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EMS Use of Benzodiazepines Safely Stops Status

ABSTRACT & COMMENTARY

Source: Alldredge BK, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001;345:631-637.

In this randomized, double-blind study, the authors attempted to determine the safety and efficacy of lorazepam and diazepam for out-of-hospital status epilepticus when administered by emergency medical service (EMS) paramedics. Adults with prolonged (lasting five minutes or more) or repetitive, generalized convulsive seizures received intravenous diazepam (5 mg), lorazepam (2 mg), or placebo. An identical second injection was given if seizures recurred or continued four minutes or more after the first injection. Patients were excluded if they had a pulse less than 60 beats per minute, a systolic blood pressure less than 100 mmHg, second- or third-degree atrioventricular block, sustained ventricular tachyarrythmia, asthma or chronic obstructive pulmonary disease, a history of long-term use of benzodiazepines, or sensitivity to benzodiazepines.

Of the 205 patients enrolled, 66 received lorazepam, 68 received diazepam, and 71 received placebo. Status epilepticus had been terminated on arrival to the emergency department (ED) in more patients treated with lorazepam (59%) or diazepam (43%) than patients given placebo (21%) (P = 0.001). After adjustment for covariates, the odds ratio for termination of status epilepticus by the time of arrival in the lorazepam group as compared with the placebo group was 4.8 (95% CI, 1.9-13.0). The odds ratio was 1.9 (95% CI, 0.8-4.4) in the lorazepam group as compared with the diazepam group, and 2.3 (95% CI, 1.0-5.9) in the diazepam group as compared with the placebo group. The rates of out-of-hospital respiratory or circulatory complications (such as manually assisted ventilation or intubation) after the study treatment was administered were 11% for the lorazepam group, 10% for the diazepam group, and 22.5% for the placebo group (P = 0.08). Most of these complications were transient and noted at the time of ED arrival; similar numbers of complications were seen in each group.

Of the 66 patients examined in the lorazepam group, 32 (48%) received two doses for a total of 4 mg. Of the 68 patients in the diazepam

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group, 27 (39%) received two doses for a total of 10 mg. There were noticeable differences in the study groups for causes of status epilepticus, but they did not reach statistical significance. Also, the randomization did not evenly disperse ethnic groups and race among the three study groups.

Finally, the authors' power calculations determined that the study had the power to detect a 25% difference between each study arm. The authors concluded that benzodiazepines are safe and effective when administered by paramedics for out-of-hospital status epilepticus in adults and that lorazepam is likely to be a better therapy than diazepam.

COMMENTARY BY RICHARD J. HAMILTON, MD, FAAEM, ABMT

Why is there such interest in the safety of benzodiazepines for status epilepticus? In spite of the intuitive notion that administering benzodiazepines to terminate a seizure is good practice, no study has demonstrated any particular benefit to the patient. Furthermore, studies have suggested that lorazepam distributes in the central nervous system more effectively than other benzodiazepines, imparting with its use a theoretical advantage to patients with status epilepticus or prolonged seizures.

These untested notions have been examined in this paper, but not without an obvious bias favoring lorazepam. The equivalent of 2 mg of lorazepam is 10 mg of diazepam, not 5 mg. It is interesting to me that the authors do not discuss or statistically analyze the finding that lorazepam patients received a second dose of drug slightly more often. In addition, if the power analysis concludes that the study can detect only a 25% difference in response rates, then clearly no conclusion can be drawn from the 17% difference between the two study drugs at this mismatched dose.

However, I commend the authors on an arduous and rewarding study and wish to underscore their truly important findings. They successfully demonstrate that benzodiazepines reduce out-of-hospital cardiorespiratory complications of status epilecticus and are safe to use in the field. Many EMS interventions that appear intuitive have failed to produce tangible benefit when studied closely. It is rewarding to find that field care makes a difference. I would encourage everyone to consider stocking a benzodiazepine in EMS units. In fact, diazepam may be a better drug for field use because it requires no refrigeration. In any case, it's not the drug that's important; the correct dose of any benzodiazepine in status epilepticus is the dose that works! ❖

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Point-of-Care Cardiac Enzyme Testing: Pushing the Envelope?

ABSTRACT & COMMENTARY

Source: McCord J, et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. *Circulation* 2001;104: 1483-1488.

The diagnosis of acute myocardial infarction (AMI) in the emergency department (ED) continues to be a challenge and remains a major source of malpractice occurrences in our specialty. Nearly half of all patients with AMI present with nondiagnostic electrocardiograms (ECGs), and anywhere from 2% to 5% are mistakenly discharged from the ED.[1] Serial cardiac marker testing, primarily creatine kinase with muscle and brain subunits (CK-MB) and, more recently, cardiac troponin I (cTnI)

and troponin T over a period of 6-18 hours, has been the primary means of excluding the diagnosis of AMI. However, this strategy leads to prolonged ED stays and unnecessary hospitalizations of large numbers of patients.

In this industry-sponsored study, investigators studied the utility of a point-of-care (POC) bedside assay (Biosite Diagnostics) for CK-MB, cTnI, and myoglobin, measured on initial presentation and at 90 minutes, three hours, and nine hours after ED arrival in patients evaluated for possible AMI. Results were compared against the final diagnosis of AMI as determined by agreement between two cardiologists reviewing the entire medical record and standard laboratory serial CK-MB levels over nine hours. Physicians caring for patients were blinded as to the bedside testing results.

