clinical management of patients with viral haemorrhagic fever: a pocket guide for the front-line health worker]

» [World Health Organization (WHO): manual for the care and management of patients in Ebola care units/community care centres - interim emergency guidance]

plus analgesia/antipyretic

Treatment recommended for ALL patients in selected patient group

Primary options

» acetaminophen: children: 10-15 mg/kg orally/rectally every 4-6 hours when required, maximum 75 mg/kg/day; adults: 325-1000 mg orally/rectally every 4-6 hours when required, maximum 4000 mg/day

Secondary options

» morphine sulfate: children: 0.2 to 0.4 mg/kg orally every 4-6 hours when required, or 0.05 to 0.1 mg/kg intravenously every 4-6 hours when required; adults: 2.5 to 10 mg orally/ intravenously every 4 hours when required

» Should be treated with acetaminophen first line (for pain and fever).[175]

» Opioid analgesics (e.g., morphine) are preferable for more severe pain.[175]

» Nonsteroidal anti-inflammatory drugs (including aspirin) should be avoided due to their associated increased risk of bleeding and potential for nephrotoxicity.

» Analgesia may help dysphagia, if present.

plus antiemetic

Treatment recommended for ALL patients in selected patient group

Primary options
Acute

» **metoclopramide**: children: consult specialist for guidance on dose; adults: 10 mg orally/intravenously every 8 hours, maximum 30 mg/day

OR

» **ondansetron**: children: consult specialist for guidance on dose; adults: 4-8 mg orally/intravenously every 8-12 hours when required, maximum 24 mg/day

plus **consider administration of broad-spectrum antibiotics**

- Treatment recommended for ALL patients in selected patient group

- In some settings, especially in endemic areas where there is poor access to diagnostic tests, patients are routinely given broad-spectrum antibiotics as part of the management protocol.

plus **consider administration of convalescent whole blood or plasma**

- Treatment recommended for ALL patients in selected patient group

- There is limited evidence from past outbreaks that transfusion of blood from convalescent patients could be beneficial in the acute phase of infection, and may reduce mortality.[9][176]
  Use of convalescent plasma is likely to be more achievable and effective than use of whole blood.[177][178]

- Trials carried out in Guinea failed to show a survival benefit in patients treated with convalescent plasma, although the treatment appeared to be safe with no severe complications documented.[179][180]

- The WHO has issued interim guidelines on the use of convalescent blood/plasma.

- [World Health Organization (WHO): use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks]

- [World Health Organization (WHO): ethics of using convalescent whole blood and convalescent plasma during the Ebola epidemic]
### Acute

<table>
<thead>
<tr>
<th>Condition</th>
<th>Plus</th>
<th>Treatment recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>with heartburn/dysphagia/abdominal pain</td>
<td>antacid or proton-pump inhibitor</td>
<td>Treatment recommended for ALL patients in selected patient group</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» omeprazole: children ≥10 years of age and adults: 20 mg orally once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Patients may benefit from administration of a suitable antacid or a proton-pump inhibitor (e.g., omeprazole).[175] Analgesia may help with dysphagia.</td>
</tr>
<tr>
<td>with diarrhea</td>
<td>supportive therapies</td>
<td>Treatment recommended for ALL patients in selected patient group</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» zinc: children &lt;6 months of age: 10 mg orally once daily for 10-14 days; children ≥6 months of age: 20 mg orally once daily for 10-14 days</td>
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<tr>
<td></td>
<td></td>
<td>» Zinc is recommended in children with diarrhea.[175]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Patients should be evaluated for gastrointestinal infections and managed accordingly.[175]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» Fecal management systems were used successfully in the 2014 outbreak in West Africa in patients with severe diarrhea. They were well tolerated and provided infection prevention and control benefits for healthcare workers.[101]</td>
</tr>
<tr>
<td>with seizures</td>
<td>benzodiazepine or anticonvulsant</td>
<td>Treatment recommended for ALL patients in selected patient group</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>» diazepam: children: consult specialist for guidance on dose; adults: 5-10 mg intravenously/intramuscularly initially, repeat every 10-15 minutes if required, maximum 30 mg/total dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» diazepam rectal: children: consult specialist for guidance on dose; adults: 0.2 mg/kg rectally as a single dose, a second dose can be given in 4-12 hours if necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» phenobarbital: children: consult specialist for guidance on dose; adults: 10 mg/kg intravenously initially, followed by 5 mg/kg</td>
</tr>
</tbody>
</table>
## Treatment

### Acute

<table>
<thead>
<tr>
<th>with agitation</th>
<th>plus</th>
<th>sedative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary options</td>
<td></td>
<td></td>
</tr>
<tr>
<td>» diazepam: children: consult specialist for guidance on dose; adults: 5 mg orally/intravenously as a single dose</td>
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<tr>
<td>OR</td>
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<tr>
<td>» haloperidol: children: consult specialist for guidance on dose; adults: 5 mg intramuscularly as a single dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>» Although uncommon, agitation may be associated with encephalopathy or possibly a direct effect of the virus on the brain, and can occur in advanced disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>» Judicious use of a sedative (e.g., haloperidol or a benzodiazepine) is imperative for keeping the patient calm and preventing needlestick injuries in healthcare workers.[175]</td>
<td></td>
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</tr>
<tr>
<td>» Repeat doses are based on clinical response.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>with respiratory distress</th>
<th>plus</th>
<th>oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>» Oxygen should be titrated to maintain SpO2 ≥90%. It should also be given if SpO2 &lt;94%. Patients should be evaluated for pneumonia, fluid overload, wheezing, and congestive heart failure and managed accordingly.[175]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

» Although uncommon, seizures are a feature of advanced disease and pose a risk to healthcare workers because they increase the risk of contact with the patient’s body fluids. 

