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 guiniea 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).

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 - 15.

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** Duration of treatment: 60 days	**Post exposure prophylaxis in case of suspected or confirmed exposure to the pathogen** Duration of prophylaxis: 60 days
Ciprofloxacin ➢ **First line treatment and as alternative for oral follow-up** ➢ **First line prophylaxis until susceptibility to other agents has been confirmed**	**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 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 500mg 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 ➢ **Alternative first line treatment and follow up when susceptibility is confirmed** ➢ **Alternative first line prophylaxis when susceptibility is confirmed**	**Posology**	**<u>Adults</u>** 100 mg iv twice daily followed by 100mg orally twice daily	**<u>Adults</u>** 100 mg orally twice daily
		<u>Children</u> > 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 followed by the same doses orally	**<u>Children</u>** > 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**	**<u>Adults</u>** 2.4 – 3 g iv, six times daily	**NA**
		<u>Children</u> > 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**	**<u>Adults</u>** 1g iv, three times daily followed by 500 mg orally three times daily	**<u>Adults</u>** 500 mg orally three times daily
		<u>Children</u> 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	**<u>Children</u>** 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.

References

1. JAMA Consensus statement. Anthrax as a biological weapon. Vol. 281 No. 18,May 12, 1999

2. 2001. CDC Update: Investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobioal therapy, October 2001. (www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a1.htm) MMWR Morb Mortal Wkly Rep. 50(42):910-19.

3. PHLS homepage, (www.phls.org.uk/facts/deliberate releases.htm) Last date accessed December 03, 2001. Anthrax, 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.

4. A. Johansson. 2001. Antrax (www.sos.se/fulltext) National Board of Health and Welfare. Sweden

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

6. Protocol for dealing with suspected anthrax in Ireland. (www.doh.ie).Version 5. October 26th, 2001.

7. Update: Recommendations for antimicrobial prophylaxis for children and breastfeeding mothers and treatment of children with anthrax. Morbidity and Mortality Weekly Report (MMWR). Vol 50 no 45 p 1015-16. November 16, 2001

8. Dixon, T. C., M. Meselson, J. Guillemin, and P. C. Hanna. 1999. Anthrax. N Engl J Med. 341(11):815-26.

9. Notice to Readers: Updated Recommendations for Antimicrobial Phophylaxis Among Asymptomatic Pregnant Women After Exposure to *Bacillus anthracis* / Interim Recommendations for Protecting Workers from Exposure to *Bacillus* anthracis in Work Sites in which Mail is Handled or Processed. Morbidity and Mortality Weekly Report (MMWR). Vol 50 no 43 p 960 - 961. November 2, 2001

10. A. Timen. 2000. Anthrax, nog steeds een bedreiging. Infectieziekten Bulletin, Vol. 11, no 12 p 272-274. December 11, 2000.

11. Doxycycline (Vibramycin, Monodos, Coryx, Cosy, Atridox, Periodox, Vibra-Tabs) Use by Pregnant and Lactating Women. FDA Drug Information page (www.fda.gov). October 30, 2001.

12. CIPRO (Ciprofloxacin) Use by Pregnant and Lactating Women. FDA Drug Information page (www.fda.gov). October 30, 2001.

13. FDA Public Health Advisory: Update on Use of Doxycycline for Anthrax Exposure. FDA News page (www.fda.gov). October 18, 2001.

14. Anthrax – Translated Summary of the Finnish recommendations.

15. M.N. Swarz. 2001. Recognition and Management of Anthrax – An Update. N Engl J Med. 345(22):1621-26, November 29, 2001.