



EUROPEAN MEDICINES AGENCY
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EMA/CHMP Guidance document on use of medicinal products for the treatment and prophylaxis of biological agents that might be used as weapons of bioterrorism

At the request of the European Commission, the EMA and its Scientific Committee, the Committee for Human Medicinal Products (CHMP) produced a guidance document on the use of medicinal products for treatment and prophylaxis of biological agents that might be used as weapons of bioterrorism. The first version of the guidance, produced on 16th January 2002, considered those agents in Category A of the US Centre for Disease Control's (CDC) list of agents that might be used for the purposes of bioterrorism. On 21 February and 21 March 2002 the document was extended to cover agents in categories B and C of the CDC's list. On 25th July 2002 the document was extended to include information on nationally authorised vaccines and immunoglobulins for the prevention or post-exposure prophylaxis of some infections. Thereafter four reviews followed in 2005, 2007, 2008 and 2010; however no revisions were made at this time. This document is not intended to be a comprehensive guideline on the management of patients and the public health measures that would be necessary in the case of such an attack. The document is confined to the possible medicines and regimens that might be useful in the case of an attack with each agent listed. It should be noted that there are differences between Member States in the content of the Summaries of Product Characteristics (SmPC) for many of the medicines that have been suggested for treatment and/or prophylaxis. In fact, few of the medicinal products mentioned are authorised for the treatment and/or prophylaxis of the specific diseases mentioned. In addition, the licensing status and the actual availability of some of the medicinal products suggested vary between EU Member states. All these factors may well influence medicines that would actually be used in the case of an attack. Moreover some medicines, including anti-toxins, may have to be obtained through special access mechanisms in individual Member States. Therefore, prescribers should always consult existing national guidance and expertise, and should always refer to the national prescribing information regarding each of the medicinal products suggested.

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

Last update: 18 November 2014

Contents:

1. Introduction
2. Anthrax
3. Plague
4. Tularaemia



5. Smallpox
6. Viral haemorrhagic fever
7. Botulism
8. Brucellosis
9. Q fever
10. Glanders and melioidosis
11. Other infectious diseases (psittacosis, epidemic typhus (*Rickettsia prowazekii*), multidrug-resistant tuberculosis, shigellosis, salmonellosis, cholera)
12. Annex (biological agents for which currently no specific treatment can be recommended)

Introduction

This guidance document is concerned with the selection of medicinal products that are potentially useful for post-exposure prophylaxis and/or treatment of infectious diseases in the context of biological warfare. The guidance is an update of previous guidances published on the EMA website in the aftermath of the 9/11 events in the United States.

This initiative started with a consensus view reached between representatives from EU Member States during and after meetings held on 14 December 2001 and 12 February 2002 at the EMA in London. The outcome of that meeting was a guidance document describing the therapies to be used in an emergency situation against pathogens that appear on the US Centre for Disease Control's (CDC) list of organisms and toxins that might be used as weapons of bioterrorism (categories A, B and C).

This initial document was further updated by the EMA in the upcoming years and the present version summarises the most recent advances in the field.

Following a known or suspected act of bioterrorism, it may take some time to confirm that an attack has occurred, to identify the pathogen, and to determine its antimicrobial susceptibility. Therefore, decisions regarding whether and when to commence therapy of exposed persons, and the choice of drug, must depend on the perceived risk. Such decisions can only be made on a case by case basis, and following urgent consultation (national and/or international) between governments and their expert advisers.

As previous guidance documents, this update is not intended to provide comprehensive guidance on the management of patients or the public health measures that would be needed. The principles agreed when the first guideline was drafted, that the availability of medicinal products, and the legal, practical and logistic considerations that might influence the selection of products in individual Member States would not be considered in these recommendations, were upheld.

The possible treatment options suggested, have been selected under the provision that the pathogens listed have not been genetically engineered so as to be resistant to some or all of the potentially useful medicinal products.

The choice of first/second line drugs for treatment and/or prophylaxis and the dose and duration recommendations have been drawn from the literature (based on in-vitro activity and in-vivo data in animals and man) and from various national recommendations. Therefore, it must be pointed out that these recommendations should not be assumed to be based on randomised controlled clinical trials in all cases. Since the contraindications and warnings regarding the use of individual drugs may vary between Member States, there is a recommendation that reference should be made to the prescribing information in each country.

Those agents on the CDC's list for which there is currently no drug treatment that can be recommended have been listed in the Annex.

It is envisaged that this guidance should be further updated in the future as appropriate to take into account new scientific knowledge.

As previously envisaged, this guidance has been updated with information made available on nationally authorised vaccines and immunoglobulins that may be useful in the prevention of or post-exposure prophylaxis against certain pathogens.

The present revised guidance document was adopted by CHMP on 18 November 2014.

INHALATION, INTESTINAL and CUTANEOUS ANTHRAX

General points on treatment

Anthrax is an acute infectious disease caused by *Bacillus anthracis*, that may be infecting man via cutaneous (the most common naturally- occurring form), pulmonary or gastrointestinal routes. In the case of a deliberate release of anthrax spores, inhalational anthrax would be the most likely mode of infection. However, person to person transmission of inhalational disease does not occur. The incubation period for inhalation anthrax ranges from 1 to 60 days and patients have frequently complained over fever, chills, drenching sweats, profound fatigue, minimally productive cough, nausea or vomiting, and chest discomfort.

Cutaneous anthrax would not be expected to be a major problem in case of deliberate release of anthrax spores, although it is not impossible that this might occur.

There are no studies in humans but data from guinea pigs and monkeys have indicated that doxycycline and ciprofloxacin are both efficacious in prophylaxis and in curative treatment (1). However, early treatment is essential.

Ciprofloxacin is the recommended first line treatment. Other quinolones such as Ofloxacin and Levofloxacin offer alternative treatment options but dose recommendations can presently only be given in adults. Doxycycline and penicillins are alternative therapies when susceptibility has been confirmed although penicillin is not bactericidal against *Bacillus anthracis*. Oral amoxicillin is also an option for late-stage therapy if the patient is improving and susceptibility has been confirmed. In this regard, preliminary data indicate that *B. anthracis* may produce penicillin-hydrolysing enzymes (2).

For post-exposure prophylaxis the same antibacterial agents are recommended. However, should susceptibility to penicillin be confirmed, amoxicillin would be the drug of choice in pregnant women and children.

Because of the mortality associated with inhalational anthrax, **two or more** antimicrobial agents predicted to be effective are recommended; however, controlled studies to support a multiple drug approach are not available (2). Other agents with *in vitro* activity suggested for use in conjunction with ciprofloxacin or doxycycline include protein synthesis inhibitors (rifampin, chloramphenicol, clindamycin, clarithromycin, erythromycin, gentamicin and streptomycin) and vancomycin, but there are no or insufficient data to confirm the utility of these agents in the treatment of inhalational *B. anthracis* infection (2). In addition, penicillin should not be used alone and combination treatment with ciprofloxacin could therefore be considered.

Natural resistance of *B. anthracis* strains exists against sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime sodium, aztreonam, and ceftazidime. Therefore, these antibiotics should not be used in the treatment or prophylaxis of anthrax infection (1).

