Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Welder's Anthrax: A Tale of 2 Cases

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Bacillus anthracis has traditionally been considered the etiologic agent of anthrax. However, anthrax-like illness has been documented in welders and other metal workers infected with *Bacillus cereus* group spp. harboring pXO1 virulence genes that produce anthrax toxins. We present 2 recent cases of severe pneumonia in welders with *B. cereus* group infections and discuss potential risk factors for infection and treatment options, including antitoxin.

Keywords. welder's anthrax; *Bacillus cereus*; *Bacillus tropicus*; welding; antitoxin.

Anthrax is a life-threatening zoonotic disease that occurs worldwide. The etiologic agent has historically been considered *Bacillus anthracis*, which is notable for its potential use as a bioterror agent. Most naturally occurring human cases are from contact with infected animal carcasses. Anthrax, caused by the bacteria *B. anthracis*, is primarily a toxin-mediated disease; *B. anthracis* toxin genes are encoded on the pXO1 plasmid and include those for edema factor (EF), lethal factor (LF), and protective antigen (PA) [1]. The pXO2 plasmid encodes for the capsule, which helps the bacteria evade the immune response. Together, these offensive (toxins) and defensive (capsule) gene products account for much of the virulence of the pathogen. Antitoxins, whether polyclonal or monoclonal, interfere with the binding of PA and internalization of EF and LF; antiserum used in the early 20th century likely had the same mechanism of action. Three anthrax antitoxins are US Food and Drug Administration approved for treatment of inhalation anthrax [2–4]. In clinical trials, these products were safe; however, patients should be monitored for the risk of hypersensitivity reactions.

Patients with inhalation anthrax often present with nonspecific constitutional symptoms followed by cough, dyspnea, and severe respiratory compromise within a few days. Mortality from inhalation anthrax has historically been high, but advances in treatment and critical care medicine have decreased mortality from approximately 92% prior to 2001 to approximately 45% since 2001 [5–7]. Most patients with inhalation anthrax have evidence of hematogenous spread to the gastrointestinal tract, and half have evidence of meningitis [8].

Recently, anthrax has been redefined. "Anthrax-like" illness in humans may also be caused by *Bacillus cereus* group pathogens, such as *B. cereus* and *Bacillus tropicus* (including strain G9241), expressing virulence genes similar to those of *B. anthracis* [9, 10]. Before the 2 cases reported here, 4 welders [11–14] and 1 metal worker [12] have been described with anthrax-like diseases related to infection with *B. cereus* group spp. that have pXO1 virulence genes (Table 1). Fatalities have also been reported in 2 welders with *B. cereus* group infections that lacked *B. anthracis* toxins [15]. It is not known why welders are at increased risk for infections with these novel pathogens. However, they are known to be at risk for respiratory infections in general [16]. At least 1 study that compared welders to the general population documented a proportional mortality ratio (ie, the proportion of deaths due to respiratory infections in welders divided by the proportion of deaths due to respiratory infections in the general population) of 255 (95% confidence interval, 192–332) for pneumonia, with most deaths attributed to pneumococcal and unspecified lobar pneumonias [17].

We report 2 geographically separated cases of severe pneumonia diagnosed in welders over a 6-month span caused by 2 genetically unrelated, toxin-expressing pathogens from the *B. cereus* group. The first patient received raxibacumab antitoxin from the Strategic National Stockpile (SNS) and survived, despite multiple episodes of pulselessness and a prolonged leukemoid reaction. The second patient succumbed in the emergency department after presenting with a 3-day history of altered mental status.

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Table 1. Admitting Characteristics of Patients With Welder's Anthrax from Anthrax Toxin–Producing Members of the *Bacillus cereus* Group

Age (Years)/ Sex	Race	Year	Worksite State	Days to Hospital	Temperature (°C)	Pulse	Blood Pressure (mmHg)	Respiratory Rate (min^{-1})	Platelets ($\times 10^9$/L)	White Blood Cell Count ($\times 10^9$/L)	White Blood Cell Count ($\times 10^9$/L) Highest	Hematocrit (%)	Cough	Dyspnea	Pleural Effusion	Hemoptysis	Fatal
42/M [11]	…	1994	LA	2	38.6[a]	132	80/66	44	49.0[b]	12.0	22.4	…[c]	Y	N	N	Y	N
39/M [12]	W	2003	TX	8	38.7	125	100/46	20	…	15.1	25.3	44.8	Y	N	N	N	Y
56/M [12][d]	B	2003	TX	8	35.7	123	124/95	36	…	25.1	…	57.4	Y	Y	N	Y	Y
47/F [13]	…	2007	LA	…	…	…	…	…	…	…	…	…	…	…	…	…	Y
39/M [14]	H	2011	TX	0.08	36.7	115	93/51	20	…	21.0	…	54.5	Y	Y	Y	Y	Y
39/M[f]	W	2020	LA	6[e]	36.9	122	85/61	16	209.0	13.7	60.0	43.1	Y	O_2 92	Y	Y	N
34/M[f]	H	2020	TX	3	36.8	130	119/75	16	…	28.0	28.0	64.7	N	O_2 70	Y	N	Y

Two additional fatal *Bacillus cereus* group infections occurred in welders and were reported by Miller in 1997, but both cases lacked *Bacillus anthracis* toxin genes [10]. The first was a 46-year-old male reported from Louisiana in December 1995 with an admission white blood cell count of 26 900/μL. The second was a 41-year-old male reported from Louisiana in January 1996 with admission and highest white blood cell counts of 8.8×10^9/L and 17.0×10^9/L and an admission hematocrit of 55.9%.

Abbreviations: LA, Louisiana; TX, Texas. W, White; B, Black; H, Hispanic.

[a]Rectal temperature.

[b]Four days after admission.

