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Distinguishing Influenza and Influenza-Like Illnesses from Inhalational Anthrax

Summary

The previous issue of the *Virginia Epidemiology Bulletin* described the prevention and control of influenza. This current article presents the reader with diagnostic considerations in distinguishing influenza and other influenza-like illnesses from inhalational anthrax. Much of this article is adapted from the November 9, 2001, issue of *Morbidity and Mortality Weekly Report* ("Notice to Readers: Considerations for Distinguishing Influenza-Like Illness from Inhalational Anthrax").[1]

Introduction

As autumn transitions into winter, most health care providers are anticipating and preparing for the usual increase in cases of influenza and other respiratory illnesses. What makes this flu season different from previous years, however, is the memory of the recent bioterrorism-related anthrax attacks and the specter of possible future attacks. From October 3 to November 28, the Centers for Disease Control and Prevention (CDC) has identified a total of 22 cases of anthrax in the U.S.[2] Of these, 11 have been inhalational anthrax (all confirmed), and 11 have been cutaneous anthrax (7 confirmed and 4 suspected) (Table 1). Five cases (all of which were inhalational anthrax) were fatal, for a case-fatality rate of 45% for inhalational anthrax. All other patients appear to have recovered or to be in the process of recovering.

As has already been observed by many physicians, it is likely that some patients this winter will be concerned that their flu-like symptoms may represent the early manifestation of inhalational anthrax infection; some of these patients, no doubt, will request antibiotics. Many physicians and other front-line providers will be faced with the new task of attempting to rule out early anthrax infection in patients with influenza or other influenza-like illnesses (ILIs). They may also be faced with the dilemma of whether or not to prescribe antibiotics to these patients.

Influenza and respiratory syncytial virus (RSV) infections generally peak during the winter; rhinoviruses and parainfluenza virus infections usually peak during the fall and spring; and adenoviruses circulate throughout the year. Respiratory infections associated with bacteria occur throughout the year; however, pneumococcal disease peaks during the winter, and mycoplasma and legionellosis are more common during the summer and fall.

The purpose of this article is to provide guidance to clinicians who may be faced with the task of differentiating influenza and other ILIs from inhalational anthrax.

Some Definitions

The term ILI generally refers to a nonspecific respiratory illness characterized by fever with cough and/or sore throat; other non-specific constitutional symptoms (e.g., malaise, fatigue, myalgias) may be present as well. While influenza is the prototype ILI, the majority of ILI cases are actually caused by a variety of other viruses, including rhinoviruses, RSV, adenoviruses, and parainfluenza viruses. Other causes of ILI include bacteria such as *Legionella spp.*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Streptococcus pneumoniae*.

Anthrax is a disease caused by the bacteria *Bacillus anthracis*, a sporulating gram-positive rod. The three commonly described types of anthrax disease in humans (cutaneous, inhalational, and gastrointestinal) reflect the different portals of entry for *B. anthracis*. As a bioterrorism threat, the inhalational form is of most concern due to its high case-fatality rate (approaching 100%, if untreated) and because the spores can be aerosolized. Inhalational anthrax typically presents as a biphasic illness, with an initial (prodromal) phase and a second (fulminant) phase. It is the prodromal phase of inhalational anthrax that may mimic the signs and symptoms of influenza and other ILIs.

In This Issue:

Distinguishing Influenza and Influenza-like Illnesses from Inhalational Anthrax 1

CDC Letter to Health Care Providers 4

Table 1. Summary of Anthrax Cases in the U.S., by Location of Exposure, 2001							
Case Status	**FL**	**NYC**	**NJ**	**DC**	**CT**	**VA**	**Total**
Confirmed	**2**	**5**	**5**	**4**	**1**	**1**	**18**
Cutaneous	0	4	3	0	0	0	7
Inhalational	2	1	2	4	1	1	11*
Suspect	**0**	**3**	**1**	**0**	**0**	**0**	**4**
Cutaneous	0	3	1	0	0	0	4
Inhalational	0	0	0	0	0	0	0
*Includes 5 deaths.							

