2001 anthrax crisis in Washington, D.C.: Pharmacists' role in screening patients and selecting prophylaxis

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Abstract: Pharmacists' development and use of a worksheet facilitating their rapid selection of patient-appropriate prophylactic antimicrobials in an anthrax clinic is described.

A clinic housed at D.C. General Hospital, in Washington, D.C., treated most of the people—many of them postal workers—who may have been exposed to anthrax in that city during the 2001 anthrax crisis. A form was needed to assist pharmacists in the rapid selection of prophylactic antimicrobials and in patient education and counseling. A team of pharmacists collaborated on the development of a form tailored to the clinical and logistical needs of the operation. The questions on the form were based largely on the two antianthrax agents most likely to be used, ciprofloxacin and doxycycline, and were designed to identify the circumstances that would most frequently require a medication change or a modification of patient education. Yes-or-no check boxes allowed pertinent data to be captured most efficiently. A positive response to any question triggered a personal interview and assessment by a pharmacist. A treatment algorithm was also developed to ensure consistent pharmacist selection of agents in the face of potentially changing policies and staff. The worksheet questions sought to establish treatment objectives, document allergies and concomitant therapies, and identify patients who were pregnant or lactating.

Pharmacists developed a patient-screening worksheet that helped determine their choice of treatment for people who may have been exposed to anthrax in Washington, D.C., during the 2001 anthrax crisis.

Index terms: Ambulatory care; Anthrax; Biological warfare; Ciprofloxacin; Diagnosis; Disaster planning; Doxycycline; Pharmacists; Protocols; Quinolones; Tetracyclines

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On October 15, 2001, a member of the staff of U.S. Senate Majority Leader Thomas Daschle opened an anthrax-contaminated letter in the Hart Senate Office Building.[1] In the weeks that followed, additional letters laced with anthrax spores were identified, and at least 22 people developed either cutaneous or inhalational anthrax.[2] Many of the afflicted were postal workers assigned to the U.S. capital region. Thousands of other federal and nonfederal personnel may have been exposed.

Agencies of the U.S. Public Health Service (USPHS), including the Centers for Disease Control and Prevention (CDC) and the Office of Emergency Preparedness, planned and implemented a rapid response to the crisis.[3] One of the primary missions of USPHS during this crisis was distributing prophylactic antimicrobials to individuals determined to be at risk for anthrax exposure. USPHS personnel stationed in a clinic housed at D.C. General Hospital, in Washington, D.C., treated most of these people. A tool to assist pharmacists in the rapid selection of the appropriate prophylactic antimicrobials and in patient education and counseling regarding the selected therapy was needed. An anthrax

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health and medication worksheet was developed to meet this need. This article describes the development of the worksheet and how pharmacists used it to help screen patients and select prophylaxis.

General development of the worksheet

Early in the crisis, an existing CDC patient-screening form was tried but found to be too complex—and then, after a quick revision, too superficial. A team of pharmacists collaborated on another revision tailored to the clinical and logistical needs of the operation. The objectives were to

1. Capture patient data for assessment and therapeutic selection,
2. Maximize comprehensibility for the public (by writing the form at an eighth-grade reading level),
3. Promote swift identification of patients with complex medical problems and those requiring intensive education or especially careful therapeutic selection,
4. Facilitate rapid assessment of whether objectives for therapeutic selection and patient education were being met,
5. Reinforce oral education of patients,
6. Minimize delays in patient processing without compromising therapeutic selection and education,
7. Record patient history, agent selection, comments, and other ancillary information (e.g., quantity of medication dispensed).
8. Collect epidemiologic data,
9. Serve as a quality assurance and quality control tool, and
10. Support training of health care workers.

The result was the anthrax health and medication worksheet (Figure 1). Clinic pharmacists considered it superior to its predecessors, and patients found it much easier to use. Throughout the mission, revisions of the worksheet continued to be made when necessary.

While the worksheet served as a valuable screening tool, it was not the only method of presenting, discussing, or capturing data on the provision of anthrax prophylaxis and patient education. All people who came to the clinic were given a 15- to 30-minute lecture that covered most of the frequently asked questions about anthrax and preventive agents.[3] Time was set aside during each presentation for people to ask questions or express concerns. In addition, each individual had the opportunity to meet personally with a health care provider, typically a pharmacist, to discuss any personal or medical matters related to the event.