[c]Patient had hemoglobin of 8.4 following a gastrointestinal bleed.

[d]Metal worker.

[e]Patient had onset of cough 6 days before hospitalization. Eleven days before hospitalization, he had dark urine and flank, back, and abdominal pain.

[f]These cases are described in the current report.

CASE PATIENT 1

During a medical visit to have his hypertension monitored in spring 2020, a 39-year-old White welder from Louisiana was referred from a clinic to a community hospital emergency department when he was noted to have oxygen saturation in the low 90s by pulse oximetry. His medical history included a 25-year history of cigarette smoking and alcohol use (approximately 8 drinks/day).

Close contacts to the patient suggested during an epidemiologic investigation that his symptoms started 11 days prior to hospitalization and included dark urine and flank, back, and abdominal pain. They reported he had cough with bloody sputum and fever 6 days before hospitalization. However, at the community hospital, the patient reported only 4 days of fever, fatigue, and cough accompanied by rusty to bloody sputum but no dyspnea. He also complained of bilateral flank pain. On admission, he had a temperature of 36.9°C, pulse rate of 122 beats/minute, respiratory rate of 16 breaths/minute, blood pressure of 85/61 mmHg, and oxygen saturation of 92% on room air. Examination of the lungs demonstrated bilateral rhonchi. Table 2 shows admission and alternate day laboratory results. Noteworthy laboratory results included leukocytosis and elevated blood urea nitrogen (BUN) and creatinine. A protein antigen test for influenza A and B and nucleic acid amplification tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on days 1 and 2 were negative. He was admitted for acute pyelonephritis and dehydration and given azithromycin and ceftriaxone empirically (Figure 1).

On hospital day 2 (HD2), marked diarrhea developed and his hypoxemia worsened; chest radiography demonstrated an airspace opacity in the right upper lobe. His hypoxemia progressed throughout the day; he ultimately required endotracheal intubation and mechanical ventilation. That day, a blood culture from admission grew gram-positive rods suspected of belonging to the *B. cereus* group. On HD3, chest radiography showed dense consolidation in his right lung that was greatest in the mid and upper fields, patchy infiltrates in his left lung, and a suspected right pleural effusion (Figure 2). He was then transferred to a tertiary care center.

On HD5, the US Centers for Disease Control and Prevention (CDC) was notified by the Mississippi State Public Health Laboratory (MSPHL), a member of the CDC Laboratory Response Network (LRN), of a bacterial isolate from blood culture submitted for *B. anthracis* rule-out. Although the isolate was negative for *B. anthracis*, the target specific for the pXO1 plasmid [18] was positive, suggesting a *B. cereus* group organism with pXO1 virulence genes. Given the severity of the patient's illness and the atypical finding, MSPHL chose to notify CDC with concerns the isolate was *B. cereus* biovar *anthracis*. Although the results were not reported until later, on hospital admission, the LF plasma level was 1220 ng/mL. It declined to 628 ng/mL on HD2 and 173 ng/mL on HD3 [19, 20].

Table 2. Alternate Day Laboratory Values for Case Patient 1

Hospital Day	White Blood Cell Count ($\times 10^9$ L)	Hematocrit (%)	Platelets ($\times 10^9$ L)	Blood Urea Nitrogen (mmol/L)	Creatinine (μmol/L)	Albumin (g/L)	Aspartate Aminotransferase (μkat/L)	Alanine Aminotransferase (μkat/L)
1	13.7	43	209	29	2.9	…	…	…
3	33.3	48	213	23	1.6	…	…	…
5	60.0	38	149	28	1.4	1.5	60	28
7	47.7	32	42	45	2.6[a]	1.5	…	…
9	47.2	26	39	43	2.6[a]	2.1	…	…
11	42.4	24	57	55	3.5[a]	1.9	133	96
13	13.7	43	209	29	2.9[a]	2.0	96	82

[a]The patient was on continuous renal replacement therapy.

The patient continued to deteriorate over the next few days. Antimicrobial therapy was changed to vancomycin and piperacillin-tazobactam. He developed a profound and persistent leukocytosis beginning on HD4, with a total white blood cell (WBC) count consistent with a leukemoid reaction (58.4×10^9 cells/L; Figure 1). Hematocrit and platelets started

