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Pediatric Anthrax: Implications for Bioterrorism Preparedness

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was requested and funded by the Health Resources and Services Administration. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

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Structured Abstract

Objectives. To systematically review the literature about children with anthrax to describe their clinical course, treatment responses, and the predictors of disease progression and mortality.

Data Sources. MEDLINE® (1966-2005), 14 selected journal indexes (1900-1966) and bibliographies of all retrieved articles.

Review Methods. We sought case reports of pediatric anthrax published between 1900 and 2005 meeting predefined criteria. We abstracted three types of data from the English-language reports: (1) patient information (e.g., age, gender, nationality); (2) symptom and disease progression information (e.g., whether the patient developed meningitis); and (3) treatment information (e.g., treatments received, year of treatment). We compared the clinical symptoms and disease progression variables for the pediatric cases with data on adult anthrax cases reviewed previously.

Results. We identified 246 titles of potentially relevant articles from our MEDLINE® search and 2253 additional references from our manual search of the bibliographies of retrieved articles and the indexes of the 14 selected journals. We included 62 case reports of pediatric anthrax including two inhalational cases, 20 gastrointestinal cases, 37 cutaneous cases, and three atypical cases. Anthrax is a relatively common and historically well-recognized disease and yet rarely reported among children, suggesting the possibility of significant under-diagnosis, under-reporting, and/or publication bias. Children with anthrax present with a wide range of clinical signs and symptoms, which differ somewhat from the presenting features of adults with anthrax. Like adults, children with gastrointestinal anthrax have two distinct clinical presentations: upper tract disease characterized by dysphagia and oropharyngeal findings and lower tract disease characterized by fever, abdominal pain, and nausea and vomiting. Additionally, children with inhalational disease may have "atypical" presentations including primary meningoencephalitis. Children with inhalational anthrax have abnormal chest roentgenograms; however, children with other forms of anthrax usually have normal roentgenograms. Nineteen of the 30 children (63%) who received penicillin-based antibiotics survived; whereas nine of 11 children (82%) who received anthrax antiserum survived.

Conclusions. There is a broad spectrum of clinical signs and symptoms associated with pediatric anthrax. The limited data available regarding disease progression and treatment responses for children infected with anthrax suggest some differences from adult populations. Preparedness planning efforts should specifically address the needs of pediatric victims.

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/clinic/tp/pedanthtp.htm.

Executive Summary

Overview

In response to the 2001 U.S. anthrax attack, there has been a proliferation of guidelines for the diagnosis and treatment of patients with anthrax. However, most of these have not specified screening and management protocols for specific populations, such as children. Efforts to prepare for and respond to future attacks of anthrax bioterrorism will be aided by detailed information about the clinical presentation and treatment responses of both adult and pediatric populations exposed to anthrax.

We performed a systematic review of case reports of pediatric anthrax to describe the clinical course, treatment responses, and predictors of disease progression and mortality for children with anthrax infection. In addition to cases of inhalational, gastrointestinal, and cutaneous anthrax, we included in our analysis case reports of primary anthrax meningoencephalitis (without an identifiable inhalational, gastrointestinal, or cutaneous source).

Key Questions

We sought to synthesize the data from English-language case reports of children with anthrax to answer three key research questions:

1. What is the evidence for an age-dependent clinical course associated with anthrax?

2. How effective are antibiotic prophylaxis and treatment for anthrax in children compared to adults? Similarly, how effective are other medical treatments in children compared to adults (e.g. ventilator/respiratory support)?

3. Based on the review of evidence for Questions 1 and 2, what are the implications for children versus adults in terms of preparedness and response planning for anthrax exposure (i.e., healthcare provider education on diagnosis and management, considerations for hospitals, vaccination strategies)?

Methodology

We sought English-language case reports of patients aged 18 years or younger with confirmed inhalational, gastrointestinal, or atypical anthrax (e.g., primary anthrax meningoencephalitis without an identifiable inhalational or cutaneous source). Because there have been hundreds of case reports of pediatric cutaneous anthrax, we selected a random sample

of 50 English-language case reports of pediatric cutaneous anthrax for abstraction. We then augmented the data abstracted from the English-language pediatric case reports with the data available from our prior Evidence Report on adult cases of inhalational anthrax. Given key physiological differences among infants, toddlers, and adolescents, we analyzed case reports in three age groups: 0 to 2 years, >2 to 13 years, and >13 to 18 years.

We identified case reports of pediatric anthrax referenced in MEDLINE® between January 1966 and June 2005 using the MeSH terms *anthrax* and *case report*. We then performed additional comprehensive searches of retrieved bibliographies and the indexes of selected journals from 1900 to 1966 (e.g., *New England Journal of Medicine, JAMA, Lancet, Medical Journal of Australia, La Presse Médicale, Deutsche Medizinische Wochenschrift, La Semana Medicale*). We also performed extensive manual searches of retrieved bibliographies.

Two investigators screened potentially relevant articles to determine whether they met inclusion criteria. One investigator independently abstracted patient data from each included case report and reviewed bibliographies for additional potentially relevant studies. Because the purpose of this project was to characterize the spectrum of pediatric anthrax disease as well as to identify the differences in disease progression and treatment responses of adults and children with anthrax, we abstracted three primary types of data from each included article: (1) patient information (e.g., age, gender); (2) symptom and clinical course information (e.g., whether the patient developed meningitis); and (3) treatment information.

We performed univariate analyses to summarize the key patient and treatment characteristics. We applied a Bonferroni correction to account for multiple comparisons.

Findings

We identified 246 titles of potentially relevant articles from our MEDLINE® search and 2253 additional references from our manual search of the bibliographies of retrieved articles and the indexes of the 14 selected journals. We identified 62 case reports of pediatric anthrax including two inhalational cases, 20 gastrointestinal cases, 37 cutaneous cases, and three atypical cases. Most of the included cases were of adolescents: we found seven cases of children aged 0 to 2 years old, 22 cases of children more than 2 years to 13 years old, and 34 cases of adolescents aged more than 13 years to 18 years old. We did not find any reports of anthrax in pregnant women or reports of prenatal cases of anthrax.

Among the 59 case reports which stated the patient's gender, only 14 (24%) were girls. This is similar to the gender discrepancy observed among adults. Several plausible explanations for this gender disparity include that anthrax has largely been an occupational disease among professions traditionally dominated by men and boys (e.g., woolsorters and butchers) and that there may be biases that result in the under-diagnosis and under-reporting of girls with anthrax.

Overall, the mortality rate was 31%. Among patients who received antibiotics, 71% survived compared to 82% of patients who received antiserum. Only one patient was treated with a fluroquinolone—a key component of the current treatment guidelines for anthrax. None of the included patients received anthrax vaccine.

Pediatric Inhalational Anthrax

Inhalational anthrax occurs when anthrax spores are inhaled into the lung. There is insufficient evidence available from the two English- and three foreign-language case reports of pediatric anthrax to classify the typical presentation of inhalational anthrax or treatment responses or to compare them to adults with inhalational disease. In particular, we have very little information about inhalational anthrax in infants or toddlers. However, the evidence that is available on pediatric inhalation anthrax does provide us with four key observations.

- Among adults, inhalational anthrax presents with a prodromal phase (often described as flu-like) for whom the most common symptoms or findings at admission are abnormal temperature, abnormal lung findings, fever or chills, tachycardia, fatigue or malaise, cough, dyspnea, and nausea or vomiting. Notably, these symptoms are typically accompanied by nonheadache neurological symptoms such as dizziness, visual changes, and syncope, which are not typical of routine influenza infection. The three children for whom we have signs and symptom data were found to have dyspnea and abnormal lung exams; however, none had either nonheadache neurological symptoms or nausea or vomiting. This suggests that screening algorithms based on adult findings may have less diagnostic accuracy for children presenting with inhalational anthrax.

- Adult patients typically have abnormal chest roentgenograms characterized by pleural effusions or widened mediastinum. Both of the pediatric patients with inhalational anthrax who had chest roentgenograms were found to have similar abnormalities.

- Prior to the introduction of antibiotics, anthrax infection was primarily treated with anti-serum, which reportedly decreased mortality by 75% compared to untreated patients. Later, effective antibiotics such as penicillin and chloramphenicol were added to anthrax treatment strategies. Current treatment guidelines for inhalational in children vary among different professional organizations; however, most recommend triple intravenous antibiotics with ciprofloxacin or doxycycline with two other antibiotics such as clindamycin, rifampin, penicillin, among others. Among adult patients, nearly all of those not given antibiotics or anthrax anti-serum during the prodromal phase progress to the fulminant phase which is a characterized by a rapidly progressive critical illness with respiratory failure, shock. Regardless of antibiotic/anti-serum therapy or other medical intervention such as mechanical ventilation, the overall mortality rate in fulminant phase is 97%. Similarly, the child who received antibiotic treatment during the fulminant phase died. The two children who survived inhalational anthrax were treated with antiserum—a treatment not typically included in current treatment guidelines or bioterrorism preparedness inventories.

- In adults, pleural fluid drainage has been significantly associated with survival after the development of fulminant inhalational anthrax. Only one child with inhalational anthrax received pleural fluid drainage and she survived.

Pediatric Gastrointestinal Anthrax

Gastrointestinal anthrax results from the ingestion of *B. anthracis* spores leading to the infection (and often ulceration) of the gastrointestinal epithelium. We found 20 English-language case reports of pediatric gastrointestinal anthrax—most of them were associated with known outbreaks, typically resulting from the consumption of contaminated meat. The average age of these patients was 10.5 years (four children were ≤ 2 years old, eight children were >2 to 13 years old; and eight children were >13 to 18 years old). Five were girls and none of the cases were from the U.S. The literature on pediatric gastrointestinal anthrax provides four key results.

- Compared to inhalational and cutaneous disease, gastrointestingal anthrax is considered quite rare among adults, especially in the U.S. However, among children, there have been more case reports of gastrointestinal disease than inhalational disease. Clearly, children are susceptible to gastrointestinal anthrax from agricultural sources—whether they would be more or less likely to present with primary gastrointestinal disease after a bioterrorism event is not known.

- Historically, gastrointestinal anthrax has been recognized as presenting in two forms: oropharyngeal disease among patients in whom the site of infection is the upper gastrointestinal tract and intestinal disease among patients in whom the site of infection is the lower gastrointestinal tract. Like adults, children seem to have two presentations of gastrointestinal anthrax: upper tract disease characterized by dysphagia and oropharyngeal findings and lower tract disease characterized by fever, abdominal pain, and nausea and vomiting.

- Of the four patients with gastrointestinal anthrax who had roentgenograms, two were found to have pulmonary abnormalities, one patient had "ascites but no other abnormalities," and one had a normal examination. From the limited evidence, we cannot determine whether roentgenograms contributed significantly to the early diagnosis of pediatric gastrointestinal anthrax.

- The mortality rate for treated gastrointestinal anthrax among adults is generally reported as approximately 40%. However, the children with gastrointestinal anthrax (both treated and untreated) had a somewhat higher case-fatality rate (63%). Among the children with gastrointestinal disease who died, many had developed meningoencephalitis, presumably as a result of hematologic dissemination.

Pediatric Cutaneous Anthrax

Cutaneous anthrax has long been recognized as an occupational hazard for adults handling contaminated animal products who introduce *B. anthracis* spores into the skin through cuts, abrasions, or insect bites. It is reported to account for more than 95% of clinical anthrax disease. We randomly selected 50 English-language case reports of children with cutaneous anthrax. Of these, only 37 provided sufficient information about individual patients to be included in our

analysis. In general, even the included reports of pediatric cutaneous anthrax were of very poor quality, often providing only a few sentences about the patient and their clinical course (and rarely even describing the skin lesions in detail). The reports of these 37 children with cutaneous anthrax provide three key findings.

- Historically, cutaneous anthrax usually begins with a small, painless, pruritic papule on an exposed area. This lesion enlarges and becomes an oval eschar surrounded by vesicles with marked, painless brawny edema and tissue necrosis. The skin lesions described for children are similar to the classical skin lesions described for adults.