Clinical Considerations

CDC has recently published a detailed description of the first 10 cases of bioterrorism-related inhalational anthrax in the U.S.[3] Table 2 lists the frequency of specific signs and symptoms among the anthrax cases in comparison with influenza and ILI from other causes. Fever, fatigue, malaise, and cough were common features among all groups. However, shortness of breath and nausea or vomiting occurred frequently in inhalational anthrax, but relatively infrequently in influenza and other ILIs. In comparison, rhinorrhea, a common feature of influenza (79%) and other ILIs (68%), was reported in only one of the 10 persons who had inhalational anthrax. Similarly, sore throat was reported in 64-84% of influenza cases and ILI from other causes but was found in only 2 out of 10 inhalational anthrax cases.

The case series by CDC also reveals some interesting ancillary findings. As shown in Table 3, all 10 persons with inhalational anthrax had abnormal chest radiographs on initial presentation. Seven had mediastinal widening, 7 had infiltrates, and 8 had pleural effusion. Similarly, 8 of 8 had abnormal chest computed tomography (CT) scans. In contrast, most cases of ILI are not associated with radiographic findings of pneumonia. Influenza-associated pneumonia occurs in approximately 1%-5% of community-dwelling adults with influenza and can occur in >20% of influenza-infected elderly. Influenza-associated pneumonia may be caused by the primary virus infection or, more commonly, by bacterial infection occurring coincident with or following influenza illness.

Laboratory Testing

No rapid screening test is widely available to diagnose inhalational anthrax in the early stages. Nasal swabs are not a good diagnostic test for anthrax and are not recommended for use in individual patients. They have been used primarily as part of epidemiologic investigations involving confirmed cases to help determine the extent of the exposure.

Blood cultures appear to be quite sensitive in diagnosing anthrax (blood cultures grew *B. anthracis* in all seven patients with inhalational anthrax who had not received previous antimicrobial therapy). However, blood cultures should not be obtained routinely on all patients with ILI symptoms who have no probable exposure to anthrax. They should be obtained for persons in whom bacteremia is suspected.

Rapid tests for influenza and RSV are available and, if used, should be conducted within the first 3-4 days of a person's illness when viral shedding is most likely. RSV antigen detection tests have a peak sensitivity of 75%-95% in infants but do not have enough sensitivity to warrant their routine use among adults. Among the rapid influenza tests available, two can be performed in any physician's office (Quidel Quickvue Influenza test and ZymeTx Zstatflu test®), and three are classified as moderately complex tests (Biostar FLU OIA; Becton-Dickinson Directigen Flu A+B; and Becton-

Table 2. Symptoms and Signs of Inhalational Anthrax, Laboratory-confirmed Influenza, and Influenza-like Illness (ILI) from Other Causes			
Symptom/Sign	**Inhalational anthrax (n=10)**	**Laboratory-confirmed influenza**	**ILI from other causes**
Fever or chills	100%	83% - 90%	75% - 89%
Fatigue/malaise	100%	75% - 94%	62% - 94%
Cough (minimal or nonproductive)	90%	84% - 93%	72% - 80%
Nausea or vomiting	90%	12%	12%
Shortness of breath	80%	6%	6%
Elevated temperature	70%	68% - 77%	40% - 73%
Chest discomfort or pleuritic chest pain	70%	35%	23%
Myalgias	60%	67% - 94%	73% - 94%
Headache	50%	84% - 91%	74% - 89%
Abdominal pain	30%	22%	22%
Sore throat	20%	64% - 84%	64% - 84%
Rhinorrhea	10%	79%	68%

Dickinson Directigen Flu A™). The clinical usefulness of these rapid influenza tests for the diagnosis of influenza in individual patients is limited because of their relatively low sensitivity (45%-90%). Therefore, the rapid influenza tests should not be performed on every patient presenting with ILI and they cannot be relied upon to differentiate influenza from inhalational anthrax. However, rapid influenza testing used in conjunction with viral cultures can help determine whether influenza viruses are circulating among specific populations, (e.g., nursing home residents).

Conclusion

In the vast majority of cases, a good history and physical exam should be all the clinician needs to distinguish influenza and other ILIs from inhalational anthrax. Barring any future anthrax attacks, and excluding those at high risk for anthrax exposure, the individual patient presenting with ILI is much more likely to have a naturally-acquired respiratory pathogen as opposed to inhalational anthrax. For the management of persons with a history of exposure to anthrax or who have an occupational or environmental risk for anthrax exposure, clinicians should refer to the most recent CDC guidelines[4,5] or visit CDC's bioterrorism web site at www.bt.cdc.gov.

