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Emergency Task Force (ETF)

EMA guidance document on the use of medicinal products for treatment and prophylaxis in case of exposure to biological agents used as weapons of terrorism, crime or warfare

This guidance replaces the previous European Medicines Agency (EMA) guidance, CPMP/4048/01, rev.6.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of Contents

Introduction

At the request of the European Commission and later as per regulation 726/2004 art 57(q), the EMA and its Committee for Human Medicinal Products (CHMP) published a guidance document on the use of medicinal products for the treatment and prophylaxis of biological agents that might be used as weapons in the context of bioterrorism in 2002. The first version of the guidance considered pathogens included in Category A of the US Centers for Disease Control and Prevention (CDC) list of agents that might be used for the purposes of bioterrorism. Subsequently, the document was extended to cover agents in categories B and C of the CDC's list and to include information on medicinal products for the treatment and prophylaxis of some infections. Thereafter five reviews followed in 2005, 2007, 2008, 2010 and 2014. (1)

In this current revision, additional changes to the structure of the guidance document were considered necessary. The old EMA classification of the biological agents, based on the availability of treatment options, was revised to align it with the current classification used by the US CDC. Relevant EU regulations, publications and guidance documents were considered, e.g., the Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work. However, it was felt that the 2000/54/EC Directive does not take into account relevant aspects related to biological agents in the context of a deliberate release. The focus of classification should lie on the dissemination and transmission potential of the pathogens, mortality and morbidity rates, the availability of treatment and prevention options and the risk for public health. A classification such as that of CDC was considered more appropriate for the scope of this guidance. If a specific EU list of pathogens relevant in biological warfare, bioterrorism and biocrime were to be developed in the future, this guidance will be updated accordingly. (2, 3)

This document is not intended to be a comprehensive guideline on the management of patients and on the public health measures that would be necessary in the case of deliberate release of the selected agents. The scope of the document is confined to the listing and description of medicines and regimens that might be used in the case of an attack with each biological agent. Treatment options should always be regarded in conjunction with existing national recommendations and public health plans. Moreover, reference should always be made to the labelling information included in the medicines' Summary of Product Characteristics (SmPCs) of each EU Member State.

It should be noted that not all of the listed medicinal products are authorised in the EU for the treatment and/or prophylaxis of the specific diseases mentioned; in such cases, information on indication, dosage and administration of medicines derives from scientific literature and product labels from authorities outside of the EU. Even in the lack of an EU centralised or national marketing authorization, medical countermeasures listed in this guidance may be made available to the population in case of need. In addition, the actual availability of some of the medicinal products suggested can be variable across the EU. All these factors may well influence choices on medicines to be used in the case of an attack. Moreover, some medicines may have to be obtained through special access mechanisms in individual Member States.

Following a known or suspected act of biowarfare, bioterrorism, or biocrime it may take some time to confirm that an attack has occurred, to identify the pathogen, and to determine its susceptibility to available drugs. Therefore, decisions regarding the choice of medicinal products need to be tailored to the actual situation. The possible treatment options suggested have been selected under the provision that the pathogens listed have not been genetically engineered to be resistant to some or all of the potentially useful medicinal products.

This guidance document will be updated on a regular basis as appropriate.

The present revised guidance document was adopted by ETF on July 12, 2024.

List of Pathogens per US-CDC categorisation

The updated classification of the list of pathogens is shown in the table below.

Category A pathogens are high-priority agents because they can be easily disseminated or transmitted from person to person, are characterized by high mortality rates, have the potential to cause major public health impact and require special attention in terms of preparedness.

Category B pathogens represent the second highest priority because they can be disseminated moderately easily, are characterized by low mortality rates but can cause moderate morbidity and require specific diagnostic capacity and enhanced disease surveillance.

Category C agents include emerging pathogens that could be engineered for mass dissemination because of their availability, ease of production and dissemination, potential for high morbidity and mortality rates and consequent public health impact.

Category	Biological agent
Category A	Anthrax (*Bacillus anthracis*)
	Plague (*Yersinia pestis*)
	Tularaemia (*Francisella tularensis*)
	Botulism *(Clostridium botulinum* toxin*)*
	Smallpox (*Variola major*)
	Viral haemorrhagic fever • Filoviruses (Ebola, Marburg) • Arenaviruses (Lassa, Machupo)
Category B	Brucellosis (Brucella species)
	Q fever (*Coxiella burnetii*)
	Epsilon toxin of *Clostridium perfringens*
	Glanders (*Burkholderia mallei*)
	Melioidosis (*Burkholderia pseudomallei*)
	Epidemic Typhus fever (*Rickettsia prowazekii*)
	Food and water safety threats: • Salmonella species • Shigellosis • *Escherichia coli* 0157:H7 • *Vibrio cholerae* • Staphylococcal enterotoxin B • *Cryptosporidium parvum*
	Psittacosis (*Chlamydia psittaci*)
	Ricin and abrin toxin
	Viral encephalitis (alphaviruses) • Eastern equine encephalitis • Venezuelan equine encephalitis • Western equine encephalitis
Category C	Nipah virus
	Hantavirus

References

1. CDC, 'CDC | Bioterrorism Agents/Diseases | Emergency Preparedness & Response' 2019, available from: https://emergency.cdc.gov/agent/agentlist-category.asp

2. 'Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC)', in: Core EU Legislation, pp. 216–261, Official Journal L 262, 17/10/2000 P. 0021 - 0045, 2015
3. Tegnell A. et al., 'Development of a matrix to evaluate the threat of biological agents used for bioterrorism', Cell. Mol. Life Sci. CMLS 63, 2223–2228 2006

Category A: Biological agents and medicinal products

Inhalation, intestinal and cutaneous anthrax (Bacillus anthracis)

Disease characteristics and general points on treatment

Anthrax is an acute infectious zoonotic disease caused by spore-producing *Bacillus anthracis* that may infect humans via cutaneous contact with infected animals (the most common naturally occurring form), inhalation, gastrointestinal or injection routes. In the case of deliberate release of anthrax spores, inhalational anthrax would be the most likely route of infection, however cutaneous anthrax may also occur. Person to person transmission does not occur.

Meningitis may complicate any form of anthrax or occur as a primary manifestation. Systemic anthrax, defined as invasive *Bacillus anthracis* infection associated with bacterial dissemination or toxin-mediated multi-organ dysfunction, may be secondary to any route of infection.

The incubation period for anthrax ranges from 1 to 60 days. Patients with inhalational anthrax develop the first symptoms on average 1 to 7 days after exposure. The median incubation period is on average 2 days for cutaneous anthrax and for primary meningitis, 3 days for ingestion anthrax, and 1 day for injection anthrax, which is associated with drug use.

Patients with inhalational anthrax frequently present with general malaise, sweats, fatigue, minimally productive cough, nausea or vomiting, chest discomfort, and dyspnoea. Fever can be low grade or absent in up to half of the cases. Pleural effusions and mediastinal widening at the chest radiography are commonly reported in inhalation anthrax. 1 in 3 cases of inhalational anthrax may develop secondary meningitis. In a literature review comprising more than 960 cases of all forms of anthrax from 1880 to 2018, more than half of hospitalised cases died. Mortality rates were higher for primary meningitis and inhalational anthrax (93% and 85% respectively). Most cases with non-systemic anthrax survived if treated. In systemically ill patients, survival substantially improved with the early administration of antimicrobials or antiserum/antitoxin. (1-2)

The available data to support the choice of antimicrobials for the treatment of anthrax derive from in-vitro or animal studies (non-clinical studies), and from single clinical cases, as no controlled clinical trials have been performed.

The choice of the appropriate regimen for the treatment and the prophylaxis of anthrax should consider the patient's characteristics, the central nervous system (CNS) involvement, the production of toxin, the potential for antimicrobial resistance, the possible presence of long-lasting spores and, in case of a deliberate release of anthrax spores, the need to treat a large number of individuals. Acceptability and adherence to long treatment regimens should also be taken into account.

Combination therapy has been shown to increase survival in cases of inhalation anthrax. The combination of bactericidal agents (BA) and other agents such as protein synthesis inhibitors (PSI) or RNA synthesis inhibitors (RSI) can be beneficial in view of the potential advantage on the inhibition of toxin production demonstrated in vitro. For cutaneous anthrax, if the patient does not have signs and symptoms of meningitis, antibacterial monotherapy is recommended. (1-5)

Among BAs, ciprofloxacin has been shown to be efficacious in both treatment and prophylactic setting and is recommended as the primary agent of choice. Other fluoroquinolones such as levofloxacin or moxifloxacin are alternative treatment options. Doxycycline, a PSI, was also shown to be efficacious in both treatment and prophylaxis.

For severe systemic disease without CNS involvement, the preferred regimen is a combination of two BA belonging to different classes, plus a PSI or RSI, however using only one BA plus a PSI or RSI may be sufficient, depending on clinical judgement.

If anthrax meningitis is suspected, a combination therapy composed by at least 3 agents with good CNS penetration (including at least one BA and one PSI) is recommended. Carbapenems (meropenem) and another class agent (doxycycline, linezolid or, in alternative, clindamycin or chloramphenicol) should be added to ciprofloxacin for at least 2 weeks. Rifampicin could be considered for its good synergistic effect if linezolid or clindamycin are not available. Penicillins can be considered for primary bactericidal activity but should be avoided before susceptibility is confirmed, because of the possibility of natural penicillin resistance, although rare. Antimicrobial drug susceptibility testing of isolates is essential, and the choice of the antibiotic regimen for treatment and prophylaxis of exposed should be guided, when possible, by the drug susceptibility test of the index case. Natural resistance of *Bacillus anthracis* strains exists against sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime, aztreonam, and ceftazidime. Therefore, these antibiotics should not be used in the treatment or prophylaxis of anthrax. Vancomycin is also an alternative option.

Intravenous combination therapy for two weeks or longer (intensive phase) is recommended for systemic anthrax. In a mass casualty setting, intravenous therapy may not be possible, and oral therapy may need to be used. After the intensive treatment phase, in case of inhalational exposure patients with compromised immune system and vulnerable populations such as children aged less than 18 years and pregnant women should transition to an oral post-exposure prophylaxis regimen that can be extended up to 60 days from onset of illness, due to the fact that some spores may stay dormant during the first onset of symptoms and may germinate later.

The duration of treatment for cutaneous anthrax is 7 to 10 days. (1-10)

Patients with systemic anthrax may also benefit from the addition of an antitoxin to the antimicrobial regimen, which prevents cellular toxin uptake and the formation of toxin complexes. The antibacterial regimen should always be combined with an antitoxin in severe anthrax with or without CNS involvement. Anthrax antitoxins may also be used to treat cutaneous anthrax if all recommended antimicrobial medicines are not available or not appropriate.

Among antitoxins, two monoclonal antibodies have so far been assessed by regulatory authorities in different jurisdictions, and are authorized in the US: obiltoxaximab and raxibacumab (licensed in the US as Anthim and Raxibacumab, respectively). Both monoclonals have been proven efficacious in animal studies, and are indicated in the US licence for the treatment of inhalational anthrax in all age groups, in combination with antibiotics. They can also be used for post-exposure prophylaxis when alternative options are not appropriate. Anthrax immunoglobulin intravenous are also licensed in the US. Post-licensure animal studies have shown that monoclonal antibodies were superior to anthrax immunoglobulins in terms of survival following aerosol exposure to *Bacillus anthracis*. (11-17)

Asymptomatic persons exposed to anthrax should immediately start antimicrobial post-exposure prophylaxis (PEP) for up to 60 days, whatever the vaccination status. Ciprofloxacin and doxycycline are the drugs of choice for PEP. (1-10)

Post-exposure immunisation can be considered in addition to antimicrobial prophylaxis, taking into account timing of administration in relation to exposure. Three anthrax vaccines currently exist that can be used for post-exposure prophylaxis. The Anthrax Vaccine Adsorbed (AVA, Biothrax or Bacithrax) is a subunit vaccine nationally authorised in some EU member states. AVA did not show interference when co-administered with raxibacumab, however, no data is available on co-administration of obiltoxaximab. The AVP vaccine, produced and licensed in UK, is a sterile filtrate of an alum

precipitated anthrax antigen in a solution for injection. Both vaccines have shown to be effective in protecting laboratory animals against inhalational anthrax. An Anthrax Vaccine Adsorbed Adjuvanted was recently approved by the FDA for post-exposure prophylaxis when administered with appropriate antibacterial drugs in adults. (5,15,18)

Recommended medicinal products for the treatment and prophylaxis of anthrax and their EU marketing authorisation status

Clinical indication	Medicinal products		EU MA status
Treatment of systemic anthrax with or without CNS involvement	**First line regimens**[4-7, 10-13, 19]		
	One or two of the following bactericidal agents (BAs) (if two agents, they must be from different classes) plus one of the following protein synthesis inhibitors (PSIs). An antitoxin can be combined with the antibacterial regimen.		All recommended antibiotics except minocycline IV are authorised at national level in MSs, some for different indications.
	Adults (≥18 years, >40 kg)	One or two BAs (if two they must be from different classes): <u>Carbapenems:</u> **Meropenem:** 2 g IV q8h for 14 days or longer, depending on clinical response. <u>Fluoroquinolones:</u> **Ciprofloxacin:** 400 mg IV q8h for 14 days or longer, depending on clinical response. **Levofloxacin:** 500 mg IV q8h for 14 days or longer, depending on clinical response. And one PSI: <u>Tetracyclines:</u> **Doxycycline:** 200 mg IV for 1 dose, then 100 mg IV q12h for 14 days or longer, depending on clinical response. **Minocycline:** 200 mg IV for 1 dose, then 100 mg IV q12h for 14 days or longer, depending on clinical response. In case of inhalational exposure, immunocompromised adults should transition to an oral post-exposure prophylaxis regimen for a total duration of treatment of 60 days from symptom onset (including the intensive phase). An antitoxin can be combined with the antibacterial regimen: **Obiltoxaximab:** 16 mg/kg IV once. Premedication with an antihistamine, e.g. diphenhydramine, is recommended 30 minutes prior to administration of obiltoxaximab.	
	Children (≥1 month to 18 years. For treatment recommendations in newborns consult CDC guidelines)	One or two BAs (if two they must be from different classes): <u>Carbapenems:</u> **Meropenem:** 40 mg/kg (max 2g/dose) IV q8h for 14 days or longer, depending on clinical response.	

		Fluoroquinolones*: **Ciprofloxacin:** 10 mg/kg (max 400 mg/dose) IV q8h for 14 days or longer, depending on clinical response. **Levofloxacin:** Body weight ≥50 kg: 750 mg IV q24h for 14 days or longer, depending on clinical response. Body weight <50 kg: 10 mg/kg (max 250 mg//dose) IV q8h for 14 days or longer, depending on clinical response. And one PSI: Tetracyclines*: **Doxycycline:** Body weight ≥45 kg: 200 mg IV loading dose, then 100 mg IV q12h for 14 days or longer, depending on clinical response. Body weight <45 kg: 2.2 mg/kg loading dose IV (max 200 mg/dose), then 2.2 mg/kg IV (maximum 100 mg/dose) q12h for 14 days or longer, depending on clinical response. **Minocycline:** 4 mg/kg IV (max 200 mg/dose) loading dose, then 2 mg/kg IV (max 100 mg/dose) q12h for 14 days or longer, depending on clinical response. In case of inhalational exposure, children should transition to an oral post-exposure prophylaxis regimen for a total duration of treatment of 60 days from symptom onset (including the intensive phase). An antitoxin can be combined with the antibacterial regimen: **Obiltoxaximab:** Body weight >40 kg: 16 mg/kg IV once Body weight >15 to 40 kg: 24 mg/kg IV once Body weight ≤15 kg: 32 mg/kg IV once Premedication with an antihistamine, e.g. diphenhydramine, is recommended 30 minutes prior to administration of obiltoxaximab.
	Pregnancy and lactation (≥18 years, >40 kg)	One or two BAs (if two they must be of different classes): Carbapenems: **Meropenem:** 2 g IV q8h for 14 days or longer, depending on clinical response. Fluoroquinolones*: **Ciprofloxacin:** 400 mg IV q8h for 14 days or longer, depending on clinical response. **Levofloxacin:** 500 mg IV q8h for 14 days or longer, depending on clinical response. And one PSI: Tetracyclines*: **Doxycycline:** 200 mg IV for loading dose, then 100 mg IV q12h for 14 days or longer, depending on clinical response. In case of inhalational exposure, pregnant women should transition to an oral post-exposure prophylaxis regimen for

		a total duration of treatment of 60 days from symptom onset (including the duration of IV treatment). An antitoxin can be combined with the antibacterial regimen: **Obiltoxaximab:** 16 mg/kg IV once. Premedication with an antihistamine, e.g. diphenhydramine, is recommended at least 30 minutes prior to administration of obiltoxaximab.	
	Notes	*In view of the life-threatening nature of the disease, and particularly for penicillin-resistant strains and when antimicrobial susceptibility tests are not yet available, the benefits of fluoroquinolones and tetracyclines for paediatric anthrax and for pregnant women are expected to overweigh the potential risks, including anticipated risks for the embryo/fetus in pregnancy.	
	Alternative regimens[4-7, 10-16, 19]		
	One or two of the following bactericidal agents (BAs) (if two agents, they must be from different classes) plus one of the following protein synthesis inhibitors (PSIs) or RNA synthesis inhibitors (RSIs). An antitoxin can be combined with the antibacterial regimen.		All recommended antibiotics are authorised at national level in MSs, some for different indications. Raxibacumab, and anthrax immune globulin are not authorised in the EU.
	Adults (≥18 years, >40 kg)	One or two BAs (if two they must be of different classes): Beta-lactams: **Penicillin G:** 4 MU IV q4h for 14 days or longer, depending on clinical response. **Ampicillin:** 2 g IV q4h for 14 days or longer, depending on clinical response. **Imipenem/cilastatin:** 1 g IV q6h for 14 days or longer, depending on clinical response. **Ampicillin/sulbactam:** 3 g IV q6h for 14 days or longer, depending on clinical response. **Piperacillin/tazobactam:** 4.5 g IV q6h for 14 days or longer, depending on clinical response. Fluoroquinolones: **Moxifloxacin:** 400 mg IV q24h for 14 days or longer, depending on clinical response. Glycopeptides: **Vancomycin:** 15 mg/kg IV q12h for 14 days or longer, depending on clinical response. Consider loading dose of 20-35 mg/kg for critically ill patients. And one PSI/RSI:	

		Clindamycin: 900 mg IV q8h for 14 days or longer, depending on clinical response. **Linezolid:** 600 mg IV q12h for 14 days or longer, depending on clinical response. **Rifampicin:** 600 mg IV q12h for 14 days or longer, depending on clinical response. **Chloramphenicol*:** 1 g IV q6-8h for 14 days or longer, depending on clinical response. An antitoxin can be combined with the antibacterial regimen: **Raxibacumab:** 40 mg/kg IV once. Remedication with diphenhydramine is recommended. **Anthrax immune globulin (Anthrasil):** 7 vials (420 units) IV once. Dose can be increased based on clinical severity.
	Children (≥1 month to 18 years. For treatment recommendations in newborns consult CDC guidelines)	One or two BAs (if two they must be of different classes): <u>Beta-lactams:</u> **Ampicillin:** 50 mg/kg (max 3 g) IV q6h for 14 days or longer, depending on clinical response. **Penicillin G:** 67.000/kg (max 4 MU/dose) IV q4h for 14 days or longer, depending on clinical response. **Imipenem/cilastatin:** 25 mg/kg (max 1 g/dose) IV q6h for 14 days or longer, depending on clinical response. **Ampicillin/sulbactam:** 50 mg/kg (ampicillin component, max 2 g/dose) IV q6h for 14 days or longer, depending on clinical response. <u>Fluoroquinolones**:</u> **Moxifloxacin:** ≥12 - ≤18 years and ≥45 kg: 400 mg IV q24h for 14 days or longer, depending on clinical response. ≥12 - ≤18 years and <45 kg: 4 mg/kg (max 200 mg/dose) q12h for 14 days or longer, depending on clinical response. 6 - <12 years: 4 mg/kg (max 200 mg/dose) q12h for 14 days or longer, depending on clinical response. 2 - <6 years: 5 mg/kg (max 200 mg/dose) IV q12h for 14 days or longer, depending on clinical response. ≥3 - ≤23 months: 6 mg/kg (max 200 mg/dose) IV q12h for 14 days or longer, depending on clinical response. <u>Glycopeptides:</u> **Vancomycin:** 20 mg/kg IV q8h for 14 days or longer, depending on clinical response. And one PSI/RSI: **Clindamycin:** 13.3 mg/kg (max 900 mg/dose) IV q8h for 14 days or longer, depending on clinical response. **Linezolid:** ≥12 years: 15 mg/kg IV (max 600 mg/dose) q12h for 14 days or longer, depending on clinical response.

		<12 years: 10 mg/kg (max 600 mg/dose) q8h for 14 days or longer, depending on clinical response. **Rifampicin:** 10 mg/kg (max 300 mg/dose) IV q12h for 14 days or longer, depending on clinical response. **Chloramphenicol*:** 25 mg/kg (max 1 g/dose) q6h for 14 days or longer, depending on clinical response. An antitoxin can be combined with the antibacterial regimen: **Raxibacumab:** >50 Kg body weight: 40 mg/kg IV once 15-50 kg body weight: 60 mg/kg IV once <15 Kg body weight: 80 mg/kg IV once Premedication with diphenhydramine is recommended. **Anthrax immune globulin (Anthrasil):** 1-7 vials (60-420 units) IV once based on patient weight. Dose can be increased based on clinical severity.
	Pregnancy and lactation (≥18 years, >40 kg)	One or two BAs (if two they must be of different classes): <u>Beta-lactams:</u> **Penicillin G:** 4 MU IV q4h for 14 days or longer, depending on clinical response. **Ampicillin:** 2 g IV q4h for 14 days or longer, depending on clinical response. **Imipenem/cilastatin:** 1 g IV q6h for 14 days or longer, depending on clinical response. **Ampicillin/sulbactam:** 3 g IV q6h for 14 days or longer, depending on clinical response. **Piperacillin/tazobactam:** 4.5 g IV q6h for 14 days or longer, depending on clinical response. <u>Fluoroquinolones**:</u> **Moxifloxacin:** 400 mg IV q24h for 14 days or longer, depending on clinical response. <u>Glycopeptides:</u> **Vancomycin:** 15 mg/kg IV q12h for 14 days or longer, depending on clinical response. Consider loading dose of 20-35 mg/kg for critically ill patients. And one PSI/RSI: **Clindamycin:** 900 mg IV q8h for 14 days or longer, depending on clinical response. **Linezolid:** 600 mg IV q12h for 14 days or longer, depending on clinical response. **Rifampicin:** 600 mg IV q12h for 14 days or longer, depending on clinical response. An antitoxin can be combined with the antibacterial regimen:

		There are data on the use of raxibacumab and anthrax immune globulin (Anthrasil) in pregnant and lactating women. Therefore, their use should be guided by clinical reasoning, and when other antitoxins are not available.	
	Notes	*Should not be used in combination with a bactericidal antimicrobial drug because the interaction might be antagonistic. **In view of the life-threatening nature of the disease, and in particular for penicillin-resistant strains of anthrax and when antimicrobial susceptibility tests are not yet available, the benefits of fluoroquinolones and tetracyclines for paediatric anthrax and for the treatment of pregnant women are expected to overweigh the potential risks, including the anticipated risks for the embryo/fetus in pregnancy.	
Treatment of cutaneous anthrax	**First line regimens**[4-6, 10-13, 19, 21]		
	Monotherapy with one of the following BA or PSI agents. An antitoxin can be used only when antibiotics are contraindicated or unavailable.		All recommended antibiotics are authorised at national level in MSs, some for different indications.
	Adults (≥18 years, >40 kg)	One of the following BA or PSI agents: **Doxycycline:** 100 mg PO q12h for 7-10 days. **Ciprofloxacin:** 500 mg PO q12h for 7-10 days. **Levofloxacin:** 750 mg PO q24h for 7-10 days. **Amoxicillin*:** 1 g PO q8h for 7-10 days. **Penicillin VK*:** 500 mg PO q6h for 7-10 days. In case of inhalational exposure, immunocompromised individuals should transition to an oral post-exposure prophylaxis regimen for a total duration of treatment of 60 days from symptom onset. An antitoxin can be used only when antibiotics are contraindicated or unavailable: **Obiltoxaximab:** 16 mg/kg IV once. Premedication with an antihistamine, e.g. diphenhydramine, is recommended 30 minutes prior to administration of obiltoxaximab.	
	Children (≥1 month to 18 years. For treatment recommendations in newborns consult CDC guidelines)	One of the following BA or PSI agents: **Ciprofloxacin**:** 15 mg/kg (max 500 mg/dose) PO q12h for 7-10 days. **Levofloxacin**:** Body weight ≥50 kg: 750 mg PO q24h for 7-10 days. Body weight <50 kg: 8 mg/kg (max 250 mg/dose) PO q12h for 7-10 days. **Doxycycline**:** ≥45 kg: 100 mg PO q12h for 7-10 days.	

		<45 kg: 2.2 mg/kg (max 100 mg/dose) PO q12h for 7-10 days. **Amoxicillin*:** 25 mg/kg (max 1 g/dose) IV q8h for 7-10 days. **Penicillin VK*:** 12.5–18.7 mg/kg (max 500 mg/dose) PO q6h for 7-10 days. **Amoxicillin/clavulanate:** ≥3 months: 22.5 mg/kg (amoxicillin component, max 875/125 mg/dose) PO q12h for 7-10 days. **Clindamycin:** 10 mg/kg (max 600 mg/dose) q8h for 7-10 days. In case of inhalational exposure, children should transition to an oral post-exposure prophylaxis regimen for a total duration of treatment of 60 days from symptom onset. An antitoxin can be used only when antibiotics are contraindicated or unavailable: **Obiltoxaximab:** Body weight >40 kg: 16 mg/kg IV once Body weight >15 - 40 kg: 24 mg/kg IV once Body weight ≤15 kg: 32 mg/kg IV once Premedication with an antihistamine, e.g., diphenhydramine, is recommended 30 minutes prior to administration of obiltoxaximab.
	Pregnancy and lactation (≥18 years, >40 kg)	One of the following BA or PSI agents: **Doxycycline**:** 100 mg PO q12h for 7-10 days. **Ciprofloxacin**:** 500 mg PO q12h for 7-10 days. **Levofloxacin**:** 750 mg PO q24h for 7-10 days. **Amoxicillin*:** 1 g PO q8h for 7-10 days. **Penicillin VK*:** 500 mg PO q6h for 7-10 days. In case of inhalational exposure, pregnant women should transition to an oral post-exposure prophylaxis regimen for a total duration of treatment of 60 days from symptom onset. An antitoxin can be used only when antibiotics are contraindicated or unavailable: **Obiltoxaximab:** 16 mg/kg IV once. Premedication with an antihistamine, e.g. diphenhydramine, is recommended 30 minutes prior to administration of obiltoxaximab.
	Notes	*Only for penicillin susceptible strains. **In view of the life-threatening nature of the disease, in particular for penicillin-resistant strains of anthrax and when antimicrobial susceptibility tests are not yet available, the benefits of therapy with fluoroquinolones and tetracyclines for paediatric anthrax and for the treatment of pregnant women are expected to overweigh the potential risks,

		including anticipated risks for the embryo/fetus in pregnancy.	
	Alternative regimens[4-6, 9-15, 18]		
	One of the following antibiotic regimens. An antitoxin can be used only when antibiotics are contraindicated or unavailable.		All recommended antibiotics are authorised at national level in MSs, some for different indications. Dalbavancin is authorised at EU level. Raxibacumab and anthrax immune globulin are not authorised in the EU.
	Adults (≥18 years, >40 kg)	One of the following BA or PSI agents: **Amoxicillin/clavulanate:** 1 g PO q12h for 7-10 days. **Moxifloxacin:** 400 mg PO q24h for 7-10 days. **Clindamycin:** 600 mg PO q8h for 7-10 days. **Ofloxacin:** 400 mg PO q12h for 7-10 days. **Linezolid:** 600 mg PO q12h for 7-10 days. **Dalbavancin:** 1.5 g IV once, followed by another 1.5 g IV one or two weeks afterwards as needed. **Meropenem:** 2 g IV q8h for 7-10 days. **Vancomycin:** 15 mg/kg IV q12h for 7-10 days. **Imipenem/cilastatin:** 1 g IV q6h for 7-10 days. An antitoxin can be used only when antibiotics are contraindicated or unavailable. **Raxibacumab:** 40 mg/kg IV once. Premedication with diphenhydramine is recommended. **Anthrax immune globulin (Anthrasil):** 7 vials (420 units) IV once. Dose can be increased based on clinical severity.	
	Children	One of the following BA or PSI agents: **Moxifloxacin*:** ≥12 - ≤18 years and ≥45 kg: 400 mg PO q24h for 7-10 days. ≥12 - ≤18 years and <45 kg: 4 mg/kg (max 200 mg/dose) PO q12h for 7-10 days. 6 - <12 years: 4 mg/kg (max 200 mg/dose) PO q12h for 7-10 days. 2 - <6 years: 5 mg/kg (max 200 mg/dose) PO q12h for 7-10 days.	