There are currently two licensed anthrax vaccines, which are produced in the UK and in the United States respectively. These vaccines have shown to be effective in protecting laboratory animals against inhalational anthrax. In certain circumstances, in addition to antimicrobial prophylaxis, post-exposure immunisation may also be indicated. With vaccination, post-exposure antibiotic prophylaxis can be reduced to 4 weeks.

Raxibacumab, a monoclonal antibody that neutralizes toxins produced by *B. anthracis*, has been licensed in US, to treat inhalational anthrax (in conjunction with antibiotherapy) and as preventive measure when alternative therapies are not available or not appropriate.

This guidance covers treatment regimens of suspected or confirmed clinical cases of inhalation, intestinal and cutaneous anthrax infections whatever the clinical presentation, and post exposure prophylaxis regimens in case of suspected or confirmed exposure to *B. anthracis*. Recommendations are compiled from references 1 - 14.

RECOMMENDATIONS

In a mass casualty setting parenteral treatment may not be an option and recommendations for oral treatment should be followed.

Otherwise oral therapy should be substituted when the patient's condition improves. In addition, some products show high bioavailability

(e.g. ciprofloxacin and doxycycline) making initial oral treatment an option.

Name of active substance. Role in therapy and prophylaxis	Section	Treatment of suspected or confirmed clinical cases of inhalation/intestinal anthrax	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen
Ciprofloxacin ➤ First line treatment and as alternative for oral follow-up ➤ First line prophylaxis until susceptibility to other agents has been confirmed	Posology	Duration of treatment: 60 days <i>Adults</i> 400 mg iv twice daily followed by 500 mg orally twice daily	Duration of prophylaxis: 60 days <i>Adults</i> 500 mg orally twice daily
		<i>Children</i> 10mg/kg IV every 12hr (change to oral therapy, 10- 15mg/kg PO when appropriate) The daily dose in children should not exceed that in adults.	<i>Children</i> 10 – 15 mg/kg orally twice daily Ciprofloxacin dose depends on age and weight, as a guide: newborn – 6 months 100mg/day 1 year – <3 years 200mg/day 3 years – <5 years 300mg/day 5 years – <7 years 400mg/day 7 years – <12 years 500mg/day 12 years+ (adult dose) 1000mg/day

	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Ofloxacin ➤ Alternative to ciprofloxacin	Posology	<i>Adults</i> 400 mg iv twice daily followed by 400 mg orally twice daily	<i>Adults</i> 400 mg orally twice daily
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Levofloxacin ➤ Alternative to ciprofloxacin	Posology	<i>Adults</i> 500 mg iv once daily, followed by 500mg orally once daily	<i>Adults</i> 500 mg orally once daily
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Doxycycline ➤ Alternative first line treatment and follow up when susceptibility is confirmed ➤ Alternative first line prophylaxis when susceptibility is confirmed	Posology	<i>Adults</i> 100 mg iv twice daily followed by 100mg orally twice daily	<i>Adults</i> 100 mg orally twice daily
		<i>Children</i> > 8years and >45 kg: adult dose > 8years and <45 kg: 2.2 mg/kg iv twice daily < 8years 2.2. mg/kg iv twice daily (maximum 200 mg per day) followed by the same doses orally	<i>Children</i> > 8years and >45 kg: adult dose > 8years and <45 kg: 2.2 mg/kg orally twice daily < 8years 2.2. mg/kg orally twice daily (maximum 200 mg per day)
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Penicillin G ➤ Alternative first line treatment if susceptibility is confirmed	Posology	<i>Adults</i> 2.4 – 3 g iv, six times daily	NA
		<i>Children</i> > 12 years: 2.4 – 3g iv, six times daily < 12 years: 30 mg/kg, four times daily	
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Amoxicillin ➤ Alternative first line treatment if confirmed susceptibility and as oral follow up. ➤ Alternative first line prophylaxis if susceptibility is confirmed	Posology	<i>Adults</i> 1g iv, three times daily followed by 500 mg orally three times daily	<i>Adults</i> 500 mg orally three times daily
		<i>Children</i> 80 mg/kg/day iv in three divided doses followed by 80 mg/kg/day orally in three divided doses (maximum dose 500 mg/dose)	<i>Children</i> 80 mg/kg/day orally in three divided doses (maximum dose 500 mg/dose)

	Contra indications	Should be considered in view of the prescribing information given in the different Member States.
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.

Cutaneous anthrax

In non-severe cases where high spontaneous recovery rates have been reported, a 7-10 days oral treatment regimen with the same products and doses as detailed in the tables is recommended. If a risk of inhalation anthrax cannot be ruled out, prophylaxis should continue for 60 days.

In more severe cases of cutaneous anthrax with signs of systemic involvement, pronounced local oedema or wounds in the head and neck region, combination treatment should be considered.

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PLAGUE

General points on treatment

Plague is a severe infectious disease caused by *Yersinia pestis*. There are many clinical forms of the disease, among which bubonic plague, septicemic plague and pneumonic plague are the most important.

In pneumonic plague, person-to-person transmission of the disease through respiratory droplets is possible. The infectious dose by respiratory droplets or aerosols is between 100 and 500 organisms. Protective measures such as masks and prophylactic antibiotic treatment (7 days) help to protect persons who have face-to-face contact with infected patients. After an incubation period of 1 to 4 days, patients with pneumonic plague present with malaise, high fever, chills, coughs, myalgia and clinical signs of sepsis.

There are very few published clinical trials that have evaluated specific agents for the treatment of plague in humans and there are limited studies in animals. Early treatment of pneumonic plague is essential. Streptomycin has historically been the preferred treatment. Gentamicin has also been used successfully in man and is currently recommended as first line therapy.

Other antibiotics have also been effective in clinical experience, including tetracycline, doxycycline, chloramphenicol and fluoroquinolones. *In vitro* studies suggest equivalent or greater activity of ciprofloxacin, levofloxacin, and ofloxacin against *Y.pestis* when compared with aminoglycosides or tetracyclines.

Antimicrobials that have been shown to have poor or only modest efficacy in animal studies have included rifampicin, aztreonam, ceftazidim, cefotetan and cefazolin as well as third generation cephalosporines (despite *in vitro* activity (1); these antibiotics should not be used.

Despite the fact that naturally occurring resistance to tetracyclines is rare, multidrug resistant strains of *Y. pestis* and quinolone resistant strains have been reported in the literature (2, 3, 10, 11), including multidrug-resistant strains of *Y. pestis*, and an isolate resistant to all antimicrobials currently recommended.

Because of the mortality that could be anticipated with pneumonic plague, combined use of two antimicrobial agents of different classes i.e. gentamicin and ciprofloxacin predicted to be effective should be considered; however, controlled studies to support a multiple drug approach are not available.

In case of meningitis caused by plague the preferred treatment option is chloramphenicol, 25-30 mg/kg iv as a loading dose, followed by 50-60 mg/kg, four times daily in both adults and children with similar oral doses for follow up treatment. In case of a favourable clinical course, the dose may be reduced to 15-30 mg/kg i.v in view of the potential bone marrow suppression. Treatment duration should be 21 days in view of the risk of relapse)

These guidance covers treatment regimens of suspected or confirmed clinical cases of plague regardless the clinical presentation, and post exposure prophylaxis in case of suspected or confirmed exposure to *Y. pestis*.