- Only seven of the included pediatric cutaneous cases were girls (the gender was unreported for three cases). This male predominance is similar to what has been observed among adults and may represent the relatively higher risk of occupational exposures among boys and men or under-diagnosis or under-treatment of girls with anthrax.

- Among adults, untreated cutaneous anthrax has been associated with a 5 to 20% case fatality rate (presumably from hematologic dissemination of disease) but is rarely fatal when treated. Only five children died (13.5% case fatality rate) which falls within the range of adult case fatality rates. All of these were boys, three of whom had not received antibiotics. One child developed meningoencephalitis before he died.

Atypical Anthrax

Historically, anthrax has been classified according to the three principal exposures: inhalational, gastrointestinal, and cutaneous. Although rare, atypical anthrax presentations do occur among adults including laryngopharyneal and nasopharyngeal disease and primary anthrax meningoencephalitis. Some authors have speculated that the port of entry for primary anthrax meningoencephalitis is either an unrecognized lower respiratory tract port of entry or transethmoid migration of occult nasopharyngeal infection.

We found 2 cases of pediatric laryngopharyngeal anthrax, one report of a girl with nasopharyngeal disease, and one English-language and five foreign language case reports of children with primary meningoencephalitis (97% of whom died). From these cases, we conclude, that, although uncommon, children can have atypical presentations of anthrax. Although we cannot determine with certainty the means by which these patients contracted anthrax, we suspect an inhalational exposure for many, if not most, of them. To prevent delays in diagnosis and therapy during future bioterrorist attacks, clinicians should recognize that anthrax infection in both adults and children might present with primary nasal, laryngeal, pharyngeal, and/or meningeal symptoms.

Discussion and Summary Answers to the Key Questions

Anthrax is a relatively common and historically well-recognized disease and yet rarely reported among children—particularly among the very young children. The paucity of pediatric anthrax case reports, particularly among the youngest children, suggests that these children may have less exposure to anthrax or that anthrax infection in this population may be under-diagnosed and/or under-reported. We note that the presenting symptoms for pediatric inhalational anthrax are very common for many childhood diseases and that naturally occurring anthrax disease is most prevalent in poor countries where children may never come to medical attention or have diagnostic cultures confirmed. Additionally, there may be a significant publication bias in this literature (e.g., cases that are unusual or fatal may be more likely to be published)..

Key Question #1: What Is the Evidence for an Age-dependent Disease Progression Associated with Anthrax?

Although children with anthrax may present with somewhat different symptoms than adults, we found no specific evidence for age-dependent differences in disease progression. Like adults, children with gastrointestinal anthrax, seem to have two distinct clinical presentations: One resulting from upper tract disease and another resulting from lower tract disease. Additionally, children with inhalational disease may have non-pulmonary presentations including primary meningoencephalitis.

Key Question #2: How Effective Are Antibiotic Prophylaxis and Treatment for Anthrax in Children Compared to Adults? Similarly, how effective are other medical treatments in children compared to adults (e.g. ventilator/respiratory support)?

Most of the children included in our analysis who received an antibiotic were given penicillin-based antibiotics which produced a 63% survival rate. Other successful treatments included antiserum, which produced an 82% survival rate. These survival rates were similar to those observed for adults.

In adults, pleural fluid drainage was significantly associated with survival after the development of fulminant inhalational anthrax. One child with inhalational anthrax received pleural fluid drainage and she survived. However, we found insufficient cases of children who received pleural fluid drainage (or other treatment modalities such at mechanical ventilation) to determine the extent which they may be more or less effective in children than they are in adults.

Key Question #3: Based on the review of evidence for Questions 1 and 2, what are the implications for children versus adults in terms of preparedness and response planning for anthrax exposure (i.e., healthcare provider education on diagnosis and management, considerations for hospitals, vaccination strategies)?

The results of our systematic review have implications for preparedness planning efforts that relate to the diagnosis and management of children with anthrax. The presenting signs and symptoms of children with anthrax are very similar to the signs and symptoms of children presenting with much more common infectious diseases. This creates a difficult diagnostic challenge both for clinicians needing to make a timely diagnosis and public health officials implementing syndromic surveillance systems. More research is needed to identify the specific signs and symptoms that distinguish common pediatric infections such as influenza from early anthrax infection.

Only one of the 62 pediatric anthrax cases was treated with a fluoroquinolone; however, penicillin-based and antiserum regimens were much more commonly used among the included cases and were associated with favorable survival rates. Antiserum is not included in current treatment guidelines or bioterrorism preparedness inventories and has been associated with serum sickness and inconsistency in effectiveness across batches. Similarly, current treatment guidelines do not include penicillin as a single agent due to concerns of penicillin-resistant organisms. Thus, we have little evidence about the use of the medical regimens currently considered first line against anthrax and more evidence about those therapies not currently being recommended

.

Future Research

To facilitate accurate diagnosis and effective treatment of children with anthrax, future pediatric anthrax case reports should provide much more detailed information about exposure, clinical presentation, and treatment responses for infants, toddlers, and adolescents with anthrax.

The finding that anthrax antiserum was associated with survival among historical cases of children with anthrax warrants additional research on the safety, efficacy, and potential availability of this therapy. Similarly, we found no reports of children having received anthrax vaccine (which is currently only available for adults)—additional research is required regarding the safety and effectiveness of anthrax vaccination for both prophylaxis and treatment of children exposed to anthrax.

The finding that children may not present with the same signs and symptoms as adults has implications for syndromic surveillance systems (e.g., the finding that non-headache neurological symptoms was a key distinguishing feature of adult inhalational anthrax was not found among children). Specifically, the development of pediatric syndromic surveillance requires additional research to identify the key presenting signs and symptoms of pediatric anthrax that distinguish patients with this disease from other common infections.

Evidence Report

Chapter 1. Introduction

Ring-a-ring-a-roses
A pocket full of posies
A-tishoo! A-tishoo!
We all fall down.[1]

In response to the intentional release of *Bacillus anthracis* by mail in 2001, there has been a proliferation of guidelines for the diagnosis and treatment of patients with anthrax.[2-10] However, most of these have not specified screening and management protocols for special populations, such as children. Children will likely be among the victims of future bioterrorism attacks on the general public as they were during the 1995 sarin attack in Tokyo (which affected 16 children and five pregnant women) and the 1984 intentional *Salmonella* contamination of salad bars in Oregon (which affected numerous high school students).[1] Additionally, children may be the specific targets of some terrorists as they were during the unsuccessful 1995 plot to release a chlorine gas bomb in California's Disneyland.[11] There is not a clear consensus as to whether children have particular physiological vulnerabilities to biological threat agents; however, young children may not be capable of seeking medical care or following the instructions of clinicians or public health officials—this can be particularly problematic if their parents or caregivers have, themselves, been incapacitated.[1, 11-13] Efforts to prepare for and respond to future attacks of anthrax bioterrorism will be aided by detailed information about the clinical presentation and treatment responses of both adult and pediatric populations exposed to anthrax.

Principally because of the paucity of pediatric cases in large case series of anthrax, observers have speculated that children are less susceptible to anthrax infection and may have different clinical courses after infection than adults. For example, during the 1979 Sverdlovsk outbreak, 70 patients were exposed and developed clinical anthrax after an airborne release of spores.[14, 15] However, there were no victims under the age of 24 reported—despite the fact that children were in the path of the plume.[16] Additionally, researchers have noted that there was no age-dependent susceptibility noted among the Sverdlovsk victims above 24 years of age.[16] However, because there are no published reports synthesizing data from all reported pediatric cases of anthrax, it is unknown to what extent patient characteristics, early detection, and early treatment affect disease progression and mortality in pediatric populations.

The development of protocols for the screening of pediatric patients with suspected anthrax and their subsequent management should be based on evaluation of the available literature regarding the clinical presentation and disease progression of children exposed to anthrax. Thus, we performed a systematic review of case reports of pediatric anthrax to describe the clinical course, treatment responses, and predictors of disease progression and mortality for children with

[1] This nursery rhyme has been attributed to the pandemic of bubonic plague of the 1340s. Specifically, the ring-a-roses refers to the rose-colored rash of plague and the posies refer to the flowers and spices put into the pockets of victims to ward off the stench of death. The last two lines refer to the sneezing that was common among the victims just before their seemingly inevitable deaths.

anthrax infection. In addition to cases of inhalational, gastrointestinal, and cutaneous anthrax, we included in our analysis case reports of primary anthrax meningoencephalitis (i.e., without an identifiable inhalational, gastrointestinal, or cutaneous source).

Key Research Questions

For a previous evidence report, "Regionalization of Bioterrorism Preparedness and Response"[17] we synthesized all cases of adult inhalational anthrax published between 1900 and 2005. For the current project, we sought to synthesize the data from English-language case reports of children with inhalational, gastrointestinal, cutaneous, and atypical anthrax to answer three key research questions:

1. What is the evidence for an age-dependent clinical course associated with anthrax?

2. How effective are antibiotic prophylaxis and treatment for anthrax in children compared to adults? Similarly, how effective are other medical treatments in children compared to adults (e.g. ventilator/respiratory support)?

3. Based on the review of evidence for Questions 1 and 2, what are the implications for children versus adults in terms of preparedness and response planning for anthrax exposure (i.e., healthcare provider education on diagnosis and management, considerations for hospitals, vaccination strategies)?

Chapter 2. Methods

We sought all English-language case reports of patients aged 18 years or younger with inhalational, gastrointestinal, or atypical anthrax (e.g., primary anthrax meningoencephalitis without an identifiable inhalational or cutaneous source). Because there have been hundreds of case reports of pediatric cutaneous anthrax, given limited resources, we selected a random sample of 50 English-language case reports of pediatric anthrax for abstraction. We then augmented the data abstracted from the English-language pediatric case reports with the data available from our prior Evidence Report on adult cases of inhalational anthrax.[17]

Inclusion and Exclusion Criteria

We considered articles eligible for inclusion if the authors of the case report established a definitive diagnosis of anthrax. To confirm the diagnosis of anthrax, we used the case criteria that we developed previously which require that patients have positive cultures, gram stain, or immunologic evidence of recent *Bacillus anthracis* infection and/or associated clinical or autopsy findings consistent with anthrax infection.[17] We present our overall inclusion strategy in Figure 1 and our separate inclusion criteria for inhalational anthrax in Table 1, gastrointestinal anthrax in Table 2, cutaneous anthrax in Table 3, primary anthrax meningoencephalitis in Table 4, and atypical anthrax in Table 5. If the authors of a case report described a patient as having a particular type of anthrax (such as gastrointestinal disease) and they did not meet our inclusion criteria for that type of anthrax, we noted this. We excluded reports in which the authors presented summary information about a group of patients with anthrax but did not include individual patient data.

Figure 1. Inclusion strategy

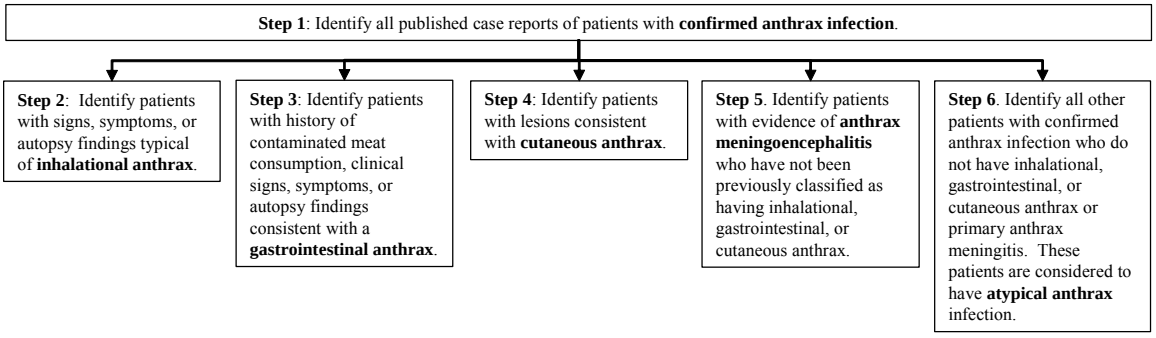

Table 1. Inclusion criteria for cases with presumed inhalational anthrax

Any one of the following:
1. Cultures[a] AND symptoms[b] or autopsy findings[c] consistent with inhalational anthrax.
2. Symptoms and gram-stain evidence[d] AND improvement with appropriate therapy or autopsy findings.
3. During an ongoing anthrax outbreak with confirmed cases (meeting criteria 1 or 2): Symptoms AND autopsy findings or improvement with appropriate therapy.[e]
4. For patients with high-risk inhalational anthrax exposure (e.g., wool mill worker) who did not receive antibiotic treatment: Symptoms AND improvement with anthrax antiserum.

