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SERRATIA LIQUEFACIENS BLOODSTREAM INFECTIONS FROM CONTAMINATION OF EPOETIN ALFA AT A HEMODIALYSIS CENTER

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ABSTRACT

Background In one month, 10 *Serratia liquefaciens* bloodstream infections and 6 pyrogenic reactions occurred in outpatients at a hemodialysis center.

Methods We performed a cohort study of all hemodialysis sessions on days that staff members reported *S. liquefaciens* bloodstream infections or pyrogenic reactions. We reviewed procedures and cultured samples of water, medications, soaps, and hand lotions and swabs from the hands of personnel.

Results We analyzed 208 sessions involving 48 patients. In 12 sessions, patients had *S. liquefaciens* bloodstream infections, and in 8, patients had pyrogenic reactions without bloodstream infection. Sessions with infections or reactions were associated with higher median doses of epoetin alfa than the 188 other sessions (6500 vs. 4000 U, $P=0.03$) and were more common during afternoon or evening shifts than morning shifts ($P=0.03$). Sessions with infections or reactions were associated with doses of epoetin alfa of more than 4000 U (multivariate odds ratio, 4.0; 95 percent confidence interval, 1.3 to 12.3). A review of procedures revealed that preservative-free, single-use vials of epoetin alfa were punctured multiple times, and residual epoetin alfa from multiple vials was pooled and administered to patients. *S. liquefaciens* was isolated from pooled epoetin alfa, empty vials of epoetin alfa, antibacterial soap, and hand lotion. All the isolates were identical by pulsed-field gel electrophoresis. After the practice of pooling epoetin alfa was discontinued and the contaminated soap and lotion were replaced, no further *S. liquefaciens* bloodstream infections or pyrogenic reactions occurred at this hemodialysis facility.

Conclusions Puncturing single-use vials multiple times and pooling preservative-free epoetin alfa caused this outbreak of bloodstream infections in a hemodialysis unit. To prevent similar outbreaks, dialysis units should use medication vials containing the doses most appropriate to their clinical needs. (N Engl J Med 2001;344:1491-7.)

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OVER 200,000 persons in the United States currently receive hemodialysis,¹ and the costs of the treatment are paid principally by Medicare. Rates of reimbursement for hemodialysis providers have remained relatively constant over the past two decades and increased only 1.2 percent last year.² The percentage of patients treated with dialysis in for-profit facilities has grown from 40 percent in 1982 to 68 percent in 1997.^{1,3} There is concern that with constraints on reimbursement and increasing privatization, dialysis providers are motivated to control costs, sometimes to the detriment of patient care.⁴

One way of reducing costs is to avoid the waste of medications. Heparin and epoetin alfa, medications that are administered to most patients who are receiving hemodialysis, are packaged in vials and withdrawn with a needle and syringe. These vials contain more than the labeled amount, and the use of all the medication, including the excess, may yield substantial cost savings. However, this may require health care workers to puncture single-use vials multiple times, which may lead to substantial bacterial growth in preservative-free medications.

Previously published reports of nosocomial infection with *Serratia liquefaciens*, a rare pathogen in humans, include bloodstream infections resulting from the receipt of contaminated red-cell concentrates⁵⁻¹⁰ and urinary tract infections due to the use of a contaminated cystometric transducer.¹¹ To date, no outbreaks of infection with *S. liquefaciens* have been re-

From the Hospital Infections Program (L.A.G., V.R.R., M.J.A., L.A.C., J.I.T., S.C.H., B.J.J., W.R.J.) and the Epidemic Intelligence Service (L.A.G., V.R.R.) and Preventive Medicine Residency (D.R.E.), Division of Applied Public Health Training, Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta; and the Colorado Department of Public Health and Environment, Denver (D.R.E., R.E.H.). Address reprint requests to Dr. Grohskopf at the Hospital Infections Program, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, Mailstop E-69, Atlanta, GA 30333, or at lkg6@cdc.gov.

ported among patients receiving hemodialysis. Between June 30 and July 30, 1999, 10 *S. liquefaciens* bloodstream infections and 6 pyrogenic reactions without bloodstream infection occurred in outpatients at a free-standing hemodialysis facility with three sections (A, B, and C). All but one episode occurred in section C of the facility. On August 3, 1999, the Hospital Infections Program at the Centers for Disease Control and Prevention (CDC) was invited by the Colorado Department of Public Health and Environment to assist in the investigation and control of the outbreak.