References

1. CDC. Notice to Readers: Considerations for Distinguishing Influenza-Like Illness from Inhalational Anthrax. *MMWR* 2001;50:984-6.
2. CDC. Update: Investigation of Bioterrorism-Related Inhalational Anthrax — Connecticut, 2001. *MMWR* 2001;50:1077-9.
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4. CDC. Update: Investigation of Bioterrorism-Related Anthrax and Interim Guidelines for Clinical Evaluation of Persons with Possible Anthrax. *MMWR* 2001;50:941-8.
5. CDC. Notice to Readers: Interim Guidelines for Investigation of and Response to *Bacillus Anthracis* Exposures. *MMWR* 2001;50:987-90.

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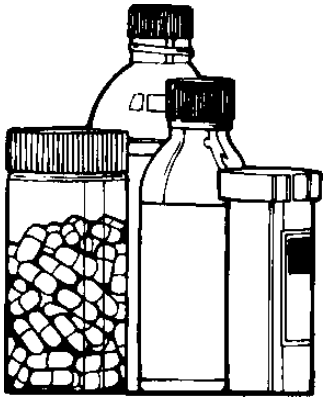

Table 3. Initial Clinical and Laboratory Findings in First 10 Patients with Bioterrorism-Related Inhalational Anthrax, October - November 2001*

Physical findings	
Fever (>37.8º C)	7/10
Tachycardia (heart rate >100/min)	8/10
Hypotension (systolic blood pressure <110 mm Hg)	1/10
Laboratory results	
White blood cell count (median)	9.8 x 10^3/mm^3
Differential - neutrophilia (>70%)	7/10
Neutrophil band forms (>5%)	4/5
Elevated transaminases† (SGOT or SGPT >40)	9/10
Hypoxemia (Alveolar-arterial oxygen gradient >30 mm Hg on room air O_2 saturation <94%)	6/10
Metabolic acidosis	2/10
Elevated creatinine (>1.5 mg/dL)	1/10
Chest X-ray findings	
Any abnormality	10/10
Mediastinal widening	7/10
Infiltrates/consolidation	7/10
Pleural effusion	8/10
Chest computed tomography findings	
Any abnormality	8/8
Mediastinal lymphadenopathy, widening	7/8
Pleural effusion	8/8
Infiltrates, consolidation	6/8

*Adapted from Jernigan JA, et al. Bioterrorism-Related Inhalational Anthrax: The First 10 Cases Reported in the United States. *Emerg Infect Dis* 2001;7:933-44.
†SGOT=serum glutamic oxalacetic transaminase; SGPT=serum glutamic pyruvic transaminase.

Flu Season 2001-02

CDC Letter to Health Care Providers

Continue to vaccinate throughout December, and beyond

December 3, 2001

Dear Colleague:

If you are seeing patients who need or want influenza vaccine, I urge you to continue to offer influenza vaccine throughout the month of December and beyond for as long as vaccine is available. As you know, distribution of a portion of this year's influenza vaccine was delayed, and insufficient quantities were available to meet all the demand during the optimal period for vaccination, October and November. **Thus, many individuals 65 and above and those with medical conditions placing them at high risk for complications from influenza remain unvaccinated.** In addition, other young, healthy persons who wish to reduce their risk from influenza this year were not vaccinated. And finally, many work-site clinics were cancelled due to unavailability of vaccine.

Now that vaccine production is complete, plentiful amounts of influenza vaccine are available for immediate shipment from the three primary suppliers of vaccine in the United States: Aventis Pasteur, Wyeth-Lederle, and Henry Schein (and its GIV and Caligor divisions) at current market prices. Other marketers may also have product available. I urge you to take advantage of this situation and continue to vaccinate until all persons who want or need influenza vaccine are vaccinated or the available supply is exhausted.