Table 2. Inclusion criteria for cases with presumed gastrointestinal anthrax

Any one of the following (exclude if patient meets cutaneous or inhalational case definition):
1. Symptoms[f] AND cultures or gram-stain AND history of contaminated meat consumption or during outbreak of gastrointestinal anthrax.
2. History of contaminated meat consumption or cases occurred during an ongoing gastrointestinal anthrax outbreak with confirmed cases (meeting criteria 1) AND Autopsy findings[g] or symptoms with improvement with appropriate therapy.

Table 3. Inclusion criteria for cases with presumed cutaneous anthrax

Any one of the following (exclude if patient meets inhalational case definition):
1. Cultures AND any skin lesion
2. Skin lesion and gram-stain[d] AND improvement with appropriate therapy
3. During an ongoing anthrax outbreak with confirmed cases (meeting criteria 1 or 2): skin lesions AND improvement with appropriate therapy
4. For patients with high-risk inhalational anthrax exposure (e.g. wool mill worker) who did not receive antibiotic treatment: skin lesions AND improvement with anthrax antiserum.

Table 4. Inclusion criteria for cases with presumed primary anthrax meningoencephalitis

The following (exclude if patient meets inhalational, gastrointestinal, or cutaneous case definitions):
Culture or gram-stain AND either cerebrospinal fluid[h] or autopsy[i] findings consistent with anthrax meningoencephalitis.

Table 5. Inclusion criteria for cases with presumed atypical anthrax

The following (exclude if patient meets inhalational, gastrointestinal, cutaneous, or primary anthrax meningitis case definitions):
Culture or gram-stain or autopsy[i] findings consistent with anthrax.

[a]Culture (any source) or immunological evidence of recent *Bacillus anthracis* infection.

[b]Clinical symptoms of inhalational anthrax included flu like symptoms, fever, cough, dyspnea, chest pain, abnormal lung exam, or mediastinal widening or pleural effusions on chest roentenogram.

[c]Autopsy findings of inhalational anthrax included excessive pleural fluid (particularly if hemorrhagic), enlarged or hemorrhagic mediastinum, mediastinal lymphadenopathy, or subpleural congestion.[14, 18, 19]

[d]Gram-stain evidence (any source) of *B. anthracis*: gram-positive, spore-forming, nonmotile, hemolytic, spore-forming bacilli measuring 1-1.3 x 3-10 μm.[20]

[e]Received appropriate antibiotics (% *B. anthracis* strains susceptible ≥70%) or anti-serum.

[f]Clinical symptoms of gastrointestinal anthrax included diarrhea (especially bloody/tarry), abdominal pain, abdominal distension and/or evidence of ascites.

[g]Autopsy findings of gastrointestinal anthrax included excessive peritoneal fluid (particularly if hemorrhagic), enlarged or hemorrhagic mesenteric lymphadenopathy, and/or small bowel/stomach ulceration(s).

[h]Cerebral spinal fluid consistent with meningoencephalitis (e.g., bloody fluid, leukocytosis, etc.)

[i]Autopsy findings consistent with meningoencephalitis (e.g., hemorrhagic meninges).

Search Strategy

We identified case reports of pediatric anthrax referenced in MEDLINE® between January 1966 and June 2005 using the MeSH terms *anthrax* and *case report*. We then performed additional comprehensive searches of retrieved bibliographies and the indexes of the following selected journals from 1900 to 1966: *New England Journal of Medicine, JAMA, AMA-Archives of Internal Medicine, Lancet, BMJ, Medical Journal of Australia, La Presse Médicale, Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris, Deutsche Medizinische Wochenschrift, Wiener Medizinische Wochesnschrift, Wiener Klinische Wochenschrift, Muenchener Medizinische Wochenschrift, Berliner Klinische Wochenschrift, La Semana Medicale*. From our previous synthesis of adult inhalational anthrax cases, we found that much of the literature on clinical anthrax was published before 1966 (the earliest publication referenced in MEDLINE®). Thus, we performed extensive manual searches of retrieved bibliographies.

Because case reports of pediatric inhalational anthrax are relatively rare, in an effort to maximize the number of included cases, we included case reports of pediatric anthrax (0 to 18 years of age) presenting from 1900 to 2005. Although medical treatment for anthrax has changed considerably since 1900 (particularly since the advent of effective antimicrobials), we were interested in presenting signs and symptoms, which would not be affected by medical interventions. We excluded articles that described cases presenting prior to 1900 because *B. anthracis* was not identified as the causative agent of clinical inhalational anthrax until 1877[21] and because the use of reliable microscopic[22] and cultural examination techniques[23] to confirm the diagnosis were not developed until the late 19th century.

Data Abstraction and Evaluation

Two investigators screened potentially relevant articles to determine whether they met inclusion criteria. One investigator independently abstracted patient data from each included English language article and reviewed bibliographies for additional potentially relevant studies. We resolved abstraction discrepancies by repeated review and discussion. If two or more studies presented the same data from a single patient, we included the data only once in our analyses.

Because the purpose of this project is to characterize the spectrum of pediatric anthrax disease as well as to identify the differences in disease progression and treatment responses of adults and children with anthrax, we abstracted three primary types of data from each included article: (1) patient information (e.g., age, gender, nationality); (2) symptom and disease progression information (e.g., whether the patient developed meningitis); and (3) treatment information (e.g., treatments received, year of treatment). Data abstractions were performed directly into a detailed Excel abstraction form. The abstracted variables and their brief definitions are provided in Appendix A (including the definitions of some of the medical terms used in the case descriptions of individual patients).

To obtain a random sample of 50 case reports of pediatric cutaneous anthrax, we used a random number generator to select 50 reference identification numbers from the more than 200 pediatric cutaneous case reports that we retrieved from our literature search.

To evaluate the quality of the included case reports, we determined the extent to which the diagnosis of anthrax was confirmed (e.g., autopsy versus cultures versus response to therapy during a known outbreak) and whether the source of infection (e.g., inhalational disease) was established.

Statistical Analysis

Given key physiological differences among infants, toddlers, and adolescents, we analyzed case reports according to three age groups: 0-2 years, 3-13 years, and 14-18 years. Univariate analyses enabled us to summarize the key patient and treatment characteristics. We computed correlation coefficients between mortality and patient and treatment factors. For single comparisons, we considered a p-value less than 0.05 statistically significant. When comparing U.S 2001 to pre-2001 cases (or patients who lived to those who died), we applied a Bonferroni correction to account for multiple comparisons (we considered a p-value less than 0.025 statistically significant (0.05/2 = 0.025)).

Peer Review Process

A draft of this Evidence Report was sent to a panel of seven experts in pediatrics, infectious diseases, public health, and bioterrorism preparedness (Appendix C). Their comments were incorporated into the final Report.

Chapter 3. Results

Summary of Included Studies

We identified 246 titles of potentially relevant articles from our MEDLINE® search and 2253 additional references from our manual search of the bibliographies of retrieved articles and the indexes of the 14 selected journals. After removing duplicate reports, we included 62 English case reports of pediatric anthrax from which we abstracted detailed patient, treatment, and disease progression information. We did not find any reports of anthrax in pregnant women or reports of prenatal cases of anthrax.

Table 6 describes the distribution of these cases by source of anthrax infection and compares them to the non-English language case reports and adult case reports for which we have limited data (previously collected).

Table 6. Distribution of anthrax case reports by source, language, and age

Source of Anthrax Infection	Number of Pediatric Cases			Number of Adult Cases		
	English	Non-English	Total	English	Non-English	Total
Inhalational	2	3	5	45	32	77
Gastrointestinal	20	2	22	42	50	92
Cutaneous	222[b]	229	451	895	1724	2619
Atypical: Laryngopharyngeal	2	0	2	0	2	2
Atypical: Nasopharyngeal	0	1	1	2	3	5
Atypical: Primary Meningoencephalitis	1	5	6	22	10	32

[a]Pediatric Cases were defined as those in persons ≤ 18 years old.
[b]Of the 222 cutaneous cases, we selected a random sample of 50 for abstraction, of which only 37 provided sufficient data for inclusion in this analysis.

Given key physiological differences among infants, toddlers, and adolescents, we analyzed the English-language case reports according to three age groups: 0 to 2 years old (7 cases), more than 2 years to 13 years old (22 cases), and more than 13 years to 18 years old (34 cases) (Table 7). We found relatively few English-language case reports of infants and young children with anthrax. This paucity of case reports among the youngest children result from several factors. First, anthrax has been historically recognized as an occupational disease so it is reasonable that only older children would have these occupational exposures. Additionally, particularly because the presenting signs and symptoms of anthrax-related disease are similar to other infectious diseases, there may be biases resulting in under-diagnosis and under-reporting of anthrax among the youngest children.

Table 7. Distribution of English-language cases by age

Age Group	Source of Anthrax Infection	Number of Cases	Number of Females	Number Surviving
0 to 2 years	Inhalational	0	0	N/A
	Gastrointestinal	4	2 (50%)	1 (25%)
	Cutaneous	3	2 (66.7%)	1 (33%)
	Atypical	0	0	N/A
>2 to 13 years	Inhalational	1[a]	1 (100%)	1 (50%)
	Gastrointestinal	8	1 (12.5%)	3 (42.8%)[b]
	Cutaneous	12	1 (8%)	12 (100%)
	Atypical: Laryngopharyngeal	1	0 (0%)	1 (100%)
>13 to 18 years	Inhalational	1	1 (100%)	0
	Gastrointestinal	8	2 (25%)	3 (37.5%)
	Cutaneous	22	4 (21%)[c]	18 (82%)
	Atypical: Laryngopharyngeal	1	0 (0%)	1 (100%)
	Atypical: Primary Meningoencephalitis	1	0 (0%)	0 (0%)

[a]This cases was 2.5 years old.
[b]One case report of gastrointestinal anthrax did not state if the patient survived.
[c]Three reports of patients with cutaneous anthrax did not state the patients' gender.
N/A = not applicable

In the sections that follow, we first present the results for each types of pediatric anthrax (e.g., inhalational, gastrointestinal) then present summary information about all reviewed cases including summary information about treatment responses.

Inhalational Anthrax

Background. Because it is assumed that during a bioterrorism event, anthrax spores would be inhaled from an aerosolized source, a comprehensive assessment of the clinical presentation of inhalational anthrax is essential for early diagnosis. We direct interested readers elsewhere for reviews of the adult literature of inhalational anthrax.[24, 25] Briefly, among adults inhalational anthrax typically presents with a prodromal phase (often described as flu-like) during which fever, chills, and cough are the most common presenting symptoms. [24, 25] Among adults, the most common symptoms and/or findings at admission are abnormal temperature, abnormal lung findings, complaint of fever or chills, tachycardia, fatigue or malaise, cough or dyspnea.[24] Non-headache neurological symptoms such as dizziness, visual changes, and syncope are also prominent and are key symptoms that distinguish patients with inhalational anthrax in the prodromal phase from patients with influenza. [24, 25] Among adult patients, with the exception of one patient (who was a veterinarian and thought to have partial immunity to anthrax from prior exposure), patients not treated during the prodromal phase progress to the fulminant phase.[26] The fulminant phase of disease is characterized by a rapidly progressive critical illness with respiratory failure, shock, and, usually, death. Regardless of antibiotic/anti-serum therapy or other medical intervention such as mechanical ventilation, the overall mortality rate in fulminant phase is 97% (only two patients are known to have survived the fulminant phase of inhalational anthrax).[27-34]All adult patients with inhalational anthrax who had chest roentenograms had abnormal findings including pleural effusions (69%) or widened mediastinum (54%).[24]

Pediatric inhalational anthrax reports. There have been two English-language case reports of pediatric inhalational anthrax (Table 8).