METHODS

Study Definitions

A patient with *S. liquefaciens* infection was defined as any patient who underwent hemodialysis in section C during the study period who had a blood culture that was positive for *S. liquefaciens* (bloodstream infection) or in whom fever (a temperature of at least 38°C [100°F]) or rigor developed during or within the two hours after hemodialysis (a pyrogenic reaction). We also identified dialysis sessions that were associated with bloodstream infections or pyrogenic reactions.

Study Period

The study period consisted of all days from June 30 through August 10, 1999, on which the staff members reported that at least one bloodstream infection or pyrogenic reaction had occurred. These days were June 30; July 6, 21, 22, 27, 28, and 30; and August 2, 4, and 10.

Cohort Study

We reviewed clinical, microbiologic, and dialysis records for all sessions in section C that took place during the study period. The data collected included the demographic characteristics of the patients, the dates of treatment, the times at which treatment was initiated and terminated, means of vascular access, the machine number, the station number, the number of times the dialyzer had been reused, the maximal recorded body temperature, any symptoms of illness, the time of the onset of symptoms, intravenous medications administered, postdialysis weight, the most recently measured hematocrit, and the results of blood cultures. All documented contacts between patients and staff members were noted.

Observational Studies

We reviewed the procedures for the treatment of municipal water, disinfection of the water-distribution system, collection and culture of water and dialysate samples, and reprocessing of dialyzers. We also observed the way in which dialysis treatments were given, the machines prepared and cleaned, and medications stored and administered.

Microbiologic Studies

Isolates of *S. liquefaciens* from infected patients were sent to the CDC to confirm their identity. Swabs of environmental surfaces and samples of tap water, soaps, and hand lotions from section C, the adjoining restroom, and the medication room were sent to the CDC for bacterial culture. Swabs for culture from the hands of staff members of section C were obtained with use of a validated method.¹² DNA typing was performed with the use of pulsed-field gel electrophoresis on selected environmental isolates of *S. liquefaciens* and isolates from infected patients, according to the procedure of Maslow et al.,¹³ with the restriction endonuclease *SpeI*. Gels were interpreted according to the criteria of Tenover et al.¹⁴ For comparison, *S. liquefaciens* isolates that were not related to the

outbreak were obtained from two clinical laboratories elsewhere in the state.

Survey of Practices for the Use of Epoetin Alfa

A survey of practices for the use of epoetin alfa was mailed to 103 randomly selected hemodialysis centers in the United States. Information collected included the center's affiliation (affiliated with a hospital or free-standing), the type of ownership (for-profit or nonprofit), the epoetin alfa preparations used (single-use or multidosed preparations), whether single-use vials were routinely punctured multiple times, whether excess epoetin alfa was routinely collected and administered to patients, and the means by which excess epoetin alfa was collected (by pooling residual medication into a vial or syringe or by some other method). The centers submitted all information anonymously.

Statistical Analysis

Data were recorded on standardized forms and entered into a computer data base. Univariate analysis was performed with the use of Epi Info (version 6; CDC, Atlanta) and SAS software (version 6.12; SAS Institute, Cary, N.C.). Categorical variables were compared with the use of the chi-square test or Fisher's exact test. Continuous variables were compared with the use of the Wilcoxon rank-sum test. Multivariate logistic-regression analysis was performed with the use of Stata software (version 6; Stata, College Station, Tex.). Sessions were grouped according to patient identification number, and the generalized estimating equation was used to control for the potential correlation of patients' characteristics in multiple sessions. The doses of epoetin alfa and heparin were evaluated both as continuous variables and as dichotomous variables, with the overall median dose used as the boundary.

RESULTS

Cohort Study

A total of 208 dialysis sessions involving 48 patients were reviewed. We identified 12 sessions associated with *S. liquefaciens* bloodstream infections and 8 associated with pyrogenic reactions for which blood cultures were negative; these 20 sessions involved 15 patients. Five patients had positive blood cultures or pyrogenic reactions during two sessions. All 15 patients were treated successfully with antimicrobial agents as outpatients. For 1 of these 15 patients and for 2 patients who did not have bloodstream infections or pyrogenic reactions, epoetin alfa was reportedly most often given subcutaneously rather than intravenously, but the route of administration was not documented; therefore, the dose of epoetin alfa was considered to be unknown for the 11 sessions involving these 3 patients.