The policy on agent selection was somewhat fluid. A flexible treatment algorithm was needed in case the drug of choice was changed. At the time of the crisis, ciprofloxacin was the only drug approved by FDA for anthrax treatment and prophylaxis. CDC recommended either ciprofloxacin or doxycycline hyclate as first-line therapy.[4] Therefore, the treatment protocol used ciprofloxacin as the drug of choice and doxycycline as a secondary agent when necessary (Appendix A). Amoxicillin was used only if there was a contraindication to both ciprofloxacin and doxycycline. Once susceptibility test results were available, the agent of choice was modified as necessary. Doxycycline soon became the preferred agent because its spectrum of activity was similar to ciprofloxacin's, it was safer, and it was available from multiple sources.

The worksheet facilitated rapid identification of the most appropriate therapy for each patient and of the patient's educational needs. The questions were based largely on the two antianthrax agents most likely to be used, ciprofloxacin and doxycycline, and were designed to identify circumstances that would most frequently require a medication switch or a modification of patient education. Yes-or-no check boxes allowed pertinent data to be captured most efficiently and served to identify individuals with more complex needs. A positive response to any question triggered a personal interview and assessment by a pharmacist, possibly leading to a change in therapy or a special emphasis on education.

Development of the treatment algorithm

During the mission, pharmacists discussed with one another their experiences and particularly complicated cases. A consensus on therapeutic selection began to form. A treatment algorithm was developed to ensure a consistent approach to agent selection in the face of possible changes in agent-selection policies and in the pharmacy staff. Similar questions were grouped to facilitate rapid completion of the document by patients and allow the provider to efficiently weigh all pertinent factors when deciding on a treatment. The algorithm was further refined as part of the postoperation debriefing. The final algorithm is shown in Appendix B.

Establishing treatment objectives. The first set of questions on the worksheet established whether the patient required definitive treatment, prophylaxis, or no therapy. Asymptomatic individuals who had completed the full anthrax vaccination series within the previous year did not require any therapy but were given the option of receiving prophylactic antimicrobials. In clinical studies designed to evaluate the efficacy of the anthrax vaccine, 83% of people had a vaccine-induced immune response (indirect hemagglutination) two weeks after the first dose, and 95% had an even stronger response (a fourfold increase in antibody titer) after three doses.[5] Since a direct correlation between antibody titer and protection from anthrax remains unproven, the authors believed that the more prudent approach was to provide antimicrobial prophylaxis to

Figure 1. Anthrax health and medication worksheet.

Name: _____ Today's Date: _____

Date of Birth: _____ Social Security Number: ___ - ___ - ____

Have you ever received the anthrax vaccine? Yes ☐ No ☐
Do you have flu-like symptoms (fever, aches, chills, cough)? Yes ☐ No ☐
Do you have a skin lesion or sore that appeared or got worse recently? Yes ☐ No ☐

Medication Information

Are you allergic to any medications? Yes ☐ No ☐
Name(s) of medications: _____
Do you currently take any medications? Yes ☐ No ☐
Name(s) of medications:
_____
_____

Do you take vitamins or supplements (calcium, iron, zinc, magnesium, multivitamins)? Yes ☐ No ☐
Do you use antacids (Tums, Maalox, Mylanta, Rolaids, Pepto-Bismol)? Yes ☐ No ☐

Disease Information

Do you have or have you had epilepsy (seizures)? Yes ☐ No ☐

Do you have or have you had liver disease or hepatitis? Yes ☐ No ☐

Do you have or have you had kidney disease? Yes ☐ No ☐

Dietary Information

Do you drink two or more drinks WITH CAFFEINE per day (coffee, tea, colas, etc.)? Yes ☐ No ☐
Do you eat dairy products (milk, yogurt, cheese, ice cream)? Yes ☐ No ☐
Do you drink orange juice WITH EXTRA CALCIUM? Yes ☐ No ☐

Females Only

Are you breast-feeding? Yes ☐ No ☐
Is it possible you are pregnant? Yes ☐ No ☐
Do you take birth-control pills? Yes ☐ No ☐

For Pharmacist Use Only

Agent/directions selected:
Ciprofloxacin 500 mg BID ☐ Doxycycline 100 mg BID ☐ Amoxicillin 500 mg TID ☐
Ciprofloxacin_____ ☐ Doxycycline _____ ☐ Amoxicillin _____ ☐
Qty Dispensed: 10 Day Supply ☐ 50 Day Supply ☐ 60 Day Supply ☐ R.Ph. Signature: _____
Notes:
_____
_____

anyone who did not complete the vaccination series.