Recommendations are compiled from references 1-11.

RECOMMENDATIONS

In a mass casualty setting parenteral treatment may not be an option and recommendations for oral treatment should be followed. Otherwise oral therapy should be substituted when the patient's condition improves. In addition the high bioavailability of some products (e.g. ciprofloxacin and doxycycline) makes initial oral treatment an option. Patients should be isolated during the first 48 hours of treatment.

Name of active substance Role in therapy and prophylaxis	Section	Treatment of suspected or confirmed clinical cases of plague Duration of treatment: 10-14 days	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen Duration of prophylaxis: 7 days
Gentamicin ➤ First line treatment ➤ First choice treatment in pregnancy	Posology	<i>Adults</i> Standard doses for severe sepsis, such as 5 mg/kg iv/im once daily or 2.5 mg/kg iv/im twice daily or 2 mg/kg loading dose followed by 1,7 mg/kg iv/im thrice daily	<i>Adults</i> NA
		<i>Children</i> 2.5 mg/kg iv three times daily	<i>Children</i> NA
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	

	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.
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Streptomycin ➤ First line treatment	Posology	<i>Adults</i> 1 g im or i.v. twice daily	<i>Adults</i> NA
		<i>Children</i> 15 mg/kg i.m. or i.v. twice daily (maximum dose, 2g)	NA
	Contra indications	Should be considered in view of the prescribing information given in the different Member States. Of note, streptomycin may not be marketed in all EU Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Ciprofloxacin ➤ Second line treatment ➤ Prophylaxis	Posology	<i>Adults</i> 400 mg iv twice daily followed by 500 mg orally twice daily	<i>Adults</i> 500 mg orally twice daily (including pregnant women)
		<i>Children</i> 10-15 mg/kg/day iv twice daily followed by 10 -15 mg/kg orally twice daily. The daily dose in children should not exceed that in adults.	<i>Children</i> 10 -15 mg/kg orally twice daily

	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Ofloxacin ➤ Alternative to ciprofloxacin	Posology	<i>Adults</i> 400 mg iv twice daily followed by 400 mg orally twice daily	<i>Adults</i> 400 mg orally twice daily
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Levofloxacin ➤ Alternative to ciprofloxacin	Posology	<i>Adults</i> 500 mg iv once daily followed by 500 mg orally once daily	<i>Adults</i> 500 mg orally once daily
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Doxycycline ➤ Third line treatment ➤ Prophylaxis	Posology	<i>Adults</i>	<i>Adults</i>
		100 mg iv twice daily followed by 100 mg orally twice daily for 7 days or 100 mg i.v. single dose	100 mg orally twice daily (including in pregnant women)
	<i>Children</i>	<i>Children</i>	
	> 8 years and >45 kg: adult dose > 8 years and <45 kg: 2.2 mg/kg iv twice daily < 8 years 2.2. mg/kg iv twice daily (maximum 200mg per day) followed by the same doses orally	> 8 years and >45 kg: adult dose > 8 years and <45 kg: 2.2 mg/kg orally twice daily < 8 years 2.2. mg/kg orally twice daily (maximum 200 mg per day)	
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Trimethoprim –sulfametoazol

Chloramphenicol can be used in adults (including in pregnant women) as post-exposure prophylactics: 25 mg/kg p.o. qid x 7 days

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TULAREMIA

General points on treatment

Tularemia is an infection caused by *Francisella tularensis*. Ulceroglandular tularemia is the most common form of the disease and is usually a consequence of a bite from an arthropod vector which has previously fed on an infected animal. The occasional naturally occurring cases of inhalation tularemia often arise from farming activities. However, the pneumonic form is the likely form of the disease should this bacterium be used as a bioterrorism agent. As few as 10 – 50 organisms can produce infection via the respiratory route but there has been no documented person-person transmission. After an incubation period that ranges from 1- 5 days for primary pneumonia (otherwise 1 – 14 days), the inhalation form of tularemia is manifested by fever, prostration, weight loss and respiratory symptoms.

Aminoglycosides are the drugs of choice and virtually all strains of *F. tularensis* are susceptible to streptomycin and gentamicin. Tetracyclines and chloramphenicol have been used successfully but are associated with higher relapse rates (1, 2). Ciprofloxacin has been successfully used in clinical setting (1, 2, 3, 4, 5) and the bacteria are sensitive *in vitro* but data in patients with tularemia are lacking (2, 3, 4). 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 (6, 7, 8).

Because of the mortality that could be anticipated with serious cases of inhalational tularemia, combined use of two antimicrobial agents of different classes, i.e. gentamicin and ciprofloxacin predicted to be effective should be considered; however, controlled studies to support a multiple drug approach are not available.

In case of tularemia meningitis, the preferred treatment option is chloramphenicol, 25 mg/kg iv, four times daily in both adults and children with similar oral doses as follow up therapy. (Treatment duration should be 21 days in view of the risk of relapse).

This guidance covers treatment regimens of suspected or confirmed clinical cases of tularemia whatever the clinical presentation and post exposure prophylaxis in case of suspected or confirmed exposure to *F. tularensis*.

Recommendations are compiled from references 1-10 9.

RECOMMENDATIONS

In a mass casualty setting parenteral treatment may not be an option and recommendations for oral treatment should be followed.

Otherwise oral therapy should be substituted when the patient's condition improves. In addition, the high bioavailability of some products (eg ciprofloxacin and doxycycline) makes initial oral therapy an option.

Name of active substance Role in therapy and prophylaxis	Section	Treatment of suspected or confirmed clinical cases of Tularemia Duration of treatment: 10 –21 days (as further indicated below under posology)	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen Duration of prophylaxis: 14 days
Gentamicin ➤ First line treatment ➤ First line in pregnancy	Posology Duration: 10 days	<i>Adults</i> Standard doses for severe sepsis, such as 5 mg/kg iv once daily or 2.5 mg/kg twice daily	<i>Adults</i> NA
		<i>Children</i> 2.5 mg/kg iv three times daily	<i>Children</i> NA
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	

	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.
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Streptomycin ➤ First line treatment	Posology Duration: 10 days	<i>Adults</i> 1 g IM twice daily	<i>Adults</i> NA
		<i>Children</i> 15 mg/kg IM twice daily (maximum dose, 2 g/day)	NA
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Ciprofloxacin ➤ Second line treatment ➤ First line prophylaxis	Posology Duration: 14 days	<i>Adults</i> 400 mg iv twice daily followed by 500 mg orally twice daily	<i>Adults</i> 500 mg orally twice daily