» Recognition and correction of contributing factors (e.g., high temperature, hypoperfusion, electrolyte disturbances, hypoglycemia) is essential.

» A benzodiazepine (e.g., intravenous/intramuscular or rectal diazepam) can be used to abort the seizure while an anticonvulsant (e.g., phenobarbital) can be given for repeated seizures.[175]

### with agitation plus sedative

Treatment recommended for ALL patients in selected patient group

Primary options

- diazepam: children: consult specialist for guidance on dose; adults: 5 mg orally/intravenously as a single dose

- haloperidol: children: consult specialist for guidance on dose; adults: 5 mg intramuscularly as a single dose

- Although uncommon, agitation may be associated with encephalopathy or possibly a direct effect of the virus on the brain, and can occur in advanced disease.

- Judicious use of a sedative (e.g., haloperidol or a benzodiazepine) is imperative for keeping the patient calm and preventing needlestick injuries in healthcare workers.[175]

- Repeat doses are based on clinical response.

### with respiratory distress plus oxygen

Treatment recommended for ALL patients in selected patient group

- Oxygen should be titrated to maintain SpO2 ≥90%. It should also be given if SpO2 <94%. Patients should be evaluated for pneumonia, fluid overload, wheezing, and congestive heart failure and managed accordingly.[175]
### Acute

- **with sepsis/septic shock**  
  + **empiric antibiotic therapy + fluid resuscitation + inotropic support + airway management**  
  - Treatment recommended for ALL patients in selected patient group  
  - Identification of sepsis or septic shock should be done rapidly using established criteria. Management follows the same principles as for bacterial sepsis. Local guidance should be followed, but should include: broad-spectrum antibiotics in the first hour after sending blood cultures; rapid intravenous fluid resuscitation with assessment of response (within 30 minutes or faster if possible); appropriate airway management and oxygen administration; and monitoring of urine output preferably by urethral catheterization, as well as vital signs and clinical features.[181]
  
  - Blood lactate levels are a useful tool to help assess perfusion and response to resuscitation.
  
  - In the absence of a response to initial management, inotropic support should be considered, preferably via a central venous catheter in an intensive care unit where invasive monitoring enables more aggressive fluid, electrolyte, and acid-base balance correction.[99] [182]
  
  - Possibility of hemorrhage should be considered, particularly in patients with skin or mucosal bleeding.
  
  - WHO guidelines should be consulted for specific recommendations on the management of sepsis/septic shock.
  
    - [World Health Organization (WHO): clinical management of patients with viral haemorrhagic fever: a pocket guide for the front-line health worker]
  
    - [World Health Organization (WHO): manual for the care and management of patients in Ebola care units/community care centres - interim emergency guidance]

- **with organ dysfunction**  
  + **supportive care**  
  - Treatment recommended for ALL patients in selected patient group  
  - Multi-organ dysfunction is a common feature of advanced infection and includes acute kidney injury, pancreatitis, adrenal failure, and liver damage.
### Acute

<table>
<thead>
<tr>
<th>with significant bleeding/ hemorrhage</th>
<th>plus</th>
<th>transfusion, vitamin K, and/or tranexamic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Primary options

- phytonadione (vitamin K1): consult specialist for guidance on dose

- OR

- tranexamic acid: consult specialist for guidance on dose

- Major bleeding occurs infrequently, but is a manifestation of advanced infection that is usually, but not always, fatal.

- When available, fresh whole blood or platelet and plasma transfusions should be given according to local protocols and guided by clinical and laboratory (if available) indicators (e.g., hemoglobin, hematocrit, INR).

- Vitamin K and tranexamic acid are reasonable treatment options in patients who are bleeding.

<table>
<thead>
<tr>
<th>with malaria</th>
<th>plus</th>
<th>antimalarial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Malaria should be tested for and treated with appropriate antimalarial therapy if present while keeping in mind the patient's risk for Ebola virus infection and the possibility of a dual infection. In endemic settings, malaria treatment is usually given as part of the routine management protocol, with or without confirmation of the infection.
**Acute**

- **pregnant**

  **plus monitoring and early treatment of complications**

  Treatment recommended for ALL patients in selected patient group

  - The general medical management of pregnant women is the same as for any other person who is infected.

  - Intrapartum hemorrhage and spontaneous abortion appear to be common in infected women; therefore, obstetric management should focus on monitoring for, and early treatment of, hemorrhagic complications.[21] [186] [187] [188] [189] Experience during the 2014 outbreak suggests that good outcomes can occasionally be achieved.[190]

  - Recommendations for PPE use by healthcare workers caring for pregnant women are the same as for healthcare workers caring for nonpregnant adults.

