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Rapid Sterilization of CSF when Antibiotics Precede LP

Source: Kanegaye JT, et al. Lumbar puncture in pediatric bacterial meningitis: Defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics* 2001;108: 1169-1174.

DESPITE A DEARTH OF RELEVANT LITERATURE, MOST CLINICIANS believe there is a minimum window of several hours after the initiation of parenteral antibiotics during which cerebrospinal fluid (CSF) can be obtained with accurate culture results. This study sought to examine the truth of this commonly held belief.

This retrospective study from Children's Hospital of San Diego examined the medical records of children discharged with final diagnoses of bacterial meningitis or suspected bacterial meningitis during a five-year period. Patients were included if they met any of the following criteria: CSF culture positive for a known bacterial pathogen; positive CSF antigen study or gram stain along with CSF white blood cell count (WBC) higher than 10/mm^3; blood culture positive with CSF WBC higher than 100/mm^3; or CSF WBC higher than 4000/mm^3 in the absence of bacterial isolate. Exclusion criteria included positive CSF viral study, neural tube defect, CSF shunt, penetrating injury, neurosurgical procedure in the last month other than lumbar puncture (LP), or incomplete medical record.

One hundred twenty-eight patients met study criteria, with 104 (81%) due to positive CSF cultures and the remainder divided equivalently among the other inclusion criteria. Patients were classified into one of three groups: 39 (30%) of patients had delayed LP (LPd) when LP occurred after the initiation of parenteral antibiotics; 34 (27%) had LP prior to parenteral antibiotics (LPp); and 55 (43%) had LP pre- and post-parenteral antibiotic administration (LPp/p). The primary outcomes measured were the yield of CSF cultures in the LPd and the LPp/p groups by organism and time from antibiotic administration.

Bacterial organisms were identified in 125 (98%) cases through CSF culture, blood culture, or CSF antigen study. *Streptococcus pneumoniae* (38%), *Neisseria meningitidis* (29%), and group B Streptococcus (16%) were the most common pathogens. Negative

INSIDE

Predicting the truly sick child with fever ***page 74***

Dispatcher-assisted CPR and impact on survival ***page 75***

Special Feature: Reversal of anticoagulant effects of warfarin by vitamin K_1 ***page 76***

See page 79 for information on our April 18 audio conference, "Avoiding Medication Errors: Saving Lives, Time, and Dollars."

CSF cultures occurred in 44% of patients in whom parenteral antibiotics were started prior to LP, compared with 8% among patients undergoing LP prior to parenteral antibiotic administration. Antibiotics used in the LPd and LPp/p groups almost always included a high-dose, third-generation cephalosporin.

Fifteen patients had LP within one hour after initiation of antibiotics, with negative CSF cultures in three of nine cases of meningococcal meningitis. The earliest sterilization of *N. meningitides* occurred at 15 minutes after the initiation of ceftriaxone infusion. Only one culture remained positive after 2.3 hours. Culture-negative pneumococcal meningitis occurred as early as 4.3 hours after initiation of antibiotics. In CSF cultured between four and 10 hours after antibiotic initiation, five of seven patients with pneumococcal meningitis had negative CSF cultures. Several pneumococcal isolates were resistant to penicillin and/or ceftriaxone. CSF cultures for group B Streptococcus obtained within eight hours of parenteral antibiotics remained positive.

The authors conclude that sterilization of CSF may occur more rapidly after antibiotic initiation than previously suspected, especially among patients with meningococcal meningitis. They also emphasize that the lack of adequate CSF cultures may lead to an inability to properly tailor therapy to susceptibility, or to unnecessarily prolonged treatment among patients with suspected bacterial meningitis. The authors suggest that hemodynamically stable patients with suspected meningitis and no evidence of herniation or cerebral edema should receive LP prior to the administration of antibiotics.

COMMENTARY BY JACOB W. UFBERG, MD

The results of this study came as a surprise to me, as I'm sure they did for most readers. However, the retrospective design of this study does lead to the usual limitations regarding the accuracy of medical records. It often is difficult to tell from nursing records whether a documented time represents the beginning or end of antibiotic administration, and rates of administration surely varied from case to case. Additionally, the dosage of administration was not uniform. This being said, a prospective study would be impossible to perform due to the ethical and practical concerns involved.

The authors point out that as more children receive the pneumococcal vaccine, an increased percentage of meningitis likely will be meningococcal. This likely will result in earlier sterility of CSF isolates and an increased need for early LP. We must note, however, the medical and legal risks of delaying antibiotics in children with suspected bacterial meningitis. The answer is not delayed antibiotics, but earlier LP. As in any critically ill patient, many things must happen simultaneously. We should be performing the LP while the infusion is being prepared and started, thus obtaining the necessary culture material without delaying antibiotic administration. ❖

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Predicting the Truly Sick Child with Fever

Source: Pulliam PN, et al. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. *Pediatrics* 2001;108:1275-1279.