		<i>Children</i> 10-15 mg/kg/day iv twice daily followed by 10 -15 mg/kg orally twice daily. The daily dose in children should not exceed that in adults.	<i>Children</i> 10 –15 mg/kg orally twice daily
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Ofloxacin ➤ Alternative to ciprofloxacin	Posology	<i>Adults</i> 400 mg iv twice daily followed by 400 mg orally twice daily	<i>Adults</i> 400 mg orally twice daily
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Levofloxacin ➤ Alternative to ciprofloxacin	Posology	<i>Adults</i> 500 mg iv once daily followed by 500 mg orally once daily	<i>Adults</i> 500 mg orally once daily
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Doxycycline ➤ Third line treatment ➤ Second line prophylaxis	Posology Duration: 21 days treatment 14 days prophylaxis	<i>Adults</i> 100 mg iv twice daily followed by 100 mg orally twice daily	<i>Adults</i> 100 mg orally twice daily
		<i>Children</i> > 8 years and >45 kg: adult dose > 8 years and <45 kg: 2.2 mg/kg iv twice daily < 8 years 2.2. mg/kg iv twice daily (maximum 200mg per day) followed by same regimen orally	<i>Children</i> > 8 years and >45 kg: adult dose > 8 years and <45 kg: 2.2 mg/kg orally twice daily < 8 years 2.2. mg/kg orally twice daily (maximum 200 mg per day)
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

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SMALLPOX

General points on treatment

Smallpox is a disease caused by a virus of the pox group (variola virus). Smallpox infection was declared eradicated by WHO in 1979, following a vaccination campaign. The usual incubation period is 10 to 14 days, is asymptomatic and during this period infected individuals do not transmit the virus. Clinical symptoms start with a flu-like syndrome (fever, myalgia, headache), followed by the appearance of a rash becoming vesiculo-pustular, most prominent on the face, arms and legs. Death occurs overall in about 30% of the cases (up to 100% of the cases in some rare forms of the disease). Smallpox is spread from one person to another by infected saliva droplets. Persons are most infectious during the first week of the rash.

At present, there is no proven treatment for smallpox. Therefore, patients must be managed solely with supportive therapy. Isolation (ideally in a negative-pressure room) is mandatory. Antibiotics may be useful for the control of secondary bacterial infections that may occur (1).

Different smallpox vaccines are currently approved in the EU Member States. In people exposed to smallpox, administration of such vaccine can lessen the severity of or even prevent illness if given within 3-4 (and up to 7) days after exposure (1). A "surveillance and containment" strategy, meaning careful monitoring and offering the vaccine to the close contacts of known patients first, is also highly important.

VIG (vaccinia immunoglobulin G) may be used to treat or prevent some vaccine complications or to attenuate smallpox disease in contacts not adequately protected by vaccination. VIG is not recommended for the treatment of post-vaccinial encephalitis or vaccinial keratitis.

Encouraging initial reports in the 1960s describing the therapeutic benefits of the thiosemicarbazones, cytosine arabinoside, and adenine arabinoside but the results were later questioned and none of these early reports were confirmed in further studies (2).

Ribavirin and cidofovir have been proposed as possible candidates for the treatment of smallpox (3).

In two reports (4,5), cidofovir (Vistide®), which has been approved via the EU centralised procedure for the treatment of cytomegalovirus retinitis in immunocompromised patients, was also found to protect mice, again when given as a single dose, against a lethal aerosolised or intranasal cowpox virus challenge. However, the potential utility of this drug in post-exposure prophylaxis is limited, given the fact that it must be administered intravenously and its use is often accompanied by serious renal toxicity (2).

Ribavirin has a broad antiviral spectrum (6) that includes small pox virus but no recommendations on treatment for small pox can be made for ribavirin or for cidofovir at the present time.

It is acknowledged that other investigational medicinal products are also being developed for the treatment of smallpox (8, 9)

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VIRAL HAEMORRHAGIC FEVER

General points on treatment

VHFs are caused by viruses of four distinct families: arena viruses (Lassa fever, Argentine haemorrhagic fever); filoviruses (Ebola and Marburg); bunyaviruses (Crimean-Congo, hantavirus); and flaviviruses (dengue) (1). Lassa fever and Crimean-Congo Haemorrhagic Fever are spread from man to man and are the only two VHFs to be considered in the context of this document. The incubation period for VHF ranges from 2 to 21 days and common presenting symptoms are fever, myalgia and prostration followed by shock and generalised mucus membrane bleeding.

Patients receive intensive supportive therapy and the characteristics of the individual case (e.g. lung involvement) should guide the doctor as to the need for treatment of contacts.

Ribavirin, an anti-viral drug, has been effective in treating some individuals with Lassa fever, Crimean-Congo Haemorrhagic Fever and Haemorrhagic Fever with Renal Syndrome (2,3,4,5). Treatment with convalescent-phase plasma has been used with success in some patients with Argentine haemorrhagic fever (1,6.)

Ribavirin, has been shown to be most effective when given early in the course of the illness. Patients should also receive supportive care consisting of maintenance of appropriate fluid and electrolyte balance, oxygenation and blood pressure, as well as treatment of any other complicating infections (1).

This guidance considers treatment of suspected or confirmed clinical cases of Lassa fever and Crimean-Congo Haemorrhagic Fever and post exposure prophylaxis regimens in case of suspected or confirmed exposure to the virus.

The Dose Recommendations given below are compiled primarily from ref. 7 (based on refs 3 and 8) and 9.

The largest seen epidemic of Ebola virus (EBOV) disease is currently ongoing in some countries in West Africa. A number of medicinal products aimed at targeting both prevention and treatment of the Ebola virus disease are currently under development and all existing regulatory tools and resources are in place to underpin the global effort of providing effective and safe medicines to prevent and treat the disease.

RECOMMENDATIONS

In a mass casualty setting parenteral treatment may not be an option and recommendations for oral treatment should be followed. Otherwise oral therapy should be substituted when the patient's condition improves.

Name of active substance Role in therapy and prophylaxis	Section	Treatment of suspected or confirmed clinical cases of VHF Duration of treatment: 10 days	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen Duration of prophylaxis: 7 days
Ribavirin	Posology	<p>Adults Two iv regimens can be used</p> <ul style="list-style-type: none"> • Initial dose of 2 g followed by 1 g every 6 hours for 4 days followed by 0.5 g every 8 hours for 6 days <p style="text-align: center;">Or</p> <p>Initial dose of 30 mg/kg followed by 15 mg/k every 6 hours for 4 days, followed by 7.5 mg/kg every 8 hours for 6 days</p> <p>Oral regimen: 2 g orally (loading dose) followed by 4g/day in 4 divided doses for 4 days followed 2g/day for 6 days</p> <p>Children No recommendations can be given</p>	<p>Adults 2 g/day orally in 4 divided doses</p> <p>Children No recommendations can be given</p>
	Contra indications	Ribavirin is embryotoxic and teratogenic. However, given the seriousness of the condition the same product as in non-pregnant adults could be considered. Patients must not breastfeed during therapy.	

	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to replace breastfeeding by artificial lactation
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BOTULISM

General points on treatment

A deliberate release may involve airborne dissemination of toxin, producing botulism through inhalation. Alternatively, it may involve contamination of food and water supplies either with toxin or with *C. botulinum* bacteria. Antibacterial agents have no role in the management of this type of botulism (may lyse *Clostridium botulinum* and increase toxic load).

Botulism is a clinical diagnosis. Effective treatment depends on provision of supportive care and rapid administration of botulinum antitoxin based on clinical presentation.

