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Guidelines for Treatment of Anthrax

Andrea Meyerhoff; Dianne Murphy; Alan D. Tice; et al.

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β-Blocker Therapy and Depression

To the Editor: In their review article, Dr Ko and colleagues¹ found no significant increased risk of depressive symptoms and only small increased risk of fatigue and sexual dysfunction associated with β-blocker therapy. They concluded that concerns about depression, fatigue, and sexual dysfunction should not deter physicians from initiating β-blocker therapy. I would like to raise the following caveats.

First, in addition to varying degrees of lipid solubility and generation, there are other pharmacological differences among β-blockers. Several β-blockers, such as pindolol, have antagonistic activity at somatodendritic 5-HT_{1A} autoreceptors, and thereby increase serotonin release.² This action may lead to an improvement in depression. Räsänen et al³ reported that treatment with pindolol was associated with a slightly but significantly lower rate of antidepressant use, suggesting that pindolol may have some beneficial effects on mood. Although Ko et al used a random-effects model to account for heterogeneity between studies, they should have considered the additional heterogeneity associated with different β-blockers.

Second, and in contrast to the above findings, Sørensen et al⁴ found that the standardized mortality ratio for suicide in users of β-blockers was 1.6 (95% confidence interval, 1.2-2.1). This suggests that β-blockers may increase the risk of suicide. If so, depression also may be increased by the use of β-blockers because most suicides are a consequence of depression. Thus, it is possible that the majority of studies in the meta-analysis of Ko et al did not have sufficient sensitivity to detect depression.

Finally, Ko et al investigated depression, fatigue, and sexual dysfunction individually, but fatigue and sexual dysfunction also may be attributed to depression. As such, the authors could have analyzed these symptoms collectively as “depressive symptoms.”

Existing studies about the risk of depressive symptoms in β-blockers yield conflicting results. This inconsistent relationship suggests that some β-blockers may improve depression, others may worsen it, and yet others may have little effect.

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1. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. β-Blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA*. 2002; 288:351-357.
2. Terao T. β-Adrenoceptor blockers and serotonin. *Br J Clin Pharmacol*. 2002; 53:407.
3. Räsänen P, Hakko H, Tihonen J. Pindolol and major affective disorders: a three-year follow-up study of 30,485 patients. *J Clin Psychopharmacol*. 1999;19:297-302.
4. Sørensen HT, Mellekjær L, Olsen JH. Risk of suicide in users of β-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors. *Br J Clin Pharmacol*. 2001;52:313-318.

To the Editor: We disagree with the conclusions of Ko et al¹ that the conventional wisdom of β-blocker therapy being associated with depressive symptoms, fatigue, and sexual dysfunction is not supported by data from clinical trials. Their data show that the withdrawal rate of β-blockers because of fatigue was more than 2 times higher, and that due to sexual dysfunction almost 5 times higher, than in patients receiving placebo. In the Medical Research Council studies,^{2,3} the withdrawal rate for patients taking β-blockers because of fatigue was between 10 and 24 times that for those receiving placebo and also significantly higher than that for those taking diuretics, which are known to have a well-documented adverse effects profile.

However, in contrast to β-blockers, diuretics have been clearly shown to reduce morbidity and mortality in hypertension.⁴ Withdrawal rates provide more reliable information than “reported symptoms,” which, according to the principle “don’t ask, don’t tell,” are often neither solicited nor volunteered. In contrast, whenever a patient concludes that he or she has to withdraw from the study, symptoms usually have reached levels that are no longer tolerable.

Ko et al attempt to diminish the significance of the 3-fold increased risk of withdrawal due to fatigue and the 5-fold increased risk of withdrawal due to sexual dysfunction by pointing out that the absolute withdrawal risks were small. Indeed they were, but the benefits were even smaller, particularly in hypertension. The risk reduction by β-blockers for stroke, myocardial infarction, and death are 0.7, 0.7, and 0.4, respectively, per 1000 patient-years.^{2,3} These values are not significantly different from placebo. For every stroke or heart attack prevented, however, 3 patients were made impotent by β-blockers, and 8 experienced fatigue to the extent that they withdrew from such therapy—hardly an acceptable risk/benefit ratio for a completely asymptomatic disease such as mild essential hypertension.