  - There are no data available to recommend one delivery method over another. Infected women or women with suspected infection are advised not to breastfeed unless breast milk has been shown to be PCR negative for Ebola virus.

  - Amniotic fluid has been shown to contain the virus, including when the level was found to be undetectable in blood. Therefore recommendations for delivery include avoiding the induction of labor, particularly rupturing of membranes.[190]

  - The CDC and WHO have produced specific guidance for caring for pregnant women:
    - [Centers for Disease Control and Prevention (CDC): guidance for screening and caring for pregnant women with Ebola virus disease for healthcare providers in US hospitals][World Health Organization (WHO): Ebola virus disease in pregnancy: screening and management of Ebola cases, contacts and survivors]

  - The CDC has also produced specific guidance for caring for neonates born to infected women:
    - [Centers for Disease Control and Prevention (CDC): care of a neonate born to a mother who is confirmed to have Ebola, is a person under investigation, or has been exposed to Ebola]
Emerging

Experimental therapies

Experimental treatments for Ebola virus infection are under development; however, they have not yet been fully tested for safety or effectiveness. As this is a rapidly developing area, the latest World Health Organization (WHO) guidance should be consulted. The Food and Drug Administration (FDA) is working to help expedite the development and availability of medical products.

rVSV-ZEBOV vaccine

rVSV-ZEBOV (also known as rVSV-ZEBOV-GP or V920) is a live attenuated vesicular stomatitis virus with 1 of its genes replaced by an Ebola virus gene. Phase I trials have confirmed the safety of this vaccine, although joint pain seems to be a common, self-limiting adverse effect. The STRIVE (Sierra Leone Trial to Introduce a Vaccine against Ebola) trial, a combined phase II and III clinical trial to assess the safety and efficacy of rVSV-ZEBOV, found that no cases of Ebola were reported in the 7998 participants who were vaccinated. An open-label, cluster-randomized, ring vaccination trial in which contacts of a suspected Ebola case were vaccinated with a single intramuscular dose of rVSV-ZEBOV was conducted in Guinea. Patients in the treatment arm received the vaccine immediately, while vaccination was delayed by 21 days in the control arm. The study found that rVSV-ZEBOV has a high protective efficacy. No patients who received the vaccine developed Ebola virus infection 10 days or more after randomization in the immediate-treatment arm; however, cases occurred in unvaccinated patients in the comparison group. The vaccine has been granted Breakthrough Therapy Designation by the FDA and PRIME status by the European Medicines Agency. rVSV-ZEBOV was used during the 2018 outbreaks in the Democratic Republic of the Congo.

Favipiravir

Formerly known as T-705, favipiravir is an experimental antiviral drug that selectively inhibits viral RNA-dependent RNA polymerase. It is active against influenza viruses, West Nile virus, yellow fever virus, foot-and-mouth disease virus, as well as other flaviviruses, arenaviruses, bunyaviruses, and alphaviruses. The drug is currently approved in Japan for influenza pandemics, but has been found to be effective against Ebola virus in mouse models. Human phase II trials in Guinea used a higher dose than that used for influenza. The JIKI trial, a multicenter nonrandomized trial undertaken in Guinea in 2014-2015, suggested good tolerability at a higher dose in a low-resource setting, as well as a potential benefit in patients with low viral loads. Favipiravir was used during the 2018 outbreaks in the Democratic Republic of the Congo on a compassionate use basis.

Remdesivir (GS-5734)

A prodrug of adenine nucleotide analog that has potent activity against a variety of filoviruses in primate cell infection models. Initial studies have demonstrated excellent effectiveness as a treatment in nonhuman primates infected with Ebola virus. It was used in the UK for a case of late Ebola virus relapse with meningoencephalitis. The patient recovered after being treated with a 14-day course given in combination with a high-dose corticosteroid. This appears to be a promising agent for further studies. Remdesivir was used during the 2018 outbreaks in the Democratic Republic of the Congo on a compassionate use basis.

ZMapp

An experimental combination of 3 humanized monoclonal antibodies targeted at 3 Ebola virus glycoprotein epitopes, engineered for expression in tobacco plants. ZMapp had been found to be protective when administered to nonhuman primates 24 to 48 hours after infection. Another study showed that the drug was able to rescue nonhuman primates when treatment is initiated up to 5 days after infection. A randomized, controlled trial in 72 patients in sites in Liberia, Sierra Leone, Guinea, and the US found that, although the use of ZMapp plus the current standard of care appeared to be beneficial
compared with current standard care alone, results did not meet the prespecified statistical threshold for efficacy and further research is required.[208] No major safety concerns were noted in this trial, and only one serious adverse effect (hypertension) was found to be related to the infusion itself. ZMapp was used during the 2018 outbreaks in the Democratic Republic of the Congo on a compassionate use basis. REGN3470-3471-3479, another combination of three monoclonal antibodies directed against different epitopes of the Ebola virus glycoprotein, has also been approved for use in the latest outbreak.

