An Outbreak of Gram-Negative Bacteremia in Hemodialysis Patients Traced to Hemodialysis Machine Waste Drain Ports

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AN OUTBREAK OF GRAM-NEGATIVE BACTEREMIA IN HEMODIALYSIS PATIENTS TRACED TO HEMODIALYSIS MACHINE WASTE DRAIN PORTS

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ABSTRACT

OBJECTIVE: To investigate an outbreak of gram-negative bacteremias at a hemodialysis center (December 1, 1996-January 31, 1997).

DESIGN: Retrospective cohort study. Reviewed infection control practices and maintenance and disinfection procedures for the water system and dialysis machines. Performed cultures of the water and dialysis machines, including the waste-handling option (WHO), a drain port designed to dispose of saline used to flush the dialyzer before patient use. Compared isolates by pulsed-field gel electrophoresis.

SETTING: A hemodialysis center in Maryland.

RESULTS: 94 patients received dialysis on 27 machines; 10 (11%) of the patients had gram-negative bacteremias. Pathogens causing these infections were *Enterobacter cloacae* (n=6), *Pseudomonas aeruginosa* (n=4), and *Escherichia coli* (n=2); two patients had polymicrobial bacteremia. Factors associated with development of gram-negative bacteremias were receiving dialysis via a central venous catheter (CVC) rather than via an arterio-venous shunt (all 10 infected patients had CVCs compared to 31 of 84 uninfected patients, relative risk [RR] undefined; $P<.001$) or dialysis on any of three particular dialysis machines (7 of 10 infected patients were exposed to the three machines compared to 20 of 84 uninfected patients, RR=5.8; $P=.005$). *E cloacae, P aeruginosa,* or both organisms were grown from cultures obtained from several dialysis machines. WHO valves, which prevent backflow from the drain to dialysis bloodlines, were faulty in 8 (31%) of 26 machines, including 2 of 3 machines epidemiologically linked to case-patients. Pulsed-field gel electrophoresis patterns of available dialysis machine and patient *E cloacae* isolates were identical.

CONCLUSIONS: Our study suggests that WHO ports with incompetent valves and resultant backflow were a source of cross-contamination of dialysis bloodlines and patients' CVCs. Replacement of faulty WHO valves and enhanced disinfection of dialysis machines terminated the outbreak (*Infect Control Hosp Epidemiol* 1999;20:746-751).

Hemodialysis is a common medical procedure. During 1996, approximately 236,000 persons received hemodialysis in the United States; of these, an estimated 183,000 (78%) received chronic hemodialysis.[1] Because of the need for repeated vascular access, patients who receive chronic hemodialysis are at increased risk for bloodstream infections (BSIs). Reported BSI rates for hemodialysis patients have ranged from 8.4 to 16.9 episodes per 100 patient-years,[2] and BSI has been identified as the cause of 6% to 18% of deaths among hemodialysis patients.[2]

Although the most frequent BSI pathogens in hemodialysis patients are gram-positive organisms, such as *Staphylococcus aureus,* numerous clusters of gram-negative bacterial BSIs have been reported. When such clusters have been reported, inadequate disinfection of water treatment or distribution systems,[3,4] errors in dialyzer reprocessing,[5-8] or improper set-up procedures[9-11] have been implicated. We describe the investigation of a cluster of gram-negative bacterial BSIs that occurred during a 2-month period at Frederick Memorial Regional Dialysis Center (FMRDC), a free-standing ambulatory hemodialysis center in Maryland. Our findings indicate that the outbreak resulted from contamination of a waste drain port unique to a particular model of hemodialysis machine.

METHODS

Case Definition

A case-patient was defined as any FMRDC patient with a blood culture positive for one or more gram-negative bacteria from December 1, 1996, through January 31, 1997 (the epidemic period). Patients with BSIs secondary to an infection at another site were excluded.

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Case Ascertainment

All blood cultures obtained at FMRDC were processed at the Franklin Memorial Regional Hospital microbiology laboratory. To identify case-patients and to determine the background BSI rate at FMRDC, we reviewed that hospital's microbiology records from January 1, 1995, through January 31, 1997 (the study period). Hemodialysis medical records of all FMRDC patients who received dialysis during the epidemic period were reviewed.

