

Is It Influenza or Anthrax? A Decision Analytic Approach to the Treatment of Patients With Influenza-like Illnesses

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See editorial, p. 329.

Study objective: We analyze the risks and benefits of alternative treatment strategies for non-septic-appearing febrile patients with influenza-like illnesses and possible exposure to anthrax.

Methods: We used a decision analytic model to evaluate 6 testing and treatment strategies in an emergency department. Patients were non-septic-appearing and had influenza-like illnesses but low likelihood of exposure to anthrax. The following interventions were used: (1) no empiric antibiotics; (2) blood culture and treatment only if the result was positive; (3) rapid testing for influenza and, for those who tested negative, treatment with 60 days of ciprofloxacin; (4) a two-test strategy in which all patients were first tested for influenza; those who tested negative had a blood culture test and were treated empirically with ciprofloxacin for 3 days while waiting for blood culture results; (5) culture test for all patients and treatment with ciprofloxacin for up to 3 days while waiting for blood culture results; and (6) treatment of all patients with ciprofloxacin empirically for 60 days. Main outcome measures were deaths, complications from anthrax, adverse events from ciprofloxacin, and ciprofloxacin patient-days.

Results: For nonzero probabilities of anthrax, patient mortality was always lowest in the strategies in which all patients were treated empirically for anthrax either for 60 days or for 3 days pending blood culture results. These strategies, however, were associated with more morbidity (more ciprofloxacin patient-days and more antibiotic adverse events) than were strategies without empiric treatment. The numbers of adverse events and antibiotic patient-days were reduced substantially with the two-test strategy, in which patients with influenza were identified early and not treated. In general, for probabilities of anthrax equaling or exceeding 2%, treating all patients empirically for 60 days was best, but for probabilities between 0.1% and 2%, the sensitivity of blood culture for anthrax determined the optimal strategy: when the sensitivity exceeded 95%, a short course of empiric ciprofloxacin until blood culture results became available was best, but for sensitivities below 95%, more aggressive empiric antibiotics use was warranted. The proportion of patients with influenza in the community affected the choice of strategy, so that seasonal variation exists.

Conclusion: During influenza season, our findings support rapid testing for influenza, followed by empiric treatment for anthrax pending blood culture results for those

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Capsule Summary**What is already known on this topic**

Early symptoms of inhalational anthrax are similar to those of influenza.

What question this study addressed

Six strategies for testing and treatment of possible inhalational anthrax were examined in a theoretical model using varying assumptions.

What this study adds to our knowledge

When anthrax exposure is a possibility, the optimal strategy during influenza season begins with rapid influenza testing. Those negative for influenza receive short-term empiric antibiotics for anthrax pending blood culture results.

How this might change clinical practice

This model provides a framework for decisions regarding empiric treatment of possible inhalational anthrax among patients with respiratory symptoms. Determining the probability of anthrax exposure for an individual patient remains a challenge.

who test negative for influenza. Our results help to highlight the importance of developing rapid and sensitive tests for anthrax and of developing improved surveillance and methods to calculate the previous probability of attacks.

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INTRODUCTION**Background**

During the mailed anthrax attacks in the fall of 2001, 11 people contracted inhalational anthrax, and 5 people died. Additionally, more than 10,000 people with possible exposure to anthrax were offered 60 days of prophylaxis with oral ciprofloxacin.¹ Most people were asymptomatic at the start of the therapy, and none developed anthrax.² Early recognition of inhalational anthrax is critical because treatment with antibiotics can prevent morbidity and mortality only if initiated within the first 24 to 72 hours of the illness. Distinguishing early-stage inhalational anthrax from influenza and other influenza-like illnesses (eg, parainfluenza, rhinovirus, community-acquired pneumonia, adenovirus), however, remains problematic. The US Centers for Disease Control and Prevention (CDC) has published data to assist clinicians in distinguishing anthrax from other respiratory infections, but there is no well-defined treatment strategy based on a constellation of signs and symptoms.^{3,4} An expert consensus panel has

published recommendations for the management of anthrax, and the CDC has published recommendations about whom to treat for suspected inhalational anthrax.^{5,6} Unless patients are part of an identified cohort of exposed individuals, as were the postal workers in 2001, there are no guidelines on how to manage flu-like illness when inhalational anthrax is part of the differential diagnosis but unlikely.

If a suspected anthrax attack were to occur during influenza season, some patients with early anthrax might be misdiagnosed as having influenza and not treated. Conversely, if the index of suspicion for anthrax were high, many with influenza could possibly be inappropriately treated with antibiotics for possible anthrax. Prolonged use of ciprofloxacin poses risks of adverse events to individuals and endangers society at large through development of antibiotic-resistant organisms and depletion of stores of a useful broad-spectrum antibiotic. The decision to treat individual patients with prophylactic antibiotics requires careful weighing of the risks and benefits. In the event of a suspected attack by bioterrorists in the midst of a seasonal outbreak of influenza, emergency and primary care physicians will have to make these choices in the face of uncertainty. To examine the individual and public health consequences of approaches to treatment of patients with possible anthrax, we developed a decision analytic model of 6 strategies for evaluating and treating non-septic-appearing febrile patients with influenza-like illness and possible exposure to anthrax.

