Multistate Outbreak of Hemolysis in Hemodialysis Patients—Nebraska and Maryland, 1998

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From May 13 through May 23, 1998, a total of 30 patients in three states developed hemolysis with or without chest pains, shortness of breath, nausea, or abdominal pain while undergoing hemodialysis (HD). Two patients died. This report summarizes the preliminary findings of investigations in Nebraska and Maryland and implicated lot number 04D15309 of Cobe Centrysystem 3 Blood Tubing sets (Gambro Healthcare, Lakewood, Colorado) as the cause of these reactions.

Nebraska

A case was defined as hypertension (an increase of ≥30 mm Hg from the baseline systolic blood pressure) and evidence of hemolysis (i.e., positive “pink test” [pink-appearing serum]) in a patient within 12 hours of initiating hemodialysis during May 13-20. A total of 13 (11%) of 118 patients at two HD centers in Lincoln, Nebraska, had illnesses that met the case definition. In addition, case-patients reported chest pain (five), shortness of breath (four), nausea (four), abdominal pain (four), vomiting (three), back pain (two), cyanosis (two), or diarrhea (one). Onset of symptoms occurred a median of 120 minutes (range: 20-272 minutes) into the dialysis session.

Case-patients ranged in age from 46 to 84 years (median: 70 years); seven were men. They had received hemodialysis for a median of 3 years (range: <1 to 8 years); 11 (85%) used reprocessed dialyzers. Of the 13 patients, 11 (85%) required hospitalization; four (31%), admission to an intensive-care unit (ICU); and three (23%), blood transfusion. The 13 case-patients were dialyzed on 12 different machines but all may have been dialyzed using a Cobe Centrysystem 3 Blood Tubing Set (lot number 04D15309) that was present at the clinic during the dialysis period. During hemodialysis, lot numbers of blood tubing are not routinely recorded. However, for six case-patients, the blood tubing lot number was 04D15309.

Examination of the implicated blood tubing revealed narrowing of the aperture through which blood was pumped during the dialysis treatment. Analyses of the water supply at one of the HD centers was within normal limits for chlorine, chloramine, endotoxin, bacteria, and trace element levels as set by the American Association for the Advancement of Medical Instrumentation.

Maryland

During May 18-23, a total of 12 (4%) of 298 patients at four HD centers in Baltimore developed abdominal pain (eight), nausea (seven), and/or erythroderma (four); all had evidence of hemolysis on admission to the hospital. Onset of symptoms occurred a median of 114 minutes (range: 22-227 minutes) into the dialysis session.

Case-patients ranged in age from 48 to 85 years (median: 67 years); seven were men. Case-patients had received hemodialysis for a median of 3 years (range: 1 to 5 years); none used reprocessed dialyzers. All case-patients required hospitalization; four, admission to ICU; and six, blood transfusion. The 12 case-patients were dialyzed on 12 different machines, but all may have been dialyzed using a Cobe Centrysystem 3 Blood Tubing Set (lot number 04D15309) that was present at the clinic during the dialysis period.

On May 25, the manufacturer issued a voluntary nationwide recall of specific lots of catalog number 003210-500 (including lot number 04D15309) of Cobe Centrysystem 3 Blood Tubing sets. On June 10, following additional reports (including two additional deaths) in Alabama and New Jersey, the manufacturer expanded the recall to all lots of Cobe Centrysystem 3 Blood Tubing sets and Cobe Hemodialysis kits containing blood tubing sets for dialysis with catalog numbers 003109-400, 003109-410, 003110-500, 003111-500, 003112-500, 003113-500, 003114-500, 003210-500, 003212-500, 003101-000, and 003212-515.

CDC Editorial Note: In the United States, approximately 225,000 persons with end stage renal disease undergo long-term hemodialysis each year. Hemolysis (i.e., premature breakdown of red blood cells [RBCs]) associated with hemodialysis is rare.2,3 The most frequent causes of hemodialysis-associated hemolysis are increased chloramine in the water used for dialysis; nitrate contamination of the dialysate, formaldehyde residue left after dialyzer reprocessing or water treatment system disinfection, use of hypotonic dialysate or dialysate exceeding 108°F (42°C), or mechanical injury of RBCs from occluded or kinked hemodialysis blood lines.2,4

In this outbreak, all episodes of hemolysis have been associated with blood tub-
ing produced by a single manufacturer. Preliminary findings suggest that the narrowed aperture of the blood tubing set caused mechanical lysis of the RBCs. 

To ascertain the extent of this problem, all episodes of hemolysis in dialysis patients using a Cobe Centrsystem 3 Blood Tubing Set or Cobe Hemodialysis Kit should be reported through state health departments to CDC’s Hospital Infections Program, National Center for Infectious Diseases, telephone (404) 639-6413, and to the Food and Drug Administration’s MedWatch program, telephone (800) 332-1088.