Analytic Epidemiology and Statistical Methods

To determine whether an outbreak was occurring, we compared the BSI rates during the pre-epidemic (January 1, 1995-November 30, 1996) and epidemic periods. To identify risk factors for gram-negative BSIs, we conducted a cohort study of all patients who received dialysis at FMRDC during the epidemic period. Hemodialysis and medical records of these patients were examined for demographic characteristics, underlying renal disease, types of vascular access, dates accesses were placed, physicians who inserted the access, dialysis day, dialysis shift, dialysis station number, dialysis machines used, dialyzer type, dialyzer reuse, parenteral medications received during the dialysis session, symptoms, blood culture results, and patient outcome.

Data were entered and analyzed using Epi Info software (version 6.02; Centers for Disease Control and Prevention [CDC], Atlanta, GA). For categorical variables, relative risks were calculated using Yates' corrected chi-square or Fisher's Exact tests. Continuous variables were compared using the Kruskal-Wallis Test.

Procedure Review

Procedures for maintenance and disinfection of the water distribution and treatment system and of dialysis machines (COBE, Centrysystem 3, GAMBRO Healthcare, Lakewood, CO) were reviewed. FMRDC practices for performing cultures of the water system and dialysate also were assessed. Setup, initiation, and termination of dialysis via central venous catheter (CVC) and via arterio-venous (A-V) graft were observed. Procedures for CVC insertion, maintenance, manipulation, and removal were reviewed.

Microbiological Studies

Water samples were obtained from several locations in the water treatment system and from numerous stations in the dialysis unit. Samples of dialysate and either surface swab or fluid from the waste-handling option (WHO) were obtained from available dialysis machines. All samples were sent to the CDC for bacterial culture. Water, dialysate, and WHO port fluid samples were cultured by the membrane filtration technique.[12] Surface swabs from the WHO were assayed using the wipe-rinse technique.[13] Membrane filters were placed aseptically on trypticase soy agar and incubated at 36°C for 48 hours.[13-15] Total viable colony counts were documented and isolates identified using standard microbial techniques.

Available case-patient blood isolates were sent to the CDC for confirmation of identification. DNA typing using pulsed-field gel electrophoresis (PFGE)[16,17] was performed on available dialysate isolates, all available case-patient blood isolates, and randomly selected *Enterobacter cloacae* isolates from nonhemodialysis patients treated at an affiliated hospital.

RESULTS

Descriptive Epidemiology

Background BSI rate. The gram-negative BSI rate was significantly greater during the epidemic than the pre-epidemic period (10 of 10,152 dialysis sessions vs 17 of 90,000 dialysis sessions, $P<.001$). In contrast, the gram-positive BSI rate was comparable during the epidemic and pre-epidemic periods (4 of 10,152 dialysis sessions vs 51 of 90,000 dialysis sessions, $P=.63$).

Case-patients. During the epidemic period, 94 patients received dialysis on 27 machines. Ten patients were excluded from the analysis: 4 because they had gram-positive BSIs during the epidemic period and 6 because they had chills or fever and received antibiotics but subsequently had negative blood cultures. Of the remaining 84 patients, 10 (12%) met the case definition. Bloodstream pathogens isolated from case-patients were *E cloacae* (6), *Pseudomonas aeruginosa* (4), and *Escherichia coli* (2); 2 patients had polymicrobial bacteremia (*E cloacae* and *P aeruginosa; P aeruginosa* and *E coli)*. The median age of the case-patients was 56.5 years old (range, 16-88). Six case-patients were male; 7 were white, and 3 were African-American. Underlying renal diseases of the case-patients were hypertension (6), diabetic nephropathy (2), glomerulonephritis (1), and cholesterol emboli (1).

As a result of the BSIs, 7 of the 10 case-patients were hospitalized. There were no deaths attributed to the bloodstream infections. All 10 case-patients required intravenous antibiotic therapy. Additionally, vascular access catheters were removed and replaced for all 10 case-patients.

