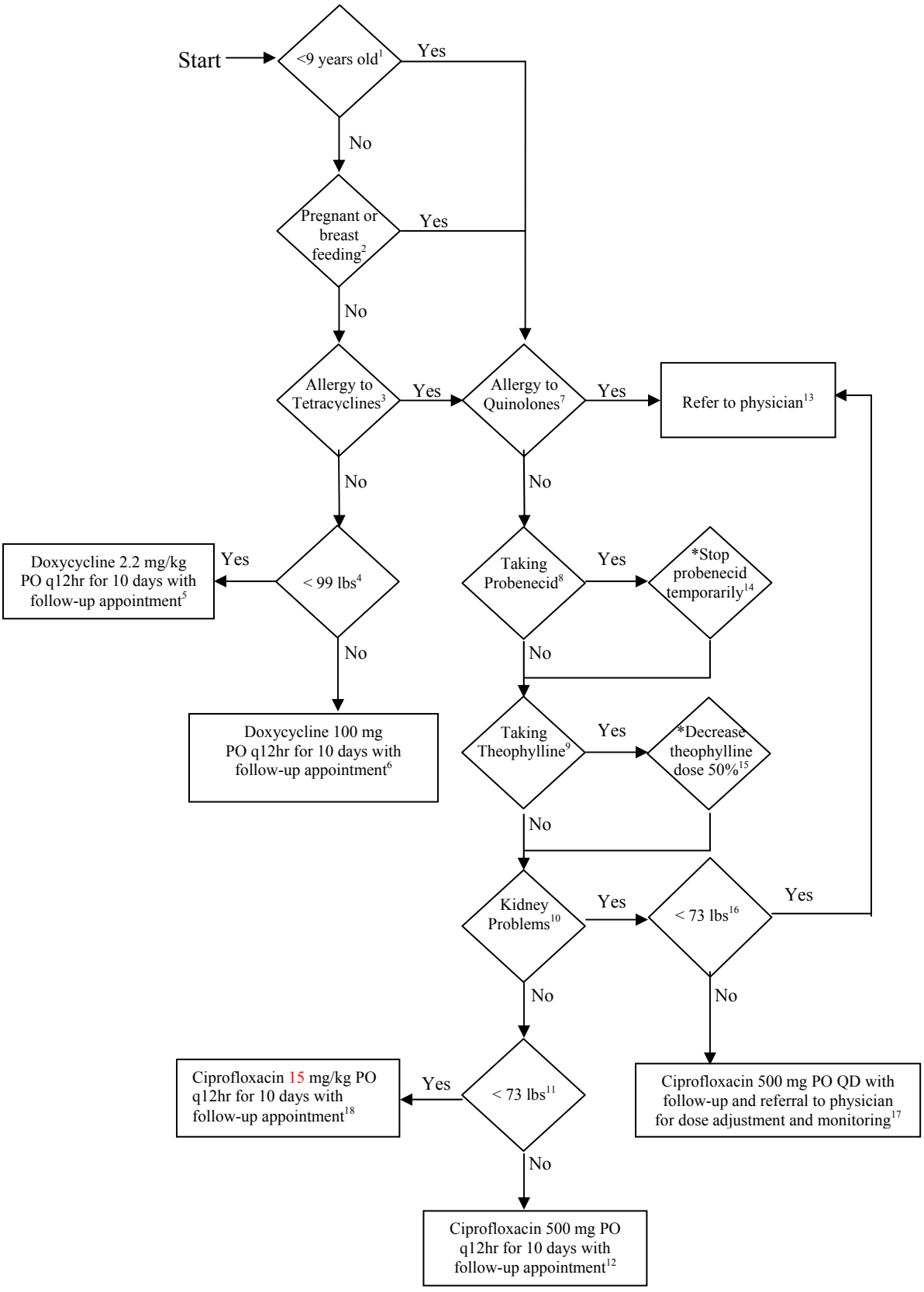
# Attachment 1: Anthrax Post-Exposure Prophylaxis Dispensing Algorithm
# Doxycycline (Primary Drug)