**mAb114**

A human IgG1 monoclonal antibody targeted to the *Zaire ebolavirus* glycoprotein. It was isolated from a human survivor of the 1995 outbreak in Kikwit (Democratic Republic of the Congo), and developed by the National Institutes of Health in the US where a first-in-human phase I clinical trial examining the safety and tolerability is currently in progress. [209] It is administered as a single dose; however, there is no human efficacy data available yet. mAb114 was used during the 2018 outbreaks in the Democratic Republic of the Congo on a compassionate use basis.

**Other vaccines**

A vaccine candidate which uses a prime-boost strategy to enhance immunogenicity and involves the use of 2 distinct viral vectors that are administered as different doses (Ad26-EBOV and MVA-EBOV), has undergone phase I clinical trials in the UK.[210] [211] ChAd3-ZEBOV is a chimpanzee-derived adenovirus vector with an Ebola virus gene inserted. A randomized, placebo-controlled phase II trial found that an antibody response to vaccination with ChAd3-ZEBOV or rVSV-ZEBOV was observed in 71% to 84% of active-vaccine recipients versus 3% of placebo recipients by 1 month. Responses were largely maintained at 12 months.[212]

**TKM-100802 (siRNA)**

Also known as TKM-Ebola. Consists of a combination of small interfering RNAs that target Ebola virus RNA polymerase-L, formulated with lipid nanoparticle technology. Has been shown to be protective in nonhuman primates, and is effective against Marburg virus in guinea pigs and monkeys.[205] [213] [214] [215] The Food and Drug Administration (FDA) granted expanded access use of this drug under an Investigational New Drug application (IND). Using emergency protocols, it was administered to a small number of patients.[159] [191] However, a phase II single-arm trial started in Sierra Leone in March 2015 was discontinued in June 2015, after 19 patients were enrolled, due to a lack of clinical benefit.[216]

**Zmab**

An experimental product composed of 3 monoclonal antibodies directed against the envelope glycoproteins of the Ebola virus, developed by the National Microbiology Laboratory (Winnipeg, Canada), through the Public Health Agency of Canada. Not made to good manufacturing practice (GMP) standards, it has been used in some patients on a compassionate basis. Concerns have been raised by reports of the rapid emergence of resistant Ebola virus mutants in primates with delayed death after treatment with monoclonal antibody preparations, emphasizing the importance of detailed monitoring of any patients treated with these products.[217]

**MIL-77**

Contains 3 monoclonal antibodies prepared in China in mammalian Chinese hamster ovary (CHO) cell-line cultures. This experimental preparation has been used on a compassionate basis in two British patients who both survived.[218]

**BCX-4430**

An experimental adenosine analog found to be active against Ebola virus in rodents. Its mechanism of action is thought to be due to the inhibition of viral RNA-dependent RNA polymerase. It is active against flaviviruses, bunyaviruses, arenaviruses, and paramyxoviruses. The drug has been shown to be protective in nonhuman primates and rodents, even when administered 48 hours after infection.[219] A phase I safety trial is under way.
FX06

One severely unwell patient in Germany was successfully given 3 doses of FX06, a fibrin-derived peptide, in addition to renal replacement therapy and high-quality intensive care.[129] This drug is currently being evaluated as a potential adjunctive treatment for sepsis with vascular leak syndrome in animal models. It has also been evaluated in humans as a potential treatment for preventing reperfusion injury after cardiac revascularization with no major negative adverse effects.[220] [221] It has been given on a compassionate-use basis to 2 patients; however, no conclusions can be drawn yet.

AVI-7537

A drug that consists of antisense phosphorodiamidate morpholino oligomers (PMOs) that target the Ebola virus VP24 gene. It has been shown to confer a survival benefit to infected nonhuman primates.[222] AVI-6002 is an experimental drug that consists of 2 PMOs (AV-7537, and AV-7539, which targets the VP35 gene). AV-6002 has undergone phase I clinical studies.[159] [191] [223]

Interferons

Interferons have been used in the past but have unproven efficacy.[159] A phase II study is under way with limited patient enrolment to date.

Brincidofovir

Formerly known as CMX-001, brincidofovir is an experimental antiviral drug currently undergoing phase III trials for the treatment of cytomegalovirus and adenovirus. It also shows activity against Ebola virus in vitro.[159] [191] [224] The manufacturer announced that it would no longer participate in clinical trials of the drug for the treatment of Ebola owing to the decline of new cases of infection in Liberia, and the drug has been deprioritized for use in Ebola treatment.[225]

Other drugs

Therapeutic agents used for other diseases, such as clomiphene, and chloroquine, inhibit Ebola virus interactions with human cells in models, but no trials are currently registered. Amiodarone has been shown to inhibit filovirus cell entry, and has been used compassionately in one treatment facility in Sierra Leone.[192] [226] [227] Atorvastatin plus irbesartan with or without clomiphene has been used to treat some patients in Sierra Leone; however, no clinical data are available. Aptamers (DNA or RNA molecules selected in vitro and capable of binding a wide range of nucleic and non-nucleic acid molecules with high affinity and specificity) are being studied for the treatment of Ebola virus infection.[228] Small molecule inhibitors of Ebola virus infection are also being studied.[229] WHO has prioritized the antimalarial drug amodiaquine for testing in non-human primates. A specifically configured, experimental RNA compound, rintatolimod, has shown positive results against Ebola in an animal model.
Recommendations