MATERIALS AND METHODS

To gather evidence for our models, we performed a MEDLINE search by using the following key words: “anthrax,” “*Bacillus anthracis*,” “ciprofloxacin,” “fluroquinolone,” “influenza,” “influenza-like illness,” “flu-like symptoms,” and “anaphylaxis.” Additionally, we included articles identified in the bibliographies of recent review articles and consensus statements.⁷⁻¹² We reviewed those articles that described signs, symptoms, and the use of diagnostic tests for the clinical syndromes of interest. For data on antibiotic effects, we reviewed articles that described rates of adverse events from short and long courses of therapy and rates of anaphylaxis. We incorporated information about the 2001 attacks published by the CDC.^{2,13,14} There were no human subjects, so institutional review board approval was not sought.

For eligible patients, whom we defined as having fever and symptoms consistent with an influenza-like

illness but not appearing to be septic and having no confirmed history of exposure to anthrax, we modeled 6 management strategies by using decision analysis software (Data 4.0; TreeAge, Williamstown, MA) to compare outcomes. Febrile patients were considered to have an influenza-like illness if they had at least 1 of the following symptoms: headache, fatigue, dry cough, sore throat, nasal congestion, and myalgias. We defined septic-appearing patients as those who were ill appearing or had signs or symptoms of cardiovascular instability. We assumed that patients with symptoms of influenza and a known exposure to anthrax would be administered antibiotics. We assumed that the baseline risk for anthrax was above zero, either because of a reported known case in the surrounding area or a strong suspicion that a bioterrorist agent had been released. We did not include septic-appearing patients, because we assumed that they all would be admitted and treated with antibiotics. Our decision tree included branches for 3 diagnoses: inhalational anthrax, influenza, and other flu-like illnesses (eg, respiratory syncytial virus, adenovirus, atypical pneumonia).

In the first strategy (Treat None), no testing is performed and none of the eligible patients is treated empirically with antibiotics. In the second strategy (Treat None Pending Culture), blood cultures are drawn from all eligible patients, with antibiotic treatment given only to those with positive cultures, necessitating a 3-day delay of therapy. In the third strategy (Influenza Testing), all patients undergo a rapid diagnostic test for influenza. If the test result is positive, they are assumed to have influenza and are not treated for anthrax. If the test result is negative, they are treated for 60 days with ciprofloxacin for anthrax. In the fourth strategy (Two Test), all patients undergo a rapid diagnostic test for influenza. If the test result is positive, they are assumed to have influenza and are not treated for anthrax.

Patients who test negative for influenza begin receiving empiric ciprofloxacin for 3 days pending the results of a blood culture. If the culture is negative after 3 days, treatment is discontinued. In the fifth strategy (Treat All Pending Culture), blood cultures are drawn from all eligible patients, and they all begin receiving empiric ciprofloxacin. If the culture is negative after 3 days, treatment is discontinued. In the sixth strategy (Treat All), all eligible patients are treated for 60 days with ciprofloxacin. We chose 60 days because it is the minimum duration of treatment recommended by the CDC.

Data on anthrax infection in human beings are sparse, so we relied on reported clinical features in the recent cohort of infected patients, as well as on a panel

of infectious disease and bioterrorism experts.¹⁵ According to published findings from the cohort of the first 10 of the 11 patients infected with anthrax in 2001, we modeled a 10% mortality for infected patients treated early (Table 1).¹⁶ Currently, blood culture is the best and only anthrax test available to most clinicians. The sensitivity of blood culture for detecting anthrax is not known precisely, but because cultures for all 8 patients with blood cultures drawn before administration of antibiotics had positive growth, it is thought to be high.¹⁷ Thus, we assumed a sensitivity of 90% and considered a range from 50% to 95%.¹¹ The specificity of blood culture was assumed to be 98%, with a range from 50% to 100%. Anthrax-infected patients with

Table 1.
Assumptions of the model.

Model Attribute	Estimates
Proportion of all patients with flu-like symptoms who have:	
Anthrax, range, %	0–10
Influenza, range, %	0–66
Other influenza-like illnesses (not influenza or anthrax), range, %	24–100
Mortality from, % (range)	
Anthrax with	
Delayed antibiotics and no blood culture drawn	90 (50–100)
Delayed antibiotics until blood culture positive	75 (40–100)
Early antibiotics discontinued because of false-negative blood culture	50 (25–75)
Early antibiotic treatment	10 (5–20)
Influenza	
Other influenza-like illnesses	18 per million
Morbidity complications from, % (range)	
Anthrax in survivors	
Influenza	87 (36–100)
Other influenza-like illnesses	0.12
Ciprofloxacin	
Minor (mild to moderate) adverse events from	
3-Day course	45
60-Day course	57
Severe adverse events from	
3-Day course	0.1
60-Day course	0.3
Test characteristics, % (range)	
Sensitivity of blood culture for anthrax	90 (50–99)
Specificity of blood culture for anthrax	98 (50–99)
Sensitivity of influenza testing	85 (65–95)
Specificity of influenza testing	95 (75–99)
Clinical outcome and utility on a scale from 0 to 1	
Death	0
Complications of anthrax and severe ciprofloxacin adverse events	0.578
Complications of anthrax and minor ciprofloxacin adverse events	0.578
Complications of anthrax	0.579
Severe adverse events from ciprofloxacin	0.998
Minor adverse events from ciprofloxacin	0.999
Disease-free survival (perfect health)	1