The 15 patients who had an infection with *S. liquefaciens* or a pyrogenic reaction did not differ significantly from the other 33 patients with respect to median age, sex, median postdialysis weight, dialysis schedule, or median hematocrit (Table 1). Dialysis sessions that were associated with infection or a pyrogenic reaction were similar to dialysis sessions that were not associated with infection or a pyrogenic reaction with respect to the median length of the session, median dose of heparin, and type of vascular access (Table 2). In contrast, the median dose of epoetin alfa was significantly higher during dialysis sessions

TABLE 1. UNIVARIATE COMPARISON OF RISK FACTORS AMONG 15 PATIENTS WITH *SERRATIA LIQUEFACIENS* INFECTION OR A PYROGENIC REACTION AND 33 PATIENTS WITHOUT INFECTION OR A PYROGENIC REACTION AT A HEMODIALYSIS CENTER FROM JUNE 30 THROUGH AUGUST 10, 1999.

VARIABLE	PATIENTS WITH INFECTION OR A PYROGENIC REACTION (N=15)	PATIENTS WITHOUT INFECTION OR A PYROGENIC REACTION (N=33)	P VALUE
Continuous			
Age — yr			0.99
Median	52.0	57.0	
Range	29.0–83.0	28.0–87.0	
Postdialysis weight — kg			0.29
Median	65.0	70.8	
Range	45.8–92.0	43.0–124.5	
Hematocrit — mg/dl			0.37
Median	36.6	38.7	
Range	31.8–46.8	27.9–43.5	
Categorical			
Male sex — no. (%)	9 (60.0)	19 (57.6)	0.88
Monday, Wednesday, and Friday dialysis schedule — no. (%)	10 (66.7)	16 (48.5)	0.24

that were associated with infection or a pyrogenic reaction than during dialysis sessions that were not associated with infection or a pyrogenic reaction. In a multivariate model that included the dose of epoetin alfa and the shift during which the session took place (morning, afternoon, or evening), treatment during the afternoon and evening shifts and doses of epoetin alfa of more than 4000 U were significant risk factors for infection (Table 3).

Univariate and multivariate analyses were repeated after the exclusion of 35 sessions during which antimicrobial agents were given (4 sessions associated with infection and 31 sessions not associated with infection). The results were similar; for doses of epoetin alfa of more than 4000 U, the multivariate model yielded an odds ratio for infection of 3.8 (95 percent confidence interval, 1.1 to 13.6). Analyses also were performed after the exclusion of sessions involving pyrogenic reactions and negative blood cultures; doses of epoetin alfa of more than 4000 U remained a significant risk factor in a multivariate analysis (odds ratio, 5.2; 95 percent confidence interval, 1.2 to 23.0).

Observational Studies

Water Treatment and Distribution

Before being used, municipal water passed through two particulate filters, an ion-exchange softener, two beds of granular activated charcoal, a reverse-osmosis unit, and an endotoxin filter. The water was supplied to the room for machine storage and dialysate prep-

TABLE 2. UNIVARIATE ANALYSIS OF RISK FACTORS FOR *SERRATIA LIQUEFACIENS* INFECTION OR A PYROGENIC REACTION AMONG 208 SESSIONS AT A HEMODIALYSIS CENTER FROM JUNE 30 THROUGH AUGUST 10, 1999.

VARIABLE	DIALYSIS SESSION ASSOCIATED WITH INFECTION OR PYROGENIC REACTION (N=20)	DIALYSIS SESSION NOT ASSOCIATED WITH INFECTION OR PYROGENIC REACTION (N=188)	P VALUE
Continuous			
Length of session — min			0.08
Median	227.5	220	
Range	170–255	135–335	
Total dose of heparin — U			0.4
Median	6500	6000	
Range	4700–10,000	2500–16,000	
Dose of epoetin alfa — U*			0.03
Median	6500	4000	
Range	3000–15,000	0–20,000	
Categorical			
Type of vascular access — no. (%)			0.4
Fistula	7 (35.0)	59 (31.4)	
Graft	13 (65.0)	115 (61.2)	
Catheter	0	14 (7.4)	
Shift — no. (%)			0.03
Morning	2 (10.0)	73 (38.8)	
Afternoon	9 (45.0)	64 (34.0)	
Evening	9 (45.0)	51 (27.1)	

*The dose of epoetin alfa was unknown for 11 sessions (1 associated with a pyrogenic reaction and 10 not associated with infection or pyrogenic reactions).

aration, then to the patient care area and to the dialyzer-reprocessing area, and finally it reentered the water-treatment system.