FEBRILE ILLNESS IS A TROUBLESOME PROBLEM FOR children seen in the emergency department (ED). Many have an identifiable source of fever, including some who are thought to have viral syndromes. For the 20% in

whom no etiology is apparent, much diagnostic uncertainty remains. Furthermore, febrile children younger than age 3 have serious infections or bacteremia documented more often than do older children. What is the best option for the ED physician? Admit for observation? Culture and treat? Culture and wait? Controversy abounds, and clinical guidelines are not applied uniformly.

In an attempt to reduce the difficulty of identifying young children with occult but serious bacterial infections (SBI), Pulliam and colleagues studied 77 children ages 1-36 months in an academic ED in Delaware. Each had a temperature exceeding 39°C but an undetectable source for fever after clinical evaluation. Each patient had a complete blood count, urinalysis, blood culture, and C-reactive protein (CRP) measured. Chest films (CXR) were done at the discretion of the attending physician.

The average age was 10 months, with a mean temperature of 39.5° C, and an average fever duration of 24 hours. Of the 77 children, 14 (18%) were diagnosed with SBI. Etiologies included urinary tract infection (UTI) in six (all were *Escherichia coli*), bacteremia in five (all were *Streptococcus pneumoniae*), and pneumonia by CXR in four (one of whom also had pneumococcal bacteremia). Comparison of laboratory data revealed an average white blood cell count (WBC) of 22,300/mm^3 for the SBI group of 14 children, vs. 12,500/mm^3 for the non-SBI children ($p = 0.003$). Absolute neutrophil counts (ANC) were 13,900/mm^3 vs. 7300/mm^3 for SBI and non-SBI cases, respectively ($p < 0.0001$). Band counts were 5.7% vs. 3.6% ($p = 0.11$). CRP concentration in SBI patients averaged 9.7 mg/dL, vs. 1.0 mg/dL for non-SBI children ($p = 0.002$).

Diagnostic performance of WBC, ANC, and CRP was analyzed by receiver operating characteristic curve to select cutoff values that maximized sensitivity and specificity. A cutoff for WBC of 15,000 had sensitivity of 64% and specificity of 67%, while an ANC cutoff of 10,200 had 71% sensitivity and 76% specificity. For CRP, a cutoff of 7.0 mg/dL was correlated with 79% sensitivity and 91% specificity, with positive and negative predictive values of 65% and 95%, respectively. A CRP value less than 5 mg/dL excluded SBI with 98% negative predictive value. The authors conclude that CRP levels are more definitive than other common tests in predicting SBI in young febrile children.

COMMENTARY BY MICHAEL FELZ, MD

The sensitivity, specificity, and predictive values of CRP exceeded those for total WBC and ANC in this cohort of 77 children younger than age 3 with high fever. While the use of CRP in the diagnosis of pediatric infections is not new, this study was performed in 2000 during an era when pneumococcal bacteremia in young children remains well-disguised, as was well documented in five of 14 cases. A cutoff CRP value of 7 mg/dL correlated strongly with pneumococcal SBI. Correlation was equally strong with UTI and radiologic pneumonia, also common occurrences in the pediatric ED. Low levels of CRP (< 5 mg/dL) predicted the absence of SBI with strong statistical significance.

I find this data quite persuasive. While no available test approaches 100% reliability, this study convincingly advances CRP as a definitive marker of SBI, outperforming more traditional tests such as WBC, ANC, and band counts—three tests upon which many of us rely heavily for diagnosis. When confronted by a febrile child with no readily apparent source of infection, we must "ride the horns" of several dilemmas in deciding how aggressively to pursue invasive evaluation (i.e., blood culture, bladder catheterization, lumbar puncture) and whether to treat, admit, discharge, or observe. In my opinion, CRP warrants addition to the list of fast-track diagnostic tools in the pediatric ED. It is rapid, easily obtained (by fingerstick), inexpensive, and reliable in documenting (value > 7 mg/dL) or excluding (value < 5 mg/dL) SBI in fever scenarios in the pediatric ED. Predictive values of CRP conceivably could render speculative empiric antibiotic therapy nearly obsolete, especially if WBC and ANC point in the same direction as CRP in predicting/excluding SBI. I welcome this new data on an "old" test. ❖

Dispatcher-assisted CPR and Impact on Survival Rates

Source: Rea TD, et al. Dispatcher-assisted cardiopulmonary resuscitation and survival in cardiac arrest. *Circulation* 2001; 104:2513-1256.

Approximately 250,000 people suffer out-of-hospital cardiac arrest each year in the United States; of those, one-third receive bystander cardiopulmonary resuscitation (CPR), and 5% survive to hospital discharge. Previous studies have demonstrated that real-time 911 dispatcher assistance and guidance with CPR increases the proportion of cardiac arrest victims who receive lay public bystander CPR. However, there has been little data on whether such dispatcher-assisted CPR in the field has any measurable outcome benefit.

