Ebola virus infection

The right clinical information, right where it's needed
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Summary

- Initial stages of infection are non-specific, 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 centred 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 centres 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 travelling, all countries should have tested and practised 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*.\[1\] 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 non-human 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).\[2\] Incubation periods may be shorter in children.\[3\] Patients are not considered infectious until they develop symptoms. Human infection carries a high case fatality rate depending on the Ebola virus species and quality of supportive care available.

Ebola virus infection is part of the group of conditions known as viral haemorrhagic fevers, and was formerly known as Ebola haemorrhagic 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.\[24\] 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.\[25\]

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.\[26\] Over 28,000 cases (confirmed, probable, and suspected) were reported in this outbreak, with over 11,000 deaths.

An outbreak was announced in the Democratic Republic of the Congo (DRC) in August 2018. As of 27 August 2019, 2997 cases (2892 confirmed and 105 probable), including 1998 deaths (a case fatality rate of 67%), have been reported in the North Kivu and Ituri provinces of the DRC. Of the total number of cases, 58% were female and 28% were children <18 years of age.\[27\] Related to this outbreak, a cluster of cases have also been confirmed in Uganda.\[28\] This outbreak 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.\[29\] Direct comparison of case fatality rates between different Ebola treatment centres 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,[30] falling to 31.5% in some treatment centres in West Africa,[31] and around 20% in patients managed outside West Africa.[32]

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).[29] There has only been 1 outbreak of *Bundibugyo ebolavirus* : in 2007 in western Uganda, and this outbreak had a case fatality rate of 25%.[33]

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.[34]

**Aetiology**

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 non-human primates; however, the natural reservoir and mode of transmission to humans has not been confirmed.[35] Laboratory testing of reservoir competence shows that successful infection is possible in bats and rodents, but not in plants or arthropods.[36] [37] [38] Animal-to-human transmission may occur during hunting and consumption of the reservoir species or infected non-human primates. The local practice of eating bush meat or food contaminated with bat faeces (3 species of tree-roosting bats have been implicated as a reservoir) is also thought to contribute.
Human-to-human transmission occurs via contact with body fluids from infected patients. In the early epidemics, the re-use of non-sterile injections was responsible for many healthcare-associated transmissions. However, while this still remains a risk, most cases result from close physical contact or contact with body fluids (e.g., sweat, blood, faeces, 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 diarrhoea, vomiting, and haemorrhage). 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. Super-spreading events in the community are also increasingly recognised as a contributing factor: a funeral of a traditional healer in Sierra Leone in 2015 was linked to 300 cases. In one study, it was found that super-spreaders were responsible for approximately 61% of infections in the 2014 outbreak.

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. 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. This means that sexual transmission may be possible long after the infection has resolved, and such cases were confirmed during and following the 2014 outbreak. Ebola virus has also been detected in vaginal fluid. 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.[42]

Infection via the inhalation route has been shown to be possible in non-human primates; however, there is no evidence for airborne transmission in humans.[14] [55] 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.[56] Travellers 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 non-human 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.[57] [58]

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] [59] 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.[60] [61] [62] [63] [64]

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 tumour necrosis factor (TNF)-alpha.[10] [14] [65] 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).[66] Infection leads to lymphocyte depletion through indirect apoptosis (since the virus does not replicate in lymphocytes), and neutrophil suppression via glycoprotein GP.[67] The most common cause of thrombocytopenia is platelet disappearance from damaged tissue or more generalised virus-induced disseminated intravascular coagulation, where coagulation factors are depleted.[68] 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.[69] Flow cytometry, which was used in a treatment
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Basics

centre in Guinea during the 2014 outbreak, demonstrated that T-cell dysregulation (characterised by higher expression of CTLA-4 and PD-1 on CD4 and CD8 cells) was associated with death. This confirms earlier suggestions that an adequate, but controlled, immune response is key to survival.[70]

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 haemorrhage.[65]

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 centres 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 haemorrhagic 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 pigs 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 following preventive measures are recommended for people in an area affected by an outbreak:

- Practise careful hygiene (e.g., wash hands with soap and water, alcohol-based hand sanitiser, 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 non-human 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 travellers (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
- Practise proper infection control and sterilisation 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.

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

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

If infection is suspected based on initial screening, immediate isolation is warranted before any further work-up 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.[74]

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:[74]

- 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
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healthcare workers. After safe doffing, a rapid risk assessment and consideration of post-exposure prophylaxis (PEP) should be undertaken.[75]

- 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 World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) produce detailed guidance on PPE:

- [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)]
- [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]

Vaccines:

- No vaccines have been licensed for use in humans.[76] See Emerging section for detail on vaccines in development.

[World Health Organization (WHO): Ebola: infection prevention and control]
[Centers for Disease Control and Prevention (CDC): Ebola prevention]

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 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 WHO and CDC are below:

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

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.
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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 World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) produce detailed guidance on PPE:

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

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.[167] 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.[71]

[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.[245] 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.[246]

- In addition to these interventions, psychological support is needed for healthcare workers exposed to dangerous pathogens.[247]

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

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

**Case history #1**

A 35-year-old man is brought to the Ebola screening centre in Liberia with a 3-day history of diarrhoea, 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 examination, 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 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 centre in Sierra Leone returned to the UK 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 centre 10 days ago. During her stay, she reports taking atovaquone/proguanil for malaria prophylaxis. There are no abnormal findings on examination except for several mosquito bites. Her vital signs are a temperature of 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, haemoptysis, easy bruising, conjunctival bleeding, haematuria, 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 diarrhoea, melaena).[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:
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- 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/diarrhoea reduces the risk; however, uncontrolled diarrhoea 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 minimise the risk of transmission while working up the patient.\[77\] \[78\]

The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) produce detailed guidance on PPE:

- [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)]
- [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]

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

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

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 travellers 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 epidemiological 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 travellers from West Africa, the presence of risk factors for acquiring malaria should be assessed (e.g., living/working in, or travelling to, endemic area; inadequate or absent chemoprophylaxis; not using insecticides or bed nets).\[79\] However,
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Diagnosis

Co-infection 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.[80]

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:[81]

- 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 organisation. Links to the case definitions by the WHO and CDC are below:

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

Symptoms

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

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

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%), diarrhoea (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.[82] Myalgia has also been reported (22%) and, in facilities that could measure this, raised creatine kinase was common (36% to 83%).[19] [80] [83] [84]
Three phases of illness are typically recognised, starting with a few days of non-specific fever, headache, and myalgia, and followed by a gastrointestinal phase where diarrhoea, vomiting, abdominal symptoms, and dehydration are prominent.\[59\] In the second week, the patient may either recover, or deteriorate with 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.\[85\] Children present with similar symptoms to adults; however, in previous outbreaks, younger children are reported to have more respiratory (e.g., cough, dyspnoea) and gastrointestinal symptoms, but less bleeding and neurological signs compared with adults.\[86\] Data were sparse for this patient group in the 2014 outbreak.\[86\] A paediatric cohort study in Sierra Leone described symptoms in 282 patients and found vomiting (60%), abdominal pain (59%), diarrhoea (45%), and conjunctivitis (38%) were common, while hiccups (5%) and bleeding (2%) were rare.\[88\] 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.\[89\]

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 examination**

A full physical examination should be undertaken with the aim of excluding a focus for sepsis while looking for signs of viral haemorrhagic 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] [90] 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,\[89\] [91] with normothermia or hypothermia occurring in the later stages of fatal infection.\[16\] [17] [86] Some patients may initially have a low-grade fever with no other symptoms, or alternatively the temperature may be near normal at first evaluation.\[92\] The temperature threshold for fever differs among countries and guidelines, and using a lower temperature threshold (e.g., ≥37.5°C) increases the sensitivity of finding cases.\[90\] [93] The World Health Organization use a threshold of >38°C.\[94\] However, in a large cohort in Sierra Leone, <30% had a fever of ≥38°C at presentation, although a history of fever was reported by 89% of patients.\[22\]

- **Blood pressure:** hypotension is a feature of pre-terminal 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:** tachypnoea, 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.\[82\]

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] [84] It is frequently described as non-pruritic, erythematous, and maculopapular. It may begin focally, then become diffuse, generalised, 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, haemoptysis, easy bruising, conjunctival bleeding, haematuria, 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] It is less common in children.[88]

• Hiccups: a sign of advanced infection, typically seen in the last 2 to 3 days of fatal infections. They are less common in children.[88] [89]

• Hepatomegaly: tender hepatomegaly with the edge of the liver palpable below the rib cage has been reported, but is uncommon.