blood cultures were assumed to have 50% mortality if they received empiric treatment for only 3 days (Treat All Pending Culture) because of false-negative cultures. If these patients were not initially treated empirically but had true-positive cultures (Treat None Pending Culture), anthrax-infected patients had 75% mortality because treatment was delayed by 3 days. For anthrax-infected patients who were not treated and for whom no culture was drawn (Treat None), the mortality was 90% because their treatment delay would likely exceed 3 days. The high mortality among infected patients whose treatment is delayed beyond the first medical visit is based on the recent experiences of patients whose condition was not recognized at the initial medical visit, as well as on previous reports. These mortality rates assumed full compliance with medication regimens. We assumed that patients with true- and false-positive cultures would be admitted for intravenous antibiotics and close monitoring. According to a detailed description of anthrax survivors published in the *New York Times*,¹⁸ we assumed that 87% of patients would develop long-term complications from anthrax, such as shortness of breath, short-term memory loss, fatigue, and nightmares. The proportion of patients with inhalational anthrax among eligible patients was modeled throughout a 4-log range from 0.01% to 10%.

On the basis of a recently published report, we assumed that during a seasonal outbreak of influenza, the proportion of patients presenting with influenza-like symptoms who actually have influenza would be 66%.¹⁹ To perform a Bayesian revision for rapid diagnostic tests for influenza, we applied a sensitivity of 85% and a specificity of 95% according to data from recent reviews.^{20,21} For patients with influenza, we estimated a death rate of 18 per million, which was based on CDC data.²²

We chose to analyze the effects of treatment with ciprofloxacin because most physicians prescribed this medication at the outset of the 2001 attack until susceptibility information was known. Adverse outcome rates from treatment with ciprofloxacin (Table 1) were based on published clinical experience with ciprofloxacin and assumed full compliance for 3 or 60 days to maintain consistency with assumptions underlying our anthrax mortality estimates. Lower levels of compliance likely would lead to higher mortality rates and lower rates of antibiotic-related adverse events. The severity of adverse events was classified according to the definitions for mild, moderate, and severe used by the CDC in its investigation of prophylactic antibiotic outcomes

after the anthrax attack. Mild and moderate adverse events included abdominal pain, nausea, diarrhea, vomiting, and dizziness. Severe adverse events included life-threatening events or those that required hospitalization or intervention to avoid hospitalization.^{2,14,23-28} In the results, mild and moderate were combined into a single outcome: minor. The death rate from anaphylaxis to ciprofloxacin was assumed to be low, according to the rarity of anaphylaxis to ciprofloxacin and the infrequent occurrence of death from anaphylaxis.²⁹⁻³¹

We modeled 7 possible clinical outcomes for each strategy: (1) death; (2) survival with residual complications from inhalational anthrax after having had severe adverse effects from ciprofloxacin; (3) survival with residual complications from inhalational anthrax after having had mild to moderate adverse effects from ciprofloxacin; (4) survival with residual complications from inhalational anthrax; (5) survival after having had severe adverse effects from ciprofloxacin; (6) survival after having had minor adverse effects from ciprofloxacin; and (7) disease-free survival, which we defined as patients who had no complications from their respiratory illness or from antibiotic treatment.

We calculated the total numbers of deaths, anthrax complications, antibiotic adverse events, number of patients treated with ciprofloxacin, and ciprofloxacin patient-days for a cohort of 100,000 patients at 4 previous probabilities of anthrax (Table 2). According to these results, we then calculated the number needed to treat and the number needed to harm (Table 3). These are useful measures of clinical effectiveness and are equal to 1 divided by the risk difference. Thus, for number needed to treat, we determined the number of patients treated with antibiotics and the number of ciprofloxacin patient-days needed to avoid 1 death, and for number needed to harm, we determined the number of antibiotic adverse events needed to avoid 1 death.

We performed these calculations for each strategy compared with Treat None but also determined the number needed to treat and the number needed to harm when each strategy was ranked in order of treatment "cost" (eg, lowest to highest proportion treated) and compared to the 1 with the next lowest "cost." To determine the optimal strategy, all 7 outcomes were assigned a quality-adjusted life expectancy. Life expectancy for a 45-year-old patient was adjusted for the duration of morbidity on a scale ranging from 0 for death to 1 for perfect health (disease-free survival) according to symptoms associated with the Quality of Well-Being states (Table 1), a previously validated measure.³² For

example, utilities for adverse events were adjusted for the duration of antibiotic adverse effect. As an illustration, a patient who experienced a minor adverse event from antibiotics would have the utility associated with nausea for 3 days subtracted from their life expectancy of 34 years. Utilities for long-term residual complications from anthrax were based on the descriptions of the survivors of the 2001 anthrax attack and were mapped into Quality of Well-Being health states. Residual complications from anthrax include shortness of breath, fatigue, nightmares, and short-term memory loss.¹⁸ Ciprofloxacin patient-days were calculated assuming full compliance of 3 or 60 days among survivors. Patients who died despite treatment were assumed to have taken ciprofloxacin for the 2 days between onset of illness and death.

anthrax of 0.01%, 0.1%, 1%, and 10%. In all scenarios, Treat None results in the most deaths and the lowest proportion treated with ciprofloxacin and, hence, the fewest adverse antibiotic effects; conversely, Treat All always results in the fewest deaths but the highest rate of ciprofloxacin adverse effects. All other strategies were intermediate with respect to deaths and in the proportion treated with antibiotics.