The first was a 1928 report of a 2½ year old girl who lived on a farm in Iowa on which several horses had died. She presented with a fever to 103°F; restlessness; coughing; bulging, erythematous tympanic membranes; and "a marked translucent edema about the eyes" that extended to the waist.[35] Her initial lung exam was notable for "numerous fine crepitant râles were superimposed over tubular breathing."[35] Her laboratory tests were significant for a leukocyte count of 18,000 and urinalysis that was frankly purulent. Chest roentenogram revealed a "diffuse pneumonic process of the right lung.[35] Because copious gram-positive organisms grew from her pleural fluid, she was given anthrax anti-serum. On hospital day ten she defervesced and was much improved; however, it was noted that she could not see. On fundoscopic examination, she was noted to have pale retinae and almost white optic cups, no visible veins, and arteries "that showed only as minute threads." [35] Her clinicians concluded that she had suffered septic emboli of her optic arteries.[35] She was discharged and on follow up examination was noted to be a healthy child who "walked and talked, and gave evidence of light perception, but no vision."[35]

The second case was a 1975 report of a 16 year old Iranian farmer girl admitted with dyspnea and painless swelling in her left axilla for two days.[36] On admission, she was afebrile but was noted to have edema of her chest wall and scattered râles of the lung bases.[36] Over the first hospital day, her axillary swelling increased in size and the skin overlying it developed petechial hemorrhages.[36] Her leukocyte count was 33,000 with 90% neutrophils and her chest roentenogram showed "marked widening of the mediastinum with smooth borders and a soft tissue swelling over the right chest wall. The lung fields were clear."[36] She became stuporous and developed severe respiratory stridor and was treated with penicillin and chloramphenicol. On hospital day three, despite this treatment, she became hypotensive and died.[36] Autopsy showed massive pulmonary edema, mediastinal widening with hemorrhage of the mediastinal lymph nodes—one of which had eroded into the carina. *B. anthracis* was cultured from the mediastinum and lungs.[36]

We also found three foreign language case reports of children aged 13 to 17 for which we were able to obtain only scant clinical, laboratory, or disease progression data from our prior Evidence Report. The child who received antiserum survived, but the two children who did not receive therapy died (Table 8).

A screening algorithm based principally on adult anthrax cases designed to distinguish patients with inhalational anthrax from those with common viral respiratory tract infections found that rhinorrhea and sore throat were the two symptoms most associated with viral illnesses (positive likelihood ratios of 0.2 [CI, 0.1-0.4] and 0.2 [CI, 0.1-0.5] respectively).[25] None of the included pediatric patients were reported to have either of these symptoms. In this screening algorithm, the symptoms most suggestive of inhalational anthrax were nonheadache neurological symptoms (no positive likelihood ratio calculated), dyspnea (positive likelihood ratio, 5.1 [CI, 3.0-8.5]), nausea or vomiting (positive likelihood ratio, 5.3 [CI, 3.7-7.4]), and any abnormality on lung auscultation (positive likelihood ratio, 8.1 [CI, 5.3-12.5]). [25] All of the children for whom we have signs and symptom data were found to have dyspnea and abnormal lung exams; however, none had either nonheadache neurological symptoms or nausea or vomiting. This suggests that this screening algorithm may have less diagnostic accuracy for children than for adults presenting with inhalational anthrax.

In adults, pleural fluid drainage was significantly associated with survival after the development of fulminant inhalational anthrax.[24] One child with inhalational anthrax received pleural fluid drainage (and she survived). However, we have insufficient cases to determine the

extent which pleural fluid drainage (or other treatment modalities) were particularly associated with survival.

Summary. In the event of an aerosolized anthrax bioterrorism attack, most of the resultant morbidity and mortality will be from inhalational disease. The five published case reports of pediatric anthrax provide insufficient evidence to classify the typical presentation or treatment responses of children with inhalational anthrax or to compare them to adults with inhalational disease. However, the little evidence that is available on pediatric inhalation anthrax does provide us with three interesting observations. First, we note that the adolescent who received treatment during the fulminant phase died. This is in keeping with the high fatality rate for patients with fulminant inhalational anthrax observed for adult cases. Second, the two children who survived were treated with antiserum—a treatment not typically included in current treatment guidelines or bioterrorism preparedness inventories (we describe the use of anti-serum in greater detail in the section on treatment response in the summary of all cases at the end of this chapter). Finally, there is a paucity of pediatric cases in the literature for what is a relatively common and historically well-recognized disease. This suggests that pediatric cases may be under-diagnosed (we note that the presenting symptoms for pediatric inhalational anthrax are very common for many childhood diseases), or that children may have decreased exposure (as this has traditionally been an occupational illness), or that a significant publication bias may exist in this literature (e.g., cases that are unusual or fatal may be more likely to be published). For example, we question whether the case of the two year old Iowa farm girl was published because of the unusual complication of septic emboli, and may not represent the typical spectrum of presentations of inhalational anthrax.

Table 8. Pediatric inhalational anthrax case reports

Yr. (Ref.)	Age, Gender	Country	Anthrax Exposure Risk	Symptoms at Presentation	Initial Physical Exam	Initial Labs	Treat-ment*	Complica-tions‡	Died	Autopsy Findings
English-Language Pediatric Cases										
1928[35]	2.5, F	U.S.	Unknown	Cough, restlessness	Febrile, abnormal lung exam, cyanosis, pharyngeal erythema & edema, abdominal distension, mottled skin, erythematous bulging tympanic membranes	WBC 18K; purulent urine	H	PE, PFD, C	No	n/a
1975[36]	16, F	Iran	Unknown	Dyspnea, axilla swelling	Abnormal lung exam, afebrile, abnormal chest roentenogram		P, Ch	-	Yes	Pulmonary edema, mediastinal widening, hemorrhagic mediastinal and axillary nodes
Foreign-Language Pediatric Cases										
1901[37, 38]	16, F	Poland	Unknown	"In agony"	-	-	None	M, PE	Yes	n/a
1929[39]	17, M	Germany	Wool	Fever, chills, pleurisy, cough, dyspnea, hemoptysis	Febrile, tachycardia, abnormal lung exam	-	As	-	No	n/a
1954[40, 41]	13,M	Russia	Dust from infected sheep and calf	-	-	-	None	M	Yes	n/a

*Treatment abbreviations: As-Anthrax anti-serum, Ch-Chloramphenicol, H-Horse anti-serum, P-Penicillin.
‡Complications: M-Meningitis, C-Cyanosis, PE-Pleural effusion(s), PFD-Pleural fluid drainage.
The symbol '-' represents either not seen prior to death or no additional signs or symptoms noted in case report at presentation.

Gastrointestinal Anthrax

Background. Gastrointestinal anthrax results from the ingestion of *B. anthracis* spores leading to the infection (and often ulceration) of the gastrointestinal epithelium. Whereas the vegetative forms of *B. anthracis* can be killed by pasteurization, anthrax spores are robust and can cause disease even after exposure to heat, cold, desiccation, and exposure to acid.[42] Thus, a bioterrorism attack in which spores were used to contaminate food or beverages could result in gastrointestinal disease. Additionally, after a mail-based attack (such as during 2001), gastrointestinal disease could occur through manual deposition of spores into the mouth or contamination of nearby consumables.

Compared to inhalational and cutaneous disease, gastrointestingal anthrax is considered quite rare among adults, especially in the U.S. Often there have been outbreaks of several patients presenting with gastrointestinal anthrax after consuming contaminated meat.[43] The mortality rate for treated gastrointestinal anthrax is generally reported as approximately 40%.[42] Historically, gastrointestinal anthrax has been recognized as presenting in two forms: oropharyngeal disease among patients in whom the site of infection is the upper gastrointestinal tract and intestinal disease among patients in whom the site of infection is the lower gastrointestinal tract.[42] Oropharyngeal anthrax presents with high fevers, ulcerations of the posterior oropharynx, severe sore throat, and cervical lymphadenopathy (often with marked swelling of the neck).[42] In a report of an outbreak of adults with oropharyngeal disease contracted from consuming contaminated meat, three of the 24 patients died.[44]

In contrast, intestinal anthrax presents with high fevers, diarrhea, severe abdominal pain, and serosanginous or frankly hemorrhagic ascites.[42] In a report of 155 people in Uganda who ate a contaminated zebu, 91% developed anthrax with gastrointestinal complaints (including nine children who died within 48 hours of onset of symptoms[2]).[45] Whereas bowel ulcerations are a common finding among adults with gastrointestinal anthrax; nonulcerative, hemorrhagic lesions of the bowel are often associated with anthrax sepsis from inhalational, cutaneous, and oropharyngeal disease.[42] Abdominal roentgenograms generally reveal nonspecific findings such as increased bowel gas patterns with air-fluid levels or evidence of ascites.[42]

Pediatric gastrointestinal anthrax reports. We found 20 English-language case reports of pediatric gastrointestinal anthrax—most of which were associated with a known outbreak, typically resulting from the consumption of contaminated meat. Seven patients survived. The average age of these patients was 10.5 years (four children were $\leq$ 2 years old, eight children were >2 to 13 years old; and eight children were >13 to 18 years old). Five were girls and none of the cases were from the U.S.

The pediatric cases presented with symptoms similar to those reported for adults:[46, 47] The most common presenting symptoms were fever (60%), abdominal pain (45%), and nausea and vomiting (45%) without any reports of hematemesis. Four patients (20%) had diarrhea and only one reported a bloody stool. Three cases presented with symptoms of oropharyngeal or upper gastrointestinal disease (Table 9). Of the three patients who went on to have abdominal surgery, all had mesenteric lymphadenopathy. Nine patients (45%) developed meningoencephalitis. Of the 19 patients for whom we were able to determine short-term survival after anthrax, 12 died (63% case fatality rate).

[2]These nine children are not included in our analysis because individual case report data have not been published for them.

Thirteen of the 14 patients who received antibiotics were given a regimen that included a penicillin-based antibiotic, ten patients received more than one antibiotic, and no patients received anti-serum. The use of penicillin-based antibiotics likely reflects the year of the case report, the country of origin of the patient, among other factors. We found no patient or treatment factors that were significantly associated with survival from gastrointestinal anthrax; however, this analysis had limited power to detect predictors of survival given the small sample size. However, it is notable that whereas all five girls with gastrointestinal anthrax died, only seven of the 14 boys with gastrointestinal anthrax died. Additionally, cases prior to 1977 were less likely to die (six of the eight pre-1977 cases lived) compared to more recent cases (ten of the 11 cases after 1977 died).

Summary. The literature on pediatric gastrointestinal anthrax (of which only eight cases were less than 10 years old) provides four key results. First, whereas gastrointestinal anthrax is much rarer than other forms of anthrax for adults, there have been many more case reports of gastrointestinal disease than inhalational disease among children. Clearly, children are susceptible to gastrointestinal anthrax from agricultural sources—whether they would be more or less likely to present with primary gastrointestinal disease after a bioterrorism event likely depends on the type of bioterrorism attack (e.g., intentional contamination of food sources or surfaces could result in gastrointestinal disease). Second, like adults, children have two presentations of gastrointestinal anthrax: upper tract disease characterized by dysphagia and oropharyngeal findings and lower tract disease characterized by fever, abdominal pain, and nausea and vomiting. Third, among the reported cases of gastrointestinal anthrax among children, there is a high case-fatality rate (63%). Among those who died, many had developed meningoencephalitis. Finally, that case reports from before 1977 were more likely to describe patients who lived is not readily explainable, and might represent publication bias among the more recent case reports.

