EPIDEMIC PARENTERAL EXPOSURE TO VOLATILE SULFUR-CONTAINING COMPOUNDS AT A HEMODIALYSIS CENTER

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ABSTRACT

OBJECTIVE: To determine the cause of acute illness on August 30, 2000, among patients at an outpatient dialysis center (center A).

DESIGN: We performed a cohort study of all patients receiving dialysis on August 30, 2000; reviewed dialysis procedures; and analyzed dialysis water samples using microbiologic and chemical assays.

SETTING: Dialysis center (center A).

PATIENTS: A case-patient was defined as a patient who developed chills within 5 hours after starting hemodialysis at center A on August 30, 2000.

RESULTS: Sixteen (36%) of 44 patients at center A met the case definition. All case-patients were hospitalized; 2 died. Besides chills, 15 (94%) of the case-patients experienced nausea; 12 (75%), vomiting; and 4 (25%), fever. Illness was more frequent on the second than the first dialysis shift (16 of 20 vs 0 of 24, $P < .001$); no other risk factors were identified. The center's water treatment system had received inadequate maintenance and disinfection and a sulfurous odor was noted during sampling of the water from the reverse osmosis (RO) unit. The water had elevated bacterial counts. Volatile sulfur-containing compounds (ie, methanethiol, carbon disulfide, dimethyldisulfide, and sulfur dioxide) were detected by gas chromatography and mass spectrometry in 8 of 12 water samples from the RO unit and in 0 of 28 samples from other areas ($P < .001$). Results of tests for heavy metals and chloramines were within normal limits.

CONCLUSIONS: Parenteral exposure to volatile sulfur-containing compounds, produced under anaerobic conditions in the RO unit, could have caused the outbreak. This investigation demonstrates the importance of appropriate disinfection and maintenance of water treatment systems in hemodialysis centers (*Infect Control Hosp Epidemiol* 2004;25:256-261).

Hemodialysis is the most commonly used treatment for patients with end-stage renal disease. In the United States, approximately 3,500 hemodialysis centers provide hemodialysis therapy to more than 250,000 patients.[1] Municipal water must be treated to remove impurities that would be toxic to patients undergoing dialysis. Almost all hemodialysis water treatment systems include a reverse osmosis unit, which removes a variety of toxic substances, and many include deionization (ie, cationic, anionic, or mixed bed) tanks, which remove positively or negatively charged ions and replace them with hydrogen and hydroxyl ions.[2]

Because reverse osmosis membranes are subject to bacterial overgrowth and scale formation, they must be routinely cleaned, disinfected, and rinsed.[3,4] Cleaning may be required as often as once a week or as infrequently as once every 2 months, depending on the type of reverse osmosis membrane and on local water supply conditions. Optimal water pressure is required for proper functioning of reverse osmosis units.[3,4] When the water pressure is too low for proper functioning of the reverse osmosis unit, the reverse osmosis unit must be switched to bypass mode to divert water around it. If the system remains in bypass mode for more than 4 hours, the reverse osmosis unit should be programmed to flush and drain for 15 minutes every 4 hours, to minimize water stagnation and prevent accumulation and growth of bacteria on the surface of the membranes.

On a single day, several patients at a freestanding hemodialysis center developed illness and required hospitalization shortly after initiating hemodialysis; two of these patients died. We describe the investigation of this cluster of illness and discuss the potential role of certain sulfur-containing compounds as a source of illness in hemodialysis centers.

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The authors thank the individuals in local and state health departments and the staff and physicians of dialysis center A who participated in the outbreak investigation.

METHODS

Case Definition and Ascertainment

A case-patient was defined as a patient of dialysis center A who developed chills during or within 5 hours of initiation of hemodialysis on the epidemic day (August 30, 2000). We reviewed the records of all patients who received dialysis at center A during August 29 and 30, 2000, to ascertain cases. We also reviewed the records of patients who received dialysis on 4 days (January 16, 2000, March 27, 2000, and August 22 and 23, 2000) when maintenance procedures (eg, disinfection, replacement of components, or cleaning and disinfection of the reverse osmosis membrane) were performed on the center's water treatment system.