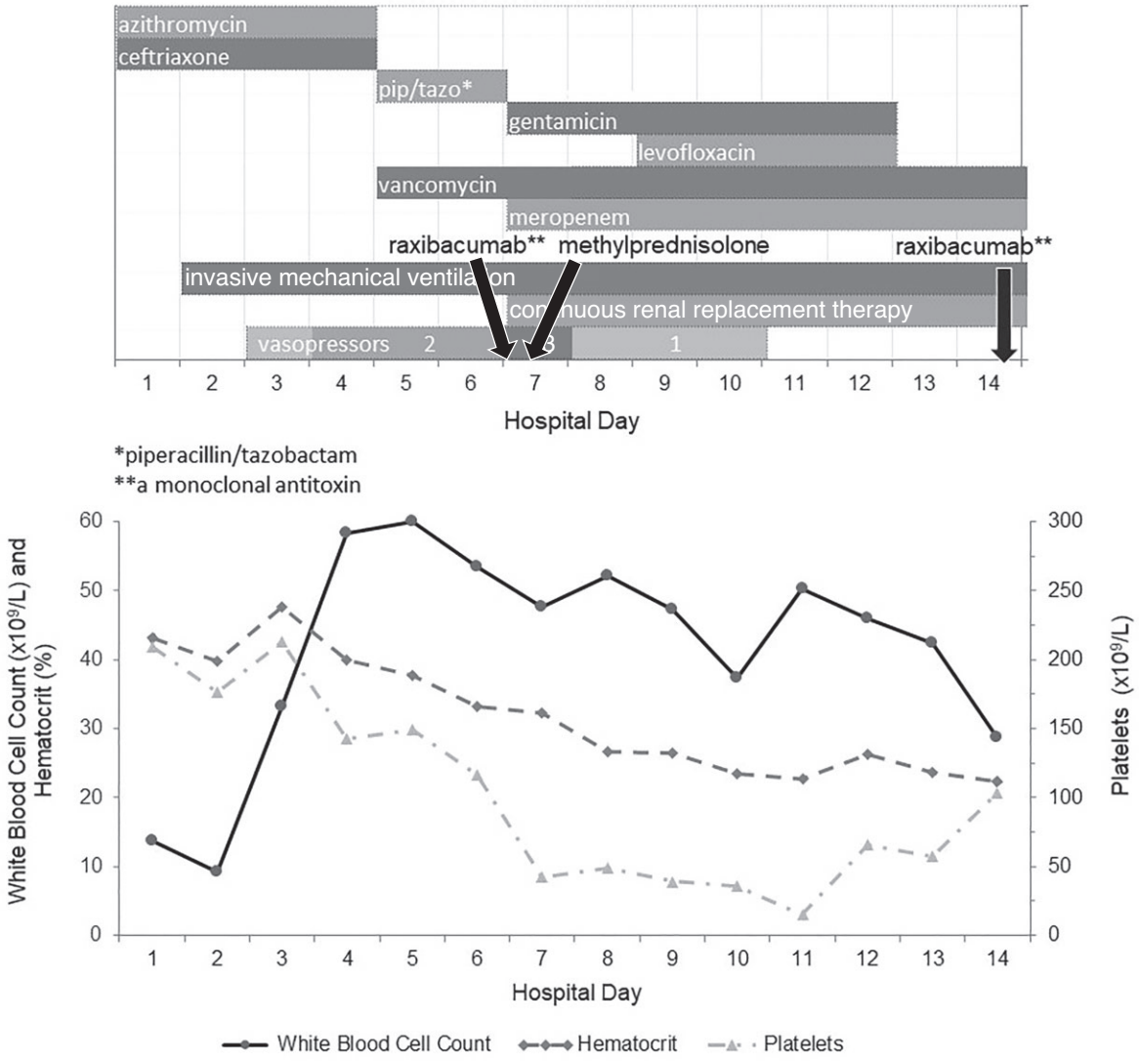

Figure 1. Supportive care and treatments and hematology results for case patient 1, hospital days 1–14.

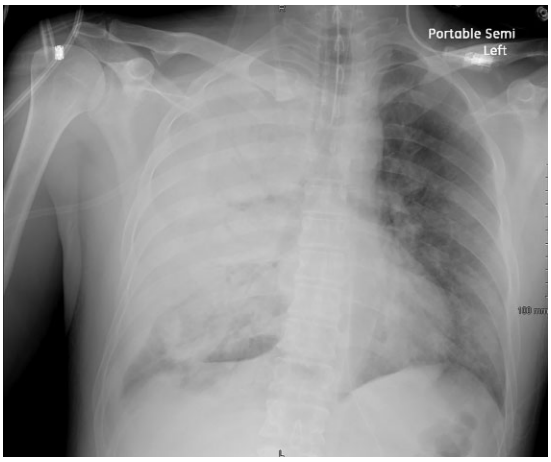

Figure 2. Portable chest radiograph for case patient 1 from hospital day 3 showing dense consolidation in the right lung, greatest in the mid and upper chest. Air bronchograms were present. Pleural fluid was possibly present, and empyema was a consideration. Patchy, milder infiltrates were seen in the left lung.

to decline, and acute kidney injury developed. Progressive shock ensued, requiring multiple vasopressors. On HD6, he experienced multiple episodes of pulselessness, requiring chest compressions and advanced cardiac life support (Figure 1). His air-space disease progressed to near-total opacification of the right hemithorax and worsening consolidation on the left (Figure 3*A*).

On HD6, within 24 hours of suspecting the patient had an anthrax toxin–expressing *B. cereus* group infection, the clinicians consulted anthrax subject matter experts at the CDC and requested the monoclonal antitoxin raxibacumab.

On HD7, raxibacumab was administered early, gentamicin and meropenem were started later, and piperacillin-tazobactam was discontinued. Supportive measures included 3 vasopressors, new onset continuous renal replacement therapy (CRRT), and methylprednisolone (Figure 1). Shortly after raxibacumab receipt, a portable chest radiograph (Figure 3*B*) was read as "no significant change in extensive confluent infiltrates throughout both lungs [compared to HD6]."

The LRN results from MSPHL suggested that the gram-positive isolate was *B. cereus*; however, it was later reclassified as *B. tropicus* at the CDC based on whole-genome sequence analysis and recent changes to the *B. cereus* group taxonomy. Susceptibility results are shown in Table 3; its genome contained virulence factor genes encoding for EF, LF, and PA but not for polyglutamate capsule.

Although the number of vasopressors required to maintain adequate blood pressure decreased from 3 to 1 in the 2 days following antitoxin receipt, the patient still required mechanical ventilation and CRRT, and his anemia and thrombocytopenia worsened (Figure 1). Due to his continued instability, LF levels were measured in serum and pleural fluid. On HD11 (5 days after antitoxin receipt), LF was nondetectable in serum but still present in pleural fluid at 1.35 ng/mL [19, 20]. Anti-PA immunoglobulin G (IgG) increased from <10 μg/mL 2 days before receipt to >1000 μg/mL 2 days after [21]. It declined slowly over the next few days (Figure 4). In consultation with the CDC, a second dose of antitoxin was administered on HD14, which bolstered anti-PA levels. No appreciable changes were noted on thoracic radiographs from 1 day before to 1 day after dose 2 (Figures 5*A* and 5*B*), suggesting no hypersensitivity or other adverse events related to administration. Anti-PA