The trivalent equine antitoxin contains antibodies to botulinum toxin types A, B and E, which are the most common toxin types associated with sporadic cases of human botulism. The quantities of antitoxin are usually expressed in International Units (IU) per unit of volume. Passive immunisation with equine antitoxin is effective in reducing the severity of symptoms if administered early in the course of the disease. No specific dose recommendations can be made due to the variability of the properties e.g. strength of the available antitoxin in different EU Member States. Therefore, the product particular supplied with the vial(s) must be consulted. Availability of antitoxin appears to be very variable across the EU and it is usually only obtainable from designated centres where limited stocks are stored. If not stocked it could be directly obtained from the supplier, i.e. equine Botulism-Antitoxin by Novartis Behring (0049 64 21 39 05).

In the US, equine derived heptavalent antitoxin (BAT Cangene) has been licensed by FDA.

An oligoclonal cocktail of 6 recombinant, super-humanized IgGs, neutralizing the neurotoxins secreted by all strains of *Clostridium botulinum* A, B and E is under development (6).

Most patients eventually recover after weeks to months of supportive care.

Recommendations are compiled from references 1-6.

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BRUCELLOSIS

General points on treatment

Four species are pathogenic to man: *B. melitensis* (acquired mainly from goats and sheep), *B. suis* (swine), *B. abortus* (mainly from cattle) and *B. canis* (dogs). The bacteria are highly infectious by aerosols. Person to person transmission does not usually occur.

The incubation period varies from 5 days to 6 months. The symptoms can be very diverse (eg. fever, night sweats, malaise cough, joint infections, hepatitis etc. have been described) and vary according to the duration of the infection at the time of clinical presentation.

For most presentations of the disease, combination treatment 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(1,2,3,4,5). Regarding the treatment duration, doxycycline and rifampicin should be administered for 6 weeks (45 days), administration of streptomycin should be made for 2 weeks and of gentamycin for 1 week (5).

A recently published systematic review and meta-analysis of randomised trials in the treatment of brucellosis (5) 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. Of note, the use of a regimen with parenteral administration may not always be the most advantageous option.

In children younger than 8 years of age, the combination rifampicin-cotrimoxazole given for 45 days can be recommended (6).

Fluoroquinolones can penetrate intracellularly and *in vitro* and *in vivo* studies have been encouraging, showing that quinolones combined with rifampicin could also be considered as alternative to the above. Other alternatives could be the combinations ofloxacin-rifampicin and doxycycline-cotrimoxazole. Triple therapy cannot be recommended at present for non-complicated brucellosis.

For complicated cases , including endocarditis, joint infections and CNS infections, a more prolonged course of multiple antibiotics (doxycycline plus two or more other active antibiotics) is required.

This guidance covers treatment regimens of suspected or confirmed clinical cases of brucellosis. Although recommendations are also given for post exposure prophylaxis in case of suspected or confirmed exposure to *Brucella*, there is not enough evidence to support this.

Recommendations are compiled from references 1-6.

RECOMMENDATIONS

In a mass casualty setting parenteral treatment may not be an option and recommendations for oral treatment should be followed.

Otherwise oral therapy should be substituted when the patient's condition improves. In addition, some products show high bioavailability (e.g. doxycycline) making initial oral treatment an option.

Name of active substance Role in therapy and prophylaxis	Section	Treatment of suspected or confirmed clinical cases Duration of treatment: 6 weeks	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen Duration of prophylaxis: 3-6 weeks
Doxycycline ➤ First line treatment in combination with rifampicin or streptomycin or with gentamicin in adults and children > 8 years of age ➤ First line prophylaxis in combination with rifampicin in adults and children > 8 years of age.	Posology	Adults 100mg iv twice daily followed by 100 mg orally twice daily Children > 8years and >45 kg: adult dose > 8years and <45 kg: 2.2 mg/kg iv twice daily followed by the same doses orally	Adults 100 mg orally twice daily Children > 8years and >45 kg: adult dose orally > 8years and <45 kg: 2.2 mg/kg orally twice daily
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Name of active substance Role in treatment and prophylaxis	Section	Treatment of suspected or confirmed clinical cases Duration of treatment: 6 weeks	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen Duration of prophylaxis: 3 – 6 weeks
Rifampicin ➤ First line treatment in combination with doxycycline in adults and children > 8 years ➤ First line prophylaxis in combination with doxycycline in adults and children > 8 years of age ➤ First line treatment and prophylaxis in combination with TMP-SMX in children < 8 years of age	Posology	Adults 10 – 15 mg/kg/day i.v in one or two doses followed by 600 – 900 mg orally once daily Children 10 – 15 mg/kg/day i.v in one or two doses followed by 10 – 15 mg/kg/day orally in one or two doses	<i>Adults</i> 600 – 900 mg orally once daily Children 10 – 15 mg/kg/day orally in one or two doses
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Name of active substance Role in treatment and prophylaxis	Section	Treatment of suspected or confirmed clinical cases Duration of treatment: 1-2 weeks (review the need for further treatment after 2 weeks with aminoglycosides; less for children)	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen Duration of prophylaxis: 3 - 6 weeks
Gentamicin ➤ Alternative first line treatment in combination with doxycycline in adults and children > 8 years	Posology	<i>Adults</i> 3-5 mg/kg iv once daily or 1.5 - 2.5 mg/kg twice daily	NA
		<i>Children</i> 1- 2.5 mg/kg iv three times daily.	
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding. First line for women who are pregnant or breastfeeding.	

Name of active substance Role in treatment and prophylaxis	Section	Treatment of suspected or confirmed clinical cases Duration of treatment: 2 weeks (review the need for further treatment after 2 weeks with aminoglycosides; less for children)	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen Duration of prophylaxis: 3 - 6 weeks
Streptomycin ➤ Alternative first line treatment in combination with doxycycline in adults and children > 8 years	Posology	<i>Adults</i> 1 g im once or twice twice daily	NA

		<i>Children</i> 15 mg/kg once or twice daily (maximum dose, 2g per day)	
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Name of active substance	Section	Treatment of suspected or confirmed clinical cases	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen
Role in treatment and prophylaxis		Duration of treatment: 6 weeks	Duration of prophylaxis: 3 weeks (ref 4)

<p>TMP-SMX (trimethoprim sulphamethoxazole)</p> <ul style="list-style-type: none"> ➤ First line treatment and prophylaxis in combination with rifampicin in children < 8 years of age and as an alternative in pregnant women ➤ Second line treatment and prophylaxis in combination with rifampicin in adults and children > 8 years 	<p>Posology</p>	<p>Adults</p> <p>TMP: 6-8 mg/kg/day and SMX: 40mg/kg/day iv in one or two divided doses followed by TMP: 6-8 mg/kg/day and SMX: 40mg/kg/day orally in one or two divided doses.) (Maximum total dose is 1440 mg twice daily. Consideration could be given to reducing the dose after 2 weeks)</p> <p>Children < 8 years</p> <p>TMP: 6-8 mg/kg/day and SMX: 30-40mg/kg/day iv in 2 divided doses followed by TMP: 6-8 mg/kg/day and SMX: 30-40mg/kg/day orally in one or two divided doses (Consideration could be given to reducing the dose after 2 weeks).</p>	<p>Adults</p> <p>960 mg <i>per os</i> twice daily</p> <p>Children < 8years</p> <p>TMP: 6-8 mg/kg/day and SMX: 30-40 mg/kg/day orally in one or two divided doses for three weeks.</p>
	<p>Contra indications</p>	<p>Should be considered in view of the prescribing information given in the different Member States.</p>	
	<p>Pregnancy and lactation</p>	<p>Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.</p>	

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Q FEVER

General points on treatment

Q fever is a zoonosis caused by *Coxiella burnetii*, an obligate intracellular gram-negative bacterium with high infectivity but with relatively low virulence.. Transmission from man to man is rare.

