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Rapid Demise of Injection Drug Users in the United Kingdom

ABSTRACTS & COMMENTARY

Synopsis: *An outbreak of soft tissue infection, sepsis, and death in injection drug users in the United Kingdom may be due to infection with Clostridium novyi.*

Sources: CDC. *MMWR Morb Mortal Wkly Rep* 2000;49:489-492; Eastern Regional Health Authority and National Disease Surveillance Centre. *Eurosurveillance Weekly*, June 22, 2000; http://www.eurosurv.org/update.

Between april 1, 2000, and the third week of june 2000, at least 88 injecting drug users (IDU) were identified with circulatory collapse, pleural effusions, soft tissue edema and necrosis, and evidence of inflammation at the site of drug injection. Forty (45.5%) died.

Twenty-one cases occurred in England and Wales, 48 in Scotland, and the remainder in Ireland. Not all these cases, however, meet the newly agreed upon International Specific Case Definition: "an injecting drug user who has been admitted to hospital or found dead since 1 April 2000 with soft tissue inflammation (abscess, cellulitis, fasciitis, or myositis) at an injection site, and with (i) severe systemic toxicity (sustained systolic blood pressure < 90 mm Hg despite fluid resuscitation and total peripheral white blood cell count > 30 × 109/L), or (ii) postmortem evidence of a diffuse toxic or infectious process including pleural effusions and soft tissue oedema or necrosis."

On June 15, the Greater Glasgow Health Board reported that an organism preliminarily identified as *Clostridium novyi* type A had been isolated from at least six patients. A week later, it was reported that the same organism had been recovered from a patient in Brighton.[1,2]

COMMENT BY STAN DERESINSKI, MD

C. novyi causes sudden death in cattle (Black disease) as the result of gas gangrene: "wet, foul smelling lesions." This organism is also involved in 10-40% of human cases of gas gangrene.[3] It has also caused, in the absence of gas gangrene, bacteremia, splenic abscess, and other site infections.[4]

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C. novyi type A produces a 250 kDa alpha toxin (CNAT) that acts as a monoglucosyltransferase, catalyzing the incorporation of N-acetylglucosamine into the Rho subfamily proteins.[5,6] Rho proteins are a family of GTP-binding proteins involved in the regulation of the actin cytoskeleton, as well as in some signal transduction processes. The acceptor amino acid in Rho, Thr-37, is located in the effector domain of the GTPases and is also the acceptor site for the *Clostridium difficile* toxins.

CNAT, in fact belongs to a family of large clostridial cytotoxins that includes toxins A and B of *C. difficile*. Like the *C. difficile* toxins, with which it has approximately 48% homology, CNAT is cytotoxic in vitro, causing the rounding up of cells as a result of redistribution of the actin cytoskeleton.

Like other clostridia, *C. novyi* is present in soil and feces. The occurrence of these cases in the United Kingdom suggests a common source of contamination of a supply of heroin. A study reported in 1983 found that 61% of 31 samples of street heroin yielded microbial growth in culture, with the two most commonly isolated organisms being *Bacillus* sp (79%) and *Aspergillus* sp (10%).[7] They found, however, no correlation between the organisms recovered from the heroin and from soft tissue infections in a group of users.

Soft tissue infection is highly revalent among IDUs, particularly those who inject into muscle or subcutaneous tissues.[8] In the United States, and particularly in California, there has been a significant increase in incidences of tetanus, as well as of wound botulism in users of black tar heroin.[9,10] *Streptococcal fasciitis* is another potentially lethal infection encountered in IDUs, but perhaps the most dramatic complication reported in this group was the patient recently encountered in Oslo, Norway, with a subcutaneous abscess, sepsis, and hemorrhagic meningitis from whose cerebrospinal fluid *B. anthracis* was isolated.[11] ❖

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Europe: Just When You Thought It Was Safe!

ABSTRACTS & COMMENTARY

Synopsis: *Tick-borne encephalitis, a vaccine-preventable disease, remains a summertime danger in Europe.*

Sources: Logar M, et al. *Infection* 2000;28:74-77; Kaiser R, Holzmann H. *Infection* 2000;28:78-84; Ruef C. *Infection* 2000; 28:65-67.

During the summer of 1997, 80 (37.6%) of 213 patients with aseptic meningitis in Ljubljana, Slove-

nia, had serum IgM antibody to tick-borne encephalitis (TBE) virus in the absence of antibody to *Borrelia burgdorferi* sensu lato and of PCR evidence of enterovirus infection in CSF. None of the 60 adults and 20 children had received TBE vaccination. Sixty-five (81.3%) had a history of tick bite. Adults were almost twice as likely as children to have peripheral blood leukocytosis and one-sixth of the adults had thrombocytopenia compared to none of the children. CSF demonstrated findings typical of aseptic meningitis, with lymphocyte predominance in 68.8%; there was no significant difference among important parameters between adults and children. A total of 64 (80%) had a biphasic illness. Fever duration was longer in adults.

Separately, laboratory findings of 100 consecutive adults with TBE admitted to the University of Freiburg hospital between 1990 and 1997 were retrospectively evaluated by Kaiser and Holzmann. Three (3%) had previously received TBE vaccine, but in each case vaccination had been incomplete. All but three of the 100 patients had serum IgM antibody to TBE virus at the time of admission. Findings compatible with intrathecal synthesis of TBE virus-specific IgM or IgG antibodies were detected by the 15th day after the onset of neurological symptoms in all patients studied. In contrast to the Slovenian experience, CSF granulocyte predominance was seen in approximately one-half of patients.