To date, influenza activity in the United States remains quite limited with only a couple of small outbreaks and a relatively small number of isolated cases reported. Influenza disease has peaked in January or later in 15 of the past 19 influenza seasons. **But even when influenza is occurring in a community, individual patients who have not yet been exposed, especially the elderly and those with risk conditions, can benefit from vaccination**. For businesses that want to protect their work forces and minimize absenteeism caused by influenza, work-site clinics in December or later can still help meet that objective. And the many young, healthy individuals who deferred vaccination earlier in the year can now be vaccinated.

The medical literature has documented that when health care providers recommend vaccination to patients, those patients almost always agree to be vaccinated. I hope that you will continue to offer influenza vaccine to your patients. If you require additional vaccine, I encourage you to contact a supplier and obtain the needed quantities. For those of you concerned about this year's Medicare payment rate for influenza vaccine, all Medicare carriers are now paying $7.12 per dose of vaccine (which exceeds the prices being offered by the three primary suppliers) plus an administrative fee that ranges from $3.00 to $5.79 depending upon locale.

Thank you for your continued effort to provide influenza vaccine to high-risk individuals and others who seek it, especially in light of the delays in distribution we have experienced these past two years. Please continue your efforts to help ensure that in 2001/2002, we achieve the highest influenza vaccine coverage levels ever and protect more individuals, especially the most vulnerable, against the ravages of influenza.

Sincerely,

Walter A. Orenstein, M.D.
Assistant Surgeon General Director
National Immunization Program

Cases of Selected Notifiable Diseases Reported in Virginia*

Total Cases Reported, September 2001

Disease	State	Regions NW	N	SW	C	E	Total Cases Reported Statewide, January through September: This Year	Last Year	5 Yr Avg
AIDS	41	9	7	2	4	19	686	577	729
Campylobacteriosis	77	22	13	22	6	14	433	457	505
E. coli O157:H7	8	6	1	0	1	0	46	56	56
Giardiasis	47	20	7	13	4	3	294	320	305
Gonorrhea	537	27	37	81	141	251	8070	7747	6988
Hepatitis A	15	0	4	1	4	6	104	118	141
B, acute	25	5	2	4	12	2	126	124	96
C/NANB, acute	0	0	0	0	0	0	0	3	12
HIV Infection	55	5	21	1	6	22	719	546	666
Lead in Children†	46	7	9	8	9	13	477	595	499
Legionellosis	2	1	1	0	0	0	19	27	20
Lyme Disease	9	2	4	0	1	2	103	124	71
Measles	0	0	0	0	0	0	1	2	2
Meningococcal Infection	2	0	0	0	1	1	33	36	39
Mumps	0	0	0	0	0	0	6	8	9
Pertussis	8	2	4	0	0	2	36	71	41
Rabies in Animals	71	26	10	8	20	7	349	450	450
Rocky Mountain Spotted Fever	1	1	0	0	0	0	16	5	17
Rubella	0	0	0	0	0	0	0	0	1
Salmonellosis	178	29	41	27	47	34	1077	768	832
Shigellosis	56	1	7	3	13	32	242	342	289
Syphilis, Early§	13	1	5	2	1	4	187	218	392
Tuberculosis	20	0	13	2	4	1	187	200	240

Localities Reporting Animal Rabies This Month: Accomack 2 raccoons; Augusta 1 raccoon, 1 skunk; Bath 1 bobcat, 1 skunk; Bedford 1 cat; Buckingham 1 raccoon, 1 skunk; Campbell 2 raccoons, 1 skunk; Charlotte 1 skunk; Chesterfield 1 bat, 2 raccoons, 1 skunk; Cumberland 1 skunk; Fairfax 1 bat, 2 foxes, 1 raccoon; Fauquier 1 bat; Fluvanna 1 dog; Frederick 1 raccoon; Fredericksburg 1 fox; Halifax 1 dog, 1 fox, 2 skunks; Hanover 1 bat, 1 raccoon; Henrico 1 skunk; Highland 1 skunk; James City 1 skunk; King and Queen 1 skunk; King George 1 fox; Loudoun 1 deer, 1 groundhog, 2 raccoons; Louisa 1 groundhog, 1 skunk; Nelson 1 raccoon; Nottoway 1 bat, 1 skunk; Page 1 bat; Pittsylvania 1 raccoon; Prince Edward 1 skunk; Prince George 1 bat, 1 cat; Prince William 2 raccoons; Roanoke City 1 skunk; Rockbridge 1 raccoon, 2 skunks; Rockingham 1 cat, 2 foxes, 1 raccoon, 2 skunks; Shenandoah 1 skunk; Stafford 1 bat; Tazewell 2 skunks; Virginia Beach 3 raccoons; Warren 1 skunk.

