2 September 2003 | Annals of Internal Medicine | Volume 139 | Number 5 (Part 1)

Annals of Internal Medicine

www.annals.org | Established in 1927 by the American College of Physicians

'Accuracy of Screening for Inhalational Anthrax after a Bioterrorist Attack'

Annals of Internal Medicine. 2003;139:337-345

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Objective

Objectives: Bioterrorism using anthrax claimed 5 lives in 2001 and remains a potential public health threat. Furthermore, in the event of a bioterrorist attack, it may be difficult to distinguish inhalational anthrax from viral respiratory tract disease.

Evidence-based triage protocols to distinguish patients at risk for inhalational anthrax (IA) may improve early management of suspected cases in the setting of a large-scale anthrax attack.

Rationale

- The 2001 anthrax attacks, in which eleven people developed the inhalational form of the disease and five died, exposed a weakness in the United States' medical response to bioterrorism.
- Physicians were largely unprepared for the task of recognizing the early symptoms and signs of this extremely rare and rapidly progressive infection in ambulatory patients
  - Four of the eleven patients initially were sent home after being seen as outpatients or in an emergency department (ED) with diagnoses that included "viral syndrome", bronchitis, and gastroenteritis .
    - POTENTIAL SCREENING DILEMMA

Rationale

- A large-scale anthrax attack has the potential to cause casualties on a scale that would quickly overwhelm local and regional tertiary care treatment capacity
- Establishment of multiple mass prophylaxis centers physically distinct from hospital emergency departments (to prevent overcrowding and potential contamination) for rapid dispensing of antibiotics to affected populations and for identification of individuals suspected of having inhalational anthrax (IA)
- Triage protocols used in these settings would need to rely on presenting symptoms and signs, since laboratory or radiographic testing may not be available in non-hospital center.

Rationale

- Viral URI: Influenza, RSV, parainfluenza and rhinoviruses/coronaviruses are appropriate comparison conditions because of prevalence and potential similarity to IA.
  - Anthrax symptoms not compared to asymptomatic persons
    - Not a screening dilemma
  - Anthrax symptoms not compared with the severe acute illnesses
    - These patients would likely not participate in mass screening

Methods

- We reviewed English-language case reports of 28 IA cases from 1923-2001 and descriptive studies reporting the presenting symptoms and signs of patients with laboratory-confirmed influenza and influenza-like illness (ILI).
- We calculated the strength of association of selected clinical features for IA versus viral respiratory infections (influenza, ILI, and CAP) using likelihood ratios (with 95% CI) and used these to propose a triage protocol.
  - Development of diagnostic algorithms for rare diagnoses by using LR and by establishing hypothetical comparison groups 'populated' by common conditions has been previously reported
    - "Clinical Features that differentiate hantavirus pulmonary syndrome from three other acute respiratory illnesses" ***CID***: **1995;21:643-9**

Likelihood Ratios

- The Likelihood Ratio (LR) is the likelihood that a given test result would be expected in a patient with the target disorder compared to the likelihood that that same result would be expected in a patient without the target disorder
  - They have advantages over sensitivity and specificity because they are less likely to change with the prevalence of the disorder
  - LR can be calculated for several levels of the symptom/sign or test
  - LR can be used to calculate post-test probability for a target disorder

Likelihood Ratios

- We can assume that there are four possible groups of patients:
- group a, who are disease positive and test positive;
- group b, who are disease negative but test positive;
- group c, who are disease positive but test negative;
- group d, who are disease negative and test negative.
- Then:

  LR+ = sensitivity / (1-specificity) = (a/(a+c)) / (b/(b+d))

  LR- = (1-sensitivity) / specificity = (c/(a+c)) / (d/(b+d))

  Post-test odds = pre-test odds * LR

Likelihood Ratios

- For this analysis:
  - Comparison of signs and symptoms between a population presenting with either IA or a URI of another etiology such as influenza, ILI, or ACAP:
    - LR+ = (Prevalence of symptom or sign among IA cases)÷(Prevalence of same symptom or sign in influenza, ILI or CAP comparison group)