COMMENT BY STAN DERESINSKI, MD, FACP

The TBE pathogen is a flavivirus whose principal vector within central Europe, southern Scandinavia, and European Russia is the hard tick, *Ixodes ricinus*, which is also the vector for *B. burgdorferi* in this region. TBE virus may also be acquired by ingestion of infected dairy products, especially unpasteurized goat milk.

Neurological disease develops during the second phase of infection but occurs in only 5-30% of symptomatic patients (and only 1 in 250 infected individuals ever develop symptoms). However, some patients present with neurological disease in the absence of a febrile prodrome.

In a typical symptomatic case, a flu-like illness develops 7-14 days after infection. Symptoms resolve within a week, but in a minority of cases, a second phase of illness occurs after a 2- to 8-day period of remission. It is during this phase that neurological involvement is likely to be observed. Residual abnormalities, including paralysis, are reported to occur in 30-60% of patients. There is evidence that the disease is more severe in adults than in children. TBE in the Far East, caused by other strains of the virus, is more severe and has significantly greater mortality.

A TBE-inactivated vaccine is available in Europe and appears to be safe and immunogenic, although a meta-analysis has concluded that its protective efficacy is, as yet, unproven.[1,2] It is administered twice within three months and once more 6-18 months after the second injection; an accelerated schedule has also been described. Protection is believed to last for three years after the last administration. Postexposure TBE virus hyperimmune globulin is also used in Europe, but its value is unproven. ❖

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GISA and Hetero-VRSA Coming Out of the Closet

ABSTRACT & COMMENTARY

Synopsis: *Reduced susceptibility to vancomycin among clinical isolates of Staphylococcus aureus continues to add to the panoply of antibiotic-resistant organisms causing serious infections.*

Source: Wong SS, et al. *Diagn Microbiol Infect Dis* 2000;36: 261-268.

Wong and colleagues in hong kong describe the clinical and microbiological aspects of four cases of bacteremia due to *Staphylococcus aureus* that demonstrated heterogenous resistance to vancomycin (hetero-VRSA). The patients were 53-78 years of age, each had severe underlying disease, and vancomycin administration failed to eradicate the organism. All four patients died.

Routine disk susceptibility testing failed to detect resistance to vancomycin (although the zone of inhibition around the teicoplanin disk was in the "intermediate" range). Heteroresistant strains were detected as satellite colonies around an aztreonam disk on the surface of Mueller-Hinton agar containing 4% NaCl and 4 µ/mL vancomycin. The vancomycin MIC of the resistant subpopulations was, in each case, 8 µ/mL, while those of teicoplanin were 8-24 µ/mL. All isolates pro-

duced beta-lactamase and all possessed the *mecA* gene, which codes for methicillin resistance. Three of the isolates, obtained from patients at a single hospital, were indistinguishable by pulsed-field gel electrophoresis, while that obtained from a patient at a second hospital differed from the other three. Electron microscopy of the hetero-VRSA strains demonstrated a thickened cell wall when compared to MRSA strains. Checkerboard titration demonstrated significant synergy between ampicillin and vancomycin.

COMMENT BY STAN DERESINSKI, MD, FACP

The National Committee for Clinical Laboratory Standards (NCCLS) guidelines for susceptibility of *S. aureus* to vancomycin are given in the table.[1] To date, there have been no reported isolations of *S. aureus* with MIC ≥ 32 μ/mL. These intermediately susceptible isolates have been termed vancomycin-intermediate *S. aureus* (VISA), but are now more generally known as glycopeptide-intermediate *S. aureus* (GISA). Wong et al distinguish between isolates with relatively homogenous reduced susceptibility for which they reserve the term GISA and those with heteroresistance, which they term hetero-VRSA.

Table

NCCLS Guidelines for Vancomycin Susceptibility[1]

Interpretation	MIC
Susceptible	≤ 4 μ/mL
Intermediate	8-16 μ/mL
Resistant	≥ 32 μ/mL

Isolates of *S. aureus* with reduced susceptibility to vancomycin were first identified in Japan in 1996.[2] Since that time, they have also been described in many areas of the world, including the United States, Germany, France, Greece, Hong Kong, the United Kingdom, Italy, and Guatemala. Their prevalence varies greatly. In 1997, hetero-VRSA were found in hospitals throughout Japan, with 9.3% of MRSA from university hospitals and 1.3% from nonuniversity hospitals having this characteristic.[2] However, only 1.1% of MRSA yielded VISA subclones at one Italian hospital.[3]

As in the currently reviewed experience, disk susceptibility testing commonly fails to detect reduced susceptibility to vancomycin in these strains. The vancomycin agar screen plates used in this study, which are commercially available, are effective in detecting colonial growth from strains with reduced susceptibility, which should be confirmed by broth dilution testing. It has been recommended that this screening agar be used in all laboratories that use disk diffusion as their primary susceptibility method. The MicroScan method and the E test perform well when incubated for 24 hours.[4]

The mechanism of reduced resistance to vancomycin, which is distinct from that seen in enterococci, remains poorly defined. To date, hetero-VRSA and GISA (and hetero-VRCNS[5]) have only been detected on a background of methicillin resistance. VRSA and hetero-VRSA strains demonstrate an increased expression of PBP2, as well as an increased rate of cell wall turnover and they have abnormally thick cell walls, which become more apparent in GISA strains when the organism is exposed to sub-MIC concentrations of vancomycin.[6,7] It has been proposed that the activity of vancomycin is impaired due to inability to reach its site of activity.[8]