Cohort Study

To assess potential risk factors associated with illness, we performed a cohort study of all 44 patients treated at dialysis center A on the epidemic day. Variables assessed included age, gender, underlying cause of renal disease, date of first dialysis, dialysis shift, type of dialyzer, number of times the dialyzer had been used, type of vascular access, and type of dialysate. For dialysis sessions on the epidemic day, we evaluated records of vital signs before and after hemodialysis, total time receiving dialysis, dialysis personnel treating each patient, medications received, symptoms and their time of onset, and blood culture results. For patients who were hospitalized, we examined records of symptoms and signs on hospital admission, laboratory test results, medications received, duration of hospitalization, and outcome.

Facility Review

We interviewed members of the dialysis staff and inspected the center's water treatment and distribution system. We reviewed the facility's water treatment logbook and methods for preparing dialysate, performing dialysis, and reprocessing dialyzers.

Laboratory Study

We reviewed the results of microbiologic and chemical assays performed by a commercial laboratory on product water and dialyzers obtained by staff of dialysis center A on the epidemic day.

On September 5, 2000, we collected water samples from multiple sites throughout the dialysis center's water treatment and distribution system in sterile, endotoxin-free plastic tubes and sent them to the Centers for Disease Control and Prevention for microbiologic, endotoxin, and chemical assays. In addition, we sent six hemodialyzers to the Centers for Disease Control and Prevention for analysis.

Water samples were cultured using the membrane filtration technique. The filters were then placed on both trypticase soy agar and Reasoner's 2 agar (R_2A) (Becton Dickinson Microbiology Systems 1, Cockeysville, MD). Trypticase soy agar plates were incubated at 36°C for 48 hours and R_2A plates were incubated at 28°C for 7 days. Colonies were counted using a stereomicroscope. Endotoxin activity was determined by the turbidimetric Limulus Amebocyte Lysate assay (LAL-5000, Associates of Cape Cod, MA) using the standard control endotoxin (Pyrotell GT Lysate, Associates of Cape Cod) and Pyros software (Associates of Cape Cod). Water was analyzed for metals, including aluminum, arsenic, barium, cadmium, calcium, copper, lead, magnesium, potassium, silver, selenium, sodium, and zinc, by inductively coupled argon plasma mass spectrometry. Volatile sulfur-containing compounds were extracted from the water samples by solid phase microextraction and analyzed by full-scan gas chromatography and mass spectrometry.[5] Volatile compounds in the water samples were identified by mass spectral library matching.

Statistical Analysis

Data were entered and analyzed using Epi-Info software (version 6.0; Centers for Disease Control and Prevention, Atlanta, GA).[6] Relative risks and 95% confidence intervals were calculated. Categorical variables were compared using the chi-square or Fisher's exact two-tailed test. Continuous variables were compared using the Kruskal–Wallis test.

RESULTS

Descriptive Epidemiology

Sixteen (36%) of 44 patients receiving dialysis on the epidemic day met the case definition. The median age of case-patients was 73 years (range, 36 to 90 years) and 56% were female. All case-patients experienced chills, 15 (94%) experienced nausea, and 12 (75%) experienced vomiting. All had received dialysis during the second shift. Only 4 patients experienced fever (oral temperature > 100.0°F), with a median time to onset of 5 hours. The median duration from the start to the end of hemodialysis was 43 minutes (range, 7 to 125 minutes). The median duration from the start of hemodialysis to the onset of symptoms was 81 minutes (range, 14 to 214 minutes). All 16 case-patients were hospitalized; 4 were admitted to an intensive care unit. One case-patient died on the day of admission and another died after 37 days of hospitalization.

