Inhalational, Gastrointestinal, and Cutaneous Anthrax in Children

A Systematic Review of Cases: 1900 to 2005

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Objective: To systematically review all published case reports of children with anthrax to evaluate the predictors of disease progression and mortality.

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

Study Selection: Case reports (any language) of anthrax in persons younger than 18 years published between January 1, 1900, and December 31, 2005.

Main Exposures: Cases with symptoms and culture or Gram stain or autopsy evidence of anthrax infection.

Main Outcome Measures: Disease progression, treatment responses, and mortality.

Results: Of 2499 potentially relevant articles, 73 case reports of pediatric anthrax (5 inhalational cases, 22 gastrointestinal cases, 37 cutaneous cases, 6 cases of primary meningoencephalitis, and 3 atypical cases) met the inclusion criteria. Only 10% of the patients were younger than 2 years, and 24% were girls. Of the few children with inhalational anthrax, none had nonheadache neurologic symptoms, a key finding that distinguishes adult inhalational anthrax from more common illnesses, such as influenza. Overall, observed mortality was 60% (3 of 5) for inhalational anthrax, 65% (13 of 20) for gastrointestinal anthrax, 14% (5 of 37) for cutaneous anthrax, and 100% (6 of 6) for primary meningoencephalitis. Nineteen of the 30 children (63%) who received penicillin-based antibiotics survived, and 9 of the 11 children (82%) who received anthrax antiserum survived.

Conclusions: The clinical presentation of children with anthrax is varied. The mortality rate is high in children with inhalational anthrax, gastrointestinal anthrax, and anthrax meningoencephalitis. Rapid diagnosis and effective treatment of anthrax in children requires recognition of the broad spectrum of clinical presentations of pediatric anthrax.

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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. However, most of these guidelines have not specified diagnostic and management protocols for 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, Japan (which affected 16 children and 5 pregnant women), and the 1984 intentional Salmonella contamination of salad bars in Oregon (which affected numerous high school students). In addition, 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. 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 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 developed clinical anthrax after an airborne release of spores, however, there were no victims younger than 24 years reported, despite the fact that children were in the path of the plume. Because there are no published studies synthesizing data from all reported pediatric cases of anthrax, it is unknown to what extent patient characteristics, early detec-
tion, and early treatment affect disease progression and mortality in pediatric populations.

The development of protocols for the evaluation and management of pediatric patients with suspected anthrax should be based on evaluations 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 in children with anthrax infection. In addition to cases of inhalational, gastrointestinal, and cutaneous anthrax, the analysis included case reports of primary anthrax meningitis (ie, without an identifiable inhalational, gastrointestinal, or cutaneous source).

DATA SOURCES AND SEARCH TERMS

We sought all case reports (all languages) of patients younger than 18 years with inhalational, gastrointestinal, cutaneous, or atypical anthrax (eg, primary anthrax meningitis without an identifiable inhalational, gastrointestinal, or cutaneous source) presenting between January 1, 1900, and December 31, 2005. We identified case reports of pediatric anthrax referenced in MEDLINE between January 1, 1966, and June 30, 2005, using the Medical Subject Headings terms anthrax and case report. We performed additional comprehensive searches of retrieved bibliographies and the indexes of selected general medical and infectious disease journals published between January 1, 1900, and January 1, 1966 (ie, New England Journal of Medicine, JAMA, Archives of Internal Medicine, Lancet, BMJ, Medical Journal of Australia, La Presse Médicale, Bulletin et Mémoires de la Société Médicale des Hôpitaux de Paris, Deutsche Medizinische Wochenschrift, Wiener Medizinische Wochenschrift, Wiener Klinische Wochenschrift, Muenchener Medizinische Wochenschrift, Berliner Klinische Wochenschrift, and La Semana Medica).

STUDY SELECTION

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 developed previously, which require that patients have positive culture, Gram stain, or immunologic evidence of recent *B anthracis* infection or associated clinical or autopsy findings consistent with anthrax infection.†,15-18 Because there have been hundreds of case reports of pediatric cutaneous anthrax we used a random-number generator to select a random sample of 50 English-language case reports of pediatric anthrax for abstraction.