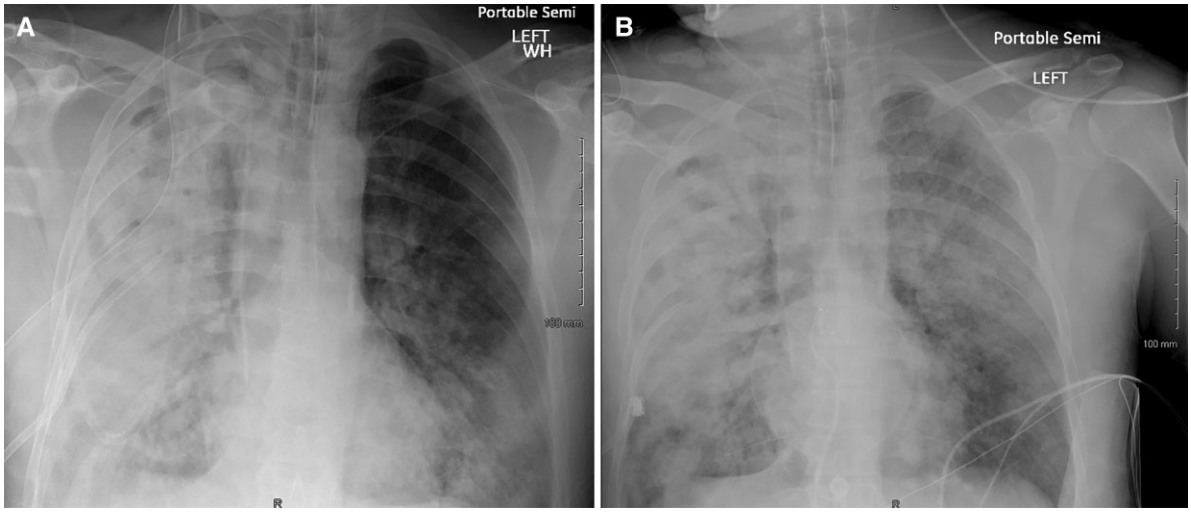

Figure 3. *A,* Portable chest radiograph for case patient 1 from the afternoon of hospital day 6, before antitoxin dose 1, showing extensive air-space consolidation throughout most of the right lung and nodular infiltrates throughout the left lung. *B,* Portable chest radiograph for case patient 1 from early morning hospital day 7, shortly after antitoxin dose 1, showing extensive confluent infiltrates throughout both lungs, with greater confluent disease of the right lung.

Table 3. Susceptibility Results for *Bacillus cereus* Group, Case Patient 1

Broth Microdilution Tests	Results (μg/mL)	Interpretation
Amikacin	2	Susceptible
Ampicillin	16	Resistant
Chloramphenicol	4	Susceptible
Ciprofloxacin	≤0.25	Susceptible
Clindamycin	≤0.25	Susceptible
Erythromycin	≤0.25	Susceptible
Gentamicin	≤0.25	Susceptible
Imipenem	≤0.5	Susceptible
Levofloxacin	≤0.12	Susceptible
Meropenem	≤0.12	Susceptible
Penicillin	>2	Resistant
Rifampin	≤0.5	Susceptible
Tetracycline	≤1	Susceptible
Trimethoprim-Sulfamethoxazole	>8/152	Resistant
Vancomycin	1	Susceptible

increased to 6080 μg/mL on HD14 following the second dose of antitoxin. By week 5 of hospitalization, anti-PA IgG declined to 683 μg/mL. Despite the positive anti-PA IgG, LF was still positive in a pleural fluid specimen (0.058 ng/mL) collected in the same timeframe (Supplementary Figure 1).

Iron levels assessed retrospectively on samples banked from HD3 and HD17 showed serum iron levels of 17 μg/dL and 19 μg/dL (normal, 49–181 μg/dL), total iron-binding capacity levels of 136 μg/dL and 143 μg/dL (normal, 250–450 μg/dL), and ferritin levels of 1524 ng/mL and 4047 ng/mL (normal, 22–322 ng/mL).

CRRT was discontinued on HD15. The patient remained on vancomycin for 24 days and meropenem for 30 days. A 9-day course of linezolid was started when vancomycin was stopped. The patient had a protracted hospital course characterized by more than 3 months of mechanical ventilatory support, *Staphylococcus aureus* and *Serratia* spp. bacteremias, a thoracoscopy with talc, and multiple transfusions of packed red blood cells. A few days after weaning from mechanical ventilation, he was discharged to a rehabilitation facility and, later, home.

CASE PATIENT 2

The patient was a 34-year-old Hispanic, male welder. In November 2020, he was evaluated at a Houston emergency department for a 2-day history of altered mental status following a fall. His past medical history included childhood epilepsy, tobacco use, and alcohol use disorder.

On examination, he was confused and had a temperature of 36.8°C, pulse rate of 130 beats/minute, respiratory rate of 16 breaths/minute, blood pressure of 119/75 mm Hg, and oxygen saturation of <80% despite supplemental oxygen by nonrebreather mask (Table 1). Rales and rhonchi were heard on auscultation. Laboratory studies were notable for leukocytosis; erythrocytosis; hypokalemia; elevated BUN, creatinine, lactic acid, and bilirubin; and mild transaminase elevations (Table 4). He was intubated for acute hypoxemic respiratory failure. A urine toxicology screen and polymerase chain reaction (PCR) test for SARS-CoV-2 were negative. A chest radiograph showed dense bilateral air-space opacities greatest in the perihilar regions and lower lobes (right greater than the left), suggesting diffuse bilateral consolidation. Computed tomography of the head, chest, abdomen, and pelvis demonstrated air-space disease but was otherwise normal (Figures 6*A* and 6*B*).