A patient with signs and symptoms that were consistent with cutaneous or inhalational anthrax and were temporally related to the exposure event received prophylactic therapy and was routed to a primary care provider for further assessment. All symptomatic patients were instructed to see a primary care provider immediately. These patients were given the option of seeing a USPHS physician at the clinic for a brief screening or their personal physician for a more extensive evaluation. The provision of prophylactic therapy to these individuals represented a prac-

tical attempt to streamline clinic operations and minimize the reprocessing of previously screened patients. To minimize interference with antimicrobial susceptibility testing, these individuals were cautioned not to take any prophylactic medications until after they had consulted a physician.

Documenting allergies and concomitant therapies. The second set of questions allowed gathering of detailed information on drug allergies and concomitant treatments that could affect therapeutic selection. Because of the potential interactions of ciprofloxacin or doxycycline with cations like calcium, aluminum, and magnesium, specific questions regarding vitamin and mineral supplements and antacids were included in the questionnaire. In general, therapy was not changed if patients answered yes to either of the questions about minerals and antacids. However, patients were counseled to avoid taking minerals or antacids with ciprofloxacin or doxycycline.

A positive response on the worksheet regarding allergies or allergic reactions elicited further investigation. If a patient was suspected to have a true allergy to the drug of choice or other agents in the same class, a suitable alternative agent was prescribed. If the patient had not tolerated, but not been allergic to, the drug of choice or similar drugs, the pharmacist decided whether an alternative agent was warranted.

The drug interaction assessment was quite complex. The pharmacists familiarized themselves with the most common and most severe drug interactions involving ciprofloxacin, doxycycline, and amoxicillin.[6,7] The approach to agent selection and counseling for patients receiving concomitant drug therapy is summarized in Appendix C. None of the antianthrax agents were considered absolutely contraindicated for use in combination with other medications.[6,7] In practice, however, it was not uncommon for a pharmacist to exercise caution and use an alternative agent. All patients were instructed to see a physician to discuss whether any further modifications to their drug therapy were necessary.

Patients already receiving antimicrobial therapy proved challenging in screening for drug interactions. Pharmacists had to determine the specific indication, the treatment start date, the duration of therapy, and the susceptibility (if any) of the anthrax strain to the currently used antimicrobial. If the agent was included in the CDC anthrax prophylaxis guidelines or if susceptibility test findings were available, the patient was instructed to complete the current course of therapy. If necessary, additional antimicrobials were dispensed to complete the prophylactic regimen.

Assessment of appropriate antimicrobial therapy for other indications (urinary-tract infections, upper-respiratory-tract infections, etc.) was beyond the scope of the operation. Therefore, for the patient currently receiving antimicrobial therapy that did not meet CDC anthrax prophylaxis guidelines or yield a positive result in susceptibility tests, pharmacists dispensed the appropriate preventive agent and instructed the patient to consult a physician before beginning treatment. The District of Columbia's health department was available to assist community health care providers in selecting appropriate therapy.

Several medical conditions contraindicated treatment with the drug of choice or at least created the need for extra caution. Ciprofloxacin is known to lower the seizure threshold.[6,7] Patients with epilepsy or who were taking antiepileptic drugs typically received doxycycline. Ciprofloxacin is excreted almost exclusively by the kidneys,[6,7]and recommendations are available for adjusting ciprofloxacin dosages on the basis of serum creatinine concentration. Since this laboratory value was unlikely to be available during the crisis, patients who indicated they had renal disease were given doxycycline, which is metabolized primarily by the liver.

The worksheet included dietary questions to remind pharmacists to reinforce patient education. Every patient was informed of dietary restrictions; this occurred during group counseling and one-on-one sessions with a pharmacist. Most patients indicated that they consumed caffeine or dairy products. Therefore, the form was designed to promote patient education without detracting from rapid assessment and appropriate therapeutic selection. Check boxes for responses in the form's dietary section were offset so that they did not line up with the other check boxes. This formatting helped providers deemphasize this section during the initial assessment and focus on questions that could result in a switch to a secondary agent.