Case-patients had received hemodialysis for a median of 27.5 months (range, 2 to 56 months). All had received dialysis with reused hollow-fiber high flux dialyzers (F-80; Fresenius AG, Bad Hamburg, Germany). The median number of times dialyzers had been reused as of the epidemic day was 7 (range, 1 to 41). There was no clustering of cases by dialysis station.

Routine hematology and chemistry panels for case-patients yielded abnormal results only for the white blood cell count. Before the outbreak, case-patients' median white blood cell count was 6.1×10^9/L (range among case-patients, 4.7 to 10.0×10^9/L; normal range, 4.5 to 10.0×10^9/L). After the onset of symptoms on the epidemic day, case-patients had a median white blood cell count of 3.2×10^9/L (range, 0.8 to 12.7×10^9/L; $P = .07$ compared with before the epidemic), and 9 (56%) of the case-patients had a white blood cell count of less than 4.5×10^9/L.

TABLE 1
POTENTIAL RISK FACTORS FOR HEMODIALYSIS-ASSOCIATED TOXICITY AT DIALYSIS CENTER A ON AUGUST 30, 2000

Risk Factor	Total No. of Patients	No. Ill (%)	RR (CI_{95})	*P*
Age, y				
< 70	21	10 (48)	1.83 (0.80–4.15)	.14
⩾ 70	23	6 (26)		
Gender				
Male	20	7 (35)	0.93 (0.42–2.06)	.86
Female	24	9 (38)		
Shift				
Second	20	16 (80)	Indeterminate	< .001
First	24	0 (0)		
Type of access				
Catheter	24	11 (46)	1.83 (0.76–4.40)	.15
Fistula, graft	20	5 (25)		
Underlying disease				
Hypertension	29	7 (24)	0.45 (0.2–1.01)	.053
Diabetes	15	8 (53)		
Treated with reused dialyzers				
Yes	40	16 (40)	Indeterminate	.28
No	4	0 (0)		
Receipt of heparin				
Yes	41	15 (37)	1.10 (0.21–5.72)	.91
No	3	1 (33)		

RR = relative risk; CI_{95} = 95% confidence interval.

Samples for blood cultures were obtained from all 16 case-patients. Two had a positive blood culture—one for *Staphylococcus epidermidis* and one for *Citrobacter* species. Both of these patients were receiving dialysis through vascular catheters.

Analytic Epidemiology

Illness was not associated with age, gender, type of vascular access, reuse of dialyzers, underlying cause of renal disease, or receipt of heparin (Table 1). However, dialysis during the second shift was associated with illness.

Facility Review

At the time of the outbreak, dialysis center A provided hemodialysis to 135 patients. Patients were treated in three shifts, from approximately 6:00 am to 11:00 am, 11:00 am to 4:00 pm, and 4:00 pm to 10:00 pm. Dialysis services were provided in one large room with centrally located chairs (n = 24) and beds (n = 2). The room was divided into 6 stations (ie, A, B, C, D, E, and F) with 4 chairs each. Patient care staff consisted of dialysis technicians and nurses. One technician worked at each station and one nurse supervised three stations consisting of 4 chairs each and 1 bed. Patients usually received dialysis at the same station, chair, and machine during each session.

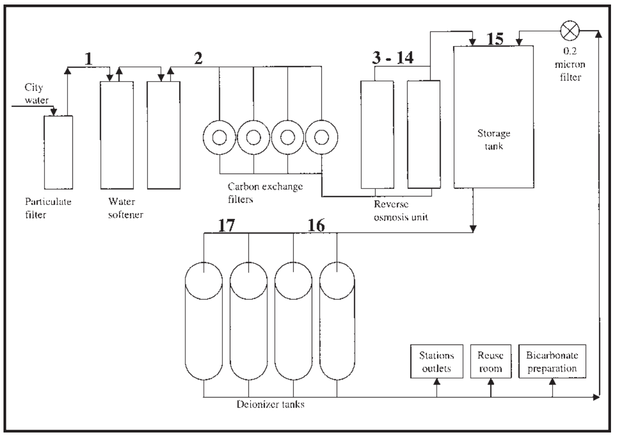

FIGURE. Water treatment system at dialysis center A. Numbers indicate sample numbers (Table 2).