This retrospective cohort analysis studied the impact of a dispatcher-assisted CPR program on the rate of hospital survival-to-discharge among victims of cardiac

arrest in the field setting. The investigators analyzed emergency medical services (EMS) and hospital records for 7945 persons who experienced a field arrest due to cardiac causes during a 17-year period (1983-2000) in Kings County, WA. Three cohorts were defined: patients who did not receive bystander CPR (no CPR, 44%); those who received bystander CPR without dispatcher assistance (unassisted CPR, 30%); and those who received bystander CPR with dispatcher assistance (assisted CPR, 26%).

The overall survival-to-discharge rate was 15%. Survival rates were greater for the unassisted CPR and assisted CPR groups (27% and 18%, respectively) vs. the no CPR group (13%). Multivariate odds ratio for survival were significantly higher in the unassisted CPR (1.69) and assisted CPR (1.45) groups when adjusted for age, sex, location, whether the arrest was witnessed, and EMS response time. In addition, there was no change in the results if researchers excluded cases in which bystander CPR was performed by medical professionals.

When analyzing the subgroup of witnessed arrests, the investigators found that the time to any CPR efforts (by bystander, EMS, or other personnel) were markedly shorter in the unassisted and assisted groups. However, the initiation of CPR with dispatcher assistance took approximately one minute longer than when initiated by bystanders who did not need assistance. Interestingly, while overall there was improved survival with unassisted CPR vs. assisted CPR, there was no difference in the subgroup of patients with prolonged EMS response times (> 5 minutes), suggesting that beyond the one-minute delay, the quality of CPR was comparable.

The authors conclude that dispatcher-assisted CPR led to greater numbers of patients receiving bystander CPR, shorter time to the initiation of CPR efforts, and improved survival for patients who suffer cardiac arrest in the field.

COMMENTARY BY THEODORE C. CHAN, MD, FACEP

This large cohort study again confirms that early CPR saves lives. More specifically, this study demonstrates that 911 dispatchers by telephone can assist and direct bystanders to initiate CPR on cardiac arrest victims, resulting in more patients receiving bystander CPR earlier and improving their chances for survival.

It should be noted that only survival-to-hospital-discharge was studied; no assessment of the patients' neurologic status and quality of life was made. Moreover, as a retrospective study, there may have been underlying biases as to who received and did not receive dispatcher assistance. Most importantly, this study was conducted in a community well-known for its outstanding public CPR training and outreach programs, as well as for tremendous arrest survival rates that have been difficult to replicate in other communities. Similarly, the success of dispatcher-assisted programs may not be easy to reproduce in other urban settings.

Despite these limitations, the findings of this study are impressive given the approximately 50% improvement in survival with dispatch-assisted CPR. Moreover, dispatch instruction in this study included ventilation and chest compression. The most recent American Heart Association guidelines recommend limiting such instructions to chest compression only, as research suggests equal efficacy.[1] Given this simplification, the potential impact of dispatch-assistance programs may even be greater in the future.

Most patients in the no CPR and assisted CPR groups suffered their arrests at private homes (81% and 94%, respectively), as opposed to the unassisted CPR group (38%). As the large majority of cardiac arrests take place at home, this finding further emphasizes the real and potential benefit of dispatcher-assisted CPR. Programs such as these, as well as other efforts expanding public access defibrillation and citizen CPR training, hopefully will make inroads into the overall dismal rate of cardiac arrest survival. ❖

Reference

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Special Feature

Reversal of Anticoagulant Effects of Warfarin by Vitamin K_1

By Richard J. Hamilton, MD, FAAEM, ABMT

Consider the following scenario: an elevated internationalized normalized ratio (INR) is called to a physician's office as a panic value from the laboratory. The patient is at home, usually asymptomatic. The INR is 9.0 and the private physician instructs the patient to go to the emergency department (ED) for a repeat INR and evaluation for bleeding complications. At the hospital, the patient encounter is preceded by a phone call to the ED physician by the referring physician explaining the referral.

It is surprising how few physicians understand the role a simple oral dose of vitamin K can play in this situation. Emergency physicians can educate each other and their referring primary care physicians about this antidote.

Background

Indeed, vitamin K is an antidote. It is used to reverse the coagulopathy of warfarin and superwarfarin rodenticides. Vitamin K is a cofactor for the activation of vitamin K-dependent coagulant proteins (prothrombin, factor VII, factor IX, and factor X) and the regulatory anticoagulant proteins (protein C and protein S). Vitamin K is recycled to its active form (vitamin K_1 or phytonadione) by a series of enzymes—vitamin K epoxide reductase and vitamin K reductase. Warfarin exerts its anticoagulant effect by inhibiting vitamin K epoxide reductase and, to a lesser extent, vitamin K reductase.