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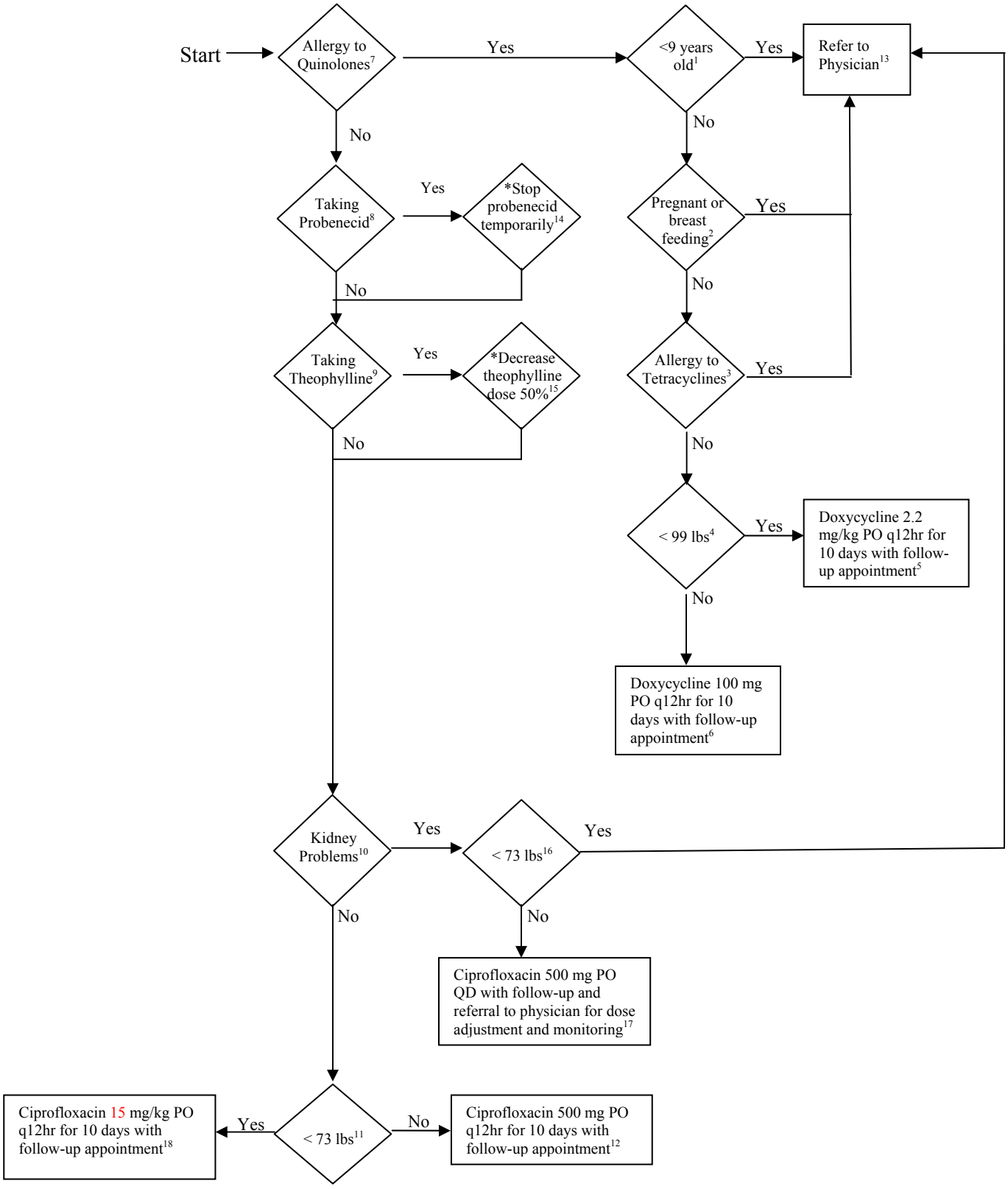


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**Post-Exposure Prophylaxis Dispensing Algorithm**

The above flow diagrams and these footnotes describe drug selection and dosing information for patients requiring post-exposure prophylaxis or preventative treatment after exposure to *Bacillus anthracis*, the bacteria that causes anthrax.