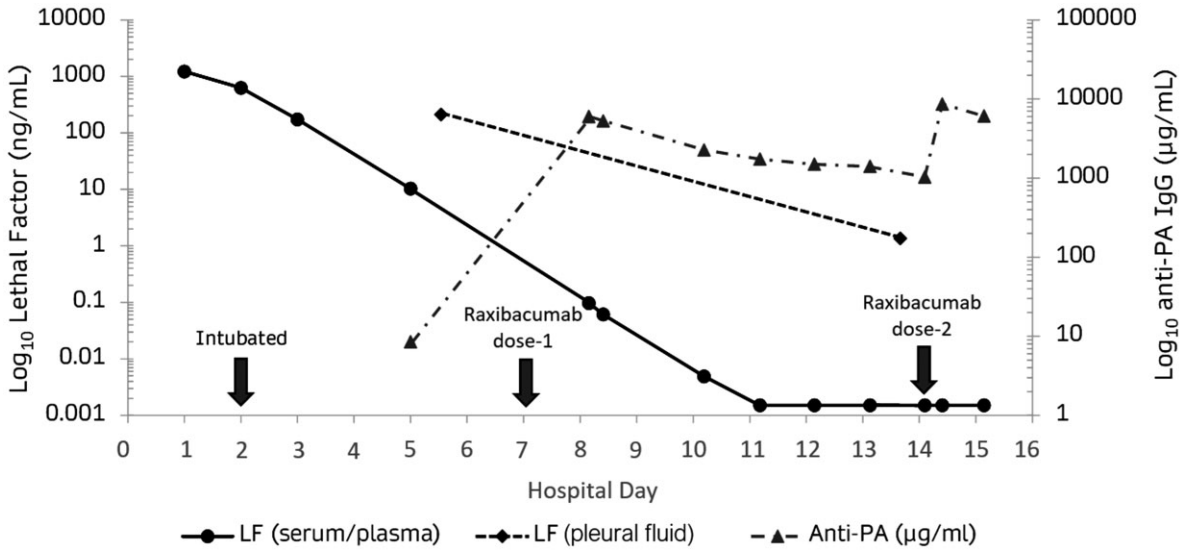

Figure 4. Anthrax lethal factor (LF) and anti-protective antigen (PA) immunoglobulin G (IgG) for case patient 1 by hospital day.

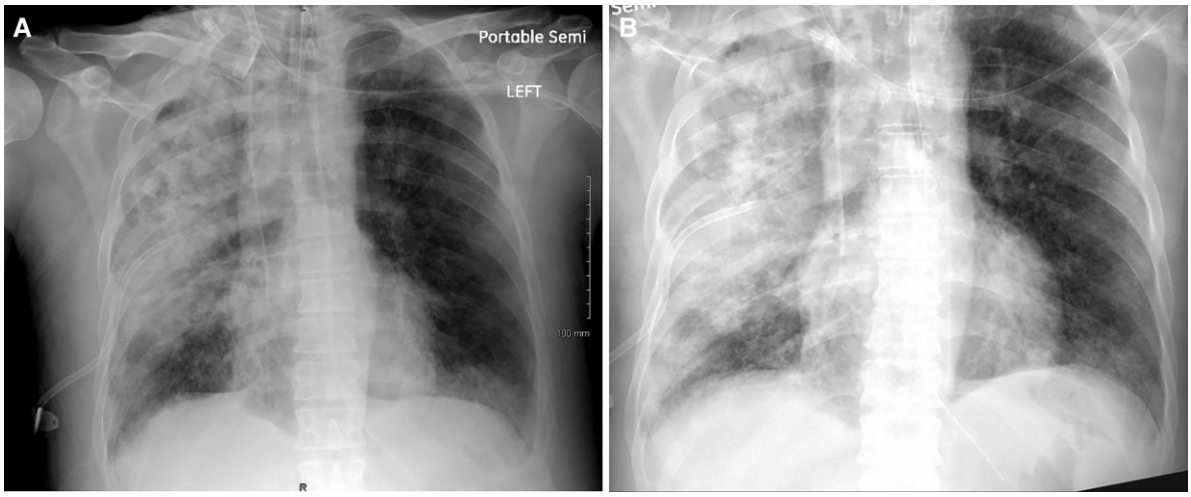

Figure 5. *A,* Portable chest radiograph of case patient 1 from hospital day 13, 1 day before antitoxin dose 2, showing slight radiographic improvement, especially on the left. *B,* Portable chest radiograph of case patient 1 from hospital day 15, 1 day after antitoxin dose 2, showing persistent bilateral pleural and parenchymal opacities, decreased aeration at right lung base, and increased aeration on left.

Table 4. Emergency Department Laboratory Values for Case Patient 2

Hospital Day	White Blood Cell Count ($\times 10^9$/L)	Hematocrit (%)	Platelets ($\times 10^9$/L)	Potassium (mmol/L)	Blood Urea Nitrogen (mmol/L)	Creatinine (μmol/L)	Albumin (g/L)	Bilirubin (mg/dL)	Total Alkaline Phosphatase (U/L)	Aspartate Aminotransferase (μkat/L)	Alanine Aminotransferase (μkat/L)
1	28	65	230	2.8	25	2.3	4.6	2.7	248	62	46

Patient was on continuous renal replacement therapy.