Warfarin is used to induce a therapeutic coagulopathy for a variety of conditions. However, precise control of the coagulopathy is frustrated by alterations in metabolism, drug-drug interactions, and dietary sources of vitamin K_1. Management is difficult, and appropriate warfarin doses frequently are achieved after a period of trial and error. Frequent monitoring of the INR allows adjustments of the dose of warfarin to maintain therapeutic values and prevent bleeding complications. When the patient is excessively anticoagulated, the traditional approach is to eliminate or reduce doses of warfarin until re-testing demonstrates a therapeutic INR. This method is unsatisfactory, as it takes as long as four days to normalize the INR from a ratio as low as the 2.0-3.0 range.[1] In addition, the goal of correction is to reverse the coagulopathy into the therapeutic range for the patient—not to normalize it to 1.0. This protects the patient from an exacerbation of whatever medical problem led them to warfarin therapy (e.g., atrial fibrillation, pulmonary embolus, deep venous thromboembolism, etc.).

As an antidote, vitamin K_1 is prescribed in large doses to confidently reverse the coagulopathy completely. When warfarin is used therapeutically, the correct dose of vitamin K_1 would be the one that restores the patient to a safe INR. Since the risk of bleeding rises sharply when the INR exceeds 5.0, vitamin K_1 should be dosed to lower the INR to at least below 5.0. If the patient has non-life threatening bleeding or requires elective or urgent surgery, then the INR should be reduced to 1.0 to 1.5. An INR of 1.0 is the goal when bleeding is serious or surgery is emergent.

A number of studies have endeavored to determine the correct dose and route of vitamin K_1. The goal is to reverse the coagulopathy without unnecessary risk of thrombosis, avoid warfarin resistance, and avoid anaphylactoid reactions (a common side effect of rapid infusion of intravenous vitamin K_1).

Evidenced-based Dosing of Oral Vitamin K_1

The effectiveness of low-dose oral vitamin K_1 was demonstrated in a randomized trial comparing 2.5 mg oral vitamin K_1 to withholding warfarin for correction of the INR to 5.0 at 24 hours. In this study, simply withholding the warfarin was inadequate, whereas oral vitamin K_1 was effective.[2] In a prospective cohort study of 62 patients on warfarin, without bleeding but with INR values between 4.5 and 10.0, a combined strategy of low-dose vitamin K_1 (1.0 mg) and omitting the next dose of warfarin was examined. Sixteen hours later, the mean INR was 2.86. None of the patients showed resistance to warfarin when it was restarted. However, three patients had an increase in INR on day two despite the vitamin K_1 therapy.[3]

In a retrospective case series study, investigators examined the efficacy of 2.5 mg of oral vitamin K_1 to reverse an INR from the 5.0-16.0 range in patients without major bleeding. Warfarin was withheld for either one or two doses, depending upon patient availability for repeat testing in 24 or 48 hours, respectively. This dose successfully reduced the INR to below 5.0 in 90% of the patients within 24-48 hours, and overcorrected the INR (i.e., < 2.0) in 14 patients (17%); yet none of these values was lower than 1.5 (only one-third of the overcorrected values were < 1.8), and no patient had thromboembolic complications. However, when the initial INR was 10.0 or more, a dose of 2.5 mg of oral vitamin K_1 was effective in only five of 10 patients.[4]

A more precise method to calculate the oral dose of vitamin K_1 is to use a regression formula based on the initial and desired INR. This formula is: *Vitamin K_1 dose in mg = 16 - (17 x [INR desired/INR initial])*.

For example, a patient with an INR of 10.0 whose therapeutic INR is 2.5 would get 11.75 mg of vitamin K_1 by mouth. This approach also has the advantage of permitting continued use of warfarin. It was studied in 65 patients who were either excessively anticoagulated or required reversal of coagulopathy for elective or urgent surgery. The formula was successful in reducing the INR to therapeutic levels for all patients but one within 48 hours. There was one bleeding complication and no thrombotic complications.[5]

Management of Supratherapeutic INR

Based on the above data and using a combined approach that withholds warfarin doses, the American College of Chest Physicians (ACCP) developed a consensus guideline. These guidelines were published in 1998 and have been reviewed and reinforced as an

Table

Management of Supratherapeutic INR[6]

INR	Serious Bleeding	Warfarin	Vitamin K1 Dose	Other
< 5 but above therapeutic	No	Lower next dose or omit one dose	None	
> 5.0 but < 9.0	No	Omit one or two doses	1-2.5 mg PO once	Use 2-4 mg if surgical procedure and INR must be reduced in 24 hrs.
> 9.0	No	Omit until INR corrected	3-5 mg PO	Expect INR to reduce to therapeutic within 24-48 hrs.
> 20	Yes	Omit	10 mg slow IV	Use fresh frozen plasma or prothrombin complex concentrate.
Any INR	Life-threatening	Omit	10 mg slow IV	Use pro - thrombin complex concentrate.

appropriate standard of care.[6] *(See Table.)* All therapy should be monitored with daily INR levels until therapeutic levels are achieved.

The route of administration is important in vitamin K_1 therapy. The efficacy of oral vitamin K_1 is equivalent to that of intravenous vitamin K_1, and dosages are the same. Intravenous vitamin K_1 has the disadvantage of producing anaphylactoid reactions that generally are related to the rate of administration. Subcutaneous administration is both common and less effective. Physicians unfortunately choose this route under the mistaken assumption that it is faster or more effective. Intramuscular administration is obviously contraindicated in coagulopathy.

