

Medical News

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Additional news items in this issue: *Reducing IV Device-Associated Infections*, page 448; *Early-Onset Versus Late-Onset Nosocomial Pneumonia in ICU*, page 454.

Anergy Testing and Tuberculin Skin Testing

Although anergy testing is commonly used to help interpret negative tuberculin skin test results, the validity of this approach has not been demonstrated. Specific issues include lack of a standardized protocol for antigen selection, number needed to evaluate reliably inability to respond, and uniform criteria for defining cutaneous reactivity, as well as regional variation in skin test reactivity. Tuberculin skin testing is used to screen for latent infection and to evaluate the need for INH prophylaxis. The presence or absence of reactivity to control antigens does not affect this decision. The results of anergy testing also do not predict the risk for progression to active disease in either HIV-negative or HIV-positive patients. In HIV-negative patients with active TB, 10% to 20% have negative tuberculin test results, and 5% to 10% have a negative tuberculin result but have a positive reaction to another antigen. A negative tuberculin skin test result does not exclude either latent infection or active disease, even in the presence of a reaction to other antigens. Neither anergy testing nor tuberculin testing obviates the need for microbiological evaluation when there is suspicion for active TB infection. Therefore, anergy testing is not useful in screening for asymptomatic tuberculous infection or for diagnosing active TB.

FROM: Slovis BS, Plitman JD, Haas DW. The case against anergy testing as a routine adjunct to tuberculin skin testing. *JAMA* 2000;283:2003-2007.

DHHS Classified ETO as Human Carcinogen

Ethylene oxide (ETO) has been identified as a known human carcinogen in the Ninth Report on Carcinogens, prepared by the National Toxicology Program and released by the Department of Health and Human Services (DHHS) on May 15. The substance, which is widely used in healthcare facilities to sterilize medical devices, had been listed in previous reports as "reasonably anticipated to be a human carcinogen."

When ETO was first listed in the Fourth Report on

Carcinogens in 1985 as a reasonably anticipated human carcinogen, only limited evidence of its carcinogenicity in humans was available. Subsequent research showing an increased risk for leukemia and non-Hodgkin's lymphoma in workers exposed to ETO, coupled with data on its genotoxic and biochemical interactions with human DNA, led to its reclassification as a known human carcinogen.

Ethylene oxide is used in hospitals to sterilize heat-sensitive medical items, surgical instruments, and other objects and fluids coming in contact with biological tissues. The report states "Exposure mostly results from peak emissions during operations such as opening the door of the sterilizer and unloading and transferring sterilized material . . . With the proper use of engineering controls and work practices, exposure levels can be very low." A Special Hazard Review by NIOSH recommended ETO exposure limits of 0.1 ppm as an 8-hour time-weighted average (TWA) and 5 ppm as a ceiling concentration for no more than 10 minutes. OSHA lowered the permissible exposure limit from 50 ppm to 1 ppm as an 8-hour TWA in 1984 and in 1988 established a short-term exposure limit of 5 ppm during a 15-minute period.

FROM: Ninth Report on Carcinogens. US Department of Health and Human Services National Toxicology Program, "The 9th Report on Carcinogens 2000": <http://ehis.niehs.nih.gov/roc>.

Hemolysis Outbreak in Hemodialysis Patients

Hemolysis associated with hemodialysis is rare. The most frequent causes of hemodialysis-associated hemolysis are chemical contamination, heat, or mechanical injury of erythrocytes from occluded or kinked hemodialysis bloodlines. When patients in three states developed hemolysis while undergoing hemodialysis between May 13 and 23, 1998, Dr. Rose Duffy and coinvestigators from the CDC's Hospital Infections Program, in collaboration with the state health departments, initiated an investigation. A case-patient was defined as any patient at healthcare facilities A (Nebraska), B (Maryland), or C (Massachusetts) during May 13 through 23, 1998 (epi-

demic period) who had hemolysis diagnosed >48 hours after undergoing hemodialysis. To identify case-patients and to determine background rates, the medical records of patients from facilities A, B, and C who were undergoing hemodialysis during the epidemic and pre-epidemic (that is, May 5-19, 1998) periods were reviewed. Experiments simulating hemodialysis with the same lot numbers of hemodialysis blood-tubing cartridge sets used on case- and control-patients were conducted.