		≥3 - ≤23 months: 6 mg/kg (max 200 mg/dose) PO q12h for 7-10 days. **Ofloxacin*:** 11.25 mg/kg (max 400 mg/dose) PO q12h for 7-10 days. **Linezolid:** ≥12 years: 15 mg/kg (max 600 mg/dose) PO q12h for 7-10 days. <12 years: 10 mg/kg (max 600 mg/dose) PO q8h for 7-10 days. **Dalbavancin:** ≥6 years to <18 years: 18 mg/kg every (max 1.5 g/dose) IV once, followed by the same dose one or two weeks afterwards if needed. ≥3 months to <6 years: 22.5 mg/kg (max 1.5 g/dose) IV once, followed by the same dose one or two weeks afterwards if needed. **Meropenem:** 20 mg/kg (max. 2 g/dose) IV q8h for 7-10 days. **Imipenem/cilastatin:** 25 mg/kg (max. 1 g/dose) IV q6h for 7-10 days. **Vancomycin:** 20 mg/kg IV q8h for 7-10 days. An antitoxin can be used only when antibiotics are contraindicated or unavailable: **Raxibacumab:** >50 Kg body weight: 40 mg/kg IV once 15-50 kg body weight: 60 mg/kg IV once <15 Kg body weight: 80 mg/kg IV once Premedication with diphenhydramine is recommended. **Anthrax immune globulin (Anthrasil):** 1-7 vials (60-420 units) based on patient weight once IV. Dose can be increased based on clinical severity.
	Pregnancy and lactation (≥18 years, >40 kg)	One of the following BA or PSI agents: **Amoxicillin/clavulanate:** 1 gr PO q12h for 7-10 days. **Moxifloxacin*:** 400 mg PO q24h for 7-10 days. **Ofloxacin*:** 400 mg PO q12h for 7-10 days. **Clindamycin:** 600 mg PO q8h for 7-10 days. **Linezolid:** 600 mg PO q12h for 7-10 days. **Dalbavancin:** 1.5 g IV once, followed by another 1.5 g IV one or two weeks afterwards as needed. **Meropenem:** 2 g IV q8h for 7-10 days. **Vancomycin:** 15 mg/kg IV q12h for 7-10 days. **Imipenem/cilastatin:** 1 g IV q6h for 7-10 days.

		An antitoxin can be used when antibiotics are contraindicated: There are data on the use of raxibacumab and anthrax immune globulin (Anthrasil) in pregnant and lactating women. Therefore, their use should be guided by clinical reasoning, and when other antitoxins are not available.	
	Notes	*In view of the life-threatening nature of the disease, in particular for penicillin-resistant strains of anthrax and when antibacterial susceptibility tests are not yet available, the benefits of therapy with fluoroquinolones and tetracyclines for paediatric anthrax and for the treatment of pregnant women are expected to overweigh the potential risks, including the anticipated risks for the embryo/fetus in pregnancy.	
Post-exposure prophylaxis after inhalational exposure to anthrax	**First line regimens**[4-8, 11, 13, 19]		
	One of the following antibiotic post-exposure prophylaxis (PEP) regimens started as soon as possible in all exposed individuals. Unvaccinated persons aged 18-65 years should receive vaccination in addition to antibiotics*.		All recommended products except obiltoxaximab are authorised at national level in MSs, some for different indications.
	Adults (≥18 years, >40 kg)	Vaccination regimen*: **Anthrax Vaccine Adsorbed (Biothrax® or Bacithrax®):** 3 doses subcutaneously at 0-, 2- and 4-weeks post exposure. And one of the following antibiotic PEP regimens: **Doxycycline:** 100 mg PO q12h **Ciprofloxacin:** 500 mg PO q12h **Levofloxacin:** 750 mg PO q24h **Amoxicillin******:** 1 g PO q8h **Penicillin VK******:** 500 mg PO q6h Antibiotic PEP duration: 42 days in total after the 1st dose of vaccine. The duration is 60 days if antibiotics are given without vaccination, and for older (≥66 years) and immunocompromised individuals, regardless of vaccination. In case of unavailability of the first line antibiotic PEP regimens, the alternative antibiotic PEP regimens can be used. An antitoxin can be used only when antibiotics are contraindicated or unavailable: **Obiltoxaximab:** 16 mg/kg IV once. Premedication with an antihistamine, e.g. diphenhydramine, is recommended 30 minutes prior to administration of obiltoxaximab.	
	Children (≥1 month to 18 years.	Vaccination regimen*:	

	For treatment recommendations in newborns consult CDC guidelines)	The safety and effectiveness of Anthrax Vaccine Absorbed have not been established in the paediatric population*. And one of the following antibiotic PEP regimens: **Ciprofloxacin*****:** 15 mg/kg (max 500 mg/dose) PO q12h for 60 days. **Levofloxacin*****:** Body weight <50 kg: 8 mg/kg (max 250 mg/dose) PO q12h for 60 days. Body weight ≥50 kg: 750 mg PO q24h for 60 days. **Doxycycline*****:** <45 kg: 2.2 mg/kg (max 100 mg/dose) PO q12h for 60 days. ≥45 kg: 100 mg PO q12h for 60 days. **Amoxicillin****: 25 mg/kg (max 1 g/dose) IV q8h for 60 days. **Penicillin VK****: 12.5–18.7 mg/kg (max 500 mg/dose) PO q6h for 60 days. **Amoxicillin/clavulanate:** ≥3 months: 22.5 mg/kg (amoxicillin component, max 875/125 mg/dose) PO q12h for 60 days. **Clindamycin:** 10 mg/kg (max 600 mg/dose) q8h for 60 days. An antitoxin can be used only when antibiotics are contraindicated or unavailable: **Obiltoxaximab:** Body weight >40 kg: 16 mg/kg IV once Body weight >15 to 40 kg: 24 mg/kg IV once Body weight ≤15 kg: 32 mg/kg IV o Premedication with an antihistamine, e.g., diphenhydramine, is recommended 30 minutes prior to administration of obiltoxaximab.
	Pregnancy and lactation (≥18 years, >40 kg)	Vaccine regimen*: Pregnant women should not be vaccinated against anthrax with Anthrax Vaccine Adsorbed unless the potential benefits of vaccination have been determined to outweigh the potential risk to the fetus*. And one of the following antibiotic PEP regimens: **Doxycycline*****:** 100 mg PO q12h for 60 days. **Ciprofloxacin*****:** 500 mg PO q12h for 60 days. **Levofloxacin*****:** 750 mg PO q24h for 60 days. **Amoxicillin****: 1 g PO q8h for 60 days. **Penicillin VK****: 500 mg PO q6h for 60 days. An antitoxin can be used when antibiotics are contraindicated:

		Obiltoxaximab: 16 mg/kg IV once. Premedication with an antihistamine, e.g. diphenhydramine, is recommended 30 minutes prior to administration of obiltoxaximab.	
	Notes	*The safety and effectiveness of Anthrax Vaccine Absorbed have not been established in the paediatric population, pregnant women, and older adults (aged >65 years). However, vaccination of these populations may be considered, based on the data available at the time of an anthrax event and when clinically justified. **Only for penicillin susceptible strains. ***In view of the life-threatening nature of the disease, in particular for penicillin-resistant strains of anthrax and when antibacterial susceptibility tests are not yet available, the benefits of therapy with fluoroquinolones and tetracyclines for paediatric anthrax and for the treatment of pregnant women are expected to overweigh the potential risks, including the anticipated risks for the embryo/fetus in pregnancy.	
	Alternative regimens[4-7, 11-16, 17-20]		
	One of the following antibiotic post-exposure prophylaxis (PEP) regimens started as soon as possible in all exposed individuals. Unvaccinated adults should receive vaccination in addition to antibiotics.		All recommended antibiotics are authorised at national level in MSs, some for different indications. Dalbavancin is authorised at EU level. Anthrax Vaccine Adsorbed Adjuvanted (Cyfendus®), raxibacumab, and anthrax immune globulin are not authorised in the EU.
	Adults (≥18 years, >40 kg)	Vaccination regimen: **Anthrax Vaccine Adsorbed Adjuvanted (Cyfendus®):** two doses IM two weeks apart. And one of the first line antibiotic PEP regimens or one of the following antibiotic PEP regimens: **Amoxicillin/clavulanate:** 1 g PO q12h **Moxifloxacin:** 400 mg PO q24h **Clindamycin:** 600 mg PO q8h **Ofloxacin:** 400 mg PO q12h **Linezolid:** 600 mg PO	

		Dalbavancin: 1.5 g IV once, followed by another 1.5 g IV one or two weeks afterwards as needed. Antibiotic PEP duration: 42 to up to 60 days in case of vaccination, depending on schedule and available data on the immune response; 60 days if antibiotics are given without vaccination, and for older (≥66 years) and immunocompromised individuals, regardless of vaccination. An antitoxin can be used only when antibiotics are contraindicated or unavailable: **Raxibacumab:** 40 mg/kg IV once. Premedication with diphenhydramine. **Anthrax immune globulin (Anthrasil®):** 7 vials (420 units). Dose can be increased based on clinical severity.
	Children	Vaccination regimen*: The safety and effectiveness of Anthrax Vaccine Absorbed Adjuvanted have not been established in the paediatric population*. One of the following antibiotic PEP regimens: **Moxifloxacin****:** ≥12 to ≤18 years and ≥45 kg: 400 mg PO q24h for 60 days. ≥12 to ≤18 years and <45 kg: 4 mg/kg (max 200 mg/dose) PO q12h for 60 days. 6 to <12 years: 4 mg/kg (max 200 mg/dose) PO q12h for 60 days. 2 to <6 years: 5 mg/kg (max 200 mg/dose) PO q12h for 60 days. ≥3 to ≤23 months: 6 mg/kg (max 200 mg/dose) PO q12h for 60 days. **Ofloxacin****:** 11.25 mg/kg (max 400 mg/dose) PO q12h for 60 days. **Linezolid:** ≥12 years: 15 mg/kg (max 600 mg/dose) PO q12h for 60 days. <12 years: 10 mg/kg (max 600 mg/dose) PO q8h for 60 days. **Dalbavancin:** ≥6 years to <18 years: 18 mg/kg (max 1.5 g/dose) IV once, followed by the same dose one or two weeks afterwards if needed. ≥3 months to <6 years: 22.5 mg/kg (max 1.5 g/dose) IV once, followed by the same dose one or two weeks afterwards if needed. An antitoxin can be used only when antibiotics are contraindicated or unavailable: **Raxibacumab:** >50 Kg body weight: 40 mg/kg IV once 15-50 kg body weight: 60 mg/kg IV once <15 Kg body weight: 80 mg/kg IV once Premedication with diphenhydramine.

		Anthrax immune globulin (Anthrasil®): 1-7 vials (60-420 units) based on patient weight. Dose can be increased based on clinical severity.
	Pregnancy and lactation (≥18 years, >40 kg)	Vaccination regimen*: The safety and effectiveness of Anthrax Vaccine Absorbed Adjuvanted have not been established in the pregnant population*. One of the following antibiotic PEP regimens: **Amoxicillin/clavulanate:** 1 gr PO q12h for 60 days. **Moxifloxacin******:** 400 mg PO q24h for 60 days. **Ofloxacin******:** 400 mg PO q12h for 60 days. **Clindamycin:** 600 mg PO q8h for 60 days. **Linezolid:** 600 mg PO q12h for 60 days. **Dalbavancin:** 1.5 g IV once, followed by another 1.5 g IV one or two weeks afterwards as needed. **Meropenem:** 2 g IV q8h for 60 days. **Vancomycin:** 15 mg/kg IV q12h for 60 days. **Imipenem/cilastatin:** 1 g IV q6h for 60 days. An antitoxin can be used when antibiotics are contraindicated: **Raxibacumab:** No adequate and well controlled studies in pregnant women were conducted. Raxibacumab should be used during pregnancy only if clearly needed. **Anthrax immune globulin (Anthrasil®):** No data available in pregnant and lactating women.
	Notes	*The safety and effectiveness of Anthrax Vaccine Absorbed Adjuvanted have not been established in the paediatric population, pregnant women, and older adults (aged >65 years). However, vaccination of these populations may be considered, based on the data available at the time of an anthrax event and when clinically justified. **In view of the life-threatening nature of the disease, in particular for penicillin-resistant strains of anthrax and when antibacterial susceptibility tests are not yet available, the benefits of therapy with fluoroquinolones and tetracyclines for paediatric anthrax and for the treatment of pregnant women are expected to overweigh the potential risks, including anticipated risks for the embryo/fetus in pregnancy.

References

1. Hendricks K. et al., 'Clinical Features of Patients Hospitalized for All Routes of Anthrax, 1880-2018: A Systematic Review', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 75, S341–S353 2022

2. Person M.K. et al., 'Systematic Review of Hospital Treatment Outcomes for Naturally Acquired and Bioterrorism-Related Anthrax, 1880-2018', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 75, S392–S401 2022
3. Maxson T. et al., 'Systematic Review of In Vitro Antimicrobial Susceptibility Testing for Bacillus anthracis, 1947–2019', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 75, S373–S378 2022
4. Kennedy J.L. et al., 'Postexposure Prophylaxis and Treatment of Bacillus anthracis Infections: A Systematic Review and Meta-analyses of Animal Models, 1947-2019', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 75, S379–S391 2022
5. Bower W.A., 'CDC Guidelines for the Prevention and Treatment of Anthrax, 2023', MMWR Recomm. Rep. 72 2023
6. Bradley J.S. et al., 'Pediatric Anthrax Clinical Management', Pediatrics 133, e1411–e1436 2014
7. Meaney-Delman D. et al., 'Prophylaxis and Treatment of Anthrax in Pregnant Women: A Systematic Review of Antibiotics', Obstet. Gynecol. 122, 885–900 2013
8. Nolen L.D. et al., 'Postexposure Prophylaxis After Possible Anthrax Exposure: Adherence and Adverse Events', Health Secur. 14, 419–423 2016
9. Holty J.-E.C. et al., 'Systematic review: a century of inhalational anthrax cases from 1900 to 2005', Ann. Intern. Med. 144, 270–280 2006
10. Louie A. et al., 'Differential effects of linezolid and ciprofloxacin on toxin production by Bacillus anthracis in an in vitro pharmacodynamic system', Antimicrob. Agents Chemother. 56, 513–517 2012
11. Hesse E.M. et al., 'Antitoxin Use in the Prevention and Treatment of Anthrax Disease: A Systematic Review', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 75, S432–S440 2022
12. Slay R.M. et al., 'Pre- and Postlicensure Animal Efficacy Studies Comparing Anthrax Antitoxins', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 75, S441–S450 2022
13. EMA, 'Nyxthracis (previously Obiltoxaximab SFL) | European Medicines Agency', EMA 2024, available from: https://www.ema.europa.eu/en/medicines/human/EPAR/nyxthracis-previously-obiltoxaximab-sfl
14. FDA, 'Products Approved for Anthrax', FDA 2023, available from: https://www.fda.gov/drugs/bioterrorism-and-drug-preparedness/products-approved-anthrax
15. FDA, 'ANTHIM (obiltoxaximab) injection', FDA Prod. Inf. 2016, available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125509lbl.pdf
16. FDA, 'ANTHRASIL', FDA 2022, available from: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/anthrasil
17. Tournier J.-N. et al., 'Questionable Efficacy of Therapeutic Antibodies in the Treatment of Anthrax', mSphere 4, e00282-19 2019
18. FDA, 'CYFENDUS', FDA 2023, available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/cyfendus
19. D. N. Gilbert et al. (eds.), 'The Sanford guide to antimicrobial therapy 2023', 53rd edition., Antimicrobial Therapy, Inc, 2023.
20. FDA, 'Biothrax', FDA 2023, available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/biothrax
21. Gatti M. et al., 'Real-World Use of Dalbavancin in the Era of Empowerment of Outpatient Antimicrobial Treatment: A Careful Appraisal Beyond Approved Indications Focusing on Unmet Clinical Needs', Drug Des. Devel. Ther. 15, 3349–3378 2021

Plague (Yersinia pestis)

Disease characteristics and general points on treatment

Plague is a severe infectious disease caused by *Yersinia pestis*. The disease may present clinically as bubonic, septicaemic, or pneumonic plague. Rarely, meningeal and pharyngitic plague can occur, and atypical and non-specific presentations of infection have been reported. Plague occurs in several countries in Africa, Asia, South America, and the USA. Between 2010 and 2015, there were 3,248 cases reported worldwide. Humans usually become infected through the bite of an infected rodent flea or by handling an infected animal. In addition to rodents, occasionally dogs and cats can be reservoirs for human transmission. These forms of transmission normally lead to primary bubonic plague, which may evolve to septicaemic or pneumonic plague if untreated. Septicaemic plague can result in secondary pneumonic plague. Pneumonic plague can cause person-to-person transmission through respiratory droplets. Pneumonic and septicaemic forms of plague are expected to be the most common presentations in case of exposition to inhalation of a preparation of bacteria.

The incubation period of bubonic plague is usually 1 to 8 days, while the incubation period of pneumonic plague can be shorter (1 to 4 days). Septicaemic plague can occur within days after exposure. Bubonic plague usually manifests with fever, malaise and most commonly one (rarely more) swollen and painful lymph nodes. Septicaemic plague can develop from an untreated bubonic plague and manifests with fever, shock, abdominal pain, and internal and skin bleeding. Patients with pneumonic plague present with malaise, high fever, chills, coughs, myalgia and clinical signs of sepsis. Plague is a very serious illness with a rapid and commonly fatal progression. The mortality rate is influenced by the dose of inhaled bacilli, the time of treatment initiation and the availability of enhanced supportive care. Without early treatment, the death rate is above 90% for pneumonic and septicaemic plague, and around 40 to 60% for bubonic plague. A recent systematic review found that information on the clinical outcomes of plague treatments come essentially from case series; of 87 articles identified, only one was a randomised control trial and three were non-randomised comparisons. In this systematic review, the overall case-fatality ratio in treated patients was as low as 15%, highlighting the importance of early and appropriate antibiotic treatment. (1-6)

Streptomycin has historically been the preferred treatment but is no longer available everywhere. Gentamicin has also been used successfully and is currently recommended as first line therapy. Other antibiotics that have shown to be effective in clinical experience include tetracycline, doxycycline, chloramphenicol, and fluoroquinolones. A systematic review of aggregate-level antimicrobial treatment and outcome data of patient cohorts with plague showed that monotherapy with tetracyclines, chloramphenicol, and aminoglycosides displayed the lowest associated case fatality rates, especially among cases where treatment was initiated at a non-severe stage of the disease. However, in case of severe disease and/or after intentional release of *Y. pestis*, dual therapy with two distinct classes of antimicrobials should be used. In vitro studies suggest equivalent or greater activity of ciprofloxacin, levofloxacin, and ofloxacin against *Y. pestis* when compared with aminoglycosides or tetracyclines. Studies conducted in monkeys have shown that treatment with levofloxacin or ciprofloxacin was more efficacious than gentamicin and doxycycline. This evidence formed the basis to support the FDA approval of fluoroquinolones (levofloxacin, ciprofloxacin, and moxifloxacin) for the treatment and prophylaxis of plague, and fluoroquinolones are listed as first line agents for treatment and prophylaxis of plague in US CDC recommendations. Antimicrobials that have been shown to have poor or only modest efficacy in animal studies have included rifampicin, aztreonam, ceftazidime, cefotetan and cefazolin as well as third generation cephalosporines (despite in vitro activity); these antibiotics should not be used. Monotherapy with penicillins was also associated with the highest fatality rates in clinical case cohorts compared to other treatments. (4-9)

In case of plague meningitis, the preferred treatment option has historically been chloramphenicol, due to its good blood-brain barrier penetration and activity against *Y. pestis.* Levofloxacin and moxifloxacin also have good central nervous system penetration and activity against *Y. pestis,* so they could be considered for treatment of plague meningitis. However, no human controlled studies on their use are available. Nevertheless, combination therapies of chloramphenicol and levofloxacin or moxifloxacin should be considered for plague meningitis. If chloramphenicol is not available, a non-fluoroquinolone first-line or alternative antimicrobial, e.g. a tetracycline, can be used. (9, 12, 14)

Despite the fact that naturally occurring resistance to tetracyclines is rare, tetracycline and quinolone resistant strains of *Yersinia pestis* have been reported in the literature, including multidrug-resistant strains and an isolate resistant to all currently recommended antimicrobials. Resistance to antibiotics should be taken into account. Because of the mortality that could be anticipated with pneumonic plague a combination of two antimicrobial agents of different classes, e.g., gentamicin and ciprofloxacin, should be considered. Literature data have shown that combination therapies had lower fatality rates compared to monotherapies, but more data on combinations that include fluoroquinolones are needed to draw firm conclusions. There are no controlled studies showing the effect of a multiple drug approach to date. In the systematic review the most frequent combinations were streptomycin and sulphonamides or streptomycin and chloramphenicol. The duration of antibiotic therapy should be 10-14 days for all forms of plague, which may be extended based on the clinical condition. The clinical presentation, drug bioavailability and the ability to tolerate oral drugs should guide clinicians on the choice between oral or parenteral drugs. Patients who show evident clinical improvement can be switched to oral treatment after initial IV treatment and de-escalate to monotherapy. (3-6, 10, 11)

Common indications for post-exposure prophylaxis are unprotected exposure to pneumonic plague and to infected animals, intentional release of *Y. pestis,* and laboratory exposure. Routine pre-exposure prophylaxis for healthcare personnel is not recommended if standard and droplets precautions are maintained. However, it can be considered in case of shortages of PPE, overcrowding, and poor ventilation. (9, 12)

There are currently no approved vaccines against plague. A live *Y. pestis* EV vaccine, previously used with benefit in Madagascar, is used in Asia and Russia, but was never licensed in EU. Several vaccines candidates are currently under pre-clinical and clinical development. (15)

Recommended medicinal products for the treatment and prophylaxis of plague and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Pneumonic or septicaemic plague	**First line regimens**[5, 6, 8-10, 12-14, 16, 18-21]		
	Dual therapy with one fluoroquinolone and one aminoglycoside		All recommended antibiotics are authorised at national level in EU MSs, some for different indications. Streptomycin may not be available in some EU MSs.
	Adults (>18 years)	One fluoroquinolone:	

		Ciprofloxacin: 400 mg IV q8h IV or 750 mg PO q12h for 10-14 days or longer, depending on clinical response. **Levofloxacin:** 750 mg IV/PO q24h for 10-14 days or longer, depending on clinical response. **Moxifloxacin:** 400 mg IV/PO q24h for 10-14 days or longer, depending on clinical response. And one aminoglycoside: **Gentamicin:** 5 mg/kg IV/IM q24h for 10-14 days or longer, depending on clinical response. **Streptomycin:** 1 gr IV/IM q 12h for 10-14 days or longer, depending on clinical response.
	Children	One fluoroquinolone*: **Ciprofloxacin:** IV: 10 mg/kg every q8-12h (max 400 mg) for 10-14 days or longer, depending on clinical response. PO: 15 mg/kg every q8-12h (max 500 mg/dose q8h PO or 750 mg/dose q12h) for 10-14 days or longer, depending on clinical response. **Levofloxacin:** Body weight <50 kg: 8 mg/kg IV/PO q12h (maximum 250 mg/dose) for 10-14 days or longer, depending on clinical response. Body weight ≥50 kg: 500–750 mg IV/PO q24h for 10-14 days or longer, depending on clinical response. And one aminoglycoside: **Gentamicin:** 4.5–7.5 mg/kg IV/IM q24h for 10-14 days or longer, depending on clinical response. **Streptomycin:** 15 mg/kg every IV/IM q12h (maximum 1g/dose) for 10-14 days or longer, depending on clinical response.
	Pregnancy and lactation	**Gentamicin:** 5 mg/kg IV q24h for 10-14 days or longer, depending on clinical response. And one fluoroquinolone: **Ciprofloxacin******:** 400 mg IV q8h or 500 mg PO q8h for 10-14 days or longer, depending on clinical response. **Levofloxacin******:** 750 mg PO/IV q24h for 10-14 days or longer, depending on clinical response.
	Notes	*Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate. **Fluoroquinolones are not recommended in pregnant/breastfeeding women. However, their use should follow clinical judgment on potential benefit and anticipated risks.
	Alternative regimens[5, 6, 8-10, 12-14, 16-20]	
	One of the following antibiotic combination regimens:	All recommended

			antibiotics are authorised at national level in EU MSs, some for different indications. Chloramphenicol parenteral formulation may not be available in some EU MSs.
	Adults	A combination of two of the following regimens: **Doxycycline:** 200 mg PO/IV for 1 dose, then 100 mg PO/IV q12h for 10-14 days or longer, depending on clinical response. **Chloramphenicol:** 12.5-25 mg/kg IV q6h for 10-14 days or longer, depending on clinical response. **Trimethoprim-sulfamethoxazole:** 5 mg/kg (trimethoprim component) PO/IV q8h for 10-14 days or longer, depending on clinical response.	
	Children	A combination of two of the following regimens: **Doxycycline*:** Body weight ≥ 45 kg: 100 mg/kg q12h for 10 days. Body weight <45 kg: 4.4 mg/kg PO/IV loading dose, then 2.2 mg /kg PO/IV q12h for 10-14 days or longer, depending on clinical response. **Moxifloxacin*:** Age 12 to ≤17 years: Weight ≥45 kg: 400 mg IV/PO q24h for 10-14 days or longer, depending on clinical response. Weight <45 kg: 4 mg/kg IV/PO q12h (maximum 200 mg/dose) for 10-14 days or longer, depending on clinical response. Age 6 to 11 years: 4 mg/kg IV/PO q12h (maximum 200 mg/dose) for 10-14 days or longer, depending on clinical response. Age 2 to 5 years: 5 mg/kg IV/PO q12h (maximum 200 mg/dose) for 10-14 days or longer, depending on clinical response. Age ≥3 to ≤23 months: 6 mg/kg IV/PO q12h (maximum 200 mg/dose) for 10-14 days or longer, depending on clinical response. **Chloramphenicol:** 12.5-25 mg/kg IV q6h for 10-14 days or longer, depending on clinical response.	
	Pregnancy and lactation	A combination of two of the following regimens: **Moxifloxacin**:** 400 mg PO/IV q24h for 10-14 days or longer, depending on clinical response. **Doxycycline**:** 200 mg IV as 1 dose, then 100 mg IV q12h for 10-14 days or longer, depending on clinical response. **Trimethoprim-sulfamethoxazole:** 5mg/kg (trimethoprim component) PO/IV q8h for 10-14 days or longer, depending on clinical response.	

		The use of chloramphenicol is not recommended in pregnant/breastfeeding women. Use late in pregnancy has been associated with adverse effects in the neonate (i.e., grey baby syndrome). Chloramphenicol should be used during pregnancy only if the expected benefits outweigh the known risks to the fetus.	
	Notes	*Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate. Treatment of children <8 years with doxycycline can be justified in severe infections when alternatives are not available or appropriate. **Fluoroquinolones and tetracyclines are not recommended in pregnant/breastfeeding women. However, their use should follow clinical judgment on potential benefit and anticipated risks.	
Plague meningitis	**First line regimens**[9, 12-14, 16]		
	Combination therapy of chloramphenicol and a fluoroquinolone		All recommended antibiotics are authorised at national level in MSs, some for different indications. Chloramphenicol parenteral formulation may not be available in some EU MSs.
	Adults (>18 years)	**Chloramphenicol*:** 25 mg/kg IV q6h (max 1 g/dose) And one fluoroquinolone: **Levofloxacin:** 750 mg IV/PO q24h for 10-14 days or longer, depending on clinical response. **Moxifloxacin:** 400 mg IV/PO q24h for 10-14 days or longer, depending on clinical response. If chloramphenicol or fluoroquinolones are added to an existing regimen, duration of treatment is 10 days.	
	Children	**Chloramphenicol:** Age 29 days - 17 years: 25 mg/kg IV (max 1 g/dose) q6h for 10-14 days or longer, depending on clinical response. Age 8 - 28 days: 25 mg/kg/dose IV q12h for 10-14 days or longer, depending on clinical response. Age <7 days: 25 mg/kg/dose IV q24h for 10-14 days or longer, depending on clinical response. And one fluoroquinolone**: **Levofloxacin**:** Age ≥28 days - 17 years: Body weight 50 kg: 500-750 mg IV/PO q24h for 10-14 days or longer, depending on clinical response.	