Despite the fact that these guidelines have been in place since 1998, compliance is low and practice patterns still are highly variable. A recent survey of internists in Ontario, Canada, showed that compliance with dose and route of vitamin K_1 recommended by ACCP varied from 1% to 10%.[7] One particularly disturbing trend was the tendency to use a subcutaneous injection when an oral dose was a more effective and reliable route. Obviously, there still is much work to be done on informing practitioners. Therefore, when a referring physician calls you about a patient with an INR that is above therapeutic, let him or her know that you are going to use the ACCP guidelines to reverse the patient's anticoagulation into the therapeutic range; use the opportunity to employ a well-conceived approach for the patient while you educate other providers. ❖

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Physician CME Questions

19. Early sterilization of cerebrospinal fluid (CSF) cultures with antibiotics is most likely to happen with which organism?

a. *Neisseria meningitidis*
b. *Streptococcus pyogenes*
c. *Streptococcus pneumoniae*
d. *Haemophilus influenzae*

20. In children ages 1-36 months with high fever without obvious source, the laboratory test most predictive of serious bacterial infection is:

a. a total white blood cell (WBC) count exceeding 10000/mm^3.
b. greater than 5% bands in WBC differential count.
c. C-reactive protein greater than 7 mg/dL.
D. an absolute neutrophil count higher than 7500/mm^3.

21. Overall, dispatcher-assisted cardiopulmonary resuscitation (CPR) for sudden cardiac arrest in the field setting resulted in:

A. improved survival over no bystander CPR, but not equivalent to unassisted bystander CPR.
B. improved survival over both no bystander CPR and unassisted bystander CPR.
C. worse rate of survival compared to both no bystander CPR and unassisted bystander CPR.
D. shortened time interval to CPR efforts over unassisted bystander CPR.

22. Anaphylactoid reactions associated with vitamin K_1 administration are most likely with what method of adminstration?

A. Intravenous
B. Intramuscular
C. Sublingual
D. Oral

23. According to the American College of Chest Physicians guidelines, how might one initially manage a patient on warfarin with an INR of 8.0 and no active bleeding?
A. Hold warfarin dose; administer vitamin K_1 2.5 mg IV.
B. Continue warfarin; administer vitamin K_1 10 mg IV.
C. Hold warfarin dose; administer vitamin K_1 10 mg IV.
D. Continue warfarin dose; administer vitamin K_1 10 mg po.
E. Hold warfarin dose; administer vitamin K_1 2.5 mg po.

24. Concerns regarding rapid sterilization of CSF cultures when antibiotics precede lumbar puncture are important because of:
A. implications for detection of antibiotic resistance.
B. possible unnecessary prolongation of treatment in cases of suspected bacterial meningitis.
C. both of the above.
D. None of the above

25. In the study by Pulliam et al of children age 1-36 months with fever higher than 39°C and no obvious source, a CRP of less than 5 mg/dL had a negative predictive value for serious bacterial illness of:
A. 98%.
B. 75%.
C. 50%.
D. 28%.

26. Which of the following is a true statement regarding vitamin K_1 and correction of warfarin-induced over-anticoagulation?
A. Subcutaneous route appears to be most effective.
B. Intramuscular route is contraindicated.
C. Intravenous route is safest and most effective in mild cases.
D. Oral route is best used in patients with life-threatening bleeding.

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.

VT on Recumbency?

By Ken Grauer, MD

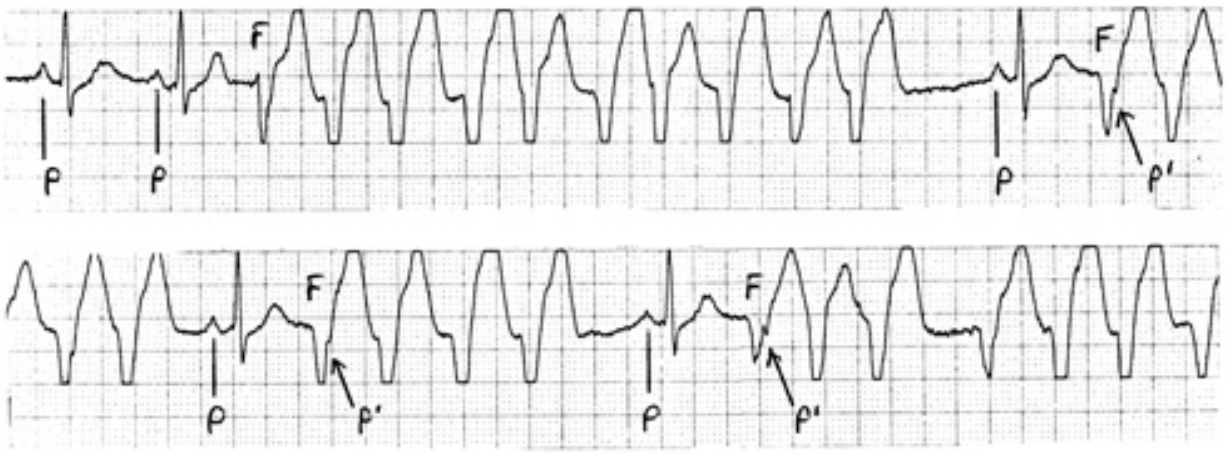

Figure. Noncontinuous telemetry rhythm strips obtained just after the patient turned onto her left side.