Overall, 817 patients were enrolled in the study during the five-month period (excluding patients with ECG findings that led to reperfusion therapy and those in whom a full nine hours of serial CK-MB levels were not obtained). Of this group, 66% had nondiagnostic ST-T wave findings and 3% had normal ECGs. The majority of patients (78%) were admitted to either a telemetry bed or observation unit. Ultimately, 65 were diagnosed with AMI.

The investigators analyzed their results utilizing receiver-operating characteristic (ROC) curves to determine optimal cutoff values, which were: myoglobin greater than 200, CK-MB greater than 6.0, and cTnI greater than 0.4 ng/mL. The combination of abnormal myoglobin or cTnI at presentation or 90 minutes had the highest sensitivity (96.7%) and negative predictive value (99.6%) for AMI. Fifty-five of the 65 AMI patients had abnormal myoglobin or cTnI on presentation; an additional eight patients had elevations at 90 minutes. Two AMI patients were not identified until the nine-hour CK-MB marker was obtained. The investigators note that POC testing results were more rapidly available to physicians than standard laboratory results (24 minutes vs 71 minutes).

The investigators conclude that bedside testing for myoglobin and cTnI during the first 90 minutes can rapidly and accurately exclude AMI in patients presenting to the ED.

COMMENTARY BY THEODORE C. CHAN, MD, FACEP

In theory, the use of multiple cardiac markers for AMI is attractive in that it combines the strengths of each marker (myoglobin's early rise, high sensitivity, and low cardiac specificity; cTnI's high specificity, prolonged elevation, and superior prognostic value; and the traditional CK-MB). This work, along with another recent study,[2] suggests that a combination of markers can safely exclude AMI within 90 minutes of presentation.

However, a number of points must be kept in mind when considering this accelerated "rule-out." First, not all assays for these markers are equal. For example, troponin assays can measure a variety of different complex and free forms, thus affecting standardization and applicability. Second, while POC testing will undoubtedly improve turnaround times, significant amounts of staff time, space, and money are required to maintain these resources in the ED.

In this study, markers were used to predict the diagnosis of AMI, rather than clinical outcome. In fact, 11% of patients were diagnosed with unstable angina (rather than AMI), and it is unknown whether the rapid markers had any utility in predicting subsequent short-term cardiac events. Methodologically, the strength of the study is limited because abnormal cut-off values were not determined until after the data was analyzed.

It is interesting that the investigators found excellent utility with myoglobin, which has been a source of controversy in the emergency medicine literature. As the investigators point out, such utility may have resulted from the later presentation (median 4.3 hours) of patients. It also is interesting to note that there was such little utility for POC CK-MB when laboratory CK-MB was one of the factors used for the diagnosis of AMI. This finding continues to affirm the utility of other, newer cardiac markers, particularly troponin, recently incorporated into the American College of Cardiology and American Heart Association guidelines on acute coronary syndromes.[3] ❖

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Chest Pain in the ED—What to Do with the Younger Folks?

ABSTRACT & COMMENTARY

Source: Walker NJ, et al. Characteristics and outcomes of young adults who present to the emergency department with chest pain. *Acad Emerg Med* 2001;8:703-708.

To better characterize the optimal evaluation of younger chest pain (CP) patients, Walker and colleagues studied 487 patients younger than age 40 with acute CP during 527 visits to the emergency department (ED)

over a 15-month period at the University of Pennsylvania. Clinical examination, electrocardiograms (ECGs), and cardiac enzyme tests were performed in each case. Patients using cocaine were excluded. ECGs were interpreted by attending ED physicians. Enzymes were interpreted as indicative of acute myocardial infarction (AMI) or unstable angina (USA) if CK-MB exceeded 10 ng/mL or 5 ng/mL, respectively, and/or troponin-I exceeded 2 ng/mL or 0.3 ng/mL, respectively. All patients were followed during ED stays or hospital admission, and were contacted 30 days later and asked if they had experienced any occurrence of acute coronary syndromes (ACS).

Ages ranged from 25 to 40 years, with 71% between the ages of 30 and 39 years. Sixty percent were female, and 73% African American. Forty-two percent had no risk factors for coronary artery disease (CAD), while 37% were smokers and 22% were hypertensive. Pressure-like or squeezing CP was present in 42%, sharp or stabbing CP in 35%, and radiation of pain to the neck or left arm in 31%. Normal or nondiagnostic ECGs were documented in 93% of cases, whereas 5% had early repolarization, 1% had bundle branch block, and 2% had evidence of ischemia or infarction.

During hospital evaluation or at 30-day follow-up, 35 of the 169 patients (21%) had further work-up for CAD, revealing five of 23 stress sestamibi scans that were abnormal and five of 12 coronary angiograms with greater than 70% stenoses. By all criteria available, an ACS (AMI or USA) was documented in a total of 25 patients, for an event rate of 4.7% (95% CI, 2.9-6.5%). Eight patients (1.5%) had AMI, five had percutaneous transluminal coronary angioplasty (PTCA) or stenting, none required coronary artery bypass graft (CABG), and four (0.7%) died—one of cardiac arrest, one with metastatic carcinoma, one with end-stage congestive heart failure, and one with diabetes and end-stage renal failure in a nursing home. Thirty-day survival was 99% for the cohort.