		Body weight <50 kg: 8 mg/kg (max 250 mg/dose) IV/PO q12h for 10-14 days or longer, depending on clinical response. Age <28 days: 10 mg/kg IV q12h for 10-14 days or longer, depending on clinical response. **Moxifloxacin******:** Age 12 to ≤17 years: Weight <45 kg: 4 mg/kg IV/PO q12h (maximum 200 mg/dose) for 10-14 days or longer, depending on clinical response. Weight ≥45 kg: 400 mg IV/PO q24h for 10-14 days or longer, depending on clinical response. Age 6 to 11 years: 4 mg/kg IV/PO q12h (maximum 200 mg/dose) for 10-14 days or longer, depending on clinical response. Age 2 to 5 years: 5 mg/kg IV/PO q12h (maximum 200 mg/dose) for 10-14 days or longer, depending on clinical response. Age ≥3 to ≤23 months: 6 mg/kg IV/PO q12h (maximum 200 mg/dose) for 10-14 days or longer, depending on clinical response.	
	Pregnancy and lactation	The use of chloramphenicol is not recommended in pregnant/breastfeeding women. Use late in pregnancy has been associated with adverse effects in the neonate (i.e., grey baby syndrome). Chloramphenicol should be used during pregnancy only if the expected benefits outweigh the known risks to the fetus. And one fluoroquinolone***: **Levofloxacin:** 750 mg IV/PO q24h for 10-14 days or longer, depending on clinical response. **Moxifloxacin:** 400 mg IV/PO q24h for 10-14 days or longer, depending on clinical response.	
	Notes	*After clinical improvement, chloramphenicol can be reduced to a lower dose of 12.5 mg/kg q6h in adults and given orally. Serum concentration monitoring should be performed when available, especially in children. If chloramphenicol is not available, a first-line non-fluoroquinolone or alternative antimicrobial with CNS penetration, e.g. doxycycline, can be used. **Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate ***Fluoroquinolones are not recommended in pregnant/breastfeeding women. However, their use should follow clinical judgment on potential benefit and anticipated risks.	
Pre- and post-exposure prophylaxis	**First line regimens**[9, 12, 16, 17, 21]		
	One of the following antibiotic regimens		All recommended antibiotics are authorised at national level in MSs, some for

			different indications.
	Adults (>18 years)	One of the following regimens: **Ciprofloxacin:** 500-750 mg PO q12h for 7 days. **Levofloxacin:** 500-750 mg PO q24h for 7 days. **Moxifloxacin:** 400 mg PO q24h for 7 days. **Doxycycline:** 100 mg PO q12h for 7 days.	
	Children	One of the following regimens: **Ciprofloxacin*:** 15 mg/kg PO q12h (maximum 750 mg/dose) for 7 days. **Levofloxacin*:** Body weight ≥50 kg: 500–750 mg PO every q24h for 7 days. Body weight <50 kg: 8 mg/kg PO q12h (maximum 250 mg/dose) for 7 days. **Doxycycline*:** Body weight ≥45 kg: 100 mg PO q12h for 7 days. Body weight <45 kg: 2.2 mg/kg PO q12h for 7 days.	
	Pregnancy and lactation	One of the following regimens: **Ciprofloxacin**:** 500 mg PO q8h or 750 mg PO q12h for 7 days. **Levofloxacin**:** 750 mg PO q24h for 7 days.	
	Notes	*Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate. Treatment with tetracyclines in children <8 years is justified in severe infections when alternatives are not available or appropriate. **Fluoroquinolones are not recommended in pregnant/breastfeeding women. However, their use should follow clinical judgment on potential benefit and anticipated risks.	
	Alternative regimens[9, 12, 16, 17, 21]		
	One of the following antibiotic regimens:		All recommended antibiotics are authorised at national level in EU MSs, some for different indications.
	Adults	One of the following regimens: **Trimethoprim-sulfamethoxazole:** 5mg/kg (trimethoprim component) PO q12h for 7 days. **Tetracycline:** 500 mg PO q6h for 7 days.	
	Children	One of the following regimens: **Moxifloxacin*:** As per treatment regimen, for 7 days.	

		Trimethoprim-sulfamethoxazole: 5mg/kg (trimethoprim component) PO q12h for 7 days
	Pregnancy and lactation	One of the following regimens: **Moxifloxacin******:** 400 mg IV/PO q24h for for 7 days. **Doxycycline******:** 100 mg PO q12h for for 7 days. **Trimethoprim-sulfamethoxazole:** 5mg/kg (trimethoprim component) PO q12h for for 7 days.
	Notes	*Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate. **Fluoroquinolones and tetracyclines are not recommended in pregnant/breastfeeding women. However, their use should follow clinical judgment on potential benefit and anticipated risks.

References

1. Rajerison M. et al., 'Plague', in: Manson's Tropical Diseases, 24th ed., pp. 447–454, Elsevier, 2023
2. CDC, 'Bioterrorism and Plague: Preparedness', Plague 2024, available from: https://www.cdc.gov/plague/bioterrorism/index.html
3. Inglesby T.V. et al., 'Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense', JAMA 283, 2281–2290 2000
4. Sebbane F., N. Lemaître, 'Antibiotic Therapy of Plague: A Review', Biomolecules 11, 724 2021
5. Godfred-Cato S. et al., 'Treatment of Human Plague: A Systematic Review of Published Aggregate Data on Antimicrobial Efficacy, 1939-2019', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 70, S11–S19 2020
6. Bourner J. et al., 'A systematic review of the clinical profile of patients with bubonic plague and the outcome measures used in research settings', PLoS Negl. Trop. Dis. 17, e0011509 2023
7. Hewitt J.A. et al., 'The African Green Monkey Model of Pneumonic Plague and US Food and Drug Administration Approval of Antimicrobials Under the Animal Rule', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 70, S51–S59 2020
8. Layton R.C. et al., 'Levofloxacin cures experimental pneumonic plague in African green monkeys', PLoS Negl. Trop. Dis. 5, e959 2011
9. Nelson C.A. et al., 'Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response', MMWR Recomm. Rep. Morb. Mortal. Wkly. Rep. Recomm. Rep. 70, 1–27 2021
10. E. Carniel, B. J. Hinnebusch (eds.), 'Plague treatment and resistance to antimicrobial agents', in: Yersinia: systems biology and control, pp. 109–114, Caister Academic Press, 2012.
11. Kiefer D. et al., 'Phenotypical characterization of Mongolian Yersinia pestis strains', Vector Borne Zoonotic Dis. Larchmt. N 12, 183–188 2012
12. D. N. Gilbert et al. (eds.), 'The Sanford guide to antimicrobial therapy 2023', 53rd edition., Antimicrobial Therapy, Inc, 2023
13. WHO, 'WHO guidelines for plague management: revised recommendations for the use of rapid diagnostic tests, fluoroquinolones for case management and personal protective equipment for prevention of post-mortem transmission' 2024, available from: https://www.who.int/publications-detail-redirect/9789240015579
14. Cooley K.M. et al., 'Plague Meningitis: A Systematic Review of Clinical Course, Antimicrobial Treatment, and Outcomes', Health Secur. 21, 22–33 2023
15. Demeure C.E. et al., 'Yersinia pestis and plague: an updated view on evolution, virulence determinants, immune subversion, vaccination, and diagnostics', Genes Immun. 20, 357–370 2019
16. EMA, 'Ciprofloxacin Bayer - Art. 30 referral | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/referrals/ciprofloxacin-bayer
17. Stultz J.S., L.S. Eiland, 'Doxycycline and Tooth Discoloration in Children: Changing of Recommendations Based on Evidence of Safety', Ann. Pharmacother. 53, 1162–1166 2019
18. Hatala R. et al., 'Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis', Ann. Intern. Med. 124, 717–725 1996

19. Barza M. et al., 'Single or multiple daily doses of aminoglycosides: a meta-analysis', BMJ 312, 338–345 1996
20. Contopoulos-Ioannidis D.G. et al., 'Extended-interval aminoglycoside administration for children: a meta-analysis', Pediatrics 114, e111-118 2004
21. Yu P.A. et al., 'Safety of Antimicrobials During Pregnancy: A Systematic Review of Antimicrobials Considered for Treatment and Postexposure Prophylaxis of Plague', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 70, S37–S50 2020

Tularaemia (Francisella tularensis)

Disease characteristics and general points on treatment

Tularaemia is an infection caused by *Francisella tularensis*. Ulceroglandular tularaemia is the most common form of the disease and is usually a consequence of a bite from an arthropod vector (ticks, mosquitoes or deer flies) which has previously fed on an infected animal. The inhalation of dust or aerosols contaminated with the bacterium can lead to the occasional naturally occurring cases of inhalation tularaemia. This mode of transmission can result in pneumonic tularaemia, which is the most severe form of the disease. Additionally, humans can become infected by direct contact with infected animals and can contract oropharyngeal tularaemia through contaminated food or water. As few as 10 to 50 organisms can produce infection via the respiratory route but there has been no documented person-person transmission. The incubation period can range from 1 to 21 days but is usually only 3 to 5 days for primary pneumonia, the inhalation form of tularaemia. Symptoms of pneumonic tularaemia include fever, prostration, weight loss and respiratory complaints. The lung involvement can evolve to a systemic disease called typhoidal tularaemia, which can manifest with high fever, asthenia, myalgia and neurological symptoms (stupor, confusion and behavioural changes). In addition to classic forms of tularemia, *F. tularensis* can cause endocarditis, osteoarticular disease, peritonitis, encephalitis and meningitis. Disease prognosis and case fatality rate is influenced by the bacterium subspecies (*F. tularensis subspecies tularensis* being the most virulent), treatment timeliness and patients' immune status. For *F. tularensis subspecies tularensis* the case fatality rate without treatment ranges from 5 to 15% and decreases to 2% with adequate treatment. Other subspecies included those that are responsible for natural infection in the northern hemisphere are associated with lower mortality rates (below 1%) even in the pre-antibiotic era. (1,3)

Aminoglycosides are the drugs of choice for severe disease, and virtually all strains of F. tularensis are susceptible to streptomycin and gentamicin. Streptomycin has traditionally been the preferred aminoglycosides, however gentamicin is more readily available. Tetracyclines and chloramphenicol have been used successfully but are associated with higher relapse rates. Ciprofloxacin has been successfully used in clinical settings, and the bacteria are sensitive in vitro; however, data in patients with tularaemia are scarce. Treatment duration varies from 10 to 21 days according to the antimicrobial agent used. In the case of meningitis, combination therapy with doxycycline, ciprofloxacin or chloramphenicol is recommended, due to the poor penetration of aminoglycosides into the cerebrospinal fluid. Duration of treatment is 14 to 21 days. Many antibiotics, including all beta-lactam products, are ineffective for the treatment of F. tularensis infections. In vitro data indicate susceptibility to rifampicin, sulphonamides, and macrolides but there is a lack of clinical data to support a recommendation for clinical use. Post-exposure prophylaxis of tularaemia may be considered. Ciprofloxacin or doxycycline are generally recommended, but clinical data supporting these recommendations are scarce. Since human-to-human transmission is not known to occur, post-exposure prophylaxis is not recommended to close contacts. (4-10)

There is currently no approved vaccine for tularaemia.

Recommended medicinal products for the treatment and prophylaxis of tularaemia and their EU marketing authorisation status

Clinical indication	Medicinal products		EU MA status
Severe tularaemia	**First line regimen**[4, 5, 9, 11-20]		
	One of the following antibiotic regimens:		All recommended antibiotics are authorised at national level in MSs, some for different indications. Streptomycin may not be available in some EU MSs.
	Adults and children (≥12 years)	One of the following antibiotic regimens: **Gentamicin***: 5 mg/kg IV q24h for 10 days. **Streptomycin***: 1 gm IM q12h for 7 to 10 days. In the case of meningitis, the treatment duration is 14 to 21 days, and a combination with one of the following antibiotics is recommended: **Doxycycline:** 100 mg IV q12h for 14 to 21 days. **Ciprofloxacin:** 400 mg IV q12h for 14 to 21 days. **Chloramphenicol:** 15-25 mg/kg dose IV q6h for 14 to 21 days.	
	Children (<12 years)	One of the following antibiotic regimens: **Gentamicin****: 2.5 mg/kg IV/IM q8h or 5-7.5 mg/kg IV q24h for 10 days. **Streptomycin*:** 15 mg/kg IM q12h (max 2 g/day) for 7-10 days. In the case of meningitis, the treatment duration is 14 to 21 days, and a combination with one of the following antibiotics is recommended: **Doxycycline*****:** Weight ≥ 45 kg: 100 mg IV q12h for 14 days. Weight <45 kg: 2.2 mg/kg IV q12h (max. 200 mg/day) for 14 to 21 days. **Ciprofloxacin******:** 15 mg/kg IV q12h (max. 1 g/day) for 14 to 21 days. **Chloramphenicol:** 15 mg/kg IV q6h (max 4g/day) for 14 to 21 days.	
	Pregnancy and lactation	Treatment is the same as for non-pregnant. Aminoglycosides, tetracyclines, quinolones and chloramphenicol are not recommended in pregnant women. However, use should follow clinical judgment on potential	

		benefit and anticipated risks. Lactation should be discontinued if possible.
	Notes	*Dosing of aminoglycosides should be optimized to achieve a rapid attainment of therapeutic concentrations, as this has been correlated with improved patient outcomes. Moreover, dosing should be tailored to minimize drug toxicity. Different product labelling information may refer to different dosing strategies: intermittent dosing (q12h or q8h) or extended-interval dosing (q24h). The two dosing strategies have demonstrated comparable efficacy in a range of infections. However, extended-interval dosing offers the potential to possibly decrease nephrotoxicity, increase ease of administration and serum concentration monitoring. **There are limited data available on extended-interval dosing of gentamicin in children. However, extended interval dosing may be the preferred option in view of the potential decreased toxicity. ***Treatment of children <8 years with doxycycline is not recommended. However, it's use can be justified in severe infections when alternatives are not available or appropriate. ****Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate.
	Alternative regimens[4, 6-8, 11, 16-20]	
	Doxycycline or ciprofloxacin	Doxycycline and ciprofloxacin are authorised at national level in MSs, some for different indications.
	Adults	One of the following antibiotic regimens: **Doxycycline:** 100 mg IV q12h for 14 days. **Ciprofloxacin:** 400 mg IV q12h for 14 days.
	Children	One of the following antibiotic regimens: **Doxycycline*:** Weight ≥ 45 kg: 100 mg IV q12h for 14 days. Weight <45 kg: 2.2 mg/kg IV q12h (max. 200 mg/day) for 14 days. **Ciprofloxacin**:** 15 mg/kg IV q12h (max. 1 g/day) for 14 days.
	Pregnancy and lactation	One of the following antibiotic regimens: **Doxycycline:** 100 mg IV q12h for 14 to 21 days. **Ciprofloxacin:** 400 mg IV q12h for 14 days. Tetracyclines and quinolones are not recommended in pregnant women. However, use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.
	Notes	*Treatment of children < 8 years with doxycycline is not recommended. However, it's use can be justified in severe infections when alternatives are not available or appropriate.

		**Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate. Use of oral antibiotics may be necessary if the number of patients exceeds the medical care capacity for individual medical management.	
	Chloramphenicol (use only in case of unavailability of other treatments)		Authorised at national level in MSs.
	Adults	15-25 mg/kg dose IV q6h for 14 days.	
	Children	15 mg/kg IV q6h (max 4g/day) for 14 to days.	
	Pregnancy and lactation	Treatment is the same as for non-pregnant. Chloramphenicol use late in pregnancy has been associated with adverse effects in the neonate (i.e., grey baby syndrome), however use during pregnancy and breast-feeding should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	None	
Mild – moderate tularaemia	**First line regimen**[4, 6-8, 11, 16-20]		
	Doxycycline or ciprofloxacin		Doxycycline and ciprofloxacin are authorised at national level in MSs, some for different indications.
	Adults	One of the following antibiotic regimens: **Doxycycline:** 100 mg PO q12h for 14 days. **Ciprofloxacin:** 500 mg PO q12h for 14 days.	
	Children	One of the following antibiotic regimens: **Doxycycline*:** Weight ≥45 kg: 100 mg PO q12h for 14 days. Weight <45 kg: 2.2 mg/kg PO q12h (max. 200 mg/day) for 14 days. **Ciprofloxacin**:** 15 mg/kg IV q12h (max. 1 g/day) for 14 days.	
	Pregnancy and lactation	One of the following antibiotic regimens: **Doxycycline:** 100 mg PO q12h for 14 days. **Ciprofloxacin:** 500 mg PO q12h for 14 days. Tetracyclines and quinolones are not recommended in pregnant women. However, use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	*Treatment of children <8 years with doxycycline is not recommended. However, it's use can be justified in severe infections when alternatives are not available or appropriate.	

		**Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate.
Post-exposure prophylaxis	**First line regimen**[4, 11, 18-20]	
	Doxycycline and ciprofloxacin have been used for post-exposure prophylaxis with the same posology and population considerations as listed as for mild to moderate tularaemia treatment.	

References

1. ECDC, 'Tularaemia' 2012, available from: https://www.ecdc.europa.eu/en/tularaemia
2. Abdellahoum Z. et al., 'Tularemia as a Mosquito-Borne Disease', Microorganisms 9, 26 2020
3. Maurin M., M. Gyuranecz, 'Tularaemia: clinical aspects in Europe', Lancet Infect. Dis. 16, 113–124 2016
4. Dennis D.T. et al., 'Tularemia as a biological weapon: medical and public health management', JAMA 285, 2763–2773 2001
5. Pérez-Castrillón J.L. et al., 'Tularemia epidemic in northwestern Spain: clinical description and therapeutic response', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 33, 573–576 2001
6. Johansson A. et al., 'Ciprofloxacin for treatment of tularemia in children', Pediatr. Infect. Dis. J. 19, 449–453 2000
7. Johansson A. et al., 'Ciprofloxacin for treatment of tularemia', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 33, 267–268 2001
8. Aranda E.A., 'Treatment of tularemia with levofloxacin', Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis. 7, 167–168 2001
9. Ikäheimo I. et al., 'In vitro antibiotic susceptibility of Francisella tularensis isolated from humans and animals', J. Antimicrob. Chemother. 46, 287–290 2000
10. Maurin M. et al., 'Bactericidal Activities of Antibiotics against Intracellular Francisella tularensis', Antimicrob. Agents Chemother. 44, 3428–3431 2000
11. WHO, 'WHO Guidelines on tularaemia', World Health Organization, 2007
12. D. N. Gilbert et al. (eds.), 'The Sanford guide to antimicrobial therapy 2023', 53rd edition., Antimicrobial Therapy, Inc, 2023
13. Hatala R. et al., 'Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis', Ann. Intern. Med. 124, 717–725 1996
14. Barza M. et al., 'Single or multiple daily doses of aminoglycosides: a meta-analysis', BMJ 312, 338–345 1996
15. Contopoulos-Ioannidis D.G. et al., 'Extended-interval aminoglycoside administration for children: a meta-analysis', Pediatrics 114, e111-118 2004
16. EMA, 'Ciprofloxacin Bayer - Art. 30 referral | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/referrals/ciprofloxacin-bayer
17. Stultz J.S., L.S. Eiland, 'Doxycycline and Tooth Discoloration in Children: Changing of Recommendations Based on Evidence of Safety', Ann. Pharmacother. 53, 1162–1166 2019
18. Stier D.M., M.P. Mercer, 'Tularemia', in: B. W. Frazee et al. (eds.): Emergency Management of Infectious Diseases, 2nd ed., pp. 506–513, Cambridge University Press, 2018
19. Penn, Robert L., 'Tularemia: Clinical manifestations, diagnosis, treatment, and prevention - Uptodate Free' 2024, available from: https://pro.uptodatefree.ir/Show/3141
20. Kimberlin D.W. et al., 'Tularemia', in: Red Book (2021): Report of the Committee on Infectious Diseases, p. 822, American Academy of Pediatrics, 2021

Botulism (Clostridium botulinum toxin)

Disease characteristics and general points on treatment

Botulism is a serious disease characterized by progressive muscle paralysis caused by the botulinum neurotoxin produced by Clostridium botulinum. These bacteria are ubiquitous most commonly as spores and can be found in soil and agricultural products but rarely cause disease. However, multiple outbreaks are reported annually in the EU. The incubation period varies depending on the route of transmission, e.g. 12 to 48 hours for ingestion and 1 to 3 days for inhalation. The clinical presentation can be mild and is due to a descending flaccid paralysis with dysphagia, blurred vision, difficulty speaking, diplopia, shortness of breath, fatigue, ptosis among the most reported signs and symptoms that if untreated can evolve in a matter of days to respiratory failure. 5 to 10% of cases are fatal. (1-5)

Treatment involves supportive care and administration of botulinum antitoxin (BAT). BAT is the only specific symptomatic treatment for botulism. There are 2 different formulations of BAT, the trivalent equine-derived antitoxin that is a mixture of F(ab')2 immunoglobulin fragments raised against 3 botulinum toxin serotypes A, B and E, and the heptavalent equine-derived, a mixture of F(ab')2 immunoglobulin fragments that neutralizes the 7 botulinum neurotoxin serotypes A, B, C, D, E, F, G. These antibodies bind and neutralize botulinum neurotoxins in the bloodstream that have not yet irreversibly bound to synaptic receptors. BAT cannot reverse existing paralysis but can halt further progression. BAT should be administered as early as possible in the course of illness. Due to the sporadic nature of cases, studies to assess the efficacy in humans could not be carried out, so effectiveness has been established in animal models with evidence from observational studies that provide additional support. Currently, there are a few BATs under development, including one in the EU. (5-9)

To date there is no available vaccine to prevent or treat botulism.

These guidelines do not address the syndrome of infant botulism.

Recommended medicinal products for the treatment of botulism and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Botulism treatment of suspected or confirmed clinical cases	**First line regimen**[5, 6, 10-12]		
	Heptavalent botulinum antitoxin (BAT)		Not authorised in the EU.
	Adults (≥17 years)	One vial IV at a starting infusion rate (first 30 minutes) of 0.5 ml/min. Double the infusion rate if tolerated (every 30 minutes). Maximum infusion rate 2 mL/min.	
	Children (1 year - <17 years)	There is limited paediatric safety data available. Dosage is based on the Salisbury rule. 20 – 100% of adult dose of 0.01mL/kg/min IV (every 30 minutes). Maximum infusion rate 0.03mL/kg/min. **Do not exceed adult rate	
	Children (<1 year)	10% of adult dose regardless of body weight of 0.01mL/kg/min IV (every 30 minutes). Maximum infusion rate 0.03 mL/kg/min.	
	Pregnancy and lactation	Treatment is the same as for nonpregnant. The safety of BAT for use during pregnancy and breastfeeding has not been well established. Use should follow clinical	

		judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	Do not give a second dose unless progression or paralysis clearly continues and suspicion for botulism is high.	
	Alternative regimen[13]		
	Trivalent Botulinum Antitoxin (Antytoksyna botulinowa ABE) (limited data available on safety profile)		Authorised in Poland.
	Adults and children	50 ml to 100 ml IV or IM.	
	Pregnancy and lactation	The safety of trivalent botulinum antitoxin for use during pregnancy and breastfeeding has not been well established. Use, with extreme caution, should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	There is a mandatory allergy test before administration.	

References

1. WHO, 'Botulism' 2024, available from: https://www.who.int/news-room/fact-sheets/detail/botulism
2. CDC, 'Bioterrorism and Botulism: The Threat', Botulism 2024, available from: https://www.cdc.gov/botulism/bioterrorism/index.html
3. ECDC, 'Botulism' 2012, available from: https://www.ecdc.europa.eu/en/botulism
4. Bossi P. et al., 'Bichat guidelines for the clinical management of botulism and bioterrorism-related botulism', Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull. 9, 31–32 2004
5. Rao A.K., 'Clinical Guidelines for Diagnosis and Treatment of Botulism, 2021', MMWR Recomm. Rep. 70 2021
6. Mensa J., 'GUÍA DE TERAPÉUTICA ANTIMICROBIANA', 2023, EDITORIAL ANTARES, 2024.
7. ANR, 'Research on and generation of a decavalent equine Antitoxin counteracting deliberate botulinum neurotoxin attacks', Agence Natl. Rech. 2024, available from: https://anr.fr/Project-ANR-20-SEBM-0003
8. Shi D.-Y. et al., 'Characterization of a novel tetravalent botulism antitoxin based on receptor-binding domain of BoNTs', Appl. Microbiol. Biotechnol. 107, 3205–3216 2023
9. Rummel A. et al., 'Generation of an equine decavalent botulism antitoxin (X-BAT) counteracting deliberate attacks with botulism neurotoxin.', available from: https://www.sifo.de/sifo/shareddocs/Downloads/Poster_Innovationsforum-2022/Poster_10.pdf?__blob=publicationFile&v=3
10. FDA, 'Package Insert - Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) - (Equine)' 2016
11. AdisInsight Drugs, 'Botulinum antitoxin heptavalent - Emergent BioSolutions' 2008, available from: https://adisinsight.springer.com/drugs/800028586
12. Ni S., M. Brady, 'Botulism Antitoxin', StatPearls 2023
13. BIOMED, 'Package leaflet: information for the user of Botulinum antitoxin ABE' 2019, available from: https://biomed.com.pl/assets/ulotki/Botulina_ABE_ulotka.pdf

Smallpox (Variola major)

Disease characteristics and general points on treatment

Smallpox is a serious disease caused by *Variola major* virus and remains the only human disease to have been eradicated; however, there is concern that it could be intentionally released as a biological attack. Transmission is from person to person by infected aerosols and air droplets spread in face-to-face contact with an infected person. The virus can also be transmitted through contaminated objects such as clothing and bedding as well as direct contact with skin pustule lesions. The incubation period is 7 to 17 days with an average of 12 days and during this period individuals are asymptomatic. The clinical presentation is fever, malaise and after few days a rash appears in the face and forearms that within 24 hours spreads with a centrifugal distribution to all parts of the body. Lesions progress to papules, vesicles, and pustules that after days form scabs that leave permanent scars. Massive viral toxaemia could lead to multi-organ failure and in haemorrhagic cases, disseminated intravascular coagulation can occur. For the unvaccinated population, smallpox has high lethality ranging from 20% to 60% for the most severe forms. (1-6)

A few antivirals are available for the treatment of smallpox and other orthopoxvirus-caused diseases. Tecovirimat is an antiviral that inhibits VP37 (the product of the F13L gene), a highly conserved protein present in all orthopoxviruses, preventing the formation and egress of enveloped virions. Cidofovir, a nucleoside analogue with broad-spectrum activity against DNA viruses including poxviruses, is primarily used to treat cytomegalovirus retinitis. Brincidofovir is a lipid-conjugated prodrug of cidofovir, that inhibits DNA polymerase and acts as a nucleotide analogue of deoxycytidine monophosphate which can be incorporated into viral DNA hindering synthesis. Because smallpox is eradicated, studies to assess the effectiveness of antivirals in humans cannot be carried out, so effectiveness has been established with in-vitro studies and multiple animal models. Low barrier resistance to tecovirimat against mpox virus mutations has been demonstrated for some cases especially in patients who are immunocompromised. The combination of tecovirimat with brincidofovir resulted in synergistic efficacy against orthopoxvirus infections in vitro and in vivo. The use of tecovirimat, alone or in combination with vaccines, has been considered for pre-exposure and post-exposure prophylaxis, because the antiviral has shown to be highly protective against mortality in multiple orthopoxvirus animal models following lethal challenges, however there are no human clinical data to support its use in such settings. (7-13)

Before worldwide eradication, antivaccinial gamma-globulins obtained from animal sera and recently vaccinated individuals were used as prophylaxis and to treat few smallpox disease cases with apparent overall encouraging results though no clear association with benefit has been demonstrated. The vaccinia immune globulin (VIGIV) is an hyperimmune globulin indicated for treatment of certain complications of vaccinia vaccination with first generation vaccines. VIGIV might provide cross-protection across orthopoxviruses and has been used in combination with other medical countermeasures in immunosuppressed patients for the treatment of severe mpox disease. (14-16)

First and second-generation smallpox vaccines had an essential role in eradication; however, they were associated with risks of serious adverse events. Newer third generation vaccines have been developed which have a much-improved safety profile though evidence for efficacy is based on animal models and immunogenicity studies. Vaccination can be used either pre-exposure or post-exposure in populations at potential risk. There are currently very few third-generation smallpox vaccines available such as MVA-BN (Imvanex) approved in EU and LC16m8 approved in Japan. First and second-generation vaccines (e.g. Pourquier, RIVM, APSV, ACAM2000) have been recommended for use in the case where

third generation vaccines are not available nevertheless safety warnings and contraindications for some populations must be considered.

First-line responders should be vaccinated. Only staff with confirmed vaccination status should provide direct care to patients with suspected or confirmed smallpox. Evidence suggests that ring vaccination is the best strategy for containment, but most available information comes from vaccination campaigns in the 1970s with first generation vaccines.

Care for contacts of known smallpox cases should begin with post-exposure vaccination within 4 days regardless of symptoms to lessen severity and protection against a fatal outcome. (17-23)

Recommended medicinal products for the treatment of smallpox and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Smallpox	**First line regimen**[6-8, 11-13, 16, 24-26]		
	Tecovirimat		Oral presentation is authorised in the EU. IV presentation is not authorised in the EU.
	Adults	Oral regimen: Weight ≥120 kg: 600 mg PO q8h for 14 days. Weight 40 - <120 kg: 600 mg PO q12h for 14 days. Weight 25 - <40 kg: 400 mg PO q12h for 14 days. Weight 13 - <25 kg: 200 mg PO q12h for 14 days. IV regimen: Weight ≥120 kg 300 mg IV q12h for 14 days. Weight 35 kg to <120 kg 200 mg IV q12h for 14 days. Weight 3 - <35 kg 6 mg/kg IV q12h for 14 days.	
	Pregnancy and lactation	Tecovirimat is not recommended during pregnancy. The use of tecovirimat during pregnancy should be based on clinical judgment of potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	Capsule contents can be administered via a nasogastric tube. IV route is contraindicated in patients with severe renal impairment (creatinine clearance below 30mL/min). Good compliance is important to avoid resistances. Combination therapy with brincidofovir and/or immunoglobulins could be considered.	
	Alternative regimens[6, 8-12, 14-16, 27-32]		
	Brincidofovir		Not authorised in the EU.
	Adults and children	Weight ≥48 kg: 200 mg (20 ml) PO once weekly for two weeks (on days 1 and 8). Weight 10 - <48 kg: 4 mg/kg PO once weekly for two weeks (on days 1 and 8). Weight <10 kg: 6 mg/kg PO once weekly for two weeks (on days 1 and 8).	
	Pregnancy and lactation	Brincidofovir may cause fetal harm based on animal reproduction studies, an alternative therapy should be used if feasible. There is no data on the presence of brincidofovir in human milk, the effects of the drug on the breastfed infant, or on milk production. Precaution should be exercised.	