Clinical Scenario: The telemetry rhythm strips shown here were obtained from a patient with a long history of alcohol abuse. Serum potassium and magnesium levels were both below normal. Runs of tachycardia similar to those shown seemed to occur each time the patient turned over on her left side. Do the runs of wide-complex tachycardia (WCT) represent ventricular tachycardia (VT)? How certain are you of your answer? Is it likely to be coincidence (or a product of the telemetry nurse's imagination) that left-sided recumbency seemed to precipitate this arrhythmia? How would you treat the rhythm?

Interpretation: Despite the paucity of narrow complexes, the underlying rhythm is sinus, as evidenced by the presence of two consecutive sinus-conducted beats at the beginning of the top rhythm strip (upright P wave, constant PR interval). Periodic isolated sinus beats punctuate both tracings. The runs of WCT are clearly VT. We say this because: 1) QRS morphology looks like VT (the QRS is wide and very different from sinus-conducted beats); 2) there is evidence of AV dissociation (despite the onset of WCT, the next sinus P wave occurs right on time at the beginning of several WCT runs, seen as a notch (P′) in the S wave of the first VT beat); 3) there is a fusion beat (F) at the onset of each run; 4) there are post-ectopic pauses after each run, which are followed by sinus capture beats; and 5) VT is by far the most common cause of WCT (and there is no reason at all in this case to suspect aberrant conduction). The runs of VT seen here are slightly irregular, which can occur with this arrhythmia.

Although the mechanism is unclear, position changes (most commonly assumption of the left lateral decubitus position) probably do precipitate VT in an occasional patient with ventricular irritability who is predisposed to ventricular ectopy (Grauer K, et al. *Fam Prac Recert* 1990;12:32-46). Therefore, I would believe the nurse's observation and avoid the left lateral decubitus position, at least until serum electrolytes were corrected. ❖

In Future Issues:

Pertussis: Back to the Future?

BIOTERRORISM WATCH

Preparing for and responding to biological, chemical and nuclear disasters

Anthrax aftermath: Adverse drug reactions, vaccine controversy undercut CDC extended treatment offer

Some 8,000 people say thanks but no thanks

Despite the lingering possibility of late-onset anthrax infection, more than 8,000 people potentially exposed in the bioterrorism attacks of 2001 have turned down offers of additional antibiotics and immunization with the controversial vaccine, *Bioterrorism Watch* has learned.

Faced with insufficient data to truly assess the risk, the Centers for Disease Control and Prevention (CDC) in Atlanta offered the additional measures but fell short of actually recommending them.

Additional treatment offered as an 'option'

Operating on a thin margin of data about anthrax exposures, incubation periods, and subsequent infections, the CDC concluded it couldn't make a formal recommendation. The additional antibiotics and vaccine were made available as "options" to those exposed.

"The feeling was that this was the best thing we could do for people, and at least, leave it up to them to make a decision," says **Ian Williams**, PhD, medical epidemiologist in the CDC national center for infectious diseases. "We don't know what the answer is, but these are the options. We were really caught between a rock and a hard place on this one."

The 10,000 people potentially were exposed to anthrax in Connecticut, Florida, New Jersey, New York City, and Washington, DC.

They were all originally recommended to take at least 60 days of post-exposure antibiotic prophylaxis, but emerging data suggest that there has been a surprising lack of compliance.

In some preliminary surveys, fewer than half of those exposed were fully adhering to their original 60-day regimen. The CDC now has undertaken a telephone survey of all 10,000 people to identify adverse reactions and other reasons for the lack of adherence. **(See related story, p. 3.)**

The vaccine and additional antibiotic options were brought into play in part because the CDC knew it had large numbers of people who had not completed the original 60-day regimen. But the offer of additional care may have been undermined to some degree by prior adverse antibiotic reactions and fear of an anthrax vaccine that has been mired in controversy for years. Then again, many of those exposed may have felt they were no longer at risk and if their status changed, they would consult a physician.

Anthrax alive at 100 days

Though no known cases of anthrax have developed in any of the individuals who were prescribed the 60-day antibiotic course, the CDC also was aware of some disturbing data in animal studies. Traces of live anthrax spores have been detected in test animals' lungs up to 100 days following exposure, raising the theoretical possibility that the spores remaining still could

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cause disease. In that regard, one of the additional options offered to the exposed people was to take antibiotics for another 40 days (bringing total therapy time out to 100 days).