DATA EXTRACTION

Three investigators (D.M.B., J.-E.C.H., and E.W.) screened potentially relevant articles to determine whether they met the inclusion criteria. The same 3 investigators 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 2 or more studies presented the same data from a single patient, we included the data only once in the analyses.

We abstracted 3 primary types of data from each included article: patient information (eg, age, sex, and nationality), symptom and disease progression information (eg, whether the patient developed meningitis), and treatment information (eg, treatments received and year of treatment). To evaluate the quality of the included case reports we determined the extent to which the diagnosis of anthrax was confirmed (eg, autopsy vs cultures vs response to therapy during a known outbreak) and whether the source of infection (eg, inhalational disease) was established.

DATA SYNTHESIS

Because there are important physiologic differences between infants, toddlers, and adolescents, we analyzed case reports in 3 age groups: 0 to 2 years, older than 2 to 13 years, and older than 13 to 18 years. We performed univariate analyses to summarize the key patient and treatment characteristics. We computed correlation coefficients between mortality and patient and treatment factors. For single comparisons we considered *P* < .05 to be statistically significant. Comparing survival in patients who received a given treatment and those who did not, we applied a Bonferroni correction to account for multiple comparisons (we considered *P* < .025 to be statistically significant (0.05/2 = 0.025)).

RESULTS

We identified 2499 titles of potentially relevant articles from literature searches. After removing duplicate reports and reports of patients 18 years and older we included 73 case reports of pediatric anthrax, including 62 English-language and 11 foreign-language reports describing 5 cases of inhalational anthrax, 22 cases of gastrointestinal anthrax, 37 cases of cutaneous anthrax, 6 cases of primary meningitis, and 3 other atypical cases (Figure).

PATIENT CHARACTERISTICS

Cases were highly heterogeneous with respect to age, year of disease onset, nationality, diagnostic workup, and treatment regimen. Most of the included cases were adolescents. We found 8 cases of children aged 0 to 2 years, 26 cases of children older than 2 to 13 years, and 37 cases of adolescents older than 13 to 18 years (Table 1). Among the 59 case reports that stated the patient's sex, only 14 (24%) were girls.

The included cases differed with respect to their treatments and treatment responses (Table 2). Overall, observed mortality was 60% (3 of 5) for inhalational anthrax, 65% (13 of 20) for gastrointestinal anthrax, 14% (5 of 37) for cutaneous anthrax, and 100% (6 of 6) for primary meningitis (survival data are not available for all cases). Among patients who received antibiotics, 71% survived compared with 82% of patients who received antiserum alone (*P* = .29). Only 1 patient (who survived) was treated with a fluoroquinolone, a key component of the current treatment guidelines for anthrax.20-22 None of the included patients received anthrax vaccine. We found no statistically significant associations between sex or age and survival.

Of the included cases, 14 developed meningitis (7 had gastrointestinal anthrax, 1 had cutaneous anthrax, and 6 had primary anthrax meningitis), and all but 1 of these patients died. Because patient characteristics and treatment responses varied with the
source of infection, we present these results according to presumed anthrax source.

**INHALATIONAL ANTHRAX**

We found 2 English-language and the 3 foreign-language case reports of children with inhalational anthrax (eTable available at: http://www.archpediatrics.com). All the children for whom we have signs and symptoms data were reported to have dyspnea and abnormal lung examination findings; however, none had neurologic symptoms other than headache, nausea, or vomiting. The 2 children with inhalational anthrax who had chest radiographs were found to have abnormal...
ties similar to those classically associated with inhalational anthrax (ie, a widened mediastinum and pleural effusions).

The 5 published case reports of pediatric anthrax provide insufficient evidence to evaluate the treatment responses of children with inhalational anthrax and to compare them with adults with inhalational disease. However, note that the 2 children who survived were treated with antiserum, a treatment not typically included in current treatment guidelines or bioterrorism preparedness inventories. In addition, the child with inhalational anthrax who received pleural fluid drainage survived (eTable).

GASTROINTESTINAL ANTHRAX

Of the 20 English-language case reports of pediatric gastrointestinal anthrax, most were associated with known outbreaks, typically resulting from the consumption of contaminated meat (Table 3). (The 2 foreign-language reports of gastrointestinal anthrax provided insufficient clinical data to be included in the analyses.) The average age of these patients was 10.5 years, 5 were girls, and none were from the United States. Compared with inhalational and cutaneous disease, gastrointestinal anthrax is considered rare in adults, especially in the United States. However, in children there have been more case reports of gastrointestinal disease than inhalational disease.