In general, Treat None Pending Culture resulted in nearly as many deaths as Treat None because the delay in treatment led to a steep increase in mortality from anthrax. The remaining 3 strategies, Two Test, Influenza Testing, and Treat All Pending Culture, resulted in nearly as many deaths avoided as Treat All but with fewer ciprofloxacin-treated patients or fewer patient-days of treatment.

To clarify the trade-offs among the various strategies, Table 3 compares each strategy with Treat None and calculates the number needed to treat with antibiotics and the number of patient-days of antibiotics to avoid 1 death (number needed to treat) and the number of

RESULTS

Table 2 shows the results for hypothetical cohorts of 100,000 patients for probabilities of inhalational

Table 2. Patient outcomes calculated from the decision model for 6 strategies on hypothetical cohorts of 100,000 patients by probability of inhalational anthrax.*

Strategy	Deaths	Anthrax Complications	Severe Adverse Events	Minor Adverse Events	Treated With Ciprofloxacin, %	Ciprofloxacin Patient Days
Probability of inhalational anthrax=0.01%.						
Treat None	10.3	0.4	0	0	0.01	78
Treat None Pending Culture	8.9	0.9	6	1,139	2	120,550
Two Test	3	3.1	44	19,081	42	175,421
Influenza Testing	2.7	3.2	127	24,041	42	3,521,959
Treat All Pending Culture	2.7	3.2	104	45,198	100	414,446
Treat All	2.3	3.3	300	56,947	100	5,999,869
Probability of inhalational anthrax=0.1%.						
Treat None	91	4	0	0.1	0.1	780
Treat None Pending Culture	78	9	6	1,139	2	121,441
Two Test	19	31	44	19,047	42	179,281
Influenza Testing	15	32	126	23,997	42	2,531,743
Treat All Pending Culture	15	32	104	45,163	100	418,484
Treat All	11	33	300	56,902	100	5,999,368
Probability of inhalational anthrax=1%.						
Treat None	901	42	0	1	1	7,800
Treat None Pending Culture	766	95	6	1,135	3	133,828
Two Test	179	306	43	18,715	42	220,450
Influenza Testing	141	320	124	23,567	42	2,526,566
Treat All Pending Culture	141	320	103	44,813	100	458,885
Treat All	101	334	297	56,449	100	5,994,127
Probability of inhalational anthrax=10%.						
Treat None	9,001	420	0	10	10	78,000
Treat None Pending Culture	7,651	945	6	1,103	12	258,299
Two Test	1,781	3,061	37	15,386	43	632,127
Influenza Testing	1,401	3,197	101	19,265	43	2,480,787
Treat All Pending Culture	1,401	3,200	97	41,308	100	862,895
Treat All	1,001	3,343	273	51,920	100	5,941,928

*Results in Table 2 are based on assumptions and estimates in Table 1.

minor antibiotic adverse events and the number of severe antibiotic adverse events to avoid 1 death (number needed to harm). Treat None Pending Culture generally results in the lowest number needed to treat and number needed to harm, whereas either Treat All strategy results in the highest number needed to treat and number needed to harm. During influenza season, Two Test and Influenza Testing result in intermediate numbers needed to treat and numbers needed to harm with similar numbers needed to treat but better numbers needed to harm for Two Test than Influenza Testing because fewer patients would be treated empirically for 60 days.

Sensitivity Analyses

One-way sensitivity analysis involves varying the value of each parameter throughout a wide range of values to determine whether the optimal strategy changes. Figure 1 shows the results for varying the previous probability that an individual patient has inhalational anthrax, in which the morbidity and mortality related to anthrax and antibiotic treatment are measured on a

common quality-adjusted life expectancy scale. Because of antibiotic adverse effects, the 2 Treat None strategies were the most effective for previous probabilities of anthrax below 0.003%. When the previous probability of anthrax exceeded 0.003%, the empiric treatment strategies (Influenza Testing, Two Test, Treat All Pending Culture, and Treat All) became preferred because of the risk of increased mortality if treatment for suspected anthrax is delayed. For previous probabilities of anthrax above 2.2%, Treat All was best. For a summer month when the probability of influenza approaches zero, Figure 2 displays a similar 1-way sensitivity analysis. The Treat None strategies were best for probabilities below 0.007%, whereas Treat All was best for probabilities of anthrax above 2.2%.

At an anthrax previous probability of 0.01%, Two Test increased quality-adjusted life expectancy by only 10 quality-adjusted hours compared with Treat None. For previous probabilities of 0.1% and 1%, Treat All Pending Culture increased life expectancy by 6 and 60 quality-adjusted months, respectively, compared with Treat None. At a 10% previous probability, Treat All

Table 3. Trade-offs between deaths, adverse events, and ciprofloxacin patient-days of each strategy compared with Treat None.*