COMMENT BY MICHAEL FELZ, MD

The authors conclude that acute CAD-related events are unusual in patients with acute CP who are younger than age 40. They emphasize certain differences in demographics and risk factors for younger patients. For example, 81-94% of AMIs prior to age 40 occur in males.[1] Risk factors in younger patients include smoking (62-94%), family history (15-84%), and hyperlipidemia (20-61%), while diabetes is rare (12%).[2] At angiography, younger AMI patients usually have single-vessel CAD, while 14-20% of cases have normal coronary anatomy, raising the question of vessel spasm.[3]

Based on the data in this study, young patients with CP have a 4.7% risk of ACS, including a 1.5% risk of AMI. Taken in obverse, this translates into a 95.3% likelihood that the under-40 CP patient in the ED has no CAD-related event, and a 98.5% chance that AMI is not present. The likelihood of survival of such patients exceeds 99% at 30 days, according to this analysis. My response to this study is three-fold. First, the rarity of ACS in younger patients is consistent with my experience in 23 years of primary care practice and teaching. Costochondritis, reflux, and muscle strain are vastly more common than CAD in this age group. Yet I remain vigilant, remembering a handful of patients younger than age 40, both men and women, who had impressive ST elevation, alarming enzyme levels, greater than 90% stenoses on catheterization, and emergent PTCA or stenting. Thankfully, nearly all recovered rapidly and went to work on risk factor modification. It is noteworthy that the incidence of AMI in cocaine-associated CP has been reported to be 6%,[4] a nearly identical rate to that in the current series. Second, the current study evaluated predominantly young, African Amercan females. Whether these data can be extrapolated to the general population is not clear. Finally, I would have been interested in physical exam information on these patients, especially how often focal, reproducable chest wall tenderness was present. This common finding in younger patients, and in older ones as well, is reassuring for exclusion of CAD, especially when the ECG is normal.[5] ❖

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Special Feature

Bioterrorism: Potential Microbiological Agents

By Maged Botros, MD

The use of biological warfare is not a new concept to Americans. Our very existence stems from a covert operation by early settlers to sell smallpox-laden

blankets to Native American Indians. It is ironic that this same weapon now has many fearing their own mortality in this land. As recently as during the first and second World Wars, America and other countries operated secret development programs for offensive biowarfare. However, in 1969 the United States terminated its offensive biological weapons program for microorganisms and has concentrated its efforts on defensive measures only.[1] In 1975, the Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriologic and Toxin Weapons and on their Destruction went into effect.[1] Despite this treaty, bioterrorism is still a real threat to humanity. To date, the former Soviet Union, Iraq, North Korea, Syria, and South Africa are signatories who are believed to have violated the treaty.[1] This article will concentrate on three potential organisms that may be encountered during an act of bioterrorism: Variola major (smallpox), *Yersinia pestis* (pneumonic plague), and *Bacillus anthracis* (inhalation anthrax).

Smallpox

Although smallpox was discounted in the past as a "rational" weapon because its spread might be uncontrollable, recent events have challenged this traditional belief. Some terrorists may be undeterred by the havoc that would result from the reintroduction of smallpox into society, the younger half of which is unvaccinated and the remainder probably not having retained immunity. Because a large proportion of the world's population is not immune to smallpox, no effective treatment exists, and the case fatality rate is between 20% and 50%, the smallpox virus is a potentially dangerous agent of biologic terrorism.[2]

Smallpox is caused by the variola virus, which is an orthopoxvirus that infects only humans. Smallpox has an incubation period of 12-13 days that is followed by the abrupt onset of fever, malaise, headache, and backache.[4] The exanthem appears within 2-4 days and evolves from macules to papules to vesicles to pustules, and finally, crusts form. All the lesions are in a similar stage at any one time. The initial lesions occur on the palms and soles and feel firm (like BB pellets) when palpated.[3] The rash is highly characteristic, with profuse involvement of the face, forearms, and lower legs, and relative sparing of the trunk and abdomen. After 8-9 days, the pustules become umbilicated and form crusts. Although this rash may be mistaken for chickenpox (varicella), its distribution and evolution (all the lesions being in the same stage) are unique.[4]

If the diagnosis of smallpox is considered, the patient should be placed immediately in respiratory isolation, patient contacts should be identified, and the Centers for Disease Control and Prevention (CDC) should be contacted. Spread of smallpox generally occurs through intimate contact, with entry through the respiratory tract, so population density as well as immunity affects the extent of spread. Infected people are contagious from the onset of illness until the last crusts are gone. In the United States, routine vaccination continued until 1971; the vaccine was given sporadically after this until 1983, when vaccine producers were urged to reserve the vaccine for military personnel only.[4] Given recent concerns about bioterrorism, there is a push in Congress to reinstate the smallpox vaccination program.

Although no proven treatment for smallpox exists, recent in vitro data and studies in animals suggest that intravenous cidofovir may shorten the course of disease in infected individuals. Clinical trials to evaluate intravenous cidofovir therapy are being planned, but until then only isolation, supportive care, and treatment of complicating bacterial infections are indicated.[2]

Plague

Since 1977 there have been 18 documented cases of *Yersinia pestis*, the etiologic agent for plague, in the United States. *Y. pestis* has three separate clinical presentations: bubonic plague (acute regional lymphadenitis), septicemic plague (blood-borne), and pneumonic plague (pulmonary). The most common clinical form is bubonic plague, which historically was contracted from rodents or cats infested with fleas carrying the microorganism. Although this would be an effective medium for bioterrorists to utilize, the pneumonic form of the plague seems to be a more likely choice given that direct, person-to-person transmission occurs only in the setting of pneumonic plague.[5]

Bubonic plague generally occurs after an incubation period of 2-6 days and results in the sudden onset of fever, chills, weakness, and headache. Shortly thereafter, patients note an intensely painful swelling in one region of lymph nodes, usually the groin, axilla, or neck. This swelling, or bubo, is typically oval, varying from 1 to 10 cm in length; the overlying skin is elevated and warm and may appear stretched or erythematous. The bubo itself is firm, extremely tender to palpation, and non-fluctuant. In the absence of therapy, the disease progresses rapidly to a septicemic phase, with marked toxicity, prostration, and shock.