	Notes	None	
	Vaccinia Immunoglobulin Intravenous (VIGIV)		Not authorised in the EU.
	Adults	6000 U/kg IV at an infusion rate no greater than 2mL/min. 9000 U/kg IV may be considered if no response to initial treatment or in case of severe disease.	
	Children	Safety and effectiveness in paediatric population has not been established.	
	Pregnancy and lactation	It is not known whether VIGIV can cause fetal harm nor if it is excreted in human milk, however other immunoglobulins have been widely used during pregnancy. The risk/benefit of VIGIV administration should be assessed for each individual case.	
	Notes	Consideration may be given to repeat dosing depending on severity of symptoms and response to treatment. Contraindicated for use in the presence of isolated vaccinia keratitis. Doses up to 24,000 U/kg were shown to be safe in clinical trials. For patients with risk factors for thrombosis, the maximum daily dose of VIGIV should not exceed 12,000 U/kg	
	Cidofovir (use only in case of unavailability of other treatments)		Authorised at national level in MSs for different indications.
	Adults (≥18 years)	Induction treatment: 5 mg/kg IV once weekly for two consecutive weeks. Maintenance treatment: 5 mg/kg IV once every two weeks.	
	Children (≤17 years)	Cidofovir is not recommended for use in children because safety and efficacy have not been established; however, it has been used to treat adenovirus infection in high-risk populations at the standard doses listed below: Induction treatment: 5 mg/kg IV once weekly for two consecutive weeks. Alternatively, 1mg/kg 3 times a week for two consecutive weeks if any concern on renal dysfunction. Maintenance treatment: 5 mg/kg IV once every two weeks. Alternatively, 1mg/kg every two weeks if any concern on renal dysfunction.	
	Pregnancy and lactation	Cidofovir is not recommended during pregnancy. The use of cidofovir during pregnancy should be based on clinical judgment of potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	To minimize the potential for renal toxicity, patients must receive oral probenecid and hydration with normal saline concurrently with cidofovir.	
Pre-exposure and post-exposure prophylaxis	**First line regimen**[17, 21-23, 33]		
	Modified Vaccinia Ankara – Bavarian Nordic (MVA-BN)		Authorised at EU level.
	Adults (≥18 years)	2 doses of 0.5ml SC separated by 28 days (on days 1 and 28).	
	Children (<18 years)	Safety and efficacy in children below 18 years have not been established.	
	Pregnancy and lactation	The safety of MVA-BN for use during pregnancy and breastfeeding has not been well established. Use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	

	Notes	First dose should preferably be administered within 4 days post-exposure	
	Alternative regimen[17-20, 23, 34]		
	First and second-generation vaccines		Not authorised in the EU.
	Notes	There is risk for transmission of vaccinia virus from the inoculation site. Live vaccinia virus vaccines, although rare, can cause life-threatening conditions such as encephalitis or myopericarditis. From a biodefense standpoint these safety concerns would be of secondary importance to the need to break the chain of transmission quickly and efficiently. These vaccines are contraindicated for those who have conditions associated with immunosuppression, during pregnancy and lactation.	

References

1. Bossi P. et al., 'Bichat guidelines for the clinical management of smallpox and bioterrorism-related smallpox', Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull. 9, 25–26 2004
2. WHO, 'Smallpox' 2024, available from: https://www.who.int/health-topics/smallpox
3. CDC, 'Smallpox | CDC' 2019, available from: https://www.cdc.gov/smallpox/index.html
4. ECDC, 'Smallpox' 2017, available from: https://www.ecdc.europa.eu/en/smallpox
5. Nath A. et al., 'Smallpox complications', Lancet Neurol. 21, 874 2022
6. Margus C., '141 - Variola Major Virus (Smallpox) Attack', in: G. Ciottone (ed.): Ciottone's Disaster Medicine, 3rd ed., pp. 795–798, Elsevier, 2024
7. Grosenbach D.W. et al., 'Oral Tecovirimat for the Treatment of Smallpox', N. Engl. J. Med. 379, 44–53 2018
8. Rao A.K. et al., 'Interim Clinical Treatment Considerations for Severe Manifestations of Mpox - United States, February 2023', MMWR Morb. Mortal. Wkly. Rep. 72, 232–243 2023
9. De Clercq E., 'Cidofovir in the treatment of poxvirus infections', Antiviral Res. 55, 1–13 2002
10. Huston J. et al., 'Brincidofovir: A Novel Agent for the Treatment of Smallpox', Ann. Pharmacother. 57, 1198–1206 2023
11. Li P. et al., 'Preventing drug resistance: combination treatment for mpox', Lancet Lond. Engl. 402, 1750–1751 2023
12. Contag C. et al., 'Treatment of Mpox with Suspected Tecovirimat Resistance in Immunocompromised Patient, United States, 2022', Emerg. Infect. Dis. J. 29, 2520 2023
13. Russo A.T. et al., 'An overview of tecovirimat for smallpox treatment and expanded anti-orthopoxvirus applications', Expert Rev. Anti Infect. Ther. 19, 331–344 2021
14. Marennikova S.S., 'The use of hyperimmune antivaccinia gamma-globulin for the prevention and treatment of smallpox', Bull. World Health Organ. 27, 325–330 1962
15. Hobday T.L., 'Antivaccinial gamma-globulin in the control of smallpox', Lancet Lond. Engl. 1, 907–908 1962
16. Grosenbach D.W. et al., 'Emerging pharmacological strategies for treating and preventing mpox', Expert Rev. Clin. Pharmacol. 16, 843–854 2023
17. Sato H., 'Countermeasures and vaccination against terrorism using smallpox: pre-event and post-event smallpox vaccination and its contraindications', Environ. Health Prev. Med. 16, 281 2011
18. Kretzschmar M. et al., 'Ring Vaccination and Smallpox Control', Emerg. Infect. Dis. 10, 832–841 2004
19. Costantino V. et al., 'Modelling of optimal vaccination strategies in response to a bioterrorism associated smallpox outbreak', Hum. Vaccines Immunother. 17, 738–746 2021
20. Meyer H., 'Summary report on first, second and third generation smallpox vaccines' 2013
21. WHO, 'Multi-country outbreak of mpox, External Situation report # 17 - 2 March 2023' 2024, available from: https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report---17---2-march-2023
22. UK Health Security Agency, 'Smallpox and mpox (monkeypox): the green book, chapter 29', in: The Green Book, UK Health Security Agency, 2022
23. Kroger A.T. et al., '321 - Immunization', in: J. E. Bennett et al. (eds.): Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition), pp. 3516-3553.e5, W.B. Saunders, 2015
24. EMA, 'Tecovirimat SIGA - SPC | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tecovirimat-siga

25. CDC, 'Guidance for Tecovirimat Use | Mpox | Poxvirus | CDC' 2024, available from: https://www.cdc.gov/poxvirus/mpox/clinicians/Tecovirimat.html
26. FDA, 'Full prescribing information TPOXX' 2024, available from: https://www.accessdata.fda.gov/spl/data/70b3a765-cf50-476b-904d-0d272bcc8a72/70b3a765-cf50-476b-904d-0d272bcc8a72.xml
27. FDA, 'Full prescribing information TEMBEXA.', available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf
28. Emergent BioSolutions, 'Vaccinia Immunoglobulin Intravenous (Human) - Product Monograph.' 2018, available from: https://www.emergentbiosolutions.com/wp-content/uploads/2022/01/VIGIV-Canada-Monograph-English.pdf
29. CDC, 'Expanded Access IND Protocol: Use of Vaccinia Immune Globulin Intravenous (VIGIV, CNJ-016) for Treatment of Human Orthopoxvirus Infection in Adults and Children.' 2023, available from: https://www.cdc.gov/poxvirus/mpox/data/vigiv-protocol.pdf
30. EMA, 'Vistide | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vistide
31. Ganapathi L. et al., 'Use of cidofovir in pediatric patients with adenovirus infection', F1000Research 5, 758 2016
32. Verma A. et al., 'Use of cidofovir in recent outbreak of adenovirus-associated acute liver failure in children', Lancet Gastroenterol. Hepatol. 7, 700–702 2022
33. EMA, 'Imvanex | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/EPAR/imvanex
34. Kennedy R.B. et al., 'Smallpox Vaccines for Biodefense', Vaccine 27S4, D73–D79 2009

Viral haemorrhagic fevers

Viral haemorrhagic fevers (VHFs) are caused by viruses of four distinct families, but only filoviruses and arenaviruses are considered as agents that could be deliberately released.

Filoviruses

Viruses in the family *Filoviridae* can cause severe haemorrhagic fever in humans and non-human primates. Bats are considered the reservoir host and may spread the virus to other animals and humans. Filoviruses are enveloped, single-stranded, negative-sense RNA viruses in a lipid (fatty) membrane and appear in several shapes. The family *Filoviridae* includes, beside others, the following species: Ebola virus (Zaire ebolavirus), Sudan virus (Sudan ebolavirus), and Marburg viruses, which are each described separately below.

Ebola virus

Disease characteristics and general points on treatment

Fruit bats of the *Pteropodidae* family are thought to be natural reservoir of ebolaviruses, and epizootics in animals lead to spillover to humans. Unprotected contact with infected faeces, blood or aerosols from bats or other intermediate hosts like monkeys is considered the most likely routes of infection from animals to humans. Human-to-human transmission occurs via direct contact (broken skin or mucous membranes) with the blood and other body fluids (urine, saliva, faeces, vomit, breast milk, amniotic fluid, and semen) of infected people, or indirect contact with contaminated surfaces and materials such as clothing, bedding, and medical equipment. Symptomatic patients can spread the disease and remain infectious as long as their blood or other bodily fluids contain the virus, even after death. Ebolaviruses can persist in the testes, interior of the eyes, placenta, and central nervous system, and the cerebrospinal fluid after a cleared acute infection. The incubation period is 2 to 21 days. The symptom onset of Ebola virus disease can be abrupt with flu-like symptoms, like high fever, fatigue, muscle pain, headache, and sore throat. These are followed by severe nausea, vomiting, watery diarrhoea, rash, and in some cases haemorrhagic fever, including internal and external bleeding. In fatal cases, death occurs most often between 8 and 9 days after symptom onset, usually preceded by dehydration, jaundice, severe blood loss, delirium, shock, and multi-organ failure. After recovering from Ebola virus disease, some people may have sequelae for two years or longer. The estimated average case fatality rate of Ebola virus is around 50% and has varied from 25% to 90% in past outbreaks, depending on circumstances and case management. (1-2)

There are no approved therapeutics for Ebola virus disease in the EU. However, the monoclonal antibodies Inmazeb (atoltivimab, maftivimab, and odesivimab) and Ebanga (mAb114 (Ansuvimab)) are approved by the FDA and recommended by WHO for the treatment of Ebola virus disease. The approval was based on the results of the randomised controlled PALM trial conducted during the 2018 Ebola virus outbreak in the Democratic Republic of Congo. Results of the PALM trial showed that remdesivir and ZMap were inferior to the above-mentioned monoclonal antibodies, and it was not possible due to the lack of a control arm to determine if remdesivir or ZMap provide benefit, therefore treatment with remdesivir or ZMap is not recommended, unless monoclonal antibodies are not available. Early supportive care can improve survival. Treatment includes oral or intravenous fluids and electrolytes, maintaining oxygen status and blood pressure, replacing blood and clotting factors and medicines for any complication provided in the hospital. Menstrual suppression, e.g. with-hormonal contraceptives, in fertile-aged, infected women to prevent haemorrhagic complications could be considered. Use or steroids as additional therapy will be tested in clinical trials. (3-8)

For post-exposure prophylaxis, monoclonal antibodies could be considered for high-risk exposures, although there are limited clinical data in this respect. Concomitant vaccination with Ervebo® might be an option, however evidence even in NHPs models is conflicting and interference with the monoclonal antibodies cannot be excluded. Recent data from an observational study in the Democratic Republic of Congo indicate that vaccination with the VSV vaccine Ervebo® alone reduces the mortality in patients with confirmed Ebola virus disease. In case monoclonal antibodies and the VSV vaccine are not available, remdesivir may be considered. (9-11)

Two vaccines for active immunisation have been approved in the EU, Ervebo® and the two-dose heterologous vaccine regimen, which consists of a dose of Zabdeno® followed by a second dose with Mvabea® 8 weeks later. The approval of Ervebo® was based on a ring vaccination study during an Ebola outbreak in Guinea in 2016, which provided evidence that the vaccine could be used to contain outbreaks. The approval of the combination vaccine was based on extrapolation of protection achieved in a non-human primate challenge model. Due to the vaccination schedule of 8 weeks, this combination vaccine would only be suitable for pre-exposure prophylaxis outside an outbreak situation. (11-16)

Recommended medicinal products for the treatment of Ebola virus disease and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Treatment of infection caused by Ebola virus (zaire ebolavirus) in adult and paediatric patients, including neonates born to a mother who is RT-PCR positive for Ebola virus (zaire ebolavirus) infection	**First line regimens**[3-7]		
	Atoltivimab, maftivimab, and odesivimab-ebgn		Recommended monoclonal antibodies are not authorised in the EU.
	Adults and children	**Atoltivimab, maftivimab, and odesivimab-ebgn:** 50 mg/kg single IV over 2-4 hours depending on body weight.	
	Pregnancy and lactation	The safety of atoltivimab, maftivimab, and odesivimab-ebgn for use during pregnancy and breastfeeding has not been established. The use of atoltivimab, maftivimab, and odesivimab-ebgn should be based on clinical judgment of potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	None	
	Ansuvimab-zykl		Not authorised in the EU.
	Adults and children	50 mg/kg single IV over 60 minutes.	
	Pregnancy and lactation	The safety of ansuvimab-zykl for use during pregnancy and breastfeeding has not been established. The use of ansuvimab-zykl should be based on clinical judgment of potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	None	
	Alternative regimen[3-7]		
	Remdesivir (only in case of unavailability of monoclonal antibodies)		Authorised at EU level for different indications.
	Adults and children (>12 years)	Day 1: 200 mg single IV loading dose Day 2-5: 100 mg IV dose q24h	
	Pregnancy and lactation	The safety of remdesivir for use during pregnancy and breastfeeding has not been established. The use of remdesivir	

		should be based on clinical judgment of potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	None	
Post-exposure prophylaxis against ebola virus disease	**First line regimen**[4-6, 9-12, 15-17]		
	One of the following regimens.		Recommended monoclonal antibodies are not authorised in the EU. rVSVΔG-ZEBOV-GP is authorised at EU level.
	Adults and children	One of the following monoclonal antibody regimens: **Atolivimab, maftivimab and odesivimab-ebgn:** 50 mg per kg each single IV over 2-4 hours depending on body weight. **Ansuvimab-zykl:** 50 mg per kg IV single IV over 2-4 hours depending on body weight. Combination with VSV vaccine may be considered*: **rVSVΔG-ZEBOV-GP, live, attenuated:** Single 1 ml IM dose.	
	Pregnancy and lactation	The safety of these medicinal products for use during pregnancy and breastfeeding has not been established. The use of these medicinal products should be based on clinical judgment of potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	*Combination of monoclonal antibodies and the VSV vaccine may be considered. However, caution is advised as a potential interference between vaccine and the monoclonal antibodies cannot be excluded. Treatment should be started as soon as possible.	
	Alternative regimen[18, 19]		
	Remdesivir (only in case of unavailability of monoclonal antibodies)		Authorised at EU level for different indications.
	Adults and children (>12 years)	100 mg IV q24h for 5 days used in PREVAIL IV. Longer administration could be considered.	
	Pregnancy and lactation	The safety of remdesivir for use during pregnancy and breastfeeding has not been established. The use of remdesivir should be based on clinical judgment of potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	None	

Sudan virus

Disease characteristics and general points on treatment

Fruit bats of the *Pteropodidae* family are thought to be natural reservoir of Ebolaviruses, and epizootics in animals lead to spillover human cases. Unprotected contact with infected bat faeces or aerosols is considered the most likely routes of infection from the bat reservoir to humans. Human-to-human transmission occurs via direct contact (broken skin or mucous membranes) with the blood and other body fluids (urine, saliva, faeces, vomit, breast milk, amniotic fluid, and semen) of infected people, or indirect contact with contaminated surfaces and materials such as clothing, bedding, and medical equipment. Symptomatic patients can spread the disease and remain infectious as long as their blood

contains the virus, even after death. The incubation period ranges from 2-21 days. The symptom onset of Sudan virus (SUDV) infection can be abrupt with flu-like symptoms such as fever, fatigue, muscle pain, headache, and sore throat, followed by vomiting, diarrhoea, rash, and/or symptoms of impaired kidney and liver function. More severe illness can include internal and external bleeding, multiorgan failure, encephalopathy, respiratory distress, shock, and spontaneous abortion in pregnant women. The estimated case fatality ratios of Sudan virus disease have varied from 39% to 100% in past outbreaks, depending on circumstances and case management. (20)

There are no approved therapeutics and vaccines at present. Some antivirals, monoclonal antibodies and vaccines are currently in clinical development. The monoclonal antibody MBP134, remdesivir and the combination MBP134 + remdesivir are ready to be tested in clinical trials in case of an outbreak. A recent study in non-human primates reported that oral obeldesivir given for ten days one day post-challenge protected all five macaques from lethal SUDV infection. Shortening the dosing to five consecutive days was associated with a survival of 60% of the animals, however, rebound of SUDV occurred shortly after cessation of obeldesivir treatment. Based on these results, obeldesivir may potentially be investigated in future in clinical trials for the treatment SUDV, and potentially, based on its shown *in vitro* antiviral activity, also for EBOV and MARV. Early supportive care can improve survival. Treatment includes oral or intravenous fluids and electrolytes, maintaining oxygen status and blood pressure, replacing blood and clotting factors and medicines for any complication. Menstrual suppression, e.g. with-hormonal contraceptives, in fertile-aged, infected women to prevent haemorrhagic complications could be considered. Use or steroids as additional therapy will be tested in upcoming clinical trials. (21-24)

Three vaccines are ready to be tested in clinical trials in case of an outbreak: the bivalent adenovirus vectored vaccine (biEBOV) which consists of the replication-deficient simian adenovirus vector ChAdOx1 encoding two antigens: EBOV glycoprotein (Zaire) and SUDV glycoprotein (Sudan), the monovalent adenovirus vectored vaccines consisting of the simian adenovirus vector ChAd3 encoding the Sudan (SUDV) glycoprotein (ChAd3-SUDV) and the monovalent vaccine which consists of the vesicular stomatitis virus (VSV) as the backbone with the VSV-G gene replaced with the Ebola-GP gene from the Sudan strain (VSV-SUDV). (25)

Marburg virus

Disease characteristics and general points on treatment

Marburg virus (MARV) is a genetically unique, zoonotic RNA virus of the filovirus family, that can cause Marburg virus disease (MVD). MVD is a rare but severe haemorrhagic fever which affects both humans and non-human primates. The Egyptian fruit bat, *Rousettus aegyptiacus*, represent the animal reservoir for the Marburg virus. Infected fruit bats do not show obvious signs of illness. Unprotected contact with infected bat faeces or aerosols is considered the most likely routes of infection from the bat reservoir to humans. Once an individual is infected, human-to-human transmission occurs via direct contact (broken skin or mucous membranes) with the blood and other body fluids (urine, saliva, faeces, vomit, breast milk, amniotic fluid, and semen) of infected people, or indirect contact with contaminated surfaces and materials such as clothing, bedding, and medical equipment. Patients remain infectious as long as their blood, semen, breastmilk, or body fluids contain the virus, even after death. The incubation period is 2 to 21 days. The onset of MVD symptoms is abrupt, with flu-like symptoms like high fever, severe headache, chills, myalgia, prostration, and malaise. Rapid debilitation occurs within 2 to 5 days, with gastrointestinal symptoms such as anorexia, abdominal discomfort, severe nausea, vomiting, and watery diarrhoea. The intensity of the disease increases on days 5 to 7, with a maculopapular rash and symptoms of haemorrhagic fever, such as petechiae, mucosal and

gastrointestinal bleeding, and bleeding from venipuncture sites. Neurological symptoms (disorientation, agitation, seizures, and coma) can occur. Disseminated intravascular coagulation, lymphopenia and thrombocytopenia typically appear within a week after the disease onset. In fatal cases, death occurs most often between 8 and 9 days after symptom onset, usually preceded by dehydration, jaundice, severe blood loss, delirium, shock, and multi-organ failure. The average MVD case fatality rate is around 50%. Case fatality rates have varied from 24% to 88% in past outbreaks depending on circumstances and case management. (26)

There are no approved drugs and vaccines available at present. Some antivirals, monoclonal antibodies and vaccines are currently in clinical development. MPB091, a monoclonal antibody and remdesivir are developed as therapeutic options to treat MARV disease and could be entering clinical trials during outbreaks. Early supportive care can improve survival. Treatment includes oral or intravenous fluids and electrolytes, maintaining oxygen status and blood pressure, replacing blood and clotting factors and medicines for any complication provided in the hospital. Menstrual suppression, e.g. with-hormonal contraceptives, in fertile-aged, infected women to prevent haemorrhagic complications could be considered. Use or steroids as additional therapy will be tested in clinical trials. (27, 28)

In addition, several vaccines are developed against MARV of which the following are being tested in phase 1 and phase 2 clinical trials: CHAd3-MARV (in phase 2), ChAdOx1 Marburg (preclinical), rVSVΔG-MARV-GP (preclinical), multivalent filovirus vaccines Ad26.Filo and MVA-BN-Filo (Phase 1), rVSVΔG-MARV (Angola) GP (preclinical/Phase 1) and rVSVN4CT1-AMARV GP1 (Angola) (preclinical). (29-31)

References

1. Jacob S.T. et al., 'Ebola virus disease', Nat. Rev. Dis. Primer 6, 1–31 2020
2. Feldmann H. et al., 'Ebola', N. Engl. J. Med. 382, 1832–1842 2020
3. FDA, 'Inmazeb - full prescribing information.', available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761169s000lbl.pdf
4. WHO, 'BT-EB001 | WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control)' 2023, available from: https://extranet.who.int/prequal/medicines/bt-eb001
5. WHO, 'Therapeutics for Ebola virus disease' 2022, available from: https://www.who.int/publications-detail-redirect/9789240055742
6. FDA, 'Ebanga - full prescribing information' 2020, available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761172s000lbl.pdf
7. Mulangu S. et al., 'A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics', N. Engl. J. Med. 381, 2293–2303 2019
8. World Health Organization, 'Optimized supportive care for Ebola virus disease: clinical management standard operating procedures', World Health Organization, 2019.
9. Jaspard M. et al., 'Post-exposure prophylaxis following high-risk contact with Ebola virus, using immunotherapies with monoclonal antibodies, in the eastern Democratic Republic of the Congo: an emergency use program', Int. J. Infect. Dis. IJID Off. Publ. Int. Soc. Infect. Dis. 113, 166–167 2021
10. Moso M.A. et al., 'Prevention and post-exposure management of occupational exposure to Ebola virus', Lancet Infect. Dis. 24, e93–e105 2024
11. Coulborn R.M. et al., 'Case fatality risk among individuals vaccinated with rVSVΔG-ZEBOV-GP: a retrospective cohort analysis of patients with confirmed Ebola virus disease in the Democratic Republic of the Congo', Lancet Infect. Dis. 24, 602–610 2024
12. EMA, 'Ervebo | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/documents/product-information/ervebo-epar-product-information_en.pdf
13. EMA, 'Zabdeno | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/documents/product-information/zabdeno-epar-product-information_en.pdf

14. EMA, 'Mvabea | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/documents/product-information/mvabea-epar-product-information_en.pdf
15. Kucharski A.J. et al., 'Effectiveness of Ring Vaccination as Control Strategy for Ebola Virus Disease', Emerg. Infect. Dis. 22, 105–108 2016
16. Henao-Restrepo A.M. et al., 'Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)', Lancet Lond. Engl. 389, 505–518 2017
17. Bushmaker T. et al., 'Limited Benefit of Postexposure Prophylaxis With VSV-EBOV in Ebola Virus-Infected Rhesus Macaques', J. Infect. Dis. 228, S721–S729 2023
18. Warren T.K. et al., 'Remdesivir is efficacious in rhesus monkeys exposed to aerosolized Ebola virus', Sci. Rep. 11, 19458 2021
19. Higgs E.S. et al., 'PREVAIL IV: A Randomized, Double-Blind, 2-Phase, Phase 2 Trial of Remdesivir vs Placebo for Reduction of Ebola Virus RNA in the Semen of Male Survivors', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 73, 1849–1856 2021
20. Tsou T.-P., 'Sudan virus disease - A quick review', J. Formos. Med. Assoc. Taiwan Yi Zhi 123, 16–22 2024
21. Cross R.W. et al., 'Combination therapy with remdesivir and monoclonal antibodies protects nonhuman primates against advanced Sudan virus disease', JCI Insight 7, e159090 2022
22. WHO, 'Solidarity trials Core protocol: Randomized trial to evaluate the efficacy and safety of select therapeutic agents in the treatment of Ebola Disease' 2022, available from: https://cdn.who.int/media/docs/default-source/blue-print/solidarity_sudan-ebolavirus_treatment-protocol_webversion.pdf?sfvrsn=fbb613ff_3&download=true
23. Cross R.W. et al., 'Oral administration of obeldesivir protects nonhuman primates against Sudan ebolavirus', Science 383, eadk6176 2024
24. WHO, 'Optimized supportive care for Ebola virus disease: clinical management standard operating procedures', World Health Organization, 2019.
25. WHO, 'WHO Technical Advisory Group on candidate vaccine prioritization. Summary of the evaluations and recommendations on the three Sudan ebolavirus vaccines that are candidates for inclusion in the planned ring vaccination trial in Uganda ("Tokomeza Ebola")' 2022, available from: https://www.who.int/publications/m/item/core-protocol-a-phase-1-2-3-study-to-evaluate-the-safety-tolerability-immunogenicity-and-efficacy-of-vaccine-candidates-against-filoviruses-disease-in-healthy-individuals-at-risk-of-filovirus-disease
26. Kortepeter M.G. et al., 'Marburg virus disease: A summary for clinicians', Int. J. Infect. Dis. IJID Off. Publ. Int. Soc. Infect. Dis. 99, 233–242 2020
27. Mire C.E. et al., 'Therapeutic treatment of Marburg and Ravn virus infection in nonhuman primates with a human monoclonal antibody', Sci. Transl. Med. 9, eaai8711 2017
28. WHO, 'Optimized supportive care for Ebola virus disease: clinical management standard operating procedures', World Health Organization, 2019.
29. Guttman M., 'Sabin Vaccine Institute Begins Phase 2 Clinical Trial for Marburg Vaccine in Uganda', Sabin Vaccine Inst. - Press Release 2023, available from: https://www.sabin.org/resources/sabin-vaccine-institute-begins-phase-2-clinical-trial-for-marburg-vaccine-in-uganda/
30. WHO, 'Marburg virus vaccine landscape' 2023, available from: https://www.who.int/publications/m/item/marburg-virus-vaccine-landscape
31. Bockstal V. et al., 'First-in-human study to evaluate safety, tolerability, and immunogenicity of heterologous regimens using the multivalent filovirus vaccines Ad26.Filo and MVA-BN-Filo administered in different sequences and schedules: A randomized, controlled study', PloS One 17, e0274906 20

Arenaviruses

Arenaviruses can cause haemorrhagic syndromes with significant morbidity and mortality. Arenaviruses naturally occur in rodent reservoirs and spread to humans through contact with infected rodent blood, urine, and faeces, through inhalation of aerosolized faecal particles, direct contact, or contamination of food. Person-to-person and laboratory transmission can also occur, particularly in households and health care settings in the absence of adequate infection prevention and control measures. These viruses are classified in two groups based on their geographical location; Old World viruses occurring in the eastern hemisphere (e.g. Lassa virus) and New World viruses occurring in the western hemisphere (e.g. Machupo virus). There are growing concerns about Lujo virus, an Old World virus, as a potential threat, but it will not be discussed for the purposes of this guidance. (1-3)

Lassa virus and Machupo virus

Disease characteristics and general points on treatment

Lassa fever

Lassa fever is caused by Lassa virus endemic in West Africa, causing seasonal outbreaks. The majority of cases are reported by Nigeria, followed by Sierra Leone and Liberia; sporadic cases are reported across other countries in West Africa. The incubation period ranges from 2 to 21 days (average 10 days). About 80% of people who become infected with the Lassa virus have no symptoms or have mild flu-like symptoms and nausea, vomiting, abdominal pain, and diarrhoea. In severe cases, the condition of the patient rapidly deteriorates with acute kidney injury, anasarca, acute respiratory distress, encephalopathy, seizures, bleeding diathesis, organ failure and death. The overall case-fatality rate is 1%. Among patients with severe disease, case-fatality range from 15% to 30% and up to 35% for imported cases in non-endemic regions. The disease is severe late in pregnancy, with maternal death and/or foetal loss in more than 80% of cases during the third trimester. (1, 2, 4-6)

Bolivian Haemorrhagic Fever (BHF)

BHF is caused by Machupo virus endemic in Bolivia. Incubation period ranges from 5 to 19 days. Onset of clinical disease is insidious with fever and mild flu-like symptoms. Erythema, petechia and facial oedema are more common in BHF than other disease caused by New World arenaviruses. Approximately one third of patients develop severe neurological, cardiovascular, and haemorrhagic symptoms within a week of the prodromal phase. Mortality is estimated to be around 25%. (1, 2, 7)

Ribavirin is a nucleoside analogue that most closely resembles guanosine in structure. Its metabolites interfere with the capping and elongation of messenger RNA. It is active in-vitro against a wide range of DNA and RNA viruses. Ribavirin has been used for arenaviruses-caused disease treatment, however the quality of evidence is very low and safety concerns are increasing. In fact, a recent meta-analysis shows that its use for mild Lassa fever may lead to increased mortality, and it has been encouraged to reconsider its role and to support the evaluation of potential new therapeutics. Ribavirin is also used as post-exposure prophylaxis in case of high-risk exposure, however there is no evidence to support this indication. Favipiravir, a purine analogue, inhibits RNA polymerase activity reducing viral load and preventing viral transcription and replication. It was licensed in 2014 in Japan for treating influenza and has demonstrated efficacy against arenaviruses in animal models. The use of favipiravir combined with ribavirin for treatment of 2 cases of moderate Lassa fever has been reported. Considering also the safety profile, neither ribavirin nor favipiravir can be recommended without further evidence from controlled clinical trials.