Whether the virulence of these strains is altered is unclear. One in vitro study found, however, that reduced susceptibility to vancomycin is associated with increased biofilm formation and adherence to artificial surfaces when the organism is exposed to this glycopeptide.[9]

Infection with *S. aureus* with reduced vancomycin susceptibility on the background of methicillin resistance (and beta-lactamase production) reduces the available therapeutic choices. However, many of the strains isolated to date are susceptible to antibiotics whose mechanism of action does not target the cell wall, such as trimethoprim-sulfamethoxazole, rifampin, tetracyclines, quinupristin-dalfopristin, daptomycin and linezolid. The observation by Wong et al of synergy between ampicillin and vancomycin has been previously reported. Ampicillin has relatively high affinity for PBP2A and ampicillin-sulbactam has been demonstrated to be bactericidal in vitro against some VISA strains.[10,11] ❖

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Antibiotics Anonymous Redux[1]

SPECIAL REPORT

By Stan Deresinski, MD, FACP

The problem of antibiotic resistance continues to worsen. An important contribution to this problem is the inappropriate prescription of antibiotics by physicians. For example, excess prescription of antibiotics for respiratory tract infections, particularly in children, has been identified as an important factor in the emergence of penicillin-resistant *Streptococcus pneumoniae*. Indeed, it has been suggested that some physicians have lost control over their antibiotic prescribing—that they have become, in effect, antibiotic dependent. I have, as a consequence, devised a questionnaire for the diagnosis of this dreaded addiction afflicting practicing physicians. If the answer to one or more of these questions is yes, you have a problem!

Are you antibiotic dependent?

1. Do you prescribe antibiotics to relieve tension?
2. Do you prescribe antibiotics more than other physicians but are able to hide it?
3. Do you sometimes feel guilty about the way you prescribe antibiotics?
4. Do you have a strong urge to prescribe antibiotics at a particular time of day?
5. Have you lost ambition since you began prescribing antibiotics in this way?
6. Has another physician advised you to stop or cut down your prescribing?
7. Are you harder to get along with when you are heavily prescribing?
8. Have you ever tried to cut back?
9. Do you have difficulty sleeping a full night?
10. Have you ever been in trouble with the antibiotic police?
11. Have you ever done anything while prescribing that you don't remember (have a blackout)?
12. Have you ever promised yourself you would cut back on your prescribing and then broken that promise?
13. Have you ever tried to convince people that you were not prescribing antibiotics when you were?
14. Do you wish people would mind their own business about your antibiotic prescribing—that they stop telling you what to do?
15. Have you ever switched from one kind of antibiotic to another in the hope that this would keep you from going over the edge?
16. Have you had to have an eye-opener, i.e., prescribed an antibiotic immediately upon awakening, in the last year?
17. Do you envy people who can prescribe antibiotics without getting into trouble?

For those who have answered yes to one or more of these questions, I have begun the development of a 12-step program. Unfortunately, I have only been able to develop half of a 12-step program.

1. You must admit that you are powerless over your antibiotic prescribing.
2. You must believe that a power (an antibiotic guru) greater than yourself can restore you to sanity.
3. You must make a decision to turn your will and life over to the care of that power.
4. You must make a searching and fearless moral inventory of yourself.
5. You must admit to the power and to yourself the exact nature of your misprescribing.
6. You must humbly ask the power to remove your antibiotic shortcomings. ❖

Reference

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Managed Care

SPECIAL REPORT

By Stan Deresinski, MD, FACP

Some months ago, i received a communication dealing with antibiotic use from Health Net. Health Net calls itself "California's Health Plan" and, on its Web site, describes itself in the following way: "We have an extensive network of nearly 45,000 physicians, 750 physician groups and affiliates, and 4200 pharma-

cies—all working together to serve nearly 2.2 million Members. Health Net has grown to become the largest subsidiary of Foundation Health Systems (FHS), the fourth largest publicly traded managed care organization in the United States."

The communication contained a listing of "Health Net Suggested Treatment for Respiratory Tract Infections." For patients with acute exacerbations of chronic bronchitis, it states "Antibiotics are usually not required" and gives as a citation *JAMA* 1995;273:957.[1] Saint and colleagues, however, state a different conclusion in that article: "These analyses suggest a small but statistically significant improvement due to antibiotic therapy in patients with exacerbations of COPD. This antibiotic-associated improvement may be clinically significant, especially in patients with low baseline flow rates."

Although there is some room for interpretation of the results of this study, they bring one to a conclusion far different from "antibiotics are usually not required." If Health Net is "California's Health Plan," it may be time to move to a state with a health plan that is more careful in its pronouncements. ❖

Reference

1. Saint S, et al. *JAMA* 1995;273:957-960.

Staff Fingernails Implicated in *Pseudomonas* Outbreak

ABSTRACT & COMMENTARY

Synopsis: *Evidence supported a possible relationship between long or artificial fingernails in the colonization of health care workers' hands and a prolonged outbreak of Pseudomonas aeruginosa in a neonatal ICU.*

Source: Moolenaar RL, et al. *Infect Control Hosp Epidemiol* 2000;21:80-85.