Pneumonic plague may result from primary person-to-person transmission or from hematogenous spread of *Y. pestis* to the lung in patients with bubos.[5] Patients develop cough and chest pain and may have hemoptysis. Radiographically, there is patchy bronchopneumonia or confluent consolidation. Sputum is purulent and contains *Y. pestis*. Pneumonic plague is highly contagious by airborne transmission; persons inhaling the organism, from either an infected person or an animal, are susceptible to infection. The diagnosis is confirmed by using Gram's stain or fluorescent antibodies to isolate *Y. pestis* from blood, a bubo aspirate, or from sputum. The Gram's stain will reveal leukocytes and gram-negative coccobacilli.

Untreated bubonic plague has an estimated mortality rate of more than 50% and can evolve into a fulminant illness complicated by septic shock.[5] Pneumonic plague is invariably fatal when antibiotic therapy is delayed more than one day after the onset of illness; therefore, the early institution of effective antibiotic therapy is mandatory after appropriate cultures. Streptomycin should be administered intramuscularly in two divided doses daily, totaling 30 mg/kg of body weight per day for 10 days. Doxycycline 200 mg IV once, followed by 100 mg orally twice a day, is a satisfactory alternative.[6] Given the risk of person-to-person transmission, all patients with suspected pneumonic plague should be placed on strict standard and airborne precautions. Close contacts of suspected or confirmed pneumonic plague cases should be provided with chemoprophylaxis with doxycycline.[5] A formalin-killed vaccine is commercially available but does not protect against the pneumonic form of the disease. New, subunit vaccines for plague are currently under development.[5]

Anthrax

B. anthracis, the etiologic agent responsible for anthrax, is a large, aerobic, gram-positive rod with a centrally located spore. There are three predominant clinical forms of anthrax which are determined by the route of entry. Cutaneous anthrax constitutes more than 95% of reported cases and results from entry of spores through skin abrasions. The remaining 5% of cases are due to gastrointestinal (never reported in the United States) or inhalation anthrax.[7]

Cutaneous anthrax becomes apparent within five days of exposure, beginning as small, painless, often pruritic papules that enlarge and become vesicular within 1-2 days. Fever, malaise, and regional adenopathy often are associated features. The lesion ulcerates near the end of the first week and progresses to the black eschar responsible for the name of this disease (from the Greek word for coal, describing the characteristic color and appearance of the eschar).[7] If it is recognized and treated promptly, the disease is rarely fatal. The case-fatality rate of cutaneous anthrax is 20% without antibiotic treatment and less than 1% with antibiotic treatment.[8]

Inhalation anthrax results from the inhalation of a large sum of aerosolized spores. The estimated infectious dose that is required to cause inhalation anthrax in humans has been estimated to be roughly 8,000-50,000 spores.[8] The large load that is required is believed to be why person-to-person transmission of inhalation anthrax has never been documented.

Aerosolized anthrax spores greater than 5 micrometers in size are deposited in the upper airways (pharynx, larynx, and trachea) and effectively trapped or cleared by the mucociliary system. Spores between 2 micrometers and 5 micrometers in size are able to reach the alveolar ducts and alveoli. These spores are engulfed by pulmonary macrophages and transported to mediastinal and hilar lymph nodes.[7] Following a period of germination, a large amount of anthrax toxin is produced. Regional lymph nodes are quickly overwhelmed and the toxin finds its way into the systemic circulation, resulting in edema, hemorrhage, necrosis, and septic shock; death soon follows. Since the organisms are initially transported to mediastinal lymph nodes, a major site of involvement is the mediastinum. Edema and lethal toxin cause the massive hemorrhagic mediastinitis that is typical of inhalation anthrax.[7]

Inhalation anthrax has an incubation period of about six days. This is followed by an initial stage that results in four days of myalgia, malaise, fatigue, nonproductive cough, sensation of retrosternal pressure, and fever. The second stage, which usually lasts 1-2 days, develops suddenly with the onset of acute respiratory distress, hypoxemia, and cyanosis, and usually culminates in death.[7] A chest radiograph typically shows normal lung parenchyma with a widening of the mediastinum and pleural effusions.

Diagnosis of inhalation anthrax during the first stage is difficult. The symptoms and signs of disease are similar to the common cold or a viral infection and often are mistaken for the latter diagnoses. Advanced disease may be recognizable by virtue of the shock-like symptoms and characteristic chest radiograph abnormality, but by then the disease progression is rapid and treatment is less likely to be effective.