Summary of Historical and Contemporary Signs and Symptoms of IA

Table 1. **Summary of Symptoms and Signs at Initial Presentation: Historical versus Contemporary Patients with Inhalational Anthrax***

Clinical Feature	Historical Patients (References 21–24, 26–32) (n = 17)	Current Patients (References 4, 17) (n = 11)	Total (n = 28)
	← % →		
Symptoms			
Cough	71	91	79
Fever or chills	59	100	75†
Fever/chills or cough	94	100	96
Dyspnea	65	73	68
Chest pain	65	55	61
Nausea or vomiting	47	82	61
Fatigue or malaise	29	100	57‡
Headache	35	36	36
Other neurologic symptoms (e.g., confusion, syncope)	35	55	43
Abdominal pain	18	27	22
Sore throat	18	18	18
Rhinorrhea	18	9	14
Hemoptysis	18	9	14
Signs			
Abnormal lung examination on admission	82	78	81
Rales or ronchi	77	44	65
Dullness to percussion or decreased breath sounds	65	44	58
Tachycardia	77	91	82
Abnormal temperature (range, 35.3–40.6 °C)	59	73	64
Profuse diaphoresis	59	64	61
Tachypnea	59	45	54
Hypotension	12	9	11
Outcome			
Death	94	45	75§

* Seventeen historical patients had all the symptoms, signs, and outcomes presented in the table. Eleven current patients had all the symptoms; the signs of tachycardia, abnormal temperature, profuse diaphoresis, tachypnea, and hypotension; and the outcome. For the sign of abnormal lung examination on admission, there were 9 current patients. In the total column, all the symptoms; the signs of tachycardia, abnormal temperature, profuse diaphoresis, tachypnea, and hypotension; and the outcome refer to 28 patients. For the sign of abnormal admission lung examination, there was a total of 26 patients.
† Fisher exact test; $P < 0.05$.
‡ Fisher exact test; $P < 0.001$.
§ Fisher exact test; $P < 0.01$.