Pregnancy and lactation. CDC's anthrax prophylaxis guidelines allow for the use of either ciprofloxacin or doxycycline in pregnant or lactating women. Before the results of any susceptibility testing were known, both ciprofloxacin and doxycycline were dispensed to pregnant or lactating women, and they were instructed to consult their obstetrician before starting to take the drugs. Once susceptibility test findings were available, these patients were prescribed amoxicillin because of its demonstrated safety in pregnant women.[7]Most antimicrobials can decrease the effectiveness of oral contraceptives. Thus, all women of childbearing age receiving oral contraceptives were advised to use an alternative method of contraception during the course of therapy.

Additional information. Space was provided at the bottom of the worksheet for pharmacists to write notes about agent selection, directions given, quantity dispensed, unique patient issues, and justification for a decision to use an alternative drug.

Discussion

While the anthrax health and medication worksheet was designed to capture the key information that might guide agent selection or patient education, it was not intended to generate an exhaustive list. Other factors arose relatively frequently that affected agent selection; many of these related to patient preference for a particular dosage form. Also, the worksheet was not designed to address pediatric matters. The affected population consisted almost entirely of adults. CDC's anthrax prophylaxis guidelines do include recommendations for children. It is unclear what modifications to the worksheet, if any, would be required to meet the needs of children.

The screening form, developed and refined by pharmacists, was effective for assessing patients' medical history. This tool was used by pharmacists to quickly determine appropriate medical treatment with reasonable assurance that the most important medical concerns had been addressed. The details of the worksheet were based on pharmacists' knowledge of drug therapy and disease management. These skills were used effectively to provide medical care during a crisis.

Conclusion

Pharmacists developed a patient-screening worksheet that helped determine their choice of treatment for people who may have been exposed to anthrax in Washington, D.C., during the 2001 anthrax crisis.

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Appendix A—Suggested antimicrobial prophylaxis after confirmed or suspected exposure to *Bacillus anthracis*[5]

Any one of the following agents may be used:

1. Ciprofloxacin 500 mg (as the hydrochloride) orally twice daily in adults or 10–15 mg/kg/day orally in divided doses every 12 hours in children;
2. Ofloxacin 400 mg orally twice daily in adults; not recommended in children;
3. Doxycycline 100 mg (as the hyclate) orally twice daily in adults; 5 mg/kg/day orally in divided doses every 12 hours in children;
4. Penicillin V: Not indicated in adults; 50 mg (as the potassium salt) per kilogram per day orally in divided doses four times daily in children;
5. Amoxicillin 500 mg (as the trihydrate) orally three times daily in adults; 80 mg/kg/day orally in divided doses two or three times daily in children.

Prophylaxis should continue until exposure to *B. anthracis* has been excluded. If exposure is confirmed and vaccine is available, prophylaxis should continue for four weeks and until three doses of vaccine have been administered; if vaccine is not available, prophylaxis should continue for 30–60 days. Use of tetracyclines and fluoroquinolones in children has potential adverse effects, including staining of teeth and cartilage damage, respectively. However, these risks must be weighed against the risk of developing anthrax. If potential exposure has occurred, treatment of children should begin as soon as susceptibility of the organism to penicillins has been confirmed. Data on the pediatric use of ofloxacin or other fluoroquinolones (except ciprofloxacin) are limited.

Appendix B—Algorithm for selection of prophylactic agent based on anthrax health and medical worksheet[a]