Strategy	NNT to Avoid 1 Death	Antibiotic Patient-Days to Avoid 1 Death	Minor Adverse Events to Avoid 1 Death (NNH)	Severe Adverse Events to Avoid 1 Death (NNH)
Previous probability of anthrax=0.01%.				
Treat None Pending Culture vs Treat None	1,421	86,051	814	4
Two Test vs Treat None	5,752	24,020	2,614	6
Influenza Testing vs Treat None	5,525	463,405	3,163	17
Treat All Pending Culture vs Treat None	13,157	54,522	5,947	14
Treat All vs Treat None	12,499	749,974	7,118	38
Previous probability of anthrax=0.1%.				
Treat None Pending Culture vs Treat None	153	9,281	88	0.5
Two Test vs Treat None	583	2,479	265	0.6
Influenza Testing vs Treat None	553	33,302	316	1.7
Treat All Pending Culture vs Treat None	1,316	5,496	594	1.4
Treat All vs Treat None	1,250	74,982	711	3.8
Previous probability of anthrax=1%.				
Treat None Pending Culture vs Treat None	15	934	8	0.04
Two Test vs Treat None	57	295	26	0.06
Influenza Testing vs Treat None	54	3,314	31	0.16
Treat All Pending Culture vs Treat None	130	594	59	0.14
Treat All vs Treat None	124	7,483	71	0.4
Previous probability of anthrax=10%.				
Treat None Pending Culture vs Treat None	1.4	134	0.8	0.004
Two Test vs Treat None	4.6	77	2	0.005
Influenza Testing vs Treat None	4.3	316	2.5	0.013
Treat All Pending Culture vs Treat None	12	103	5	0.013
Treat All vs Treat None	11	733	6	0.03

NNT, Number needed to treat; NNH, number needed to harm.

*Results in Table 3 are based on assumptions and estimates in Table 1.

increased life expectancy by 1.7 quality-adjusted years of life compared with Treat None.

Figure 3 presents a 2-way sensitivity analysis varying 2 parameters simultaneously: the previous probability of inhalational anthrax (0% to 1.5%) and the sensitivity (80% to 100%) of blood culture for anthrax. When the sensitivity of blood culture was below 95%, the empiric treatment strategies (Treat All if Influenza Test Negative and Treat All) were best. For blood culture sensitivities above 95%, blood culture could be used to stop therapy in patients whose culture results were negative (Treat All Pending Culture and Two Test) because false-negative cultures would be few. When the previous probability of anthrax exceeded 2%, Treat All dominated at any sensitivity of blood culture.

Two-way sensitivity analysis was also performed to examine the effect of varying the previous probability of inhalational anthrax and of influenza (Figure 4) to account for seasonal and geographic variation in influenza. For low probabilities of influenza, empiric treatment of anthrax was preferred if the previous probability of anthrax exceeded 0.1%. At higher probabili-

ties of influenza, testing for influenza to limit unnecessary exposure to antibiotics becomes preferred.

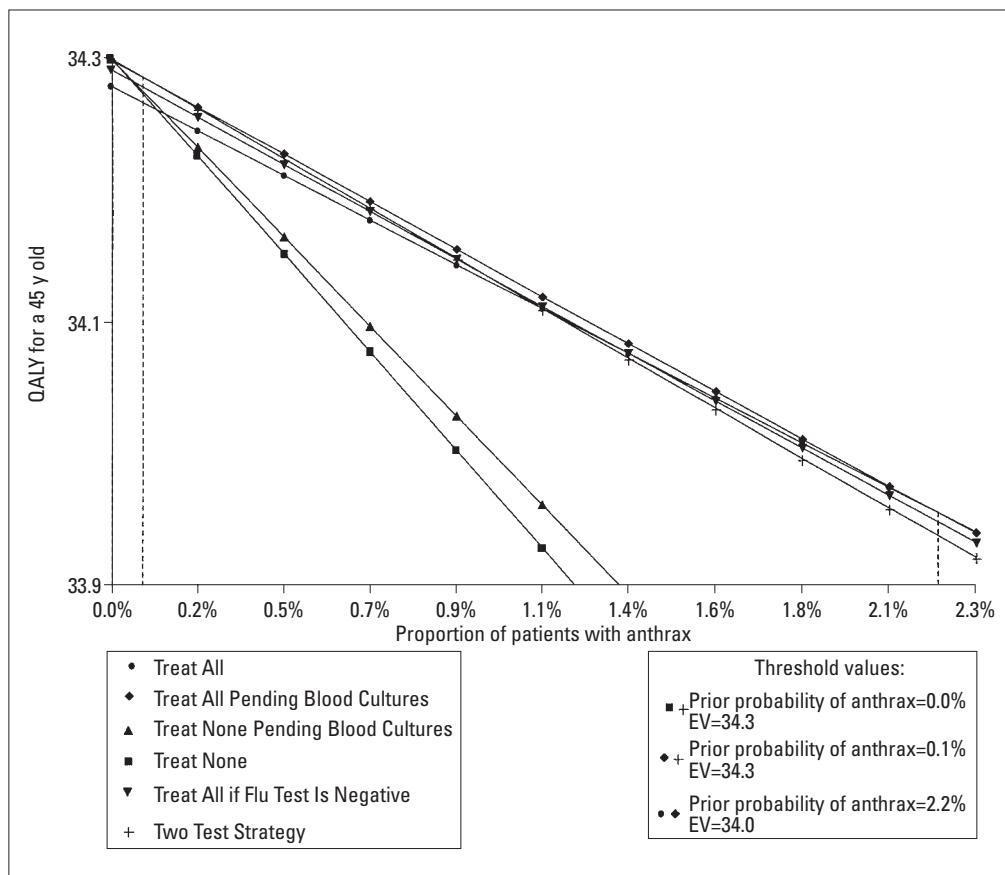
From an individual's standpoint, our analysis suggests that the clinical suspicion at which physicians should treat empirically (Two Test, Treat All Pending Culture, and Treat All) is low. For any likelihood above 0.003% during influenza season or 0.007% during the summer, physicians should treat because of the high mortality associated with delayed antibiotic treatment. These individuals, however, are likely to experience substantial antibiotic morbidity. For the 100,000 such persons treated when the proportion that has anthrax is 0.003%, we would expect more than 45,000 antibiotic adverse effects. From a public health standpoint, such strategies would result in more than 300,000 patient-days of ciprofloxacin.