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Statewide Surveillance for Ehrlichiosis—Connecticut and New York, 1994-1997

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IN THE United States, human monocytic ehrlichiosis (HME) and human granulocytic ehrlichiosis (HGE) represent two clinically indistinguishable yet epidemiologically and etiologically distinct diseases caused by Ehrlichia chaffeensis and a bacterium similar or identical to E. equi, respectively. Infection with these emerging tickborne pathogens results in acute, influenza-like illnesses with fever, headache, malaise, and frequently leukopenia and/or thrombocytopenia. Connecticut and New York have initiated statewide laboratory-based surveillance to determine the magnitude and geographic extent of ehrlichiosis. This report summarizes results from the first 3 years of surveillance, which showed that rates of ehrlichiosis were similar in counties in both states where the disease occurs, and highest age-specific rates occurred among persons aged >40 years.

In New York, since 1994, physicians have been encouraged to submit serum specimens and clinical data from patients with signs and symptoms consistent with ehrlichiosis. Ehrlichiosis became reportable in Connecticut in January 1995 and in New York in March 1996; public health laboratories in both states have provided confirmatory serologic testing for ehrlichiosis since 1995. State laboratories tested serum specimens by indirect fluorescent antibody (IFA) assay to detect antibodies against E. chaffeensis and E. equi, and tested whole blood or serum using polymerase chain reaction (PCR) assays to detect Ehrlichia spp. DNA. A probable case was defined in New York as the presence of a single antibody titer ≥1:80 to E. chaffeensis or ≥1:50 to E. equi. A confirmed case was defined in both states as a fourfold or greater increase in antibody titer between acute-phase and convalescent-phase serum specimens, visualization of intracytoplasmic ehrlichiae (i.e., morulae) in peripheral blood leukocytes (plus, in New York, at least one antibody titer ≥1:80), or identification of DNA sequences of E. chaffeensis or the agent of HGE by PCR assay.

Connecticut
From 1995 through 1997, a total of 173 ehrlichiosis cases were reported in Connecticut; 191 (76%) were confirmed, and 42 (24%) were probable. Of the 173 confirmed and probable cases, 155 (90%) were HGE and nine (5%) were HME; nine (5%) persons had antibodies reactive with both E. chaffeensis and E. equi. Cases were identified by IFA (83), PCR (69), both assays (19), and visualization of morulae (two).

Frequencies of specific signs and symptoms were similar to frequencies identified in previous case series.1-3 Information about fever (defined as ≥100.4 F [≥38.0 C]) was known for 162 patients; of the 138 (85%) with fever, the median temperature was 102.4 F (39.1 C). Information about leukopenia (defined as white blood cell count [WBC] <5.0 × 10^9/L) was known for 130 patients; of the 79 (61%) with leukopenia, the median WBC was 3.2 × 10^9/L. Information about thrombocytopenia (defined as platelet count <150 × 10^9/L) was known for 130 patients; of the 92 (68%) patients with thrombocytopenia, the median platelet count was 87 × 10^9/L.

Ehrlichiosis cases occurred in all months except January; 133 (77%) of the 173 cases occurred during May–September. Illnesses occurred equally in males and females (mean age: 61.9 years; range: 2 days–90 years). The 19 (11%) patients who were hospitalized were substantially older (mean age: 61.9 years) than patients who were not hospitalized (mean age: 44.7 years). One patient died with cancer as the primary diagnosis at the time of death. Treatment information was available for 66 cases. Reported antibiotic therapy began at a median of 4.5 days from symptom onset; 59 of the 66 patients received doxycycline.

The statewide average annual reporting rate for 1995-1997 was 1.8 cases per 100,000 population (range: 1.1 in 1995 to 2.9 in 1997). In 1997, a total of 96 cases were reported, an increase from 40 in 1996 and 37 in 1995. Ehrlichiosis cases were reported in all eight Connecticut counties; the highest average annual reporting rate was in Middlesex and New London counties (9.3 and 4.8, respectively). Age-specific rates were higher among persons aged >40 years; the highest rate (3.9) was among those aged 70–79 years.

New York
From 1994 through 1997, a total of 225 ehrlichiosis cases were reported in New York; 135 (60%) were confirmed, and 90 (40%) were probable. Of the 225 confirmed and probable cases, 197 (88%) were HGE, and 28 (12%) were HME. Cases were identified by IFA (138), PCR (57), and both assays (30); nine with a positive IFA titer also had visualization of morulae.

Frequencies of specific signs and symptoms were similar to those reported for Connecticut patients. All 218 patients for whom fever information was available had fever (median temperature: 102.5 F [39.2 C]). Information about leukopenia was known for 177 patients; of the 110 (62%) with leukopenia, the median WBC was 4.0 × 10^9/L. Information about thrombocytopenia was known for 171 patients; of the 122 (71%) with thrombocytopenia, the median platelet count was 114 × 10^9/L. Ehrlichiosis cases occurred during all months; 182 (81%) of

1*No data were available for five patients in Massachusetts.
2Use of trade names and commercial sources is for identification only and does not imply endorsement by CDC or the U.S. Department of Health and Human Services.
the 225 cases occurred during May-September. Most (123 [55%] of 225) cases occurred in males. The mean patient age was 58 years (range, 1-86 years). Ninety-three patients were hospitalized; one person with a probable case died from multiple organ failure.