Of the 20 presentations of gastrointestinal anthrax, 3 presented with symptoms of upper tract disease characterized by dysphagia and oropharyngeal findings, and the remaining presented with lower tract disease characterized by abdominal pain and vomiting. The most common presenting symptoms were fever (60%), abdominal pain (45%), and vomiting (45%); however, none had hematemesis. Four patients (20%) had diarrhea, and only 1 reported a bloody stool. All 3 patients who went on to have abdominal surgery had mesenteric lymphadenopathy. Of the 4 patients with gastrointestinal anthrax who had radiographs, 2 were found to have pulmonary abnormalities, 1 had “ascites but no other abnormalities,” and 1 had normal examination findings.

Seven patients (35%) developed meningoencephalitis, presumably as a result of hematologic dissemination. The development of secondary meningoencephalitis was a poor prognostic indicator, present in 6 of the 12 children with gastrointestinal disease who died.

Thirteen of the 14 patients who received antibiotic agents were given a regimen that included a penicillin-based antibiotic, 10 patients received more than 1 antibiotic, and no patients received antiserum. The use of penicillin-based antibiotics likely reflects the year of the case report and 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. It is notable that whereas all 5 girls with gastrointestinal anthrax died, only 7 of the 14 boys with gastrointestinal anthrax died.

| CUTOUS ANTHRAX |

Of the 50 randomly selected English-language case reports of children with cutaneous anthrax, only 37 provided sufficient information about individual patients to be included in this analysis. In general, the included reports of pediatric cutaneous anthrax were of very poor quality, often providing only a few sentences about the patients and their clinical course (and rarely describing the skin lesions in detail). The clinical course of cutaneous anthrax typically progressed as has historically been described from a small, painless, pruritic papule on an exposed area to an enlarging lesion that becomes an oval eschar surrounded by vesicles with marked, painless brawny edema and tissue necrosis. Findings from chest radiographs available from 4 patients with cutaneous anthrax were normal.

Sixteen children received penicillin, and 8 had surgical debridement of their lesions. Only 5 children with cutaneous anthrax died (14% case fatality rate), which is within the range of adult case fatality rates. All cases of fatal cutaneous disease were boys, 3 of whom had not received antibiotic agents. One child with cutaneous anthrax developed meningoencephalitis before he died.

| ATYPICAL ANTHRAX |

Historically, anthrax has been classified according to the 3 principal exposures—inhalational, gastrointestinal, and cutaneous—that result in the described presentations. Although rare, atypical anthrax presentations, including la-
ryngopharyngeal and nasopharyngeal disease and pri-
mary anthrax meningoencephalitis, do occur in adults.77
Some researchers have speculated that the port of entry for
primary anthrax meningoencephalitis is either an unrec-
ognized lower respiratory tract port of entry78 or transeth-
moidal migration of occult nasopharyngeal infection.79-81
We found 2 nonfatal cases of laryngopharyngeal an-
thrax. Both were boys, aged 6 and 11 years, from the same
East African case report from 1944.82 Other than noting
signs of respiratory distress and laryngeal obstruction on
hospital admission, no other signs, symptoms, or other
clinical data are available. The 6-year-old required a tra-
cheostomy, but no additional procedure or treatment data
were reported.

We found 1 report of a 17-year-old Argentinian girl
suspected of inhaling horsehair in a bristle mill who de-