Table 9. English-language pediatric gastrointestinal anthrax case reports

Yr. (Ref.)	Age, Gender	Country	Type of GI disease[§]	Initial Symptoms	Initial Physical Exam	Treatment*	Complications[‡]	Died	Autopsy Findings
2002[48]	15, M	Iran	LG	Fever, abd pain, diarrhea	Febrile but vital signs otherwise normal. Abdomen tender, no splenomegaly.	P	Sh, DIC	Yes	Subendocardial petechiae non hemorrhagic effusion. Stomach, small bowel, mesentery and spleen had edema, hemorrhage, adenopathy but no ulcerations. Esophagus hemorrhagic spots
1991	2, F	Iran	LG	Fever, abd pain, emesis	Febrile, tachycardic, tachypneic, hypotensive Cyanosis, abd tender, distended, no bowel sounds, no skin lesions	A, G, Ch		Yes	None reported
2002[48,49]	8, M	Iran	LG	None reported	None reported	None reported		Yes	None reported
1989[50]	11, M	India	LG		No info	Antibiotics, type not specified		Not stated	None reported
1976[51]	17, M	Bangladesh	LG	Fever, anorexia, abd pain	Febrile, no lung findings, abd tender, no distention, no hepato/splenomegaly, slight R flank tenderness, bowels sounds slightly decreased	P, A, Ch, S, T, E	T, Sh	No	Not applicable
1965[43]	7, M	Lebanon	LG	Periumbilical pain, fever, vomiting	Distended abd, palpable mass in R iliac fossa ascites, hypotension	P	S	No	Not applicable
1962[43]	17, M	Lebanon	LG	Fever, abd pain	Tender distended abdomen, ascites	P, S	S	No	Not applicable

Table 9. English-language pediatric gastrointestinal anthrax case reports, continued

Yr. (Ref.)	Age, Gender	Country	Type of GI disease[§]	Initial Symptoms	Initial Physical Exam	Treatment*	Complica-tions[‡]	Died	Autopsy Findings
1974[43]	15, M	Lebanon	LG	None reported	Ascites, oculofacial congestion	P	S, Sh	No	Not applicable
1965[52]	14, M	Thailand	LG	Fever, abd pain, emesis, diarrhea	On admission vital signs were stable, respiratory distress, delerium, abd tender, distended, ascites	"antimicro-bials not given"	Sh, RF	Yes	No cerebral findings, lung hemorrhage; small bowel, mesentery and spleen edema and hemorrhage; small bowel ulcerations; mesenteric adenopathy
1932[53]	7, M	Philippines	LG	Fever, abd pain	None reported	None reported		No	Not applicable
1989[54]	6, M	Iran	LG	Fever, emesis	Febrile, tachypneic, nuchal rigidity, kernigs sign	P, S	PE, PFD, Sh, M	No	Not applicable
1989[54]	2, F	Iran	LG		Febrile, tachypneic, coma, seizure, nuchal rigidity, + kernigs, ptosis, dilatation rt pupil	P, S	M	Yes	None reported
1997[55]	13, M	Asia	LG	Emesis	Febrile, dehydrated, RLQ tenderness, no rebound or guarding, decreased bowel sounds, no meningeal or skin signs	Cf,A, Cm	MV, Sh, RF, DIC, M	Yes	Grossly swollen brain with focal subarachnoid hemorrhage, lots of gram + bacteria; cecum hemorrhagic and necrotic with polys, macrophages, bacteria
1996[56]	11, F	Europe	LG	Fever, abd pain, emesis	Febrile, ALOC, no nuchal rigidity,no skin signs	None reported	MV, RF, M	Yes	None reported
1953[57]	15, M	Africa	LG	Emesis	Febrile, coma, no focal neuro, no nuchal rigidity	P	M	Yes	Petechial, subarachnoid hemorrhage, no hemorrhagic lesions of mouth, no lung findings, small bowel hemorrhage and small ulcer, no splenic findings, mild jaundice of all tissues
1994[58]	13, M	Asia	LG	Fever, abd pain, emesis	None reported	A, Cx, Cm,M, Fl, Ac	M	Yes	Meningial involvement of anthrax bacilli
2003[59]	2, M	Asia	LG	Fever, abd pain, emesis	ALOC, coma	None reported	M	Yes	None reported

Table 9. English-language pediatric gastrointestinal anthrax case reports, continued

Yr. (Ref.)	Age, Gender	Country	Type of GI disease§	Initial Symptoms	Initial Physical Exam	Treatment*	Complica-tions‡	Died	Autopsy Findings
1977[47]	3 mos, M	India	UG	Emesis	No fever on admission (abx prior), blebs, ulceration and sloughing of gums and hard palate, ulcerations covered with "dirty looking slough"	P		No	Not applicable
1981[46]	18, F	Turkey	UG	Fever, dyspnea, dysphagia	None reported	P,G	RF	Yes	Brain, lung hemorrhage, tonsillar findings, ENT adenopathy, no abdominal findings noted
1983[46]	16, F	Turkey	UG	Fever, dysphagia	Febrile, lethargic, orolaryngeal edema, large tonsil with pseudomembrane and right-sided neck mass	None reported	Sh	Yes	Brain, lung hemorrhage, tonsillar findings, ENT adenopathy, small bowel hemorrage, hyperemia kidneys and liver

§Type of GI disease refers to whether the primary source of infection was the upper (UG) or lower (LG) gastrointestinal tract.

*Antibiotics or anthrax anti-serum. Abbreviations: A-Ampicillin, Ac-Acylovir, Ag-Amoxicillin/Clavulanate, Am-Ambramycin, As-Anthrax anti-serum, Ax-Amoxicillin, Au-Aureomycin, Az-Azithromycin, C-Ciprofloxacin, Ce-Cefamandol, Cf-Cefuroxime, Ch-Chloramphenicol, Cl-Clindamycin, Cm-Cefotaxime, Cn-Ceftriaxone, Cx-Cloxacillin, Cz-Ceftazidime, D-Doxycycline, E-Erythromycin, F-Flucloxacillin, Fl-Fluconazole, G-Gentamicin, H-Horse anti-serum, L-Levofloxacin, M-Metronidazole, N-Naficillin, P-Penicillin, R-Rifampin, Re-Reverin, S-Streptomycin, Sd-Sulfadiazine, Sf-Sulfanilamide, St-Sulfathiazole, T-Tetracycline, Ts-Trimethoprim/Sulfamethoxazole, U-Ampicillin/Sulbactam, V-Vancomycin.

‡Complications: M-Meningitis, C-Cyanosis, DIC-disseminated intravascular coagulation, PE-Pleural effusion(s), PFD-Pleural fluid drainage, S-surgery, Sh-shock, MV-mechanical ventilation, RF-Respiratory failureT-transfusion(s)

Cutaneous Anthrax

Background. Cutaneous anthrax has long been recognized as an occupational hazard for adults handling contaminated animal products who introduce *B. anthracis* spores into the skin through cuts, abrasions, or insect bites.[60] It is reported to account for more than 95% of clinical anthrax disease.[61] Historically, after an incubation period of less than three days, cutaneous anthrax usually begins with a small, painless, pruritic papule on an exposed area.[61] Classically, this lesion enlarges and becomes "oval eschar surrounded by vesicles with painless and marked edema."[62] Subcutaneously inoculated anthrax produce toxins resulting in the marked "brawny edema" and tissue necrosis characteristic of this disease.[63] Anthrax bacilli can usually be easily demonstrated on gram stain smears of fluid from these lesions.[61] Among adults, untreated cutaneous anthrax has been associated with a 5 to 20% case fatality rate (usually from haematologic dissemination of disease) but is rarely fatal when treated.[61] During an aerosolized bioterrorism event with anthrax, children touching a contaminated surface may present with cutaneous disease.

Pediatric cutaneous anthrax reports. We randomly selected 50 English-language case reports of children with cutaneous anthrax. Of these, 13 provided insufficient information about individual patients to be included in this analysis, 37 reports (74% of the randomly selected sample of cases) provided sufficient detail that data could be abstracted (Table 10). In general, even the included reports of pediatric cutaneous anthrax were of very poor quality, often providing only a few sentences about the patient and their clinical course (and rarely even describing the skin lesions in detail).

The average age of these patients was 11.8 years (range: 1.5 to 18 years)—15 were less than 10 years old (Table 7). Only seven were girls (the gender was unreported for three cases). This male predominance is similar to what has been observed among adults. Generally the lesions described were similar to the classical description of adult skin lesions with eschars surrounded by edema. Sixteen children received penicillin and eight had surgical debridement of their lesions. Only five children died (13.5% case fatality rate) which is similar to the ranges of adult cases. All of these were boys, three of whom had not received antibiotics. One child developed meningoencephalitis before he died.

Summary. The data from our sample of 37 cases of pediatric cutaneous anthrax are limited by very poor reporting of disease progression, patient characteristics, and treatment information. Among these included cases, the skin lesions described for children are similar to the classical skin lesions historically described for cutaneous anthrax. Similarly, the male predominance of disease and case fatality rates for children were similar to what has been described for adults with cutaneous anthrax.

Table 10. English-language pediatric cutaneous anthrax case reports

Yr. (Ref.)	Age, Gender	Country	Symptoms at Presentation	Initial Physical Exam	Treatment*	Died
1905 [64]	17, F	G.B.	Throat swelling, skin lesion	Skin pustule, vesicle with edema	As	No
1906[65]	18, M	G.B.	Painless skin lesion	Fever, mildly tachycardic, pustule and edema	As, FFP	Yes
1922[66]	16,F	U.S.	Skin lesion	Circumscribed papulopustule	Surgical debridement	No
1923[67]	17, ?	U.S.	Cheek lesion	Cheek lesion	H	No
1923[67]	14, ?	U.S.	Skin lesion	Skin lesion	H	No
1946[68]	12, M	Mexico	Skin lesion	Skin eschar and edema	Cutaneous radiation rx	Not stated
1999[69]	16, M	Turkey	Fever, throat swelling, skin lesion with pruritis	Febrile, tachycardic, tachypneic, skin lesion	P; Flouroquinolone not specified. Steroids, surgical debridement	No
1971[70]	2, F	Africa	Fever, swelling on left side of face	Febrile, left face and mouth lesion	Ch; E	No
2002[71]	6, M	Turkey	Fever, skin lesion	Febrile, Forehead lesion	P	No
2002[71]	5, M	Turkey	Fever, skin lesion	Febrile, Forehead lesion	P	No
1998[63]	3, F	Turkey	Skin lesion forehead; Throat swelling	Forehead lesion	P	No
1998[63]	17, M	Turkey	Skin lesion on fingers	Finger lesion	P	No
1998[63]	17, F	Turkey	Skin lesions on fingers	Finger lesion	P	No
1939[72]	17, M	G.B.	Fever, skin lesion	Fever, pustule	Sulfa; As	No
1906[73]	17, M	G.B.	Neck lesion	Neck lesion	General antiserum, surgical debridement	Yes

Table 10. English-language pediatric cutaneous anthrax case reports, continued

Yr. (Ref.)	Age, Gender	Country	Symptoms at Presentation	Initial Physical Exam	Treatment*	Died
1906[73]	17, M	G.B.	Right cheek lesion	Right cheek lesion	General antiserum; surgical debridement	Not stated
1906[73]	16, M	G.B.	2 pustules on arm and foot	2 pustules on arm and foot	General antiserum; surgical debridement	Not stated
1986[74]	3, M	Africa	Ectropion, no corneal scar	Ectropion, no corneal scarring	Left upper ectropian surgery	Not stated
1983[75]	2, M	Africa	No sx reported	Edema and eschar	P	Yes
1958[76]	15, M	G.B.	Skin lesion	Nothing documented	P and aminoglycoside	No
1934[77]	15, M	Africa	Fever, skin lesion	Fever, tachycardic, tachypneic, pustule and edema	Other abx unspecified	No
1987[78]	9, M	Turkey	Fever and skin lesion	Pustule and edema	P, steroids	No
1932[79]	17, M	India	Fever, malaise, painful pruritic skin lesion	Fever on admission, tender pustule initially, on admission evolved into vesicle	Neosalvarsan intravenously	No
1961[62]	7, M	U.S.	No complaints	Fever, rd on admission, circular black lesion on neck with vesicles	P, aminoglycoside	Not stated
1901[80]	16, M	Italy	Pustule on chin with swelling	Pustule and edema	As	Not stated
2000[81]	7, M	Turkey	Pruritic skin lesion	Erythematous pustule of eyelid, with edema	P	No
1996[82]	4, M	Turkey	Periorbital swelling, eyelid lesion, visual acuity ok	Edema and eschar, eye and vision not affected	P	No
1958[83]	17, M	Mexico	Right hand and forearm lesion	Skin lesion on hand	Aminoglycoside	No
1944[84]	5, M	Canada	Fever, right chin blister with edema and induration	Fever, tachycardia, nontender R submental blister surrounded by induration and pitting edema	P, sulfathiazole	No
1999[60]	18, F	India	None reported	Edema and eschar	P	No