C. burnetii could be used as a biological weapon in an aerosolised form or as a contaminant of food, water or potentially mail or other items. Although this would not cause high mortality, it would result in large numbers of acute and chronically ill people.

The incubation period normally varies from 2 to 14 days (1). Up to 50% of infected individuals remain asymptomatic. In acute presentations, symptoms such as headache, malaise, fever, night sweats, cough and pneumonia with pleuritic pain may develop, but the disease is often self-limiting. Alternatively, symptoms may not appear until long after initial infection, so that the patient presents with the chronic forms of the disease.

Doxycycline is recommended for first line treatment. Both successes and failures with erythromycin in the treatment of Q fever have been reported (2,3). However, clinical data have indicated that the times to defervescence that may be achieved with erythromycin, roxithromycin and clarithromycin are similar to that of doxycycline, and that macrolides can be used empirically as second line therapy for acute Q fever (4). Quinolones have been used (2,3,5), and these agents and chloramphenicol may be useful in meningoencephalitis (see chapters on plague and tularemia for dosing recommendations on chloramphenicol).

In chronic infection with *Coxiella burnetii*, which may manifest as endocarditis, the choice of drug and duration of treatment (usually prolonged) has to be considered on an individual basis (2). Combination therapy is normally administered, such as rifampicin and doxycycline or doxycycline and fluoroquinolones

This guidance covers possible treatment regimens for suspected or confirmed acute clinical cases of Q fever and post exposure preventive therapy. It has been proposed that post-exposure preventive treatment may be effective if begun at 8 –12 days post exposure, (6). If given within 7 days of exposure, chemoprophylaxis is not effective and may prolong the onset of disease.

Recommendations are compiled from references 1-8.

RECOMMENDATIONS

In a mass casualty setting parenteral treatment may not be an option and recommendations for oral treatment should be followed.

Otherwise oral therapy should be substituted when the patient's condition improves. In addition, some products show high bioavailability (e.g. ciprofloxacin and doxycycline) making initial oral treatment an option.

Name of active substance Role in treatment and prophylaxis	Section	Treatment of suspected or confirmed clinical cases Duration of treatment: 1 - 3 weeks	Post exposure preventive treatment in case of suspected or confirmed exposure to the pathogen Duration of preventive treatment: 1 week (ref 6)
Doxycycline ➤ First line treatment in adults and children ➤ First line preventive treatment in adults and children	Posology	Adults 100mg iv twice daily followed by 100 mg orally twice daily	<i>Adults</i> 100 mg orally twice daily
		Children > 8years and >45 kg: adult dose > 8years and <45 kg: 2.2 mg/kg iv twice daily < 8years 2.2. mg/kg iv twice daily (maximum 200mg per day) followed by the same doses orally	Children > 8years and >45 kg: adult dose orally > 8years and <45 kg: 2.2 mg/kg orally twice daily < 8years 2.2. mg/kg orally twice daily <i>(maximum 200mg per day)</i>

	Contra indications	Should be considered in view of the prescribing information given in the different Member States.
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.

Name of active substance Role in treatment and prophylaxis	Section	Treatment of suspected or confirmed clinical cases	Post exposure preventive treatment in case of suspected or confirmed exposure to the pathogen
Erythromycin ➤ Second line treatment in adults and children ➤ Second line preventive treatment in adults and children	Posology	Duration of treatment: 1- 3 weeks Adults Up to 1g iv 4 times daily followed by 500 mg orally four times daily.	Duration of preventive treatment: 1 week (ref 6) <i>Adults</i> 500mg orally four times daily
		Children 50 mg/kg/day i.v in four divided doses followed by >35 kg: 500 mg orally, four times daily < 35 kg: 50 mg/kg/day orally in two divided doses daily (not to exceed 500 mg four times daily)	<i>Children</i> >35 kg: 500 mg orally, four times daily < 35 kg: 50 mg/kg/day orally in two divided doses daily (not to exceed 500 mg four times daily)
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Name of active substance Role in treatment and prophylaxis	Section	Treatment of suspected or confirmed clinical cases	Post exposure preventive treatment in case of suspected or confirmed exposure to the pathogen
Clarithromycin ➤ Alternative to erythromycin	Posology	Adults 500 mg i.v twice daily followed by 500 mg orally twice daily	<i>Adults</i> 500 mg orally twice daily
		Children The iv formulation is not recommended in children 7.5 mg/kg twice daily orally; max 250 mg twice daily. Over 40 kg give adult dose.	<i>Children</i> 7.5 mg/kg twice daily orally; max 250 mg twice daily. Over 40 kg, give adult dose.
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Name of active substance Role in treatment and prophylaxis	Section	Treatment of suspected or confirmed clinical cases	Post exposure preventive treatment in case of suspected or confirmed exposure to the pathogen
	Posology	Adults 150 mg orally twice daily	<i>Adults</i> 150 mg orally twice daily

Roxithromycin ➤ Alternative to erythromycin		Children 8 mg/kg/day orally in two divided doses	<i>Children</i> 8 mg/kg/day orally in two divided doses
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Name of active substance. Role in therapy and prophylaxis	Section	Treatment of suspected or confirmed clinical cases Duration of treatment: 2 -3 weeks	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen
Ciprofloxacin ➤ First line treatment in case of meningococcal meningitis.	Posology	<i>Adults</i> 400 mg iv twice daily followed by 500 mg orally twice daily	NA
		<i>Children</i> 10 – 15 mg/kg iv twice daily followed by 10-15 mg/kg orally twice daily	<i>Children</i> NA
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Ofloxacin Alternative to ciprofloxacin	Posology	<i>Adults</i> 400 mg iv twice daily followed by 400 mg orally twice daily	NA

	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Levofloxacin Alternative to ciprofloxacin	Posology	<i>Adults</i>	NA
		500mg iv once daily, followed by 500mg orally once daily	
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

For pregnant women and children a further alternative therapy in acute Q-fever has been proposed:

Women who are pregnant or breast-feeding

Co-trimoxazole 960mg (800mg sulfamethoxazole/160mg trimethoprim) oral twice daily Until term/ delivery

Children under 12

Co-trimoxazole (sulfamethoxazole 40mg/kg and trimethoprim 8mg/kg) Oral daily 14 days

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GLANDERS and MELIOIDOSIS

General points on treatment

The causative agents of glanders and melioidosis are the non-fermenting gram-negative bacilli *Burkholderia mallei* and *Burkholderia pseudomallei*, respectively. Exposure by inhalation is considered most likely in the context of biological warfare and the infective dose is assumed to be low. The probability of transmission from person to person is low.