Water Treatment and Distribution System. At the center, chlorinated municipal water was heated to 78°C and then pumped through a 7.5-µm particulate filter, a water softener (where citric acid was added to regulate pH), carbon filters, and a reverse osmosis unit (Figure). The water next flowed into a storage tank and then passed through 8 deionization tanks, post-deionizer 0.2-µm bacterial filters, and the center's water distribution system to be distributed to the dialysis stations, the dialyzer reuse room, and, finally, the bicarbonate preparation area. Unused water was recirculated back to the storage tank.

The entire water treatment and distribution system was disinfected with hypochlorite solution (500 ppm) once annually. The last such disinfection had been performed 8 months before the epidemic.

The manufacturer recommended monitoring the water pressure before and after the return distribution loop, and replacing the post-deionizer 0.2-µm filters every 3 months or if the difference in water pressure between the two filters was more than 10 psi. During our facility review, we found that 0.2-µm filters had not been changed as recommended and that the difference in water pressure was greater than 10 psi (range, 34 to 90 psi).

All 10 membranes on the reverse osmosis unit of the water treatment system were replaced on March 27, 2000, and 4 were replaced on June 22, 2000. The reverse osmosis membranes were disinfected on August 22, 2000, and cleaned the day after that for the first time in 2000. A review of the facility's water treatment logbook indicated that on August 28, 29, and 30, 2000, the reverse osmosis unit was on bypass mode (ie, water was diverted around the reverse osmosis unit and storage tank directly to the deionizer unit) for 1 to 13 hours per day. The reverse osmosis unit was on bypass mode for at least 2 hours on August 28, 2000; from 6:15 pm on August 29, 2000, to 7:30 am on August 30, 2000; and from 9:30 to 10:45 am on August 30, 2000. At 12:30 pm on August 30, 2000, 48 minutes after the first patient symptoms were reported, the system again went into bypass mode due to low pressure. There was no evidence that the reverse osmosis unit was flushed to prevent bacterial growth after it had been in bypass mode on these occasions.

On August 30, 2000, at 9:30 am, the reverse osmosis unit went into bypass mode due to low water pressure. At 10:45 am, as part of routine maintenance, a technician from an outside company that had been contracted to maintain the water treatment system changed four of the eight deionization tanks. After changing the tanks, the technician took the reverse osmosis unit out of bypass mode, but did not notice any other problems. However, at 11:42 am, the first patient on the second shift experienced chills, nausea, and vomiting during hemodialysis. Within an hour, several other patients on the second shift experienced similar symptoms while receiving or shortly after hemodialysis. All dialysis treatments where stopped by 12:48 pm and the center voluntarily closed.

On September 5, 2000, when we opened the reverse osmosis unit to obtain water samples, we noted a distinct sulfur odor. The technician at dialysis center A reported that a similar odor had been reported approximately 3 weeks before the epidemic.

Dialyzer Reprocessing. Dialyzers were reprocessed for reuse on the same patient by rinsing with product water and disinfecting with 3.5% peracetic acid–hydrogen peroxide solution (Renalin, MinnTech Corp., Minneapolis, MN). Our inspection revealed no problems with dialyzer reprocessing.

Dialysis Machines. All dialysis machines used at center A were COBE Centrysystem 3 machines (Gambro Healthcare, Lakewood, CO). Each machine was used by as many as three patients each day, one per shift. After each use, the exterior of each machine was cleaned with a 1:10 dilution of 5.25% bleach. After the third shift, the machines were set on an automatic disinfection cycle with a 1:10 solution of 12% bleach. Once a week, the machines were disinfected overnight with Actril (Renal Systems, MinnTech Corp.). The machines were equipped with alarms that signaled a variety of problems, including incorrect pH or bicarbonate concentration, or blood leakage. On the outbreak day, only one machine alarm was activated; this was due to a blood leak in a reprocessed dialyzer, which was replaced with a new dialyzer.