Other small-molecule drugs and monoclonal antibodies are under evaluation to treat Lassa Fever and BHF such as LHF-535 and ARN-75039, which are already in clinical phases. The use of convalescent immune plasma from survivors has been utilized as treatment for BHF and other New World arenavirus, however no clinical trials have been completed and there has been no identification of a treatment time frame in which it would be protective. Immune plasma treatment of Lassa fever has not been as successful, and this may be related to the fact that neutralizing antibodies appear weeks after recovery and are generally of low titre and avidity. (8-20)

Currently there are no available vaccines against Lassa virus and Machupo virus, but several candidates are under development. Notably, a live-attenuated measles-Lassa virus (MV-LASV V182-001) and a vesicular stomatitis virus vectored vaccine (VSVΔG-LASV-GPC) are already in clinical phases. A live-attenuated vaccine against AHF is approved in Argentina and animal models suggest that this vaccine could be efficacious against Machupo virus. (9, 15, 21)

References

1. Ciottone G.R. et al., 'Viral Hemorrhagic Fever Attack', in: Ciottone's Disaster Medicine, 3rd Edition. 2024
2. Seregin A. et al., 'Lymphocytic Choriomeningitis Virus, Lassa Virus, and the South American Hemorrhagic Fevers (Arenaviruses)', in: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Ninth Edition, 9th ed., pp. 2177-2184.e2, Elsevier, ClinicalKey, 2020
3. ECDC, 'Facts about arenavirus' 2017, available from: https://www.ecdc.europa.eu/en/arenavirus-infection/facts
4. WHO, 'Lassa fever' 2024, available from: https://www.who.int/health-topics/lassa-fever
5. CDC, 'About Lassa Fever', Lassa Fever 2024, available from: https://www.cdc.gov/lassa-fever/about/index.html
6. Wolf T. et al., 'Fifty years of imported Lassa fever: a systematic review of primary and secondary cases', J. Travel Med. 27, 2020
7. Patterson M. et al., 'Epidemiology and pathogenesis of Bolivian hemorrhagic fever', Curr. Opin. Virol. 5, 82–90 2014
8. Kimberlin D.W., 'Antiviral Agents', in: Principles and Practice of Pediatric Infectious Diseases, 5th ed., pp. 1551–1567, Elsevier, ClinicalKey, 2024
9. Garry R.F., 'Lassa fever — the road ahead', Nat. Rev. Microbiol. 21, 87–96 2023
10. WHO, 'Clinical management of patients with viral haemorrhagic fever: A pocket guide for front-line health workers' 2016, available from: https://www.who.int/publications/i/item/9789241549608
11. Merson L. et al., 'Clinical characterization of Lassa fever: A systematic review of clinical reports and research to inform clinical trial design', PLoS Negl. Trop. Dis. 15, e0009788 2021
12. Raabe V.N. et al., 'Favipiravir and Ribavirin Treatment of Epidemiologically Linked Cases of Lassa Fever', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 65, 855–859 2017
13. Nigeria Center of Disease Control, 'National Guidelines for Lassa Fever Case Management - Nigeria | ReliefWeb' 2018, available from: https://reliefweb.int/report/nigeria/national-guidelines-lassa-fever-case-management
14. Bossi P. et al., 'Bichat guidelines for the clinical management of haemorrhagic fever viruses and bioterrorism-related haemorrhagic fever viruses', Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull. 9, 29–30 2004
15. Silva-Ramos C.R. et al., 'Bolivian hemorrhagic fever: A narrative review', Travel Med. Infect. Dis. 40, 102001 2021
16. ClinicalTrials.gov, 'Search for: Lassa Fever | Card Results | ClinicalTrials.gov' 2024, available from: https://clinicaltrials.gov/search?cond=Lassa%20Fever&page=2
17. Frank M.G. et al., 'South American Hemorrhagic Fevers: A summary for clinicians', Int. J. Infect. Dis. IJID Off. Publ. Int. Soc. Infect. Dis. 105, 505–515 2021
18. Salam A.P. et al., 'Ribavirin for treating Lassa fever: A systematic review of pre-clinical studies and implications for human dosing', PLoS Negl. Trop. Dis. 16, e0010289 2022
19. Eberhardt K.A. et al., 'Ribavirin for the treatment of Lassa fever: A systematic review and meta-analysis', Int. J. Infect. Dis. IJID Off. Publ. Int. Soc. Infect. Dis. 87, 15–20 2019
20. Salam A.P. et al., 'Time to reconsider the role of ribavirin in Lassa fever', PLoS Negl. Trop. Dis. 15, e0009522 2021
21. ClinicalTrials.gov, 'Search for: Lassa Fever, Other terms: vaccine | Card Results | ClinicalTrials.gov' 2024, available from: https://clinicaltrials.gov/search?cond=Lassa%20Fever&term=vaccine

Category B: Biological agents and medicinal products

Brucellosis (Brucella species)

Disease characteristics and general points on treatment

Brucellosis is a zoonotic infection caused by Brucella bacteria. Four species are pathogenic to humans: *B. melitensis* (the most pathogenic in humans and acquired mainly from goats and sheep), *B. suis* (swine are the principal host), *B. abortus* (cattle are the principal host) and *B. canis* (dogs are the principal host). Transmission can occur via direct or indirect contact with infected animals or with contaminated animal products (e.g., unpasteurized milk and dairy products) or by inhalation of aerosols. Person to person transmission does not usually occur. The incubation period varies from 5 days to 6 months, with an average of 1 to 2 months. The route of transmission does not influence the clinical presentation. Symptoms can appear acutely or insidiously and be very diverse. General constitutional symptoms (e.g. fever, night sweats, malaise, chronic fatigue, weight loss, body pain and arthralgias) may be accompanied by organ specific localizations (bone or joint infections, hepatitis, orchitis, endocarditis, ocular or nervous system involvement) and vary according to the duration of the infection at the time of clinical presentation. With adequate and timely treatment, the prognosis is generally good with low risk of relapse or chronic disease. Mortality is overall less than 2% to 5% and is usually the result of Brucella endocarditis or severe CNS involvement. (1-3)

For most presentations of the disease, a combination of doxycycline and rifampicin or an aminoglycoside is recommended as first line treatment of uncomplicated brucellosis in adults and children older than 8 years of age. A systematic review and meta-analysis of randomised trials in the treatment of brucellosis has concluded that the regimen doxycycline-streptomycin was superior to doxycycline-rifampicin in terms of relapse rate and combined relapse-treatment failure and could therefore be proposed as the regimen of choice, with the regimen doxycycline-rifampicin as an alternative. Comparable outcomes have been observed with doxycycline-streptomycin and doxycycline-gentamicin. Of note, the use of a regimen with parenteral administration may not always be the most advantageous option. Fluoroquinolones can penetrate intracellularly, and in vitro and in vivo clinical studies have been encouraging, showing that quinolones combined with rifampicin could also be considered as alternative to the above. Neurobrucellosis, osteoarticular brucellosis and brucella endocarditis could require surgical interventions and should be treated with a combination of 3 or more antibacterial drugs during long periods of time. Localized disease will not be discussed for the purposes of this guidance and specific guidelines should be consulted for more details. (3-8)

Antimicrobial post-exposure prophylaxis has been shown to prevent brucellosis in case of laboratory exposure and should be started within 24 weeks after a high-risk exposure. (9)

Some live attenuated vaccines are available for prevention of *Brucella abortus* and *Brucella melitensis* in animals (cattle, sheep and goats). There are no vaccines available for prevention of Brucella infections in humans.

Recommended medicinal products for the treatment and prophylaxis of brucellosis and their EU marketing authorisation status

Clinical indication	Medicinal products		EU MA status
Brucellosis	**First line regimen**[3-8, 10-12]		
	One of the following antibiotic regimens		All recommended antibiotics are authorised at national level in MSs, some for different indications. Streptomycin may not be available in some EU MSs.
	Adults	**Doxycycline:** 100 mg PO q12h for 6 weeks. And one of the following antibiotic regimens: **Gentamicin***: 5 mg/kg IV q24h for 7 days. **Streptomycin***: 15-40 mg/kg (max. 1 g) IV/IM q24h for 14-21 days. **Rifampicin:** 600-900 mg PO q24h for 6 weeks.	
	Children (≥8 years)	**Doxycycline:** Weight ≥45 kg: Same as adult regimen. Weight <45 kg: 2.2 mg/kg IV/OS q12h for 6 weeks. And one of the following antibiotic regimens: **Gentamicin****: 5 mg/kg IV q24h for 7 days. **Rifampicin:** 15-20 mg/kg (max 900 mg/day) PO divided in one or two doses for 6 weeks.	
	Children (<8 years)	**Trimethoprim-sulfamethoxazole:** 5 mg/kg (trimethoprim component) PO q12h for 6 weeks. **Rifampicin:** 15-20 mg/kg (max 900 mg/day) PO divided in one or two doses for 6 weeks.	
	Pregnancy and lactation	**Pregnancy ≥36 weeks:** Rifampicin 600-900 mg PO q24h for 4 weeks. **Pregnancy <36 weeks:** Trimethoprim-sulfamethoxazole 5 mg/kg (trimethoprim component) PO q12h for 4 weeks. Rifampicin 600-900 mg PO q24h for 4 weeks. The safety of trimethoprim-sulfamethoxazole and rifampicin for use during pregnancy and breastfeeding has not been well established. Use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	*Dosing of aminoglycosides should be optimized to achieve a rapid attainment of therapeutic concentrations, as this has been correlated with improved patient outcomes. Moreover, dosing should be tailored to minimize drug toxicity. Different product labelling information may refer to different dosing strategies: intermittent dosing (q12h or q8h) or an extended-	

		interval dosing (q24h). The two dosing strategies have demonstrated comparable efficacy in a range of infections. However, extended-interval dosing offers the potential to possibly decrease nephrotoxicity, increase ease of administration and serum concentration monitoring, reduce administration and monitoring related costs. **There are limited data available on extended-interval dosing of gentamicin in children. However, extended interval dosing may be the preferred option in view of the potential decreased toxicity.	
	Alternative regimen[5-7]		
	Ciprofloxacin and either doxycycline or rifampicin		All recommended antibiotics are authorised at national level in MSs, some for different indications.
	Adults	**Ciprofloxacin:** 500 mg PO q12h for 6 weeks. And one of the following antibiotics: **Doxycycline:** 100 mg PO q12h for 6 weeks. **Rifampicin:** 600-900 mg PO q24h for 6 weeks.	
	Children	None	
	Pregnancy and lactation	None	
	Notes	None	
Post-exposure prophylaxis	**First line regimen**[9-13]		
	One of the following antibiotic regimens:		All recommended antibiotics are authorised at national level in MSs, some for different indications.
	Adults	**Doxycycline:** 100 mg PO q12h for 3-6 weeks. **Rifampicin:** 600 mg PO q24h for 3-6 weeks.	
	Children (≥8 years)	**Doxycycline:** Weight ≥45 kg: same as adults. Weight <45 kg: 2.2 mg/kg OS q12h for 3-6 weeks. **Rifampicin:** 10-15 mg/kg (max 600 mg/day) PO divided in one or two doses for 3-6 weeks.	
	Children (<8 years)	**Trimethoprim-sulfamethoxazole:** 5 mg/kg (trimethoprim component) PO q12h for 3-6 weeks **Rifampicin**: 15-20 mg/kg (max 900 mg/day) PO divided in one or two doses for 3-6 weeks.	
	Pregnancy and lactation	**Trimethoprim-sulfamethoxazole:** 160 mg (trimethoprim component) PO q12h for 3-6 weeks. **Rifampicin:** 600-900 mg PO q24h for 3-6 weeks. The safety of trimethoprim-sulfamethoxazole and rifampicin for use during pregnancy and breastfeeding has not been well established. Use should follow clinical judgment on potential	

		benefit and anticipated risks. Lactation should be discontinued if possible. Pregnant women with high-risk exposures should be considered for PEP in consultation with their obstetricians.	
	Notes	Prophylaxis can be initiated up to 24 weeks after exposure.	
	Alternative regimen[9-13]		
	Trimethoprim-sulfamethoxazole and rifampicin		Trimethoprim-sulfamethoxazole and rifampicin are authorised at national level in MSs, some for different indications.
	Adults	**Trimethoprim-sulfamethoxazole:** 160 mg (trimethoprim component) PO q12h for 3-6 weeks. **Rifampicin:** 600-900 mg PO q24h for 3-6 weeks.	
	Children	None	
	Pregnancy and lactation	The safety of trimethoprim-sulfamethoxazole and rifampicin for use during pregnancy and breastfeeding has not been well established. Use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	Prophylaxis can be initiated up to 24 weeks after exposure. If exposure to B. abortus strain RB51 (resistant to rifampicin), use doxycycline alone or in combination with trimethoprim-sulfamethoxazole.	

References

1. ECDC, 'Brucellosis' 2010, available from: https://www.ecdc.europa.eu/en/brucellosis
2. Hoover D.L., A.M. Friedlander, 'Brucellosis', in: Medical Aspects of Chemical and Biological Warfare, pp. 513–521, Washington, DC: US Department of the Army, Surgeon General, and the Borden Institute, 1997
3. Bossi P. et al., 'Bichat guidelines for the clinical management of brucellosis and bioterrorism-related brucellosis', Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull. 9, 33–34 2004
4. Agalar C. et al., 'Ciprofloxacin and rifampicin versus doxycycline and rifampicin in the treatment of brucellosis', Eur. J. Clin. Microbiol. Infect. Dis. Off. Publ. Eur. Soc. Clin. Microbiol. 18, 535–538 1999
5. Solís García del Pozo J., J. Solera, 'Systematic review and meta-analysis of randomized clinical trials in the treatment of human brucellosis', PloS One 7, e32090 2012
6. Hasanjani Roushan M.R. et al., 'Efficacy of gentamicin plus doxycycline versus streptomycin plus doxycycline in the treatment of brucellosis in humans', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 42, 1075–1080 2006
7. D. N. Gilbert et al. (eds.), 'The Sanford guide to antimicrobial therapy 2023', 53rd edition., Antimicrobial Therapy, Inc, 2023
8. Khuri-Bulos N.A. et al., 'Treatment of childhood brucellosis: results of a prospective trial on 113 children', Pediatr. Infect. Dis. J. 12, 377–381 1993
9. Traxler R.M. et al., 'Review of brucellosis cases from laboratory exposures in the United States in 2008 to 2011 and improved strategies for disease prevention', J. Clin. Microbiol. 51, 3132–3136 2013
10. Hatala R. et al., 'Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis', Ann. Intern. Med. 124, 717–725 1996
11. Barza M. et al., 'Single or multiple daily doses of aminoglycosides: a meta-analysis', BMJ 312, 338–345 1996

12. Contopoulos-Ioannidis D.G. et al., 'Extended-interval aminoglycoside administration for children: a meta-analysis', Pediatrics 114, e111-118 2004
13. Ashford D.A. et al., 'Adverse events in humans associated with accidental exposure to the livestock brucellosis vaccine RB51', Vaccine 22, 3435–3439 2004

Q fever (Coxiella burnetii)

Disease characteristics and general points on treatment

Q fever is caused by the pleomorphic gram-negative, obligate intracellular bacteria *Coxiella burnetii. C. burnetii* is maintained in a large natural reservoir within mammals, birds, and arthropods. The organism is shed in urine, faeces, milk, placentas, and birth fluids from infected livestock. Person-to-person transmission has been reported but is believed to be extremely rare. *C. burnetii* is a highly infectious agent, resistant to heat, drying, and many common disinfectants, and has high innate airborne infectivity. Inhalation of a single particle is thought to be sufficient to cause clinical disease in some patients. Incubation period is 2 to 3 weeks. The most common clinical presentation is a nonspecific febrile illness with chills, malaise, myalgia, fatigue, anorexia, and headache. People who develop severe disease may experience pneumonia or hepatitis. Endocarditis, myocarditis, meningoencephalitis, and osteomyelitis occur in less than 1% of acute cases of Q fever. 1% to 5% of infected individuals progress to chronic Q fever, and of these, 60% to 73% develop an endocarditis. For pregnant individuals there is a risk for miscarriage, stillbirth, pre-term delivery, or low infant birth weight. The case-fatality rate of acute Q fever is only about 1% in untreated patients. Untreated chronic Q fever endocarditis is always fatal. Adequate antibiotic treatment reduces the mortality rate for Q fever endocarditis to <5%. (1-5)

Most of the cases of acute Q fever are asymptomatic and resolve spontaneously without specific treatment. Nevertheless, treatment can shorten the duration of illness and decrease the risk of complications such as endocarditis. All pregnant individuals with acute Q fever should be treated, even if asymptomatic. Doxycycline, a tetracycline antibiotic that inhibits bacterial growth is considered the drug of choice for acute Q fever. Macrolides, quinolones, and trimethoprim/sulfamethoxazole have also been shown to have effect. Acute Q fever in patients with high-risk of chronic disease, chronic Q fever and Q fever endocarditis should be treated with a combination of antibiotics for no less than 12 months. These guidelines do not address chronic Q fever treatment. Post-exposure prophylaxis can be considered in cases of suspected intentional release for at high-risk individuals and has proven to be effective if started 8 to 12 days after exposure. (6-10)

An inactivated whole cell vaccine (Q-VAX) is available. A single vaccination is 95% effective against aerosolized *C. burnetii*, and it offers protection for up to 5 years. It is licensed for use in Australia, but worldwide use is limited due to its reactogenic nature. (11)

Recommended medicinal products for the treatment and prophylaxis of Q fever and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Acute Q fever (except in case of meningoencephalitis)	**First line regimen**[5-9, 12]		
	Doxycycline		Authorised at national level in MSs.
	Adults	100 mg PO/IV q12h for 14 to 21 days.	
	Children (≥8 years and <8 years with severe disease and/or high-risk factors)	2.2 mg/kg PO/IV q12h (maximum 100 mg per dose) for 14 to 21 days.	
	Pregnancy and lactation	Tetracyclines are not recommended in pregnant/breastfeeding women. However, use should follow	

		clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	Treatment is most effective if given within the first 3 days of symptoms.	
	Alternative regimens[5-9, 13]		
	Trimethoprim-sulfamethoxazole		Authorised at national level in MSs for different indications.
	Adults (≥8 years, >40 kg)	160/800 mg PO/IV q12h for 14 to 21 days.	
	Children	8 – 12 mg/kg PO/IV q24h (based on trimethoprim) divided in 2 doses (maximum 320 mg/day) for 14 to 21 days.	
	Pregnancy and lactation	The safety of trimethoprim/sulfamethoxazole for use during pregnancy and breastfeeding has not been well established. Use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	Concomitant use of folic acid is recommended during pregnancy.	
	Clarithromycin		Authorised at national level in MSs for different indications.
	Adults and children (≥40 kg)	500 mg PO/IV q12h for 14 to 21 days.	
	Children (<40 kg)	7.5 mg/kg PO q12h (max 500 mg q12h). There is no data supporting intravenous use in children for 14 to 21 days.	
	Pregnancy and lactation	The safety of clarithromycin for use during pregnancy and breastfeeding has not been well established. Use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
Meningoencephalitis	**First line regimen**[6, 7, 9, 14]		
	Ciprofloxacin		Authorised at national level in MSs for different indications.
	Adults	400 mg IV or 500 mg PO q12h for 14 to 21 days.	
	Adolescents and children (≥ 5 years)	10-15 mg/kg PO or IV q12h (max 500 mg per dose) for 14 to 21 days.	
	Children (<5 years)	10 mg/kg PO or IV q12h for 14 to 21 days.	
	Pregnancy and lactation	Quinolones are not recommended in pregnant/breastfeeding women. However, use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	Use with caution in children due to potential risk of articular damage	
Post-exposure prophylaxis	**First line regimen**[6, 9, 10]		
	Doxycycline has been used for post-exposure prophylaxis with the same dosing and population considerations as listed as for treatment. However, the recommended duration is shorter, 5 to 7 days.		
	Alternative regimen[6, 9, 10]		
	Trimethoprim/Sulfamethoxazole has been used for post-exposure prophylaxis with the same dosing and population considerations as listed as for treatment. However, the recommended duration is shorter, 5 to 7 days.		

References

1. ECDC, 'Facts about Q fever' 2010, available from: https://www.ecdc.europa.eu/en/q-fever/facts
2. CDC, 'Signs and Symptoms of Q fever', Q Fever 2024, available from: https://www.cdc.gov/q-fever/signs-symptoms/index.html
3. Bryan D. et al., 'WHO/BS/2023.2456 WHO 1st International Standard for anti-Q Fever serum (human)' 2024, available from: https://www.who.int/publications/m/item/who-bs-2023.2456
4. Petri W.A., 'Q Fever - Infectious Diseases', MSD Man. Prof. Ed. 2022, available from: https://www.msdmanuals.com/professional/infectious-diseases/rickettsiae-and-related-organisms/q-fever
5. Cetaruk E.W., 'Coxiella burnetii (Q Fever) Attack', in: Ciottone's Disaster Medicine, 3rd ed., pp. 754–756, Elsevier, 2023
6. Bossi P. et al., 'Bichat guidelines for the clinical management of Q fever and bioterrorism-related Q fever', Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull. 9, 37–38 2004
7. Fariñas M.T.F., C.M. Collado, '[Infection by Coxiella burnetii (Q fever)]', Enferm. Infecc. Microbiol. Clin. 28 Suppl 1, 29–32 2010
8. Nunes-Silva C. et al., 'Guidelines for the Treatment and Follow-Up of Patients with Q Fever', Acta Med. Port. 35, 494–503 2022
9. Anderson A. et al., 'Diagnosis and management of Q fever--United States, 2013: recommendations from CDC and the Q Fever Working Group', MMWR Recomm. Rep. Morb. Mortal. Wkly. Rep. Recomm. Rep. 62, 1–30 2013
10. Moodie C.E. et al., 'Prophylaxis after Exposure to Coxiella burnetii', Emerg. Infect. Dis. 14, 1558–1566 2008
11. Sam G. et al., 'Q fever immunology: the quest for a safe and effective vaccine', NPJ Vaccines 8, 133 2023
12. Sovereign Medical, 'Summary of Product Characteristics DOXICLAT 100 mg Capsules [Spanish]' 2024, available from: https://cima.aemps.es/cima/dochtml/ft/50404/FT_50404.html
13. Almirall S.A., 'Summary of Product Characteristics SOLTRIM 160MG/ 800MG Powder for injection [Spanish]' 2024, available from: https://cima.aemps.es/cima/dochtml/ft/54920/FichaTecnica_54920.html
14. AEP, 'Ciprofloxacino | Asociación Española de Pediatría' 2020, available from: https://www.aeped.es/comite-medicamentos/pediamecum/ciprofloxacino

Epsilon toxin of Clostridium perfringens

Disease characteristics and general points on treatment

Clostridium perfringens is a Gram-positive, spore-forming, anaerobe bacillus which resides in water, soil, and in the gastrointestinal tracts of various mammals, including humans. The bacterium can produce different types of toxins which represent the most important virulence factor and have diverse mode of action. There are 7 toxinotypes (A-G) of *C. perfringens* based upon the production of one or more major protein toxins. The most important and lethal toxins are Alpha, Beta, Epsilon, Iota and enterotoxins. The Epsilon toxin (ETX) is the most potent of all *C. perfringens* toxins and is produced by *C. perfringens* types B and D, usual commensal of sheep and occasionally other herbivores and humans. Natural infections with ETX producing *C. perfringens* occur in livestock. Only few reports of human disease from ETX exist. The mechanism of action of ETX is mainly based on its ability to stimulate presynaptic neurons leading to excessive release of glutamate. In animals the disease manifests as an enterotoxaemia facilitated by an increased intestinal permeability that allows toxins, and subsequently bacteria, to spread via the systemic circulation from the gut to other organs, primarily brain, lungs, and kidneys. Of note, person-to-person transmission by respiratory route has not been shown. Inhalation of ETX can lead to high-permeability pulmonary oedema and haematogenous spread to the kidneys, heart, and CNS. Ataxia, weakness, dizziness, trembling, and seizures and eventually coma may represent the most important clinical signs and symptoms, due to the high affinity of the toxin with the CNS and the capacity to cause neurological stimulation. Other clinical manifestations may include respiratory irritation, cough, bronchospasm, dyspnoea, respiratory failure, tachycardia, cardiovascular collapse, nausea, vomiting, diarrhoea, severe abdominal cramping and distention, renal failure, and pancytopenia. Onset of illness is anticipated to be within 1 to 12 hours of exposure. Death can occur within 30 to 60 minutes of symptom onset in affected animals; therefore, a rapid fatal course could be expected also in humans. (1-4)

There are no vaccines, antitoxins, or specific treatment against ETX for humans and clinical management should rely on supportive care. ETX vaccines for use in sheep and goats are commercially available. They are constituted by toxoided *C. perfringens* type D culture filtrate usually with an aluminium hydroxide adjuvant. They are effective in preventing enterotoxaemia in animals; however, they elicit variable, and not always optimal, immune responses and can cause important inflammatory reactions. Therefore, since they are manufactured from relatively crude preparations of the toxin, they do not constitute good candidates for human use. Differently, recombinant vaccines against ETX, constituted by toxin subunits or mutants where several residues have been substituted to eliminate all toxin activity, seem to be the most appropriate and promising approach for a future human use. Other approaches under investigation are polyclonal and monoclonal antibodies targeting epitopes close of the pore-forming domains of the toxin and chemical inhibitors. (5-6)

In the event that *C. perfringens* is the biological agent disseminated, high dose penicillin (3 to 4 million units intravenously every four hours) and clindamycin (900 mg intravenously every eight hours) might be indicated, although a primary role for antibiotic therapy has not been established. The combination of penicillin and clindamycin is the most favourable based on animal models; clinical trials evaluating the efficacy of these agents in humans have not been performed. For patients with penicillin allergy, clindamycin can be used alone. (7-8)

References

1. Ciottone G. et al., 'Ciottone's Disaster Medicine', 3rd ed., Elsevier, 2023
2. Rood J.I. et al., 'Expansion of the Clostridium perfringens toxin-based typing scheme', Anaerobe 53, 5–10 2018

3. Popoff M.R., 'Epsilon toxin: a fascinating pore-forming toxin', FEBS J. 278, 4602–4615 2011
4. Stiles B.G. et al., 'Clostridium perfringens Epsilon Toxin: A Malevolent Molecule for Animals and Man?', Toxins 5, 2138–2160 2013
5. Titball R.W., 'Clostridium perfringens vaccines', Vaccine 27 Suppl 4, D44-47 2009
6. Robinson T.M. et al., 'Inhibition of Clostridium perfringens epsilon toxin by β-cyclodextrin derivatives', Int. J. Pharm. 531, 714–717 2017
7. Stevens D.L. et al., 'Comparison of single and combination antimicrobial agents for prevention of experimental gas gangrene caused by Clostridium perfringens.', Antimicrob. Agents Chemother. 31, 312–316 1987
8. D. N. Gilbert et al. (eds.), 'The Sanford guide to antimicrobial therapy 2023', 53rd edition., Antimicrobial Therapy, Inc, 2023

Glanders (Burkholderia mallei) and Melioidosis (Burkholderia pseudomallei)

Disease characteristics and general points on treatment

The causative agents of glanders and melioidosis are the non-fermenting gram-negative bacilli *Burkholderia mallei* and *Burkholderia pseudomallei*, respectively. Infections can result from percutaneous inoculation, inhalation, or ingestion. The probability of transmission from person to person is very low for melioidosis and only few cases are reported in the literature. However, glanders is a contagious disease transmitted from horses, its natural reservoir and host. The incubation period is influenced by strain virulence, mode of infection and presence of risk factors in the host usually range from 1 to 21 days. However, there have been well-documented cases in which the first clinical manifestations of infection have occurred years after exposure. Both diseases can have a protean clinical presentation, ranging from acute pneumonia and overwhelming sepsis to localised organ infections that can take a chronic course. It has been documented that over half of the patients can present with bacteraemia and up to one fifth develop septic shock. Both diseases may be fatal without treatment. However, since the large majority of patients presenting with naturally occurring infections have risk factors for the disease (such as diabetes mellitus, chronic pulmonary disease, chronic renal failure, alcoholism, glucocorticoid therapy and cancer) the fatality rate is expected to be lower in healthy individuals if effective antibiotic therapy is promptly initiated and intensive supportive care is available. (1, 2)

B. pseudomallei is inherently resistant to penicillin, ampicillin, first and second generation cephalosporins, aminoglycosides and polymyxins. The antibiotic susceptibility pattern profile of *B. mallei* resembles that of *B. pseudomallei* with the difference that *B. mallei* shows in vitro susceptibility to gentamicin. Both pathogens are usually susceptible *in vitro* to ceftazidime, imipenem, meropenem, doxycycline. There have been reports of high minimum inhibitory concentrations (MIC) of ciprofloxacin, moxifloxacin, ertapenem and tigecycline for some strains of *B. pseudomallei*. The MIC for doripenem has been shown to be similar to the one of imipenem. For *B. pseudomallei* resistance to carbapenems is yet to be documented and primary resistance to ceftazidime is very uncommon. However, treatment emergent resistance to ceftazidime can rarely appear. Primary resistance to trimethoprim-sulfamethoxazole is less uncommon. The possibility of genetic manipulation should be considered, and treatment recommendations should be adapted, when possible, to the in-vitro susceptibility tests of available isolates. The addition of trimethoprim-sulfamethoxazole to ceftazidime therapy during initial treatment of severe melioidosis did not reduce the acute mortality rate in two randomized clinical trials. There is little experience in treating glanders in humans. Treatment of glanders should follow the same recommendations for melioidosis. (1, 3–9)

Following successful initial therapy, a prolonged oral eradication course is recommended. Trimethoprim-sulfamethoxazole oral for 3-6 months is the drug of choice. An open label randomized controlled trial showed that 12 weeks of eradication therapy was not inferior to 20 weeks therapy in terms of overall mortality and composite of mortality and disease recurrence. Amoxicillin/clavulanic acid is to be considered in case of resistance or intolerance to trimethoprim-sulfamethoxazole and in pregnant women. There is no evidence of the protective efficacy of post-exposure antibiotic prophylaxis in preventing human melioidosis or glanders. However, following known exposure of people with risk factors, a 21-day regimen of trimethoprim-sulfamethoxazole or amoxicillin/clavulanic acid should be considered. (6, 10, 11)

Human vaccines are currently not available for either disease.