Although a vaccine exists for human use, it currently is recommended only for military use and for patients with documented exposure. Primary vaccination consists of three subcutaneous injections at 0, two, and four weeks, and three booster vaccinations at six, 12, and 18 months. To maintain immunity, the manufacturer recommends an annual booster injection.[1]

Postexposure prophylaxis for exposure to *B. anthracis* consists of chemoprophylaxis and vaccination. Oral fluoroquinolones (e.g., ciprofloxacin 500 mg twice daily) are the drugs of choice for adults, including pregnant women. If fluoroquinolones are not available or are contraindicated, doxycycline (100 mg twice daily) is acceptable. Children should receive prophylaxis with oral ciprofloxacin or oral doxycycline. Since tetracyclines and fluoroquinolones have well known side effects, children should receive oral amoxicillin as soon as penicillin susceptibility of the organism has been confirmed. If exposure is confirmed, prophylaxis

should continue for four weeks if three doses of vaccine have been administered, or for eight weeks if vaccine is not available.[1,9]

Conclusion

A biologic attack on a major city can approximate the devastation of a nuclear weapon. The Office of Technology Assessment estimated that 100 kg of anthrax spread over Washington, DC, could kill between 1 million and 3 million people. When comparing this to nuclear warfare, a 1-megaton nuclear warhead detonating over Washington would result in only 759,000 to 1.9 million deaths.[1] Biologic weaponry also has the added advantage of easier acquisition, storage, and transport. It is for these reasons that the fear of bioterrorism has surfaced as a major concern for the American public as well as health care workers. For health care workers to fight bioterrorism, we need to become familiar with the possible agents that may be used and become comfortable with aiding in the early recognition, reporting, and treating of these diseases. *(Dr. Botros is an Assistant Professor of Emergency Medicine at Temple University School of Medicine, and serves as the Assistant Research Director for Sponsored Projects within the Department of Emergency Medicine at Temple University Hospital, Philadelphia, PA.)* ❖

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CME Questions

1. For prehospital cessation of seizures in patients with status epilepticus:
a. diazepam is clearly superior to lorazepam.
b. lorazepam is clearly superior to diazepam.
c. benzodiazepines are clearly superior to placebo.
d. benzodiazepines are no better than placebo.

2. When confronted by a chest pain patient younger than age 40 in the ED, physicians should:
a. dismiss CAD as too rare to consider in such cases.
b. implicate all cases as due to cocaine abuse.
c. expect abnormal ECGs and enzymes in 30-40% of cases.
d. estimate the likelihood of CAD to be approximately 5%.

3. Smallpox differs from chicken pox in that the characteristic rash of smallpox:
a. is hemorrhagic.
b. never crusts.
c. evolves so that all lesions are simultaneously in the same phase.
d. spares the face.

4. Which of the following is *not* felt to be contagious by aerosol route, and thus does not mandate immediate respiratory isolation?
a. Smallpox
b. Anthrax
c. Pneumonic plague

5. Drugs most effective in the prophylactic treatment of anthrax exposure include which of the following pairs?
a. Dicloxacillin and cephalexin
b. Doxycycline and cephalexin
c. Dicloxacillin and ciprofloxacin
d. Doxycycline and ciprofloxacin

6. A methodological flaw in the study by McCord and colleagues on point-of-care cardiac enzyme testing for acute myocardial infarction that limits the application of the data to clinical practice is the:
a. choice of troponin I rather than troponin T.
b. sole reliance on myoglobin rather than combining myoglobin with troponin I.
c. exclusion of all patients presenting without chest pain.
d. post-hoc determination of threshold values for cardiac enzymes.

Emergency Medicine Alert CME Objectives

To help physicians:

- Summarize the most recent significant emergency medicine-related studies;
- Discuss up-to-date information on all aspects of emergency medicine, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to emergency department care; and
- Evaluate the credibility of published data and recommendations.

Reciprocal Acuity

By Ken Grauer, MD

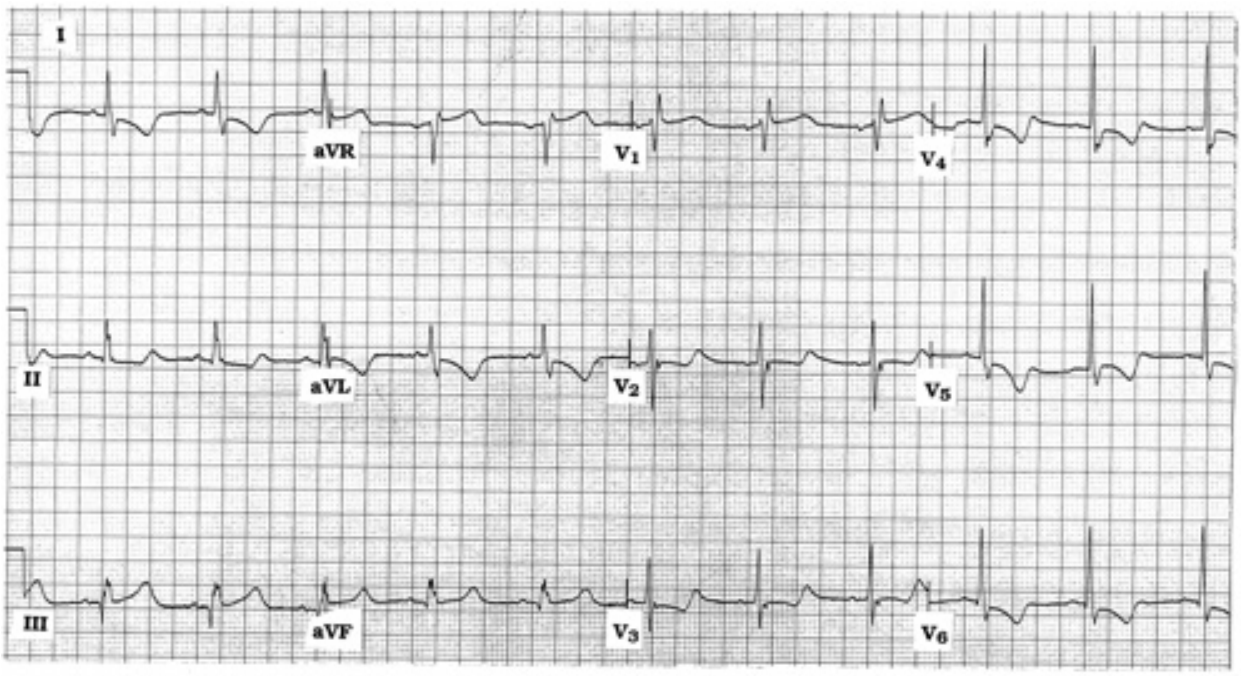

Figure. ECG obtained from an 86-year-old woman with new-onset shortness of breath.