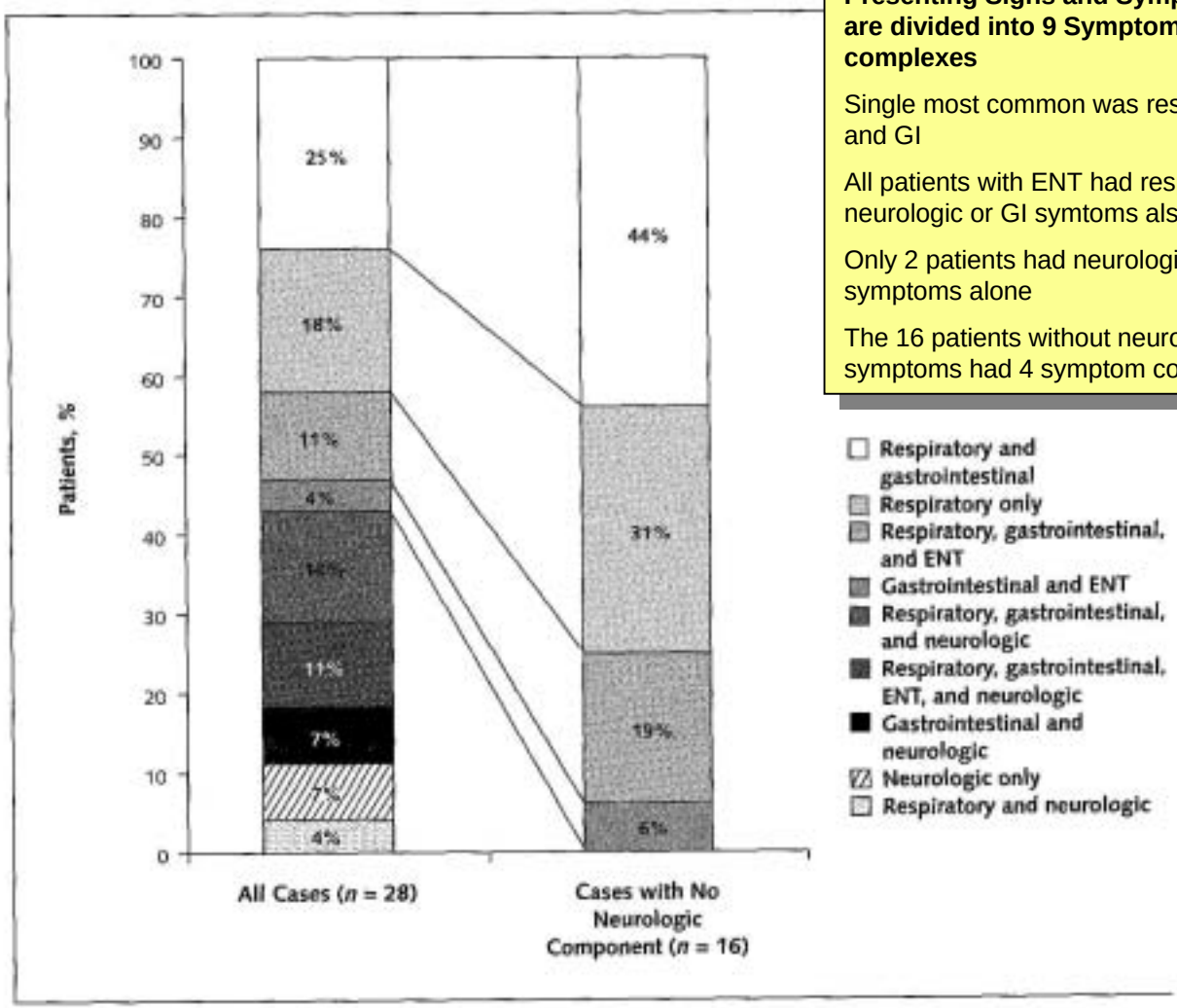
Fever/Chills or cough has a high prevalence in both historical and contemporary cases of Inhalational Anthrax

Abnormal lung examination has a high prevalence in both historical and contemporary cases of Inhalational Anthrax

Non-headache neurologic symptoms, dyspnea, UGI symptoms are notably present in IA

No contemporary or historical patients with IA had **fever or cough AND ENT symptoms** in **the absence** of other, more serious symptoms

Figure 1. **Presenting clinical symptoms of inhalational anthrax for case-patients with and without nonheadache neurologic symptoms between 1920 and 2001.**



Presenting Signs and Symptoms are divided into 9 Symptom complexes

Single most common was respiratory and GI

All patients with ENT had respiratory, neurologic or GI symtoms also

Only 2 patients had neurologic symptoms alone

The 16 patients without neurologic symptoms had 4 symptom complexes

Different proportions in the left and right columns for case-patients without neurologic symptoms reflect a change in the denominator only. Percentages may add up to more than 100% because of rounding. ENT = ear, nose, and throat.

Prevalence of Signs and Symptoms in Influenza

Table 2. **Prevalence of Signs and Symptoms in Influenza**

Clinical Feature	Studies of Patients with Laboratory-Confirmed Influenza					
	Monto et al. (35) (*n* = 2470)	Hall (33) (*n* = 59)	Carrat et al. (34) (*n* = 158)	van Elden et al. (37) (*n* = 40)	Oliveira et al. (38) (*n* = 35)	Total Patients
	← *n* (%) →					*n*/*n* (%)
Fever	1680 (68)	43 (73)	133 (84)	–	25 (71)	1881/2722 (68)
Feverish	2223 (90)	–	131 (83)	35 (88)	25 (71)	2414/2703 (89)
Cough	2294 (93)	47 (80)	132 (84)	39 (98)	29 (83)	2541/2762 (92)
Dyspnea	–	–	9 (6)	6 (15)	17 (49)	23/233 (14)
Chest pain	–	–	55 (35)	–	–	55/158 (35)
Nausea/vomiting	–	–	18 (12)	–	–	18/158 (12)
Rhinorrhea	2248 (91)	46 (78)	124 (79)	27 (68)	10 (29)	2455/2762 (89)
Sore throat	2075 (84)	32 (54)	101 (64)	32 (80)	–	2240/2727 (82)
Headache	2248 (91)	48 (81)	133 (84)	28 (70)	–	2457/2727 (90)
Abnormal lung examination	–	5 (9)	17 (11)	–	–	22/217 (10)