LIMITATIONS

Estimating the previous probability of anthrax in a population of patients is difficult and is a main limitation of our analysis. A clinical prediction rule to estimate the

Figure 1.

One-way sensitivity analysis for the previous probability of anthrax ranging between 0% and 2.3% during an influenza outbreak (proportion of patients with influenza is 66%). The vertical dashed lines represent thresholds where the optimal strategy changed. Treat None is the best strategy until the previous probability of anthrax reaches 0.003%. Two Test is best between 0.003% and 0.09%. Treat All Pending Culture is best between 0.09% and 2.2%. Treat All is best above 2%. QALY, Quality-adjusted life year.

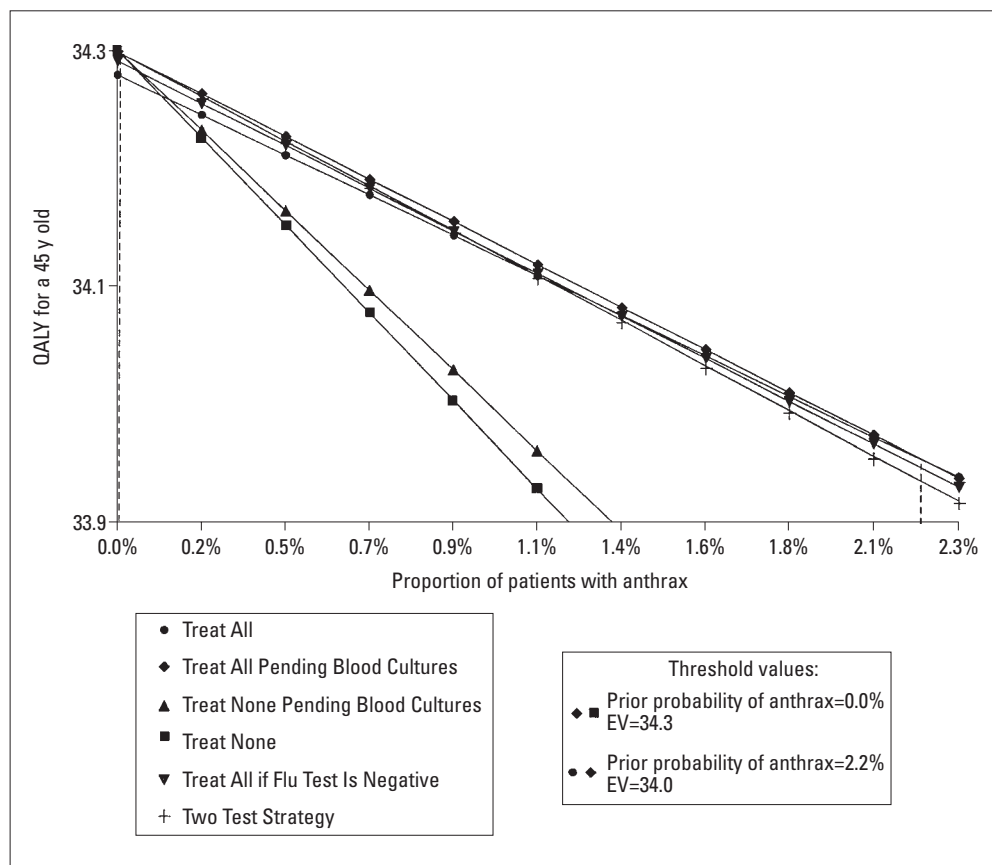


individual likelihood of anthrax would require patient-level data on history, physical examination, or simple diagnostic test results that distinguish patients with anthrax from those with influenza or influenza-like illnesses. Such a rule is not available, but a 3-tier screening protocol has been proposed according to reports of 28 patients with anthrax.³³ Even here, data on the presence or absence of combinations of symptoms were unavailable from reports of anthrax and from studies delineating the presentations of other diseases that could be confused with anthrax.³⁴ Improvement in the discrimination of anthrax from other diseases would likely require another bioterrorist attack with detailed characterization of patients with inhalational anthrax and of those who have other illnesses that could mimic anthrax. Moreover, such a clinical protocol would need to have a high sensitivity to reduce the postprotocol likelihood of anthrax to below 0.007% or 0.003%, depending on the season. Such research will require cooperation between hospitals and public health departments to enhance our abilities to estimate the previous probability of anthrax and other infectious agents.