Clinical Scenario: The ECG shown in the figure was obtained from an 86-year-old woman who presented with new-onset shortness of breath. How would you interpret this tracing? Can you explain the title of this ECG review?

Interpretation: Despite the absence of chest pain, the ECG in the figure is highly suggestive of acute infarction. The title of this ECG review tells all. The rhythm is sinus at a rate of 65 beats/minute. The PR and QRS intervals are normal, and the QT is borderline prolonged. The mean QRS axis is approximately +40°. There is no evidence of chamber enlargement. An incomplete right bundle-branch block (RBBB) pattern is present.

Although there is no ST elevation in lead II, the inferior leads otherwise show changes suggestive of acute infarction (small q waves are seen in leads II and aVF, a larger Q wave is seen in lead III, and T waves in leads III and aVF appear to be hyperacute in that they are peaked and accompanied by slight but definite ST elevation). Support that these changes in leads III and aVF are truly acute is forthcoming from the "mirror-image" picture of reciprocal ST depression and T wave inversion in the high lateral and lateral precordial leads (leads I, aVL, and V_4, V_5, and V_6, respectively). The mirror-image nature of these changes can be most easily appreciated by turning the tracing over and holding it up to the light—which results in the ST segment and T waves of leads III and aVF now taking on the appearance of the ST segment and T waves of leads I, aVL, V_4-V_6—and vice versa. The clinical significance of recognizing *reciprocal* ST-T wave changes such as these is that this finding strongly suggests acuity of the process. ❖

In Future Issues:

Droperidol vs. prochlorperazine for benign headache

BIOTERRORISM WATCH

Preparing for and responding to biological, chemical and nuclear disasters

Flu or anthrax? First inhalational cases yield clues for clinicians to make the critical call

Use case history, blood work, X-rays, rapid tests

There is a postal worker in your emergency department (ED) with flulike symptoms.

That once insignificant observation about occupation and illness now triggers a detailed algorithm created by the Centers for Disease Control and Prevention (CDC) in Atlanta. **(See algorithm, p. 2.)** Is it flu or inhalational anthrax? Whether a realistic question or not, it is what many of your incoming patients may be asking — particularly if another wave of anthrax scares coincides with a nasty influenza season. Many of the initial symptoms are similar, but investigators dealing with the first inhalational anthrax cases have gleaned out key indicators that will help clinicians make the call.

"It is important to take a careful history from the [patients] when they present," says **Julie Gerberding**, MD, acting deputy director of CDC's National Center for Infectious Diseases. "If the [patients are] mail handlers in a professional environment — where they're dealing with large amounts of mail that is not their own — then the index of suspicion should be raised and more testing should be done to be sure there aren't additional clues to suggest that it is not a common viral infection."

Using the first 10 cases of inhalational anthrax as a baseline patient profile, the CDC reports that the median age of the patients was 56 years (range: 43-73 years), and seven were men.[1]

The incubation period from the time of exposure to onset of symptoms when known (seven cases) was seven days (range: five to 11 days).

The initial illness in the patients included fever (nine) and / or sweats / chills (six). Severe fatigue or malaise was present in eight, and minimal or nonproductive cough in nine. One had blood-tinged sputum. Eight patients reported chest discomfort or pleuritic pain. Abdominal pain or nausea or vomiting occurred in five, and five reported chest heaviness. Other symptoms included shortness of breath (seven), headache (five), myalgias (four), and sore throat (two). The mortality rate was 40% for the 10 patients, much lower than historical data indicated. Indeed, one of the critical reasons to recognize inhalational anthrax early is that it is far more treatable than originally thought.

The CDC gathered comparative data on the symptoms and signs of anthrax and influenza, finding, for example, that only 20% of the anthrax patients reported sore throat.[2] Flu sufferers report a sore throat in 64% to 84% of cases. Likewise, 80% of the anthrax cases reported symptoms of nausea and vomiting. That symptom is reported in only 12% of flu cases. Shortness of breath appears to be another key distinguishing symptom, affecting 80% of the anthrax patients but seen in only 6% of flu patients.