• Lymphadenopathy: enlarged lymph nodes have been reported, but are uncommon.

• Neurological signs: depressed consciousness, encephalopathy, and seizures are rare but their presence indicates advanced infection. Confusion was more common in the 2014 outbreak.[84] Confusion may be multifactorial in children and is associated with a poor prognosis.[89] [91]

**Initial investigations**

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

- [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 collection, transport and submission of specimens for Ebola virus testing]
- [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.[95] 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.[96] 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 diarrhoea, 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).[95] Higher viral load correlates with adverse outcome and increased mortality.[20] [21] [22] [66] [80] [95] [97]

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 travellers who have returned from, an endemic area and should be ruled out.\[98\] Co-infection 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.\[80\] 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 recognised 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 work-up 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 urea and abnormal electrolytes may indicate acute kidney injury. This may be seen at the end of the first week of infection. Hypokalaemia or hyperkalaemia, due to vomiting and diarrhoea or acute kidney injury, was seen in approximately 33% of cases in the 2014 outbreak. Hypocalcaemia has been associated with fatal infection. Haematuria and proteinuria may also be seen in severe disease. Oliguria that does not respond to fluid resuscitation is a poor prognostic sign.

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. Elevated lactate was one indicator of gram-negative sepsis at day 15 in a patient treated in Germany.

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.

FBC:

- 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 normalisation 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 haemoglobin levels were reported in 24% of patients in the 2014 outbreak and have been associated with bleeding in previous outbreaks.

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.

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. The AST:ALT ratio peaked at 15:1 on days 6 to 8 of infection in fatal cases when compared with non-fatal cases, which had a peak of 5:1. Bilirubin, GGT, and ALP are often slightly elevated. Highly elevated ALT with severe jaundice suggests an alternative diagnosis (e.g., viral hepatitis).

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

Serum blood glucose:

• Hypoglycaemia 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.[88] [89]

Blood cultures:

• Negative blood cultures are helpful as they rule out other non-viral infectious causes (e.g., sepsis, enteric fever). Gram-negative bacteraemia, presumably from gut translocation, has been identified as a complication of the disease course in two patients.[102] [42] However, a study in Sierra Leone where blood cultures were taken from patients on admission to an Ebola treatment centre found that only one of the 22 cultures was positive with a presumed contaminant.[103] 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.[47] 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 titre is strong evidence for recent Ebola virus infection.[47]

Chest x-ray

• 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.[104]

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 centres.

[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.[105] [106] 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.[107] [108] Rapid sequencing of Ebola virus using these new technologies during an outbreak could allow real-time understanding of viral dynamics.[109]

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 minimising staff training requirements, risk of infection, and cross contamination.[110] 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:

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

**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 travellers 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, faeces, vomit, saliva, genital secretions [including semen], and breast milk) from infected patients.[39] [45] 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] Contact 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
Ebola virus infection

Diagnosis

equipment. Household contacts of infected patients are at a higher risk of infection if there is active diarrhoea, vomiting, or bleeding.[39]

• 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.[71] Super-spreading events in the community are also increasingly recognised as a contributing factor: a funeral of a traditional healer in Sierra Leone in 2015 was linked to 300 cases.[43] In one study, it was found that super-spreaders were responsible for approximately 61% of infections in the 2014 outbreak.[44]

• 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.[48] This means that sexual transmission may be possible long after the infection has resolved,[45] [46] [47] [49] [50] and such cases were confirmed during the 2014 outbreak.[51] [52] [53]

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 non-sterile needles was responsible for the nosocomial spread of the first epidemic in 1976.[40] 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] [46]

• 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.[72]

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.[73]

History & examination factors

Key diagnostic factors

presence of risk factors (common)

• Key risk factors include: living or working in, or arrival from, an endemic area in previous 21 days; contact with infected body fluids; occupational exposure; or butchering/consumption of meat from infected (or potentially infected) animals.

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

Diagnosis

- Human-to-human transmission occurs via contact with body fluids (e.g., sweat, blood, faeces, vomit, saliva, genital secretions [including semen], and breast milk) from infected patients. 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). Incubation periods may be shorter in children.
- 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 diarrhoea, vomiting, or bleeding.
- 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 recognised as a contributing factor: a funeral of a traditional healer in Sierra Leone in 2015 was linked to 300 cases. In one study, it was found that super-spreaders were responsible for approximately 61% of infections in the 2014 outbreak.
- People who have travelled 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 >39.0°C with a remitting pattern. Some patients may initially have a low-grade fever with no other symptoms, or alternatively the temperature may be near normal at first evaluation.
- The temperature threshold for fever differs among countries and guidelines, and using a lower temperature threshold (e.g., ≥37.5°C) increases the sensitivity of finding cases. The World Health Organization use a threshold of >38°C. However, in a large cohort in Sierra Leone, >30% had a fever of ≥38°C at presentation, although a history of fever was reported by 89% of patients. Another study in Sierra Leone found that 25% of children did not have a history of fever, or a temperature ≥38°C at the time of admission.
- Reported in 87% to 89% of patients in the 2014 outbreak.
- Presence is enough to raise concern for infection in the appropriate epidemiological context.
- Wide variations in body temperature can be observed, especially in children. Patients are often normothermic or hypothermic in the later stages of fatal infection.

myalgia (common)

- Common feature of infection, present in up to 80% of patients in previous outbreaks.
- Reported in 22% to 38% of patients in the 2014 outbreak. Raised creatine kinase was common (36% to 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.

Other diagnostic factors

fatigue (common)

- Severe tiredness and lethargy is a common feature in up to 90% of cases in previous outbreaks.
Ebola virus infection

Diagnosis

• Reported in 76% of patients in the 2014 outbreak.\[18\]

**diarrhoea (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 diarrhoea in undeveloped countries. [Fig-5]

**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)**

• Non-specific feature of early infection, present in 10% to 70% of patients in previous outbreaks.\[17\] [86]
• 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 oesophagitis.

**cough, dyspnoea, 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.\[82\]
• 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.\[86\] [87] Difficulty breathing was reported in 14% of children in the 2014 outbreak.\[89\]

**sore throat (common)**

• Pharyngitis is a non-specific feature, present in 10% to 58% of patients in previous outbreaks.\[17\] [86]
• 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.\[84\]

**tachypnoea (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.\[84\]
• May reflect metabolic acidosis due to uraemia and hypoperfusion.

