Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science
Volume 5, Number 1, 2007 © Mary Ann Liebert, Inc.
DOI: 10.1089/bsp.2006.0011

Bioterrorism-Related Inhalational Anthrax: Can Extrapolated Adult Guidelines Be Applied to a Pediatric Population?

Rick C. Place, Dan Hanfling, John M. Howell, and Thom A. Mayer

Objective: Since the 2001 anthrax attacks, an extensive body of literature has evolved, but there has been a limited focus on the management of pediatric-specific issues. We looked at the symptom complexes of all pediatric patients presenting to the emergency department of our hospital during this period and examined whether their presentations would likely allow current guidelines to be used as potential screening criteria to identify children infected with anthrax. ***Methods:*** We retrospectively reviewed emergency department records of all adult and pediatric patients (up to the age of 21 years) at Inova Fairfax Hospital during this time, when a large, and at the time ill-defined, group in the Washington, DC, metropolitan area was at risk for pulmonary anthrax. Two cases of anthrax infection were identified at this hospital in exposed adult postal workers. Screening algorithms (described by Mayer et al. and Hupert et al.) were applied to adult and pediatric patients with the presence of fever (38°C), tachycardia, or other symptoms compatible with pulmonary anthrax. Specifically, the usefulness of these guidelines as potential screening tools to identify possibly infected children was examined. ***Results:*** Of 767 pediatric patients seen in the emergency department during the study period, 312 met criteria for review (41%; 95% CI: 37–44%). Four adult patients (0.4%; 95% CI: 0.1–0.9%) had at least five clinical symptoms, fever, and tachycardia; two of them had inhalational anthrax. No pediatric patient presented with five or more clinical symptoms. Twelve children (3.9%; 95% CI: 2–6.6%) presented with four clinical symptoms; five of the 12 had neither fever nor tachycardia. Children, particularly infants and toddlers, presented with nonspecific symptom complexes primarily limited to fever, vomiting, cough, and trouble breathing. ***Conclusions:*** Existing guidelines are likely to be unreliable as a screening tool for inhalational anthrax in children, largely because of the children's inability to adequately communicate a suggestive symptom complex.

In October and November of 2001, 11 patients were identified in the United States with inhalational anthrax.[1–3] Although the total number of confirmed patient exposures to anthrax was limited, the number of patients seeking medical attention with concerns of "possible exposure" was extensive, severely straining existing healthcare services. This sudden surge in demand for patient care, especially in the context of a bioterror agent that was rela-

Rick C. Place, MD, is Pediatric Medical Director, Department of Emergency Medicine; Dan Hanfling, MD, FACEP, is Director, Emergency Management and Disaster Medicine; and John M. Howell, MD, FACEP, is Director of Academic Affairs, Department of Emergency Medicine; all are at Inova Fairfax Hospital, Falls Church, Virginia. Dr. Place and Dr. Hanfling are also Clinical Associate Professors, Department of Emergency Medicine, and Dr. Howell is Clinical Professor of Emergency Medicine, George Washington University, Washington, DC. Thom A. Mayer, MD, FACEP, FAAP, is Clinical Professor, Department of Emergency Medicine, George Washington University and University of Virginia (Charlottesville) Schools of Medicine, and Senior Lecturing Fellow, Duke University School of Medicine, Durham, NC.

tively unstudied and unfamiliar to the majority of healthcare practitioners, highlighted the importance of proactively planning for medical surge capacity, as well as familiarity with screening large numbers of patients who might have been exposed to agents of bioterrorism. Moreover, significant healthcare and economic resources were expended to distinguish the few infected people from the vast numbers of those who were not infected.[4]

The limited focus of the attacks kept this particular outbreak from more dramatically affecting the healthcare delivery system. However, as Danzig has noted in an insightful and penetrating monograph, the possibility of broader and more sustained releases of bioterrorism agents points to the critical importance of developing guidelines and training scenarios for likely bioterrorism agents that might be used in the future. These guidelines and scenarios should include consideration of pediatric victims of bioterrorism.[5]

A significant body of recent literature has focused on the medical, epidemiological, and national security aspects of these attacks.[2,3,6,7] Little focus has been placed on the ability of the healthcare delivery system to address specific pediatric diagnostic, treatment, and management aspects of intentional anthrax dissemination.