The water-distribution system was disinfected monthly with a mixture of 1 percent peracetic acid and hydrogen peroxide (Renalin, Minntech, Plymouth, Minn.). Because of the outbreak, additional disinfections were performed on July 10 with the 1 percent peracetic acid–hydrogen peroxide solution, on July 30 with a 2 percent peracetic acid–hydrogen peroxide solution, and on August 4, 5, and 8 with sodium hypochlorite. The levels of bacteria and endotoxin in the water samples were within acceptable limits according to the standards of the Association for the Advancement of Medical Instrumentation¹⁵; no species of *serratia* were isolated. Culture of an endotoxin filter and three reverse-osmosis membranes yielded no species of *serratia*.

Dialyzer Reprocessing

Dialyzers (model 80A, Fresenius Medical Care North America, Lexington, Mass.) were reprocessed after use by machine (Renatron, Minntech) with peracetic acid–hydrogen peroxide solution. The reuse of dialyzers was suspended in section C on July 30.

TABLE 3. MULTIVARIATE ANALYSIS OF RISK FACTORS FOR *SERRATIA LIQUEFACIENS* INFECTION OR A PYROGENIC REACTION AMONG 208 SESSIONS AT A HEMODIALYSIS CENTER FROM JUNE 30 THROUGH AUGUST 10, 1999.

VARIABLE	DIALYSIS SESSION ASSOCIATED WITH INFECTION OR PYROGENIC REACTION (N=20)	DIALYSIS SESSION NOT ASSOCIATED WITH INFECTION OR PYROGENIC REACTION (N=188)	ODDS RATIO (95% CI)*
	no. (%)		
Dose of epoetin alfa†			
≤4000 U‡	4 (20)	92 (49)	1.0
>4000 U	15 (75)	86 (46)	4.0 (1.3–12.3)
Shift			
Morning‡	2 (10)	73 (39)	1.0
Afternoon	9 (45)	64 (34)	12.2 (1.3–113.0)
Evening	9 (45)	51 (27)	12.7 (1.4–118.1)

*CI denotes confidence interval.

†The totals are less than 100 percent, because the dose of epoetin alfa was unknown for 11 sessions (1 associated with a pyrogenic reaction and 10 not associated with infection or pyrogenic reactions).

‡This group served as the reference category.

Dialysis Treatment Procedures

Several dialysis sessions were observed. No obvious breaches of aseptic technique were noted.

Medications

Medications or solutions given during the reviewed sessions included heparin, epoetin alfa, activated vitamin D, and hypertonic saline. Only heparin and epoetin alfa were given during all dialysis sessions that were associated with infection or a pyrogenic reaction. Heparin was stocked in multidose vials. Epoetin alfa (Epoegen, Amgen, Thousand Oaks, Calif.) at a concentration of 10,000 U per milliliter was stocked in preservative-free 1-ml vials with rubber diaphragms that were designated as single-use vials by the manufacturer. Multiple doses were drawn from these vials. When the vials were almost empty, they were refrigerated overnight. The next morning, a needle and syringe were used to extract the remaining medication from these vials. The needle was not changed between vials, but the tops of all the vials were cleaned with alcohol pads before the needle was inserted. Residual medication was pooled into one vial for use that day. Pooling was generally performed by one health care worker.

Microbiologic Studies

No species of *serratia* were isolated from 20 swabs of environmental surfaces (including 1 specimen from the faucet in the medication room), 1 sample of the tap water from the sink in the medication room, or 15 cultures of samples obtained with swabs from the hands of the staff, including the health care worker responsible for pooling residual epoetin alfa. All iso-

lates from patients with bloodstream infections were confirmed to be *S. liquefaciens*. Antibacterial soap from several dispensers mounted on the walls in section C and an unopened container yielded no *serratia* isolates. However, a sample of the same soap from the dispenser in the medication room yielded *S. liquefaciens*. A review of maintenance procedures revealed that staff members refilled the soap dispensers by periodically adding soap to them without emptying and cleaning them first. In addition, *S. liquefaciens* was isolated from a pump bottle of hand lotion, which was also located in the medication room. No other bottles of this hand lotion were present at the facility.