Cohort study. Case- and non–case-patients were similar in gender, age, ethnicity, underlying renal disease, dialysis day, dialysis shift, type of dialyzer, dialyzer reuse, and frequency of dialysis line manipulation during dialysis. In contrast, receiving dialysis via a CVC rather than via an A-V shunt (all 10 infected patients had CVCs compared to 31 of 84 uninfected patients; relative risk [RR], undefined; $P<.001$) and exposure to dialysis on any of three particular dialysis machines (7 of 10 infected patients were exposed to machines A, B, or C, compared to 20 of 84 uninfected patients; RR=5.8; $P=.001$) were associated with acquiring a gram-negative BSI. These two risk factors remained significant even when the analysis was repeated with two modified non-case populations: for one analysis, patients with gram-positive BSIs were included in the non–case-patient group, and for another analysis, all patients who did not have gram-negative BSIs were included in the non–case-patient group (ie, the entire cohort of patients who received hemodialysis at FMRDC during the study period was analyzed).

Procedure Review

Water system. At FMRDC, city water passed through carbon filters, a particulate filter, and a reverse osmosis (RO) unit before being distributed to the dialysis unit in a closed-loop circuit. Water could exit the system to hemodialysis machines at 24 stations. Once monthly, on a Saturday evening, the RO unit was disinfected with a 1% Renalin solution (Minntech Corp, Minneapolis, MN), containing hydrogen peroxide and peroxyacetic acid, which was circulated through the RO unit for 20 to 30 minutes and then allowed to sit in the unit for 2 hours before being rinsed out. At the same time, 1% Renalin was circulated through the dialysis unit loop for 1 hour, and each of the 24 station connectors were opened and closed to allow Renalin to rinse through each station port. Renalin remained in the loop from Saturday evening until Monday morning, when it was rinsed out.

Water did not circulate in the closed-loop circuit overnight, and therefore the loop was flushed with water for 30 minutes every morning before the dialysis machines were used. Water obtained from various stations in the loop was sent for culture each month, using a commercially available kit (HPC Sampler, Millipore Corp, Bedford, MA). All treatment-system water cultures at FMRDC during the pre-epidemic and epidemic periods were reported to show bacterial counts of <200 colony-forming units/mL, which is the Association for the Advancement of Medical Instrumentation (AAMI) standard for acceptable dialysis water.

Dialysis machines. Twenty-seven COBE hemodialysis machines were used at FMRDC; one machine was at each of the 24 stations, and three were available to replace machines undergoing maintenance or repairs. Since there were two dialysis shifts per day (23 or 24 patients per shift), each machine was used by 0, 1, or 2 patients per day.

Before each dialysis session, the dialyzer and dialysis tubing must be primed (flushed) with saline. Each machine has a WHO port, designed solely to dispose of the saline used to prime the dialysis machine (Figure). During priming, the arterial dialysis line is attached via a WHO priming connector to the WHO port to discard the saline prime. After priming, the arterial dialysis line is connected to the patient's arterial vascular access. At this point, the venous dialysis line is attached via a WHO priming connector to the WHO port to discard remaining saline in the dialysis tubing before being connected to the patient's venous vascular access. When the WHO port is not connected to dialysis lines for saline disposal, it is designed to be covered by a device called the rinse arm. When the rinse arm is properly closed, spent dialysate flows through the rinse arm to the WHO drain line. The WHO drain line eventually joins the machine's dialyzer drain line. Two check valves in the WHO drain line are designed to prevent dialyzer drain-line waste from refluxing up the WHO drain line into the WHO port. Specific quality control procedures for the WHO are recommended by the manufacturer. The manufacturer recommends testing the competency of WHO check valves daily by filling a 30-cc syringe with water, injecting the contents into the WHO port, and attempting to draw back fluid from the WHO; competent check valves should prevent any backflow. As a preventive maintenance procedure, the manufacturer also recommends replacing the two WHO check valves with new ones after every 2,000 hours of hemodialysis.