Table 10. English-language pediatric cutaneous anthrax case reports, continued

Yr. (Ref.)	Age, Gender	Country	Symptoms at Presentation	Initial Physical Exam	Treatment*	Died
1920[85]	15, M	US	Fever on admission , initial headache, odynophasia and throat swelling (no skin findings reported)	Febrile, tachycardic, tachypneic, coma and pharynx read and edematous		Yes**
1950[86]	10, M	India	No reports	Barely febrile, mild tachycardia and tachypnea. Vessicle, edema on back of knee, inguinal lymphadenopathy	Ch	Not stated
2001[87]	5, M	India	Febrile, no respiratory distress, abdominal pain, swelling of rt cheek, painless lip ulcer	Febrile, nontoxic, extensive gelatinous edema of right cheek, nontender eschar, superficial lip lesion, no mouth involvement and cervical adenopathy	P	No
1974[88]	2, F	Africa	No sx reported	Vessical and edema on admission	P, Ch	No
1933[89]	<5, ?	Australia	Fever, skin lesions	Afebrile with eschar, surrounding edema and blebs. No lymphadenopathy.	Carbolic ointment	No
1900[90]	16, M	China	On admission “patient looked and felt very ill” with indurated mass on upper lip and black scab	Febrile, ill-appearing with indurated mass and edema on upper lip with central eschar on admission.	Perchloride topically, carbolic acid orally, surgical debridement	No
1911[91]	17, M	U.S.	Fever, lip and cheek lesion	Febrile and tachycardic. Mouth, lip pustules with surrounding edema	Antistreptococcal serum	Yes

* Treatment with antibiotics or anthrax anti-serum. Abbreviations: A-Ampicillin, Ac-Acylovir, Ag-Amoxicillin/Clavulanate, Am-Ambramycin, As-Anthrax anti-serum, Ax-Amoxicillin, Au-Aureomycin, Az-Azithromycin, C-Ciprofloxacin, Ce-Cefamandol, Cf-Cefuroxime, Ch-Chloramphenicol, Cl-Clindamycin, Cm-Cefotaxime, Cn-Ceftriaxone, Cx-Cloxacillin, Cz-Ceftazidime, D-Doxycycline, E-Erythromycin, F-Flucloxacillin, Fl-Fluconazole, G-Gentamicin, H-Horse anti-serum, L-Levofloxacin, M-Metronidazole, N-Naficillin, P-Penicillin, R-Rifampin, Re-Reverin, S-Streptomycin, Sd-Sulfadiazine, Sf-Sulfanilamide, St-Sulfathiazole, T-Tetracycline, Ts-Trimethoprim/Sulfamethoxazole, U-Ampicillin/Sulbactam, V-Vancomycin.

**This patient developed meningitis.

Atypical Anthrax

Background. Historically, anthrax has been classified according to the three principal exposures: inhalational, gastrointestinal, and cutaneous. Historical reports[92] and more recent animal data[93, 94] suggest that two distinct inhalational anthrax syndromes may occur—one characterized by the typical and well-documented lower respiratory tract port of entry and another that develops after upper respiratory tract port of entry. Furthermore, some authors have speculated that the port of entry for primary anthrax meningoencephalitis is either an unrecognized lower respiratory tract port of entry [95] or transethmoid.[96-98] If the variety of inhalational anthrax presentations is not well recognized, misdiagnosis or delayed diagnosis and treatment may result, thereby increasing anthrax-associated morbidity and mortality.

In our prior Evidence Report, we found that although rare, atypical anthrax presentations do occur among adults.[99] Specifically, we found two case reports of adults presenting with laryngopharyngeal anthrax, five cases of adults with nasopharyngeal anthrax, and 26 cases of adults presenting with anthrax meningoencephalitis without inhalational, gastrointestinal, or cutaneous lesions.[99] (If patients presented with these atypical symptoms but were known to have exposure to contaminated meat, we classified them as having gastrointestinal disease.)

Not surprisingly, patients with atypical anthrax were less likely to have a cough, chest pain, or abnormal lung exam than patients with typical inhalational disease.[99] Adults with primary nasopharyngeal involvement experienced more rhinorrhea, nasal congestion or epistaxis than patients with typical inhalational disease.[99] Patients with primary meningoencephalitis were more likely to experience non-headache neurologic complaints than patients with typical inhalational anthrax.[99] The mortality rate for patients with primary anthrax meningoencephalitis was 97%.[99]

Pediatric laryngopharyngeal case results. We found 2 cases of pediatric laryngopharyngeal anthrax (Table 11). Both were from the same 1944 case series of East African presentations of atypical anthrax. Both were boys, aged 6 and 11 years, who survived. The 6 year old required a tracheostomy, but neither experienced disseminated intravascular coagulation, meningitis, respiratory failure, or septic shock. Other than noting signs of respiratory distress and laryngeal obstruction on admission, no other signs, symptoms, treatments or other clinical data are available for these boys.

The two reports of adults with laryngopharyngeal anthrax are reviewed in detail elsewhere. [99] Briefly, one patient was a 20 year old African man (1970) while the other was a 41 year old German man (1904). Both of these adults with laryngeal disease presented with neck swelling and ultimately died of their disease. The German patient had autopsy evidence of leptomengingitis, laryngeal and pharyngeal edema with epithelial necrosis but no skin, tracheal, bronchial, lung, or small bowel abnormalities. Given the paucity of available clinical and treatment details in the case reports of these four patients, we are unable to conclude whether adults and children with laryngopharyngeal anthrax are likely to either present or progress differently.

Pediatric nasopharyngeal case results. We found one pediatric case report from 1942 of a 17 year old Argentinean girl suspected of inhaling horsehair in a bristle mill. She went on to develop nasopharyngeal disease (Table 13). This patient initially presented with epistaxis, nasal

obstruction, and neck swelling, and she survived. Detailed treatment information is not available from this case report. Among the five adults presenting between 1902 and 1942 with nasal/nasopharyngeal anthrax, three worked directly with animal hair or skins, most were thought to have either inhaled or deposited spores directly into their noses, and most presented with nasal obstruction and facial swelling. Three of the six adults died. We have no treatment data available for any of these adult cases. Again, based on the single case report of a girl with nasopharyngeal disease, we cannot evaluate the salient differences between pediatric and adult presentations of this type of anthrax.

Pediatric primary mengingoencephalitis case results. Of the 6 pediatric case reports of primary meningoencephalitis only 1 was an English-language report for which complete data are available.[100] This patient was a 14 year old Mexican boy who was thought to have been exposed in a slaughterhouse. He presented with high fever but otherwise normal vital signs, headache, delirium, seizures, and emesis. Initial physical exam was notable for the absence of pulmonary symptoms. Neurological findings included meningeal signs, eye deviation with horizontal nystagmus and nonreactive pupils, and coma. His initial significant laboratory results included an elevated white blood cell count with predominance of neutrophils and a lumbar puncture with a markedly elevated opening pressure and elevated cerebrospinal fluid protein. He had a normal chest roentenogram. The patient received penicillin and chloramphenicol but succumbed nevertheless. At autopsy, he was found to have hemorrhagic meningoencephalitis, lung and splenic edema, and small bowel ulcerations.

Among the five children described in the foreign language reports of patients with primary meningoencephalitis we have little patient or treatment information; however, fever, headache, and abdominal complaints including emesis and diarrhea were common presenting complaints. All five died.

Summary: Although rare, children (particularly adolescents) do present with atypical presentations of anthrax. Although we cannot determine with certainty the means by which these patients contracted anthrax, we suspect an inhalational exposure for many, if not most, of them. However, some of the atypical cases may be due to unrecognized cutaneous or gastrointestinal exposures. We attempted to limit this situation by excluding patients with skin lesions, histories of consuming contaminated meat, or symptoms or autopsy findings highly suggestive of gastrointestinal anthrax. Additionally, the consumption of contaminated meat is unlikely to cause nasal or nasopharyngeal involvement. To prevent delays in diagnosis and therapy during future bioterrorist attacks, clinicians should recognize that anthrax infection in both adults and children might present with atypical presentations.

Table 11. Pediatric laryngopharyngeal anthrax case reports

Yr. (Ref.)	Age, Gender	Country	Symptoms at Presentation	Initial Physical Exam	Treament	Complications	Died	Autopsy Findings
1944 [101]	6, M	East Africa	Dyspnea	Afebrile, laryngeal obstruction	Tracheostomy	None reported	No	N/A
1944 [101]	11, M	East Africa	Dyspnea	Febrile, laryngeal obstruction	N/S	None reported	No	N/A

Table 12. Pediatric nasopharyngeal anthrax case report (non-English)

Yr. (Ref.)	Age, Gender	Country	Symptoms at Presentation	Initial Physical Exam	Died	Autopsy Findings	Suspected route of entry[‡‡]
1942 [102, 103]	17, F	Argentina	Epistaxis, odynophagia, nasal obstruction, coryza, neck swelling	Tachycardia, febrile, pharyngitis; Face, palate & neck edema; Nasal serosanguinous discharge; Cervical adenopathy; No skin or tonsil lesions	No	N/A	Inhaled

Table 13. Pediatric primary meningoencephalitis anthrax case report

Yr. (Ref.)	Age, Gender	Country	Anthrax Exposure Risk	Symptoms at Presentation	Initial Physical Exam	Died	Autopsy Findings
English language case							
1975 [100]	14, M	Mexico	Slaughter-house	Headache, emesis, delirium, malaise, fever, seizures	Febrile, comatose, neurologic deficits, meningeal signs; No skin or abdominal abnormalities; Normal chest roentenogram	Yes	Congested lungs[§§], patchy bronchopneumonia, splenic congestion, cerebral, hemorrhagic meningoencephalitis, few bowel ulcerations; No skin lesions
Foreign language cases							
1981 [104]	16, M	Iran	Unknown, food product salesman[§]	Headache, emesis, fever, convulsions	Febrile, comatose, neurologic deficits, meningeal signs; No skin, lung or abdominal abnormalities	Yes	N/P

Table 13. Pediatric primary meningoencephalitis anthrax case report, continued

Yr. (Ref.)	Age, Gender	Country	Anthrax Exposure Risk	Symptoms at Presentation	Initial Physical Exam	Died	Autopsy Findings
Foreign language cases, continued							
1951 [105]	1, F	Italy	N/S	Fever, diarrhea, restlessness	Febrile; Tonsillar & oral cavity erythema/edema without ulceration/plaques; No skin, lung or abdominal abnormalities	Yes	N/P
1940 [106]	17, M	Germany	N/S	Fever, headache, back pain, stomach complaints	Febrile; No skin, lung or abdominal abnormalities; No neurologic deficits	Yes	N/P
1936 [107]	18, M	Romania	N/S	Fever, headache, abdominal pain, delirium	Comatose, cyanosis, abnormal lung exam, abdominal distension, neurologic deficits; No skin lesions	Yes	Hemorrhagic meningoencephalitis; Ascites and mesenteric adenopathy without bowel ulcerations; No lung or skin lesions
1927 [108]	11, M	France	Horses, cattle	Anorexia, headache, chills, malaise, fatigue, emesis, delirium	Febrile, tachycardia, neurologic deficits, menigeal signs; No skin, throat, lung or abdominal abnormalities	Yes	N/P

* We classified cases according to one of three anatomical sites: nasal/nasopharyngeal, larygeal/laryngopharyngeal, or primary meningoencephalitis (without known cutaneous, gastrointestinal, or respiratory port of entry). Cases were classified primary according to the primary author(s) suspicion for the port of entry as well the anatomical site(s) of mucosol and lymph node abnormalities on exam or at autopsy.