Reports have been published of engineered strains of tetracycline-resistant and quinolone-resistant *Bacillus anthracis*.[1,2] There is also a possibility for resistance to penicillins through induction of beta-lactamase enzymes. For these reasons, public health officials will test the antibiotic susceptibility of clinical specimens (blood, sputum, etc.), to determine drug selection. The most widely available, efficacious, and least toxic antibiotic will be dispensed for post-exposure prophylaxis based upon these susceptibility results.[1]

Until antibiotic susceptibility results of the implicated strain are available, initial therapy for post-exposure prophylaxis for prevention of anthrax after intentional exposure of *Bacillus anthracis* is doxycycline or ciprofloxacin.[3] Following a terrorist attack, the Missouri Department of Health and Senior Services (DHSS) will designate which of these two drugs will be the primary drug to use for prophylaxis.

Doxycycline and other tetracyclines are not normally recommended for children and pregnant women due to the risk of dental staining of the primary teeth, concerns about possible depressed bone growth, defective dental enamel, and rare liver toxicity. Therefore, children and pregnant and lactating women will not normally receive doxycycline.

Ciprofloxacin and other quinolones are not normally recommended in children and pregnant women due to the risk of arthropathy (joint disease).[1,4,5] This recommendation is based on studies in animals. Data in humans have not confirmed this risk. Therefore, children and pregnant and lactating women without an allergy to quinolones will receive ciprofloxacin according to this algorithm. The risks associated with the serious and life-threatening complications from anthrax outweigh any risks from taking ciprofloxacin.

The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice recommend the use of ciprofloxacin in pregnant or lactating women for post-exposure prophylaxis for prevention of anthrax after intentional exposure of *Bacillus anthracis*.[6] On August 30, 2000, the Food and Drug Administration (FDA) approved ciprofloxacin for use in anthrax postexposure prophylaxis for children as well as for adults. FDA and its Anti-infectives Advisory Committee have stated that the risk-benefit assessment for use of ciprofloxacin for anthrax postexposure prophylaxis is such that it is presently recommended for use in children. The ciprofloxacin label states: "Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established, except for use in inhalational anthrax (post-exposure). . . . For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate."[12]

As soon as penicillin susceptibility is confirmed, prophylactic therapy for children and pregnant women should be changed to amoxicillin.[3] (Although amoxicillin has not been approved by the Food and Drug Administration (FDA) as therapy for anthrax postexposure prophylaxis, it is often recommended for these indications. FDA has published a commentary on its Web site that describes dosing regimens that should be avoided for adults and children who have been exposed to inhalational anthrax to avoid underdosing [see http://www.fda.gov/cder/drugprepare/amox-anthrax.htm].[12])

This algorithm does not include the use of anthrax vaccine. At the time this algorithm was developed, anthrax vaccine for post-exposure prophylaxis was an investigational new drug. It is quite possible that once the release of anthrax has been confirmed the vaccine will be made available to the affected population. If so, DHSS will provide guidelines for administration.

All patients who have been potentially exposed to anthrax should receive an initial course of drug therapy (10 days). Public health officials will advise people to return for follow-up in 7-10 days to obtain an additional supply (50 days) of medication to complete a full course of therapy (60 days). The initial course of 10 days is recommended based upon the normal twice a day regimen of ciprofloxacin and doxycycline and the availability of 20 tablets in unit-of-use containers from the Strategic National Stockpile Program. At the follow-up visit, susceptibility data will be available and drugs may be changed.

The following steps and numbered paragraphs support and correspond to the flow diagram entitled "Post-Exposure Prophylaxis Dispensing Algorithm".

1. Is the patient younger than 9 years (yrs)? Due to the risk of teeth discoloration associated with tetracyclines, children without a quinolone allergy, who have not received all of their permanent teeth, should be prescribed ciprofloxacin. Since the age at which a child obtains his/her permanent teeth varies, it is possible for children under the age of 9 years to receive doxycycline. The parent or guardian of the child should be asked whether the child has a full-set of permanent teeth.