On a daily basis, after the first dialysis shift, the external surfaces of the dialysis machines were wiped down with 1% bleach. Additionally, between the first and second shifts, dialysis technicians flushed bleach into the WHO port, but did not routinely test the check valves. After the second shift, the external surfaces of the machines again were wiped down with bleach. The machines then were put in a rinse mode, and vinegar was run through, followed by a bleach rinse. Each Saturday evening, machines were disinfected by running Actril (Minntech Corp), containing hydrogen peroxide and peroxyacetic acid, through the machines for a 15-minute cycle; the Actril remained in the machines until the following Monday morning, when a 15-minute rinse cycle was used to remove it.

During our investigation, we assessed the competency of the WHO check valves on 26 machines, using the procedure outlined by the manufacturer. Backflow occurred in 8 (31%) of 26 machines. Furthermore, review of the preventive maintenance procedure for the WHO revealed that only check valve 2 was being changed every 2,000 hours. Schematic diagrams provided by COBE to the hospital engineering department, which performed routine dialysis machine maintenance, showed only check valve 2. Check valve 1, which is located in the WHO plastic casing and is not visible unless the casing is removed, was not shown on the COBE diagram and was not changed by the hospital engineers. Since FMRDC dialysis machines were 2 to 5 years old, all machines contained at least one check valve that was overdue to be changed.

During preparation of the machines for dialysis, it frequently was observed that technicians would prime the dialysis lines, insert the arterial dialysis line with the WHO priming connector into the WHO port to drain saline, then connect the arterial dialysis line to the venous dialysis line to allow for recirculation during the time interval before the patient's arrival and while the technician was obtaining vascular access to the patient. Often technicians left the WHO priming connector inserted in the WHO port, preventing the rinse arm from properly closing over the WHO port to allow flushing of the WHO. When this occurred, the same previously used WHO priming connector, rather than a clean new WHO priming connector, was used to connect the venous dialysis line to the WHO port to drain saline prime.

Patient care and vascular access. The routine procedures for accessing patient CVCs or A-V shunts were appropriate, and only occasional minor breaks in standard procedure and aseptic technique were observed. Similarly, procedures for dressing the CVC site were performed appropriately. CVC endcaps were discarded each time a CVC was accessed; a CVC was covered with a new endcap

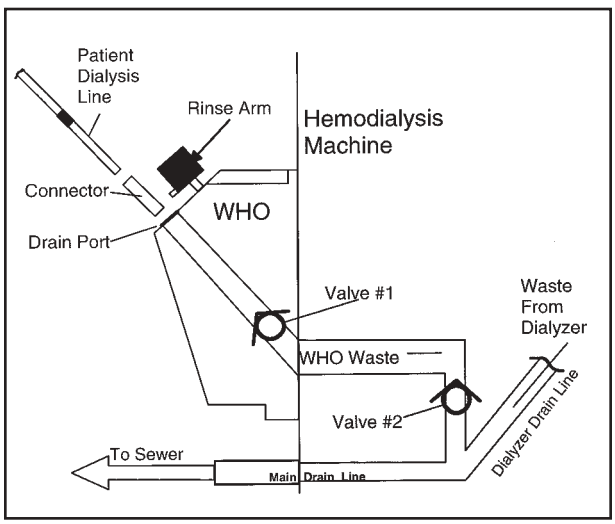

FIGURE. Waste-handling option (WHO) of a COBE Centrysystem 3 hemodialysis machine. A WHO is a waste port that is attached to the front of COBE Centrysystem 3 hemodialysis machines. It is designed to dispose of the saline used to flush the dialyzer before the machine is used for a patient. The waste drain line of the WHO joins the dialyzer waste drain line inside the dialysis machine to become one main drain line that empties into the sewer. Two valves along the WHO waste drain line are designed to prevent reflux of waste to the WHO drain port. Side view not to scale.

at the end of each dialysis session. Patients with CVCs were instructed not to change their CVC dressings at home and not to shower; however, some patients reportedly did not adhere to those instructions.

Administration of parenteral medications was performed by nurses using aseptic technique. Only one multidose-vial medication was used (Epogen, Amgen Inc, Thousand Oaks, CA); however, any single Epogen vial was used completely within one or two dialysis sessions.