The other option was to take the additional drug regimen and also be vaccinated against anthrax. The latter option included three doses of anthrax vaccine over a four-week period, but antibiotics still had to be taken as the vaccine took effect.

The vaccine was not designed for post-exposure prophylaxis, but the theory is that it may provide additional protection by inducing an immune response to anthrax.

"People were unclear what the upper limit [for the onset of infection] was," Williams says. "That is what really drove both the vaccine and the antibiotic [offer]. We thought that 40 additional days to make 100 days looked sufficient based on our scant data. The vaccine was added because, is 100 days enough? I can't tell you absolutely for sure that it is enough."

Thousands took their chances

Most people were willing to take their chances that late onset anthrax will not occur.

Of the exposed cohort of some 10,000 people, 1,547 elected to receive more antibiotics after their 60-day regimen. Another 192 opted to be immunized with the anthrax vaccine and take additional antibiotics while the series of shots is given. Are the other 8,000-plus people at any real risk?

"Our feeling is that there shouldn't be any late cases of anthrax, based on what we know," Williams says.

"But that very well might be dose-dependent. We can't quantify the dose. If you go back and look at the animal studies that were done, they were actually done with probably lower doses than we have seen in the [U.S. Senate] Hart office building. But based on the data we can draw from animal models, it looks like there shouldn't be late onset cases," he explains.

If such an event occurred, the disease presumably still could be treated — provided the person seeks medical care. Still, making assumptions about anthrax can be tricky.

The CDC has been on a steep learning curve throughout the bioterrorism attack, with officials caught off guard by the ability of anthrax to disperse and spread during mail handling.

In addition, the ability to predict risk of infection in an exposed individual remains elusive, said **Julie Gerberding**, MD, director of the CDC division of healthcare quality improvement.

"We know that the exposure dose probably varies depending on how close you are to the source when it's released and how long you are in the [area] of release," Gerberding reported at a recent CDC meeting on post-exposure prophylaxis for anthrax.

> *"This is not an experiment to help us later. We don't have a control group. All we are doing is using the best science we have, which suggests that this is best way to give protection to people."*

"[But] despite our capacity to think about populations, we cannot accurately identify individual exposure, and we cannot accurately quantify individual risk," she explained.

Faced with that conundrum, the CDC put the same options on the table for all 10,000 people potentially exposed.

"The risk was probably different in different places," Williams says. "If you look at Capitol Hill, the concentration of anthrax released was probably much higher than say, Connecticut, where a letter just went through a post office. But that's group risk. Individual risk is different. [We] can't tell you exactly what your risk is. We'll give you the best available data, but you are going to have to make that decision."

Of the 190 people receiving anthrax vaccine, 80 had some political connection in Washington, DC, and 44 were postal workers in that city. Another 49 people in New Jersey were vaccinated; and the remainder were in New York City (12), Florida (four), and Connecticut (three). Of those who chose additional antibiotics only, 849 were in Washington, DC; 354 in New Jersey; 248 in New York City; 55 in Connecticut; and 41 in Florida.

A mixed message?

The CDC has drawn criticism for its approach, particularly for making a controversial vaccine available but leaving the immunization decision up to patients and their providers.

"It would have been much better if they had come out and said, 'Yes, we think in order to have as much protection as possible against the potential of developing disease, you should receive both

Side effects undermine anthrax drug adherence

More than half dropped drugs by 30 days

Amid the hype and horror of the 2001 anthrax attacks, it seemed a given that the people potentially exposed would be particularly diligent in completing their antibiotic regimens. But as time passed — and side effects continued or worsened for some — compliance fell off dramatically for many of the 10,000 people put on 60-day regimens for ciprofloxacin and doxycycline, according to preliminary data from the Centers for Disease Control and Prevention (CDC).

None of the people who started on antibiotics have developed anthrax, but the CDC wants some answers on the lack of adherence. To that end, the CDC is conducting a telephone survey project that will attempt to reach all 10,000 people for whom post-exposure antibiotic prophylaxis was recommended. The interviews began in late January and are expected to continue through March 2002. The people were potentially exposed to anthrax in Connecticut, Florida, New Jersey, New York City, and Washington, DC.

"We are making sure we get in touch with all of these people to evaluate how they did in terms of taking antibiotics," says **Ian Williams**, PhD, medical epidemiologist in the CDC national center for infectious diseases. "We have data showing adherence definitely wasn't as high as people, prior to this outbreak, would have thought it would be."

The CDC attempted a variety of methods to assess compliance prior to the phone survey, including tracking individuals who did not return to refill their medication. Other methods include giving a sample of those exposed questionnaires that were self-administered, given by a nurse, or by telephone, according to **Nancy Rosenstein**, MD, medical epidemiologist in the CDC national center for infectious diseases.

"In general, adherence has declined over the course of the [first] 30 days to as low as 45%," Rosenstein said at a recent CDC meeting on post-exposure prophylaxis for anthrax.

