PLAGUE

General points on treatment

Plague is an infectious disease caused by *Yersinia pestis*. The infectious dose by respiratory droplets or aerosols is between 100 and 500 organisms. Person-to person transmission occurs and 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 pneumatic plague present with malaise, high fever, chills, coughs, myalgia and clinical sepsis.

There are no 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 inhalation 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, chloramphenicol and quinolones. *In vitro* studies suggest equivalent or greater activity of ciprofloxacin, levofloxacin, and ofloxacin against *Y.pestis* when compared with aminoglycosides or tetracyclines, but dose recommendations for ofloxacin and levofloxacin can presently only be given for adults. 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. Naturally occurring resistance to tetracyclines is rare. Multidrug resistant strains of *Y. Pestis* and quinolone resistant strains have been considered in the literature and in the context of genetic engineering (2, 3). . Because of the mortality that could be anticipated with inhalation 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 mg/kg iv, four times daily in both adults and children with similar oral doses for follow up treatment. (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 whatever the clinical presentation, and post exposure prophylaxis in case of suspected or confirmed exposure to *Y. pestis***.**

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 the high bioavailability of some products (e.g. ciprofloxacin and doxycycline) makes initial oral treatment an option.

Name of active substance **Role in therapy and prophylaxis**	**Section**	**Treatment of suspected or confirmed clinical cases of plague** Duration of treatment: 10 days	**Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen** Duration of prophylaxis: 7 days
Gentamicin ➢ **First line treatment**	**Posology**	**<u>Adults</u>** Standard doses for severe sepsis, such as 5 mg/kg iv once daily or 2.5 mg/kg iv twice daily	**<u>Adults</u>** NA
		<u>Children</u> 2.5 mg/kg iv three times daily	**<u>Children</u>** 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.	

Streptomycin ➢ **First line treatment**	**Posology**	**<u>Adults</u>** 1 g im twice daily	**<u>Adults</u>** NA
		<u>Children</u> 15 mg/kg im twice daily (maximum dose, 2g)	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**	**<u>Adults</u>** 400 mg iv twice daily followed by 500 mg orally twice daily	**<u>Adults</u>** 500 mg orally twice daily
		<u>Children</u> 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.	**<u>Children</u>** 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**	**<u>Adults</u>** 400 mg iv twice daily followed by 400 mg orally twice daily	**<u>Adults</u>** 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**	**<u>Adults</u>** 500 mg iv once daily followed by 500 mg orally once daily	**<u>Adults</u>** 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**	**<u>Adults</u>** 100 mg iv twice daily followed by 100 mg orally twice daily	**<u>Adults</u>** 100 mg orally twice daily
		<u>Children</u> > 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	**<u>Children</u>** > 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.	

References

1. Byrne WR and al. Antibiotic treatment of experimental pneumonic plague in mice. Antimicrobial agents and chemotherapy 1998, Mars: 675-681.

2. CDC web page (http://www.bt.cdc.gov/DocumentsApp/FactSheet/Plague/About.asp: Facts about Pneumonic Plague. December 2001.

3. JAMA Consensus statement. Plague as a biological weapon. Vol. 283 No.17, May 3, 2000

4. Afssaps homepage. Plan Biotox (www.agmed.sante.gouv.fr/htm/10/indbio.htm).
AFSSAPS. France, 2001

5. PHLS homepage, (www.phls.org.uk/facts/deliberate releases.htm) Last date accessed December 03, 2001. Plague, Interim PHLS guidelines for action in the event of a deliberate release, Issue 3 / Version 2 ed, vol. 2001. Public Health Laboratory Service, United Kingdom.

6. P. Russel, S.M. Eley, M.Green, A.J. Stagg, R.R. Taylor, M. Nelson, R.J. Beedham, D.L. Bell, D. Rogers, D. Whittington and R.W. Titball. 1997. Jounal of Antimicrobial Chemotharpy (JAC), Vol. 41, p. 301-305, 1998.