**maculopapular rash (uncommon)**

• Developed early in the course of illness in approximately 25% to 52% of patients in previous outbreaks.\[16\]
Ebola virus infection

**Diagnosis**

- Reported in 1% to 5% of patients in the 2014 outbreak.[18] [19] [84]
- Frequently described as non-pruritic, erythematous, and maculopapular. It may begin focally, then become diffuse, generalised, 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, haemoptysis, easy bruising, conjunctival bleeding, haematuria, 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., melaena, bloody diarrhoea).[16] In a previous outbreak, melaena 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.[88]

**hepatomegaly (uncommon)**

- In a previous outbreak, tender hepatomegaly with the edge of the liver palpable below the rib cage 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 uraemia, hypokalaemia, hyponatraemia, hypocalcaemia, 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] [84]
- Less common in children.[88] [89]

**tachycardia (uncommon)**

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

**hypotension (uncommon)**

- Feature of pre-terminal 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.[91] [89] [84] Confusion may be multifactorial in children and is associated with a poor prognosis.[89] [91]
- Often co-exist with bleeding and hypotension making fluid resuscitation hazardous.
Encephalopathy is possibly related to electrolyte disturbances, uraemia, 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 infection while the patient is in isolation.[95]</td>
<td></td>
</tr>
<tr>
<td>• Returns result 24 to 48 hours before ELISA testing.</td>
<td></td>
</tr>
<tr>
<td>• Several different commercial PCR kits are available with varying sensitivity, specificity, and limits of detection.[96]</td>
<td></td>
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<td>• 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.</td>
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<td>• 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 diarrhoea, vomiting, or bleeding.</td>
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<td>• 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).[95]</td>
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<td>• Higher viral load correlates with adverse outcome and increased mortality.[20] [21] [22] [66] [80] [95] [97]</td>
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</tr>
</tbody>
</table>

### malaria investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giemsa-stained thick and thin blood smears and rapid diagnostic tests are the tests of choice for malaria screening.</td>
<td>negative (may be positive if dual infection)</td>
</tr>
<tr>
<td>A negative result makes Ebola virus infection more likely in the appropriate epidemiological context; however, co-infection 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.[80]</td>
<td></td>
</tr>
</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.[99]</td>
<td></td>
</tr>
<tr>
<td>• Especially useful in patients with diarrhoea and vomiting.</td>
<td></td>
</tr>
<tr>
<td>• Hypokalaemia or hyperkalaemia, due to vomiting and diarrhoea or acute kidney injury, was seen in approximately 33% of cases in the 2014 outbreak.[80]</td>
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</tr>
<tr>
<td>• Hypocalcaemia has been associated with fatal infection.[16]</td>
<td></td>
</tr>
<tr>
<td>• Useful to guide correction of electrolytes and fluid replacement.</td>
<td></td>
</tr>
</tbody>
</table>
### Test

<table>
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<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>serum creatinine and urea</td>
<td>may be elevated</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, which was common in the 2014 outbreak.\cite{22} \cite{99} and was associated with death.\cite{80}</td>
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</tr>
<tr>
<td>• Especially useful in patients with diarrhoea and vomiting.</td>
<td></td>
</tr>
<tr>
<td>blood lactate</td>
<td>variable</td>
</tr>
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<td></td>
</tr>
<tr>
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<td>• Elevated lactate was one indicator of gram-negative sepsis at day 15 in a patient treated in Germany.\cite{42}</td>
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<td>ABG</td>
<td>variable</td>
</tr>
<tr>
<td>• 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.\cite{100}</td>
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<tr>
<td>FBC</td>
<td>thrombocytopenia, marked lymphopenia; decreased haemoglobin (if bleeding manifestations)</td>
</tr>
<tr>
<td>• 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 normalisation of thrombocytopenia. Leukocytosis may persist and show immature forms.\cite{16}</td>
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<td>• Patients with severe disease may show a progressive decline in platelet count as a manifestation of disseminated intravascular coagulation (DIC).</td>
<td></td>
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<tr>
<td>• Decreased haemoglobin levels were reported in 24% of patients in the 2014 outbreak,\cite{80} and have been associated with bleeding in previous outbreaks.\cite{16}</td>
<td></td>
</tr>
<tr>
<td>coagulation studies</td>
<td>prolonged PT or aPTT, elevated D-dimer level (if bleeding manifestations)</td>
</tr>
<tr>
<td>• Prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT) is associated with more severe infection and bleeding manifestations such as DIC.</td>
<td></td>
</tr>
<tr>
<td>• 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.\cite{101}</td>
<td></td>
</tr>
<tr>
<td>urinalysis</td>
<td>may show haematuria or proteinuria</td>
</tr>
<tr>
<td>• Haematuria or proteinuria may be seen in severe disease.\cite{16}</td>
<td></td>
</tr>
<tr>
<td>• Oliguria that does not respond to fluid resuscitation is a poor prognostic sign.</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>LFTs</strong></td>
<td></td>
</tr>
<tr>
<td>• 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. [80]</td>
<td>high AST:ALT ratio; bilirubin, GGT, and ALP may be slightly elevated</td>
</tr>
<tr>
<td>• AST:ALT ratio peaked at 15:1 on days 6 to 8 of infection in fatal cases when compared with non-fatal cases, which had a peak of 5:1. [8] [16] [101]</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></td>
</tr>
<tr>
<td>• Elevated levels have been reported in several studies and indicates the presence of pancreatitis, an indicator of severe infection. [16]</td>
<td>may be elevated</td>
</tr>
<tr>
<td><strong>serum blood glucose</strong></td>
<td></td>
</tr>
<tr>
<td>• Hypoglycaemia 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. [88] [89]</td>
<td>may be low</td>
</tr>
<tr>
<td><strong>blood cultures</strong></td>
<td></td>
</tr>
<tr>
<td>• Negative blood cultures are helpful as they rule out other non-viral infectious causes (e.g., sepsis, enteric fever).</td>
<td>negative</td>
</tr>
<tr>
<td>• Gram-negative bacteraemia, presumably from gut translocation, has been identified as a complication of the disease course in two patients. [102] [42] However, a study in Sierra Leone where blood cultures were taken from patients on admission to an Ebola treatment centre found that only one of the 22 cultures was positive with a presumed contaminant. [103]</td>
<td></td>
</tr>
<tr>
<td>• Therefore, blood should be collected for culture at baseline and/or at the time of the onset of gastrointestinal symptoms or other clinical deterioration.</td>
<td></td>
</tr>
<tr>
<td><strong>antigen-capture enzyme-linked immunosorbent assay (ELISA)</strong></td>
<td>positive for Ebola virus antibodies</td>
</tr>
<tr>
<td>• Useful diagnostic test with high specificity; however, it is not universally available. Can be used to confirm the diagnosis along with a positive RT-PCR result.</td>
<td></td>
</tr>
<tr>
<td>• 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. [47]</td>
<td></td>
</tr>
<tr>
<td><strong>IgM and IgG antibodies</strong></td>
<td></td>
</tr>
<tr>
<td>• Useful in later stages of the infection.</td>
<td>positive</td>
</tr>
<tr>
<td>• 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. IgG response develops between day 6 and 18 and can persist for several years. [47]</td>
<td></td>
</tr>
<tr>
<td>• A positive IgM or a rising IgG titre is strong evidence for recent Ebola virus infection.</td>
<td></td>
</tr>
<tr>
<td><strong>chest x-ray</strong></td>
<td></td>
</tr>
<tr>
<td>• Useful in patients with respiratory symptoms.</td>
<td>negative</td>
</tr>
<tr>
<td>• Pulmonary infiltrates are not typical of infection and suggest an alternative (or comorbid) diagnosis.</td>
<td></td>
</tr>
<tr>
<td>• May be difficult to arrange in an isolation unit and should only be ordered judiciously to avoid contamination. [104]</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 centres.
- 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. [World Health Organization (WHO): interim guidance on the use of rapid Ebola antigen detection tests]
- 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. [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. [107] [108] [109]
- 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 minimising staff training requirements, risk of infection, and cross contamination. [110] This test was used in the field during the 2018 outbreak in the Democratic Republic of the Congo.
- The US 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 authorisation, but is the first that uses a portable battery-operated reader which can provide results outside of laboratories. [112]
- This is a rapidly evolving field and different kits are approved according to the country and settings in which they are to be deployed. WHO and Food and Drug Administration (FDA) recommendations are available: [World Health Organization (WHO): Ebola vaccines, therapies, and diagnostics] [Food and Drug Administration (FDA): 2014 Ebola virus emergency use authorizations]
# 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 non-specific febrile illness in returning travellers.[98]</td>
<td>• Giemsa-stained thick and thin blood smears: positive for <em>Plasmodium</em> species.</td>
</tr>
<tr>
<td></td>
<td>• Inadequate or no malaria chemoprophylaxis.</td>
<td>• Rapid diagnostic tests: positive for <em>Plasmodium</em> 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>• Co-infection 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.[80]</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>• Epidemiological features can help differentiate between the viral haemorrhagic fevers (i.e., exposure to bats, caves, or mining).[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>Crimean-Congo haemorrhagic 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>• Epidemiological features can help differentiate between the viral haemorrhagic fevers (i.e., animal butchering, tick bite, or exposure to animals).[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>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>• Epidemiological features can help differentiate between the viral haemorrhagic fevers (i.e., exposure to rats in endemic areas).[115]</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>
</tbody>
</table>
| Rift Valley fever          | • There are no differentiating signs and symptoms.  
                              • Epidemiological features can help differentiate between the viral haemorrhagic fevers (i.e., mosquito exposure, livestock handling, consuming raw animal fluids/tissues). | • RT-PCR: positive for Rift Valley fever virus RNA.  
                              • 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. |
| Yellow fever               | • There are no differentiating signs and symptoms.  
                              • Epidemiological features can help differentiate between the viral haemorrhagic fevers (i.e., mosquito exposure, lack of immunisation). | • RT-PCR: positive for yellow fever virus RNA.  
                              • 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. |
| Typhoid infection          | • There are no differentiating signs and symptoms.                                               | • Blood or stool culture: positive for *Salmonella enterica*.  
                              • 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. |
| Rickettsial infections     | • Includes murine typhus, African tick-bite fever, and epidemic typhus.[116]  
                              • Eschar is typical.  
                              • Lymphadenopathy may be present.  
                              • Discrete rash.                                                          | • Serology: positive for *Rickettsia* species.  
                              • Eschar PCR: positive for *Rickettsia* species.  
                              • 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. |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<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>• Non-structural 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's 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.[117]</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 infection</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></td>
<td></td>
<td>• FBC: 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenteritis</td>
<td>• 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.</td>
<td>• 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.</td>
</tr>
<tr>
<td>Sepsis</td>
<td>• 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. • Diarrhoea is often absent.</td>
<td>• 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.</td>
</tr>
</tbody>
</table>