Table Abbreviations: Ref=Reference(s); Yr=Year; F=Female; M=Male; U.S.=United States; G.B.=Great Britain; N/A=Not applicable; N/S=Not specified; N/P=Not performed; GI=Gastrointestinal; CT=Computed tomography

‡‡ What the primary author(s) of the case report suspected as the route of entry for *Bacillus anthracis* spores.

§§ The primary author suspected a primary nasopharyngeal infection with a secondary stomach/intestinal infection from swallowing nasal secretions.

¶¶ Throat swabs cultured *Bacillus anthracis* with no other pathogenic organisms.

Summary Analyses Including All Cases

The included cases were highly heterogeneous in terms of their clinical presentations and treatments received.

Clinical Presentations

Among the 59 case reports which stated the patient's gender, only 14 (24%) were girls. This is similar to the gender discrepancy observed among adults and has historically been attributed to the fact that anthrax has largely been an occupational disease among professions (e.g., woolsorters and butchers) traditionally dominated by men. However, other biases may be contributing to the under-diagnosis and under-reporting of anthrax in girls relative to boys.

Eleven patients were reported to have had chest roentgenograms. Both of the patients with inhalational anthrax were found to have abnormalities on chest roentenogram. Of the four patients with gastrointestinal anthrax who had roentgenograms, two were found to have pulmonary abnormalities, one patient had "ascites but no other abnormalities," and one had a normal examination. All four of the patients with cutaneous anthrax had normal chest roentgenograms. We conclude that the role of roentgenograms for diagnostic decision making in pediatric anthrax is not well established.

Among the included cases, nine developed meningoencephalitis (seven of these had gastrointestinal anthrax, one had cutaneous anthrax, and one had primary anthrax meningoencephalitis). All but one of these patients died.

Treatment Responses

Prior to the introduction of antibiotics, anthrax infection was primarily treated with anti-serum.[109] Anthrax anti-serum reportedly decreased mortality by 75% compared to untreated patients.[110-115] and its efficacy is supported by recent animal data.[116] However, anaphylactic reactions and serum sickness were major side-effects. [117] Because anthrax virulence is caused by the production of two bacterial toxins, lethal factor and edema factor,[10] it has been theorized that therapeutics (such as antiserum) directed against these toxins could be superior to antimicrobial agents.[117-122] Additionally, the efficacy of anthrax immune therapy is supported by recent animal data using neutralizing monoclonial antibodies.[116, 123-125] In the 1940's effective antibiotics such as penicillin and chloramphenicol were added to anthrax treatment strategies.[86, 126] Anthrax anti-serum is no longer commercially available in most western countries including the U.S., but is still available in the Russian Federation and in China.[117, 127, 128] Recently, the U.S. Department of Health and Human Services awarded a contract to the Cangene Corporation (Winnipeg, Canada), to produce anthrax immune globulin between 10,000 and 100,000 doses for the Strategic National Stockpile.[129-134] Anthrax immune globulin is a highly purified human antibody that is specific to anthrax and is collected from the plasma of soldiers who were inoculated with the anthrax vaccine.[123, 135] Additionally, Human Genome Sciences, Inc. (Rockville, Maryland) was awarded a similar contract to develop a monoclonal antibody inhibitor specific for anthrax protective antigen to also be included within the Strategic National Stockpile.[12, 131-134, 136, 137]

The included cases differed with respect to their treatments and treatment responses (Table 14). Overall, the mortality rate was 31% (19 of 61; note, survival information was not available for one patient). There was no significant association between gender or age and survival. Among those patients who received antibiotics, 71% survived compared to 82% survival among those patients who received antiserum. Only one patient was treated with a fluroquinolone. Current treatment guidelines for inhalational or gastrointestinal anthrax in children vary among different professional organizations; however, most recommend triple intravenous antibiotics with ciprofloxacin or doxycycline with two other antibiotics such as clindamycin, rifampin, penicillin, among others.[9, 12, 138-141] Recommended treatment for cutaneous anthrax is with one oral antibiotic: penicillin, amoxicillin, ciprofloxacin, or doxycycline.[9, 12, 138-141]

None of the included patients received anthrax vaccine. The currently licensed, Anthrax Vaccine Adsorbed (AVA, Bioport Corporation, Lansing, MI) may have a role in post-exposure prophylaxis;[142] however, it is currently only approved for 18 to 65 year olds.[1, 12]

We had initially hoped to be able to evaluate the effect of time to onset of treatment on disease progression; however, insufficient evidence was available from the case reports to perform this analysis.

Table 14. Summary of treatments received

Treatment Received	Number of Patients	Number who Lived (%)	P value*
Any antibiotic vs. no antibiotic or antiserum	38	27 (71%)	0.78
Penicillin or penicillin-based antibiotic (e.g., ampicillin) vs. all other treatments	30	19 (63%)	0.89
Antiserum vs. all other treatments	11	9 (82%)	0.29
Aminoglycosides (most often streptomycin) vs. all other treatments	10	7 (70%)	0.85
Chloramphenicol vs. all other treatments	8	5 (63%)	0.91
Fluoroquinolones vs. all other treatments	1	1 (100%)	0.44

*P value for the comparison of whether patients who received this treatment were more likely to survive than those who did not receive this treatment.

Summary Answers to the Key Questions

Key Question #1: What Is the Evidence for an Age-dependent Disease Progression Associated With Anthrax?

Although children with anthrax may present with somewhat different symptoms than adults, we found no specific evidence for age-dependent differences in disease progression. Like adults, children with gastrointestinal anthrax, seem to have two distinct clinical presentations: One resulting from upper tract disease and another resulting from lower tract disease. Additionally, children with inhalational disease may have non-pulmonary presentations including primary meningoencephalitis.

Key Question #2: How Effective Are Antibiotic Prophylaxis and Treatment for Anthrax in Children Compared to Adults? Similarly, How Effective Are Other Medical Treatments in Children Compared to Adults (e.g. Ventilator/Respiratory Support)?

Most of the children included in our analysis who received an antibiotic were given penicillin-based antibiotics which produced a 63% survival rate. Other successful treatments included antiserum, which produced an 82% survival rate. These survival rates were similar to those observed for adults.

In adults, pleural fluid drainage was significantly associated with survival after the development of fulminant inhalational anthrax.[24, 143] One child with inhalational anthrax received pleural fluid drainage and she survived. However, we found insufficient cases of children who received pleural fluid drainage (or other treatment modalities such at mechanical ventilation) to determine the extent which they may be more or less effective in children than they are in adults.

Key Question #3: Based on the Review of Evidence for Questions 1 and 2, What Are the Implications for Children Versus Adults in Terms of Preparedness and Response Planning for Anthrax exposure (i.e., Healthcare Provider Education on Diagnosis and Management, Considerations for Hospitals, Vaccination Strategies)?

The results of our systematic review have implications for preparedness planning efforts that relate to the diagnosis and management of children with anthrax. The presenting signs and symptoms of children with anthrax are very similar to the signs and symptoms of children presenting with much more common infectious diseases. This creates a difficult diagnostic challenge both for clinicians needing to make a timely diagnosis and public health officials implementing syndromic surveillance systems. More research is needed to identify the specific signs and symptoms (e.g., rhinorrhea) that distinguish common pediatric infections such as influenza from early anthrax infection.[144]

Only one of the 62 pediatric anthrax cases was treated with a fluoroquinolone; however, penicillin-based and antiserum regimens were much more commonly used among the included cases and were associated with favorable survival rates. Antiserum is not included in current treatment guidelines or bioterrorism preparedness inventories and has been associated with serum sickness and inconsistency in effectiveness across batches. Similarly, current treatment guidelines do not include penicillin as a single agent due to concerns of penicillin-resistant organisms.[9, 138-141] Thus, we have little evidence about the use of the medical regimens currently considered first line against anthrax and more evidence about those therapies not currently being recommended.

Chapter 4. Discussion

This is the first published synthesis of the literature describing the spectrum of clinical anthrax in children. The 62 English-language pediatric cases included in this review provide four key findings.

First, children with anthrax present with a wide range of clinical signs and symptoms—which differ somewhat from the presenting features of adults with anthrax. Like adults, children with gastrointestinal anthrax have two distinct clinical presentations: One resulting from upper tract disease characterized by dysphagia and oropharyngeal findings and another resulting from lower tract disease characterized by fever, abdominal pain, and nausea and vomiting. Additionally, children with inhalational disease may have atypical presentations including primary meningoencephalitis. Clinicians and public health officials need to recognize the broad spectrum of potential presentations of anthrax in children for timely diagnosis and for the design of syndromic surveillance systems.[144]

Second, whereas children with inhalational anthrax did have abnormal chest roentgenograms, children with other forms of anthrax often had normal roentgenograms. Thus, the usefulness of roentgenograms in the early diagnosis of non-inhalational anthrax disease may be limited.

Third, most of the children included in our analysis who received an antibiotic were given penicillin-based antibiotics which produced a 63% survival rate. Other successful treatments included antiserum, which produced a 82% survival rate. Antiserum is not typically included in current treatment guidelines or bioterrorism preparedness inventories. Similarly, current treatment guidelines do not include penicillin as a single agent due to concerns of penicillin-resistant organisms.[9, 138-141] Only one child received a fluoroquinolone—which is a key component of current treatment guidelines for children with anthrax. In the event of shortfalls in stockpiles of the currently recommended antibiotics, penicillin or antiserum may provide some therapeutic benefit.

Finally, anthrax is a relatively common and historically well-recognized disease and yet rarely reported among children. We did not find evidence to support or refute the claim that children may be less susceptible to anthrax infection. In general, the relatively small number of pediatric cases of anthrax may reflect that this has traditionally been an occupational disease so that, particularly young children, may not have the same degree of exposure to anthrax spores. Additionally, the paucity of pediatric anthrax case reports suggests that anthrax may be under-diagnosed in children. Under-diagnosis and under-reporting of anthrax is likely to occur for several reasons: The presenting symptoms for pediatric inhalational anthrax are very common for many childhood diseases and since acute respiratory infections are the second leading cause of death worldwide for children under five years old, it is highly likely that naturally occurring pediatric anthrax has been attributed to one of the common childhood respiratory infections.[145, 146] Additionally, naturally occurring anthrax disease is most prevalent in poor countries with few healthcare resources and high infant mortality rates, where children may never come to medical attention or have diagnostic cultures confirmed.[147] Also, clinicians may be unlikely to report a case without culture confirmation which can be difficult since *B. anthracis* is quickly cleared after the initiation of antibiotics.

Limitations

This review has several limitations. First, because we did not have access to the original hospital and medical records, our analyses are dependent upon the data presented in the case reports. Second, because most of the patients in our review are presumed to have contracted anthrax from an occupational exposures or direct contact with contaminated animal products, our results may have limited generalizability to anthrax infection that occurs from bioterrorism. However, we cannot assess the extent to which differences in virulence and inoculating doses between anthrax infection from bioterrorism and from occupational exposure may result in differences in clinical presentations and treatment responses. Third, among the included cases, most were of older children. Thus, our results may not be generalizable to infants and toddlers with anthrax. Finally, the general paucity of pediatric cases suggests that there may be a significant publication bias in this literature.

Future Research

In order to facilitate accurate diagnosis and effective treatment of children with anthrax, future pediatric anthrax case reports should provide much more detailed information about exposure, clinical presentation, and treatment responses (such as those data described in Appendix A).