Symptoms are non-specific and include cough, headache, subjective fever, rhonorrhea, sore throat and fever

Note: Abnormal lung examination is noted in a minority of studies and patients

Since these studies did not collect uniform clinical data, the calculated prevalence rates for individual signs and symptoms presented here rely on different combinations of studies and therefore have varying denominators

Prevalence of Signs and Symptoms in Laboratory Documented Noninfluenza Viral Respiratory Tract Disease

Table 3. Prevalence of Signs and Symptoms in Influenza-Like Illness

Clinical Feature	Studies of Patients with Laboratory-Documented Noninfluenza Viral Respiratory Tract Disease				
	Monto et al. (35) (n = 1274)	Hall (33) (n = 177)	Carrat et al. (34) (n = 442)	van Elden et al. (37) (n = 39)	Total
	← n (%) →				n/n (%)
Fever	510 (40)	50 (28)	321 (73)	–	881/1893 (47)
Feverish	1134 (89)	–	331 (75)	33 (85)	1498/1755 (85)
Cough	1019 (80)	150 (85)	316 (72)	30 (77)	1515/1932 (78)
Dyspnea	–	–	27 (6)	11 (28)	38/481 (8)
Chest pain	–	–	103 (23)	–	103/442 (23)
Nausea/vomiting	–	–	54 (12)	–	54/442 (12)
Rhinorrhea	1032 (81)	157 (89)	299 (68)	23 (59)	1511/1932 (78)
Sore throat	1070 (84)	102 (58)	283 (64)	27 (69)	1482/1932 (77)
Headache	1134 (89)	70 (40)	326 (74)	22 (56)	1552/1932 (80)
Abnormal lung examination	–	28 (16)	49 (11)	–	77/619 (12)

ILI is associated with non-specific symptoms such as subjective fever, headache, cough, rhinorrhea, sore throat and fever

Note: Abnormal lung examination is noted in a minority of studies and patients

Table 4. Inhalational Anthrax Compared with Influenza, Influenza-like Illness, and Ambulatory Community-Acquired Pneumonia: Selected Clinical Variables*

Selected Symptoms and Signs	Inhalational Anthrax	Influenza	Positive Likelihood Ratio for Inhalational Anthrax vs. Influenza (95% CI)	Influenza-like Illness	Positive Likelihood Ratio for Inhalational Anthrax vs. Influenza-like Illness (95% CI)	Ambulatory Community-Acquired Pneumonia (44)	Positive Likelihood Ratio for Inhalational Anthrax vs. Ambulatory Community-Acquired Pneumonia (95% CI)
	n/n (%)			*n/n (%)*		*n/n (%)*	
Nonheadache neurologic symptoms	12/28 (43)	–	Presumed high	–	Presumed high	–	Presumed high
Abnormal lung examination	23/28 (81)	22/217 (10)	8.1 (5.3–12.5)	77/619 (12)	6.6 (5.0–8.7)	–	–
Dyspnea	19/28 (68)	23/233 (14)	5.3 (3.7–7.4)	38/481 (8)	8.6 (5.8–12.8)	97/149 (65)	1.0 (0.8–1.4)
Nausea or vomiting	17/28 (61)	18/158 (12)	5.1 (3.0–8.5)	53/442 (12)	5.1 (3.4–7.5)	57/149 (38)	1.6 (1.1–2.3)
Chest discomfort or pleuritic pain	17/28 (61)	55/158 (35)	1.7 (1.2–2.5)	103/442 (23)	2.6 (1.9–3.7)	72/149 (48)	1.3 (0.9–1.8)
Cough	22/28 (79)	2541/2762 (92)	0.9 (0.7–1.0)	1515/1932 (78)	1.0 (0.8–1.2)	135/149 (91)	0.9 (0.7–1.1)
Abnormal temperature	16/28 (57)	1881/2722 (68)	0.8 (0.6–1.1)	881/1893 (47)	1.2 (0.9–1.7)	115/149 (77)	0.7 (0.5–1.0)
Subjective fever or chills	21/28 (75)	2414/2703 (89)	0.8 (0.7–1.0)	1498/1755 (85)	0.9 (0.7–1.1)	126/149 (85)	0.9 (0.7–1.1)
Headache	10/28 (36)	2457/2727 (90)	0.4 (0.2–0.6)	1552/1932 (80)	0.4 (0.3–0.7)	100/149 (67)	0.5 (0.3–0.9)
Sore throat	5/28 (18)	2240/2727 (82)	0.2 (0.1–0.5)	1482/1932 (77)	0.2 (0.1–0.5)	–	–
Rhinorrhea	4/28 (14)	2455/2762 (89)	0.2 (0.1–0.4)	1511/1932 (78)	0.2 (0.1–0.5)	–	–