We agree, however, with the authors’ contention that “the risk of the adverse effects should be put in the context of the documented benefits.” In the case of hypertension in patients older than 60 years, such benefits have not been documented,⁴ and therefore the substantial risk of adverse effects

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Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

clearly argues against the use of β -blockers for the treatment of this disease.

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1. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. β -Blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA*. 2002;288:351-357.
2. Medical Research Council (MRC) Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ (Clin Res Ed)*. 1985;291:97-104.
3. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ*. 1992;304:405-412.
4. Messerli FH, Grossman E, Goldbourt U. Are β -blockers efficacious as first-line therapy for hypertension in the elderly? a systematic review. *JAMA*. 1998;279:1903-1907.

In Reply: Dr Terao cautions that factors other than lipid solubility and generation may influence the risks of adverse effects of β -blockers, and that there may be an inconsistent relationship between β -blockers and depressive symptoms. We acknowledge that there is evidence of a beneficial effect of pindolol in combination with paroxetine on depression.¹ Of the trials in our meta-analysis, only the STOP-Hypertension (Swedish Trial in Old Patients with Hypertension) trial² tested pindolol. Although there was no significant difference in the risk of depression between the treatment groups, the sample size was too small to confirm (or disprove) any protective effect.

With respect to the cohort study³ cited by Terao suggesting an increased risk of suicide and therefore presumably depression in users of β -blockers, we combined data from the randomized controlled trials because they provide the strongest evidence about benefits and risks. Our finding that β -blockers were not associated with an increased risk of depression does not support a mechanism for a suicide risk for these medications.

Drs Messerli and Grossman disagree with our conclusion that substantially increased risks of depression, fatigue, and sexual dysfunction are not supported by the clinical trial data. It was not our intent to diminish the significance of the relative increases in risks of withdrawal for fatigue and sexual dysfunction. Rather, we sought to appropriately interpret these risks taking into account the relative increases in risks as well as absolute excess risks. If an event is rare, even a sizable relative risk may nonetheless be associated with a small absolute excess risk. This was true for withdrawals due to fatigue and sexual dysfunction in our analysis, in which the respective 3- and 5-fold relative increases in risk were associated with absolute excess risks of only 4 withdrawals per 1000 patients per year for fatigue and 2 per 1000 patients per year for sexual dysfunction.

We disagree with Messerli and Grossman that risks of withdrawal provide more reliable information than risks of reported symptoms. Reported symptoms in clinical trials are

generally assessed in a standardized fashion in both treatment groups. We believe that both withdrawals and reported symptoms should be examined, as we did in our meta-analysis.

Finally, Messerli and Grossman suggest that diuretics (as opposed to β -blockers) are a better choice of therapy for elderly patients with mild hypertension. Our aim was not to compare the efficacy of different classes of drugs in specified conditions, but rather to quantify the risks of adverse symptoms assessed in patients randomized to receive β -blockers as compared with placebo for the treatment of myocardial infarction, heart failure, and hypertension. We believe that this information will be helpful to clinicians in placing the adverse effects of β -blockers within the context of their documented benefits.

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1. Perez V, Gilaberte I, Faries D, Alvarez E, Artigas F. Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. *Lancet*. 1997;349:1594-1597.
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3. Sørensen HT, Mellemkjaer L, Olsen JH. Risk of suicide in users of beta-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors. *Br J Clin Pharmacol*. 2001;52:313-318.