The finding that children may not present with the same signs and symptoms as adults has implications for syndromic surveillance systems. An evaluation of a drop-in syndromic surveillance system compared the syndromic categorization by emergency department staff in 11 Phoenix hospitals with chief complaints and discharge diagnoses.[148] Overall, agreement between the syndromic categorization and the discharge diagnoses was moderate (κ =0.63; [CI, 0.59-0.67]) with the greatest agreement for the gastroenteritis/diarrheal syndrome and lowest for the febrile respiratory tract infection syndrome.[148] However, pediatric chief complaints showed lower agreement for the febrile respiratory tract infection syndrome when compared with adults (κ = 0.34 [95% CI = 0.20 to 0.47] versus κ = 0.44 [95% CI = 0.28 to 0.59], respectively). [148] This suggests that additional research is needed on the presenting signs and symptoms of pediatric anthrax to inform the development of pediatric syndromic surveillance categories.

Additionally, to determine the extent to which children and adults differ with respect to the prevention and treatment of anthrax-associated morbidity and mortality, comprehensive evaluations are required of the safety and efficacy of prophylactic vaccines, the role of various antibiotics (including those not currently recommended in prophylaxis and treatment guidelines), and the role of non-antibiotic therapies such as antiserum and pleural fluid drainage.

Conclusions

The limited data available on children with anthrax suggest that their clinical presentation and treatment responses differ somewhat from adults with anthrax. Clinicians and public health officials should be aware of these differences for the timely diagnosis of children with anthrax and for the development of syndromic surveillance tools for populations that include pediatric patients.

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Appendix A. Data Abstracted

Reference ID		
Patient Identification	Age	
	Year	
	Gender	
	Country	
	Type	
	Source	
	Language	
	Pregnant woman or prenatal case	
	Case part of a known anthrax outbreak	
	Confirmed case	
Treatments (Abstracters noted whether patients received any of these treatments and, if so, whether they received them in the early phase of illness or late in the patient's course of disease.)	**Antibiotics**	Penicillin
		Other penicillinoid antibiotics (e.g., amoxicillin)
		Chloramphenicol
		Fluoroquinolone
		Cephalosporin
		Aminoglycoside
		Sulfa-based antibiotics
		Tetracycline antibiotic
		Macrolide antibiotic (e.g. Erythromycin)
		Carbapenem (e.g. Imipenem)
		Other antibiotic
	Serum	Anti-anthrax serum (i.e., Sclavo's serum)
		General serum (e.g., bovine or horse serum)
	Intrathecal	Antibiotics
		Serum
		Steroids
		Other
	Other	Steroids
		Radiation therapy
		Surgical debridement
		Pressor support
	Pleural	Thoracentesis
		Chest tube placement
	Airway	Intubation
		Tracheostomy
		Mechanical ventilation
	Transfusions	Red blood cells
		Plasma
		Platelets
		Other
Clinical Outcome(s) (Abstracters noted whether any of these occurred at any time during the patient's anthrax-related illness.)	Meningitis	
	Shock	
	Respiratory Failure	
	Disseminated intravascular coagulation	
	Laryngeal edema/Compromise of the airway from swelling	
	Died	

Appendix A. Data Abstracted, Continued

Serum/Blood Laboratory Studies (Abstracters noted the results of these tests on admission, and again if they were done later in the course of the patient's anthrax-related illness.)	**Hematology**	White Blood Cell Count
		%Neutrophils
		%Lymphocytes
		%Monocytes
		%Eosinophils
		Hemoglobin
		Hematocrit
		Platelets
		Erythrocyte Sedimentation Rate
		C-Reactive Protein
	Chemistries	Sodium
		Potassium
		Bicarbonate
		Creatinine
		BUN
		Glucose
		Calcium
	Liver Function Tests	Albumin
		Protein
		AST
		ALT
		Total bilirubin
	Coagulation Tests	INR
		Prothrombin Time
		Partial Thromboplastin Time
		D-dimer
		Fibrinogen
Lumbar puncture/Cerebrospinal fluid analysis	Opening Pressure	
	White Blood Cell Count	
	% Neutrophils	
	% Lymphocytes	
	% Monocytes	
	Red Blood Cell Count	
	Glucose	
	Total Protein	
	Gross Appearance	
Thoracentesis/Pleural fluid analysis	White Blood Cell Count	
	%Neutrophils	
	%Lymphocytes	
	%Monocytes	
	Red Blood Cell Count	
	Glucose	
	Total Protein	
	Gross Appearance	

Appendix A: Data Abstracted, Continued

Radiological Studies	**Chest Roentengram**	Widened mediastimum
		Pleural effusion
		Focal airspace opacity or infiltrates
		Hilar masses or opacities
		Other findings
	Head/Brain Computed Tomography	Findings
	Chest Computed Tomography	Findings
	Abdominal or pelvic Computed Tomography	Findings
Microbiology from samples taken while patient was alive (Abstracters noted whether these results were obtained before or after the administration of antibiotics or anti-sera.)	**Blood**	Gram Stain Findings
		Culture Findings
	CSF	Gram Stain Findings
		Culture Findings
	Pleural Fluid	Gram Stain Findings
		Culture Findings
	Skin/Cutaneous Lesion	Gram Stain Findings
		Culture Findings
	Sputum	Gram Stain Findings
		Culture Findings
	Other (Specify)	Gram Stain Findings
		Culture Findings
Autopsy Microbiology	**Blood**	Gram Stain Findings
		Culture Findings
	CSF	Gram Stain Findings
		Culture Findings
	Pleural Fluid	Gram Stain Findings
		Culture Findings
	Brain Tissue	Gram Stain Findings
		Culture Findings
	Lung/Pleura	Gram Stain Findings
		Culture Findings
	Mediastinum	Gram Stain Findings
		Culture Findings
	Stomach	Gram Stain Findings
		Culture Findings
	Small Intestines	Gram Stain Findings
		Culture Findings
	Mesentery	Gram Stain Findings
		Culture Findings
	Other (Specify)	Gram Stain Findings
		Culture Findings

Appendix A: Data Abstracted, Continued

Autopsy Findings	**Brain**	Evidence of Encephalitis
		Hemorrhage
	Meninges	Evidence of Meningitis
		Hemorrhage
	Head	Nasal or nasopharyngeal lesion/edema
		Oral lesion or edema
		Tonsilar lesion/edema
		Laryngeal lesion/edema
		Sinus lesion or hemorrhage
		Head or neck adenopathy
		Face or neck edema
	Lungs	Edema or congestion
		Hemorrhage
		Infiltrates
	Pleura	Effusion
		Hemorrhagic
	Mediastinum	Edema
		Hemorrhage
		Adenopathy
	Stomach	Edema
		Hemorrhage
		Ulceration
	Small Bowel	Edema
		Hemorrhage
		Ulceration
	Mesentery	Ascites
		Edema
		Hemorrhage
		Adenopathy
	Spleen	Edema
		Hemorrhage
	Skin	Lesions
	Other relevant findings	
Symptoms	**General Complaints**	Fever
		Chills or rigors
		Diaphoresis or night sweats
		Malaise
		Fatigue, weakness or exhaustion
		Myalgias, muscle pain, non-joint extremity pain
		Arthralgia
		Anorexia
		Back pain
		If report stated that the patient had "Common cold symptoms"
		If report stated that the patient had "flu-like symptoms"
		Ear pain
		Red eye
		Irritability
		Decreased PO Intake
		Decreased urine output
		Infants with grunting, flaring, or retractions

Appendix A: Data Abstracted, Continued

Symptoms Continued	**Respiratory Complaints**	Cough
		Productive sputum
		Hemoptysis
		Shortness of breath or dyspnea
		Chest pain
		Pleurisy or pleuritic chest pain
		Wheezing
		Respiratory distress
	Nasal/Sinus Complaints	Nasal congestion or stuffiness
		Coryza: A "cold in the head" caused by inflammation of the mucous membrane lining the nose (usually associated with nasal discharge)
		Rhinitis - an inflammation of the mucous membrane lining the nose (usually associated with nasal discharge).
		Rhinorrhea: Nasal discharge (i.e. runny nose) of any mucus-like material that comes out of the nose.
		Nasal pain
		Sinus complaints
	Gastrointestinal Complaints	Abdominal pain, irritation or indigestion
		Nausea
		Emesis
		Hematemsis
		Diarrhea
		Hemtochezia or tarry stools
	Neurological Complaints	Headache
		Dizziness, giddiness or vertigo
		Syncope
		Agitation or restlessness
		Insomnia
		Focal neurologic (motor or sensory) complaints
		Altered mental status, delirium, confusion
		Visual complaints
	Neck or Throat Complaints	Odynophagia (mouth pain) or pharyngitis (sore throat)
		Dysphagia or difficulty swallowing
		Laryngeal obstruction or choking
		Trismus: Inability to open the mouth fully
		Neck swelling
	Skin lesions	Any skin lesion (note location(s))
		If skin lesions are present, are they painful
		Pruritus
	Other relevant symptoms	
Clinical Findings	**Vital signs**	Temperature (or note if article states “febrile”, etc.)
		Heart rate (or note if article states “tachycardia”, etc.)
		Systolic blood pressure (or note if article states “hypotensive”, etc.)
		Respiratory rate (or note if article states “tachypnea”, etc.)
		Either O2Sat or PaO2 (state if on room air or if on oxygen)
	General findings	Cyanosis
		Respiratory distress
		Cold or clammy skin
		Diaphoretic
		Infants with grunting, flaring nostrils or retractions

Appendix A. Data Abstracted, Continued

Clinical Findings Continued	**Lung Exam**	Rales or rhonchi
		Wheezing
		Dullness to percussion
		Decreased breath sounds
		Bronchial or tubular breath sounds
		Any other pulmonary abnormality
	Abdominal exam	Abdominal tenderness
		Abdominal distension
		Spenomegaly
		Enlarged liver
		Ascites
		Any other abdominal abnormality
	Neurological deficits	Orthostatic dizzy
		Altered mental status or lethargy
		AMS
		Coma or stupor
		Focal neurologic (motor or sensory) deficits
		Hypperreflexia
		Cranial nerve deficits
		Seizure
		Opithotonus: arching of back (also seen with meningitis) due to irritated meninges.
		Nuchal rigidity
		Positive Kernig or Brudzinski
		Photophobia
		Other neurological abnormalities
	Nasal exam	Congestion
		Nasal obstruction
		Internal nasal lesion or abscess
		Other nasal abnormality
	Skin	Pustule
		Vesicle
		Malignant edema (erysipelatous)
		Eschar
		If a skin lesion is present, is it tender
		Any other skin/cutaneous abnormality
	Pharyngeal (oral/naso/laryngo)	Erythema or injection
		Edema
		Abscess
		Any other pharyngeal abnormalities
	Lymph nodes	Cervical
		Axillary
		Any other adenopathy
	Eye	Conjunctivitis
		Any other eye abnormalities
	Ear	Otitis/tympanic membrane abnormalities
		Any other ear abnormalities

Appendix B: Adult Anthrax Case Reports Not Included in This Analysis

Adult Inhalational Cases

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Appendix C: Peer Reviewers

Peer Reviewer	Organizational Affiliation
Ann M. Arvin, MD	Lucile Salter Packard Professor of Pediatrics Associate Dean of Research Professor of Microbiology & Immunology Stanford University Chief, Pediatric Infectious Diseases
Krista M. Scardina, Pharm.D.	Public Health Analyst; Health Resources and Services Administration; Healthcare Systems Bureau; Division of Healthcare Preparedness; National Bioterrorism Hospital Preparedness Program
Nathaniel Hupert, M.D., M.P.H.	Assistant Professor of Medicine and Public Health Weill Medical College, Department of Public Health
Gregory Moran, M.D.	Clinical Professor of Medicine, UCLA School of Medicine Department of Emergency Medicine and Division of Infectious Diseases, Olive View-UCLA Medical Center
Mike Osterholm, Ph.D.	Director of the Center for Infectious Disease Research and Policy (CIDRAP), Associate Director of the Department of Homeland Security's National Center for Food Protection and Defense (NCFPD), and Professor of Public Health, University of Minnesota
Irwin Redlener, M.D.	Professor of Clinical Public Health and Pediatrics Associate Dean & Director, The National Center for Disaster Preparedness Columbia University Mailman School of Public Health
Dean Wilkening, Ph.D.	Science Director, Center for International Security and Cooperation, Stanford University