This study was initiated when 34 patients in a neonatal ICU (NICU) developed a bloodstream infection or endotracheal tube (ETT) colonization with *Pseudomonas aeruginosa*, resulting in 11 deaths. The process of investigation involved: 1) computing attack and case-fatality rates for the period of the outbreak; 2) cultures of potential environmental sources (ventilator equipment, sink drains, faucets, hand lotion, cleaning agents) and the hands and external ear canals of 104 unit staff (nurses, physicians, nurse practitioners, respiratory therapists, clerical and housekeeping staff) on an unscheduled basis; 3) genotyping all available *P. aeruginosa* isolates from stored specimens (ETT, blood, wound) and the environmental survey; and 4) a case-control study.

A case-patient was defined as an infant from whom *P. aeruginosa* was isolated from the blood or ETT within 14 days of NICU admission. Controls were randomly selected from the NICU admission log and matched with case-patients based on birth weight. To be considered a control, the infant had to be admitted to the NICU during the same time as the case-patients and hospitalized in the NICU for 14 days or longer. The ratio of controls per case was 2:1.

Of the 519 infants admitted to the NICU during the study period, 46 met the case definition, resulting in an attack rate of 10.5%. *P. aeruginosa* was isolated from two sink drains and several other areas in the hospital; however, these isolates were a distinct genotype unrelated to any of the human specimens. Of the 104 health care workers, three nurses had *P. aeruginosa* isolated from their hands. Two (Nurse A1 and Nurse A2) were positive for genotype A. A third (Nurse B) was positive for genotype B. Most case-patients also had genotype A (75%) or B (15%). Nurse A1 had long natural fingernails, Nurse B had long artificial fingernails, and Nurse A2 had short, natural fingernails.

Case-patients were more likely than controls to have Nurse A1 or Nurse B provide care during the exposure period, after adjusting for birth-weight category (odds ratio [OR], 11.4; CI_{95}, 3.3-40.0; $P = 0.0001$; and OR, 3.6; CI_{95}, 1.3-9.7; $P = 0.01$). The number of ventilator days during the exposure period, and hours exposed to nurses with long natural fingernails, were also factors associated with being a case-patient. No other exposure to a health care worker, including Nurse A2, was associated with being a case-patient. When all significant variables were entered into a multivariate model, only exposure to Nurse A1 (OR, 10.37; CI_{95}, 2.86-37.58; $P < 0.001$) or Nurse B (OR, 3.08; CI_{95}, 1.02-9.32; $P < 0.05$) remained as independent risk factors for acquiring colonization of infection with *P. aeruginosa* within the first 14 days of NICU admission.

During the survey period, a policy was introduced that restricted use of artificial fingernails and limited nail length to short or medium. The importance of infection control measures (e.g., careful hand washing and glove use) was emphasized. Afterward, ETT colonization persisted, but no *P. aeruginosa* bloodstream infections were reported for three months. However, they recurred in the

fourth month after the policy change and educational intervention.

COMMENT BY LESLIE A. HOFFMAN, PhD, RN

The major finding of this study was the statistically significant association between colonization or infection with *P. aeruginosa* and contact with two specific nurses who had *P. aeruginosa* isolated from their hands. The evidence linking the two nurses to the outbreak included: 1) microbiological evidence—culture of their hands yielded the epidemic organism; 2) genetic evidence—the isolates recovered from the nurses' fingertips were identical by pulsed-field electrophoresis; and 3) epidemiological evidence—case-control analysis demonstrated a significant association between exposure to these two nurses and acquiring *P. aeruginosa*.

The association was deemed sufficiently strong in this Oklahoma City hospital to implement a new policy restricting nurses in the NICU from wearing long (either natural or artificial) fingernails as an infection control measure. Concurrently, an educational program was provided that stressed the importance of hand washing and glove use. The policy was initially effective (0 cases for 3 months); however, the problem recurred in the fourth month.

Because the institution implemented the nail length policy and educational program at the same time, it is impossible to determine whether one or both was responsible for the diminished number of cases. Most likely, the solution was multifactorial, given that the incidence of *P. aeruginosa* declined to zero for the three months after the policy and the educational program were introduced and then relapsed.

There are several limitations to this study. The mechanism by which the nurses initially became contaminated was not identified. Their hand contamination may have been the cause or the result of the outbreak. Handwashing practices were not observed, so it is not known if these individuals' practices differed from other health care workers. All health care workers with long or artificial nails did not have positive cultures. Accordingly, findings of this study suggest, but do not prove, that the presence of long or artificial fingernails may play a role in the transmission of infection. Further study is needed to better define the problem. In the interim, short natural nails are a reasonable choice that may reduce the risk for hospital-acquired infection. (*Leslie Hoffman is Professor, Medical-Surgical Nursing Chair, Department of Acute/Tertiary Care, University of Pittsburgh School of Nursing, Pittsburgh, Penn.*)

(***Editor's note:*** *See also Passaro DJ, et al. J Infect Dis 1997;175:992-995; and Deresinski SC. Infect Dis Alert 1997;22:173.*) ❖

CME Questions

1. **Which one of the following is correct?**
   a. Tick-borne encephalitis virus is a member of the hepadnaviruses.
   b. Tick-borne encephalitis virus may be transmitted by ingestion of contaminated dairy products.
   c. The principal vector of tick-borne encephalitis virus is *Ixodes dammini*.
   d. Encephalitis occurs in the first phase of illness caused by the tick-borne encephalitis virus.