The statewide average annual reporting rate for 1994-1997 was 0.4 cases. In 1997, a total of 67 cases were reported, a decrease from 69 in 1996 but an increase from 51 in 1995 and 14 in 1994. Ehrlichiosis cases were reported in 19 of the 62 counties in New York. Most cases occurred in the lower Hudson River Valley and eastern Long Island; the highest yearly reported rates were in Westchester and Putnam counties (5.5 and 3.6, respectively). As in Connecticut, age-specific rates were higher among persons aged >40 years; the highest rates were among those aged 70-79 years.

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CDC Editorial Note: Since 1985, approximately 500 ehrlichiosis cases have been confirmed by CDC. The occurrence of these diseases reflects the seasonal activities and geographic distributions of the tick vectors. The preponderance of ehrlichiosis cases are observed between mid-spring and mid-summer. *E. chaffeensis* infections occur most frequently in southeastern and midwestern states with abundant lone star ticks (*Amblyomma americanum*). The black-legged tick (*Ixodes scapularis*) is the principal vector of the HGE agent in the northeast and upper midwestern United States. This tick also transmits *Borrelia burgdorferi*, which causes Lyme disease, and most recognized HGE cases have originated from states with high rates of Lyme disease, particularly Connecticut, Minnesota, New York, and Wisconsin.

The findings in this report are subject to an important limitation. Surveillance case definitions developed for new or emerging infections such as ehrlichiosis are usually highly specific. Accordingly, case definitions used in the surveillance studies described in this report captured only those patients with recognized clinical findings; patients with less severe disease were excluded from confirmatory testing. The reported rates of disease therefore underestimate the true incidence of disease. When the clinical spectrum of ehrlichiosis is better defined and improved diagnostic tests for ehrlichial infections are available, the surveillance case definition can be expanded.

Passive surveillance data for ehrlichial infections are sparse, collected from a few small geographic regions in a limited number of states where *Ehrlichia* spp. are endemic. Although ehrlichiosis is reportable in 21 states, few statewide summaries of ehrlichiosis cases are large enough for meaningful analysis. Surveillance for the ehrlichioses in Connecticut and New York is part of the CDC's Emerging Infections Program, and CDC's Tick-Borne Diseases Initiative is supporting active, population-based surveillance for these diseases in Connecticut, Missouri, and Wisconsin.

The findings in Connecticut and New York underscore the expanding recognition of these diseases and unresolved issues concerning the ehrlichioses. In these two states combined, <30% of persons with ehrlichiosis required hospitalization. Previous patient series in which 55%-60% of ehrlichiosis patients were hospitalized possibly overrepresented seriously ill patients. The decline in hospitalizations also might represent increasing physician awareness of these diseases and broader use of appropriate therapy. The finding that reported rates of ehrlichiosis increase with age is consistent with previous studies and contrasts with age-specific incidences for Lyme disease and Rocky Mountain spotted fever, tickborne diseases that frequently occur in children. Age-associated host factors may account for severity of disease; however, fatal ehrlichial infections have occurred in otherwise healthy young adults and children.

Serologic cross-reactivity between *E. chaffeensis* and *E. equi* is well recognized and can hinder epidemiologic distinction between HME and HGE. There are 10 recognized species of *Ehrlichia*, and substantial serologic cross-reactivity exists among individual species within subgroups of this genus. Some “serologically confirmed” cases of HME and HGE may represent infections with the alternate agent or infections with other, antigenically-related ehrlichial species. Although IFA is the principal diagnostic tool for detecting ehrlichial infection, neither this assay nor PCR-based diagnostics are standardized. New techniques, including enzyme immunoassays using recombinant ehrlichial antigens and multiplex fluorescence-detection PCR, are under investigation.

Doxycycline is the drug of choice for persons infected with ehrlichiosis. The optimal duration of therapy has not been established, but current regimens recommend continuation of treatment for at least 3 days following defervescence, for a minimum total course of 5 to 7 days. Severe or complicated disease can require longer treatment courses. Because tetracyclines are contraindicated in pregnancy, rifampin has been used successfully in a limited number of pregnant women with documented HGE.

Limiting exposure to ticks reduces the likelihood of ehrlichial infection. In persons exposed to tick-infested habitats, prompt careful inspection for and removal of crawling or attached ticks remains an important method of preventing disease because *Ehrlichia*-infected ticks appear to require 24-48 hours of attachment to the host before the agent can be transmitted. As with Lyme disease, peridomestic activities account for many of the tick exposures responsible for HGE in the northeastern United States, and strategies to reduce vector tick densities through area-wide application of acaricides and control of tick habitats (e.g., leaf litter and brush) have been effective in small-scale trials. New methods being developed include applying acaricides to rodents and deer and using baited tubes, boxes, and deer feeding stations in areas where these pathogens are endemic. Community-based integrated tick management strategies may be an effective public health response to reduce the incidence of tick-borne infections.

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