<table>
<thead>
<tr>
<th>Source b</th>
<th>Sex/Age, y/ Country</th>
<th>Type of GI Disease</th>
<th>Initial Symptoms</th>
<th>Initial Physical Examination Findings</th>
<th>Treatment b</th>
<th>Complications</th>
<th>Died</th>
<th>Autopsy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mansour-Ghanaei et al,30 2002</td>
<td>M/15/Iran</td>
<td>LG</td>
<td>Fever, abdominal pain, diarrhea</td>
<td>Febrile but vital signs otherwise normal; abdominal tenderness, no splenomegaly</td>
<td>P</td>
<td>Sh, DIC</td>
<td>Yes</td>
<td>Subendocardial petechiae, nonhemorrhagic effusion; stomach, small-bowel, mesentery, and spleen had edema, hemorrhage, and adenopathy but no ulcerations; esophagus hemorrhagic spots</td>
</tr>
<tr>
<td>Alizad et al,31 1991</td>
<td>F/2/Iran</td>
<td>LG</td>
<td>Fever, abdominal pain, emesis</td>
<td>Febrile, tachycardic, tachypnea, hypotensive, cyanotic, abdominal tenderness with distension and absent bowel sounds, no skin lesions</td>
<td>A, G, Ch</td>
<td>None reported</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mansour-Ghanaei et al,32 and Alizad et al,33 2002</td>
<td>M/8/Iran</td>
<td>LG</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
<td>Yes</td>
<td>None reported</td>
</tr>
<tr>
<td>Sekhar et al,34 1989</td>
<td>M/11/India</td>
<td>LG</td>
<td>None reported</td>
<td>No info</td>
<td>None reported</td>
<td>None reported</td>
<td>Not stated</td>
<td>None reported</td>
</tr>
<tr>
<td>Nalin et al,35 1976</td>
<td>M/17/Bangladesh</td>
<td>LG</td>
<td>Fever, anorexia, abdominal pain</td>
<td>Febrile, no lung findings, abdominal tenderness without distention, slight right flank tenderness, bowel sounds slightly decreased</td>
<td>P, A, Ch, Sm, Tr, E</td>
<td>T, Sh</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Kanafani et al,36 1985</td>
<td>M/7/Lebanon</td>
<td>LG</td>
<td>Periumbilical pain, fever, vomiting</td>
<td>Distended abdomen, palpable mass in right iliac fossa, ascites, hypotension</td>
<td>P</td>
<td>S</td>
<td>No</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Kanafani et al,37 1962</td>
<td>M/17/Lebanon</td>
<td>LG</td>
<td>Fever, abdominal pain</td>
<td>Tender distended abdomen, ascites</td>
<td>P, Sm</td>
<td>S</td>
<td>No</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Kanafani et al,38 1974</td>
<td>M/15/Lebanon</td>
<td>LG</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
<td>No</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Tantachumroon and Panas-Ampol,39 1965</td>
<td>M/14/Thailand</td>
<td>LG</td>
<td>Fever, abdominal pain, emesis, diarrhea</td>
<td>Vital signs were stable on admission but progressed rapidly to respiratory distress, delirium, abdominal tenderness with distension and ascites</td>
<td>P</td>
<td>S, Sh</td>
<td>No</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Case report,40 1932</td>
<td>M/7/Philippines</td>
<td>LG</td>
<td>Fever, abdominal pain</td>
<td>None reported</td>
<td>None reported</td>
<td>None reported</td>
<td>No</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Tabatabaie and Syadati,41 1989</td>
<td>M/6/Iran</td>
<td>LG</td>
<td>Fever, emesis</td>
<td>Febrile, tachypnea, right lower quadrant tenderness, no rebound or guarding, decreased bowel sounds, no meningeval or skin signs</td>
<td>P, Sm</td>
<td>PE, PFD, Sh, M</td>
<td>No</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Tabatabaie and Syadati,42 1989</td>
<td>F/2/Iran</td>
<td>LG</td>
<td>Fever, tachypnea, coma, seizures, right lower quadrant tenderness, positive Kernig sign, ptosis, dilation of right pupil</td>
<td>P, Sm</td>
<td>M</td>
<td>Yes</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td>Kwong,43 1997</td>
<td>M/13/Asia</td>
<td>LG</td>
<td>Emesis</td>
<td>Febrile, dehydrated, right lower quadrant tenderness, no rebound or guarding, decreased bowel sounds, no meningeval or skin signs</td>
<td>Cf, A, Cm</td>
<td>MV, Sh, RF, DIC, M</td>
<td>Yes</td>
<td>Grossly swollen brain with focal subarachnoid hemorrhage, lots of gram-positive bacteria; cecum hemorrhagic and necrotic with poly, macrophages, bacteria</td>
</tr>
</tbody>
</table>

(continued)
veloped nasopharyngeal disease.83,84 She presented initially with epistaxis, nasal obstruction, and neck swelling, similar to what was observed among the 5 adults presenting between 1902 and 1942 with nasal/nasopharyngeal anthrax.77 She survived.