CVC insertion. Of the 94 patients receiving dialysis during the epidemic period, 34 (36%) had CVCs, and 60 (64%) had fistulas or grafts for hemodialysis access. Whereas some patients had CVCs because their fistulas or grafts had failed, others had CVCs because they had requested them for cosmetic reasons or to avoid frequent needlesticks. Because all gram-negative BSIs occurred in patients with CVCs, we reviewed procedures for CVC insertion.

CVC insertion was performed in the hospital radiology suite, under fluoroscopy. CVCs were either long-term tunneled catheters (Tesio, Medcomp, Harleysville, PA) or short-term nontunneled catheters (Quinton, Quinton Instrument Co, Bothwell, WA) placed in internal jugular veins. Quinton catheters were scheduled for routine changes every 3 weeks. The Quinton catheter generally was exchanged over a guidewire if no infection was present.

Microbiological Studies

Before the CDC investigation took place, a commercial laboratory had tested dialysate and WHO samples from 26 of the 27 dialysis machines. *E cloacae* was recovered from samples obtained from 24 machines (92%), and *P aeruginosa* was recovered from 17 machines (65%); 13 (50%) of the machines were positive for both *E cloacae* and *P aeruginosa.*

During our investigation, we sampled treated water before it entered the dialysis unit loop; the water was within AAMI standards, and no *E cloacae, P aeruginosa,* or *E coli* was isolated. Elevated bacterial counts were found in water exiting the loop in the room where dialyzers were reprocessed and in water sampled at five of seven stations; however, none of these samples grew *E cloacae, P aeruginosa,* or *E coli.*

At the time of our investigation, only 10 of 27 dialysis machines were available for culture; the remainder were undergoing high-level disinfection. Of the 10 dialysis machines we sampled, 4 grew *E cloacae* and 4 grew *P aeruginosa.* Following high-level disinfection, 5 dialysis machines were tested; 1 grew *E cloacae* and 2 grew *P aeruginosa.* A check valve removed from one WHO port also grew *P aeruginosa.*

PFGE was performed on the 5 dialysis machine *E cloacae* isolates and on three case-patient *E cloacae* isolates; these FMRDC patients had *E cloacae* BSIs in March, April, and June 1997. All had identical PFGE patterns. However, these isolates differed from *E cloacae* isolates obtained from nonhemodialysis patients at the regional hospital affiliated with HCA. No case-patient *P aeruginosa* isolates were available, so PFGE could be performed only on dialysis machine *P aeruginosa* isolates. The genome patterns of each of the *P aeruginosa* isolates were unique.

DISCUSSION

Outbreaks of gram-negative bacterial BSIs in hemodialysis units have commonly been due to inadequate disinfection of water treatment or distribution systems, reprocessed dialyzers, or other dialysis equipment.[3-11] During this outbreak, evidence suggests that gram-negative bacterial BSIs were caused by cross-contamination of hemodialysis CVCs from the WHO port, a waste drain port unique to a particular model of hemodialysis machine.

Two mechanisms for cross-contamination from the WHO are likely: (1) reflux from the waste drain line into the WHO, and (2) bacterial growth in the nutrient-rich environment of the WHO. Our investigation suggests several factors that could lead to reflux problems. First, only one of the two check valves in the WHO system of each dialysis machine was routinely changed during each manufacturer-recommended 2,000-hour preventive-maintenance assessment. The other check valve, which was hidden in the WHO plastic casing, was not replaced because schematics provided by the manufacturer did not indicate its existence. Second, daily assessment of the competence of the WHO check valves before patient use was not performed, and our investigation revealed backflow into WHO ports on 8 of 26 machines. Faulty WHO check valves were found in 7 of 24 machines with positive cultures and 2 of 3 machines epidemiologically linked to case-patients. Third, dialysis technicians commonly created a "break" in the WHO port sys-

tem by leaving WHO priming connectors, which were not connected to dialysis lines, in WHO ports. Without the rinse arm in proper position, the continuous flushing of the WHO was disrupted, thus allowing opportunities for backflow. Fourth, dialysis technicians commonly re-used WHO priming connectors that had been attached to arterial dialysis lines and then left briefly in the WHO ports, to connect venous dialysis lines to the WHO. Thus, a dialysis line that connected directly to a patient's vascular access was temporarily being connected to a "dirty" WHO priming connector, which had been sitting in an open WHO port where reflux may have occurred.