### Diagnostic criteria

#### Case definitions

- **World Health Organization case definition for Ebola or Marburg virus disease:**[81]
  - [World Health Organization (WHO): case definition recommendations for Ebola or Marburg virus diseases]

- **Centers for Disease Control and Prevention (CDC) case definition for Ebola virus disease (EVD):**[78]
  - [Centers for Disease Control and Prevention (CDC): case definition for Ebola virus disease (EVD)]
Step-by-step treatment approach

Ebola virus infection is a notifiable disease. 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.[30] [118]

Cases imported to developed countries such as Spain, Germany, France, Norway, Italy, Switzerland, the UK, and the US present a different scenario with comprehensive supportive care available in these settings, including organ support in intensive care units.[119] [120] Despite this, the lack of specific, proven therapies means that fatalities occur even in developed countries where best supportive care is available.[121] [122] [123]

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.[124] [125] [126] 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.[127] [123] [125] [128] [129]

Children should be managed by teams of health care workers with paediatric expertise. Planning for the care of children in non-endemic settings is complex and early involvement of intensivists has been advocated whenever feasible.[130] [131] [132]

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.[133]

Isolation and infection control

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

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

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 WHO and CDC produce detailed guidance on PPE:
### Treatment

- [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)]
- [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]

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

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

Specimens for laboratory investigations (e.g., Ebola RT-PCR, FBC, serum creatinine and urea, 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 minimising the risk of needlestick injuries.[134] The WHO and CDC produce detailed guidance on specimen collection:

- [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 collection, transport and submission of specimens for Ebola virus testing]

### Fluid and Electrolyte Replacement

The high frequency of vomiting and diarrhoea means that patients are often dehydrated and hypovolaemic, 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's solution.[118] [135]

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.[133]

The volume of intravenous fluids required should be assessed based on clinical examination (i.e., level of dehydration, signs of shock) and fluid losses (i.e., volume of diarrhoea and/or vomitus). Large volumes
Ebola virus infection

Treatment

of fluid replacement (up to 10 L/day) may be required in febrile patients with diarrhoea.\footnote{119} \footnote{136} \footnote{137} Large amounts of potassium replacement (e.g., 5-10 mmol [5-10 mEq/L] potassium chloride per hour) may also be required.\footnote{138} \footnote{120} \footnote{139}

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 hypovolaemia.\footnote{133}

Oral loperamidine may help reduce profuse diarrhoea, but further evidence is required to determine its role and it is not currently recommended by the WHO.\footnote{140} \footnote{141} \footnote{142} \footnote{143}

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.\footnote{127} Electrolyte monitoring should be performed daily, and repletion given as necessary.\footnote{118} 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.\footnote{127}

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 paracetamol first line. Opioid analgesics (e.g., morphine) are preferable for more severe pain. Non-steroidal anti-inflammatory drugs (including aspirin) should be avoided due to their associated increased risk of bleeding and potential for nephrotoxicity.\footnote{143}

Gastrointestinal symptoms:

- Fluid replacement is required for vomiting and diarrhoea as per the recommendations above.
- Oral or intravenous anti-emetics (e.g., ondansetron, metoclopramide) are recommended for nausea/vomiting.\footnote{143}
- Zinc is recommended in children with diarrhoea.\footnote{143}
- Patients should be evaluated for gastrointestinal infections and managed accordingly.\footnote{143}
- Faecal management systems were used successfully in the 2014 outbreak in West Africa in patients with severe diarrhoea. They were well tolerated and provided infection prevention and control benefits for healthcare workers.\footnote{144}

Heartburn/dysphagia/abdominal pain:
• Patients may benefit from administration of a suitable antacid or a proton-pump inhibitor (e.g., omeprazole).[143]

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, hypoglycaemia) is essential. A benzodiazepine can be used to abort the seizure while an anticonvulsant (e.g., phenobarbital) can be given for repeated seizures.[143] 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.[143]

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.[143]

Intraosseous access may be required in some patients.