While only one child was known to have been exposed to anthrax spores in the 2001 attack,[8] a more indiscriminate spread of anthrax spores could potentially expose a large number of children who, like their adult counterparts, would require rapid triage and risk stratification. Unfortunately, pediatric-specific guidelines have not been developed. What little there is merely reiterates the adult experience.[9,10] As part of our post-hoc analysis of the Washington, DC, area anthrax attacks, we looked at the symptom complexes of all pediatric patients presenting during this period and examined whether their presentations would likely allow current guidelines to be used as potential screening criteria to identify children infected with anthrax.[1,11]

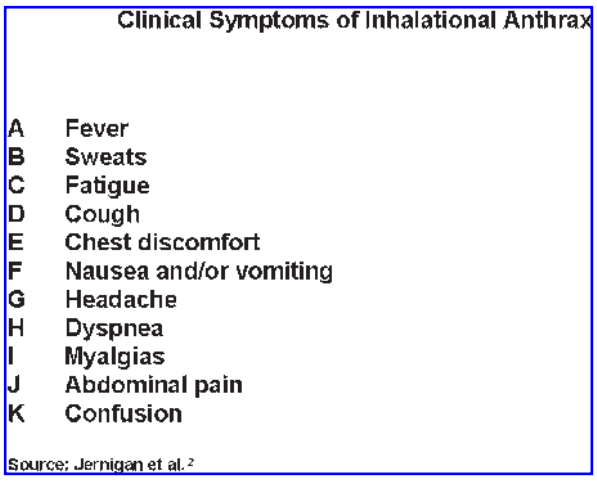
Screening for Anthrax in an Exposed Population

Our total emergency department census (i.e., adult and pediatric) for the study period was 4,259 patients. Of those, 1,127 adult and pediatric records met the criteria for review (*any* symptoms consistent with pulmonary anthrax, listed in the sidebar; fever; or tachycardia). Of the 312 pediatric charts that met the criteria for review (41% of pediatric patients presenting to the department), 195 (63%) were aged 0–3 years, 82 (27%) were aged 4–10 years, and 35 (10%) were aged 11–21 years. While no pediatric patient was diagnosed with inhalational anthrax, blood samples of two adult patients had positive PCR tests for anthrax. Four adult patients (0.4%; 95% CI: 0.1–0.9%) had at least five clinical symptoms and fever and tachycardia, thus meeting adult screening guidelines, and two of the four had inhalational anthrax.[1] No pediatric patient presented with five or more clinical symptoms, and only 12 children (3.9%) presented with four clinical symptoms; 50 pediatric patients (16%) had three symptoms, 124 (40%) had two symptoms, 104 (33%) had one symptom, and 22 (7%; 95% CI: 4.5–10.5%) had no clinical symptoms suggestive of inhalational anthrax (they had only fever or tachycardia).

It is important to note that the majority of children evaluated during the study period were preverbal infants and toddlers (63%), with a minority of more verbal school-age children (27%) and adolescents (10%). Of infants and toddlers presenting during this time period, 46% had fever. The vast majority had only two or three clinical symptoms, with none having the requisite five symptoms that would trigger the diagnostic screening in adults suggested by Mayer et al.[1] Furthermore, the aggregate symptoms in infants and toddlers were extremely limited in scope and nonspecific: fever, vomiting, cough, and trouble breathing (Figure 1). The relative paucity of symptoms that young children present with is quite evident when compared with adults presenting over the same time period, and when compared to the symptoms seen in *all* patients with documented inhalational anthrax in the U.S. during the study period and those with documented anthrax infection (Figures 1–3).[2] The scope of the symptom complex visibly changes across the entire age range of pediatric patients (Figures 4–6).