Recommended medicinal products for the treatment and prophylaxis of glanders and melioidosis and their EU marketing authorisation status

Clinical indication	Medicinal products		EU MA status
Melioidosis and glanders	**First line regimen**[1, 6, 9, 10, 12-15]		
	Initial IV therapy followed by oral eradication therapy		All recommended antibiotics are authorised at national level in MSs, some for different indications.
	Adults	Initial IV therapy: **Ceftazidime*:** 2 g IV q6-8h for 10 to 14 days. **Meropenem:** 1 g IV q8h. For CNS disease: 2 gm IV q8h for 10 to 14 days. **Imipenem:** 1 g IV q6h for 10 to 14 days. In case of bacteraemia and single or multiple lobe infiltrates, duration of treatment is 3 to 4 weeks. In case of osteoarticular or CNS disease duration of treatment is 4 to 8 weeks. Oral eradication therapy: **Trimethoprim-sulfamethoxazole:** 6-8 mg/kg (trimethoprim component) PO q12h for 3 to 6 months.	
	Children	Initial IV therapy: **Ceftazidime*** (age >2 months): 50 mg/kg IV q6-8h (max 6 g/day) for 10 to 14 days. **Meropenem** (age ≥3 months-11 years): 20-25 mg/kg IV q8h. For CNS disease: 40 mg/kg IV q8h for 10 to 14 days. **Imipenem** (age ≥1 year of age): 25 mg/kg IV q6h for 10 to 14 days In case of bacteraemia and single or multiple lobe infiltrates duration of treatment is 3 to 4 weeks. In case of osteoarticular or CNS disease duration of treatment is 4 to 8 weeks. Oral eradication therapy: **Trimethoprim-sulfamethoxazole:** 6-8 mg/kg (trimethoprim component) PO q12h for 3 to 6 months. **Amoxicillin-clavulanate:** 20mg/5mg/kg PO q8h for 3 to 6 months.	
	Pregnancy and lactation	Initial IV therapy: Same as for non-pregnant. Oral eradication therapy:	

		Amoxicillin-clavulanate: 20mg/5mg/kg PO q8h for 3 to 6 months. **Trimethoprim-sulfamethoxazole:** 6-8 mg/kg (trimethoprim component) PO q12h for 3 to 6 months. The safety of trimethoprim-sulfamethoxazole for use during pregnancy and breastfeeding has not been well established. Use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	*A switch to meropenem should be considered if clinical condition worsens, a new focus of infection develops, and repeated blood cultures are positive at 7 days of treatment. In case of mass casualty setting and for mild diseases oral therapy with trimethoprim-sulfamethoxazole and doxycycline could be considered.	
	Alternative regimen[1, 6, 8-10, 12-14]		
	Oral eradication therapy		All recommended antibiotics are authorised at national level in MSs, some for different indications.
	Adults (≥8 years, >40 kg)	**Amoxicillin-clavulanate:** 20mg/5mg/kg PO q8h for 3 to 6 months. **Doxycycline:** 100 mg PO q12h for 3 to 6 months.	
	Children	None	
	Pregnancy and lactation	None	
	Notes	For the treatment of glanders, gentamicin 5mg/kg once daily for 2 weeks plus oral trimethoprim-sulfamethoxazole 40/8 mg/kg/day continued for 2 weeks (or longer depending on response) could be considered in adults based on in-vitro susceptibility tests.	
Burkholderia pseudomallei post-exposure prophylaxis	**First line regimens**[11]		
	Amoxicillin-clavulanate		Authorised at national level in MSs for different indications.
	Adults and children	20mg/5mg/kg PO q8h for 21 days.	
	Pregnancy and lactation	20mg/5mg/kg PO q8h for 21 days.	
	Notes	None	
	Trimethoprim-sulfamethoxazole		Authorised at national level in MSs for different indications.
	Adults and children	6-8 mg/kg (trimethoprim component) PO q12h for 21 days.	
	Pregnancy and lactation	6-8 mg/kg (trimethoprim component) PO q12h for 21 days. The safety of trimethoprim-sulfamethoxazole for use during pregnancy and breastfeeding has not been well established. Use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	None	

References

1. Wiersinga W.J. et al., 'Melioidosis', N. Engl. J. Med. 367, 1035–1044 2012
2. Currie B.J. et al., 'The epidemiology and clinical spectrum of melioidosis: 540 cases from the 20 year Darwin prospective study', PLoS Negl. Trop. Dis. 4, e900 2010
3. Kenny D.J. et al., 'In Vitro Susceptibilities of Burkholderia mallei in Comparison to Those of Other Pathogenic Burkholderia spp.', Antimicrob. Agents Chemother. 43, 2773–2775 1999
4. Russell P. et al., 'Comparison of efficacy of ciprofloxacin and doxycycline against experimental melioidosis and glanders', J. Antimicrob. Chemother. 45, 813–818 2000
5. Harris P. et al., 'Comparative in vitro susceptibility of Burkholderia pseudomallei to doripenem, ertapenem, tigecycline and moxifloxacin', Int. J. Antimicrob. Agents 37, 547–549 2011
6. Chantratita N. et al., 'Antimicrobial resistance to ceftazidime involving loss of penicillin-binding protein 3 in Burkholderia pseudomallei', Proc. Natl. Acad. Sci. U. S. A. 108, 17165–17170 2011
7. Wuthiekanun V. et al., 'Survey of Antimicrobial Resistance in Clinical Burkholderia pseudomallei Isolates over Two Decades in Northeast Thailand ▿', Antimicrob. Agents Chemother. 55, 5388–5391 2011
8. Anunnatsiri S. et al., 'A Comparison Between 12 Versus 20 Weeks of Trimethoprim-sulfamethoxazole as Oral Eradication Treatment for Melioidosis: An Open-label, Pragmatic, Multicenter, Non-inferiority, Randomized Controlled Trial', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 73, e3627–e3633 2021
9. Cheng A.C. et al., 'Consensus guidelines for dosing of amoxicillin-clavulanate in melioidosis', Am. J. Trop. Med. Hyg. 78, 208–209 2008
10. The National Archives, 'Guidelines for Action in the Event of a Deliberate Release: Glanders & Melioidosis' 2008
11. Peacock S.J. et al., 'Management of Accidental Laboratory Exposure to Burkholderia pseudomallei and B. mallei', Emerg. Infect. Dis. 14, e2 2008
12. Sullivan R.P. et al., '2020 Review and revision of the 2015 Darwin melioidosis treatment guideline; paradigm drift not shift', PLoS Negl. Trop. Dis. 14, e0008659 2020
13. Chetchotisakd P. et al., 'Randomized, double-blind, controlled study of cefoperazone-sulbactam plus cotrimoxazole versus ceftazidime plus cotrimoxazole for the treatment of severe melioidosis', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 33, 29–34 2001
14. Chierakul W. et al., 'Two randomized controlled trials of ceftazidime alone versus ceftazidime in combination with trimethoprim-sulfamethoxazole for the treatment of severe melioidosis', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 41, 1105–1113 2005
15. EMA, 'Meronem - Art.30 referral | European Medicines Agency', available from: https://www.ema.europa.eu/en/medicines/human/referrals/meronem

Epidemic Typhus fever (Rickettsia prowazekii)

Disease characteristics and general points on treatment

Epidemic typhus is caused by an obligate gram-negative bacillus *Rickettsia prowazekii*, transmitted between humans through contact with infected body lice. Infected faeces are deposited on the skin and clothes and are introduced into the new host by scratching into the louse-bitten skin, by rubbing into mucous membranes or through inhalation. *R. prowazekii* is highly infectious, environmentally stable and known to remain virulent in louse faecal matter for several months. Crowding, extreme poverty, cold climate, and poor hygiene can lead to a high prevalence of louse infestation and ignite an epidemic. Incubation period ranges from 8 to 16 days. Common symptoms are headaches, fever, myalgias, and cough. The classic maculopapular, blanching rash starts on the trunk before spreading to the extremities. The face, palms, and soles are usually spared. Severe cases lead to marked delirium, vasculitis haemorrhagic rash, gangrene, coma, and death. The case fatality rate increases with age, being about 3% in infants, 30% in the 40 to 50 age group and 50% in elderly. (1-8)

Early and correct antibiotic therapy is estimated to reduce the need for hospitalization by 50% and mortality by 70% in developed settings. Doxycycline is considered the drug of choice for epidemic typhus for all individuals not allergic or not pregnant. Chloramphenicol is also effective. Antibiotics used for other pathogenic rickettsiae such as sulphonamides, macrolides or quinolones have not proven to be efficacious. The use of doxycycline 200 mg once weekly until risk exposure ends may be highly effective in interrupting typhus outbreaks, however there is very limited evidence. There is no vaccine available to prevent epidemic typhus. (3, 4, 7-12)

Recommended medicinal products for the treatment and prophylaxis of epidemic typhus fever and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Epidemic typhus	**First line regimen**[3, 4, 7, 8, 12]		
	Doxycycline		Authorised at national level in MSs.
	Adults and children (≥45kg)	100 mg PO/IV q12h for 5 to 7 days or until the patient has been afebrile for at least 48 hours. In chaotic circumstances a single dose of 200 mg for adults has been shown to be effective, although a small portion of patients may relapse.	
	Children (<45kg)	2.2 mg/kg PO/IV q12h (max. 100 mg per dose) for 5 to 7 days or until the patient has been afebrile for at least 48 hours.	
	Pregnancy and lactation	Tetracyclines are not recommended in pregnant/breastfeeding women. However, use should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	Treatment is most effective if given within the first 3 days of symptoms. Short courses of doxycycline can be used in children without causing dental staining or weakening tooth enamel, however, if treatment is longer, alternative treatment should be evaluated in children aged <8 years.	
	Alternative regimen[3, 7, 9-12]		

	Chloramphenicol		Authorised at national level in MSs.
	Adults	500mg IV q6h for 5 to 7 days.	
	Children (≥30 days)	12.5mg/kg IV q6h for 5 to 7 days (max. 500 mg per dose)	
	Neonates (<30 days)	>7 days, >2000g: 50mg/kg/day IV divided in 2 doses for 5 to 7 days. >7 days, ≤2000g: 25mg/kg/day IV q24h for 5 to 7 days. ≤7 days: 25mg/kg/day IV q24h for 5 to 7 days.	
	Pregnancy and lactation	Chloramphenicol use late in pregnancy has been associated with adverse effects in the neonate (i.e. grey baby syndrome), however use during pregnancy and breast-feeding should follow clinical judgment on potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	The use of oral chloramphenicol is not recommended.	

References

1. ECDC, 'Lice (Phthiraptera) - Factsheet for health professionals' 2022, available from: https://www.ecdc.europa.eu/en/all-topics-z/disease-vectors/facts/factsheet-lice-phthiraptera
2. CDC, 'Epidemic Typhus | Typhus Fevers | CDC', Typhus Fevers 2024, available from: https://www.cdc.gov/typhus/about/epidemic.html
3. Blanton L.S., D.H. Walker, 'Rickettsia prowazekii (Epidemic or Louse-Borne Typhus)', in: J. E. Bennett et al. (eds.): Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition), pp. 2217-2220.e1, W.B. Saunders, 2015
4. Smith D.M. et al., 'Rickettsia prowazekii Attack (Typhus Fever)', in: G. Ciottone (ed.): Ciottone's Disaster Medicine (Third Edition), pp. 757–758, Elsevier, 2024
5. WHO, 'Health aspects of chemical and biological weapons : report of a WHO group of consultants', Santé publique et armes chimiques et biologiques : rapport d' un Groupe de consultants de l' OMS 1970
6. Azad A.F., 'Pathogenic Rickettsiae as Bioterrorism Agents', Clin. Infect. Dis. 45, S52–S55 2007
7. Sexton D.J., M.T. McClain, 'Epidemic typhus', UpToDate 2022, available from: https://pro.uptodatefree.ir/Show/7905
8. Petri W.A., 'Epidemic Typhus - Infectious Diseases', MSD Man. Prof. Ed. 2024, available from: https://www.msdmanuals.com/professional/infectious-diseases/rickettsiae-and-related-organisms/epidemic-typhus
9. UpToDate, 'Chloramphenicol: Drug information' 2024, available from: https://pro.uptodatefree.ir/Show/9241
10. AEP, 'Cloranfenicol | Asociación Española de Pediatría' 2024, available from: https://www.aeped.es/comite-medicamentos/pediamecum/cloranfenicol
11. Drugs.com, 'Chloramphenicol Use During Pregnancy', Drugs.com 2024, available from: https://www.drugs.com/pregnancy/chloramphenicol.html
12. Vallano A., J.M. Arnau, 'Antimicrobianos y embarazo', Enfermedades Infecc. Microbiol. Clínica 27, 536–542 2009

Food and water safety threats

Salmonella

Disease characteristics and general points on treatment

Salmonellae are enterobacteria. One of the two *Salmonella* species, *Salmonella enterica subsp. Enterica* is spread by contaminated water and food. Of all existing serotypes, those which cause enteric fever are human-specific: *S.typhi* and *S. paratyphi.* However, also non-typhoidal *Salmonella* serovars can cause severe invasive disease in vulnerable individuals. (1-3)

The incubation period in infections due to the typhi serotype is normally 10 to 14 days (range 3 to 60 days). The incubation period for paratyphoid fever is usually shorter, 1 to 10 days.

When the disease is diarrhoeal (as in infections due to the non-typhi serotypes and occasionally also in typhoid fever) person-to-person spread occurs in poor hygiene situations and secondary cases are common. In infections due to the typhi and paratyphi serotypes, diarrhoea may or may not occur, but person-to-person spread from cases and carriers is still possible through the contact with infected faeces and urine. (1-4)

In typhoid and paratyphoid salmonellosis, and sometimes in salmonellosis due to other serotypes, the organism invades into the blood and the complications can include bowel perforation, generalised sepsis as well as localised infections in various organs and bones. Mortality rates in untreated cases of typhoid fever can reach 26%. (4)

Antibiotic treatment is routinely given for typhoid and paratyphoid salmonellosis and is sometimes necessary for other serotypes. Due to increasing resistance to the drugs that were traditionally used for the therapy of typhoid fever, the empiric treatment choice must be based on the epidemiology of the circulating Salmonella strains in the region where the disease was acquired. Most isolates from South and Southeast Asia are resistant to fluoroquinolones and often resistant to trimethoprim-sulfamethoxazole, third generation cephalosporins, ampicillin and chloramphenicol. A large-scale emergence and spread of XDR *S. typhi* (resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones and third generation cephalosporins) has been reported since 2016 in Pakistan. Ideally, definitive antimicrobial therapy for enteric fever should be based on results of susceptibility testing. For drug-susceptible disease, fluoroquinolones are the treatment of choice. For fluoroquinolones non-susceptible infections, azithromycin, third generation cephalosporins and carbapenems are the alternative options. Patients with uncomplicated disease with no evidence of systemic toxicity can be treated with oral therapy. For patients with severe disease, therapy with a parenteral agent should be considered. (5-8)

Vaccines against typhoid fever are nationally authorised in all EU member states for pre-exposure prophylaxis. Two types of vaccines are available: the oral live attenuated vaccine (Ty21a) three-dose regimen (Vivotif®) and the purified Vi polysaccharide vaccine given intramuscularly (Typhim Vi®). No vaccines for *S. paratyphi* or invasive non-typhoidal Salmonella are currently authorised, but a few are under development (9-10).

Recommended medicinal products for the treatment of Salmonella enteric fever and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Treatment of typhoid and paratyphoid enteric fever without signs of complication (GI manifestations only)	**First line regimen**[4, 6, 7]		
	One of the following antibiotic regimens according to confirmed or expected antimicrobial susceptibility.		All recommended antibiotics are authorised at national level in MSs, some for different indications.
	Adults	One of the following antibiotics: **Ciprofloxacin:** 500 mg PO q12h for 7-10 days. **Ofloxacin:** 400 mg PO q12h for 7-10 days. **Azithromycin:** 1 g PO as 1 dose, then 500 mg PO q24h for 5-7 days. **Ceftriaxone:** 2 g IV q24h for 7-14 days.	
	Children	One of the following antibiotics: **Azithromycin:** 10-20 mg/kg PO q24h (max 1 g/day) for 5-7 days. **Ceftriaxone:** 50-100 mg/kg IV in one or two doses/day for 10-14 days.	
	Pregnancy and lactation	One of the following antibiotics: **Azithromycin:** 1 g PO as 1 dose, then 500 mg PO q24h for 5-7 days. **Ceftriaxone:** 2 g IV q24h for 7-14 days.	
	Notes	None	
	Alternative regimen[4, 6, 7]		
	One of the following antibiotic regimens according to confirmed or expected antimicrobial susceptibility.		All recommended antibiotics are authorised at national level in MSs, some for different indications.
	Adults	One of the following antibiotics: **Cefotaxime:** 1-2 g IV q6-8h for 10-14 days. **Levofloxacin:** 750 mg IV/PO q24h for 7-14 days. **Trimethoprim-sulfamethoxazole:** 160 mg (trimethoprim component) PO q12h for 10-14 days.	
	Children	One of the following antibiotics: **Cefotaxime:** Age >28 days: 150-200 mg/kg/day divided q6-8h for 10-14 days. Age 8-28 days: 150 mg/kg/day IV divided q8h. Age 0-7 days: 100 mg/kg/day IV divided q12h.	

		Trimethoprim-sulfamethoxazole: 8 mg/kg (trimethoprim component, max 320 mg/day) PO divided q12-6h for 10-14 days.
	Pregnancy and lactation	**Cefotaxime:** 1-2 g IV q6-8h for 10-14 days.
	Notes	None
Treatment of complicated typhoid/paratyphoid fever (bowel perforation, mycotic aneurysm, shock) or severe infections	**First line regimen**[4, 6, 11, 12]	
	One of the following antibiotic regimens according to confirmed or expected antimicrobial susceptibility:	All recommended antibiotics are authorised at national level in MSs, some for different indications.
	Adults	One of the following antibiotics: **Ceftriaxone:** 2 g IV q24h for 7-14 days. **Meropenem:** 1-2 g IV q8h for 7-14 days. **Imipenem:** 500 mg IV q6h or 1g q8h IV for 7-14 days. **Ertapenem:** 1g q24h IV for 7-14 days.
	Children	One of the following antibiotics: **Ceftriaxone:** 50-100 mg/kg IV in one or two doses/day for 10-14 days. **Meropenem:** 20-40 mg/kg IV q8h (max 6 g/day). **Ciprofloxacin***: 15 mg/kg (max 500 mg) PO q12h or 10 mg/kg (max 400 mg) IV q12h for 7-10 days. **Ofloxacin***: 7.5-15 mg/kg (max 400 mg) PO/IV q12h for 7-10 days.
	Pregnancy and lactation	One of the following antibiotics: **Ceftriaxone:** 2 g IV q24h for 7-14 days. **Meropenem:** 1-2 g IV q8h for 7-14 days. **Imipenem:** 500 mg IV q6h or 1g q8h IV for 7-14 days. **Ertapenem:** 1g q24h IV for 7-14 days.
	Notes	*Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate.

References

1. ECDC, 'Salmonellosis' 2012, available from: https://www.ecdc.europa.eu/en/salmonellosis
2. CDC, 'Clinical Overview of Typhoid Fever and Paratyphoid Fever', Typhoid Fever Paratyphoid Fever 2024, available from: https://www.cdc.gov/typhoid-fever/hcp/clinical-overview/index.html
3. Crump J.A. et al., 'Nontyphoidal Salmonella Invasive Disease: Challenges and Solutions', Open Forum Infect. Dis. 10, S32–S37 2023
4. Wain J. et al., 'Typhoid fever', Lancet Lond. Engl. 385, 1136–1145 2015
5. Bhutta Z.A., 'Current concepts in the diagnosis and treatment of typhoid fever', BMJ 333, 78–82 2006

6. Klemm E.J. et al., 'Emergence of an Extensively Drug-Resistant Salmonella enterica Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins', mBio 9, e00105-18 2018
7. D. N. Gilbert et al. (eds.), 'The Sanford guide to antimicrobial therapy 2023', 53rd edition., Antimicrobial Therapy, Inc, 2023
8. Kuehn R. et al., 'Treatment of enteric fever (typhoid and paratyphoid fever) with cephalosporins', Cochrane Database Syst. Rev. 11, CD010452 2022
9. WHO, 'Paratyphoid fever' 2022, available from: https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/paratyphoid-fever
10. WHO, 'Nontyphoidal salmonella disease' 2022, available from: https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/nontyphoidal-salmonella-disease
11. EMA, 'Meronem - Art.30 referral | European Medicines Agency' 2009, available from: https://www.ema.europa.eu/en/medicines/human/referrals/meronem
12. EMA, 'Ciprofloxacin Bayer - Art. 30 referral | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/referrals/ciprofloxacin-bayer

Shigellosis

Disease characteristics and general points on treatment

Dysentery is a term used to define diarrhoea containing blood and mucus. Although several organisms can cause dysentery, the species of the genus *Shigella* are the most important. *S. dysenteriae* infection is usually responsible for the most severe cases, but also other species (*S. sonnei, S. flexneri and S. boydii*) can cause disease in humans. (1, 2)

The initial mode of transmission would be via contamination of food or water supplies. Further, person-to-person spread could result in very many secondary cases. The incubation period varies from 1 to 7 days. Symptoms include diarrhoea with blood and mucus, fever, stomach pain and rectal tenesmus and normally last up to 7 days. *S. dysenteriae* infections can be lethal due to complications such as bloodstream infections, toxic megacolon, haemolytic uraemic syndrome (HUS) and severe dehydration. (1, 2)

Dehydration should be treated with oral rehydration salts or, if severe, with intravenous fluids. (1)

Antibiotics are not always necessary and should in principle be reserved for severe cases or the treatment of immunocompromised patients, as antibiotic therapy shorten the duration of symptoms only of 1 to 2 days and increases the risk of resistance. However, due to public health reasons and in the context of outbreaks, treatment might be extended to milder cases. Specific therapy for more severe cases of bloody diarrhoea may reduce the duration of the illness, the risk of complications and the risk of transmission to others. (3, 4)

Fluoroquinolones constitute the first choice for treatment. However, the prevalence of resistance to fluoroquinolones is increasing worldwide (in Europe and US fluoroquinolone resistance reached 30% and 18% respectively for *Shigella spp* in 2020) and outbreak of MDR/XDR isolates are becoming increasingly frequent. Therefore, treatment should preferably be based on susceptibility tests. Fluoroquinolones, macrolides, beta-lactams, and trimethoprim-sulfamethoxazole all have established efficacy for susceptible *Shigella* isolates. Treatment duration is 3 to 5 days. (2-6)

There are no vaccines yet available for the prevention of Shigellosis. Several vaccines are under development, some covering more than one subtype. Three multivalent vaccines (altSonflex1-2-3, SV4-EPA and ZF0901) are currently under investigation in 2 to 3 randomized clinical trials. (7-11)

Recommended medicinal products for the treatment of Shigellosis and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Treatment of Shigella gastroenteritis	**First line regimens**[3, 4, 6]		
	One of the following antibiotic regimens according to confirmed or expected antimicrobial susceptibility:		All recommended antibiotics are authorised at national level in MSs, some for different indications.
	Adults	One of the following antibiotics: **Ciprofloxacin:** 500 mg PO q12h or 750 mg PO q24h for 3 days. **Levofloxacin:** 500 mg PO q24h for 3 days.	

		Azithromycin: 500 mg PO q24h for 3 days. **Ceftriaxone:** 1-2 g IV q24h for 5 days. **Trimethoprim-sulfamethoxazole:** 160 mg (trimethoprim component) PO q12h for 5 days. **Ampicillin:** 500 mg PO q6h for 5 days.
	Children	One of the following antibiotics: **Ceftriaxone:** 50 mg/kg (max 1.5 g) IV/IM q24h for 5 days. **Azithromycin:** 12 mg/kg PO q24h on day 1 (max 500 mg/day), 6 mg/kg PO (max 250 mg) q24h from day 2 to 5 (total duration 3 to 5 days). **Trimethoprim-sulfamethoxazole:** 10 mg/kg (trimethoprim component, max 320 mg/day) PO divided q12h for 3-5 days. **Ampicillin:** 100 mg/kg (max 2 g/day) PO divided q6h for 3-5 days.
	Pregnancy and lactation	One of the following antibiotics: **Ceftriaxone:** 1-2 g IV q24h for 5 days. **Azithromycin:** 500 mg PO q24h for 3 days. **Ampicillin:** 500 mg PO q6h for 5 days.
	Notes	None
	Alternative regimens[5-7 3, 4, 6, 12-14]	
	One of the following antibiotic regimens.	All recommended antibiotics are authorised at national level in MSs, some for different indications.
	Adults	For patients with severe disease (bacteraemia, intestinal or extraintestinal complications) and/or who are immunocompromised and in case of multidrug resistant isolates: **Ertapenem:** 1 g IV q24h according to clinical response. **Imipenem:** 500 mg IV q6h according to clinical response. **Meropenem:** 1 g IV q8h according to clinical response.
	Children	**Ciprofloxacin*:** 10 mg/kg (max 400 mg) IV q12h or 10 mg/kg (max 500 mg) q12h for 3 to 5 days. For patients with severe disease (bacteraemia, intestinal or extraintestinal complications) and/or who are immunocompromised and in case of multidrug resistant isolates: **Ertapenem:** 15 mg/Kg/dose IV q12h according to clinical response. **Imipenem:** 15-25 mg/Kg/dose IV q6h according to clinical response.

		Meropenem: 20 mg/Kg/dose IV q8h according to clinical response.
	Pregnancy and lactation	For patients with severe disease (bacteraemia, intestinal or extraintestinal complications) and/or who are immunocompromised and in case of multidrug resistant isolates: **Ertapenem:** 1 g IV q24h according to clinical response. **Imipenem:** 500 mg IV q6h according to clinical response. **Meropenem:** 1 g IV q8h according to clinical response.
	Notes	*Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate.