Monitoring

There are no specific requirements for monitoring after discharge; however, eligible patients may be asked to donate blood from 28 days after the date of discharge to be used in the treatment of patients with active infection.[239]

Patient instructions

Education:

- A fact sheet is available from the Centers for Disease Control and Prevention (CDC) [Centers for Disease Control and Prevention (CDC): Ebola (Ebola virus disease) fact sheet]
- A fact sheet is available from the World Health Organization (WHO) [World Health Organization (WHO): Ebola virus disease fact sheet]
- Bushmeat from Africa should not be imported into other countries [Centers for Disease Control and Prevention (CDC): facts about bushmeat and Ebola]
- Household pets are not thought to be at significant risk for infection [World Health Organization (WHO): Ebola virus disease and household pets]
- Patients should be educated about the likely course of convalescence and the possibility of long-term complications.

Sexual health:

- The WHO provides guidance on safe sex practices for survivors and their partners: [World Health Organization (WHO): interim advice on the sexual transmission of the Ebola virus disease]
- Women should be advised not to breastfeed during infection,[44] unless breast milk has been shown to be PCR negative for Ebola virus. However, the risks of not breastfeeding may outweigh the risks of breastfeeding if the infant is symptomatic. More detailed guidance is available here: [Infant feeding in the context of ebola]
- The WHO recommends that men should be offered semen testing every month from 3 months after symptom onset and be abstinent or use condoms ideally until two negative semen tests taken one month apart (or at least 12 months after resolution of symptoms).[47]

Travel:

## Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td><strong>acute kidney injury</strong></td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Frequent in severe disease. May be caused by dehydration initially, but may be a consequence of disseminated intravascular coagulation or direct damage to the kidneys by the Ebola virus in later stages.[16] [64] [79] Early recognition by monitoring urine output and blood biochemistry enables prompt action to be taken.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>sepsis/septic shock</strong></td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Etiology in Ebola virus infection is still not well understood. Multiple factors may contribute, including: bacterial sepsis, possibly through gut translocation of bacteria; a direct effect of the virus; disseminated intravascular coagulation; and hemorrhage.[64] Management follows the same principles as for bacterial sepsis.[181]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>disseminated intravascular coagulation</strong></td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Predisposes patient to bleeding complications. Major bleeding occurs infrequently, but is a manifestation of advanced infection that is usually fatal. When available, fresh whole blood or platelet and plasma transfusions should be given according to local protocols guided by clinical and laboratory (if available) indicators (e.g., hemoglobin, hematocrit, INR).[175] [185]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>miscarriage/maternal death</strong></td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Pregnant women have a high incidence of miscarriage, and infection is frequently fatal in these women.[21] [186] [187] [188]</td>
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### Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>late convalescence complications</td>
<td>variable</td>
<td>low</td>
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</table>

Patients who survive commonly exhibit a protracted recovery characterized by asthenia, weight loss, and migratory arthralgia. Skin desquamation and transient hair loss also occur frequently.

Late manifestations during convalescence are uncommon but may include orchitis, myelitis, parotitis, pancreatitis, hepatitis, psychosis, and hearing loss/tinnitus.[17] Survivors are also at risk of uveitis (anterior, posterior, or panuveitis), which may lead to secondary structural complications, vision impairment, or blindness.[255] One retrospective, uncontrolled, cross-sectional study found that approximately 28% of survivors developed Ebola-associated uveitis, and 3% developed Ebola-associated optic neuropathy. In patients with uveitis, 38.5% of patients were blind.[256] One survivor had acute uveitis with detection of viable Ebola virus 14 weeks after the onset of infection and 9 weeks after the clearance of the virus from the blood.[257] Unilateral white cataracts and a novel retinal lesion following the anatomic distribution of the optic nerve axons have also been reported.[259]

One expatriate healthcare worker presented with Ebola virus meningoencephalitis (RT-PCR of CSF and plasma were positive for Ebola virus) 9 months after recovering from severe primary Ebola virus disease in 2015. Full genome sequencing was performed comparing the initial virus detected in the blood at presentation to the virus detected in the CSF at 10 months, revealing no changes in the coding regions. The authors of this study concluded that they were not able to discern whether the virus remained latent and reactivated, or continually replicated, but were able to confirm, through sequencing, that an immune escape variant had not emerged.[260] A case of late-onset encephalitis and polyarthritis has also been reported.[261]

The etiology of these manifestations is unclear but could be related to immune complex phenomena or the persistence of Ebola virus in immune-privileged sites.

### Prognosis

The natural clinical course of Ebola virus infection varies markedly between the different viral species and according to the level of supportive medical care available. The most lethal species is *Zaire ebolavirus*, which has a reported case fatality rate of up to 90%. The average case fatality rate was approximately 50% in most treatment centers in the 2014 outbreak in West Africa, although rates have varied from 25% to 90% in other past outbreaks.[2] Most epidemics have taken place in resource-poor settings that have little supportive care; therefore, the case fatality rate in other settings could be <40%.[99]

Younger children (<5 years of age) and adults over 40 years of age have a higher mortality rate compared with adolescents and younger adults. Women have a slightly better survival rate compared with men.[242] High viral load, acute kidney injury, and neurologic involvement are also predictors of poor outcome.[18] [6] [20] [21] [22] [85] [86] [98] [243] [244] [245]

An observational study from an outbreak in 1995 showed a marked decrease in the case fatality rate from 93% to 69% between the initial and final phases of the outbreak.[246] This suggests that later cases were recognized earlier, and possibly received higher quality of care.