* Very dark gray area = presumed high positive likelihood ratio for inhalational anthrax; dark gray area = positive likelihood ratio > 3; medium gray area = positive likelihood ratio < 3 and > 0.3; light gray area = positive likelihood ratio < 0.3.

We calculated positive likelihood ratios (LR+) with 95% confidence intervals for the presence of selected signs and symptoms in IA versus influenza, ILI, and ACAP.

The LR+ is the multiplicative factor that increases or decreases the odds of having a target disease (in this case IA) as opposed to a comparison disease given the presence (LR+) or absence (LR-) of a clinical feature

LR+ = (Prevalence of symptom or sign among IA cases)÷(Prevalence of same symptom or sign in influenza and ILI comparison group)

Comparison Summary

- **Fever/Chills or cough** has a high prevalence in both historical and contemporary cases of Inhalational Anthrax and is commonly seen in Influenza and ILI
  - This would be a sensitive yet not specific screening tool for IA
- **Abnormal lung examination** has a high prevalence in both historical and contemporary cases of Inhalational Anthrax. This was uncommonly reported in Flu/ILI.
  - This is associated with an increased LR+ for IA
- **Non-headache neurologic symptoms, dyspnea, UGI symptoms** are notably present in IA and absent in Flu/ILI.
  - This is associated with an increased LR+ for IA
- No contemporary or historical patients with IA had **fever or cough AND ENT symptoms** in **the absence** of other, more serious symptoms

For those EXPOSED to Anthrax:

How are they best triaged in order to decide whether to administer prophylaxis as an outpatient vs. admission to a hospital for treatment?