2. If the patient is female, is she pregnant or breast-feeding? The American College of Obstetricians and Gynecologists Committee on Obstetric Practice recommend the use of ciprofloxacin in pregnant or lactating women for anthrax post-exposure prophylaxis.[6]

3. Has the patient had an allergic reaction to any medication in the tetracycline class?

   Allergic reactions may include: hives, redness of the skin, rash, difficulty breathing, or worsening of lupus after taking one of the tetracycline class drugs, including: demeclocycline (Declomycin); doxycycline (Adoxa, Bio-Tab, Doryx, Doxy, Monodox, Periostat, Vibra-Tabs, Vibramycin); minocycline (Arestin, Dynacin, Minocin, Vectrin); oxytetracycline (Terak, Terra-Cortril, Terramycin, Urobiotic-250); tetracycline (Achromycin V, Sumycin, Topicycline, Helidac).[7,8]

   Patients that are allergic to any medication in the tetracycline class should receive another form of therapy such as ciprofloxacin.

4. Does the patient weight less than 99 pounds (lbs) or 45 kilograms (kg)?

5. Patients less than 99 pounds (45 kilograms), should receive an initial supply (10 days) of doxycycline 2.2 mg/kg (as described in the chart below) by mouth every 12 hours with a mandatory follow-up appointment within 10 days. At that time, information about the effectiveness of certain medications in preventing anthrax will be available and the drug may be changed. A minimum of 60 days of drug therapy is necessary for the full protective effect.[3]

| Weight (lbs) | Weight (kg) | Dose (mg) | Available Dosage Forms of Doxycycline | | | | |
|---|---|---|---|---|---|---|---|
| | | | 20 mg tablet | 50mg tablet or capsule | 100mg tablet* or capsule | 25mg/5mL suspension* | 50mg/5mL syrup |
| 5-10 | 2-5 | 10 | | | | 2 mL | 1 mL |
| 11-20 | 6-9 | 20 | 1 | | | 4 mL | 2 mL |
| 21-30 | 10-14 | 30 | | | | 6 mL | 3 mL |
| 31-40 | 15-19 | 40 | 2 | | | 8 mL | 4 mL |
| 41-50 | 20-22 | 50 | | 1 | ½ | 10 mL | 5 mL |
| 51-60 | 23-27 | 60 | 3 | | | 12 mL | 6 mL |
| 61-70 | 28-32 | 70 | | | | 14 mL | 7 mL |
| 71-80 | 33-36 | 80 | 4 | | | 16 mL | 8 mL |
| 81-90 | 37-41 | 90 | | | | 18 mL | 9 mL |
| 91-100 | ≥ 42 | 100 | 5 | 2 | 1 | 20 mL | 10 mL |

*Dosage Forms available through the CDC National Pharmaceutical Stockpile Program

6. Patients greater than 99 pounds should receive an initial supply (10 days) of doxycycline 100 mg by mouth every 12 hours with a mandatory follow-up appointment within 10 days. At that time, information about the effectiveness of certain medications in preventing anthrax will be available and the drug may be changed. A minimum of 60 days of drug therapy is necessary for the full protective effect.[3]

7. Has the patient had an allergic reaction to any medication in the quinolone class?

   Allergic reactions may include: difficulty breathing, rash, itching, hives, yellowing of the eyes or skin, swelling of the face or neck, cardiovascular collapse, loss of consciousness, hepatic necrosis (death of liver cells), or eosinophilia (a rare skin disease) after taking a quinolong class drug, including: acrosoxacin or rosoxacin (Eradacil); cinoxacin (Cinobac); ciprofloxacin (Cipro, Ciloxan); gatafloxacin (Tequin); grepafloxacin (Raxar); levafloxacin (Levaquin, Quixin); lomefloxacin (Maxaquin); moxifloxacin (Avelox, ABC Pak); nadifloxacin (Acuatim); norfloxacin (Chibroxin, Noroxin); nalidixic acid (NegGram); ofloxacin

(Floxin, Ocuflox); oxolinic acid; pefloxacin (Peflacine); rufloxacin; sparfloxacin (Zagam, Respipac); temafloxacin; trovafloxacin or alatrofloxacin (Trovan).[8]

Patients that have had an allergic reaction to any medication in the quinolone class should be referred to a physician to receive another form of therapy.