[Sfig-10]

**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:[145]

• 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 catheterisation, 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 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.[127] [129]

The possibility of haemorrhage 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/haemorrhage**

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., haemoglobin, haematocrit, INR).[143] [146]

Vitamin K and tranexamic acid are reasonable treatment options in patients who are bleeding.[143]

**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.[147] Renal dysfunction is common, but can be reversed with adequate fluid resuscitation in the initial stages.[147] 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.[119] [121] [120] [123] [148]

**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.[33] [149] Use of convalescent plasma is likely to be more achievable and effective than use of whole blood.[150] [151] 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.[152] [153]

[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]
Experimental therapies

An ethics committee convened by WHO have approved the use of five investigational therapies under the framework of compassionate use during the current outbreak in the Democratic Republic of the Congo: ZMapp, remdesivir, REGN-EB3, mAb114, and favipirivir.[154]

Interim analysis of randomised controlled trial data from 499 participants in two Congo provinces found that REGN-EB3 and mAb114 were associated with a higher likelihood of survival compared to ZMapp and remdesivir. Approximately 6% of patients who received REGN-EB3 and 11% of patients who received mAb114 died, compared to 24% of patients who received ZMapp and 33% of patients who received remdesivir.[155] As a consequence, it has been recommended that the study be stopped and an extension phase continued where all future patients will be randomised to receive either REGN-EB3 or mAb114.[156]

See Emerging section for more detail on experimental therapies.

Malaria co-infection

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 non-pregnant women in previous outbreaks.[157]

The general medical management of pregnant women is the same as for any other person who is infected. Intrapartum haemorrhage and spontaneous abortion appear to be common in infected women; therefore, obstetric management should focus on monitoring for, and early treatment of, haemorrhagic complications.[158] [157] [159] [160] [161] Experience during the 2014 outbreak suggests that good outcomes can occasionally be achieved.[162]

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 labour, particularly rupturing of membranes.[162]

Recommendations for PPE use by healthcare workers caring for pregnant women are the same as for healthcare workers caring for non-pregnant 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 WHO, CDC, and Public Health England have produced specific guidance for caring for pregnant women and neonates.

[World Health Organization (WHO): Ebola virus disease in pregnancy: screening and management of Ebola cases, contacts and survivors]

[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]

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 mobile phones or the internet) in order to reduce psychological distress without increasing the risk of infection.[133]

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>
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<tbody>
<tr>
<td>all patients</td>
<td>1st isolation and infection control</td>
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<tr>
<td></td>
<td>plus fluid and electrolyte management</td>
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<td>plus analgesia/antipyretic</td>
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<td>plus anti-emetic</td>
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<td>plus consider experimental therapies</td>
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<td>plus consider broad-spectrum antibiotics</td>
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<td>plus consider convalescent whole blood or plasma</td>
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<td></td>
<td>plus antacid or proton-pump inhibitor</td>
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<td>with heartburn/ dysphagia/ abdominal pain</td>
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<tr>
<td>with diarrhoea</td>
<td>plus supportive therapies</td>
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<tr>
<td>with seizures</td>
<td>plus benzodiazepine or anticonvulsant</td>
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<tr>
<td>with agitation</td>
<td>plus sedative</td>
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<tr>
<td>with respiratory distress</td>
<td>plus oxygen</td>
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<tr>
<td>with sepsis/septic shock</td>
<td>plus empirical antibiotic therapy + fluid resuscitation + inotropic support + airway management</td>
</tr>
<tr>
<td>with organ dysfunction</td>
<td>plus supportive care</td>
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<tr>
<td>with significant bleeding/ haemorrhage</td>
<td>plus transfusion, vitamin K, and/or tranexamic acid</td>
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# Treatment

## Acute

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<tr>
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<tr>
<td>with malaria</td>
<td>antimalarial therapy</td>
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<tr>
<td>pregnant</td>
<td>monitoring and early treatment of complications</td>
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</tbody>
</table>
Ebola virus infection

Treatment

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>
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<tr>
<th>Acute</th>
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<td>all patients</td>
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1st isolation and infection control

» Patients who are identified as being at risk of infection as per the World Health Organization (WHO) or Centers for Disease Control and Prevention (CDC) case definitions should immediately be isolated in a room with private bathroom facilities.[78] [81]

» All healthcare personnel attending to the patient must wear appropriate personal protective equipment (PPE) that conforms to published protocols. [World Health Organization (WHO): personal protective equipment for use in a filovirus disease outbreak - rapid advice guideline] [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]

» All contaminated materials (e.g., clothes, bed linens) should be treated as potentially infectious.

» Specimens for laboratory investigations (e.g., Ebola RT-PCR, FBC, serum creatinine and urea, 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. [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 collection, transport and submission of specimens for Ebola virus testing]

» Placement of a central line early in the patient stay (if possible) allows bloods to be taken and fluids to be given while minimising the risk of needlestick injuries.[163]

» 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.\[164\]

» Healthcare workers should facilitate communication with family and friends (e.g., use of mobile phones or the internet) in order to reduce psychological distress without increasing the risk of infection.\[164\]

» Ebola virus infection is a notifiable disease.

**plus fluid and electrolyte management**

Treatment recommended for ALL patients in selected patient group

» 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’s solution.\[20\] Options include the peripheral or central intravenous route, or the intraosseous route.\[164\]

» The volume of intravenous fluids required should be assessed based on clinical examination (i.e., level of dehydration, signs of shock) and fluid losses (i.e., volume of diarrhoea and/or vomitus). Large volumes of fluid replacement (up to 10 L/day) may be required in febrile patients with diarrhoea.\[42\]

» 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 hypovolaemia.\[164\]

» 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.\[100\] Electrolyte monitoring should be performed daily, and repletion given as necessary.\[20\] 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 [5-10 mEq/L] potassium chloride per hour) may be required.\[22\] \[165\] \[166\]
## Acute

» High blood lactate levels can be a reliable measure of hypoperfusion and can help guide fluid resuscitation.[100]

» 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]

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<tr>
<th>plus</th>
<th>analgesia/antipyretic</th>
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<td>Treatment recommended for ALL patients in selected patient group</td>
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### Primary options

» **paracetamol**:
  - children: 10-15 mg/kg orally/rectally every 4-6 hours when required, maximum 75 mg/kg/day;
  - adults: 500-1000 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 paracetamol first line (for pain and fever).[167]

» Opioid analgesics (e.g., morphine) are preferable for more severe pain.[167]

» Non-steroidal 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.

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<th>plus</th>
<th>anti-emetic</th>
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<td>Treatment recommended for ALL patients in selected patient group</td>
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</table>

### 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

» Oral or intravenous anti-emetics (e.g., ondansetron, metoclopramide) are recommended.[167]

**plus consider experimental therapies**

Treatment recommended for ALL patients in selected patient group

» An ethics committee convened by WHO have approved the use of five investigational therapies under the framework of compassionate use during the current outbreak in the Democratic Republic of the Congo: ZMapp, remdesivir, REGN-EB3, mAb114, and favipirvir.[154]

» Interim analysis of randomised controlled trial data from 499 participants in two Congo provinces found that REGN-EB3 and mAb114 were associated with a higher likelihood of survival compared to ZMapp and remdesivir. Approximately 6% of patients who received REGN-EB3 and 11% of patients who received mAb114 died, compared to 24% of patients who received ZMapp and 33% of patients who received remdesivir.[155] As a consequence, it has been recommended that the study be stopped and an extension phase continued where all future patients will be randomised to receive either REGN-EB3 or mAb114.[156]

» See Emerging section for more detail on experimental therapies.