We found 1 English-language and 5 foreign-language case reports of children with primary meningoencephalitis; all 6 patients died (Table 4). The patient described in greatest detail 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 examination was notable for the absence of pulmonary symptoms. Neurologic findings included meningeal signs, eye deviation with horizontal nystagmus and nonreactive pupils, and coma. He had normal findings on chest radiography.

Among the 5 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 at presentation. The single patient with primary anthrax meningoencephalitis for whom we have treatment information received penicillin and chloramphenicol but died despite treatment.

This study is the first published synthesis of the literature describing the spectrum of clinical anthrax in children. The 73 pediatric cases included in this review provide 4 key findings.

First, children with anthrax present with a wide range of clinical signs and symptoms. Although there have been very few case reports of children with inhalational anthrax, most children at presentation were febrile and complained of cough and dyspnea, and all had abnormal lung findings on examination. None presented with nonheadache neurologic symptoms (eg, altered mental status or coma), which are key symptoms that have been shown among adults to distinguish inhalational anthrax from more common illnesses, such as influenza.91 Given the paucity of inhalational pediatric cases, the significance of this finding is unknown. Similar to adults, children with gastrointestinal anthrax have 2 distinct clinical presentations: one resulting from upper respiratory tract dis-
ease characterized by dysphagia and oropharyngeal findings and another resulting from lower respiratory tract disease characterized by fever, abdominal pain, and vomiting. In addition, children with inhalational disease may have atypical presentations, including primary meningoecephalitis. Physicians 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.92 Second, mortality is high in children with inhalational anthrax, gastrointestinal anthrax, and anthrax meningoecephalitis. In particular, children aged 0 to 2 years had the highest observed mortality (71%), and all children with primary meningoecephalitis died. In addition, children with gastrointestinal anthrax (treated and untreated) had a somewhat higher observed mortality rate (65%) than what has typically been reported for adults (40%).93 Most children included in this analysis who received an antibiotic drug were given penicillin-based antibiotics, which produced a 63% survival rate. Current treatment guidelines do not include penicillin as a single agent due to concerns of penicillin-resistant organisms.8,18-21 Other successful treatments included antiserum, which was associated with 82% survival.

Antiserum is not currently included in treatment guidelines or bioterrorism preparedness inventories; however, before the introduction of antibiotic agents anthrax infection was primarily treated with antiserum.94 Anthrax antiserum used in adults reportedly decreased mortality by 75% compared with untreated patients.95-100 However, anaphylactic reactions and serum sickness were major adverse effects.101 Because anthrax virulence is caused by the production of bacterial toxins,9 it has been theorized that therapeutics, such as antiserum, that are directed against these toxins could be superior to antimicrobial agents.101-106 Further evidence supporting this rationale for the efficacy of anthrax immunotherapy includes recent animal data using neutralizing monoclonal antibodies.107-110 Anthrax antiserum is no longer commercially available in most Western countries, including the United States, but it is still available in the Russian Federation and in China.9,101,111 Recently, the US Department of Health and Human Services awarded a contract to Can- gene Corp (Winnipeg, Manitoba, Canada) to produce anthrax immunoglobulin for the Strategic National Stockpile.112-117 Anthrax immunoglobulin is a highly purified human antibody that is specific to anthrax and is collected from the plasma of soldiers who were inoculated