The patient was intubated and started on mechanical ventilation. After intubation, arterial blood gas testing was consistent with severe hypoxemic respiratory failure and a profound mixed metabolic and respiratory acidosis. Shock developed, and vasopressors were initiated. Empiric antimicrobial therapy included vancomycin, piperacillin-tazobactam,

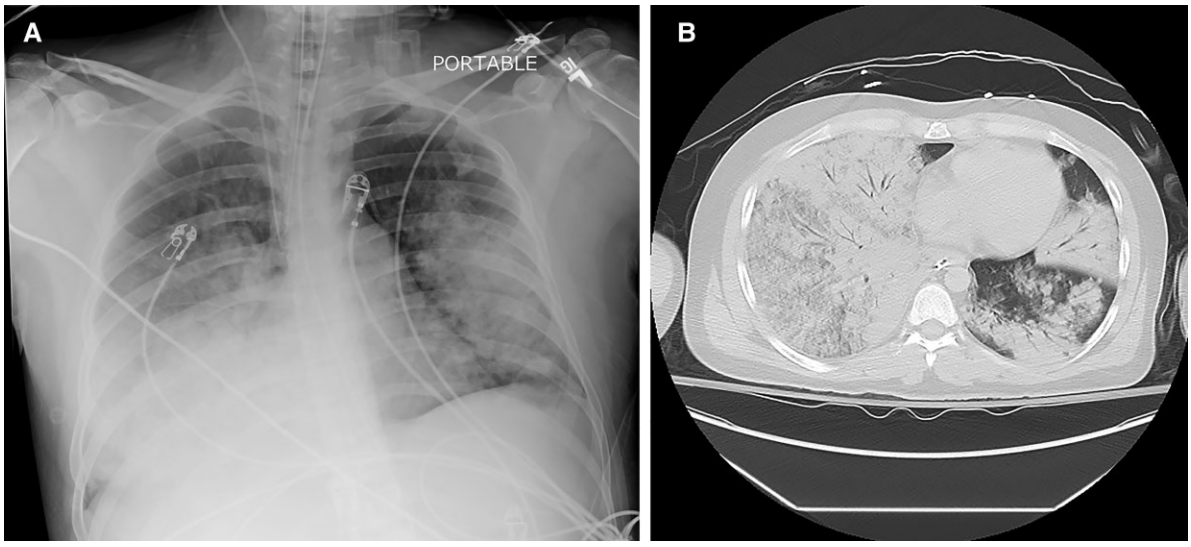

Figure 6. *A,* Chest radiograph for case patient 2 showing bilateral alveolar infiltrates consistent with pneumonia. *B,* Computed tomography abdomen lung window in case patient 2 showing diffuse bilateral consolidation.

cefepime, azithromycin, and clindamycin. Shortly after admission, and despite maximal support and resuscitative efforts, the patient deteriorated, developed ventricular fibrillation, and died.

Within 24 hours of initial presentation, the Houston Health Department, a partner in the CDC LRN, reported that an isolate had grown an organism equivocal for *B. anthracis* that most closely resembled *B. cereus*. Results of PCR testing performed by the Houston LRN showed the sample was positive for the pXO1 plasmid, and the LRN suggested it might contain a strain of *B. anthracis* cured of 1 or more virulence factors, such as the Sterne strain. At the CDC, genome sequencing identified the presence of a pXO1 plasmid and the absence of a pXO2 plasmid, confirming this was a *B. cereus* group organism with pXO1 virulence genes.

An autopsy was performed; large serosanguinous effusions were found in the pleural cavities (right, 300 mL; left, 250 mL). The lungs were severely congested and edematous, with a combined weight of 2560 g (normal combined weight for male lungs, 267–1395 g). Mild anthracotic pigment deposition was noted on the pleural surfaces, and serial sectioning showed diffusely patchy consolidation involving all lobes. The brain was congested, but the cerebrospinal fluid and leptomeninges were clear.

Microscopic examination of lung tissue revealed acute necrotizing bronchopneumonia with associated intraalveolar hemorrhage, fibrin, edema, and admixed clusters of gram-positive bacilli (Figure 7*A*–*C*). Immunohistochemistry staining with a monoclonal anti-*B. anthracis* group cell wall antibody that cross-reacts with *B. cereus* group antigens showed *B. cereus* staining [22]. Extracellular bacilliform, intracellular, and granular immunostaining were observed in the areas of the bronchopneumonia (Figures 7*D* and 7*E*). The lungs also showed abundantly scattered intraalveolar clusters of hemosiderin-laden macrophages containing coarse, intracytoplasmic hemosiderin pigment, confirmed by Prussian blue staining (Figure 7*F*). No significant interstitial fibrosis suggestive of long-term chronicity was present, indicating a pattern of intraalveolar hemorrhage associated with his current illness.

The liver had moderate centrilobular mixed steatosis consistent with early alcoholic liver disease (Figure 7*G*). The heart and kidneys exhibited mild hypertensive changes, including few hypertrophic myocytes, mild perivascular fibrosis, and mild intimal fibrosis of the arterioles. The brain showed no acute hemorrhage or evidence of meningitis or encephalitis. Multiple sections of the upper gastrointestinal tract revealed no significant hemorrhage or inflammation. No immunostaining evidence of *B. cereus* group antigens was seen in heart, liver, kidneys, intestine, or brain using a *B. anthracis* anti–cell wall antibody. Following the protocol described previously [23, 24], pan-eubacterial 16S PCR sequences amplified from lung tissue showed a *B. cereus* group organism.