2. **Which one of the following is correct?**
   a. Reduced susceptibility to vancomycin in *S. aureus* can be reliably detected by disk diffusion susceptibility testing.
   b. *S. aureus* strains with reduced susceptibility to vancomycin have increased cell wall thickness.
   c. *S. aureus* isolates that are fully susceptible to vancomycin have MICs to this drug which are 8 µ/mL or less.
   d. Vancomycin resistance in *S. aureus* is caused by the same mechanism as vancomycin resistance *Enterococcus faecium*.

3. **In the outbreak of *Pseudomonas aeruginosa* colonization and infection in a neonatal ICU, the factor that best predicted risk of infection with *P. aeruginosa* was care provided by:**
   a. nurses with positive hand cultures.
   b. a positive culture of the external ear canal.
   c. need for total parenteral nutrition.
   d. length of stay in the NICU.
   e. None of the above

4. **Which one of the following is correct?**
   a. *Clostridium novyi* infections accounts for a minority of reported cases of gas gangrene.
   b. *Clostridium novyi* is a frequent cause of food poisoning.
   c. The toxin produced by *Clostridium novyi* blocks acetylcholine secretion at neuronal synapses.
   d. *Clostridium novyi* has frequently been recovered from culture of street heroin.

5. **Antibiotics should not be administered to children suspected of having gastroenteritis due to *E. coli* 0157:H7:**
   a. because of severe side effects.
   b. until the results of cultures are available.
   c. because of a decreased risk of Shiga toxin release.
   d. None of the above

In Future Issues:

Familial Mediterranean Fever

UPDATES

By Carol A. Kemper, MD, FACP

Did PEP Prevent HIV Infection in this Girl?

Source: Katzenstein TL, et al. *Ann Intern Med* 2000;133:31-34.

This report documents the remarkable story of an unfortunate 13-year-old girl who failed to develop evidence of HIV infection following receipt of HIV-contaminated blood and extended postexposure prophylaxis (PEP). The blood donor presented with acute HIV infection and a high viral load 25 days following a bloody head butting incident in a gay bar in Copenhagen, Denmark. It was subsequently learned that he had donated blood one week earlier.

Packed cells from the donation had already been administered two days earlier to a 13-year-old girl undergoing corrective orthopedic surgery. Immediate testing of the donor's fresh frozen plasma still available in storage demonstrated a positive HIV RNA with about 11,000 copies/mL but a negative p24 antigen. The girl's viral load was barely detectable at 3 copies/mL—possibly a false-positive test result, although entirely feasible given the circumstances. Within 48 hours of the transfusion, she was started on PEP with zidovudine, lamivudine, and indinavir. Within days, ritonavir and then nelfinavir were substituted for indinavir because of intolerance. "PEP" was continued for nine months, during which time there was no further evidence of HIV infection by antibody assay, PCR, or culture. She was found to be homozygous for the CCR5 gene (indicating that she was not refractory to HIV infection). Laboratory studies remained negative for six months after discontinuation of PEP therapy.

Infusion of HIV-infected blood is believed to be uniformly associated with the development of infection in the recipient. It therefore seems likely that infection would have occurred in the absence of PEP, although the initial pretreatment HIV test results in the recipient were inconclusive. Whether a more commonly used PEP regimen, administered for one to four weeks, would have been sufficient or whether the extended PEP administered in this high-risk situation was necessary to successfully thwart infection remains uncertain. ■

45-Year Outcome of HCV Infection

Source: Seeff LB, et al. *Ann Intern Med* 2000;132:105-111.

Reports suggest that up to 20% of patients with hepatitis C virus (HCV) infection may progress to chronic liver disease. Using archived serum samples collected between 1948 and 1954, Seeff and colleagues at the Veterans Affairs Medical Center in Washington, DC, were able to assess the natural history of HCV infection on 8568 military personnel originally recruited for a study of group A streptococcal infection. Antibodies to HCV were detected in 17 (0.2%) of the banked sera using ELISA and recombinant immunoblot assay.

More than 45 years later, liver disease had been diagnosed in two of 17 HCV-positive persons (11.8%) vs. 205 of those who were HCV-negative (2.4%). Seven (41%) of the HCV-positive persons had died compared with 2226 (26%) of those who were HCV negative (relative risk, 1.5; CI, 0.8-2.6). Of those who were HCV-positive, one (5.9%) had died due to liver disease (42 years after the original phlebotomy); five had died from unrelated causes and one for unknown reasons a median of 37 years later. In comparison, 119 HCV-negative persons (1.4%) had died of liver disease. Although retrospective studies are often fraught with problems, this extended natural history study suggests that the risk of progression to chronic liver disease in apparently healthy individuals infected with HCV may be less than suggested by other reports. ■

Avoid Antibiotics in Children with *E. coli* 0157:H7

Source: Wong CS, et al. *N Engl J Med* 2000;342:1930-1936.

Earlier reports suggested that the administration of antibiotics to cultures of *Escherichia coli* 0157:H7 increased the risk of Shiga toxin release. In order to assess the possibility that hemolytic-uremic syndrome (HUS) may be increased because of the administration of antibiotics, Wong and colleagues conducted a prospective cohort study of 71 children younger than 10 years of age with diarrhea due to *E. coli* 0157:H7. Among the 71 subjects, nine received antimicrobial therapy and 10 developed HUS. Surprisingly, the administration of antibiotics was significantly associated with the risk of HUS (relative risk = 14.3; CI = 2.9-70.7). HUS developed in five of nine patients (56%) receiving antibiotics compared with four of 62 (8%) who did not receive antibiotics ($P < 0.001$).