## Table 4. Pediatric Primary Meningoecephalitis Anthrax Case Reportsa

<table>
<thead>
<tr>
<th>Source</th>
<th>Sex/Age, y/ Country</th>
<th>Anthrax Exposure Risk</th>
<th>Symptoms at Presentation</th>
<th>Initial Physical Examination Findings</th>
<th>Died</th>
<th>Autopsy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marandian and Kamali, 1981</td>
<td>M/16/Iran</td>
<td>Unknown, food product salesmanc</td>
<td>Headache, emesis, fever, convulsions</td>
<td>Febrile, comatose, neurologic deficits, meningeal signs; no skin or abdominal abnormalities; normal chest radiographic findings</td>
<td>Yes</td>
<td>Congested lungs, patchy bronchopneumonia, splenic congestion, cerebral, hemorrhagic meningoecephalitis, few bowel ulcerations, no skin lesions</td>
</tr>
<tr>
<td>Bezzi, 1951</td>
<td>F/1/Ireland</td>
<td>Not reported</td>
<td>Fever, diarrhea, restlessness</td>
<td>Febrile; tonsillar and oral cavity erythema/edema without ulceration/plaques; no skin, lung, or abdominal abnormalities</td>
<td>Yes</td>
<td>Not reported</td>
</tr>
<tr>
<td>Gross and Plate, 1940</td>
<td>M/17/Germany</td>
<td>Not reported</td>
<td>Fever, headache, back pain, stomach complaints</td>
<td>Febrile; no skin, lung, or abdominal abnormalities; no neurologic deficits</td>
<td>Yes</td>
<td>Not reported</td>
</tr>
<tr>
<td>Stalineanu, 1936</td>
<td>M/18/Romania</td>
<td>Not reported</td>
<td>Fever, headache, abdominal pain, delirium</td>
<td>Comatose, cyanosis, abnormal lung examination findings, abdominal distention, neurologic deficits; no skin lesions</td>
<td>Yes</td>
<td>Hemorrhagic meningoecephalitis; ascites and mesenteric adenosopathy without bowel ulcerations; no lung or skin lesions</td>
</tr>
<tr>
<td>Aguiah, 1927</td>
<td>M/11/France</td>
<td>Horses, cattle</td>
<td>Anorexia, headache, chills, malaise, fatigue, emesis, delirium</td>
<td>Febrile, tachycardia, neurologic deficits, meningeal signs; no skin, throat, lung, or abdominal abnormalities</td>
<td>Yes</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>English-Language Case</strong></th>
<th><strong>Foreign-Language Cases</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Headache, emesis, delirium, malaise, fever, seizures</strong></td>
<td><strong>Fever, diarrhea, restlessness</strong></td>
</tr>
<tr>
<td><strong>Febrile, comatose, neurologic deficits, meningeal signs; no skin or abdominal abnormalities; normal chest radiographic findings</strong></td>
<td><strong>Febrile, tonsillar and oral cavity erythema/edema without ulceration/plaques; no skin, lung, or abdominal abnormalities</strong></td>
</tr>
</tbody>
</table>

a We classified cases according to 1 of 3 anatomical sites: nasal/nasopharyngeal, laryngeal/laryngopharyngeal, or primary meningoecephalitis (without a known cutaneous, gastrointestinal, or respiratory port of entry). Cases were classified primarily according to the authors’ suspicion of the port of entry and the anatomical sites of mucosal and lymph node abnormalities on examination or at autopsy.

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

c What the authors of the case report suspected as the route of entry for *Bacillus anthracis* spores.
with the anthrax vaccine. In addition, 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 in the Strategic National Stockpile. In the event of shortfalls in stockpiles of the currently recommended antibiotics, penicillin and therapeutic agents directed against anthrax toxins may provide some therapeutic benefit.

Third, anthrax is reported relatively rarely in the youngest children and in girls (only 2.4% of the included cases). The sex discrepancy is similar to that observed in adults and has historically been attributed to the fact that anthrax has largely been an occupational disease among professions dominated by men and boys (eg, woolsorters and butchers); however, other biases may be contributing to the underdiagnosis and underreporting of anthrax in girls relative to boys.

Finally, 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 children may not have the same degree of exposure to anthrax spores as adults through occupational and environmental exposures (eg, young children may be more likely to be indoors than adults, whereas older children may be more likely to be outdoors than adults) or that anthrax may be underdiagnosed or underreported in children.

The potential for underdiagnosis of anthrax in children has implications for syndromic surveillance systems. The presenting symptoms for inhalational and gastrointestinal anthrax are common for many childhood diseases, and it is likely that naturally occurring pediatric anthrax has been attributed to one of the common childhood infections. Thus, effective surveillance systems require data sources that can readily distinguish anthrax from other common childhood infectious diseases.

This review has several limitations. First, because we did not have access to the original hospital and medical records the analyses depend on the data presented in the case reports. Second, because most of the included cases are presumed to have contracted anthrax from occupational exposures or direct contact with contaminated animal products, the results may have limited generalizability to anthrax infection that occurs from bioterrorism. Third, most included cases were older children; thus, these results may not be generalizable to infants and toddlers with anthrax. Finally, the general paucity of inhalational pediatric cases suggests that there may be substantial publication bias in this literature.