References

1. Mandell G.L. et al., Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition), W.B. Saunders, 2015
2. CDC, 'About Shigella Infection', Shigella - Shigellosis 2024, available from: https://www.cdc.gov/shigella/about/index.html
3. Gilbert D. N. et al. (eds.), 'The Sanford guide to antimicrobial therapy 2023', 53rd edition., Antimicrobial Therapy, Inc, 2023
4. Christopher P.R. et al., 'Antibiotic therapy for Shigella dysentery', Cochrane Database Syst. Rev. 2010, CD006784 2010
5. ECDC, 'Shigellosis - Annual Epidemiological Report for 2020', Eur. Cent. Dis. Prev. Control 2022, available from: https://www.ecdc.europa.eu/en/publications-data/shigellosis-annual-epidemiological-report-2020
6. Gharpure R. et al., 'Azithromycin and Ciprofloxacin Treatment Outcomes During an Outbreak of Multidrug-Resistant Shigella sonnei Infections in a Retirement Community-Vermont, 2018', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 74, 455–460 2022
7. MacLennan C.A. et al., 'The Shigella Vaccines Pipeline', Vaccines 10, 1376 2022
8. WHO, '2023 meeting: WHO Product Development for Vaccines Advisory Committee Meeting (PDVAC)' 2023, available from: https://www.who.int/news-room/events/detail/2023/12/12/default-calendar/2023-meeting-who-product-development-for-vaccines-advisory-committee-meeting-pdvac
9. Study Details | A Study on the Safety and Immune Responses to the GVGH altSonflex1-2-3 Vaccine Against Shigellosis in Adults, Children, and Infants, available from: https://clinicaltrials.gov/study/NCT05073003
10. Study Details | A Study to Determine If a New Shigella Vaccine is Safe, Induces Immunity and The Best Dose Among Kenyan Infants, available from: https://clinicaltrials.gov/study/NCT04056117
11. Study Details | Efficacy, Immunogenicity and Safety of S. Flexneriza-S. Sonnei Bivalent Conjugate Vaccine in Volunteers Aged From 6 Months to 5 Years, available from: https://clinicaltrials.gov/study/NCT05156528
12. EMA, 'Tienam - Art. 30 referral | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/referrals/tienam
13. EMA, 'Invanz | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/EPAR/invanz
14. EMA, 'Ciprofloxacin Bayer - Art. 30 referral | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/referrals/ciprofloxacin-bayer

Escherichia coli 0157:H7

Disease characteristics and general points on treatment

Escherichia coli bacteria producing Shiga toxin 1 and/or 2 (STEC) are also called enterohemorrhagic strains (EHEC) and can cause bloody diarrhoea. A particular serotype, E. coli O157:H7, can cause severe disease often characterized by painful bloody diarrhoea that can be complicated by the haemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Transmission is often caused by poor handwashing techniques, unhygienic food handling (poorly cooked meat, milk products, vegetables, and fruits) and contaminated water reservoirs (e.g. water parks). (1)

After an incubation period of 3 to 9 days, patients develop gastroenteric symptoms such as abdominal cramping and pain, flatulence, fever, and voluminous, watery diarrhoea that can eventually become bloody. Children, elderly, and immunocompromised individuals can present severe disease. Infants and children in particular are at higher risk of developing HUS, a complication characterized by a triad of acute renal failure, thrombocytopenia, and microangiopathic haemolytic anaemia. Patients with the additional findings of fluctuating neurological symptoms and fever are classified as having TTP. (1-2)

Treatment should be limited to hydration and supportive care. In case of confirmed or suspected STEC infections (either E. coli O157:H7 or non-O157:H7) antibiotics are contraindicated because they are associated with increased risk of HUS, in particular in children. Moreover, antibiotics have not been shown to reduce symptoms or other complications associated with STEC infections. (3-4)

There are no vaccines available.

References

1. Ciottone G. et al., 'Ciottone’s Disaster Medicine', 3rd ed., Elsevier, 2023
2. Freedman S.B. et al., 'Shiga Toxin-Producing Escherichia coli Infection, Antibiotics, and Risk of Developing Hemolytic Uremic Syndrome: A Meta-analysis', Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 62, 1251–1258 2016
3. Tarr P.I., S.B. Freedman, 'Why antibiotics should not be used to treat Shiga toxin-producing Escherichia coli infections', Curr. Opin. Gastroenterol. 38, 30–38 2022
4. Proulx F. et al., 'Randomized, controlled trial of antibiotic therapy for Escherichia coli O157:H7 enteritis', J. Pediatr. 121, 299–303 1992

Vibrio cholerae

Disease characteristics and general points on treatment

Cholera is an acute diarrheal illness caused by toxigenic strains of *Vibrio cholerae*. There are 200 serological groups of *V. cholerae*, but only *V. cholerae O1* and *O139* can cause epidemics. The disease is spread by contaminated water and food. Direct person-to-person transmission does not occur. The incubation period is normally 1 to 5 days. (1)

Depending on the serotype, up to 75% of infected individuals are asymptomatic. Of the other 25%, the majority have a mild diarrheal illness not requiring medical attention and 2% develop cholera gravis. Cholera gravis is characterized by a gradual to sudden onset of vomiting, malaise, headache, intestinal cramping, mild or no fever and painless and voluminous diarrhoea that looks like rice water.

The overall mortality rate in infected persons is 1 to 1.5%, but in those with cholera gravis mortality can reach 50 to 75% without appropriate clinical management. (1,2)

Rehydration is the mainstay for the treatment of cholera. During an epidemic, the vast majority of patients with diarrhoea can be treated by oral rehydration solutions (ORS) alone. Either the standard World Health Organization (WHO) or commercially available ORSs, that are approved at national level in MSs, can be used, as difference in composition do not appear to be clinically significant. Intravenous (IV) rehydration should be started in patients who have lost more than 10% of their body weight because of dehydration or who are not able to drink because of vomiting or mental status changes. (1-3)

Antibiotic treatment as an adjuvant to rehydration can be considered in severe cases, for pregnant women and individuals with malnutrition or underlining medical conditions. In outbreak settings, treatment could also be extended to moderate cases, acknowledging that extensive antibiotic treatment can increase the risk of developing resistance. An effective antibiotic can reduce the volume and duration of diarrhoea by about one day and a half and the period of Vibrio excretion by almost three days if compared to no treatment. Tetracyclines, macrolides and fluoroquinolones are the best therapeutic options, and the choice should ideally rely on susceptibility data. Antibiotic resistance to all tetracyclines is common. There are rare reports of macrolide resistance and reduced susceptibility to fluoroquinolones has been reported in Asia and Africa. Antibiotics should be given once initial rehydration is completed and the patient is able to take oral medications. (4-8)

In addition, zinc supplementation (10 to 30 mg daily) should be considered to reduce the duration and volume of stool in children with cholera. (9)

The role and optimal use of cholera vaccines during an outbreak is still debated. While access to safe water and sanitation should remain the pillars of infection control, there are data demonstrating the effectiveness of some types of vaccines to reduce the risk of cholera in outbreak settings. (10-13)

There are two types of killed whole-cell oral cholera vaccines (OCV):

Dukoral® is a killed whole cell monovalent (O1) vaccine with a recombinant B subunit of cholera toxin. It is WHO prequalified and centrally approved in the EU. It is administered with a buffer solution that, for adults, requires 150 ml of clean water. Dukoral can be given to all individuals over the age of 2 years. Adults should take two doses minimum 7 days apart, and children aged 2 to 5 require a third dose. A booster should be given after 2 years. Dukoral® has shown effectiveness h in outbreak settings. (14)

Shanchol™, Euvichol® and Euvichol Plus® are WHO prequalified vaccines that contain killed whole cells of several biotypes and serotypes of *V. cholerae* O1 and *V. cholerae* O139. They are not licensed in the EU. They can be given to all individuals over the age of one year. Two doses should be administered with a minimum of two weeks interval. Two doses of Shanchol™ and Euvichol® provide protection against cholera for 3 years, while a single dose provides short term protection. They have been proven effective in outbreak control. They are currently available for mass vaccination campaigns through the Global OCV Stockpile and prevalently used in endemic areas. (11)

A live attenuated cholera vaccine CVD 103-HgR (Vaxchora™) is authorized for use in the EU and is indicated for prevention of cholera caused by serogroup O1 in patients aged 2 and older. In a clinical trial including 197 healthy adult volunteers randomly assigned to receive an oral dose of the vaccine or placebo, followed by oral challenge with a V. cholerae O1 strain (10 days after vaccine), diarrhoea occurred less frequently among vaccine recipients (vaccine efficacy 90 percent). No data from effectiveness studies is currently available. (15)

Recommended medicinal products for the treatment of Cholera and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Treatment of cholera with moderate to severe volume depletion; treatment of cholera in pregnant women, individuals with acute malnutrition and chronic health conditions	**First line regimens**[2, 4, 16]		
	Azithromycin		Authorised at national level in MSs for different indications.
	Adults (≥8 years)	1 g PO as a single dose.	
	Children (<8 years)	20 mg/kg (max 1 g) PO as a single dose.	
	Pregnancy and lactation	1 g PO as a single dose.	
	Notes	None	
	Doxycycline		Authorised at national level in MSs for different indications.
	Adults (≥8 years)	300 mg PO as a single dose.	
	Children (<8 years)	2-4 mg/kg PO as a single dose.	
	Pregnancy and lactation	300 mg PO as a single dose.	
	Notes	Treatment of children <8 years with doxycycline is not recommended. However, it's use can be justified in severe infections when alternatives are not available or appropriate. Tetracyclines are not recommended in pregnant/breastfeeding women. However, their use should follow clinical judgment on potential benefit and anticipated risks.	
	Alternate regimens[2, 4, 17]		
	One of the following antibiotic regimens.		Ciprofloxacin and erythromycin are authorised at national level in MSs, some for different indications.
	Adults	One of the following antibiotics: **Ciprofloxacin:** 500 mg OS q12h for 3 days.	

		Erythromycin: 500 mg PO q6hfor 3 days.
	Children	One of the following antibiotics: **Erythromycin:** 12.5 mg/Kg (max 500 mg) PO q6h for 3 days. **Ciprofloxacin*:** 15 mg/kg PO q12h.
	Pregnancy and lactation	**Erythromycin:** 500 mg PO q6h for 3 days.
	Notes	*Treatment of children and adolescents with fluoroquinolones can be justified in severe infections when alternatives are not available or appropriate.

References

1. Ciottone G. et al., 'Ciottone's Disaster Medicine', 3rd ed., Elsevier, 2023
2. Kanungo S. et al., 'Cholera', Lancet Lond. Engl. 399, 1429–1440 2022
3. WHO, 'Oral rehydration salts' 2006, available from: https://www.who.int/publications/i/item/WHO-FCH-CAH-06.1
4. Leibovici-Weissman Y. et al., 'Antimicrobial drugs for treating cholera', Cochrane Database Syst. Rev. 2014, CD008625 2014
5. Farmer P. et al., 'Meeting cholera's challenge to Haiti and the world: a joint statement on cholera prevention and care', PLoS Negl. Trop. Dis. 5, e1145 2011
6. Weber J.T. et al., 'Epidemic cholera in Ecuador: multidrug-resistance and transmission by water and seafood', Epidemiol. Infect. 112, 1–11 1994
7. Yamamoto T. et al., 'Survey of in vitro susceptibilities of Vibrio cholerae O1 and O139 to antimicrobial agents.', Antimicrob. Agents Chemother. 39, 241–244 1995
8. Islam M.S. et al., 'Susceptibility to fluoroquinolones of Vibrio cholerae O1 isolated from diarrheal patients in Zimbabwe', JAMA 302, 2321–2322 2009
9. Roy S.K. et al., 'Zinc supplementation in children with cholera in Bangladesh: randomised controlled trial', BMJ 336, 266–268 2008
10. Luquero F.J. et al., 'Use of Vibrio cholerae vaccine in an outbreak in Guinea', N. Engl. J. Med. 370, 2111–2120 2014
11. WHO, 'Cholera vaccines: WHO position paper – August 2017' 2017, available from: https://www.who.int/publications/i/item/who-wer9234-477-500
12. Lucas M.E.S. et al., 'Effectiveness of mass oral cholera vaccination in Beira, Mozambique', N. Engl. J. Med. 352, 757–767 2005
13. Khatib A.M. et al., 'Effectiveness of an oral cholera vaccine in Zanzibar: findings from a mass vaccination campaign and observational cohort study', Lancet Infect. Dis. 12, 837–844 2012
14. EMA, 'Dukoral | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/EPAR/dukoral
15. EMA, 'Vaxchora | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vaxchora#ema-inpage-item-product-info
16. Stultz J.S., L.S. Eiland, 'Doxycycline and Tooth Discoloration in Children: Changing of Recommendations Based on Evidence of Safety', Ann. Pharmacother. 53, 1162–1166 2019
17. EMA, 'Ciprofloxacin Bayer - Art. 30 referral | European Medicines Agency' 2024, available from: https://www.ema.europa.eu/en/medicines/human/referrals/ciprofloxacin-bayer

Staphylococcal enterotoxin B

Disease characteristics and general points on treatment

Staphylococcal enterotoxin B (SEB) is one of the seven toxins produced by *S. aureus*. It can cause harm to humans if inhaled or ingested.

When ingested, SEB is one of the most common causes of gastroenteritis. Food, especially dairy products, contaminated with *S. aureus* and not properly handled, are normally the source of exposure to SEB, which is also resistant to heat and boiling. Gastrointestinal symptoms include diarrhoea, nausea, vomiting and abdominal pain accompanied with fever. Symptoms manifest within 30 minutes to 6 hours after ingestion and last normally no longer that 24 hours. (1)

Inhalation of SEB can occur only in the context of a laboratory accident or deliberate release. The effect on human beings in case of exposure to SEB by inhalation is not well documented. However, the clinical picture could be similar to a febrile respiratory syndrome with abrupt onset (within 24 hours) associated with chest pain and myalgia. In case of severe inhalation respiratory distress, pulmonary oedema and shock can occur. The toxin can in fact cause an intense inflammatory response in host tissues, due to its ability to act as a superantigen and stimulate a cascade of proinflammatory cytokines. (1)

Person-to-person transmission of SEB intoxication is not possible. (1)

There are no treatments with demonstrated efficacy against SEB intoxication. Hydration and supportive care are currently the mainstay of treatment. Antibiotics have not shown to be effective. However, doxycycline and dexamethasone may have a role as adjunctive therapy as in-vitro and mice studies have demonstrated their ability to downregulate the inflammatory cascade caused by SEB. There are monoclonal antibodies under development that showed promising results in vitro and in early treatment in macaques. (1-5)

References

1. Ciottone G. et al., 'Ciottone’s Disaster Medicine', 3rd ed., Elsevier, 2023
2. Krakauer T., M. Buckley, 'Doxycycline is anti-inflammatory and inhibits staphylococcal exotoxin-induced cytokines and chemokines', Antimicrob. Agents Chemother. 47, 3630–3633 2003
3. Krakauer T., M. Buckley, 'Dexamethasone Attenuates Staphylococcal Enterotoxin B-Induced Hypothermic Response and Protects Mice from Superantigen-Induced Toxic Shock', Antimicrob. Agents Chemother. 50, 391–395 2006
4. Larkin E.A. et al., 'Inhibition of Toxic Shock by Human Monoclonal Antibodies against Staphylococcal Enterotoxin B', PLoS ONE 5, e13253 2010
5. Verreault D. et al., 'Effective Treatment of Staphylococcal Enterotoxin B Aerosol Intoxication in Rhesus Macaques by Using Two Parenterally Administered High-Affinity Monoclonal Antibodies', Antimicrob. Agents Chemother. 63, e02049-18 2019

Cryptosporidium parvum

Disease characteristics and general points on treatment

Cryptosporidium parvum is an intracellular protozoon whose reservoir is humans, domesticated and wild animals (e.g., cows, goats, sheep, deer). The typical route of transmission is by ingestion of food or water contaminated by Cryptosporidium oocysts. Person-to-person transmission via the orofecal route can occur and oocysts can still be excreted for up to 5 weeks after the clinical symptoms end. In immunocompetent individuals, after an incubation period of 1 to 2 weeks, the infection leads to a gastroenteritis (watery diarrhoea, abdominal cramps, anorexia, nausea, vomiting and low-grade fever). The disease is usually self-limited with an average duration of 9 to 12 days. In immunocompromised hosts (in particular in those living with AIDS) and children, the disease can be more severe and evolve to chronic diarrhoea and wasting syndrome. In some rare cases the infection can have extra-intestinal complications such as biliary involvement, sclerosing cholangitis, pulmonary involvement or cirrhosis. (1)

Immunocompetent patients normally require only supportive care. However, in some severe cases treatment with nitazoxanide or paromomycin can be considered. In immunocompromised individuals living with AIDS the mainstay of treatment is the initiation of antiretroviral therapy (ART) to restore immunity. In severe cases or when persistent symptoms do not resolve with ART, antiprotozoal therapies can be used in addition to ART. However, nitazoxanide was shown to be less effective than in immunocompetent hosts and the clinical benefit of antimicrobial therapy in patients living with HIV is uncertain as data are limited and mixed. (2-7)

Recommended medicinal products for the treatment of cryptosporidium parvum-caused disease and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Treatment of immunocompetent individuals with severe acute symptoms causing significant morbidity and dehydration (stool volumes of >10 L per day), or persistent symptoms (i.e. diarrhoea lasting >2 weeks)	**First line regimen**[2, 3, 8]		
	Nitazoxanide		Not authorised in the EU.
	Adults (≥12 years)	500 mg PO q12h for 3 days.	
	Children (4-11 years)	200 mg PO with food q12h for 3 days.	
	Children (1-3 years)	100 mg PO q12h with food for 3 days.	
	Pregnancy and lactation	There are no data in humans regarding the use of nitazoxanide in pregnancy and during lactation. No teratogenicity or fetotoxicity was observed in animal reproduction studies.	
	Notes	The only contraindication is hypersensitivity.	
	Alternative regimen[2, 4]		
	Paromomycin		Authorised at national level in MSs for different indications.
	Adults	500 mg (max 35-50 mg/kg/day) PO q8h for 7 days.	
	Children	25-35 mg/kg/day in 3 doses PO for 7 days.	
	Pregnancy and lactation	To be used only in case of necessity and under medical supervision.	

	Notes	The only contraindication is hypersensitivity. No clinical data that demonstrate efficacy in immunocompetent hosts.	
Patients with AIDS with severe acute symptoms or persistent non-severe symptoms. Other immunocompromised hosts.	**First line regimens**[2-8]		
	Nitazoxanide		Not authorised in the EU.
	Adults (≥12 years)	500-1000 mg PO q12h for 2-8 weeks.	
	Children (4-11 years)	200 mg PO with food q12h for 2-8 weeks.	
	Children (1-3 years)	100 mg PO q12h with food for 2-8 weeks.	
	Pregnancy and lactation	There are no data in humans regarding the use of nitazoxanide in pregnancy and during lactation. No teratogenicity or fetotoxicity was observed in animal reproduction studies.	
	Notes	Initiation of ART is the mainstay of therapy. Antimicrobial therapy can be initiated in addition to ART in case of severe symptoms while waiting for immune restoration or in case of persistent symptoms. Immune restoration with ART is critical to symptom eradication and prognosis. For other immunocompromised hosts (e.g., solid organ transplantation) reduce immunosuppressive medication. The only contraindication is hypersensitivity.	
	Alternative regimen[2-9]		
	Paromomycin		Authorised at national level in MSs for different indications.
	Adults	**Paromomycin:** 500 mg (max 35-50 mg/kg/day) PO q8h for 2-8 weeks. In case of monotherapy failure: **Nitazoxanide:** 500-1000 mg PO q12h until immunologic recovery or clinical response. **Paromomycin:** 500 mg (max 35-50 mg/kg/day) PO q8h until immunologic recovery or clinical response. **Azithromycin:** 500 mg PO q24h until immunologic recovery or clinical response.	
	Children	25-35 mg/kg/day in 3 doses PO for 7 days.	
	Pregnancy and lactation	To be used only in case of necessity and under medical supervision.	
	Notes	The only contraindication is hypersensitivity. No clinical data that demonstrate efficacy in immunocompetent hosts.	

References

1. Ciottone G. et al., 'Ciottone's Disaster Medicine', 3rd ed., Elsevier, 2023
2. Gilbert D.N. et al. (eds.), 'The Sanford guide to antimicrobial therapy 2023', 53rd edition., Antimicrobial Therapy, Inc, 2023
3. Rossignol J.F. et al., 'Treatment of diarrhea caused by Cryptosporidium parvum: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide', J. Infect. Dis. 184, 103–106 2001

4. Sparks H. et al., 'Treatment of Cryptosporidium: What We Know, Gaps, and the Way Forward', Curr. Trop. Med. Rep. 2, 181–187 2015
5. EACS, 'EACS Guidelines for the management of people living with HIV, v.12.0', EACSociety 2023, available from: https://www.eacsociety.org/guidelines/eacs-guidelines/
6. Abubakar I. et al., 'Prevention and treatment of cryptosporidiosis in immunocompromised patients', Cochrane Database Syst. Rev., CD004932 2007
7. Amadi B. et al., 'High dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial', BMC Infect. Dis. 9, 195 2009
8. FDA, 'Nitazoxanide Tablets. Prescribing information' 2021, available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021497s017lbl.pdf
9. Smith N.H. et al., 'Combination drug therapy for cryptosporidiosis in AIDS', J. Infect. Dis. 178, 900–903 1998

Psittacosis (Chlamydia psittaci)

Disease characteristics and general points on treatment

Chlamydia psittaci infection can be transmitted to humans by direct contact with infected birds, or by inhalation of avian nasal discharge or faecal material. The disease is considered an occupational hazard for employees of pet shops, poultry farmers, but also abattoir workers and veterinarians. Pet owners can also be affected. Although all birds are susceptible, poultry and those from the parrot family are frequently incriminated. Household cats and breeding catteries have also been identified as potential sources of human *C. psittaci* infection but cases of transmission to humans have not been proven. Person-to-person transmission is rare but has been observed in outbreaks. The incubation period is 5 to 15 days. Human disease presents with a flu-like illness characterised by fever, chills, headache, and less frequently, cough, myalgia, rash, arthralgia, and joint swelling. Patients may progress to develop atypical pneumonia. Glomerulonephritis, endocarditis, encephalitis, and hepatitis may also complicate more severe cases. Mortality is reported to be less than 1% with early diagnosis and appropriate treatment. (1-4)

Tetracyclines are the recommended first line treatment for psittacosis, while macrolides represent the second choice. Fluoroquinolones are active *in vitro,* but clinical data is limited. (1,4)

There are no vaccines available at present to prevent *Chlamydia psittaci* infection.

Recommended medicinal products for the treatment of psittacosis and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Treatment of psittacosis pneumonia	**First line regimens**[4-8]		
	Doxycycline		Authorised at national level in MSs for different indications.
	Adults and children (>8 years)	100 mg IV/PO q12h for 7-10 days.	
	Pregnancy and lactation	100 mg IV/PO q12h for 7-10 days. Doxycycline is not recommended during pregnancy. The use of doxycycline during pregnancy should be based on clinical judgment of potential benefit and anticipated risks. Lactation should be discontinued if possible.	
	Notes	Treatment of children <8 years with doxycycline is not recommended. However, the use may be clinically justified in severe infections when alternatives are not available or appropriate.	
	Azithromycin		Authorised at national level in MSs for different indications.
	Adults	500 mg PO on day 1, then 250 mg PO q24h for 4 days.	
	Children	Body weight ≥45 kg: 500 mg IV/PO on day 1, then 250 mg PO for 4 days. Body weight <45 kg: 10 mg/kg PO on day 1, then 5 mg/kg PO for 4 days.	

	Pregnancy and lactation	500 mg PO on day 1, then 250 mg PO q24h for 4 days.	
	Notes	None	
	Alternative regimen[5]		
	Clarithromycin		Authorised at national level in MSs for different indications.
	Adults and children (≥12 years)	500 mg PO q12h for 7-10 days.	
	Children (>28 days - 12 years)	7.5 mg/kg PO q12h for 7-10 days.	
	Pregnancy and lactation	The safety of clarithromycin for use during pregnancy and breastfeeding has not been established. The use of clarithromycin should be based on clinical judgment of potential benefit and anticipated risks. Clarithromycin and its active metabolite are excreted in breast milk Lactation should be discontinued if possible.	
	Notes	None	

References

1. Bennett J.E. et al., 'Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases', 9th ed., Elsevier, 2019
2. Dembek Z.F. et al., 'Psittacosis: An Underappreciated and Often Undiagnosed Disease', Pathog. Basel Switz. 12, 1165 2023
3. Wallensten A. et al., 'Multiple human-to-human transmission from a severe case of psittacosis, Sweden, January-February 2013', Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull. 19, 20937 2014
4. Ojeda Rodriguez J.A. et al., 'Psittacosis Pneumonia', in: StatPearls, StatPearls Publishing, 2024.
5. D. N. Gilbert et al. (eds.), 'The Sanford guide to antimicrobial therapy 2023', 53rd edition., Antimicrobial Therapy, Inc, 2023
6. Yung A.P., M.L. Grayson, 'Psittacosis--a review of 135 cases', Med. J. Aust. 148, 228–233 1988
7. Khatib R. et al., 'Severe psittacosis during pregnancy and suppression of antibody response with early therapy', Scand. J. Infect. Dis. 27, 519–521 1995
8. Stultz J.S., L.S. Eiland, 'Doxycycline and Tooth Discoloration in Children: Changing of Recommendations Based on Evidence of Safety', Ann. Pharmacother. 53, 1162–1166 2019

Ricin and abrin toxin

Disease characteristics and general points on treatment

Ricin is a lectin, a toxic glycoprotein, that can be naturally found in the seeds of the ordeal or ornamental castor plant (*Ricinus communis L*). The Jequirity bean (*Abrus precatorius*) also has a lectin called abrin which is similar to ricin, and both are potent biological toxins. It can be inactivated by heat above 80 degrees Celsius. Castor beans are processed throughout the world to make castor oil. There are two lectins in the fibrous part of the seed of the Castor bean – Ricin I and Ricin II, of which Ricin II is the most toxic lectin. It contains two chains of amino acids, A and B, which are linked together by di-sulphide bonds. The B-chain (MW-33.000-Daltons) binds to the cell membrane and facilitates the endocytosis of the A chain (MW- 30.000 Daltons) into the cell. In the cytosol, the A chain is a strong inactivator of ribosomes and blocks irreversibly the protein biosynthesis. The seeds of the Jequirity bean contain four lectins called isoabrins. They also consist of two amino acid chains, which are linked by di-sulphide bonds. One of the four isoabrins, isoabrin-a, has the highest inhibitory effect on the protein biosynthesis. The incubation period is dependent on whether ricin was inhaled, ingested, or injected. As ricin toxin inhibits protein synthesis in cells, clinical signs and symptoms of ricin poisoning will slowly evolve. Initial manifestation of symptoms likely occurs within 4 to 10 hours following ingestion, within 4 to 8 hours following inhalation and within 12 to 24 hours following injection. After ingestion of ricin, it is extremely unlikely that signs and symptoms of poisoning would begin more than 10 hours after exposure. After inhalational exposure to ricin powder, it is very unlikely that signs and symptoms of poisoning would begin more than 24 hours after exposure. The extent of manifestations depends on the amount of ricin to which a person was exposed, route of exposure, and extent of organ involvement. Significant exposure to ricin would result in a relatively rapid, progressive worsening of symptoms over approximately 4 to 36 hours. The initial symptoms most likely affect the gastrointestinal system and include nausea, vomiting, and abdominal pain. The symptoms of ricin poisoning will likely progress rapidly (generally over 12 to 24 hours) and include severe dehydration, kidney, and liver toxicity. Death may occur within 36 to 72 hours of exposure. This rapid progression of symptoms and illness is notably different than what typically occurs with most commonly encountered infectious foodborne illnesses, which generally resolve within a day or two. (1-7)

If exposure cannot be avoided, ricin should be removed as quickly as possible from and out of the body (decontamination measures), and supportive medical care to minimise effects of the poisoning should be provided. The level of supportive care is related to the degree of cellular disruption, and prolonged intensive care and complex medical management may be required. (2, 3)

There are no approved treatments or vaccines available at present. Some antidotes based on antibodies and therapeutic vaccines are currently in clinical development. Monoclonal antibodies in clinical development are PhD9, PB10, 43RCA-G1, RB34 and RB37 and the bispecific antibody JJX12. The anti-ricin product FBT-002 is in phase-1 clinical development. Anti-abrin neutralizing antibody (S008) and mAb 10D8, are abrin antidotes in clinical development. RiVax®, an inactivated protein component of the ricin toxin combined with an alum adjuvant, has been evaluated in two phase 1 studies. In December 2023, the ovine polyclonal fragment antigen-binding against ricin was designated as an orphan medicine for the treatment of ricin poisoning in the EU. (8-16)

References

1. CDC, 'Response to a Ricin Incident: Guidelines for Federal, State, and Local Public Health and Medical Officials' 2006
2. CDC, 'CDC information on Ricin incidence' 2019, available from: https://emergency.cdc.gov/agent/ricin/