Making Sense of the Data

Current screening recommendations are extrapolated largely from the adult literature, based on risk-stratifying adult patients with anthrax exposure. What little literature that exists regarding pediatric-specific concerns discusses them as generalities (e.g., children may experience greater



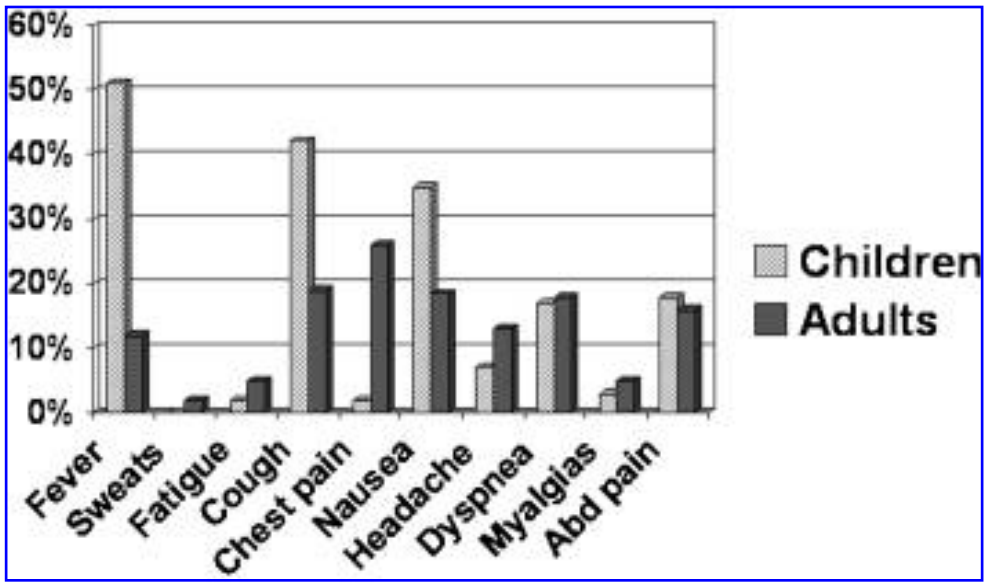


Figure 1. Frequency of Clinical Symptoms: Screened Children and Screened Adults

risks of inhalation because their minute volumes are greater).[12,13] Applying guidelines to potential pediatric inhalational anthrax victims has been a poorly developed process, particularly as it applies to infants and young children.[9,12] Whereas a number of resource documents have been made available that highlight recommended therapies and anthrax prophylaxis in children, an evidence-based diagnostic approach for potential pediatric exposure to aerosolized anthrax currently does not exist.[3] Therefore, accurate or not, pediatric guidelines are based on adult signs, symptoms, medical evaluations, and theoretical extrapolations.[9,14]

Screening and evaluation for inhalational anthrax during the fall 2001 attacks, while not formally restricted to individuals at occupational risk, were made much easier by the fact that the exposure was limited in scope. Should a more