8. Is the patient taking probenecid (Benemid)? Probenecid may decrease the renal excretion of ciprofloxacin, therefore increasing the risk of ciprofloxacin toxicity.

9. Is the patient taking theophylline (Theo-Dur, Slo-BID, Slo-Phyllin, Uniphyl)? Ciprofloxacin may increase the theophylline levels by inhibiting hepatic metabolism, and thus increase the risk of theophylline toxicity

10. Does the patient have known kidney (or renal) problems?

    Patients with kidney problems include those receiving dialysis, with known kidney failure (end-stage renal disease) or who have reduced kidney function. Patients who have chronic kidney infections or kidney stones do not need an adjusted dose, unless they have been told by a health care professional that they have kidney damage. Patients with kidney problems who weigh less than 73 pounds should be referred to a physician.

11. Does the patient weigh less than 73 pounds (lbs) or 33 kilograms (kg)?

12. Patients 73 pounds (33 kilograms) or greater should receive ciprofloxacin 500 mg by mouth every 12 hours for 10 days with a mandatory follow-up appointment within 10 days. At that time, information about the effectiveness of certain medications in preventing anthrax will be available and the drug may be changed. A full course of therapy (60 days) is necessary for the full protective effect.[3]

13. Refer the patient to a physician for further assessment and drug selection. If a patient has had allergic reactions to drugs in the quinolone and tetracycline classes, other options for prophylactic (preventative) therapy include: amoxicillin/clavulanate, clindamycin, rifampin, imipenem, aminoglycosides, chloramphenicol, vancomycin, cefazolin, tetracycline, linezolid, or a macrolide (clarithromycin, erythromycin).[1,10] These other drugs are not approved by the Food and Drug Administration for preventative treatment of anthrax and require individual prescribing by a medical doctor or dispensing under an investigational new drug application.

14. Due to the interaction between probenecid and ciprofloxacin, probenecid should be temporarily stopped. The patient should be referred to their primary physician regarding when to restart probenecid and whether a dosage adjustment is necessary.

15. Due to the interaction between theophylline and ciprofloxacin, the dose of theophylline should be decreased by 50%. The patient should be referred to their primary physician regarding drug monitoring.

16. Does the patient weigh less than 73 pounds (lbs) or 33 kilograms (kg)? Patients less than 73 lbs should be referred to a physician for drug selection and monitoring.

17. Give patients 73 pounds (32 kilograms) or greater with kidney problems ciprofloxacin 500 mg by mouth **ONCE** a day and refer them to a physician for further assessment. Use the chart[11] below to determine the dose of ciprofloxacin required for patients with kidney problems when creatinine clearance is known or can be determined. Give all patients an initial supply of medication (10 days supply) and schedule a follow-up appointment within 10 days. At that time, information about the effectiveness of certain medications in preventing anthrax will be available and the drug may be changed. A minimum of 60 days of drug therapy is necessary for the full protective effect.[3]

| Kidney Function | Ciprofloxacin Dose (milligrams=mg) |
|---|---|
| Creatinine Clearance >50 mL/min | 500 mg every 12 hours |
| Creatinine Clearance = 30-50 mL/min | 250 mg every 12 hours |
| Creatinine Clearance = 5-29 mL/min | 250 mg every 18 hours |
| Hemodialysis | 250 mg every 24 hours |

18. Patients less than 73 pounds (33 kilograms) should receive an initial supply (10 days) of ciprofloxacin 15 mg/kg by mouth every 12 hours with a mandatory follow-up appointment in 7-10 days. At that time, information about the effectiveness of certain medications in preventing anthrax will be available and the drug may be changed. A minimum of 60 days of drug therapy is necessary for the full protective effect.[3]

**References:**


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