"One of the other clues that we are noticing is that the patients with inhalation anthrax actually do not have nasal congestion or a runny nose,"

(Continued on page 3)

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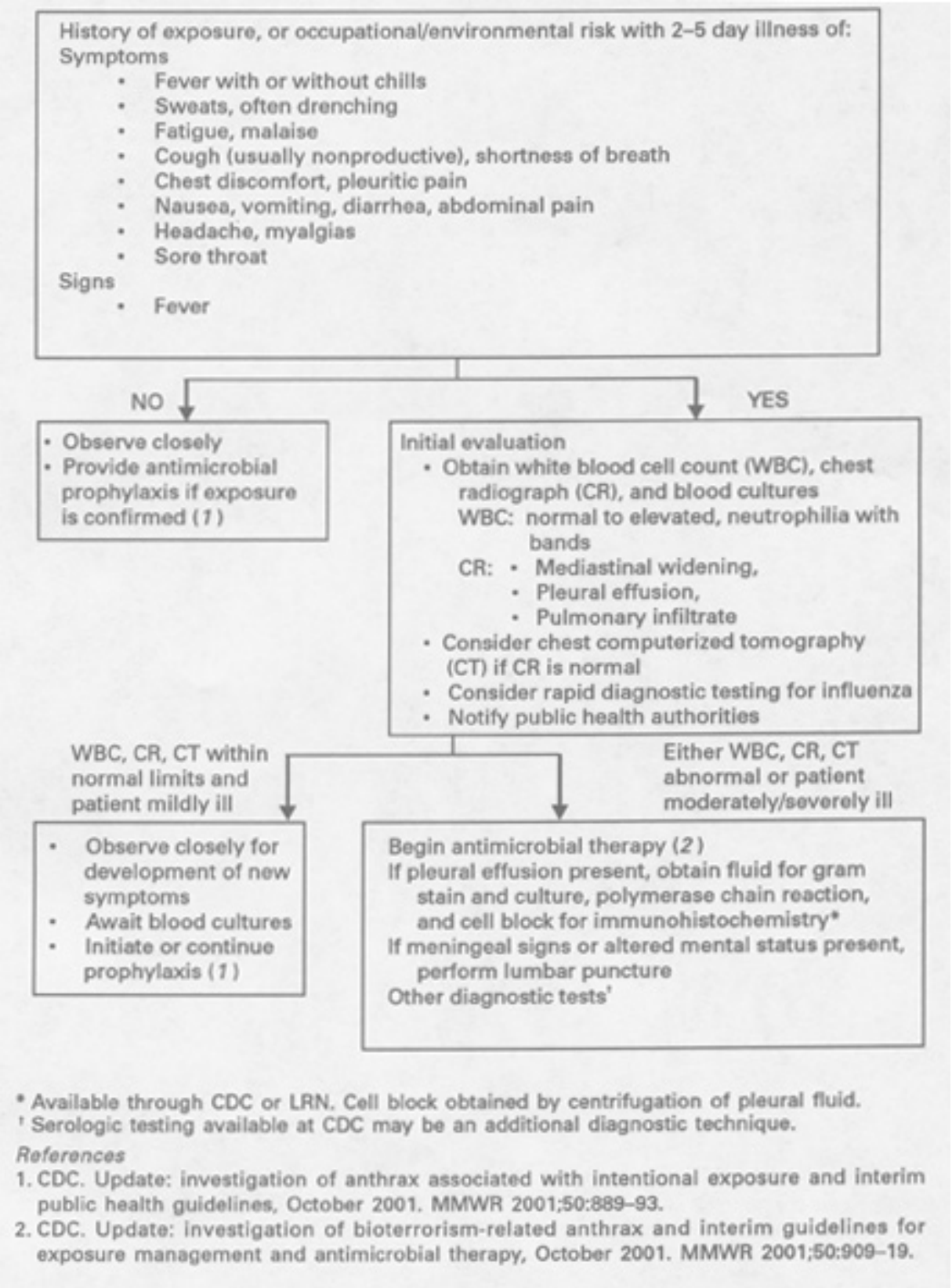
Clinical Evaluation of People with Possible Inhalational Anthrax



Source: Centers for Disease Control and Prevention. Update: Investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax. *MMWR* 2001; 50:945.

Gerberding says. "They don't have the symptoms of an upper-respiratory tract infection. They have a more systemic chest presentation, and that may be another distinguishing characteristic."

Another finding on initial blood work is that none of the inhalational anthrax patients had a low white blood cell count (WBC) or lymphocytosis when initially evaluated. Given that, CDC officials note that future suspect cases with low WBC counts may have viral infections such as influenza. Chest X-rays were abnormal in all patients, but in two an initial reading was interpreted as within normal limits. Mediastinal changes including mediastinal widening were noted in all eight patients who had CT scans. Mediastinal widening may be subtle, and careful review of the chest radiograph by a radiologist may be necessary, the CDC advises.

Complementing the CDC's effort, are the observations of the few clinicians who have actually seen inhalational anthrax cases come into their hospital systems. Two inhalational anthrax cases, both of which survived, were admitted to the Inova Healthcare System in Fairfax, VA (near Washington, DC).

"Clinically, I think the history of the people who presented here is useful," says **Allan J. Morrison Jr.**, MD, MSc, FACP, health care epidemiologist for the Inova system. "They stutter-stepped toward their pulmonary symptoms. That had some mild symptoms and then they were sort of 'meta-stable.' They were not relentlessly progressing. Then they progressed with symptoms more aggressively. Whereas with influenza — in our experience — once you start to get sick, it just keeps on progressing with very high fevers, chills, muscle aches, and pains. As a consequence, we feel there should be a good way to differentiate the two."

Since anthrax is a realistic concern in the Washington, DC, area, what about the aforementioned scenario of symptomatic postal workers in the ED?

"We would take a very aggressive history, not only of occupation but physically where they have been," Morrison says. "If they are symptomatic and have been in or work around a 'hot zone' — a location from which anthrax has either been cultured environmentally or patients have come from there — we will err on the side of being very aggressive about working up anthrax. By that I mean chest X-rays, chemistry profile, [etc.]"