Pregnant women have a high incidence of miscarriage, and infection is frequently fatal in these women.[21] [186] [187] [188]

Data on the effects of HIV infection on prognosis are being awaited. One study suggests that infection with GB virus C, an immunomodulatory pegivirus that is present in up to 28% of West Africans, is associated with better survival from acute Ebola virus disease.[247]
**Infection course**

Patients who die tend to develop clinical signs early on in the infection, with death usually attributed to shock and multi-organ failure, typically occurring between days 6 and 16 of infection.[6] [13] [14] [15] Patients who eventually recover exhibit isolated fever for several days with improvement typically around days 6 to 11.[98]

**Prognostic indicators**

Observational studies have shown that patients with fatal disease develop advanced features of infection (e.g., prostration, obtundation, hypotension, neurologic involvement) earlier in the course of infection compared with patients who survived with an observed median survival of 9 days from symptom onset.[6] [13] Acute kidney injury and higher viral load both correlate with adverse outcome and increased mortality.[20] [21] [22] [65] [94] [96] Biomarkers as prognostic indicators require further study.[13] [79] [98]

**Recovery and convalescence**

Patients who live through the second week of infection have a >75% chance of surviving.[16] Patients are usually discharged from the isolation facility when they are ambulant, self-caring, lack significant symptoms (e.g., diarrhea, vomiting, bleeding), and have 2 negative reverse transcriptase-polymerase chain reaction (RT-PCR) results for Ebola virus taken 48 hours apart.[94] Viral shedding in seminal fluid may continue for more than a year and a half after recovery.[44] [45] [46] [248] [48] [49] [51] [52] [249] [250] The virus was detected in semen in 62% of men 4 to 6 months after recovery from acute infection.[248] Another study found that 63% of men tested positive for the virus in their semen 12 months or longer after recovery, with the longest interval between discharge from a treatment unit and sample collection being 565 days.[249] It has also been detected in semen for up to 548 days after disease onset in 5% of men.[250] Sexual transmission of the virus from a man to his sexual partner has been confirmed by genomic studies in Liberia.[50] Ebola virus has also been detected in vaginal fluid.[53] The World Health Organization (WHO) recommends that men should be offered semen testing every month from 3 months after symptom onset and be abstinent or use condoms ideally until two negative semen tests taken one month apart (or at least 12 months after resolution of symptoms).[47] Virus has been detected in sweat (up to day 40), urine (up to day 30), conjunctival fluid (up to day 22), feces (up to day 19), and breast milk (up to day 17), even in the absence of viremia.[251]

Patients who survive commonly exhibit a protracted recovery characterized by arthralgias (76% to 77%), fatigue (69%), ocular symptoms (14% to 60%), headache (48% to 54%), abdominal pain (54%), anemia (50%), skin disorders (49%), and auditory symptoms (24%).[252] [253] [254]

Late manifestations during convalescence may include orchitis, myelitis, parotitis, pancreatitis, hepatitis, and psychosis.[17] Survivors are also at risk of uveitis (anterior, posterior, or panuveitis), which may lead to secondary structural complications, vision impairment, or blindness.[255] One retrospective, uncontrolled, cross-sectional study found that approximately 28% of survivors developed Ebola-associated uveitis, and 3% developed Ebola-associated optic neuropathy. In patients with uveitis, 38.5% of patients were found to be blind (visual acuity >20/400).[256] One survivor had acute uveitis with detection of viable Ebola virus 14 weeks after the onset of infection and 9 weeks after the clearance of the virus from the blood.[257] [258] Unilateral white cataracts and a novel retinal lesion following the anatomic distribution of the optic nerve axons have also been reported.[259] The etiology of these manifestations is unclear but could be related to immune complex phenomena or the persistence of Ebola virus in immune-privileged sites. Regular checkups of survivors are recommended for at least 18 months after recovery.[250]

It is likely that survivors of infection acquire lifetime immunity to the same strain of Ebola virus. As a consequence of this, patients who have recovered from infection have been invaluable in caring for patients with active infections. However, our understanding of viral persistence in sanctuary sites remains incomplete. One expatriate healthcare worker presented with Ebola virus meningoencephalitis (RT-PCR of CSF) and plasma were positive for Ebola virus) 9 months after recovering from severe primary Ebola virus disease in 2015.[260] A case of late-onset encephalitis and polyarthritis has also been reported,[261] as has a case of possible transmission from a persistently infected survivor over a year after recovery.[262] The possibility of prolonged persistence and late re-emergence of clinical disease will probably alter the epidemiologic and clinical approach to survivors who present with subsequent illnesses. This is also a theoretical concern for the management of women who become pregnant soon after recovery from acute Ebola infection.
Survivors and orphans of those who have died face stigma and ostracism in many communities. This can be associated with psychological issues.\textsuperscript{[263]} \textsuperscript{[264]}
# Diagnostic guidelines