Medical Residents' Emotional Well-being

To the Editor: In their On Call article, Dr Bellini and colleagues¹ described the relationship between mood and empathy in a sample of interns. My colleagues and I recently reported a relationship between emotional distress in residents and the quality of the care they deliver.²

While Bellini et al state they were unaware of previous longitudinal studies reporting on variations in mood during the course of the internship, we are aware of 2 studies that reported similar data.^{3,4} Like the study by Bellini et al, one of these studies found that depression and fatigue in residents was greatest in February.³ Over the last 2 decades, the negative emotional consequences of residency training have been well documented. In an effort to improve the situation, the Accreditation Council for Graduate Medical Education (ACGME) recently published new guidelines that restrict resident work hours.⁵ While these regulations represent an effort toward meaningful progress, little evidence was available to guide these changes, and the extent to which they will improve emotional distress in residents remains unknown. Future studies of resident dis-

tress should focus on identifying causes and solutions for resident distress rather than just further describing the problem. More important, studies exploring how to promote residents' well-being are needed to understand not only how to eliminate the problem but also how to promote residents' emotional health.

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1. Bellini LM, Baime M, Shea JA. Variation of mood and empathy during internship. *JAMA*. 2002;287:3143-3146.
2. Shanafelt TD, Bradley KA, Wipf JE, Back AL. Burnout and self-reported patient care in an internal medicine residency program. *Ann Intern Med*. 2002;136:358-367.
3. Girard DE, Elliot DL, Hickam DH, et al. The internship: a prospective investigation of emotions and attitudes. *West J Med*. 1986;144:93-98.
4. Reuben DB. Depressive symptoms in medical house officers: effects of level of training and work rotation. *Arch Intern Med*. 1985;145:286-288.
5. Accreditation Council for Graduate Medical Education (ACGME). *Report of the ACGME Work Group on Resident Duty Hours*. 2002. Available at: <http://www.acgme.org>. Accessibility verified September 4, 2002.

In Reply: The studies that Drs Shanafelt and Habermann cite were published 17 years ago and suggest that mood disturbances were as prevalent then as they are now. We agree that we should have cited them. Many changes have been implemented in graduate medical education at the direction of the ACGME since those studies were done, including night float systems, less critical care time, less frequent call, fewer hours per week worked and more time off.¹ It is quite disconcerting that, despite these regulations, the level of mood disturbance remains similar.

Further research must explore how to reverse or at least lessen the negative effect of residency training on mood and empathy. As Shanafelt and Habermann suggest, promoting resident well-being should be a fundamental principle of graduate medical education.

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1. Accreditation Council for Graduate Medical Education (ACGME). *Program Requirements for Internal Medicine*. 2002. Available at: <http://www.acgme.org>. Accessibility verified September 4, 2002.

Anesthesia and Preeclampsia

To the Editor: In their *Contempo Updates* article on preeclampsia, Drs Lain and Roberts¹ did not mention the role of regional analgesia and anesthesia (eg, spinal, epidural, and combined spinal-epidural) in high-risk patients. Although controversial, many investigators have recommended the use of epidural anesthesia in severe preeclampsia and eclampsia to help control blood pressure and pain and increase uterine

and renal perfusion.² One study has also found a higher Apgar score in infants whose mothers received epidural anaesthesia.³ It is a common practice to use these regional techniques (when they are not contraindicated) in such patients for peripartum care.⁴

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1. Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. *JAMA*. 2002;287:3183-3186.
2. Shnider SM, Levinson G. Anesthesia for obstetrics. In: Miller RD, ed. *Anesthesia*. 4th ed. New York, NY: Churchill Livingstone; 1994:2031-2076.
3. Moodley J, Jjuuko G, Rout C. Epidural compared with general anaesthesia for caesarean delivery in conscious women with eclampsia. *Br J Obstet Gynaecol*. 2001;108:378-382.
4. Hood DD, Curry R. Spinal versus epidural anesthesia for caesarean section in severely preeclamptic patients: a retrospective survey. *Anesthesiology*. 1999;90:1276-1282.