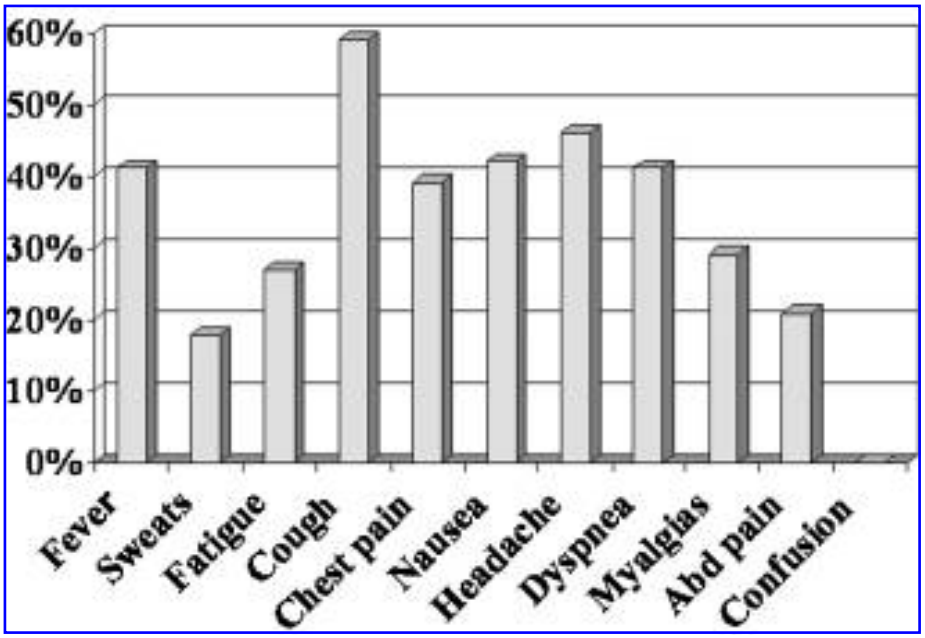


Figure 2. Frequency of Symptoms: Screened Adults with 4 or More Symptoms

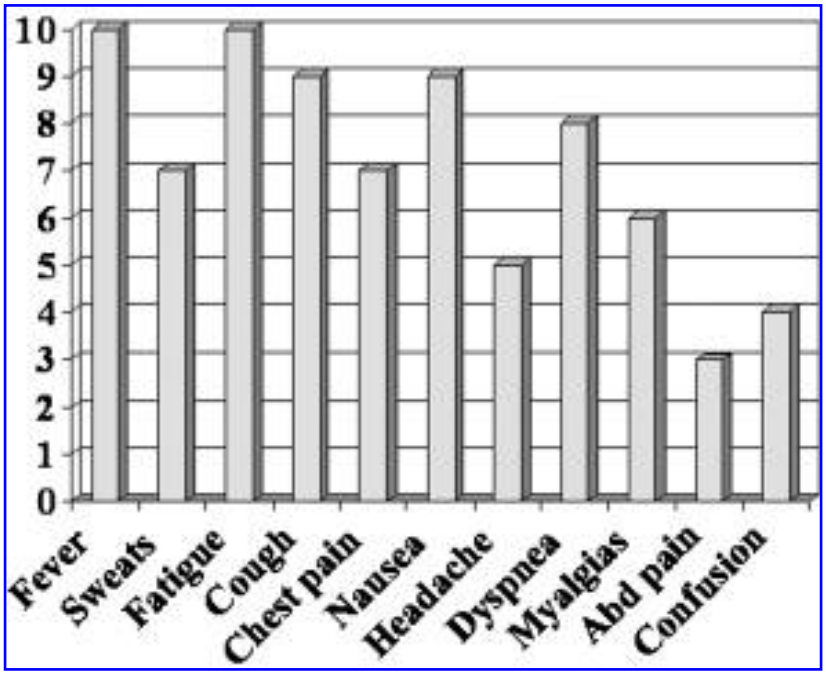


Figure 3. Frequency of Symptoms in First 10 Anthrax Cases in 2001[2]

indiscriminate, aerosolized delivery of weaponized anthrax spores take place, thereby limiting epidemiologic risk factors as a discriminator of risk, pragmatic guidelines will be necessary to better focus screening on patients truly at risk. Mayer et al. provided one approach, concluding that using five or more clinical symptoms with fever and tachycardia is a prudent approach to screening patients in the absence of defined epidemiologic risk factors.[1] Hupert and colleagues used an algorithm to assess the efficacy of screening patients with possible exposure and signs or symptoms of pulmonary anthrax.[11] A previous publication indicated that nearly 10–70 times as many patients would be screened using this algorithm as opposed to the criteria of Mayer et al.[11] We argue that both approaches may be ineffective for pediatric patients, particularly for very young children.

The literature on pediatric anthrax is sparse, with numerous case reports scattered over the past century consisting of localized, cutaneous disease and atypical presentations or outcomes (e.g., survival from anthrax meningitis).[8,10,15–20] There was only one known pediatric infection in the 2001