**plus consider 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 convalescent whole blood or plasma**

Treatment recommended for ALL patients in selected patient group
### Acute

<table>
<thead>
<tr>
<th>with heartburn/ dysphagia/ abdominal pain</th>
<th>plus</th>
<th>antacid or proton-pump inhibitor</th>
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<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td><strong>Primary options</strong></td>
<td></td>
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<tr>
<td>✷ omeprazole: children ≥10 years of age and adults: 20 mg orally once daily</td>
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<tr>
<td>✷ Patients may benefit from administration of a suitable antacid or a proton-pump inhibitor (e.g., omeprazole). Analgesia may help with dysphagia.</td>
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<tr>
<th>with diarrhoea</th>
<th>plus</th>
<th>supportive therapies</th>
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<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td><strong>Primary options</strong></td>
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</tr>
<tr>
<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>✷ Zinc is recommended in children with diarrhoea.</td>
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<tr>
<td>✷ Patients should be evaluated for gastrointestinal infections and managed accordingly.</td>
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## Acute

<table>
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<tr>
<th>with seizures</th>
<th>plus</th>
<th>benzodiazepine or anticonvulsant</th>
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<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td><strong>Primary options</strong></td>
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<tr>
<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>
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<tr>
<td>-or-</td>
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<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>
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<td>--AND/OR--</td>
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<td>» phenobarbital: children: consult specialist for guidance on dose; adults: 10 mg/kg intravenously initially, followed by 5 mg/kg every 30-60 minutes until seizures under control, maximum total loading dose 30 mg/kg</td>
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<tr>
<th>with agitation</th>
<th>plus</th>
<th>sedative</th>
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<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td><strong>Primary options</strong></td>
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<tr>
<td>» diazepam: children: consult specialist for guidance on dose; adults: 5 mg orally/intravenously as a single dose</td>
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<td>OR</td>
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</table>
Ebola virus infection

Acute

» 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.[167]

» 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.[167]

with sepsis/septic shock plus empirical 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 catheterisation, as well as vital signs and clinical features.[173]

» 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.[100] [174]
<table>
<thead>
<tr>
<th>Acute</th>
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<tbody>
<tr>
<td>» Possibility of haemorrhage should be considered, particularly in patients with skin or mucosal bleeding.</td>
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<tr>
<td>» WHO guidelines should be consulted for specific recommendations on the management of sepsis/septic shock.</td>
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<tr>
<td>» [World Health Organization (WHO): clinical management of patients with viral haemorrhagic fever: a pocket guide for the front-line health worker]</td>
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<tr>
<td>» [World Health Organization (WHO): manual for the care and management of patients in Ebola care units/community care centres - interim emergency guidance]</td>
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<tr>
<td>with organ dysfunction</td>
<td>plus supportive care</td>
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<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td>» Multi-organ dysfunction is a common feature of advanced infection and includes acute kidney injury, pancreatitis, adrenal failure, and liver damage.</td>
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<tr>
<td>» Liver damage (e.g., hepatitis) is common; however, jaundice is not a common feature.[65]</td>
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<tr>
<td>» Renal dysfunction is common in the advanced stages, but can be reversed with adequate fluid resuscitation in the initial stages.[65] 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.[42] [93] [165] [175] [176]</td>
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<tr>
<td>with significant bleeding/haemorrhage</td>
<td>plus transfusion, vitamin K, and/or tranexamic acid</td>
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<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td>Primary options</td>
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<tr>
<td>» phytomenadione: consult specialist for guidance on dose</td>
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<td>OR</td>
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<tr>
<td>» tranexamic acid: consult specialist for guidance on dose</td>
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</table>
### Acute

- **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., haemoglobin, haematocrit, INR).[167] [177]
  - Vitamin K and tranexamic acid are reasonable treatment options in patients who are bleeding.[167]

### with malaria plus antimalarial therapy

- Treatment recommended for ALL patients in selected patient group
  - 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 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 haemorrhage and spontaneous abortion appear to be common in infected women; therefore, obstetric management should focus on monitoring for, and early treatment of, haemorrhagic complications.[21] [178] [179] [180] [181] Experience during the 2014 outbreak suggests that good outcomes can occasionally be achieved.[182]

- Recommendations for PPE use by healthcare workers caring for pregnant women are the same as for healthcare workers caring for non-pregnant 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
**Acute**

<table>
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<tr>
<th></th>
<th>recommendations for delivery include avoiding the induction of labour, particularly rupturing of membranes.[182]</th>
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<tbody>
<tr>
<td>» The WHO and CDC have produced specific guidance for caring for pregnant women:</td>
<td>[World Health Organization (WHO): Ebola virus disease in pregnancy: screening and management of Ebola cases, contacts and survivors] [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]</td>
</tr>
<tr>
<td>» Public Health England (PHE) have also produced guidance:</td>
<td>[Public Health England (PHE): Ebola in pregnancy - information for healthcare workers]</td>
</tr>
<tr>
<td>» The CDC has also produced specific guidance for caring for neonates born to infected women:</td>
<td>[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]</td>
</tr>
</tbody>
</table>
Emerging

REGN-EB3

REGN-EB3 (also known as REGN3470-3471-3479) is an antibody cocktail consisting of three fully human monoclonal antibodies targeted at three non-overlapping *Zaire ebolavirus* glycoprotein epitopes. An interim analysis of a randomised controlled trial found that REGN-EB3 was associated with a higher likelihood of survival compared to ZMapp and remdesivir. Approximately 6% of patients who received REGN-EB3 died, compared to 24% of patients who received ZMapp and 33% of patients who received remdesivir.[155] REGN-EB3 has received orphan drug designation from both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and is administered as a single intravenous dose. It is being used on a compassionate use basis as one of the two treatments of choice in the current outbreak in the Democratic Republic of the Congo.

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. Interim analysis of a randomised controlled trial found that mAb114 was associated with a higher likelihood of survival compared to ZMapp and remdesivir. Approximately 11% of patients who received mAb114 died, compared to 24% of patients who received ZMapp and 33% of patients who received remdesivir.[155] mAb114 has received orphan drug designation from the FDA, and is administered as a single intravenous dose. It is being used on a compassionate use basis as one of the two treatments of choice in the current outbreak in the Democratic Republic of the Congo.

ZMapp

An experimental combination of 3 humanised monoclonal antibodies targeted at 3 Ebola virus glycoprotein epitopes, engineered for expression in tobacco plants.[183] [184] [185] ZMapp had been found to be protective when administered to non-human primates 24 to 48 hours after infection. Another study showed that the drug was able to rescue non-human primates when treatment is initiated up to 5 days after infection.[186] A randomised, 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 pre-specified statistical threshold for efficacy and further research is required.[187] 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. It is being used on a compassionate use basis in the current outbreak in the Democratic Republic of the Congo.

Remdesivir

A prodrug of adenine nucleotide analogue that has potent activity against a variety of filoviruses in primate cell infection models. Initial studies have demonstrated excellent effectiveness as a treatment in non-human primates infected with Ebola virus.[188] 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. It is being used on a compassionate use basis in the current outbreak 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.[189] Human phase II trials in Guinea used a higher dose than that used for influenza. The JIKI trial, a multi-centre non-randomised 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.[190] It is being used on a compassionate use basis in the current outbreak in the Democratic Republic of the Congo.

rVSV-ZEBOV vaccine

The rVSV-ZEBOV vaccine (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.[191] [192] [193] [194] 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.[195] An open-label, cluster-randomised, 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 randomisation in the immediate-treatment arm; however, cases occurred in unvaccinated patients in the comparison group.[196] The vaccine has been granted PRIME status by the EMA and breakthrough therapy designation by the FDA. The World Health Organization's Strategic Advisory Group of Experts (SAGE) on immunization recommends a ring vaccination strategy and vaccination of health care workers and other frontline workers with rVSV-ZEBOV for the prevention of Ebola virus infection, and it is being used in the current outbreak in the Democratic Republic of the Congo. [World Health Organization: interim recommendations on vaccination against Ebola virus disease (EVD)] Preliminary results on the efficacy of rVSV-ZEBOV using a ring vaccination strategy in the current outbreak found the vaccine to be more than 97% effective.[197]

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.[198] [199] ChAd3-ZEBOV is a chimpanzee-derived adenovirus vector with an Ebola virus gene inserted. A randomised, 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.[200]

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 non-human primates, and is effective against Marburg virus in guinea pigs and monkeys.[184] [201] [202] [203] The 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.[149] [183] 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.[204]

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, emphasising the importance of detailed monitoring of any patients treated with these products.[205]

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.[206]

**BCX-4430**

An experimental adenosine analogue 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 non-human primates and rodents, even when administered 48 hours after infection.[207] 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.[120] 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 revascularisation with no major negative adverse effects.[208] [209] It has been given on a compassionate-use basis to 2 patients; however, no conclusions can be drawn yet.