Question	Agent if Response Is Yes	Comments
1. Have you received the anthrax vaccine?	No agent if schedule is complete. If schedule is incomplete, dispense ciprofloxacin, doxycycline, or amoxicilin.	[a]Determine when anthrax vaccine was received and how much of the schedule was completed. Recommended vaccination schedule: s.c. injection at 0, 2, and 4 wk, then 6, 12, and 18 mo. An annual booster injection is necessary if immunity is to be maintained.[5]
2. Do you have flu-like symptoms (fever, aches, chills, cough)?	Ciprofloxacin, doxycycline, or amoxicillin	Determine the nature of the complaint and its duration. Dispense antianthrax agent but recommend that the individual not take a first dose until he or she has seen a primary health care provider. If signs or symptoms and temporal relationship are consistent with anthrax, schedule immediate medical follow-up.
3. Do you have a skin lesion or sore that appeared or got worse recently?	Ciprofloxacin, doxycycline, or amoxicillin	Determine the nature of the complaint and its duration. Dispense antianthrax agent but recommend that the individual not take a first dose until he or she has seen a primary health care provider. If signs or symptoms and temporal relationship are consistent with anthrax, schedule immediate medical follow-up.
4. Are you allergic to any medications?	If the patient is allergic to (or intolerant of) the drug of choice, switch to secondary medication.	Validate that an allergic reaction has occurred. Discontinue the antianthrax agent and contact a primary health care provider if there are any signs or symptoms consistent with an allergic reaction.
5. Do you currently take any medications?	Ciprofloxacin, doxycycline, or amoxicillin unless contraindication (Appendix C)	See Appendix C.
6. Do you take vitamins or supplements (calcium, iron, zinc, magnesium, multivitamins)?	Ciprofloxacin, doxycycline, or amoxicillin	Give ciprofloxacin or doxycycline 2 hr before or 2 hr after vitamin or supplement.
7. Do you use antacids (e.g., Tums, Maalox, Mylanta, Rolaids, Pepto-Bismol)?	Ciprofloxacin, doxycycline, or amoxicillin	Give ciprofloxacin or doxycycline 2 hr before or 2 hr after antacid.
8. Do you have or have you had epilepsy (seizures)?	Doxycycline or amoxicillin	Ciprofloxacin is contraindicated (lowers seizure threshold and interacts with phenytoin). Doxycycline is indicated, but phenytoin, carbamazepine, and barbiturates decrease serum doxycycline concentrations (see Appendix C).
9. Do you have or have you had liver disease or hepatitis?	Ciprofloxacin or amoxicillin	Determine the nature of any hepatic injury or dysfunction. Doxycycline's half-life is prolonged in liver disease (significance unknown).
10. Do you have or have you had kidney disease?	Doxycycline or amoxicillin	Determine the nature of any renal injury or dysfunction. Doxycycline is unaffected by renal disease. Ciprofloxacin is excreted primarily by the kidneys. Ciprofloxacin dosage guidelines for renal impairment are available in the package insert.
11. Do you drink two or more drinks with caffeine per day (coffee, tea, colas, etc.)?	Ciprofloxacin, doxycycline, or amoxicillin	Determine the amount of caffeine consumed per day. If the drug of choice is ciprofloxacin, recommend reducing the caffeine intake. Ciprofloxacin inhibits the metabolism of xanthines (e.g., caffeine). If the drug of choice is ciprofloxacin and caffeine consumption raises concern, give doxycycline.
12. Do you eat dairy products (milk, yogurt, cheese, ice cream)?	Ciprofloxacin, doxycycline, or amoxicillin	Give ciprofloxacin 6 hr before or 2 hr after dairy products.
13. Do you drink orange juice with extra calcium?	Ciprofloxacin, doxycycline, or amoxicillin	Give ciprofloxacin 6 hr before or 2 hr after calcium-fortified orange juice.
14. Are you breast-feeding?	Ciprofloxacin, doxycycline, or amoxicillin	If possible, the drug should be taken immediately after breast-feeding to reduce risk to the newborn. Amoxicillin is the drug of choice once positive susceptibility test data become available. Until susceptibility test results are available, ciprofloxacin and doxycycline are the drugs of choice during breast-feeding.
15. Is it possible you are pregnant?	Ciprofloxacin, doxycycline, or amoxicillin	Amoxicillin is the drug of choice once positive susceptibility test data become available. Until susceptibility test results are available, ciprofloxacin and doxycycline are the drugs of choice during pregnancy.
16. Do you take birth-control pills?	Ciprofloxacin, doxycycline, or amoxicillin	Advise patient to use an alternative method of contraception. Ciprofloxacin, doxycycline, and amoxicillin can decrease the effectiveness of birth-control drugs.

[a]Ciprofloxacin and doxycycline are the drugs of choice until susceptibility test data become available. Amoxicillin may be used *only* if there are contraindications to ciprofloxacin or doxycycline.