Other factors associated with an increased risk of HUS included how quickly a stool culture was obtained during the initial illness and a higher initial white blood cell count—both of which are probably reflective of the severity of illness at presentation. While 35% of patients with white blood cell (WBC) counts ranging from 14.3-24.6 cells/mm^3 developed HUS, only 6% of those with WBC counts of 8800-11,000 cells/mm^3 and none with lower WBC counts did. The sex of the child, the presence of fever, vomiting, or bloody diarrhea, or the type of antibiotic administered were not predictive of HUS. Each of the *E. coli* strains recovered in children with HUS were sensitive to the agent received. This report strongly suggests that antibiotics should not be administered to children suspected of having gastroenteritis due to *E. coli* 0157:H7 until the results of cultures are available. ■

INFECTIOUS DISEASE ALERT®

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United States Unprepared for Bioterrorism Attack, Experts Warn

Better Education Urged for Health Care Providers

By Stephen Lewis

When the united states is attacked with a biological agent (and a growing number of experts believe "when" is much more appropriate than "if"), it will be clinicians, emergency room physicians, and nurses who will be on the front lines. However, those health care providers need education on spotting and responding to a bioterrorism (BT) attack.

BT is defined by the Atlanta-based Centers for Disease Control and Prevention (CDC) as "The intentional or threatened use of viruses, bacteria, fungi, toxins from living organisms, or other chemicals, to produce death or disease in humans, animals, or plants."

BT agents can be "deliberately released into the population, the food supply, released into the air, or through infected persons," noted Scott Lillibridge, MD, director of the CDC's Bioterrorism Preparedness and Response Program. "And the first responders will be health care providers."

Lillibridge made his remarks during the International Conference on Emerging Infectious Diseases 2000, held in Atlanta July 16-19. The conference was organized by the CDC, the Council of State and Territorial Epidemiologists, the American Society for Microbiology, the Association of Public Health Laboratories, and the National Foundation for CDC.

"Initial detection and initial response, will be local," added Ali S. Kahn, MD, MPH, who is also affiliated with the Bioterrorism Preparedness and Response Program. "Clinical diagnostics at the point of care will be critical; astute clinicians will be invaluable. We need physician education."

Emergency room visits will be a critical point of identification, Kahn noted, adding: "We will be very dependent on calls from individuals such as infection control nurses."

Other presenters at the conference agreed. "The first place BT victims will be treated will be in emergency rooms and clinics," said Stephen S. Morse, PhD, a program manager in the Defense Sciences Offices of DARPA, the Defense Advanced Research Project Agency of the Defense Department, based in Arlington, Va.

A Different Kind of Emergency

BT presents the prospect of a disaster with which most responders would be unfamiliar, noted Lillibridge. "Whole cities and regions could be in peril," he warned. "We could be looking at a major medical emergency—far different from those that FEMA [Federal Emergency Management Agency], for example, has been dealing with, and with which we are more familiar."

The most likely biological agents used in an attack would be anthrax, smallpox, plague, botulism, tularemia, or VHF. These have been identified by the CDC as "Critical Biologic Agents," said Kahn. This is not necessarily because a terrorist would

more likely choose these over other agents, but because "if released, we would have a major public health issue."

The treatment and outcomes, noted Lillibridge, may not be that different from what would be seen with an emerging infectious disease. "But it's been a long time since we've had to respond to a situation like this; we've had little experience here with epidemics involving the population at large—a major federal outbreak."

Yet Lillibridge is convinced the threat is very real. He noted the accessibility of biotechnology information to terrorist groups such as Aum Shinrykyo, "which, in addition to releasing nerve gas in Tokyo's subway, experimented with botulism and anthrax," he said in a September 22, 1999, statement before the Subcommittee on National Security, Veterans Affairs and International Relations Committee on Government Reform, U.S. House of Representatives.

"An attack with an agent such as smallpox could pose threats to large populations because of the potential for person-to-person transmission, enabling spread to other cities and states . . . would quickly culminate in a nationwide emergency. International involvement would be sure to follow," he said in his statement.

Time is of the Essence

The ability to recognize and respond quickly to a BT outbreak was stressed time and again by speakers at the Atlanta conference.

"There could potentially be many casualties, and there is a short window for intervention," noted Kahn.

"If we delay, we could pay a terrible price," added Martin I. Meltzer, PhD, of the CDC, who gave a presentation on smallpox—which has only been identified as a potential weapon in the last 18-24 months.

Meltzer presented a frightening graphic, which showed that if 10 people were initially infected and untreated, and each of them in turn infected three more individuals per day, that 774 billion people would be infected in one year's time.

Meltzer went on to note that vaccine and quarantine have worked well in combination against smallpox, since history shows an average of 1.48 people infected by each initially infected person. Nevertheless, he added, rapid response is essential. "The difference between 25 days and 45 days is unbelievable," he said. "We have to be prepared."

The subsequent "Q&A" session demonstrated that even the experts are not clear on what it would take to win such a war. Meltzer suggested that 40 million doses of vaccine should be stockpiled to be adequately prepared for a BT attack of smallpox. But Meltzer said that individuals vaccinated more than 30 years ago still have sufficient immunity that the virus would not kill them.

"I believe 80% of the individuals are susceptible in this population," argued a questioner. "And 40 million doses is not enough." In either case, with the virus "eradicated" years ago, the current stockpile is negligible.