3. Olsnes S. et al., 'Mechanism of action of the toxic lectins abrin and ricin', Nature 249, 627–631 1974
4. Moshiri M. et al., 'Ricin Toxicity: Clinical and Molecular Aspects', Rep. Biochem. Mol. Biol. 4, 60–65 2016
5. Lord J.M. et al., 'Ricin: structure, mode of action, and some current applications', FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 8, 201–208 1994
6. Sharma S. et al., 'Trends in the analysis of abrin poisoning for forensic purposes', J. Forensic Leg. Med. 98, 102564 2023
7. Buehler J.W., 'Public Health Response to Biological and Chemical Weapons: WHO Guidance', Emerg. Infect. Dis. 11, 186–187 2005
8. Rasetti-Escargueil C., A. Avril, 'Medical Countermeasures against Ricin Intoxication', Toxins 15, 100 2023
9. AntoXa, 'AntoXa Corporation and SwiftPharma Sign Exclusive Collaboration Agreement to Support the Development and Commercialization of a Plant-Made Antibody Against Ricin Exposure' 2023, available from: https://antoxacorp.com/antoxa-corporation-and-swiftpharma-sign-exclusive-collaboration-agreement-to-support-the-development-and-commercialization-of-a-plant-made-antibody-against-ricin-exposure/
10. Peng J. et al., 'A Novel Humanized Anti-Abrin A Chain Antibody Inhibits Abrin Toxicity In Vitro and In Vivo', Front. Immunol. 13, 831536 2022
11. Li Z. et al., 'Neutralizing Monoclonal Antibody, mAb 10D8, Is an Effective Detoxicant against Abrin-a Both In Vitro and In Vivo', Toxins 14, 164 2022
12. Vitetta E.S. et al., 'A pilot clinical trial of a recombinant ricin vaccine in normal humans', Proc. Natl. Acad. Sci. U. S. A. 103, 2268–2273 2006
13. Vitetta E.S. et al., 'Pilot Phase IB Clinical Trial of an Alhydrogel-Adsorbed Recombinant Ricin Vaccine', Clin. Vaccine Immunol. CVI 19, 1697–1699 2012
14. Roy C.J. et al., 'Serum antibody profiling identifies vaccine-induced correlates of protection against aerosolized ricin toxin in rhesus macaques', Npj Vaccines 7, 1–10 2022
15. EMA, 'Search for clinical trials - EMA. A study to evaluate the safety, tolerance and changes in blood levels of an anti-toxin drug (FBT-002) in healthy male and female subjects. EUCT number:2023-505745-16-00', available from: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-505745-16-00
16. EU/3/23/2872 - orphan designation for treatment of ricin poisoning | European Medicines Agency (EMA) (europa.eu)

Viral encephalitis (Alphaviruses)

Encephalitic alphaviruses, including Eastern equine encephalitis virus (EEEV), Western equine encephalitis virus (WEEV) and Venezuelan equine encephalitis virus (VEEV), infect cells in the central nervous system and cause meningitis and encephalitis, often with long-term debilitating neurological sequelae. These viruses are mosquito-borne and are transmitted by Aedes, Culiseta and Culex mosquito species, which facilitates infection of a range of mammalian and avian hosts. The New World alphaviruses (Venezuelan, Eastern and Western equine encephalitis (VEEV, EEEV and WEEV)) are mainly found in the Americas and are largely characterised as causing encephalitic disease. The same applies to WEEV and EEEV. (1-3)

Venezuelan equine encephalitis

Disease characteristics and general points on treatment

Several species of mosquitos are capable of transmitting both the enzootic and epizootic strains of Venezuelan equine encephalitis virus (VEEV). *Ochlerotatus taeniorhynchus* appears to be the primary mosquito vector during epizootics, while *Culex* species transmit enzootic strains. Mosquitos feed on infected rodents or equines, infecting the mosquito midgut. Following initial infection, the virus accumulates in the salivary glands, and blood-feeding releases virions through the mosquito into the new host. Infected equines are viral amplification hosts for epizootic strains, while sylvatic rodents are the primary reservoir hosts for enzootic strains. Infected equines and humans develop high viraemia that can be a source of further mosquito infections. Infected horses shed the virus in body fluids, and humans can become infected by direct contact or aerosolised fluids. The incubation period is approximately 1 to 5 days and can vary dependent on the route of infection but is often short. Overall case fatality rate is less than 1%, in children with encephalitis it may reach up to 20% to 35%. Abrupt symptom onset with malaise, high fever, severe headache, rigors, photophobia, myalgia (especially in legs and lumbosacral area), cough, sore throat, and vomiting. In 4% to 14% of the cases, it can progress to a more serious encephalitic disease characterised by photophobia, confusion, seizures, convulsions, stupor, behavioural changes, alterations of consciousness, unilateral paralysis, and coma. The incidence of seizures increases inversely related to age. Serious neurological disease can occur in up to ~15% of infected patients. Incidence of nervous system disease may be higher after respiratory infection. 25% of the hospitalised patients may develop long-lasting neurological sequelae, including headaches, severe fatigue, and depression. (1, 2, 4)

There are currently no approved treatments or vaccines available. Supportive therapy should be given. Some patients may be treated with analgesics to relieve headaches and myalgias. Patients who develop encephalitis may require anticonvulsant and intensive care to maintain fluid and electrolyte balance, and ventilatory support. BDGR-49 is one antiviral in non-clinical development that showed efficacy in treatment of encephalitis in a mouse model. (3-5)

There is a vaccine that has been used in humans and equines, the TC-83, a live-attenuated vaccine strain. The vaccine is available for personnel at high risk of exposure. (6)

Eastern equine encephalitis

Disease characteristics and general points on treatment

Eastern equine encephalitis virus (EEEV) is maintained in a cycle between *Culiseta melanura* mosquitoes and avian hosts in freshwater hardwood swamps. *Culiseta melanura* is not considered to be an important vector of EEEV to humans because it feeds almost exclusively on birds. Transmission

to humans requires another mosquito species to create a "bridge" between infected birds and uninfected mammals, such as humans or horses. Most of the bridge species are within the *Aedes*, *Coquillettidia*, and *Culex* genera. EEEV has been documented to be transmitted through organ transplantation with one organ donor transmitting the infection to three organ transplant recipients. EEEV is found in North America and the Caribbean, with the remaining three circulating in South and Central America Northeastern United States and northward expansion into regions where the virus was historically rare or previously unknown, including northern New England and eastern Canada. The incubation period for EEEV disease ranges from 3 to 10 days and can be several weeks in immunocompromised people. EEEV symptomatic infection is associated with a case fatality rate between 30% to 70% and results in neurologic sequelae (such as seizure disorders, hemiplegia, and cognitive dysfunction) in more than 50% of survivors. Most persons infected with EEEV remain asymptomatic. Symptomatic patients typically develop a systemic febrile illness that can progress to meningitis or encephalitis. Signs and symptoms in patients with neuroinvasive disease include headache, vomiting, confusion, focal neurologic deficits, meningitis, seizures, or coma. Neuroinvasive disease results in neurologic sequelae in more than 50% of survivors. (1, 7–9)

There are no approved treatments or vaccines available at present. Supportive care for patients with severe meningeal symptoms often requires analgesics for headaches, antiemetic therapy and rehydration for associated nausea and vomiting. Patients with encephalitis require close monitoring for the development of elevated intracranial pressure, seizures, and inability to protect their airway. BDGR-49 is one antiviral in non-clinical development that showed efficacy in treatment of encephalitis in a mouse model. (5, 9)

However, the U.S. Army Medical Research Institute of Infectious Diseases—the military medical research institute at Fort Detrick in Maryland—developed an early-generation experimental human EEE vaccine in the mid-1980s, which is investigated in clinical trials, but it is not licensed and only available under a US Army Investigational New Drug programme. (10)

Western equine encephalitis

Disease characteristics and general points on treatment

Western equine encephalitis virus (WEEV) mainly circulates in the western regions of Canada and the United States and the southern cone of South America. WEEV is a naturally occurring recombinant virus derived from EEEV and a SINV-like virus. WEEV is transmitted among avian vertebrate hosts by mosquito vectors. The principal enzootic host and vector for WEEV are house sparrows (*Passer domesticus*) (HOSPs) and *Culex* (Culex) *tarsalis Coquillett* mosquitoes. During years of high enzootic activity, WEEV can also infect a variety of mammals and initiate an independent mammal/Aedes spp. cycle. Humans and horses are considered to be dead-end hosts. The incubation period for WEEV disease ranges from 2 to 7 days. The reported death fatality rate for WEEV varies between 3% to 15% depending on the specific epizootic/epidemic event. WEEV infection can result in a broad spectrum of disease outcomes ranging from subclinical, febrile symptoms to encephalitis/encephalomyelitis and death. Abrupt onset fever, chills, headache, nausea, and vomiting. Neurological signs and symptoms, including lethargy, drowsiness, neck stiffness, photophobia, vertigo, and mental status changes can manifest within a few days. Infants are more prone to irritability, convulsions, upper motor neuron deficits, and tremor. Neurological sequelae are often seen in patients recovering from neurological complications and is more often in younger individuals. (11–13)

There are currently no approved treatments or vaccines available. Supportive care for patients should be provided.

References

1. Azar S.R. et al., 'Epidemic Alphaviruses: Ecology, Emergence and Outbreaks', Microorganisms 8, 1167 2020
2. Lundberg L. et al., 'Venezuelan Equine Encephalitis Virus Capsid—The Clever Caper', Viruses 9, 279 2017
3. Croddy E., 'Chemical and Biological Warfare: A Comprehensive Survey for the Concerned Citizen', Springer Science & Business Media, 2002
4. Crosby B., M.E. Crespo, 'Venezuelan Equine Encephalitis', in: StatPearls, StatPearls Publishing, 2024
5. Cao X. et al., 'Efficacy of a brain-penetrant antiviral in lethal Venezuelan and eastern equine encephalitis mouse models', Sci. Transl. Med. 15, eabl9344 2023
6. Pittman P.R. et al., 'Long-term duration of detectable neutralizing antibodies after administration of live-attenuated VEE vaccine and following booster vaccination with inactivated VEE vaccine', Vaccine 14, 337–343 1996
7. Morens D.M. et al., 'Eastern Equine Encephalitis Virus - Another Emergent Arbovirus in the United States', N. Engl. J. Med. 381, 1989–1992 2019
8. Banda C., D. Samanta, 'Eastern Equine Encephalitis. [Updated 3 Jul 2023]', in: StatPearls, StatPearls Publishing, 2024
9. CDC, 'Clinical Signs and Symptoms of Eastern Equine Encephalitis', East. Equine Enceph. Virus 2024, available from: https://www.cdc.gov/eastern-equine-encephalitis/hcp/clinical-signs/index.html
10. Pittman P.R., S.A. Plotkin, 'Biodefense and Special Pathogen Vaccines', Plotkins Vaccines, 149-160.e7 2018
11. Bergren N.A. et al., '"Submergence" of Western equine encephalitis virus: Evidence of positive selection argues against genetic drift and fitness reductions', PLoS Pathog. 16, e1008102 2020
12. Reisen W., T. Monath, 'Western equine encephalomyelitis', in: The arboviruses: epidemiology and ecology, pp. 89–137, CRC Press, Boca Raton, FL, 1988
13. Medovy H., 'Western equine encephalomyelitis in infants', J. Pediatr. 22, 308–318 1943

Category C: Biological agents and medicinal products

Nipah virus

Disease characteristics and general points on treatment

Fruit bats of the *Pteropodidae* family are the natural host of Nipah virus. Nipah virus (NiV) can be transmitted to humans from direct contact with infected animals like bats or pigs or their body fluid (blood, urine or saliva), consuming food products that have been contaminated by body fluids of infected animals, like palm sap or fruit, and close contact with a person infected with NiV or their body fluids, including nasal or respiratory droplets, urine or blood. Human to human transmission has been reported from Bangladesh and India, most commonly in families and caregivers of NiV-infected patients and in health care settings. The incubation period (interval from infection to the onset of symptoms) is believed to range from 4 to 14 days. However, an incubation period as long as 45 to 60 days has been reported. Infection with NiV can cause asymptomatic infection to acute respiratory infection (mild, severe) and potentially fatal encephalitis. Initial symptoms include fever, vomiting, headache, cough, difficulty in breathing and muscle aches. A phase of encephalitis may follow, where symptoms can include drowsiness, disorientation, mental confusion, and seizure which can rapidly progress to coma within 24 to 48 hours. Approximately 20% of survivors develop long-term side effects, including persistent convulsions and personality changes. Dormant or latent infections that lead to delayed onset of encephalitis and sometimes death much later after exposure have also been reported months or even years after exposure. The case fatality rate is estimated at 40% to 75%. This rate can vary by outbreak depending on the virus strain, local capabilities for epidemiological surveillance and clinical management, and possibly mode of transmission. (1-6)

There are currently no approved treatments or vaccines available. Supportive care, including rest, hydration, and treatment of symptoms as they occur is often the only treatment option. Intensive supportive care is recommended to treat severe respiratory and neurologic complications. Some antivirals and monoclonal antibodies are presently in different phases of pre-clinical and clinical development. The monoclonal antibody, m102.4, has completed phase 1 clinical trials and has been used on a compassionate use basis in recent outbreaks. The antiviral remdesivir has proved effective in preventing severe disease in non-human primates when given as post-exposure prophylaxis after 3 days and may be complementary to immunotherapeutic treatments. The drug ribavirin was used to treat a small number of patients in the initial Malaysian NiV outbreak, but its efficacy in patients is unclear. (5-9)

Vaccines in development include the HeV-sG-V Nipah vaccine (Phase 1), rVSVΔG-EBOV GP/NiV G (Phase 1), NiV mRNA Vaccine, mRNA-1215 (Phase 1), and ChAdOx1 NipahB (Phase 1). (10-12)

References

1. Bradel-Tretheway B.G. et al., 'Nipah and Hendra Virus Glycoproteins Induce Comparable Homologous but Distinct Heterologous Fusion Phenotypes', J. Virol. 93, e00577-19 2019
2. Talukdar P. et al., 'Molecular Pathogenesis of Nipah Virus', Appl. Biochem. Biotechnol. 195, 2451–2462 2023
3. Goh K.J. et al., 'Clinical features of Nipah virus encephalitis among pig farmers in Malaysia', N. Engl. J. Med. 342, 1229–1235 2000
4. Hassan M.Z. et al., 'Nipah virus disease: what can we do to improve patient care?', Lancet Infect. Dis. 24, e463–e471 2024
5. WHO, 'Nipah virus', available from: https://www.who.int/news-room/fact-sheets/detail/nipah-virus
6. WHO, 'Nipah virus infection', available from: https://www.who.int/health-topics/nipah-virus-infection

1. Playford E.G. et al., 'Safety, tolerability, pharmacokinetics, and immunogenicity of a human monoclonal antibody targeting the G glycoprotein of henipaviruses in healthy adults: a first-in-human, randomised, controlled, phase 1 study', Lancet Infect. Dis. 20, 445–454 2020
2. de Wit E. et al., 'Late remdesivir treatment initiation partially protects African green monkeys from lethal Nipah virus infection', Antiviral Res. 216, 105658 2023
3. Chong H.T. et al., 'Treatment of acute Nipah encephalitis with ribavirin', Ann. Neurol. 49, 810–813 2001
4. ClinicalTrials.gov, 'Study Details | Safety and Immunogenicity of a Nipah Virus Vaccine', available from: https://clinicaltrials.gov/study/NCT04199169
5. van Doremalen N. et al., 'ChAdOx1 NiV vaccination protects against lethal Nipah Bangladesh virus infection in African green monkeys', NPJ Vaccines 7, 171 2022
6. ClinicalTrials.gov, 'Study Details | Dose Escalation, Open-Label Clinical Trial to Evaluate Safety, Tolerability and Immunogenicity of a Nipah Virus (NiV) mRNA Vaccine, mRNA-1215, in Healthy Adults', available from: https://clinicaltrials.gov/study/NCT05398796

Hantavirus

Disease characteristics and general points on treatment

Hantaviruses are a family of viruses spread mainly by rodents and can cause varied disease syndromes in humans worldwide. Infection with any hantavirus can cause hantavirus disease. Hantaviruses in the Americas are known as "New World" hantaviruses and may cause hantavirus cardiopulmonary syndrome (HCPS). Other hantaviruses, known as "Old World" hantaviruses, are found mostly in Europe and Asia and may cause haemorrhagic fever with renal syndrome (HFRS). (1–3)

Each hantavirus serotype has a specific rodent host species and is spread to humans via aerosolised virus that is shed in the urine, faeces, and saliva, and less frequently by a bite from an infected host.

Hantavirus cardiopulmonary syndrome (HCPS)

Hantavirus cardiopulmonary syndrome (HCPS) is a group of clinically similar illnesses caused by hantaviruses from the family *Bunyaviridae*. Cases of human hantavirus infection occur sporadically, usually in rural areas where forests, fields, and farms offer suitable habitat for the virus's rodent hosts. The virus is mainly transmitted to human through airborne transmission, when fresh rodent urine, droppings, nesting materials, and saliva are stirred up and inhaled. Other routes of transmission from rodents to humans include rodent bites, touching the nose or mouth after contact with objectives contaminated with rodent urine, droppings, salvia and potentially by consuming contaminated food. Human to human transmission is not commonly reported but has been reported among close contacts in patients with Andes virus. Due to the low number of reported cases, the incubation time is not known. HCPS-causing hantaviruses mainly target the respiratory and cardiovascular systems. Three phases are associated with HCPS the prodromal, cardiopulmonary, and convalescent phases. Symptoms appear to develop between one to eight weeks after exposure. Early symptoms include myalgia, headaches, chills, abdominal pain, vomiting, diarrhoea, arthralgia, conjunctival injection, and retro-ocular pain. Some patients may progress to the cardiopulmonary phase characterised by sudden onset of cough, dyspnoea, tachycardia, and hypotension followed by non-cardiogenic pulmonary oedema, respiratory failure and often cardiogenic shock often resulting in death. During the convalescent phase all previous symptoms subside except for dyspnoea, which can persist up to 1 to 2 years. HCPS case fatality rate is depending on the virus causing the HCPS and can vary between 12% (Choclo virus) and 44% (Ararquara virus). (1–4)

There are no approved treatments or vaccines available at present. Some antivirals and monoclonal antibodies are currently in clinical development. Early care in an intensive care unit with oxygen support and extracorporeal membrane oxygenation (ECMO) capability increases survival. For HCPS, ribavirin could protect hamsters from lethal ANDV challenge without toxicity. However, two clinical studies did not demonstrate any improvement in survival rates compared to placebo. Overall, there is not sufficient evidence to recommend the use of ribavirin for the treatment of HCPS. The efficacy of favipiravir remains unclear. Some studies suggest that Favipiravir reduces viral load in fatal and non-fatal hamster models of ANDV and SNV. However, other studies indicate no effect of favipiravir, if viraemia has started. No clinical data is available to support the use of favipiravir. (4-8)

Haemorrhagic fever with renal syndrome (HFRS)

Haemorrhagic fever with renal syndrome (HFRS) is a group of clinically similar illnesses caused by hantaviruses from the family *Bunyaviridae*. HFRS includes diseases such as Korean haemorrhagic fever, epidemic haemorrhagic fever, and nephropathia epidemica. The viruses that cause HFRS include Hantaan, Dobrava, Saaremaa, Seoul, Tula and Puumala. Rodents are the natural reservoir for

hantaviruses. Known carriers include the striped field mouse (*Apodemus agrarius*), the reservoir for both the Saaremaa and Hantaan virus; the brown or Norway rat (*Rattus norvegicus*), the reservoir for Seoul virus; the bank vole (*Clethrionomys glareolus*), the reservoir for Puumala virus; and the yellow-necked field mouse (*Apodemus flavicollis*), which carries Dobrava virus. Transmission to humans occurs after exposure to aerosolised urine, droppings, or saliva of infected rodents or after exposure to dust from their nests. Transmission may also occur when infected urine or these other materials are directly introduced into broken skin or onto the mucous membranes of the eyes, nose, or mouth. In addition, individuals who work with live rodents can be exposed to hantaviruses through rodent bites from infected animals. Human to human transmission may occur but is extremely rare. The incubation period is one to two weeks after exposure to infectious material, in rare cases, up to 8 weeks. HFRS is divided into five stages, the febrile, hypotensive, oliguric, diuretic and convalescent. However, the course and severity of infection is depending on the hantavirus type causing the disease. Increased vascular permeability, coagulation, dysregulation, and acute kidney injury are typical features of HFRS. Initial symptom onset is abrupt with high fever, headaches, nausea, myalgia and back and abdominal pain. Late symptoms include hypotension, ocular symptoms, acute shock, vascular leakage, and acute kidney failure, which can cause severe fluid overload. The oliguric phase occurs in half of the HFRS patients and can be associated with hypertension, complications of renal insufficiency, and pulmonary oedema. Depending upon which virus is causing the HFRS, the case fatality rate ranges between 1% (Puumala virus) and 15% (Dobrava virus). (1–3, 8, 9)

There are currently no approved treatments. Supportive therapy includes careful management of the patient's fluid (hydration) and electrolyte (e.g., sodium, potassium, chloride) levels, maintenance of correct oxygen and blood pressure levels, and appropriate treatment of any secondary infections. Dialysis may be required to correct severe fluid overload. Some antivirals and monoclonal antibodies are currently in early clinical development. The mAb cocktail containing JL16 and MIB22 has demonstrated complete or partial protection in a hamster model against lethal ANDV challenge. The broadly neutralising antibody ADI-65534, isolated from a PUUV virus-experienced donor, demonstrated pan-hantavirus activity by protecting hamsters against a lethal challenge with PUUV and ANDV. Intravenous ribavirin has been shown to decrease progression to the oliguric stage and death associated with HFRS if used as post-exposure prophylaxis in a clinical trial conducted in China. However, a clinical trial in Russia for HFRS caused by PUUV infection showed no clinical efficacy of ribavirin but an increase of adverse events. Overall, there is not sufficient evidence to recommend the use of ribavirin for the treatment of HFRS. (3, 8–15)

There are currently no approved vaccines in the EU. However, inactivated hantavirus vaccines are licensed for human use in China (bivalent inactivated vaccines against HTNV and SEOV infection and Korea (Korean HFRS vaccine Hantavax) and some vaccines are currently in clinical development. Hantavirus vaccines against HFRS have been produced by growing hantavirus (Hantaan or Seoul virus strains) in rodent brain or cell cultures followed by inactivation by either formalin or beta-propiolactone. The inactivated virus suspension is then formulated with aluminum hydroxide adjuvant. These vaccines have contributed to the reduction of HFRS in countries in Asia, however the vaccines do not provide long-lasting humoral immune response and require frequent revaccination. (16–18)

References

1. Afzal S. et al., 'Hantavirus: an overview and advancements in therapeutic approaches for infection', Front. Microbiol. 14, 1233433 2023
2. Vial P.A. et al., 'Hantavirus in humans: a review of clinical aspects and management', Lancet Infect. Dis. 23, e371–e382 2023
3. Liu R. et al., 'Vaccines and Therapeutics Against Hantaviruses', Front. Microbiol. 10, 2989 2020

4. CDC, 'Clinician Brief: Hantavirus Pulmonary Syndrome (HPS)', Hantavirus 2024, available from: https://www.cdc.gov/hantavirus/hcp/clinical-overview/hps.html
5. Safronetz D. et al., 'In vitro and in vivo activity of ribavirin against Andes virus infection', PloS One 6, e23560 2011
6. Ogg M. et al., 'Ribavirin Protects Syrian Hamsters against Lethal Hantavirus Pulmonary Syndrome — After Intranasal Exposure to Andes Virus', Viruses 5, 2704–2720 2013
7. Safronetz D. et al., 'Antiviral Efficacy of Favipiravir against Two Prominent Etiological Agents of Hantavirus Pulmonary Syndrome', Antimicrob. Agents Chemother. 57, 4673–4680 2013
8. CDC, 'Clinician Brief: Hemorrhagic Fever with Renal Syndrome', Hantavirus 2024, available from: https://www.cdc.gov/hantavirus/hcp/clinical-overview/hfrs.html
9. WHO, 'Haemorrhagic fever with renal syndrome', available from: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/hfrs
10. Williamson B.N. et al., 'Therapeutic Efficacy of Human Monoclonal Antibodies against Andes Virus Infection in Syrian Hamsters', Emerg. Infect. Dis. 27, 2707–2710 2021
11. Munir N. et al., 'Hantavirus diseases pathophysiology, their diagnostic strategies and therapeutic approaches: A review', Clin. Exp. Pharmacol. Physiol. 48, 20–34 2021
12. Garrido J.L. et al., 'Two recombinant human monoclonal antibodies that protect against lethal Andes hantavirus infection in vivo', Sci. Transl. Med. 10, eaat6420 2018
13. Mittler E. et al., 'Structural and mechanistic basis of neutralization by a pan-hantavirus protective antibody', Sci. Transl. Med. 15, eadg1855 2023
14. Huggins J.W. et al., 'Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome', J. Infect. Dis. 164, 1119–1127 1991
15. Malinin O.V., A.E. Platonov, 'Insufficient efficacy and safety of intravenous ribavirin in treatment of haemorrhagic fever with renal syndrome caused by Puumala virus', Infect. Dis. Lond. Engl. 49, 514–520 2017
16. National Pharmacopoeia Committee, 'Pharmacopoeia of the People's Republic of China 2005', People's Medical Publishing House, 80-88 2005, available at: https://www.scribd.com/document/339741066/Pharmacopoeia-of-the-People-s-Republic-of-China-2005-Vol-1-pdf
17. Cho H.-W. et al., 'Review of an inactivated vaccine against hantaviruses', Intervirology 45, 328–333 2002
18. Song J.Y. et al., 'Immunogenicity and safety of a modified three-dose priming and booster schedule for the Hantaan virus vaccine (Hantavax): A multi-center phase III clinical trial in healthy adults', Vaccine 38, 8016–8023 2020

Glossary

Biowarfare

Biowarfare is the intentional use of biological agents (e.g. micro-organisms, and toxins) as weapons in war scenarios. It is referring to a deliberated biological attack. The use is motivated or justified by ideological reasons, i.e. political or religious reasons. The biological agents can be used as they naturally occur or be genetically modified to improve mass dissemination (e.g., higher mortality or resistance to currently available medicines and vaccines) and could involve weapons of mass destruction when associated with an appropriate delivery system, as specialized munitions on the battlefield and for covert use. (1)

Bioterrorism

Bioterrorism is the intentional use of biological agents (e.g. micro-organisms and toxins) against a civilian population. The use is motivated or justified by ideological objectives (either political or religious) intending to cause panic, mass casualties, or economic loss. The biological agents can be used as they naturally occur or be genetically modified to improve mass dissemination (e.g., higher mortality or resistance to currently available medicines and vaccines). (1)

Biocrime

Biocrime is the intentional use of biological agents against a specific individual. Biocrime can be defined as the use of a disease-causing agent or toxin to kill, debilitate, or cause panic for a specific individual or a limited group of individuals. The use is motivated by personal reasons such as revenge, jealousy, or the desire for monetary gain. Therefore, the main differences between Biocrime and Bioterror are the number of people affected and the motivation behind the attack. (1)

References

1. Oliveira M. et al., 'Biowarfare, bioterrorism and biocrime: A historical overview on microbial harmful applications', Forensic Sci. Int. 314, 110366 2020

Abbreviations

CHMP - Committee for Human Medicinal Products

CDC - Centers for Disease Control and Prevention

SmPC - Summary of Product Characteristics

CNS - Central nervous system

BA - Bactericidal agent

PSI - protein synthesis inhibitors

RSI - RNA synthesis inhibitors

PEP - Post-exposure prophylaxis

AVA - Anthrax Vaccine Adsorbed

FDA - Food and Drug Administration

IV - Intravenous

MS - Member State

PO - Orally

PPE - Personal protective equipment

IM - Intramuscular

MA – Marketing authorization

MAH – Marketing authorization holder

BAT - Botulinum antitoxin

VIGIV - Vaccinia immune globulin

VHF - Viral haemorrhagic fever

NHP – Non-human primate

VSV – Vesicular stomatitis virus

SUDV - Sudan virus

EBOV – Ebola virus

MARV - Marburg virus

biEBOV - bivalent adenovirus vectored vaccine

MVD - Marburg virus disease

BHF - Bolivian Haemorrhagic Fever

ETX - Epsilon toxin

MIC - minimum inhibitory concentrations

STEC - Shiga toxin 1 and/or 2

EHEC - Enterohemorrhagic strains

HUS - Haemolytic uremic syndrome

TTP - Thrombotic thrombocytopenic purpura

ORS - Oral rehydration solutions

WHO - World Health Organization

SEB - Staphylococcal enterotoxin B

ART - Antiretroviral therapy

EEEV - Eastern equine encephalitis virus

WEEV - Western equine encephalitis virus

VEEV - Venezuelan equine encephalitis virus

NiV - Nipah virus

HCPS - Hantavirus cardiopulmonary syndrome

HFRS - Haemorrhagic fever with renal syndrome

ECMO - Extracorporeal membrane oxygenation

ANDV – Andes hantavirus

SNV – Sin Nombre virus

PUUV – Puumala (Hanta) virus

SEOV – Seoul virus