In Reply: We agree with Dr Mandal that the anesthesiologist is an important member of the care team for women with preeclampsia. Several studies have evaluated maternal and fetal safety of regional anesthesia by comparing the maternal hemodynamic response, maternal outcomes, and neonatal outcomes among patients who received epidural, spinal, general, or patient-administered analgesia. Wallace et al¹ compared general, epidural, and combined spinal-epidural and found differences in the use of ephedrine for hypotension and volume of intravenous fluids administered but no differences in Apgar scores, umbilical artery pH, or respiratory distress. They also found an increase in special care nursery admissions with epidural anesthesia.¹ The study by Hood and Curry² also supports the use of regional anesthesia. They demonstrated similar maternal and neonatal outcomes with epidural compared with spinal anesthesia with the exception of the spinal group receiving more intravenous fluids and antihypertensives. Overall change in blood pressure was similar. A retrospective study by Moodley et al³ noted comparable outcomes with general and epidural anesthesia and noted a higher 1-minute Apgar score in infants whose mothers received epidural anesthesia. In patients in labor, epidural anesthesia was superior to patient-administered analgesia but did not produce additional therapeutic benefit.⁴

Although these studies showed a decrease in mean arterial pressure in the range of 15% to 25% with anesthesia, the hypertension associated with preeclampsia should not be managed primarily with regional anesthesia.^{1,2,4} Hypotension is a risk and not a benefit. Acute severe hypertension should be managed with antihypertensive agents with consideration of potential effects of anesthesia.

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- Wallace DH, Leveno KJ, Cunningham FG, et al. Randomized comparison of general and regional anesthesia for cesarean delivery in pregnancies complicated by severe preeclampsia. *Obstet Gynecol.* 1995;86:193-199.
- Hood DD, Curry R. Spinal versus epidural anesthesia for cesarean section in severely preeclamptic patients: a retrospective survey. *Anesthesiology.* 1999;90:1276-1282.
- Moodley J, Jjuuko G, Rout C. Epidural compared with general anaesthesia for caesarean delivery in conscious women with eclampsia. *Br J Obstet Gynaecol.* 2001;108:378-382.
- Lucas MJ, Sharma SK, McIntire DD, et al. A randomized trial of labor analgesia in women with pregnancy-induced hypertension. *Am J Obstet Gynecol.* 2001;185:970-975.

Guidelines for Treatment of Anthrax

To the Editor: We wish to provide the following factual corrections in response to the article by Dr Inglesby and colleagues¹ about anthrax as a biological weapon.

First, Inglesby et al state that there are no US Food and Drug Administration (FDA)-approved postexposure antibiotic regimens following exposure to a *Bacillus anthracis* aerosol. In fact, on August 30, 2000, the FDA approved ciprofloxacin for use in inhalational anthrax (postexposure) for both adults and children. (Inhalational anthrax postexposure is also referred to as anthrax postexposure prophylaxis [PEP].)

Second, the FDA and its Anti-infectives Advisory Committee have stated that the risk-benefit assessment for use of ciprofloxacin for inhalational anthrax PEP is such that it is presently recommended for use in children.² The members of the agency believe clinicians should be informed that ciprofloxacin is approved by the FDA for pediatric use in inhalational anthrax PEP. Specifically, 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.³

Third, in contrast to prophylaxis, the FDA has not approved any therapy specifically for the treatment of inhalational anthrax. The authors state that "penicillin, doxycycline, and ciprofloxacin are approved by the FDA for the treatment of inhalational anthrax infection." For clarification, penicillin G procaine and doxycycline are both approved by the FDA for the treatment of disease due to *B anthracis*, as well as for anthrax PEP. Ciprofloxacin is only approved for "inhalational anthrax (post-exposure)" and is not approved by the FDA for the treatment of inhalational anthrax.

Finally, although amoxicillin has not been approved by the FDA as therapy for inhalational anthrax PEP or for treatment of symptomatic anthrax, it is often recommended for these indications. The 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.

More information about the recommended treatment of *B anthracis* is available from the FDA at (301) 827-7711, (301)

827-7777, <http://www.fda.gov/oc/opacom/hottopics/default.htm>. (Accessibility verified September 13, 2002.)