The incubation period normally ranges from 10 to 14 days but there have been well-documented cases in which the first clinical manifestations of infection have occurred years after exposure.

Both diseases can present with acute pneumonia or as an overwhelming sepsis. Both diseases may be fatal without treatment.

The antibiotic susceptibility pattern profile of *B. mallei* resembles that of *B. pseudomallei* and both pathogens are usually susceptible *in vitro* to ceftazidime, imipenem, meropenem, doxycycline. (1). There have been reports of high MICs of ciprofloxacin for some strains of *B. pseudomallei* (2).

Although initial treatment with imipenem or meropenem, or with ceftazidime, for 2-3 weeks has been recommended for both infections, there is little experience in treating glanders in humans. In severe cases, combination therapy with doxycycline or cotrimoxazole may be considered (3,4). In mild cases, initial oral therapy with an active agent (such as doxycycline, co-amoxiclav, fluoroquinolones or TMP/SMZ) may be sufficient.

Following successful initial therapy, a prolonged oral eradication course has been proposed. This includes up to 12-24 weeks of doxycycline 4mg/kg/day plus co-trimoxazole (sulfamethoxazole 40mg/kg and trimethoprim 8mg/kg) oral daily or co-amoxiclav 20/5mg/kg orally three times daily.

There is no evidence of the protective efficacy of post-exposure antibiotic prophylaxis in preventing human melioidosis or glanders. However, following known heavy exposure, a 7 to 10 days regimen of doxycycline or co-trimoxazole could be considered.

The recommendations below are compiled from references 1 – 9.

RECOMMENDATIONS

In a mass casualty setting parenteral treatment may not be an option and recommendations for oral treatment should be followed.

Otherwise oral therapy should be substituted when the patient's condition improves. In addition, some products show high bioavailability (e.g. ciprofloxacin and doxycycline) making initial oral treatment an option.

Name of active substance Role in treatment and prophylaxis	Section	Treatment of suspected or confirmed clinical cases	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen
Imipenem > First line treatment	Posology	Duration of initial treatment: 2 to 3 weeks Adults 50 mg/kg/day, up to 1 g iv four times daily Children >3 years: 15mg/kg, four times daily (up to max 2 g daily). Over 40 kg, use adult dose 3 months – 3 years: 15 – 25 mg/kg, four times daily.	No recommendations can currently be given (see introduction)
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Name of active substance	Section	Treatment of suspected or confirmed clinical cases	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen
Role in treatment and prophylaxis		Duration of initial treatment: 2 to 3 weeks	
Meropenem ➤ Alternative to Imipenem	Posology	Adults 500 mg – 1g iv, three times daily Children >3 months: 10 - 20 mg/kg, three times daily Adult dose for 50 kg and over.	No recommendations can currently be given (see introduction)
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Name of active substance	Section	Treatment of suspected or confirmed clinical cases	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen
Role in treatment and prophylaxis		Duration of initial treatment: 2 – 3 weeks	
Ceftazidime ➤ Alternative first line treatment	Posology	Adults 2 g iv, three times daily. Children > 2 months: 100 mg/kg/day in three divided (maximum dose is 6g) < 2months: 60 mg/kg/day in two divided doses	No recommendations can currently be given (see introduction)
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	

	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	
Name of active substance	Section	Treatment of suspected or confirmed clinical cases	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen
Role in treatment and prophylaxis		Duration of initial treatment: 2-3 weeks	
Doxycycline ➤ Combination treatment with imipenem, /meropenem or ceftazidime in severe cases	Posology	Adults 100 mg iv twice daily Children > 8years and >45 kg: adult dose > 8years and <45 kg: 2.2 mg/kg iv twice daily < 8years 2.2. mg/kg iv twice daily (maximum 200mg per day)	No recommendations can currently be given (see introduction)
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

Name of active substance Role in treatment and prophylaxis	Section	Treatment of suspected or confirmed clinical cases Duration of initial treatment: 2-3 weeks	Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen
TMP-SMX (trimethoprim sulphamethoxazole) ➤ Combination treatment with imipenem/meropenem or ceftazidime in severe cases	Posology	<u>Adults</u> TMP: 6-8 mg/kg/day and SMX: 40mg/kg/day iv in one or two divided doses followed by TMP: 6-8 mg/kg/day and SMX: 40mg/kg/day orally in one or two divided doses.) (Maximum total dose is 1440 mg twice daily. Consideration could be given to reducing the dose after 2 weeks) <u>Children < 8 years</u> TMP: 6-8 mg/kg/day and SMX: 30-40mg/kg/day iv in 2 divided doses followed by TMP: 6-8 mg/kg/day and SMX: 30-40mg/kg/day orally in one or two divided doses (Consideration could be given to reducing the dose after 2 weeks).	No recommendations can currently be given (see introduction)
	Contra indications	Should be considered in view of the prescribing information given in the different Member States.	
	Pregnancy and lactation	Given the seriousness of the condition the same product as in non-pregnant adults should be considered. It is recommended, when possible, to cease breastfeeding.	

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3. CDC. Editorial. Laboratory-Acquired Human Glanders --- Maryland, May 2000. *MMWR* 2000; 49(24); 532-5.
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OTHER BACTERIAL INFECTIONS

Psittacosis

Chlamydophila psittaci infection, acquired through respiratory droplet transmission of chlamydophila from infected birds, has been considered for many years an occupational hazard for employees of pet shops, poultry farmers, but also abattoirs workers and veterinarians (1). Pet owners can also be affected. Although all birds are susceptible, 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. 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 characterized by fever, chills, headache, and less frequently, cough, myalgia, rash, arthralgia and joint swelling. The patient may progress to develop atypical pneumonia, and glomerulonephritis and endocarditis may also occur in more severe cases.

Treatment Recommendation

The recommended treatment for *C. psittaci* infection is doxycycline *per os* 100 mg twice daily or tetracycline *per os* 500 mg four times daily for 10 to 21 days (1). Erythromycin (doses as described for Q fever) offers an alternative treatment option but may be less efficacious (1).

1. Mandell GL, Bennett JE, Dolin R, Principles and practice of infectious diseases, 7th edition, Chapter 181, 2010.

Epidemic or Louse-borne Typhus (*Rickettsia prowazekii*)

Rickettsiae are obligate intracellular bacteria and are difficult to grow in a laboratory setting. Rickettsiae move through mammalian reservoirs and are transmitted by insects or tick vectors. Epidemic typhus is very predominantly a louse-borne infection due to *R.prowazekii*. Unusually, among the rickettsioses, humans are the primary reservoir and there is transmission of lice from person to person. The incubation period is 8 to 16 days. Mortality rates are variable but up to 40% in untreated cases have been reported, with even higher rates for those over 50 years of age. Recrudescence can occur many years after the primary infection (Brill-Zinsser disease).

Treatment Recommendation

The treatment of choice is doxycycline 100 mg b.i.d for 7 to 100 days (1). Doxycycline as a single 200 mg dose has been reported to be effective (1,2,3,4) and should only be used when availability of the antibiotic is limited (risk of relapse!). Chloramphenicol, 60 – 75 mg/kg in 4 divided doses until 2 to 3 days after defervescence and tetracycline 25-50 mg/kg/day in 4 divided doses can be used as alternative treatment options (1,4).