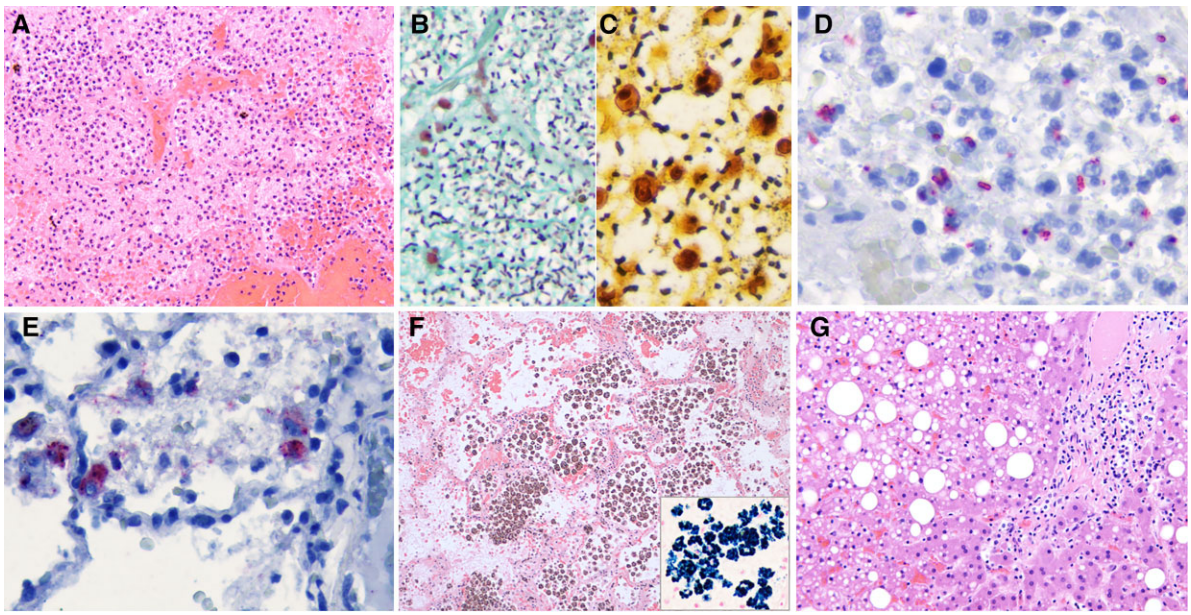

Figure 7. Histopathological, special stain, and immunohistochemical findings for case patient 2. *A*, Low magnification of lung showing bronchopneumonia with neutrophilic inflammatory hemorrhage and necrosis. *B*, Lillie-Twort Gram stain showing abundant gram-positive bacilli. *C*, Warthin–Starry stain in the same area showing many bacilli. *D*, Abundant immunostaining of granular and bacilliform antigens seen using *Bacillus anthracis* cell wall immunohistochemistry assay. *E*, Immunostaining of *B. anthracis* cell wall antibody present within histiocytic cells. *F*, Area of lung showing abundant hemosiderin-laden macrophages; inset image shows iron-rich granules highlighted by Prussian blue stain. *G*, Liver showing small and large droplet steatosis and mild mononuclear inflammatory infiltrate in the portal area.

DISCUSSION

Therapy for the systemic disease associated with the anthrax toxins, whether caused by *B. anthracis* or *B. cereus* group pathogens harboring a pXO1 plasmid, should include a bactericidal antimicrobial and an adjunctive antitoxin. Toxin production should cease with the death of the pathogen, and levels should decline as the toxin is metabolized. According to CDC anthrax treatment guidelines, one of the antitoxins available through the SNS should be added to combination antimicrobial drug treatment for anthrax patients with systemic illness. Up to 3 doses may be given as determined by clinical judgment and discussion with CDC subject matter experts. Signs of systemic involvement include tachycardia, tachypnea, hypotension, hyperthermia, hypothermia, and leukocytosis [25]. Anthrax is being redefined to include infection with anthrax toxin–producing *B. cereus* group pathogens. As the 2 welders in these case reports had severe anthrax toxin–producing pneumonias with signs of systemic involvement, both were candidates for antitoxin.

Case patient 2 died in the emergency department. Case patient 1 survived and received antitoxin twice: approximately 1 week into his hospitalization and again 1 week later. Despite severe refractory shock, including multiple episodes of pulselessness prior to antitoxin receipt, he experienced hemodynamic improvement after dose 1. As he still required CRRT and had marked hematologic abnormalities, a second dose of antitoxin was administered approximately 1 week after the first. He also appeared to benefit from this dose, as CRRT was discontinued within a few days. Antitoxin administration may have played a role in his improvement.

Limited historic data are available regarding human efficacy for antiserum or antitoxin use for systemic anthrax. For cutaneous anthrax prior to the antimicrobial era, treatment with antiserum reduced the fatality rate from 24% for untreated patients to 8% for treated patients [25]. Less information is available for antiserum or antitoxin treatment of other types of systemic anthrax, including inhalation anthrax. For inhalation anthrax, 2 of 3 patients treated with anthrax immune globulin intravenous (AIGIV) survived [26–28]. Adult respiratory distress syndrome did develop in 1 of the 2 survivors a day after AIGIV receipt, though this was not attributed to the antitoxin [27]. Worsening of chest radiographs was not observed with either dose of antitoxin for case patient 1. For patients with injection anthrax, antitoxin benefit is challenging to interpret; 10 of 15 (66.7%) patients who received AIGIV survived compared with 22 of 28 (78%) who did not. Survival for recipients and nonrecipients remained similar, even after stratification for severity [29, 30].

Inhalation anthrax results from inhalation of *B. anthracis* spores, which are carried to mediastinal lymph nodes where they germinate to initially cause a mediastinitis rather than a true pneumonia. Patients with severe *B. cereus* group, anthrax toxin–producing pneumonias present similarly to those with inhalation anthrax [31]. Data on signs, symptoms, and onset are available for 6 of 7 patients with *B. cereus* group pneumonias (Table 1). Fever or chills, cough, and dyspnea or low oxygenation were each present in 5 of 6 patients. Symptom onset to presentation ranged from less than 1 day to 8 days. Of the 5 with laboratory information, all had significant leukocytosis and 3 had elevated hematocrits. Only 2 of the 7 survived. For comparison, of 90 patients with inhalation anthrax described in the literature from 1880 through 2018, 76% had fever or chills; 57%, cough; 67%, dyspnea; 48%, leukocytosis; and 32%, elevated hematocrit. Of the 43 reported since 1960, survival occurred in 28%, and median time to presentation was 3 days (Q1–Q3, 3–5) [31].