Because anthrax in children has a high mortality rate, clinical and public health measures should emphasize the rapid diagnosis and initiation of effective therapies for this population. However, more research is needed to clarify the optimum management. The broad spectrum of clinical presentations in children with anthrax and the similarity of many of these presenting symptoms to other common pediatric infectious diseases pose serious challenges to current diagnostic criteria and surveillance systems.

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Author Contributions: Dr Bravata had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bravata, Holty, McDonald, and Owens. Acquisition of data: Bravata, Holty, Wang, Lewis, and Owens. Analysis and interpretation of data: Bravata, Wang, Wise, and Owens. Drafting of the manuscript: Bravata, Holty, and Owens. Critical revision of the manuscript for important intellectual content: Bravata, Holty, Wang, Lewis, Wise, McDonald, and Owens. Statistical analysis: Bravata and Holty. Obtained funding: Bravata, McDonald, and Owens. Administrative, technical, and material support: Bravata and Lewis. Study supervision: Bravata and Owens.

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Role of the Sponsor: The funders had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

Additional Information: The eTable is available at http://www.archpediatrics.com.

Additional Contributions: Rebecca Kim, BS, assisted with searching the indices of selected journals, Emilee Wilhelm, BA, helped with article retrieval, and Corinna Haberland, MD, provided translations.

REFERENCES


5. Updated recommendations for antimicrobial prophylaxis among asymptomatic pregnant women after exposure to Bacillus anthracis [From the Centers for Disease Control and Prevention]. JAMA. 2001;286(19):2396-2397.


<table>
<thead>
<tr>
<th>Source</th>
<th>Sex/Age, y/ Country</th>
<th>Anthrax Exposure Risk</th>
<th>Symptoms at Presentation</th>
<th>Initial Physical Examination</th>
<th>Initial Laboratory Values</th>
<th>Treatment</th>
<th>Complications</th>
<th>Died</th>
<th>Autopsy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>English-Language Pediatric Cases</strong></td>
<td></td>
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<tr>
<td>McKitterick and Pearson,23 1928</td>
<td>F/2½/US</td>
<td>Unknown</td>
<td>Cough, restlessness</td>
<td>Febrile, abnormal lung examination, cyanosis, pharyngeal erythema and edema, abdominal distention, mottled skin, erythematous bulging tympanic membranes</td>
<td>WBC count, 18 000/µL; purulent urine</td>
<td>PE, PFD, C</td>
<td>No</td>
<td>Not applicable</td>
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<tr>
<td>Vessal et al,24 1975</td>
<td>F/16/Iran</td>
<td>Unknown</td>
<td>Dyspnea, axilla swelling</td>
<td>Abnormal lung examination findings, afebrile, abnormal chest radiographic findings</td>
<td>–</td>
<td>P, Ch</td>
<td>–</td>
<td>Yes</td>
<td>Pulmonary edema, mediastinal widening, hemorrhagic mediastinal and axillary nodes</td>
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<tr>
<td><strong>Foreign-Language Pediatric Cases</strong></td>
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<tr>
<td>Krzyszkowski,25,26 1901</td>
<td>F/16/Poland</td>
<td>Wool</td>
<td>“In agony” Fever, chills, pleurisy, cough, dyspnea, hemoptysis</td>
<td>–</td>
<td>–</td>
<td>None</td>
<td>M, PE</td>
<td>Yes</td>
<td>None reported</td>
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<td>Schereffetin,27 1929</td>
<td>M/17/Germany</td>
<td></td>
<td></td>
<td></td>
<td>–</td>
<td>As</td>
<td>–</td>
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<tr>
<td>Skolubovich and Ruban,28,29 1954</td>
<td>M/13/Russia</td>
<td>Dust from infected sheep and calf</td>
<td></td>
<td></td>
<td>–</td>
<td>None</td>
<td>M</td>
<td>Yes</td>
<td>None reported</td>
</tr>
</tbody>
</table>

Abbreviations: As, anthrax antiserum; C, cyanosis; Ch, chloramphenicol; H, horse antiserum; M, meningitis; P, penicillin; PE, pleural effusion(s); PFD, pleural fluid drainage; WBC, white blood cell; –, either not seen before death or no additional signs or symptoms noted in case report at presentation.