1. Mandell GL, Bennett JE, Dolin R, Principles and practise of infectious diseases, 7th edition, Chapter 190. 2010.
2. Raoult D.and Roux V. Rickettsioses As Paradigms of New or Emerging Infectious Diseases - Clinical Microbiology Reviews, , Vol 16, N° 4 : p.694-719, Oct.1997.
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Multidrug-resistant tuberculosis (MDR-TB)

M. tuberculosis is commonly transmitted from an infected patient to other persons by coughing aerosolised droplets. Untreated infections are often fatal. Some mycobacteria are resistant to isoniazide and rifampicin, two of the major existing antimycobacterials, and disease caused by these strains is called multi-drug resistant TB (MDR-TB).

The successful medical management of patients with MDR-TB or of exposed individuals depends on the rapid availability of drug susceptibility test results. Before and after these results are available, the choice of treatment must also take into consideration the likely availability of specific drugs and regional specialised treatment guidelines (e.g. ^{1,2}). General management considerations must also take into account the proportion of the population that have already received BCG and the availability of BCG vaccine.

It is not considered to be appropriate or possible to provide general treatment guidance in this document. However, the following list includes the anti-tuberculosis drugs that may need to be used to combat MDR-TB: kanamycin, streptomycin, amikacin, capreomycin, rifabutin, levofloxacin, moxifloxacin, ofloxacin, ethionamide, prothionamide, cycloserine, PAS (para-aminosalicylic acid), terizidone, clofazimine, delamanid.

There are several different BCG vaccines (containing different daughter strains of Bacillus Calmette Guerin) authorised in various EU member states.

1. CDC. Treatment of Tuberculosis, <http://www.cdc.gov/tb/topic/treatment/default.htm> .
2. WHO Guidelines for treatment of tuberculosis, fourth edition, 2010.

Shigellosis

Dysentery was a term used by the ancient Greeks to define diarrhoea containing blood and mucus. Although several organisms can cause dysentery, the species of the genus *Shigella* are the most important (1). The most severe cases are usually associated with *S. dysenteriae*.

The initial mode of transmission in the context of bioterrorism would be via contamination of food or water supplies. However, person-to-person spread could result in very many secondary cases. The incubation period varies from 1 to 7 days.

Dehydration should be treated with oral rehydration salts or, if severe, with intravenous fluids (2). Antibiotics are not always necessary and should in principle be reserved for the severe cases, but due to public health reasons 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. When considered necessary, ciprofloxacin, or another fluoroquinolone, may be administered. However, the prevalence of resistance to fluoroquinolones is now a major problem in some parts of the world, so that the pathogen cannot be assumed to be always susceptible to all members of this class. Treatment duration is 3-5 days, and the dosage regimens which can be used are as below:

Adults:

- Ciprofloxacin 500 mg twice daily, 3 days
- Levofloxacin 500 mg once daily, 3 days
- Azithromycin 500 mg once daily, 3 days

Children:

- Ceftriaxone 50 mg/kg once daily, 5 days (up to max 2g/day)
- Azithromycin 10 mg/kg once daily, 3 days

1. WHO. Communicable Disease Surveillance and Response (CSR). <http://www.who.int>.
2. Mandell GL, Bennett JE, Dolin R, Principles and practise of infectious diseases, 7th edition, Chapter 190. 2010.

Salmonellosis

Salmonellae are enterobacteria. One of the two *Salmonella* species, *Salmonella enterica subsp. enterica* (which contains almost every bacteria belonging to this genus which is pathogenic for humans) is spread by contaminated water and food. Of all existing serotypes, those which cause enteric fever are human-specific: *S. typhi* and *S. paratyphi*.

The incubation period in infections due to the typhi serotype is normally 10 to 14 days.

When the disease is diarrhoeal (as in infection due to the non-typhi serotypes and occasionally also in typhoid) person-to-person spread occurs in poor hygiene situations and secondary cases are common (1).

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.

In typhoid and paratyphoid, and sometimes in salmonellosis due to other serotypes, the organism invades into the blood and the complications include generalised sepsis as well as localised infections in various organs and bones.

Treatment is routinely given for typhoid and paratyphoid 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 treatment choice has to be based on the epidemiology of the circulating *Salmonella* strains in the region where the disease was acquired.

For drug-susceptible disease, fluoroquinolones are the treatment of choice (ciprofloxacin 500 mg or ofloxacin 400 mg twice daily for 5 to 7 days). Quinolones can also be used in the treatment of uncomplicated MDR-typhoid. Unfortunately, resistance to fluoroquinolones is now a major problem and those cases have to be treated with azithromycin 1g *per os* once daily for 7 days or ceftriaxone i.v. 2g/day for 10 to 14 days (2).

Vaccines against typhoid are authorised in all EU member states.

1. Public Health England, UK: <http://www.hpa.org.uk/> January 21, 2013.
2. Mandell GL, Bennett JE, Dolin R, Principles and practise of infectious diseases, 7th edition, Chapter 190. 2010.

Cholera

Cholera is spread by contaminated water and food. The incubation period is normally 1 to 3 days.

Rehydration is the mainstay for the treatment of cholera. During an epidemic, 80-90% of diarrhoea patients can be treated by oral rehydration alone, but patients who become severely dehydrated must be given intravenous fluids (1).

Antibiotic treatment is just an adjuvant to rehydration - in severe cases, an effective antibiotic can reduce the volume and duration of diarrhoea and the period of *Vibrio* excretion.

When necessary, a single dose treatment with doxycycline (300 mg) is the first line treatment in adults and children > 8 years of age.

In younger children trimethoprim-sulfamethoxazole, erythromycin or furazolidone for 3 days can be recommended when appropriate. Unfortunately, drug resistance is now a considerable problem such that susceptibility to these medicinal products cannot be assumed. An alternative is the administration of azithromycin 20 mg/kg single dose (2).

Both parenteral and oral vaccines are authorised in some EU member states. The parenteral inactivated vaccine is not recommended by the WHO due to its limited degree and duration of protection.

1. Communicable Disease Surveillance and Response (CSR). WHO. <http://www.who.int/> January 21, 2002.
2. Mandell GL, Bennett JE, Dolin R, Principles and practise of infectious diseases, 7th edition, Chapter 190, 2010.

ANNEX

Biological agents for which currently no specific treatment can be recommended.

Enterohaemorrhagic E coli (EHEC)

Cryptosporidiosis

Viral encephalitis

- Venezuelan equine encephalitis, Eastern equine encephalitis and Western equine encephalitis
- Nipah virus
- Tick borne encephalitis virus. A vaccine and an immunoglobulin are authorised in some EU member states.
- Japanese encephalitis. A vaccine is authorized in the EU through centralized procedure.

Additional viral haemorrhagic fevers

- Tick-borne haemorrhagic fever virus
- Yellow fever virus. A vaccine is authorised in some EU member states.
- Hantaviruses
- Marburg and Ebola viruses

Staphylococcal enterotoxin B

Clostridium perfringens epsilon toxin

Ricin toxin