**AVI-7537**

A drug consisting of antisense phosphorodiamidate morpholino oligomers (PMOs) that target the Ebola virus VP24 gene. It has been shown to confer a survival benefit to infected non-human primates.[210] 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.[149] [183] [211]

**Interferons**

Interferons have been used in the past but have unproven efficacy.[149] 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.[149] [183] [212] 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 deprioritised for use in Ebola treatment.[213]

**Other drugs**

Therapeutic agents used for other diseases, such as clomifene, 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.[214] [215] [216] Atorvastatin plus irbesartan with or without clomifene 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.[217] Small molecule inhibitors of Ebola virus infection are also being studied.[218] The World Health Organization has prioritised 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.[244]

Patient instructions

Education:

- A fact sheet is available from the World Health Organization (WHO) [World Health Organization (WHO): Ebola virus disease fact sheet]

- 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]

- 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,[45] 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).[48]

Travel:

- The WHO and CDC produce guidance for travellers: [World Health Organization (WHO): travel and transport risk assessment] [Centers for Disease Control and Prevention (CDC): Ebola - travel notices]

[World Health Organization (WHO): Ebola virus disease]

[Centers for Disease Control and Prevention (CDC): Ebola (Ebola virus disease)]
### Complications

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<tr>
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<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>acute kidney injury</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][65][80] Early recognition by monitoring urine output and blood biochemistry enables prompt action to be taken.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sepsis/septic shock</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Aetiology 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 haemorrhage.[65] Management follows the same principles as for bacterial sepsis.[173]</td>
<td></td>
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</tr>
<tr>
<td>disseminated intravascular coagulation</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., haemoglobin, haematocrit, INR).[167][177]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miscarriage/maternal death</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][178][179][180]</td>
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</table>
Follow up

Complications | Timeframe | Likelihood
--- | --- | ---
late convalescence complications | variable | low

Patients who survive commonly exhibit a protracted recovery characterised 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.[234] 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.[235] 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.[236] Unilateral white cataracts and a novel retinal lesion following the anatomical distribution of the optic nerve axons have also been reported.[238]

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.[239] A case of late-onset encephalitis and polyarthritis has also been reported.[240]

The aetiology 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 centres 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%.[100]

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.[219]

High viral load, acute kidney injury, and neurological involvement are also predictors of poor outcome.[18] [6] [20] [21] [22] [86] [87] [99] [220] [221] [222]

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.[223] This suggests that later cases were recognised 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] [178] [179] [180]

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.[224]
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.[99]

Prognostic indicators

Observational studies have shown that patients with fatal disease develop advanced features of infection (e.g., prostration, obtundation, hypotension, neurological 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] [66] [95] [97] Biomarkers as prognostic indicators require further study.[13] [80] [99]

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., diarrhoea, vomiting, bleeding), and have 2 negative reverse transcriptase-polymerase chain reaction (RT-PCR) results for Ebola virus taken 48 hours apart.[95] Viral shedding in seminal fluid may continue for more than a year and a half after recovery.[45] [46] [47] [225] [48] [50] [52] [53] [226] [227] The virus was detected in semen in 62% of men 4 to 6 months after recovery from acute infection.[225] 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.[226] It has also been detected in semen for up to 548 days after disease onset in 5% of men.[227] Shedding of Ebola virus in semen may be intermittent; one study reported the reappearance of viral Ebola virus RNA in the semen of 30 male patients after two consecutive negative test results.[228] Sexual transmission of the virus from a man to his sexual partner has been confirmed by genomic studies in Liberia.[51] Ebola virus has also been detected in vaginal fluid.[54] 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).[48] Virus has been detected in sweat (up to day 40), urine (up to day 30), conjunctival fluid (up to day 22), faeces (up to day 19), and breast milk (up to day 17), even in the absence of viraemia.[229]

Patients who survive commonly exhibit a protracted recovery characterised by arthralgias (76% to 77%), fatigue (69%), ocular symptoms (14% to 60%), headache (48% to 54%), abdominal pain (54%), anaemia (50%), skin disorders (49%), and auditory symptoms (24%).[230] [231] [232] A longitudinal study that compared Ebola virus antibody-positive survivors with antibody-negative close contacts (controls) over a period of 12 months found that six symptoms were reported significantly more often among survivors compared to controls: urinary frequency (14.7% versus 3.4%); headache (47.6% versus 35.6%); fatigue (18.4% versus 6.3%); muscle pain (23.1% versus 10.1%); memory loss (29.2% versus 4.8%); and joint pain (47.5% versus 17.5%). More survivors also had abnormal chest, abdominal, neurological, and musculoskeletal findings compared to controls.[233]

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.[234] 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).[235] 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.[236] [237] Unilateral white cataracts and a novel retinal lesion following the anatomical distribution of the optic nerve axons have also been reported.[238] The aetiology of these manifestations is unclear but could be related to immune complex phenomena or the persistence of Ebola virus in immune-privileged sites. Regular check-ups of survivors are recommended for at least 18 months after recovery.[227]

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. A case of late-onset encephalitis and polyarthritis has also been reported, as has a case of possible transmission from a persistently infected survivor over a year after recovery. The possibility of prolonged persistence and late re-emergence of clinical disease will probably alter the epidemiological 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.
## Diagnostic guidelines

### Europe

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<td><strong>Viral haemorrhagic fever: sample testing advice</strong></td>
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<td><strong>Implementation and management of contact tracing for Ebola virus disease</strong></td>
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<td>World Health Organization</td>
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<td><strong>Infection prevention and control (IPC) guidance summary: Ebola guidance package</strong></td>
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<td><strong>Guidance for collection, transport and submission of specimens for Ebola virus testing</strong></td>
<td>Centers for Disease Control and Prevention</td>
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### North America

**Guidance for U.S. laboratories for managing and testing routine clinical specimens when there is a concern about Ebola virus disease**

**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2015

### Treatment guidelines

### Europe

**Ebola response anthropology platform**

**Published by:** Institute of Development Studies; University of Sussex; University of Exeter; London School of Hygiene and Tropical Medicine  
**Last published:** 2018

**Management of hazard group 4 viral haemorrhagic fevers and similar human infectious diseases of high consequence**

**Published by:** Public Health England Advisory Committee on Dangerous Pathogens  
**Last published:** 2015

**Ebola virus disease: clinical management and guidance**

**Published by:** Public Health England  
**Last published:** 2015

**Guidance paper Ebola Treatment Centre (ETC): pregnant & lactating women**

**Published by:** Royal College of Obstetricians and Gynaecologists  
**Last published:** 2014

**Ebola guidance for emergency departments**

**Published by:** The College of Emergency Medicine; Public Health England  
**Last published:** 2014

**Safe use of personal protective equipment in the treatment of infectious diseases of high consequence**

**Published by:** European Centre for Disease Prevention and Control  
**Last published:** 2014

**Public health management of healthcare workers returning from Ebola-affected areas**

**Published by:** European Centre for Disease Prevention and Control  
**Last published:** 2014

**Public health management of persons having had contact with Ebola virus disease cases in the EU**

**Published by:** European Centre for Disease Prevention and Control  
**Last published:** 2014

**Assessing and planning medical evacuation flights to Europe for patients with Ebola virus disease and people exposed to Ebola virus**