During the investigation, staff members were asked to save empty vials of parenteral medication for possible culture. Cultures from three vials of heparin that were being used in section C; two empty, undated vials; and four empty, dated vials (opened between July 30 and August 3) were negative, as was a culture from one empty, undated vial of hypertonic saline. However, *S. liquefaciens* was isolated from 61 of 97 empty vials of epoetin alfa (after pooling of residual medication). Vials with positive cultures were from two different lot numbers; not all vials within each lot were positive. In addition, one of three vials of pooled epoetin alfa obtained for culture grew *S. liquefaciens*. Empty vials and vials of pooled epoetin alfa had been saved for an unknown period and were not dated to indicate when they had been opened or used. Representative *S. liquefaciens* isolates from patients and vials were shown to be identical by pulsed-field gel electrophoresis and differed from four isolates that were not associated with the outbreak that had been obtained from clinical laboratories elsewhere in the state (Fig. 1).

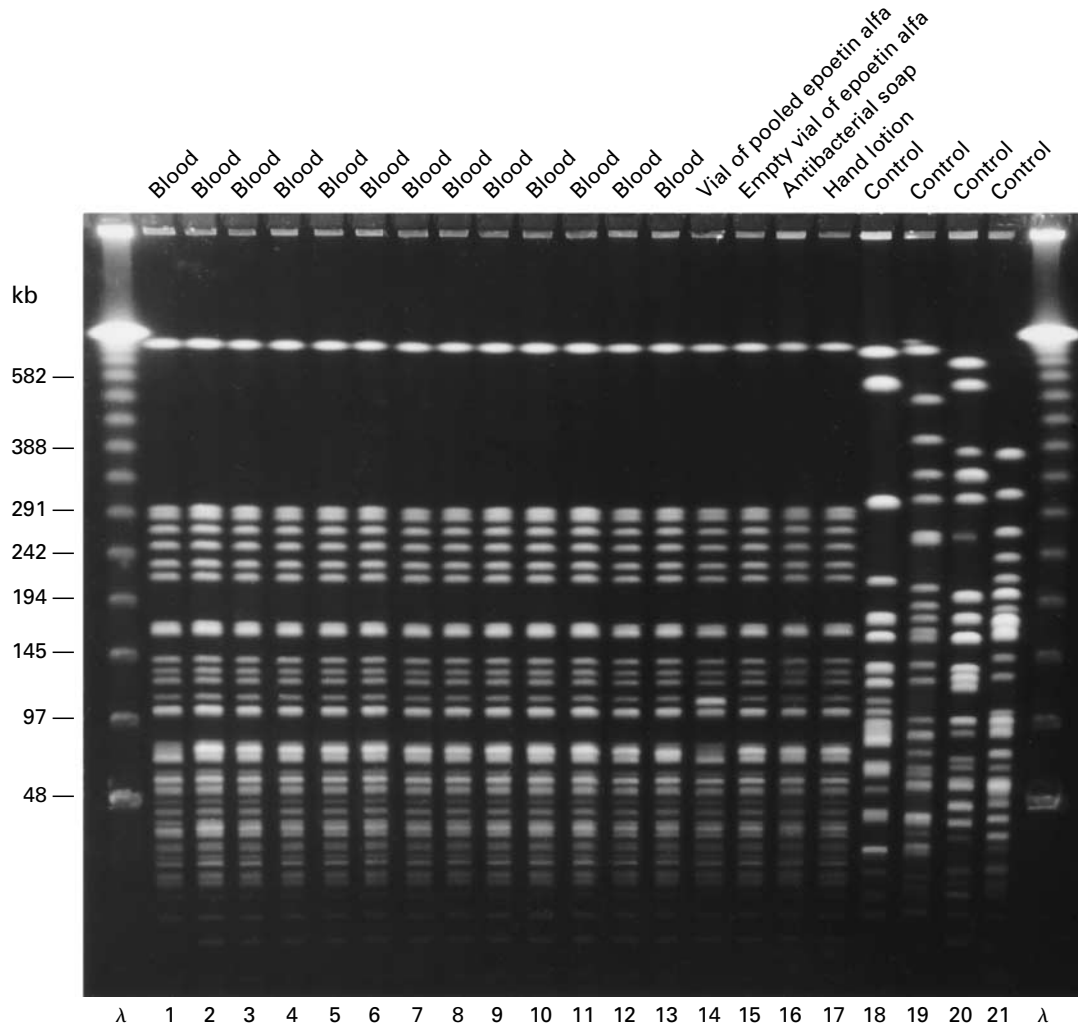


Figure 1. Pulsed-Field Gel Electrophoresis of *Serratia liquefaciens* Isolates.