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- Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA.* 2002;287:2236-2252.
- Food and Drug Administration, Center for Drug Evaluation and Research, Anti-Infective Drugs Advisory Committee meeting [transcript]. July 28, 2000; Parklawn Building, Rockville, Md. Available at: <http://www.fda.gov/ohrms/dockets/AC/CDER00.htm>. Accessed May 14, 2002. Accessibility verified September 13, 2002.
- Cipro (ciprofloxacin hydrochloride) tablets, Cipro oral suspension, and Cipro IV for intravenous infusion [package insert]. West Haven, Conn: Bayer Corp; 2002.

To the Editor: Dr Inglesby and colleagues¹ emphasize the importance of prompt and appropriate antimicrobial therapy for inhalational anthrax.

I was concerned, however, that the authors did not recommend loading doses of antibiotics. Without a loading dose, serum levels do not reach a steady state until after several doses of the drug have been administered. For compartments such as infected lymph nodes and the mediastinum, effective concentrations would be even more difficult to achieve. This may be a particular problem for doxycycline, which has a half-life of 18 hours.² A loading dose of twice the standard intermittent dose should carry no more likelihood of toxicity than a regular dose and may be appropriate for ciprofloxacin as well.

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- Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA.* 2002;287:2236-2252.
- Fabre J, Milek E, Kalfopoulos P, et al. The kinetics of tetracyclines in man: digestive absorption and serum concentrations. In: *Doxycycline (Vibramycin): A Compendium of Clinical Evaluation*. New York, NY: Pfizer Laboratories; 1973:13-18.

In Reply: We appreciate the clarifications from Drs Meyerhoff and Murphy. The accompanying corrections clarify the status of FDA approval for specific medication indications and adjust the Working Group's recommended doses for 3 drugs used in the treatment or postexposure prophylaxis of anthrax. Although these corrections do not substantively change any of the key Working Group recommendations, they are important enough to warrant specific notice.

Meyerhoff and Murphy emphasize that ciprofloxacin has been approved by the FDA for both children and adults for postexposure prophylaxis for inhalational anthrax. They also state that the FDA has not approved any therapy specifically for the treatment of inhalational anthrax while "penicillin G procaine and doxycycline are both approved by the FDA for the treatment of disease due to *B anthracis*, as well as for anthrax PEP. Cipro-

floxacin is only approved for "inhalational anthrax (postexposure)" and is not approved by the FDA for the treatment of inhalational anthrax." At this time, then, clinicians have no options that have been approved by the FDA for the treatment of inhalational anthrax. In the absence of FDA approval for any specific treatment for inhalational anthrax, clinicians must rely on other sources of guidance regarding treatment recommendations for this disease process.

Dr Tice recommends consideration of a loading dose of doxycycline and ciprofloxacin in the treatment of inhalational anthrax. We do not believe there is sufficient evidence to support changing our recommendations to include these recommendations. Tetracyclines exhibit persistent time-dependent bactericidal effects; the time above minimum inhibitory concentration (MIC) predicts therapeutic outcome.¹ Fluoroquinolone antibiotics, on the other hand, exhibit persistent concentration-dependent killing with persistent effects; the ratio of the area under the curve to the MIC predicts therapeutic outcome.² These factors are more important clinically than steady state levels of these drugs. In addition, we are aware of no information that suggests improvement in clinical outcome using loading doses of these classes of antibiotics, and the therapeutic efficacy of the standard recommended dosing regimen for these antibiotics (the same regimens that appear in our consensus paper) have been demonstrated in numerous clinical settings. Until more data regarding improvement in clinical outcomes following the use of loading doses for these antimicrobials exists, we are reluctant to propose any changes in the guidelines.

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1. Craig W. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26:1-10.

2. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother*. 1993;37:1073-10781.