The rates of hemolysis among patients at facilities A, B, and C were significantly higher during the epidemic than the pre-epidemic period (13/118 vs 0/118, $P<.001$; 12/298 vs 0/298, $P=.001$; and 5/62 vs 0/65, $P=.03$, respectively). All case-patients had hemolysis. Twenty (66%) had hypertension, 18 (60%) had abdominal pain, and 10 (36%) were admitted to an ICU. There were two deaths. The only commonality among the three outbreaks was the use of the same lot of disposable hemodialysis blood-tubing from one manufacturer. Examination of the implicated hemodialysis blood-tubing cartridge sets revealed narrowing of an aperture through which blood was pumped before entering the dialyzers. In vitro experiments with the hemodialysis blood tubing revealed that hemolysis was caused by increased pressure on erythrocytes as they passed through the partially occluded hemodialysis blood tubing.

The investigation traced the multiple hemolysis outbreaks to partially occluded hemodialysis blood tubing produced by a single manufacturer. On May 25, 1998, the manufacturer issued a voluntary nationwide recall of the implicated lots of hemodialysis blood-tubing cartridge sets.

FROM: Duffy R, Tomashek K, Spangenberg M, Spry L, Dwyer D, Safranek TJ, et al. Multistate outbreak of hemolysis in hemodialysis patients traced to faulty blood tubing sets. *Kidney Int* 2000;57:1668-1674.

Modeling Biofilm Antimicrobial Resistance

In the past 20 years, there has been a great deal of research on biofilms, the slime layers that are deposited on surfaces by microorganisms growing in liquids ranging from water to blood. The organisms are protected by the matrix of the biofilm, and they are, in essence, resistant to germicides or antibiotics.

In a recent paper, Dodds and coinvestigators, from the Center for Biofilm Engineering, Department of Chemical Engineering, Montana State University, in Bozeman, described a computer model capable of integrating mechanisms of biofilm resistance to disinfection by antimicrobial agents. Resistance mechanisms considered included retarded penetration due to a stoichiometric reaction between the antimicrobial agent and biomass, incomplete penetration due to a catalytic reaction between the antimicrobial agent and the biomass, and the existence of a fraction of the cells in a resistant phenotypic state. Mathematical models of these processes were

derived and solved in a computer simulation package. Four sets of fitted experimental data on the disinfection of *Pseudomonas aeruginosa* biofilms were fit to each of the three models. No one model fit all of the data sets adequately. Killing of a 2-day old biofilm by tobramycin was best described by the physiological limitation model. Killing by hypochlorite was best described by the stoichiometric transport model. Killing by hydrogen peroxide was best simulated by the catalytic transport model.

These results suggest that multiple mechanisms of biofilm reduced susceptibility are manifested even in biofilms of the same species and that the particular resistance mechanism depends on the biofilm age, antimicrobial agent, and biofilm thickness. The models presented in this article may be useful for diagnosing mechanisms of biofilm resistance from experimental data.

FROM: Dodds MG, Grobe, KJ, Steward PS. Modeling biofilm antimicrobial resistance. *Biotechnol Bioeng* 2000;68:456-465.

Aged Dialyzers Cause Outbreak of Severe Reactions

An event in which seven patients at one hospital developed decreased vision and hearing, conjunctivitis, headache, and other severe neurological symptoms 7 to 24 hours after hemodialysis drew attention to the issue of the long-term integrity of dialysis machines and materials. Hutter and colleagues, from the FDA's Center for Devices and Radiological Health, and the CDC's Hospital Infections Program conducted an investigation to determine the cause of the adverse reactions that occurred during this event. A retrospective cohort study was conducted of all nine patients who received hemodialysis at hospital A on September 18, 1996, the day of the outbreak. A case-patient was defined as any hospital A patient with acute onset of decreased vision and hearing and conjunctivitis after dialysis on that day. Non-case-patients were all others who underwent dialysis at hospital A on that day but did not develop adverse reactions. In an attempt to reproduce the conditions of the event, cellulose acetate dialysis membranes of various ages were retrieved from other sources and tested for physical and chemical degradation, and degradation products were identified, characterized, and injected intravenously into rabbits. The primary outcome measures were clinical signs and symptoms, time to resolution of symptoms, mortality, and dialyzer type and age, for case- versus non-case-patients.

Seven of the nine patients met the case definition. In addition to diminished vision and hearing, conjunctivitis, and headache, some case-patients had blood-leak alarm activation ($n=6$), confusion/lethargy ($n=5$), corneal opacification ($n=4$), cardiac arrest ($n=2$), or other neurological signs and symptoms. One case-patient died during hospitalization after the event; five of seven case-patients died within 13 months. Resolution of signs and symptoms varied but persisted more than 3 years or until death in three