Some groups were more compliant than others. For example, employees who worked in the American Media Building in Boca Raton, FL, were closer to 70% compliant, she said. But only 45% compliance at 30 days was also found in a "high risk group" of mail handlers in New York City, she added.

"Adherence experts tell me that when we actually count pills, the self-reporting numbers probably overestimate real adherence by as much as 20%," Rosenstein said. "So the real estimates of adherence — taking the antibiotics every day — are obviously substantially lower."

In terms of self-reported adverse events, within two weeks of taking ciprofloxacin, 19% were reporting severe nausea, vomiting, abdominal pain, and diarrhea. At 30-day surveys, many people had switched to doxycycline, but self-reported adverse events increased to 45%.

Again, the predominant symptoms were severe nausea, vomiting, diarrhea, and abdominal pain. About 12% of the people reporting adverse events required additional follow-up with medical chart review and physician interviews, she said.

"I don't want to in any way minimize the impact of these symptoms on people's daily life, but when we actually investigated further, we were unable to identify anybody who actually required hospitalization or an emergency room visit for their adverse events," Rosenstein said.

Thus, based on Food and Drug Administration criteria, no serious adverse events have been linked to taking antibiotics for anthrax exposure. A more complete picture of the adherence problems should emerge from the CDC telephone survey of all recipients. Preliminary surveys have found that 6% to 12% of respondents reported at least missing some of their doses because of the side effects, she said. ■

antibiotic and vaccine,'" says **Phillip Brachman**, MD, a professor in the Rollins School of Public Health at Emory University in Atlanta.

The vaccine has been embroiled in a safety dispute since the military began a mandatory immunization policy several years ago, with some veterans saying it made them sick and others refusing to take it.

"A number of [the exposed people] undoubtedly read about the problems some of the military

folks claimed they had experienced after having the vaccine," Brachman says.

"They associated their problem with the vaccine. Remember, that those people in the military who have made those complaints are a very small number, considering the total number of doses given," he adds. "So there are very few voices creating a lot of concern."

Brachman did what remains the only clinical trail on the safety and efficacy of an anthrax vaccine precursor when he worked for the CDC in the 1950s.

In a study of goat's-wool workers — which was once an occupational risk group for anthrax in the United States — he found the vaccine safe and effective. He reported few side effects to vaccination and an efficacy rate of 92.5%.[1] The vaccine used in the study was a protective-antigen variety similar to the current vaccine. However, the manufacturing process has since changed and a different strain of anthrax is now used.

"There have been a few minor changes, and some people make a lot more out of it then it really should be," he says. "A different strain is being used to prepare the vaccine, but that should make no difference because the organism is not in the vaccine. It is the protein product from the organism."

Dearth of data

An Institute of Medicine committee that convened to look at the current anthrax vaccine cited a dearth of data in concluding: "The published studies have found transient local and systemic effects (primarily erythema, edema, or induration) of the anthrax vaccine.

"There have been no studies of the anthrax vaccine in which the long-term health outcomes have been systematically evaluated with active surveillance. . . . The committee concludes that in the peer-reviewed literature, there is inadequate/insufficient evidence to determine whether an association does or does not exist between anthrax vaccination and long-term adverse health outcomes. . . . To date, published studies have reported no significant adverse effects of the vaccine, but the literature is limited to a few short-term studies,"[2] the committee said.

For its part, the CDC would not have made the vaccine an option for those exposed if it had any doubts about its safety, Williams says.

"It seems to be a very safe, efficacious vaccine," he says. "[The] CDC reviewed the data with the military, which has the most experience with this."

Still, some people may have been confused because the CDC did not roll out the vaccine right after the exposures occurred. Thus, the response was somewhat tepid to a vaccine "add-on" option 60 days after the potential exposure. One problem is that the U.S. military, which controls the dispersal of anthrax vaccine, did not release any stocks in the immediate aftermath of the bioterror attacks, he says.

"One of the lessons we have learned is that if the vaccine had been available when this first started, I think the post-exposure prophylaxis would have been approached much differently," Williams says.

With the military now more amicable on the issue, if a bioterrorist strikes again with anthrax, the vaccine could play an important role from the onset, he emphasizes.

"If this should happen again, the vaccine might be used closer to day zero," Williams says. "After a series of doses over a month or so, most people will develop an antibody response, so it would obviate the need for additional antibiotics. It will be used in more of a true post-exposure fashion."

Those who have been recently vaccinated will be followed over time. Indeed, the CDC is discussing following the whole cohort of 10,000 people. It is an interesting group, having been potentially exposed to anthrax, taken prolonged antibiotic regimens, and in some cases, received a vaccine whose long-term safety is in some question.

Another curious fact — as with other post-exposure regimens for diseases — is that no one will ever know if the additional measures taken by 1,739 of these people actually prevent a late-onset anthrax infection.

"This is not an experiment to help us later," Brachman says. "We don't have a control group. All we are doing is using the best science we have, which suggests that this is best way to give protection to people."

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