Bacterial growth may occur readily in the WHO system, because the WHO is designed to have spent (ie, used) dialysate flow through it. The spent dialysate provides a rich environment for microbial growth. Although routine weekly disinfection recommended by the manufacturer allows disinfectant to circulate through the WHO, this disinfection method (1) would likely be ineffective in removing any biofilm that could form, and (2) does not disinfect the outer rim of the WHO port or the tip of the WHO rinse arm. When the WHO is in use and saline is being discarded through the WHO drain port, cross-contamination of patient dialysis lines may readily occur, because the dialysis lines, the WHO connector, the rim of the WHO drain port, and the tip of the WHO rinse arm are all in contact with each other or in such close proximity that it would be impossible for a technician's hands not to come in contact with all these parts when performing routine manipulation of the dialysis lines.

In this outbreak, patients with CVCs may have been at greater risk for developing BSIs than were patients with fistula or graft access, because dialysis lines directly contact indwelling CVCs and may have "seeded" them, providing a potential ongoing source of infection. In contrast, for a patient with a fistula or graft, the dialysis line was attached to 30-cm–long vascular access tubing that was percutaneously inserted into a fistula or graft. The vascular access tubing was discarded at the end of the dialysis shift, eliminating any ongoing patient contact with a contaminated device.

The risk for BSIs among hemodialysis patients is known to be higher for patients using CVCs than for patients using A-V shunts.[2,18] At FMRDC, 36% of patients received hemodialysis through CVCs; nationwide in the United States, only 13% of hemodialysis patients used CVCs for vascular access in 1995.[19] The disproportionate number of patients being dialyzed via CVCs at this center may have been a contributor to the outbreak. That the gram-positive BSI rate remained stable throughout the pre-epidemic and epidemic periods suggests that the usual sources of CVC contamination (eg, healthcare worker hands, patient skin) were not the cause of the outbreak; CVC-related BSIs from such sources usually involve gram-positive organisms from skin flora. Furthermore, the single *E cloacae* PFGE pattern suggests that the gram-negative BSIs shared a common etiology.

The WHO port and the COBE Centrysystem 3 hemodialysis machine have been implicated in four other outbreaks of gram-negative bacterial BSI: one in Montreal, Quebec, Canada,[20,21] one in Jerusalem, Israel,[21] one in Chicago, Illinois,[22] and one in Nottingham, United Kingdom.[23] The five outbreaks have resulted in 58 bloodstream infections in 54 patients. All five outbreaks demonstrate that the design of the WHO may allow bacterial contamination of vascular access devices that lead to BSIs in hemodialysis patients.

In addition to the problems associated with the design of the WHO, insufficient training of hemodialysis personnel about the design and proper handling and maintenance of WHOs probably contributed to the BSI outbreak. The WHO is a unique device for saline prime disposal not present on other brands of hemodialysis machine. For any medical device, and particularly for unique medical devices, it is important that the manufacturer provide clear and sufficient educational materials so that users can readily understand proper handling, maintenance, and quality-control procedures. Such educational materials also should clearly indicate any major cautions about the device. In the case of the WHO, because patient dialysis lines were inserted into WHO ports, dialysis technicians generally treated WHO ports as though they were "clean" when the ports should have been treated as the dirty areas they are.

Today, more complex healthcare is increasingly being provided outside of hospitals. This report underscores the importance of surveillance and infection control in the ambulatory healthcare setting. In hospitals, both surveillance and infection control are conducted as standard practice; outside of the hospital setting, surveillance is often nonexistent, and infection control may be variable. The detection of this outbreak and identification of the likely cause was aided by the brief time frame during which multiple infections were identified.

The outbreak reported here terminated when all check valves were replaced and dialysis machine disinfection procedures were enhanced; the use of the WHO at this hemodialysis center also was subsequently discontinued.

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