Complicating the issue is that in the early stages of infection, BT agents are difficult to identify. "Many of the early symptoms are flu-like," said Morse, noting that they can include headache, muscle aches, chills, and loss of appetite. "Biological warfare agents are often indistinguishable from flu and from each other."

Morse then added this chilling admission: "By the time the symptoms appear, it may be too late to save the patient; we need to determine who was exposed before the symptoms appear."

All of this makes the case for better education that much more compelling. Health care providers with an intimate knowledge of how these agents behave will be in a better position to determine whether one of them is behind a certain constellation of symptoms.

A Nationwide Effort

With the CDC at the helm, a growing group of federal public health and military agencies is working together to better identify and respond to possible BT outbreaks. For example, the National Notifiable Disease Surveillance System (NNDSS) reports weekly to the CDC. Armed with data on previous outbreaks of infectious diseases, they are alerted by infections that occur "outside normal areas, or with unusual or unexplained [population] distribution," explained the CDC's Man-huei Chang, MPH.

But, Chang reported, there is no single U.S. system for the baseline data that are needed, underscoring the fact that national preparedness efforts are also in a race against time.

"Since 1973, at least 30 new viral agents have been identified, and there are new threats all the time," noted Lillibridge, who cited HIV, resistant TB, and West Nile as some of the more recent threats. "The tools of bioscience are increasingly available. There exists the ability to alter pathogens or to create new ones, and we are not prepared."

Kahn noted that several medical groups, including the American Medical Association and the American College of Emergency Physicians, are taking the lead in working with the CDC to educate their members and to help prepare for an event that may be more likely than many would like to admit.

A high state of preparedness could help ensure the public safety on more than one level, said Lillibridge. "After all," he noted, "in a BT attack, the health care provider population could be decimated as well."

*(**Editor's Note:** For more information about the CDC's Bioterrorism Preparedness and Response Program, visit their Web site at: http://www.bt.cdc.gov/index.asp. Or, contact: Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333. Telephone: (404) 639-3311.)* ❖

Infectious Diseases Make More Resistant Comeback

By Kim Coghill

A premature complacency in the battle against infectious diseases in the United States and throughout the world has allowed new and old diseases to make a deadly comeback, speakers told a gathering of infectious disease experts in Atlanta, at the International Conference on Emerging Infectious Diseases held July 16-19.

"Despite all the progress we are making, disease still seems to have the upper hand," said Sen. William Frist, MD, (R-TN) during his keynote address. "New diseases keep emerging and old diseases are making a comeback, stronger and more resistant to treatment than ever before."

Frist was one of several speakers who opened the second annual conference sponsored by the Atlanta-based Centers for Disease Control and Prevention that was expected to draw upward of 2000 scientists and clinicians from around the world.

Jim Hughes, MD, director of the Atlanta-based National Center for Infectious Diseases and a second keynote speaker, said many scientists believed that the middle of the 20th century marked the end of one of the most important social revolutions in history with the virtual elimination of infectious diseases as a significant factor in social life.

"But a complacency has developed which explains why we have gotten behind in dealing with infectious diseases," Hughes said. More than 30 new infections have been identified in the past 20 years.

Spread of Disease Creating Desperate Situation

The results of that complacency are all too familiar, says Frist, who recently returned from a second medical mission to Africa, where he experienced first-hand poverty, infectious diseases, and a lack of hope among villages of people who live in unhealthy circumstances.

Sudan is a classic example of what has come to be known as "humanitarian warfare," a type of aggression characteristic of the post-Cold War era. This type of warfare, Frist said, deliberately seeks to inflict pain and suffering on civilian noncombatants by denying them vital human necessities.

Unlike other wars, where collateral damage is unintentional, "humanitarian warfare" uses starvation, forced migration, and the manipulation of medical resources and food supplies as an integral part of its military strategy, Frist said. "This is the place where health and national security really intersect."

It has been reported widely in recent months that the spread of HIV/AIDS in Africa is threatening the national security of the United States and that of other countries. And while infectious diseases are considered diseases of poverty, they also present obstacles to growth and development, said David Heymann, MD, executive director of communicable diseases for the Geneva-based World Health Organization. In low-income countries, about 45% of deaths are due to infectious diseases vs. 44% worldwide.

Just as one disease is eradicated, often another surfaces particularly affecting Third World nations, said Heymann. This is the case with smallpox, which has cost the world 1.5 million lives and millions of dollars. In the early 1980s, smallpox was under control worldwide at the same time AIDS became a threat.

Throughout sub-Saharan Africa, more than 23 million adults and children are infected with HIV. With an overall infection rate of about 8%, as compared to 1.1% worldwide, almost 14 million Africans have died from AIDS. "And this is the only region in the world where women are infected at a higher rate than men," Frist said. "About 55% of the HIV-positive adult population are women, and girls and young women are particularly at risk with an infection rate of 15% to 23%."

As a result, 600,000 infants also have become infected through mother-to-child transmissions, either at birth or through breast feeding, causing 8 million children to have lost one or both parents due to AIDS.

But the AIDS virus is not the only infectious disease threatening Africa or other parts of the world including the United States. Tuberculosis—the great killer of the 19th Century—has re-emerged "with a vengeance, stronger and more resistant to drugs than ever before," Frist said. "It claims a million African lives each year and today there are 16 million cases of TB worldwide. Of those, at least 1% to 2% are multi-drug resistant," he added.