Bicarbonate Solution Preparation. Bicarbonate solution was prepared in jugs before each shift using powdered bicarbonate mix and product water. All jugs were disinfected with bleach nightly.

Follow-Up. As a result of this outbreak, the entire water treatment system at dialysis center A was replaced. The center has reopened and no reactions similar to those experienced during the outbreak have occurred.

Laboratory Results

Routine water samples collected from the water treatment system during January through August 2000 were within the limits specified by the Association for the Advancement of Medical Instrumentation for chlorine, chloramine, endotoxin, bacteria, and trace elements.[7] However, the routine endotoxin testing was not done in August 2000 because center A did not have the correct tubes for sample collection. The level of 50 trace substances, including metals, was measured once yearly, most recently on March 26, 2000; all results were within the limits of the Association for the Advancement of Medical Instrumentation.

Several water samples collected on September 1, 2000, 2 days after the epidemic day, showed elevated bacterial counts ranging from 10,000 to 107,000 colony-forming units per milliliter.

Water samples collected on September 5, 2000 (7 days after the epidemic) had levels of trace metals within the standards of the Association for the Advancement of Medical Instrumentation. However, several water samples collected near the reverse osmosis unit had bacterial counts greater than 200 colony-forming units per milliliter, the Association for the Advancement of Medical Instrumentation standard (Table 2). In addition, volatile sulfur-containing compounds were identified in 8 (67%) of 12 water samples obtained from the reverse osmosis unit. These compounds included sulfur dioxide, methanethiol, dimethyldisulfide, and carbon disulfide (Table 2).

TABLE 2
RESULTS OF ANALYSES OF PRODUCT WATER COLLECTED ON SEPTEMBER 5, 2000, AT DIALYSIS CENTER A

Sample No.	Bacteria (CFU/mL)	Endotoxin (EU/mL)	Sulfur Dioxide	Methanethiol	Dimethyldisulfide	Carbon Disulfide
1	< 100	N/T	-	-	-	-
2	21,300*	N/T	-	-	-	-
3	4,200*	7.68†	-	-	-	-
4	< 10	< 1.96	+	-	-	+
5	< 10	< 0.96	+	-	-	+
6	70	< 2	+	+	+	+
7	< 100	N/T	+	+	-	+
8	200	N/T	+	+	+	+
9	400*	N/T	+	+	+	+
10	< 100	N/T	+	-	+	+
11	< 100	N/T	+	-	+	+
12	1,120*	< 3.84	N/T	N/T	N/T	N/T
13	610*	< 3.84	N/T	N/T	N/T	N/T
14	530*	< 3.84	N/T	N/T	N/T	N/T
15	20	N/T	N/T	N/T	N/T	N/T
16	< 100	N/T	-	-	-	-
17	< 100	N/T	-	-	-	-

CFU/mL = aerobic colony-forming units per milliliter; EU/mL = endotoxin units per milliliter; + = positive results on qualitative test for the substance; - = negative results on qualitative test for the substance; N/T = not tested.
*Exceeds Association for the Advancement of Medical Instrumentation standard (< 200 CFU/mL).
†Exceeds Association for the Advancement of Medical Instrumentation standard (2 EU/mL).
Note. Sample numbers refer to the location of sample collection as shown in the figure.

DISCUSSION

We investigated a cluster of unusual reactions among 16 patients receiving hemodialysis at a single dialysis center.

We considered several potential causes for the outbreak. An infectious etiology was unlikely because only four case-patients were febrile and only two had positive blood cultures, for two different microorganisms. Endotoxin produced by gram-negative bacteria has been a frequent cause of hemodialysis-associated outbreaks. However, endotoxin typically causes onset of fever within 1 to 2 hours and is accompanied by hypotension. An endotoxin reaction seemed unlikely because only four patients had fever, the median time to the onset of fever was 5 hours in these patients, and none was hypotensive.