The λ denotes the molecular-weight marker. Lanes 1 through 11 show blood isolates from patients in section C; lanes 12 and 13 show blood isolates from patients in section A; lane 14 shows an isolate from a full vial of pooled epoetin alfa; lane 15 shows an isolate from an empty vial; lane 16 shows an isolate from antibacterial soap; lane 17 shows an isolate from hand lotion; and lanes 18 through 21 show *S. liquefaciens* isolates from other centers in the state that were not associated with the outbreak.

Survey of Practices for the Use of Epoetin Alfa

Seventy-one of 103 centers (69 percent) returned the survey. Fifty-eight of these 71 (82 percent) reported using the single-use preparation of epoetin alfa. Of these 58, 45 (78 percent), reported routinely puncturing these vials more than once to obtain multiple doses. Only 1 of these 45 centers (2 percent) reported using the vial until it was empty and then disposing of it immediately; 39 (87 percent) reported that the maximal interval between opening a vial and either emptying the vial or discarding its contents ranged from three hours to two weeks (Table 4). Nine of the 58 centers (16 percent) reported that they routinely

pooled the residual contents of multiple single-use vials in a common container for later use. There was no significant association between the practice of either pooling residual medication or using single-use vials multiple times with for-profit status.

Recommendations and Termination of Outbreak

After the study period, during the processing of cultures, two additional bloodstream infections with *S. liquefaciens* occurred in section A on August 30 and September 1. These *S. liquefaciens* isolates were identical to those from the previous bloodstream infections (Fig. 1). It was recommended that the center

TABLE 4. MAXIMAL INTERVAL BETWEEN THE OPENING OF A SINGLE-USE VIAL OF EPOETIN ALFA AND THE DISPOSAL OF ITS CONTENTS AMONG 45 CENTERS REPORTING MULTIPLE PUNCTURES OF SINGLE-USE VIALS.

INTERVAL BETWEEN OPENING AND DISPOSAL	No. OF CENTERS (%)
Specified	
Epoetin alfa accessed immediately, drained, and administered	1 (2)
3–12 Hr	5 (11)
13–24 Hr	20 (44)
36 Hr	1 (2)
48 Hr	3 (7)
2 Wk	1 (2)
Not specified	
Opened, unused medication discarded at the end of the day	6 (13)
Opened, unused medication administered the next morning	3 (7)
Not reported	5 (11)

cease pooling epoetin alfa and using the contaminated soap and hand lotion and that they begin using disposable soap containers rather than refillable dispensers. These recommendations were implemented on September 2. No additional bloodstream infections or pyrogenic reactions occurred on or after this date.

DISCUSSION

We traced an outbreak of *S. liquefaciens* bloodstream infections and pyrogenic reactions among patients receiving hemodialysis to extrinsically contaminated epoetin alfa. We found a significant epidemiologic association between doses of epoetin alfa of more than 4000 U and dialysis sessions that were associated with infection or a pyrogenic reaction. Moreover, *S. liquefaciens* that was genotypically identical to the isolates from patients was present in empty vials of epoetin alfa from multiple lot numbers, pooled epoetin alfa, soap, and hand lotion. Other potential sources of contamination that can be associated with bloodstream infection in hemodialysis facilities,¹⁶ such as inadequately treated water or improper dialyzer reprocessing, appear unlikely to have been involved in this outbreak; no strains of *S. liquefaciens* were isolated from components of the water-treatment system or water samples, and infections continued to occur after the reuse of dialyzers was stopped.

There are several limitations to our investigation. We could not obtain any vials of medication that were known to have been administered to affected patients, since no vials were saved until late in the outbreak. The vials we examined had no label to indicate when they were opened or for whom doses were withdrawn. However, the finding by pulsed-field gel electrophoresis that isolates from patients and vials of epoetin alfa

were identical strongly points to contamination of the vials as the means of transmission of *S. liquefaciens* to the patients.