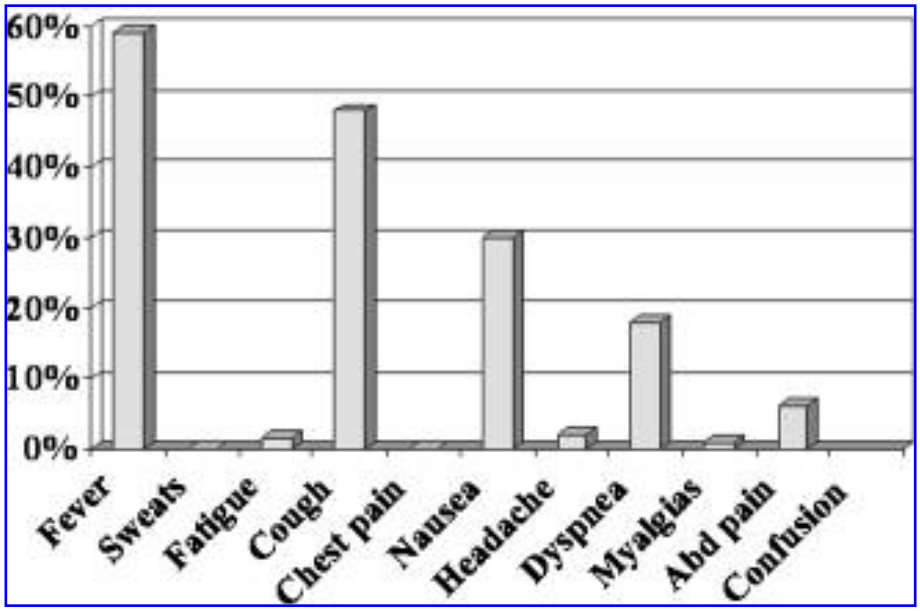


Figure 4. Frequency of Symptoms: Screened Children Ages 0–3 Years

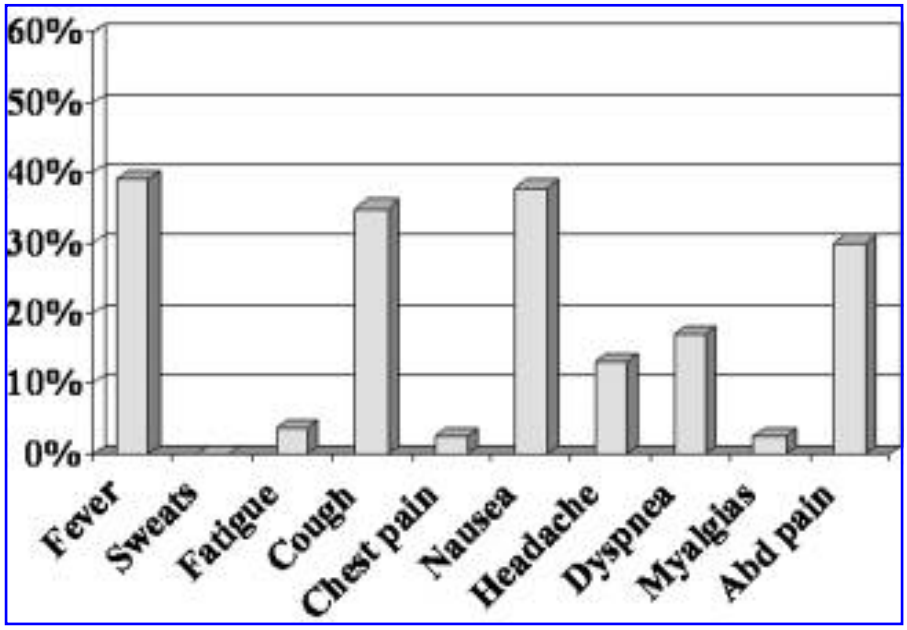


Figure 5. Frequency of Symptoms: Screened Children Ages 4–11 Years

anthrax attacks, and this patient had cutaneous anthrax, the most easily identifiable and treatable form of the disease.[8] We could find no cases of pediatric inhalational anthrax in the literature from which to draw conclusions as there were with their adult counterparts.[1–3,10] The few cases of invasive disease reported in pediatric patients were fatalities and descriptions that did not focus on the early (and potentially treatable) phases of the disease.[15–17,21–23]

One serious problem with applying adult anthrax guidelines to pediatric patients is that, like other infectious illnesses (e.g., chicken pox, mumps, severe acute respiratory syndrome), inhalational anthrax may present differently in children than in adults. A recent observational study of children with severe acute respiratory syndrome (SARS) clearly illustrated differences in clinical presentation between adults and children.[24] Even if this disease process *is* similar, it is possible that the clinical manifestations of inhalational anthrax in children may be