Toxic Substance-related Illnesses: Asbestosis 74; Lead Exposure 9; Nitrogen Oxide Poisoning 1; Pneumoconiosis 7.

*Data for 2001 are provisional. †Elevated blood lead levels ≥10µg/dL.

§Includes primary, secondary, and early latent.

Update: Influenza in Virginia

Since the last week of November, sporadic influenza activity has been reported in Virginia. To date, 3 laboratory-confirmed cases, all influenza type A, have been reported to the Office of Epidemiology. They were reported from the Richmond area.

Cases of Selected Notifiable Diseases Reported in Virginia*

Total Cases Reported, October 2001

Disease	State	Regions NW	N	SW	C	E	Total Cases Reported Statewide, January through October: This Year	Last Year	5 Yr Avg
AIDS	80	4	23	11	13	29	766	641	820
Campylobacteriosis	23	3	5	8	2	5	456	495	567
E. coli O157:H7	1	1	0	0	0	0	47	61	64
Giardiasis	34	7	11	6	5	5	328	355	357
Gonorrhea	1034	57	91	158	194	534	9094	8787	7875
Hepatitis A	8	1	1	2	4	0	112	130	160
B, acute	24	1	1	3	11	8	150	137	105
C/NANB, acute	0	0	0	0	0	0	0	3	13
HIV Infection	72	5	28	5	8	26	792	614	737
Lead in Children†	90	4	3	16	39	28	550	676	586
Legionellosis	1	0	0	1	0	0	20	31	26
Lyme Disease	11	4	5	1	0	1	114	133	80
Measles	0	0	0	0	0	0	1	2	4
Meningococcal Infection	3	0	0	0	2	1	36	37	43
Mumps	0	0	0	0	0	0	6	9	10
Pertussis	0	0	0	0	0	0	36	97	55
Rabies in Animals	50	16	6	5	11	12	399	509	512
Rocky Mountain Spotted Fever	7	4	1	0	2	0	23	7	21
Rubella	0	0	0	0	0	0	0	0	1
Salmonellosis	73	11	19	12	16	15	1149	847	959
Shigellosis	58	0	4	1	14	39	299	394	331
Syphilis, Early§	15	0	3	5	2	5	202	236	431
Tuberculosis	27	0	16	0	1	10	214	220	266

Localities Reporting Animal Rabies This Month: Accomack 2 raccoons; Albemarle 1 skunk; Amelia 1 raccoon; Augusta 1 skunk; Bath 1 skunk; Botetourt 2 skunks; Charlotte 1 skunk; Chesterfield 1 raccoon; Culpeper 1 skunk; Fairfax 1 bat, 4 raccoons; Fauquier 1 fox; Frederick 1 raccoon; Gloucester 2 raccoons; Halifax 2 skunks; Hanover 1 raccoon; Henrico 1 raccoon; James City 1 skunk; King and Queen 1 cat, 1 raccoon; King George 1 raccoon; King William 1 raccoon; Loudoun 1 skunk; Louisa 1 skunk; Mathews 1 raccoon; Nelson 1 raccoon; Nottoway 1 bobcat; Pittsylvania 1 raccoon, 1 skunk; Prince Edward 1 skunk; Prince George 1 raccoon; Rockingham 2 skunks; Shenandoah 1 fox, 1 skunk; Southampton 1 raccoon; Spotsylvania 1 skunk; Stafford 2 raccoons; Sussex 1 raccoon; Virginia Beach 1 raccoon; Wythe 1 cat; York 1 raccoon.

Toxic Substance-related Illnesses: Asbestosis 43; Lead Exposure 6; Mesothelioma 2; Pneumoconiosis 6.

*Data for 2001 are provisional. †Elevated blood lead levels ≥10µg/dL.

§Includes primary, secondary, and early latent.

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