Appendix C—Drug interactions involving antianthrax agents

Antianthrax Agent and Interacting Drug	Use Another Antianthrax Agent?	Comments
Ciprofloxacin		
Antacids	No	Antacids containing aluminum, magnesium, or calcium decrease oral absorption of ciprofloxacin, resulting in decreased bioavailability of ciprofloxacin. Give ciprofloxacin 2 hr before or 2 hr after antacids.
Probenecid	Yes	Probenecid interferes with renal tubular excretion of ciprofloxacin, resulting in a 50% increase in systemic ciprofloxacin concentrations and a prolonged serum half-life. Switch to an alternative antianthrax agent (e.g., doxycycline). If other antianthrax agents are contraindicated, dispense ciprofloxacin and adjust the dosage.
Warfarin	No	Prolongation of prothrombin time and hematemesis may occur. Use combination with caution. Monitor prothrombin time.
Iron, zinc, or calcium supplements	No	Mineral supplements or multivitamins containing iron, zinc, or calcium decrease oral absorption of ciprofloxacin, resulting in decreased bioavailability of ciprofloxacin. Administer ciprofloxacin 2 hr before or 2 hr after mineral supplements.
Other antiinfectives	Possibly	Assess for therapeutic duplication, synergism, or antagonism. Determine the intent and duration of use of the other antiinfective. Dispense ciprofloxacin and recommend that the patient discuss therapeutic options with a primary care provider.
Theophylline	Yes	Ciprofloxacin alters theophylline's pharmacokinetics, resulting in elevated theophylline concentrations and increased risk of theophylline toxicity. Switch to an alternative antianthrax agent (e.g., doxycycline). If there are contraindications to other antianthrax agents, dispense ciprofloxacin, adjust the theophylline dosage, and monitor serum drug levels.
Sucralfate	No	Sucralfate decreases oral absorption of ciprofloxacin, resulting in decreased bioavailability of ciprofloxacin. Administer ciprofloxacin 2 hr before or 2 hr after sucralfate.
Oral contraceptives	No	Decreased bioavailability and effectiveness of oral contraceptives. Advise the patient to use an alternative method of contraception.
Doxycycline		
Antacids	No	Antacids containing aluminum, magnesium, or calcium decrease oral aborption of doxycycline, resulting in decreased bioavailability of doxycycline. Administer doxycycline 2 hr before or 2 hr after antacids.
Iron, zinc, or calcium supplements	No	Mineral supplements or multivitamins containing iron, zinc, or calcium decrease oral absorption of doxycycline, resulting in decreased bioavailability of doxycycline. Administer doxycycline 2 hr before or 2 hr after mineral supplements.
Warfarin	No	Prolongation of prothrombin time and hematemesis may occur. Use combination with caution. Monitor prothrombin time.
Other antiinfectives	Possibly	Assess for therapeutic duplication, synergism, or antagonism. Determine the intent and duration of use of the other antiinfective. Dispense doxycycline and recommend that the patient discuss therapeutic options with a primary care provider.
Oral contraceptives	No	Bioavailability and effectiveness of oral contraceptives decrease. Advise the patient to use an alternative method of contraception.
Barbiturates, phenytoin, or carbamazepine	Possibly	Serum half-life and serum concentrations of doxycycline decrease. Switch the patient to an alternative antianthrax agent if there is no other contraindication. If other antianthrax agents are contraindicated, dispense doxycycline.
Amoxicillin		
Oral contraceptives	No	Bioavailability and effectiveness of oral contraceptives decrease. Advise the patient to use an alternative method of contraception.
Probenecid	No	Probenecid interferes with renal tubular excretion of penicillins, resulting in a 30–60% increase in systemic penicillin concentrations and a prolonged serum half-life. This interaction has been used to therapeutic advantage.
Allopurinol	No	Rash is more frequent when allopurinol and amoxicillin are administered together. It is unclear if the rash is associated with increased allergenicity. Inform the patient of the increased risk of rash. If a rash develops, the patient should discontinue amoxicillin immediately and inform a primary care provider.
Other antiinfectives	Possibly	Assess for therapeutic duplication, synergism, or antagonism. Determine the intent and duration of use of the other antiinfective. Dispense amoxicillin and recommend that the patient discuss therapeutic options with a primary care provider.