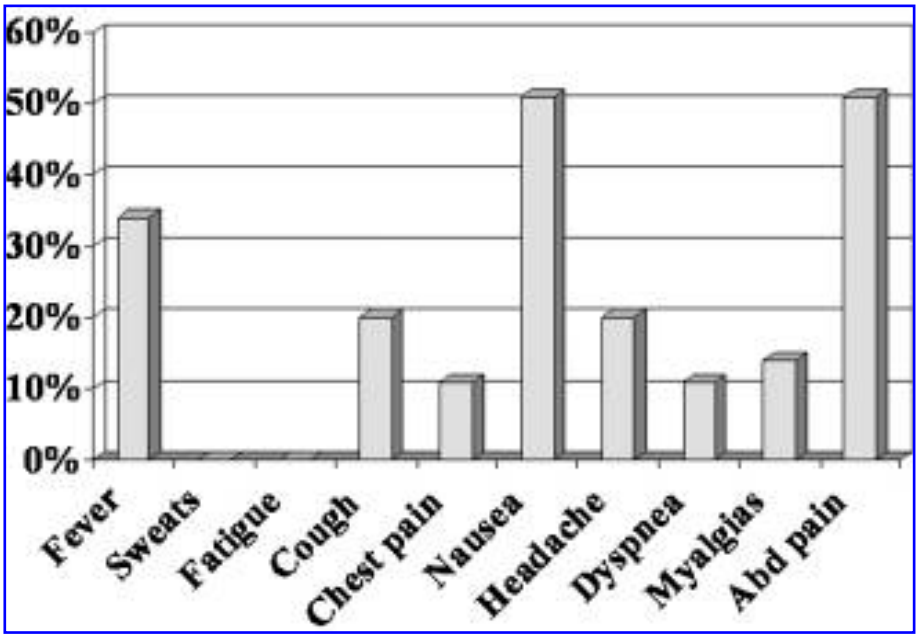


Figure 6. Frequency of Symptoms: Screened Children Ages 12–16 Years

far less specific. For example, few 2-year-olds complain of chest discomfort, but many have nonspecific vomiting with febrile illnesses. Many febrile children are reported by parents to have a minor, dry cough, thus limiting the discriminatory value of important clues specific to adult pulmonary anthrax. The pediatric literature on anthrax bioterrorism simply fails to adequately address these limitations.[9,12]

Formal Screening Guidelines Not Reliable

Unfortunately, young children are unable to verbally express a symptom complex broad enough for useful clinical discrimination (Figures 4 and 5). Many of the key symptoms noted by Jernigan et al. (Fig. 3) required both somatic insight and verbal expressiveness (e.g., dyspnea, chest discomfort, nausea, myalgias, headache).[2] The verbal ability of screened children and their symptom complexes are clearly correlated. Of all the screening criteria, in addition to fever, only a few were found in significant numbers of infants and toddlers (cough, vomiting, shortness of breath). As children advanced in age and verbal ability, the number of symptoms shifted toward a higher number with the addition of headache and stomach ache. In the pre-adult adolescent years, where verbal expressiveness is more sophisticated, a greater percentage of children presented with potentially discriminatory complexes of four symptoms (17%). Fully 63% of our pediatric patients were in the 0–3-year age group, when somatic insight and verbal expression are limited or nonexistent.

We also believe that the extrapolated workup recommended in adult guidelines may prove to be problematic. The typical approach in an adult patient is to obtain a complete blood count (CBC), blood culture (which is not timely), and a chest radiograph. Chest radiography is perhaps the one test that truly drives further evaluation in the absence of clinical toxicity, dramatically improves post-test probability, and affects prognosis.[2] Patients with a widened mediastinum or pleural effusion have evidence of potential mediastinitis, the initial (and treatable) phase of the disease.[1,2,10,25] It is recommended that such patients undergo thoracic CT imaging to confirm or eliminate the possibility of mediastinitis.[1] However, the normal pediatric radiograph may differ significantly from that of an adult. The thymic shadow in infants may cover half of the diameter of the lungs and obliterate mediastinal features. While a normal radiograph may be reassuring, the usefulness of this study to discriminate potential bioterrorism victims is likely to be more limited in young children. On the other hand, radiographic abnormalities in pediatric patients at risk for inhalational anthrax need to be taken very seriously.