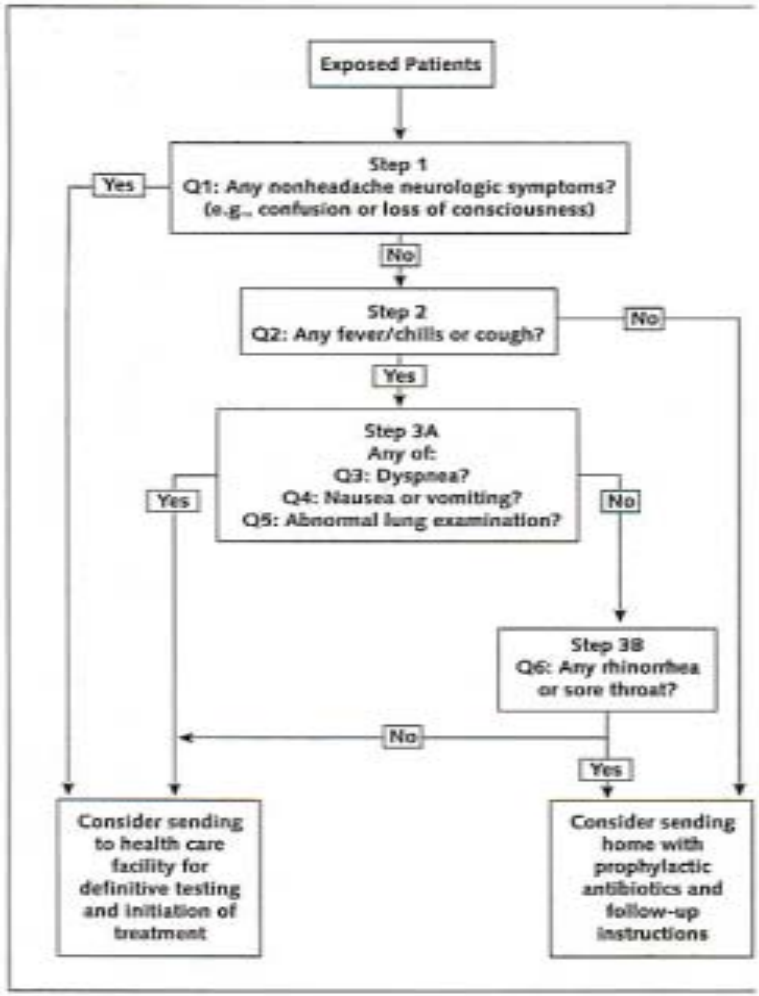
When symptoms are present, how do we differentiate early IA vs a viral respiratory tract infection during the course of triage and prophylaxis?

Neurologic Symptoms have a presumed high LR+

3 symptoms/findings help differentiate IA from Flu/ILI:

1. Abnormal lung examination
2. Dyspnea
3. UGI symptoms

Figure. Proposed three-tier screening protocol to identify potential early inhalational anthrax cases in the setting of a large-scale anthrax attack.



Fever/Chills or cough? Highly sensitive (yet not specific) single item for identifying patient's at risk for Anthrax

Absence of rhinorrhea/sore throat in the presence of fever/chiils/or cough is associated with an 4-5 increase in odds of IA

No contemporary or historical patients with IA had fever or cough AND ENT symptoms in the absence of other, more serious symptoms

Limitations

- Comparisons of IA with influenza or ILI are limited by the general paucity of clinical data on the presenting features of common viral respiratory diseases.
- Differences in baseline characteristics between these samples and the populations from which IA cases arose may introduce bias in the likelihood ratio calculations.
- These patients may not be representative of those who might be seen in an outpatient triage center in the event of an anthrax attack.
- Despite our use of historical cases, our analyses remain limited by the small number of adequately reported inhalational anthrax cases in the medical literature.
- Our review of historical anthrax cases revealed important limitations of contemporary case reports, chiefly the lack of descriptions of physical exam findings.
- We limited our literature review to English-language reports, which may have led to the exclusion of additional IA cases.

Criticisms

- Letter to the editor: *Annals of Internal Medicine*. 2003;139:337-345
- A key step in developing a diagnostic algorithm is verifying the probabilities by using the algorithm in an independent sample of patients
  - 'Circumstances forced Hupert et al to take a pragmatic, less satisfactory approach'
- On the utility of LR
  - 'That approach does not help to calculate a probability when several diagnoses in addition to anthrax are being considered. Therefore, I do not have confidence in the likelihood ratios shown in this article."
- "Analyses of alternative diagnoses is weak because published studies do not report the frequency of combination of findings that they found useful"
- "We do not know how the probability of anthrax at any decision point changes as the overall prevalence of anthrax changes in persons seen in emergency departments"

Conclusion

- Inhalational Anthrax has characteristic clinical features that are distinct from those seen in common viral respiratory tract infections.
- These symptoms include neurologic, gastrointestinal symptoms and dyspnea.
- Screening protocols based on these features may improve rapid identification of patients with presumptive inhalational anthrax in the setting of a large-scale anthrax attack.