**Published by:** European Centre for Disease Prevention and Control  
**Last published:** 2014
### Europe

**Infection prevention and control measures for Ebola virus disease: entry and exit screening measures**  
*Published by:* European Centre for Disease Prevention and Control  
*Last published:* 2014

### International

**Optimized supportive care for Ebola virus disease**  
*Published by:* World Health Organization  
*Last published:* 2019

**Clinical care for survivors of Ebola virus disease**  
*Published by:* World Health Organization  
*Last published:* 2016

**Clinical management of patients with viral haemorrhagic fever: a pocket guide for the front-line health worker**  
*Published by:* World Health Organization  
*Last published:* 2016

**Ebola virus disease in pregnancy: screening and management of Ebola cases, contacts and survivors**  
*Published by:* World Health Organization  
*Last published:* 2015

**Guidance for immunization programmes in the African Region in the context of Ebola**  
*Published by:* World Health Organization  
*Last published:* 2015

**Rapid guidance on the decommissioning of Ebola care facilities**  
*Published by:* World Health Organization  
*Last published:* 2015

**Manual for the care and management of patients in Ebola care units/community care centres - interim emergency guidance**  
*Published by:* World Health Organization  
*Last published:* 2015

**Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks**  
*Published by:* World Health Organization  
*Last published:* 2014

**Filovirus haemorrhagic fever guideline**  
*Published by:* Medecins Sans Frontieres  
*Last published:* 2008

### North America

**CDC yellow book: viral hemorrhagic fevers**  
*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2019
## North America

**Interim guidance for management of survivors of Ebola virus disease in U.S. healthcare settings**

*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2016

**Ebola virus disease information for clinicians in U.S. healthcare settings**

*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2016

**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**

*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2015

**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**

*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2015

**Ebola clinical care guidelines**

*Published by:* Canadian Critical Care Society  
*Last published:* 2014

## Asia

**Infection prevention and control guidelines for Ebola virus disease (EVD)**

*Published by:* Ministry of Health (Sultanate of Oman)  
*Last published:* 2014

## Oceania

**Ebola virus: information for health professionals**

*Published by:* Department of Health (Australia)  
*Last published:* 2018
## 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. World Health Organization (WHO): personal protective equipment for use in a filovirus disease outbreak - rapid advice guideline ([external link](#))

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

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

9. 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](#))

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

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

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

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

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

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

16. World Health Organization (WHO): how to safely collect blood samples from persons suspected to be infected with highly infectious blood-borne pathogens ([external link](#))
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Key articles


Ebola virus infection

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</thead>
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73. Strauss S. Ebola research fueled by bioterrorism threat. CMAJ. 2014;186:1206. Full text Abstract

74. Centers for Disease Control and Prevention. 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 US
Ebola virus infection


77. Fletcher TE, Brooks TJ, Beeching NJ. Ebola and other viral haemorrhagic fevers. BMJ. 2014;349:g5079. Full text Abstract


112. Food and Drug Administration. FDA authorizes emergency use of first Ebola fingerstick test with portable reader. November 2018 [internet publication]. Full text


156. National Institute of Allergy and Infectious Diseases (NIAID). Independent monitoring board recommends early termination of Ebola therapeutics trial in DRC because of favorable results with two of four candidates. August 2019 [internet publication]. Full text


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212. Guillard A. Clinical trials of Ebola therapies to begin in December. BMJ. 2014;349:g6827. [Abstract]


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

Figure 2: Ebolavirus ecology showing enzootic and epizootic cycles

Centers for Disease Control and Prevention
Figure 3: Healthcare worker in personal protective equipment at an Ebola treatment centre 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 work-up 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 diarrhoea at an Ebola treatment centre in West Africa, 2014

From the personal collection of Catherine F. Houlihan, MSc, MB ChB, MRCP, DTMH; used with permission
Figure 6: Ward area at an Ebola treatment centre in West Africa, 2014

From the personal collection of Chris Lane, MSc; used with permission
Figure 7: Healthcare worker in personal protective equipment at an Ebola treatment centre in Sierra Leone, 2014

From the personal collection of Chris Lane, MSc (Public Health England/World Health Organization); used with permission.
Figure 8: Oral rehydration solution supplies at an Ebola treatment centre in West Africa, 2014

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Figure 9: Insertion of an intravenous line in an adult with Ebola virus disease (West Africa)

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Figure 10: Insertion of an intraosseous line in a critically-ill adult with Ebola virus disease (West Africa)

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Contributors:

// Authors:

Nicholas J. Beeching, MA, BM BCh, FRCP, FRACP, FFTM RCPS (Glasg), FESCMID, DCH, DTM&H
Senior Lecturer (Honorary Consultant)
Liverpool School of Tropical Medicine and Royal Liverpool University Hospital, Liverpool, UK
DISCLOSURES: NJB is an author of several references cited in this monograph. NJB is partially supported by the National Institute of Health Research Health Protection Unit in Emerging and Zoonotic Infections at the University of Liverpool and Public Health England. He is affiliated with the Liverpool School of Tropical Medicine. Views expressed in this monograph are those of the contributor and do not necessarily represent the official position of the National Health Service, the National Institute for Health Research, the Department of Health, or Public Health England.

Manuel Fenech, MD, MRCP, DTM&H
Specialist Trainee in Infectious Diseases
Royal Liverpool University Hospital, Liverpool, UK
DISCLOSURES: MF declares that he has no competing interests.

Tom E. Fletcher, MBE, MBChB, MRCP, DTM&H
Wellcome Trust/MoD Research Fellow
Liverpool School of Tropical Medicine, Liverpool, UK
DISCLOSURES: TEF is an author of a number of references cited in this monograph. TEF is a consultant/expert panel member to the World Health Organization, and is funded by the UK Surgeon General and the Wellcome Trust. TEF has received research grants from the Medical Research Council and the UK Public Health Rapid Support Team (UK-PHRST).

Catherine F. Houlihan, MSc, MB ChB, MRCP, DTM&H
Clinical Lecturer
University College London, Honorary Clinical Lecturer, London School of Hygiene and Tropical Medicine, London, UK
DISCLOSURES: CFH declares that she has no competing interests.

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// Peer Reviewers:

William A. Petri, Jr, MD, PhD, FACP
Wade Hampton Frost Professor of Epidemiology
Professor of Medicine, Microbiology, and Pathology, Chief, Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, VA
DISCLOSURES: WAP declares that he has no competing interests.

Luis Ostrosky-Zeichner, MD, FACP, FIDSA, FSHEA
Contributors:

Professor of Medicine and Epidemiology
UT Health Medical School, Medical Director of Epidemiology, Memorial Hermann Texas Medical Center, Houston, TX
DISCLOSURES: LO-Z declares that he has no competing interests.

Stephen Mepham, MRCP (UK), FRCPATH, DTM&H, MD
Consultant in Microbiology and Infectious Diseases
Royal Free London NHS Foundation Trust, London, UK
DISCLOSURES: SM declares that he has no competing interests.