Our model required the estimation of several parameter values. For example, the true sensitivity of blood culture is unknown but is thought to be high in patients with inhalational anthrax. Clinical knowledge about the presentation and outcome of victims of weaponized anthrax remains limited to a handful of recent cases and the Sverdlovsk experience, where the accuracy of the data is unknown.¹² There are many commercially available rapid diagnostic tests for influenza, but we chose the ones with the best testing characteristics to address efficacy even though many emergency departments may not have access to these tests. More experience with anthrax infection in human beings would be needed to improve model estimates but likely would occur only in the context of another attack. In the absence of more clinical data, decision analytic techniques provide guidance with the best available data. For now, our sensitivity analyses, evaluating the model throughout a wide range of values for each parameter, identify the critical variables, such as blood culture sensitivity. Decision analysis has

Figure 2.

One-way sensitivity analysis for the previous probability of anthrax ranging between 0% and 2.3% during a summer month when the proportion of patients with influenza is zero. Vertical dashed lines represent thresholds where the optimal strategy changed. Treat None is the best strategy until the previous probability of anthrax reaches 0.007%. Treat All Pending Culture is best from 0.007% to 2.2%. Treat All is best above 2.2%.



some inherent limitations as a methodology: the assumption of independent probabilities, the assumption that assigned utilities are fixed and do not vary from one patient to another, and the fluidity of economic cost.

DISCUSSION

Evaluating the trade-off between the consequences of antibiotic use and the consequences of failure to treat anthrax poses a dilemma to the treating physician. To

Figure 3.

Two-way sensitivity analysis at varying sensitivities of blood culture and previous probabilities of anthrax. Each point on the graph represents a unique combination of 2 values, so the shaded regions identify the preferred strategy for each combination.

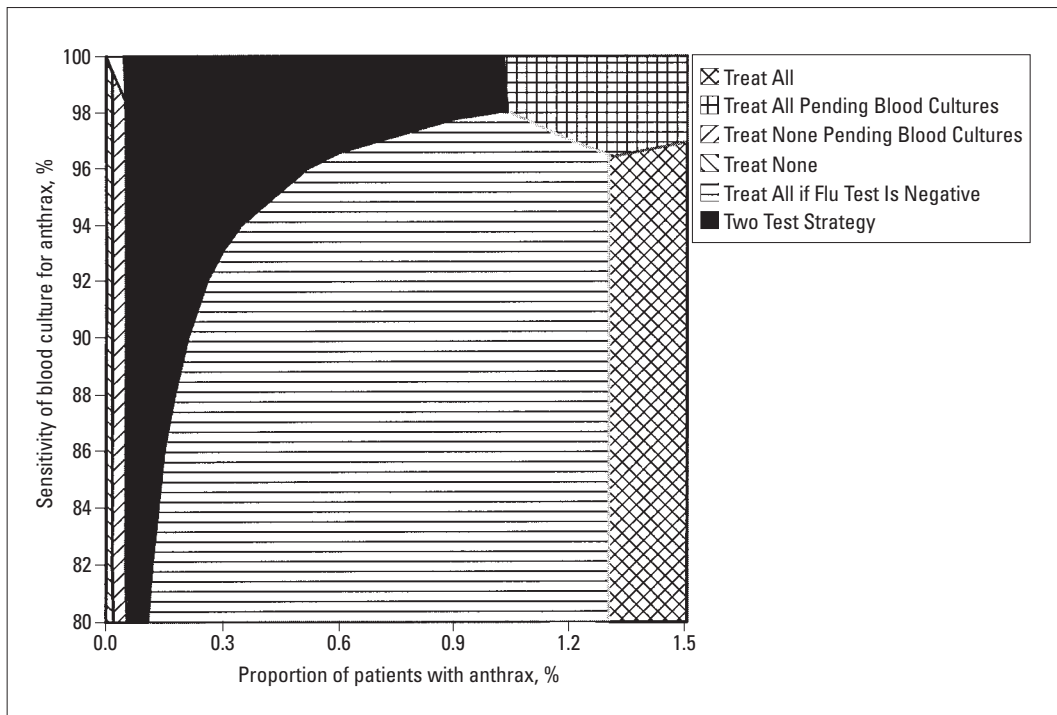
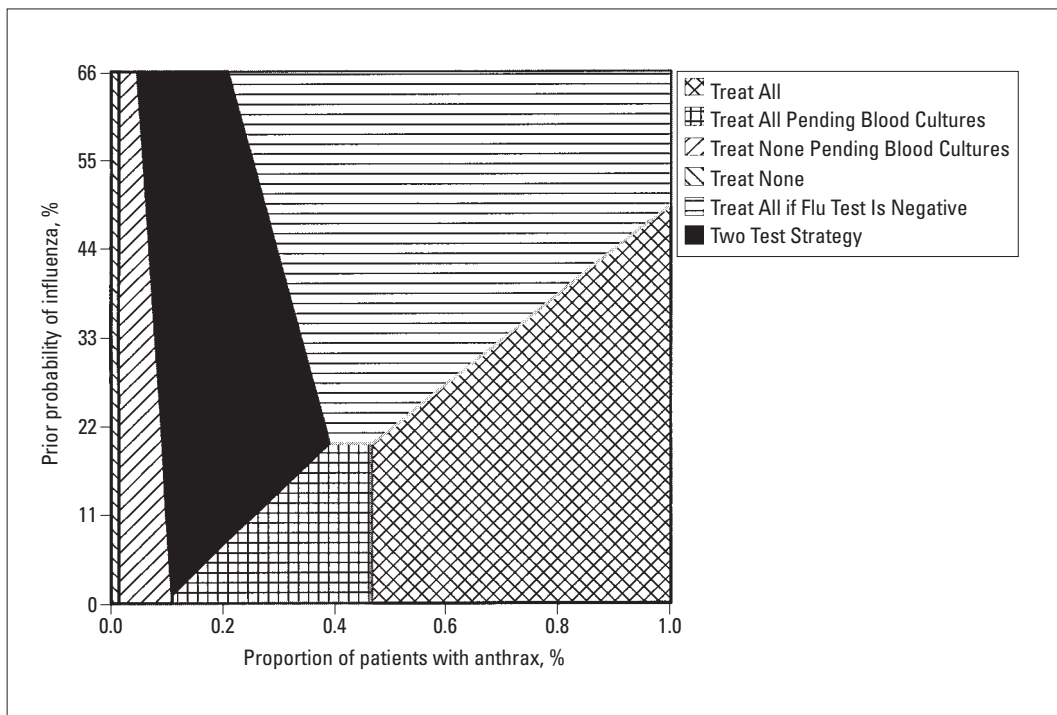