## International

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<tr>
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<tr>
<td>Guidance for collection, transport and submission of specimens for Ebola virus testing [117]</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>Guidance for U.S. laboratories for managing and testing routine clinical specimens when there is a concern about Ebola virus disease [118]</td>
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<tr>
<td>How to safely ship human blood samples from suspected Ebola or Marburg cases within a country by road, rail and sea [119]</td>
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<tr>
<td>Implementation and management of contact tracing for Ebola virus disease [120]</td>
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<tr>
<td>Interim guidance on the use of rapid Ebola antigen detection tests [121]</td>
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<td>Viral haemorrhagic fever: sample testing advice [125]</td>
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## Treatment guidelines

### International

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<tr>
<td>Yellow book chapter 3 - infectious diseases related to travel: Ebola virus disease and Marburg virus disease</td>
<td>Centers for Disease Control and Prevention</td>
<td>2017</td>
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<tr>
<td>Yellow book chapter 3 - infectious diseases related to travel: viral hemorrhagic fevers</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>Interim guidance for management of survivors of Ebola virus disease in U.S. healthcare settings</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>Ebola virus disease information for clinicians in U.S. healthcare settings</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>Guidance on personal protective equipment to be used by healthcare workers during management of patients with confirmed Ebola or persons under investigation for Ebola who are clinically unstable or have bleeding, vomiting, or diarrhea in U.S. hospitals, including procedures for donning and doffing PPE</td>
<td>Centers for Disease Control and Prevention</td>
<td>2015</td>
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<tr>
<td>Interim guidance for U.S. hospital preparedness for patients under investigation (PUIs) or with confirmed Ebola virus disease (EVD): a framework for a tiered approach</td>
<td>Centers for Disease Control and Prevention</td>
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<td>Ebola clinical care guidelines</td>
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<td>Clinical management of patients with viral haemorrhagic fever: a pocket guide for the front-line health worker</td>
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<td>Ebola virus disease in pregnancy: screening and management of Ebola cases, contacts and survivors</td>
<td>World Health Organization</td>
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<td><strong>International</strong></td>
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<tr>
<td><strong>Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks</strong> [239]</td>
<td>World Health Organization</td>
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<td><strong>Filovirus hemorrhagic fever guideline</strong> [240]</td>
<td>Medecins Sans Frontieres</td>
<td>2008</td>
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<tr>
<td><strong>Management of hazard group 4 viral haemorrhagic fevers and similar human infectious diseases of high consequence</strong> [241]</td>
<td>Public Health England Advisory Committee on Dangerous Pathogens</td>
<td>2015</td>
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## Online resources

1. BMJ Best Practice podcast: Ebola - medical guidance and lessons from West Africa with Dr Tom Fletcher ([external link](#))

2. Centers for Disease Control and Prevention (CDC): Ebola transmission ([external link](#))

3. Centers for Disease Control and Prevention (CDC): infection control for viral haemorrhagic fevers in the African health care setting ([external link](#))

4. World Health Organization (WHO): aide-memoire for infection prevention and control in a health care facility ([external link](#))

5. Centers for Disease Control and Prevention (CDC): the buddy system ([external link](#))

6. Centers for Disease Control and Prevention (CDC): guidance on personal protective equipment (PPE) to be used by healthcare workers during management of patients with confirmed Ebola or persons under investigation (PUIs) for Ebola ([external link](#))

7. World Health Organization (WHO): personal protective equipment for use in a filovirus disease outbreak - rapid advice guideline ([external link](#))

8. World Health Organization (WHO): steps to put on personal protective equipment (PPE) ([external link](#))

9. World Health Organization (WHO): steps to remove personal protective equipment (PPE) ([external link](#))

10. Centers for Disease Control and Prevention (CDC): Ebola prevention ([external link](#))

11. World Health Organization (WHO): Ebola: infection prevention and control ([external link](#))

12. Centers for Disease Control and Prevention (CDC): international infection control for healthcare workers (non-US healthcare settings) ([external link](#))

13. World Health Organization (WHO): infection prevention and control (IPC) guidance summary ([external link](#))

14. Centers for Disease Control and Prevention (CDC): case definition for Ebola virus disease (EVD) ([external link](#))

15. World Health Organization (WHO): case definition recommendations for Ebola or Marburg virus diseases ([external link](#))

16. Centers for Disease Control and Prevention (CDC): guidance for collection, transport and submission of specimens for Ebola virus testing ([external link](#))
17. World Health Organization (WHO): how to safely collect blood samples from persons suspected to be infected with highly infectious blood-borne pathogens (external link)

18. Centers for Disease Control and Prevention (CDC): guidance for US laboratories for managing and testing routine clinical specimens when there is a concern about Ebola virus disease (external link)

19. World Health Organization (WHO): interim guidance on the use of rapid Ebola antigen detection tests (external link)

20. Food and Drug Administration (FDA): 2014 Ebola virus emergency use authorizations (external link)

21. World Health Organization (WHO): Ebola vaccines, therapies, and diagnostics (external link)

22. Centers for Disease Control and Prevention (CDC): Ebola diagnosis (external link)

23. World Health Organization (WHO): clinical management of patients with viral haemorrhagic fever: a pocket guide for the front-line health worker (external link)