On the outbreak day, eight staff members treated the case-patients, and all case-patients were treated with different machines. Therefore, it is unlikely that machine dysfunction, or errors by the staff members performing dialysis, caused the outbreak. The lack of association with parenteral medication ruled out a contaminated medication as an etiology.

We conclude that the presence of volatile sulfur-containing compounds of known toxicity (eg, disulfides) in the water near the reverse osmosis unit was the most probable cause of the outbreak. Disulfides were found in water samples collected near the reverse osmosis unit, but not in water samples collected from other areas of the water treatment and distribution system. Additionally, the distinct sulfur odor was noted only from water samples taken near the reverse osmosis unit. Disulfides were likely produced by sulfate-reducing bacteria[8,9] on the improperly maintained reverse osmosis unit membranes. The sulfate-reducing bacteria converted the low (safe) level of sulfate normally present in the water to toxic levels of disulfides in the anaerobic and septic environment. Sulfate-reducing bacteria carry out the dissimilative reduction of sulfate to hydrogen sulfide only in anaerobic environments; the inappropriate maintenance of the reverse osmosis unit would have provided an anaerobic environment where these bacteria could have flourished. This also can explain why the aerobic bacterial count from the reverse osmosis unit was not proportional to the level of volatile sulfides.

Toxic reactions due to disulfides (eg, carbon disulfide) are well described. However, previous toxicologic data are based on inhalation,[10] ingestion,[11] or dermal exposures.[10,12] Exposure to disulfides by inhalation or ingestion has been reported to cause gastrointestinal (eg, nausea, vomiting, or diarrhea), cardiovascular (eg, hypertension), respiratory (eg, cough, bronchoconstriction, cyanosis, and dyspnea), and central nervous system (eg, dizziness, headache, respiratory paralysis, seizures, and coma) effects.[13-15] Dermal exposure to carbon disulfide can result in blistering with second-degree and third-degree burns,[11] and intradermal absorption of this compound can cause anorexia, nausea, vomiting, fatigue, and headache.[12] Because disulfides are usually rapidly metabolized and excreted in the urine,[11] patients with renal failure at center A may have been especially vulnerable. Previous reports of exposure to these compounds have not mentioned chills, which were a prominent clinical feature in this outbreak.

To our knowledge, this is the first reported hemodialysis outbreak linked to sulfide exposure. Toxins that have been previously implicated in hemodialysis-associated outbreaks include aluminum,[16] chloramines,[17] copper,[18] hydrogen peroxide,[19] fluorides,[20] and formaldehyde.[21] This outbreak may have been caused by exposure to toxins produced by bacterial overgrowth. Our investigation had several limitations. Water samples from the time of the outbreak were unavailable for testing. We collected samples from the water treatment system, which had been shut off for 5 days, possibly allowing growth of bacteria. However, water samples collected 1 day after the outbreak also showed high colony counts. The reverse osmosis membrane was not disassembled and inspected for evidence of bacterial growth. The assay for sulfur-containing compounds was qualitative rather than quantitative, and no samples from reverse osmosis units in other dialysis centers were available for comparison. We have no definite explanation as to what specific event triggered the release of toxins on August 30, but it may have been a surge of water pressure associated with replacement of the deionization tanks. The nonspecific symptoms and lack of characteristic laboratory abnormalities associated with sulfur-containing compounds make it difficult to be certain that those compounds caused the outbreak.

Patients receiving hemodialysis are exposed to approximately 150 L of fluid during a typical dialysis session and their bloodstream has direct access across the semipermeable membrane to the dialysate.[22] Therefore, even small amounts of toxic substances in dialysis fluids may produce adverse effects. Responsibility for ensuring a safe water supply is shared by the center's administration, medical director, and technical personnel. This report of human parenteral exposure to volatile sulfur compounds demonstrates the importance of appropriate monitoring and maintenance of water treatment systems in hemodialysis centers in preventing potentially fatal reactions.

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