In addition, the hospital system pushed early flu vaccination programs for staff and the surrounding community. "We want to move toward herd immunity," he says. "We are also working with our local hospitals to make sure that they have access to the rapid influenza tests. So for diagnosis — for obvious reasons — it is very helpful to make that distinction early."

One such rapid test is ZstatFlu (ZymeTX Inc., Oklahoma City), which the company claims can yield a diagnosis of influenza A or B some 20 minutes after a throat swab. The test detects neuraminidase, an influenza viral enzyme. However, Gerberding cautions clinicians not to rely solely on such tests. Rather, they should use the results of tests in combination with the patient history and clinical presentation, she says.

"So it is a constellation of history, clinical findings, and laboratory tests," she says. "Hopefully, when we get these all together, we'll be able to at least reduce the anxiety among some people and help clinicians diagnose those patients who really do require the antibiotic treatment. What we don't want to have happen is for everybody coming in with the flu to get an antibiotic because that undermines a whole other set of public health issues relating to antimicrobial resistance and proper management of influenza."

Even the vaccinated can still have flu

Complicating the issue is the fact that the flu vaccine efficacy can vary annually, but is usually 70% to 90% protective, says **Keiji Fukuda**, MD, a medical epidemiologist in the CDC influenza branch. Thus, depending on how well the vaccine matches the circulating strain, a certain portion of flu patients will tell clinicians they have been immunized. But in addition to vaccine breakthrough infections, there is a plethora of other viral and respiratory pathogens that will be creating similar symptoms, he says. In a somewhat sobering reminder — given that at this writing, the total anthrax cases remained in the double digits — Fukuda notes that a typical flu season will send 114,000 people to the hospital and 20,000 to their graves.

"There has been an awful lot of attention on the [anthrax] cases, but the bottom line is that there have been few cases, and these cases generally have occurred in a limited number of communities within a limited number of groups," he says. "And so the epidemiologic message is that anthrax really has not been diagnosed in most parts of the country, whereas we expect to see millions and millions of flu cases all over the place."

If facilities are faced with an onslaught of patients with respiratory illness there are several measures they can take, he notes. Those include:

- Reduce or eliminate elective surgery.
- Relax staff-to-patient ratios within the limits of your licensing agency.
- Emphasize immunizing staff so more staff are available.
- Identify ways to bring in extra staff to help out with the patients.
- Set up walk-in flu clinics to triage the patients.

Reference

1. Centers for Disease Control and Prevention. Update: Investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax. *MMWR* 2001; 50:941-948.

2. Centers for Disease Control and Prevention. Consideration for distinguishing influenza-like illness from inhalational anthrax. *MMWR* 2001; 50:984-986. ■

CDC moving quickly on smallpox front

Immunizations, training, vaccine dilution studied

Though officially stating it has no knowledge of any impending use of smallpox as a bioweapon, the Centers for Disease Control and Prevention (CDC) is scrambling with conspicuous speed to be ready for just such an event.

CDC workers from a variety of specialties are not only receiving smallpox vaccinations, they are being trained to give them to others using the old bifurcated needle scarification technique. And, even as creation of a new vaccine is fast-tracked, researchers are trying to determine if the current stockpile of 15.4 million doses can be expanded fivefold by simply diluting the vaccine.

Based on such actions, it is fair to say the agency is at least highly suspicious that the known stocks of smallpox virus are not safely ensconced in their official repositories in Russia and the United States.

"CDC is putting together a number of teams, which will probably total [more than] 100 employees, that could be quickly dispatched in a moment's notice to assist state and local health departments and frontline clinicians investigate suspect cases of smallpox," **Tom Skinner**, a spokesman for the CDC, tells *Bioterrorism Watch.*

"They are Epidemic Intelligence Service (EIS) officers, laboratorians, and others. Part of this includes vaccinating them against smallpox," he explains.

But while confirming that the CDC teams are being trained to administer the vaccine, Skinner would not specify who would be vaccinated following a smallpox bioterror event. "We have a smallpox readiness plan," he says. "Issues around vaccination are covered in that plan. That plan is being finalized. It is considered an operational plan. If we have a case tomorrow, it could be implemented. It covers who should be vaccinated and when."

The general consensus among bioterrorism experts is that those exposed would be vaccinated because the vaccine can prevent infection and possibly death even if given several days out. Likewise, health care workers and their family members would want vaccine if they were expected to care for the infected. Some aspect of quarantine would no doubt come into play because, unlike anthrax, it will be critical to separate the first smallpox cases and their contacts from the susceptible population.

Another aspect of CDC preparations includes the smallpox vaccine dilution study, which is being headed up by **Sharon E. Frey**, MD, associate professor of infectious diseases and immunology at Saint Louis University School of Medicine.

The vaccine, known as Dryvax, is no longer produced, but there are 15.4 million doses left. Frey and colleagues are looking at dilution studies that could maintain vaccine efficacy while increasing the available stock by millions of doses. In a study last year, Frey tried a one to 10 vaccine dilution, which would create a stockpile of more than 150 million doses. However, the resulting vaccine had only a 70% effective rate.

"The undiluted vaccine has about a 95% take rate," she tells *BW*. "It is not perfect, but we would like to be as close to that as we could be."

The new study will include a one to five dilution, which should show greater efficacy while increasing the stockpile to more than 75 million doses.

"We are looking at a 'take' rate for the vaccine, in other words how many people actually develop a typical lesion and whether they have a strong neutralizing antibody response to the vaccine," Frey says. "We know that the vaccine is still good. We actually titered the vaccine and it is very similar to its original titer," she adds. ■