Yet still another re-emerging disease is malaria, which each year kills more than 1 million people—mostly children. Resistance to chloroquine, the former treatment of choice, is now widespread in 80% of the 92 countries where malaria is a major killer, Frist said. "It doesn't take a surgeon to understand the threat of infectious disease, whether locally grown or borne on silent wings from a far-off corner of the world," he said. "It is a threat that is real and growing. And when you couple it with the potential that exists for our adversaries to deliberately target Americans through bioterrorist attack, the enormity of the problem becomes alarmingly apparent. Bioterrorism is not a question of if—but when."

Meeting the Challenges of the Threats

Research and drug development are necessary to meet the growing challenges emerging infectious diseases pose. As a senator, Frist has the ability to help obtain funding necessary to fight diseases.

To help stop the spread of HIV/AIDS, TB, and other infectious diseases, last week Frist offered the Global AIDS and Tuberculosis Relief Act of 2000, an amendment that would provide $460 million for HIV/AIDS. Of that money, $300

million would go toward prevention and education; testing and counseling; medications to prevent transmission; and care for those living with HIV and AIDS.

And in an effort to both improve the public health infrastructure and address the growing threats of antimicrobial resistance and bioterrorism, Frist recently introduced the Public Health Threats and Emergencies Act of 2000. If passed as submitted, the bill will:

- Enhance the CDC's ability to improve core capacities for basic surveillance technologies in labs at the federal, state, and local levels;
- Expand National Institutes of Health research for the development of improved diagnostics tools and therapies for resistant pathogens. ❖

Smallpox: A Single Case is a Medical Emergency

By Gary Evans

The centers for disease control and prevention (CDC) currently recommends the following infection control precautions for smallpox. The CDC is expected to issue a new guidance on smallpox response in the near future, and some of the information may be updated. The guidelines summarized below were developed in conjunction with the Association for Professionals in Infection Control and Epidemiology.[1]

Smallpox is an acute viral illness caused by the variola virus. Smallpox is a bioterrorism threat due to its potential to cause severe morbidity in a nonimmune population and because it can be transmitted via the airborne route. A single case is considered a public health emergency. Acute clinical symptoms of smallpox resemble other acute viral illnesses, such as influenza. Skin lesions appear, quickly progressing from macules to papules to vesicles. Smallpox is transmitted via both large and small respiratory droplets. Patient-to-patient transmission is likely from airborne and droplet exposure, and by contact with skin lesions or secretions. Patients are considered more infectious if coughing or if they have a hemorrhagic form of smallpox.

Preventive measures. A live-virus intradermal vaccination is available for the prevention of smallpox. Since the last naturally acquired case of smallpox in the world occurred more than 20 years ago, routine public vaccination has not been recommended. Vaccination against smallpox does not reliably confer lifelong immunity. Even previously vaccinated persons should be considered susceptible to smallpox.

Infection control practices. For patients with suspected or confirmed smallpox, both airborne and contact precautions should be used in addition to standard precautions. Airborne precautions require health care providers and others to wear respiratory protection when entering the patient room. (Appropriate respiratory protection is based on facility selection policy; must meet the minimal standards for particulate [N95] respirators). Contact precautions require health care providers and others to wear clean gloves upon entry into patient rooms; and wear a gown for all patient contact and for all contact with the patient's environment. Based on local policy, some health care facilities require a gown be worn to enter the room. Gowns must be removed before leaving the patient's room. Wash hands using an antimicrobial agent.

Patient placement. Patients with known or suspected smallpox should be placed in rooms that meet the ventilation and engineering requirements for airborne precautions, including a door that remains closed; monitored negative air pressure in relation to the corridor and surrounding areas; and 6-12 air exchanges per hour. Health care facilities without patient rooms appropriate for the isolation and care should have a plan for transfer of suspected or confirmed smallpox patients to neighboring facilities with appropriate isolation rooms. Patient placement in a private room is preferred. However, in the event of a large outbreak, patients who have active infections may be cohorted in rooms that meet appropriate ventilation and airflow requirements.

Post-exposure issues. Post-exposure immunization with smallpox vaccine (vaccinia virus) is available and effective. Vaccination alone is recommended if given within three days of exposure. Passive immunization (i.e., for complications of vaccination) is available in the form of vaccinia immune-globulin (VIG) (0.6 mL/kg IM). If more than three days has elapsed since exposure, both vaccination and VIG are recommended. Vaccination is generally contraindicated in pregnant women, and persons with immunosuppression, HIV-infection, and eczema who are at risk for disseminated vaccinia disease. However, the risk of smallpox vaccination should be weighed against the likelihood for developing smallpox following a known exposure. VIG should be given concomitantly with vaccination in these patients. Following prophylactic care, exposed individuals should be instructed to monitor themselves for development of flu-like symptoms or rash during the incubation period (i.e., 7-17 days after exposure) and immediately report to designated care sites selected to minimize the risk of exposure to others. Facilities should ensure that policies are in place to identify and manage health care workers exposed to infectious patients. In general, maintenance of accurate occupational health records will facilitate identification, contact, assessment, and delivery of post-exposure care to potentially exposed health care workers. ❖

Reference

1. Association for Professionals in Infection Control and Epidemiology Bioterrorism Task Force and Centers for Disease Control and Prevention Hospital Infections Program Bioterrorism Working Group. Bioterrorism readiness plan: A template for healthcare facilities. 1999. http://www.cdc.gov/ncidod/hip/Bio/bio.htm.