Autopsies were performed on 3 of 4 *B. cereus* group fatalities with clinical information, including case patient 2 [12, 14]. Pleural fluid was present in all 3 and was serosanguinous in case patient 2 and 1 other [14]. Serosanguinous pericardial effusion and a subarachnoid hemorrhage were seen in 1 patient [14]. The lungs of all 3 showed extensive areas of necrosis, and 2, including case patient 2, showed anthrax-like edema and hemorrhage [14].

Welders and other metal workers appear to have increased susceptibility to *B. cereus* group pathogens. In 1979, an accidental aerosol release of *B. anthracis* spores from a bioweapons facility in Sverdlvosk in the former Soviet Union resulted in at least 77 anthrax patients and 66 deaths. Among the inhalation anthrax patients with occupational or risk factor information in this outbreak, 7 of 35 (20%) were welders and nearly half of the males were described as moderate or heavy drinkers [32]. Because the severe pneumonias caused by *B. cereus* group members described in these 2 case patients and previously reported patients have been limited to welders (and 1 metal worker), we refer to this presentation as "welder's anthrax" (Table 1).

Several factors could influence why welders and other metal workers appear more susceptible than nonwelders to B. cereus group pathogens. For example, their internal iron availability might also influence growth of *B. cereus* group organisms [33]. Like many other pathogens, both *B. cereus* and *B. anthracis* have mechanisms for acquiring the iron needed for growth from their hosts. Both produce 2 catecholate siderophores: the 3,4-dihydrobenzoic acid (DHB) siderophore petrobactin and the 2,3-DHB–based siderophore bacillibactin [34]. *Bacillus cereus* iron acquisition is facilitated by a surface protein (IlsA) [35, 36] that binds heme, hemoglobin, and ferritin [37]. *Bacillus anthracis* iron acquisition is served by a more selective surface protein (IsdX1 [the smallest gene in the *isd* locus]) that facilitates the removal of heme from hemoglobin or haptoglobin [38]. Some host iron-binding proteins inhibit, rather than promote, the growth of *B. cereus* and *B. anthracis*.

Specifically, transferrin in its apo (empty), but not holo (full), state inhibits in vitro growth of *B. cereus* [39] and *B. anthracis* [40] in a dose-dependent manner. When iron-binding proteins such as transferrin are saturated (full), as was demonstrated by the low total iron-binding capacity of case patient 1, the antibacterial activity, including phagocytic activity, of plasma may be significantly diminished [41].

It is noteworthy that groups that experience *B. cereus* infections, such as welders, patients with alcohol-use disorders or acute leukemias [42], and premature infants [43], are also at risk for iron overload. In a study in China, welders had mean serum iron levels that were almost twice as high compared with factory food workers (300 ± 137 μg/dL vs 160 ± 79 μg/dL) [33]. In a population-based study in the United States that compared drinkers with nondrinkers, serum ferritin, transferrin saturation, and iron levels increased linearly with alcohol consumption [44], partly due to altered gastrointestinal uptake of iron [45]. In a prospective study of patients with acute leukemias or myelodysplastic syndromes, the median serum ferritin was 1549 ng/mL (ie, 5–6 times the upper limit of normal) [46]. In one study of 24- to 32-week premature infants, 19% were observed to have iron overload. Those most at risk had lower birthweights and higher numbers of transfusions [47].

The 2 case patients described here shared 2 potential sources of iron overload: welding and significant alcohol exposure. In addition to increasing the potential uptake of iron and the likelihood of iron overload, alcohol exposure can interfere with the phagocytic capacity of alveolar macrophages [48], which are considered a first line of defense against *B. anthracis* [49].

Both patients had profound leukocytosis, with an overt leukemoid reaction noted in case patient 1. Leukemoid reactions are variously defined as WBC counts that exceed 30.0×10^9/L [50], 35.0×10^9/L [51], or 50.0×10^9/L [52, 53] in the absence of hematologic malignancy. They are well described in other toxin-mediated infections such as those caused by *Clostridioides difficile*, *Bordetella pertussis* [52], and *Shigella sonnei* [53]. Although none of the previously reported cases of severe *B. cereus* group pneumonias had WBC counts $\geq 30.0 \times 10^9$/L (Table 1), leukemoid reactions have been observed in adults and children with systemic anthrax [31]. Higher or more prolonged leukemoid reactions are ominous prognostic signs. Of 65 *C. difficile* patients with leukemoid reactions, death occurred in 100% of those whose WBC counts exceeded 50.0×10^9/L and in half of those whose counts exceeded 35.0×10^9/L [51].

CONCLUSIONS

Infection with species of the *B. cereus* group harboring pXO1 virulence genes can produce pulmonary disease with similarities to that produced by *B. anthracis*, especially in terms of severity. Despite small case numbers, available data suggest welders are at unique risk for these infections. Thus, welder's anthrax should always be included in the differential for welders who present with pneumonias accompanied by hemoptysis or bloody sputum. Although mediastinitis is usually seen in inhalation anthrax from *B. anthracis*, it is not typical in welder's anthrax.

Because of its severity, welder's anthrax will usually need to be treated empirically before it can be confirmed. Anthrax antitoxin should be considered as a treatment option in all such cases. Antitoxin may be obtained from the SNS following a consultation with the Bacterial Special Pathogens Branch at CDC. Laboratory confirmation of welder's anthrax requires both the presence of anthrax toxin genes and the recognition of *B. cereus* group pathogens by a reference laboratory.

Iron overload and alcohol-use disorder might predispose patients to *B. cereus* group infections. *Bacillus cereus* group infections should be added to the list of infections that can cause leukemoid reactions, which are associated with increased mortality.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC or the authors' affiliated institutions.

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