24. Centers for Disease Control and Prevention (CDC): considerations for discharging people under investigation (PUIs) for Ebola virus disease (EVD) (external link)

25. World Health Organization (WHO): Ebola surveillance in countries with no reported cases of Ebola virus disease (external link)

26. Centers for Disease Control and Prevention (CDC): guidance for screening and caring for pregnant women with Ebola virus disease for healthcare providers in US hospitals (external link)

27. World Health Organization (WHO): Ebola virus disease in pregnancy: screening and management of Ebola cases, contacts and survivors (external link)

28. Centers for Disease Control and Prevention (CDC): current Ebola treatment centers (external link)

29. World Health Organization (WHO): manual for the care and management of patients in Ebola care units/community care centres - interim emergency guidance (external link)

30. World Health Organization (WHO): use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks (external link)

31. World Health Organization (WHO): ethics of using convalescent whole blood and convalescent plasma during the Ebola epidemic (external link)

32. Centers for Disease Control and Prevention (CDC): care of a neonate born to a mother who is confirmed to have Ebola, is a person under investigation, or has been exposed to Ebola (external link)

33. Centers for Disease Control and Prevention (CDC): Ebola treatment (external link)
34. World Health Organization (WHO): Ebola R&D landscape of clinical candidates and trials (external link)

35. US Food and Drug Administration: Ebola response updates from FDA (external link)


37. World Health Organization (WHO): Ebola virus disease fact sheet (external link)

38. Centers for Disease Control and Prevention (CDC): facts about bushmeat and Ebola (external link)

39. World Health Organization (WHO): Ebola virus disease and household pets (external link)

40. World Health Organization (WHO): interim advice on the sexual transmission of the Ebola virus disease (external link)

41. Infant feeding in the context of ebola (external link)

42. Centers for Disease Control and Prevention (CDC): Ebola - travel notices (external link)

43. World Health Organization (WHO): travel and transport risk assessment (external link)

44. Centers for Disease Control and Prevention (CDC): Ebola (Ebola virus disease) (external link)

45. World Health Organization (WHO): Ebola virus disease (external link)

46. World Health Organization (WHO): implementation and management of contact tracing for Ebola virus disease (external link)

47. World Health Organization (WHO): how to conduct safe and dignified burial of a patient who has died from suspected or confirmed Ebola virus disease (external link)
Key articles

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119. World Health Organization. How to safely ship human blood samples from suspected Ebola or Marburg cases within a country by road, rail and sea. 2017 [internet publication]. Full text

120. World Health Organization; Centers for Disease Control and Prevention. Implementation and management of contact tracing for Ebola virus disease. September 2015 [internet publication]. Full text

121. World Health Organization. Interim guidance on the use of rapid Ebola antigen detection tests. March 2015 [internet publication]. Full text


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Ebola virus infection


204. Warren T, Jordan R, Lo M, et al. Nucleotide prodrug GS-5734 is a broad-spectrum Filovirus inhibitor that provides complete therapeutic protection against the development of Ebola Virus Disease (EVD)


224. Gulland A. Clinical trials of Ebola therapies to begin in December. BMJ. 2014;349:g6827. Abstract


239. World Health Organization. Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks. September 2014 [internet publication]. Full text


Figure 1: Transmission electron micrograph showing some of the ultrastructural morphology displayed by an Ebola virus virion

Centers for Disease Control and Prevention
Ebola virus infection

**Ebola virus ecology showing enzootic and epizootic cycles**

*Centers for Disease Control and Prevention*
Figure 3: Healthcare worker in personal protective equipment at an Ebola treatment center in Sierra Leone, 2014

From the personal collection of Chris Lane, MSc (Public Health England/World Health Organization); used with permission
Figure 4: Diagnostic pathway for the workup of suspected Ebola virus infection

Produced by the BMJ Evidence Centre
Figure 5: Cholera beds with central hole in mattress to manage patients with profuse diarrhea at an Ebola treatment center in West Africa, 2014

From the personal collection of Catherine F. Houlihan, MSc, MB ChB, MRCP, DTMH; used with permission
Figure 6: Multidisciplinary ward rounds at the Save The Children Ebola treatment center in Kerrytown, Sierra Leone (Ministry of Health representative, Cuban Medical Brigade representative, and a UK clinician)

From the collection of Tom E. Fletcher, MBE, MBChB, MRCP, DTM&H; used with permission
Figure 7: General conditions at an Ebola treatment center in West Africa, 2014

From the personal collection of Catherine F. Houlihan, MSc, MB ChB, MRCP, DTMH; used with permission
Figure 8: Ward area at an Ebola treatment center in West Africa, 2014

From the personal collection of Chris Lane, MSc; used with permission
Figure 9: Healthcare worker in personal protective equipment at an Ebola treatment center in Sierra Leone, 2014

From the personal collection of Chris Lane, MSc (Public Health England/World Health Organization); used with permission.
Figure 10: Oral rehydration solution supplies at an Ebola treatment center in West Africa, 2014

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Figure 11: Insertion of an intravenous line in an adult with Ebola virus disease (West Africa)

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Figure 12: Insertion of an intraosseous line in a critically-ill adult with Ebola virus disease (West Africa)

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