CORRECTION

Incorrect Wording: Subsequent to the publication of the Consensus Statement entitled "Anthrax as a Biological Weapon, 2002: Updated Recommendations for Management," published in the May 1, 2002, issue of THE JOURNAL (2002;287:2236-2252), the authors wish to make available the following updates based on information from the US Food and Drug Administration and the Centers for Disease Control and Prevention (CDC).

In Table 3 on page 2246, the pediatric dosage of ciprofloxacin for "Initial IV [intravenous] Therapy" for inhalational anthrax in the contained casualty setting should read, "10 mg/kg every 12 h (maximum of 400 mg per dose)" and subsequent oral therapy under "Duration" should be "15 mg/kg per dose taken orally every 12 h (maximum of 500 mg per dose)." The doxycycline dosages for children should be based on weight (ie, > or ≤ 45 kg) and not on age.

In Table 4 on page 2247, the pediatric dosage of ciprofloxacin for "Initial Oral Therapy" of inhalational anthrax infection in the mass casualty setting or for postexposure prophylaxis should read, "15 mg/kg per dose taken orally every 12 h (maximum of 500 mg per dose)." The correct dosage of amoxicillin for children

who weigh less than 20 kg in a mass casualty setting or for postexposure prophylaxis is "80 mg/kg to be taken orally in 3 divided doses every 8 h."

The footnote marked by a section mark (§) in Table 4 should read as follows: "According to the CDC recommendations for the bioterrorist attacks in 2001, in which *B anthracis* was susceptible to penicillin, amoxicillin was a suitable alternative for postexposure prophylaxis in infants, children, and women who were pregnant or who were breastfeeding. Amoxicillin was also a suitable alternative for completion of 60 days of antibiotic therapy for patients in these groups with cutaneous or inhalational anthrax whose clinical illness had resolved after treatment with a ciprofloxacin- or doxycycline-based regimen (14-21 days for inhalational or complicated cutaneous anthrax; 7-10 days for uncomplicated cutaneous anthrax). Such patients required prolonged therapy because they were presumably exposed to aerosolized *B anthracis*."

In Table 5 on page 2247, the pediatric dosage of ciprofloxacin for treatment of cutaneous anthrax infection should be "15 mg/kg per dose taken orally every 12 h (maximum of 500 mg per dose)." Pediatric doxycycline dosage should be based on weight (ie, > or ≤ 45 kg) not age.

The most current versions of Tables 3, 4, and 5 are available online at: <http://jama.ama-assn.org/issues/v287n17/full/jst20007.html>.

The textual changes are as follows: On page 2245, the sentence "Penicillin, doxycycline, and ciprofloxacin are approved by the FDA for the treatment of inhalational anthrax infection,^{56,89,90,94} and other antibiotics are under study" should read, "Penicillin and doxycycline are approved by the FDA for the treatment of anthrax.^{56,89,90,94} Although neither penicillin, doxycycline, nor ciprofloxacin are specifically approved by the FDA for the treatment of inhalational anthrax, these drugs may be useful when given in combination with other antimicrobial drugs."

On page 2247, the sentence in the "Postexposure Prophylaxis" section of the text that says, "There are no FDA-approved postexposure antibiotic regimens following exposure to a *B anthracis* aerosol" should read, "Ciprofloxacin, doxycycline, and penicillin G procaine are approved by the FDA for postexposure prophylaxis of inhalational anthrax."

On page 2248 in the "Children" subsection, the sentence that begins "According to CDC recommendations . . ." should read "According to the CDC recommendations for the bioterrorist attacks in 2001, in which *B anthracis* was susceptible to penicillin, amoxicillin was a suitable alternative for postexposure prophylaxis in infants and children (Table 4)." In the "Pregnant Women" subsection, the sentence that begins, "According to the CDC recommendations . . ." should read, "According to the CDC recommendations for the bioterrorist attacks in 2001, in which *B anthracis* was susceptible to penicillin, amoxicillin was a suitable alternative for postexposure prophylaxis in women who were pregnant or who were breastfeeding (Table 4)."

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