The same limitations likely apply to the use of the CBC, a decidedly poor discriminator of serious bacterial illness in children. While written monographs on anthrax suggest a uniformly elevated leukocyte count, it is not at all clear that this is the case in the prodromal (i.e., treatable) stage of the illness.[10,26] Even then, descriptions of pediatric anthrax find a variable leukocytosis, including relatively normal values, in critically ill children, potentially limiting its usefulness.[9,15,20] Indeed, white blood cell counts were invariably normal in the recently described adult patients with inhalational anthrax who presented in the prodromal phase of the illness.[2]

Even treatment decisions are problematic. Which antibiotic is indicated for the infant with potential (but not clear) anthrax exposure, low grade fever, and nonspecific symptoms while blood cultures are pending? Sensitivity testing of the 2001 anthrax strain demonstrated the presence of a cephalosporinase and intermediate sensitivity to ceftriaxone, making it an inappropriate choice.[6] Thus, standard of care treatment for the ubiquitous pediatric fever without a source must necessarily be altered in the setting of anthrax release. Ciprofloxacin and doxycycline have both been recommended for both treatment and oral prophylaxis in children,[14] but neither of these treatments is recommended and they may not be appropriate in febrile children.

Conclusion

The recent recommendations published by the National Advisory Committee on Children and Terrorism demonstrate the urgent need to focus on improving the readiness of all healthcare facility settings to manage injured, ill, or potentially exposed pediatric patients.[27] Among a number of very important priorities is the recommendation to develop a set of diagnostic "pediatric algorithms for the most common conditions, and make them available to every hospital and location that cares for children."[27] Any febrile infant or young child presenting for evaluation during an indiscriminate aerosolized anthrax attack should be considered at risk and in need of a workup. Extrapolation of adult criteria to the pediatric patient presents difficulties. It would be wise to consider that children with very early, prodromal anthrax may present with a nonspecific febrile illness with vague constitutional symptoms—as would their adult counterparts. But there will be fewer and perhaps less specific associated findings to discriminate anthrax from more common circulating infectious illnesses. Furthermore, the diagnostic workup is likely to be less clear than in adults.

In retrospect, this study would have provided more accurate information if it had been performed in a prospective

fashion. As with all chart abstraction, results are limited to what is written on the chart. A prospective evaluation would more completely identify patient symptoms. In addition, certain other characteristics, such as a child's verbal ability, could be more clearly explored.

In summary, based on our experience screening children for inhalational anthrax in October 2001, we believe that, in cases where anthrax infection cannot be excluded and regardless of the symptom complex, febrile pediatric patients at even minimal risk of anthrax exposure should be treated empirically with ciprofloxacin or doxycycline prophylaxis after a blood culture has been obtained and follow-up arranged for the following day. All positive blood cultures drawn before the initiation of antibiotics in the 2001 attacks yielded positive results within 24 hours.[2] Indeed, recent work by Fine et al., using the more theoretical approach of decision analytic modeling, suggests that, during an event, treating all febrile patients in whom influenza has been excluded, regardless of age, may be the safest approach until blood cultures are known to be negative.[28] The sheer number of febrile children presenting to emergency departments is likely to render any other approach impractical during an indiscriminate attack. Given what is known about the course of inhalational anthrax in adults, this is likely the most reasonable approach to a child who does not appear acutely ill but might have unrecognized inhalational anthrax in the early, insidious stage.

While these data specifically target current guidelines regarding the approach to pediatric anthrax, similar limitations exist with regard to pediatric guidelines extrapolated from adult data for other chemical and bioterrorism agents.[24] We must recognize the paucity of specific pediatric data as we struggle to tailor our approach to this population.