Our study design focused only on sessions occurring on days when staff members reported bloodstream infections or pyrogenic reactions and may not have been sufficiently sensitive to identify associations between specific staff members and dialysis sessions that were associated with infection or a pyrogenic reaction. However, the staff members at this center work very consistent schedules and often care for the same patients; it is unlikely that obtaining samples on all days of the study period would have enhanced our ability to detect significant differences in the extent of exposure to specific staff members between dialysis sessions that were associated with infection or a pyrogenic reaction and dialysis sessions that were not associated with infection or a pyrogenic reaction.

Finally, we were unable to obtain unopened vials of epoetin alfa from the same lots that yielded *S. liquefaciens*, and therefore we cannot eliminate the possibility of intrinsic contamination. However, intrinsic contamination appears unlikely for several reasons. The vials that were positive for *S. liquefaciens* came from two different lots, and not all empty vials from each lot were positive. Genetically identical isolates of *S. liquefaciens* were present in soap and hand lotion; it seems unlikely that contamination would spread from the medication to these products. Moreover, if the epoetin alfa had been intrinsically contaminated, similar events would probably have been noted elsewhere, particularly since *S. liquefaciens* is a rare human pathogen. We are aware of no additional reports at other facilities.

We are uncertain of the original source of the *S. liquefaciens*. It seems likely that the *S. liquefaciens* passed from the hands of health care personnel that were transiently contaminated by soap or hand lotion to the epoetin alfa. This hypothesis is supported by the cessation of bloodstream infections and pyrogenic reactions after the cessation of pooling of epoetin alfa and the switch to single-use antibacterial soaps. The finding that significantly more dialysis sessions that were associated with infection or a pyrogenic reaction occurred in the afternoon or evening (i.e., the second or third shift) is consistent with the ability of *S. liquefaciens* to multiply even while refrigerated.^{17,18} The predominance of dialysis sessions that were associated with infection or a pyrogenic reaction in section C may have been due to the fact that this section of the facility was nearest to the room where the medication was stored and was the last to receive patients in the morning (roughly four hours after the facility opened); therefore, bacteria introduced into vials used in this section had more time to multiply.

We were unable to ascertain where or how the practice of multiple puncturing of vials and pooling of preservative-free epoetin alfa originated. However, these

procedures apparently were suggested to the center's nursing and technical staff as a way to recover as much epoetin alfa as possible from the vials and were used routinely at the facility. Epoetin alfa is expensive, and avoiding waste has important economic ramifications for hemodialysis facilities. Each 1-ml vial of 10,000 U cost the facility approximately \$85 at the time of the investigation. The reimbursement allowed by Medicare to dialysis centers for epoetin alfa is currently \$10 per 1000 U administered, of which 80 percent is reimbursed by Medicare and the remaining 20 percent must be borne by the patient or any secondary insurance.

For a facility serving 150 patients, 90 percent of whom receive 4000 U of epoetin alfa three times per week, assuming an average cost of \$9 and a reimbursement of \$10 per 1000 U,¹⁹ efficiently and consistently recovering excess medication equal to 15 percent of the labeled amount can result in a maximal reimbursement of over \$180,000 annually above the cost of the drug. Conversely, using single-use 1-ml vials of 10,000 U only once can lead to the waste of \$1.1 million worth of medication annually, for which no reimbursement is received.

In our surveyed sample of dialysis centers in the United States, the practice of puncturing single-use vials of epoetin alfa multiple times appears to be relatively common, despite labels on each vial and prescription information specifying that the product is intended for a single use. A multidose formulation of epoetin alfa with preservatives is available; however, its retail price is slightly higher. Furthermore, there is a belief among dialysis providers that the single-use preparation contains a higher percentage of excess medication than the multidose preparation.

Our data demonstrate that repeated use of single-use vials and pooling of preservative-free epoetin alfa can cause extrinsic bacterial contamination and potentially serious adverse events. In response to the outbreak, the manufacturer of the epoetin alfa, in conjunction with the Food and Drug Administration, issued a letter to dialysis providers advising that the manufacturer's instructions pertaining to single-use epoetin alfa be followed to avoid similar outbreaks. If multiple patients are to receive epoetin alfa from a single vial, multidose vials should be used.

We are indebted to the staff of the dialysis facility for their assistance in the investigation of this outbreak.

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