Figure 4.

Two-way sensitivity analysis of the performance of the 6 strategies at varying previous probabilities of influenza and at varying previous probabilities of anthrax. Each point on the graph represents a unique combination of 2 values, so the shaded regions identify the preferred strategy for each combination.



quantify this trade-off, our decision analysis examined the consequences of alternative clinical treatment strategies for patients with influenza-like illnesses in the setting of possible, but low probability, anthrax exposure. From the standpoint of an individual patient, ciprofloxacin is a safe drug with relatively minor adverse effects, whereas untreated anthrax is lethal. From a societal perspective, inhalational anthrax is rare, and massive use of ciprofloxacin will cause some adverse events, contribute to antibiotic resistance, and require resources. Because quantifying the public health impact of antibiotic use in a single patient is problematic, we have presented our results in terms of the number of ciprofloxacin patient-days and ciprofloxacin adverse events that result from each strategy, as objective measures.

The number needed to treat and number needed to harm analyses show the incremental benefits of the more aggressive treatment strategies. At the lowest previous probability of anthrax that we tested (0.01%), the number needed to treat to save 1 additional life is high, in the 1,000 to 100,000 range.³⁵ Many public health officials would consider this number excessive. To weigh the harms and benefits on a single scale, we adjusted length of life for the duration, morbidity, and possible mortality of antibiotics and anthrax. For previous probabilities of anthrax ranging from 0.01% to 10%, the optimal strategy increased life expectancy by 10 hours to 1.7 quality-adjusted life years compared with Treat None. For comparison, screening for ovarian cancer would increase life expectancy by 17 hours,³⁶ vaccination for measles, rubella, or pertussis would increase life expectancy by 3 days, and treatment of hypertension would increase life expectancy by about a year.³⁷ Thus, the crucial determinant is the likelihood of anthrax.

In the case of an intentional release of anthrax from a point source over a metropolitan area, there may be a well-defined plume with estimable risk of exposure according to geographic location.³⁸ In this type of scenario, clinicians could interact with public health officials to generate the previous probability that a patient was exposed to anthrax, according to the distance from exposure.

Rhinorrhea and productive cough are uncommon with anthrax, but other presenting symptoms for anthrax are consistent with influenza-like illness. Anthrax is rare, so developing a clinical prediction rule to estimate the likelihood of anthrax is difficult. Several published algorithms^{3,4} attempt to help practitioners

distinguish between anthrax and other respiratory illnesses, but the previous probability of anthrax in a given population remains unknown. In the absence of a clinical prediction rule based on symptoms and signs, an accurate rapid test for anthrax would be helpful.³⁹⁻⁴¹ Blood cultures appear to be sensitive but may delay treatment for up to 3 days, leading to substantial mortality in the interim. In the event that some patients return earlier than 3 days, either for a second opinion or for a culture that grew in less than 3 days, we would expect the overall patient-day usage of ciprofloxacin to decrease, but this decrease would not have other substantial effects on our results. Hence, early empiric antibiotic treatment for at least 3 days leads to the fewest deaths but relies on early detection of bioterrorist activity. Effectively applying the results of our decision analysis would be accomplished best under a model of cooperation between public health officials and the individual clinician, where local, regional, and national information could be used to estimate and communicate the previous probabilities and, hence, inform the decision about optimal treatment strategies. Syndromic surveillance efforts also may aid in the estimation of previous probabilities of anthrax.

In conclusion, by using the best available current data, our analysis allows clinicians and public health officials to weigh the risks and benefits of alternative treatment strategies for patients with flu-like symptoms and possible, but not definite, exposure to anthrax. Because of the relatively favorable therapeutic index for ciprofloxacin and the high mortality of anthrax, our findings tend to support early initiation of empiric antibiotics in patients with negative test results for influenza. The treat-first strategies are superior in preventing mortality across a 4-log range. If the probability of anthrax is low and the sensitivity of testing is high, our findings support starting a short course of ciprofloxacin until blood culture results are available. When the blood culture sensitivity is low or the previous probability of anthrax is suspected to be higher, more aggressive use of antibiotics is warranted. During influenza season, an accurate rapid test for influenza can avoid the need for blood cultures or empiric treatment for anthrax for many patients. These results highlight the need to develop a rapid accurate test for anthrax.³⁹⁻⁴¹ Improved surveillance methods⁴² and better methods for estimating the previous probability of anthrax exposure also are needed.

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