REFERENCES

1. Mayer TA, Morrison A, Bersoff-Matcha S, et al. Inhalational anthrax due to bioterrorism: would current Centers for Disease Control and Prevention guidelines have identified the 11 patients with inhalational anthrax from October through November 2001? *Clin Infect Dis* 2003;36:1275–1283.
2. Jernigan JA, Stephens DS, Ashford DA, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis* 2001;7:933–944.
3. Inglesby TV, O'Toole T, Henderson DA. Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA* 2002;287:2236–2252.
4. Howell JM, Mayer TA, Hanfling D, et al. Screening for inhalational anthrax due to bioterrorism: evaluating proposed screening protocols. *Clin Infect Dis* 2004;39(12):1842–1847.
5. Danzig R. *Catastrophic Bioterrorism—What Is To Be Done?* Washington, DC: Center for Technology and National Security Policy; 2003:1.
6. Borio L, Frank D, Mani V, et al. Death due to bioterrorism-related inhalational anthrax: report of 2 patients. *JAMA* 2001;286:2554–2559.
7. Heyman D. *Lessons from the Anthrax Attacks: Implications for U.S. Bioterrorism Preparedness: A Report on a National Forum on Biodefense.* Washington, DC: Center for Strategic and International Studies; April 2002. Available at: http://www.fas.org/irp/threat/cbw/dtra02.pdf. Accessed on August 4, 2004.
8. Freedman A, Afonja O, Chang MW, et al. Cutaneous anthrax associated with microangiopathic hemolytic anemia and coagulopathy in a 7-month-old infant. *JAMA* 2002;287:869–874.
9. Patt HA, Feigin FD. Diagnosis and management of suspected cases of bioterrorism: a pediatric perspective. *Pediatrics* 2002:109;685–692.
10. Nopar RE. Plagues on our children: the threat of biological warfare. *Clin Ped* 1967:6;63–73.
11. Hupert N, Bearman GM, Mushlin AI, Callahan MA. Accuracy of screening for inhalational anthrax after a bioterrorist attack. *Ann Intern Med* 2003:139;337–345.
12. American Academy of Pediatrics; Committee on Environmental Health and Committee on Infectious Diseases. Chemical-biological terrorism and its impact on children: a subject review. *Pediatrics* 2000;105:662–670.
13. Cieslak TJ, Henretig FM. Ring-a-ring-a-roses: bioterrorism and its peculiar relevance to pediatrics. *Curr Opin Pediatr* 2003;15:107–111.
14. Update: Interim recommendations for antimicrobial prophylaxis for children and breastfeeding mothers and treatment of children with anthrax. *MMWR Morb Mortal Wkly Rep* 2001;50:1014–1016.
15. Tahernia AC, Hashemi G. Survival in anthrax meningitis. *Pediatrics* 1972:50;329–333.
16. Tabatabaie P, Syadati A. *Bacillus anthracis* as a cause of bacterial meningitis. *Pediatr Infect Dis J* 1993:12;1035–1037.
17. Alizad A, Ayoub E, Makki N. Intestinal anthrax in a two-year-old child. *Pediatr Infect Dis J* 1995;14:394–395.
18. Kaya A, Tasyaran MA, Erol S, Ozkurt Z, Ozkan B. Anthrax in adults and children: a review of 132 cases in Turkey. *Eur J Clin Microbiol Infect Dis* 2002;21:258–261.
19. Lamb R. Anthrax. *Br Med J* 1973;1:157–159.
20. Manios S, Kavaliotis I. Anthrax in children: a long forgotten, potentially fatal infection. *Scand J Infect Dis* 1979;11:203–206.
21. Rosenfield RL, Bernardo LM. Pediatric implications in bioterrorism part II: postexposure diagnosis and treatment. *Int J Trauma Nurs* 2001;7:133–136.
22. Çiftçi E, İnce E, Ülker D. Traditions, anthrax, and children. *Pediatr Derm* 2002;19:36–38.
23. Brtheir M, Gaucherie J, Perrin J, Gringo B, Riot D. Fulminant meningitis due to *bacillus anthracis* in 11-year-old girl during Ramadan. *Lancet* 1996;347:828.
24. Puthucheary J, Lim D, Chan I, Chay OM, Choo P. Severe acute respiratory syndrome in Singapore. *Arch Dis Child* 2004;89:551–556.
25. Vessal K, Yeganehdoust J, Dutz W, Kohout E. Radiological changes in inhalation anthrax: a report of radiological and pathological correlation in two cases. *Clin Radiol* 1975;26:471–474.

26. Edwards MS. Anthrax. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases, Vol. 1.* 4th ed. Philadelphia: Saunders; 1998.
27. National Advisory Committee on Children and Terrorism. *Recommendations to the Secretary of the Department of Health and Human Services.* Atlanta: Centers for Disease Control and Prevention; June 12, 2003. Available at: http://www.bt.cdc.gov/children/recommend.asp. Accessed on August 4, 2004.
28. Fine AM, Wong JB, Fraser HSF, Fleisher GR, Mandl KD. Is it influenza or anthrax? A decision analytic approach to the treatment of patients with influenza-like illnesses. *Ann Emerg Med* 2004;43:318–328.

Manuscript received July 25, 2006;
accepted for publication January 4, 2007.

Address reprint requests to:
Rick C. Place, MD
Emergency Medicine
Inova Fairfax Hospital
3300 Gallows Road
Falls Church, VA 22042

E-mail: linsonplace@aol.com