Enterobacter cloacae Bloodstream Infections Traced to Contaminated Human Albumin

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In August 1996, a patient in Kansas developed an *Enterobacter cloacae* bloodstream infection (BSI) shortly after receiving Albuminar, a brand of human albumin. Albuminar contamination was suspected. A case-control study of patients with primary gram-negative bacterial BSIs showed that patients with *E. cloacae* BSIs were significantly more likely than patients with non–*E. cloacae* gram-negative BSIs to have received Albuminar within 3 days of developing their BSIs (3 of 5 vs. 0 of 9; OR, undefined; $P = .03$). The *E. cloacae* isolate from the Kansas patient was found by pulsed-field gel electrophoresis to be identical to the isolate from the patient's Albuminar vial, to isolates from 2 previously unopened Albuminar vials, and to an isolate from a Wisconsin patient who had received Albuminar. A worldwide recall of ~116,000 Albuminar vials took place. This multistate outbreak was detected because of clinical astuteness and prompt reporting. Combined epidemiological and laboratory approaches are valuable when investigating potentially contaminated blood components and plasma derivatives.

Albumin constitutes >60% of blood plasma proteins [1]. Human albumin, a licensed biological product, may be purified from the plasma of human donors by cold ethanol fractionation. Albumin has frequently been used as a resuscitation fluid for shock, as a nutritional intervention for protein malnutrition, and as a treatment for hepatic cirrhosis with ascites or nephrotic syndrome with edema. However, the appropriate clinical indications for the use of albumin have been debated since the product was developed in the 1940s [2], and a recent review suggests that administration of albumin to critically ill patients may increase mortality [3]. It is more expensive than other products used for the same indications, such as nonprotein colloid (e.g., hetastarch and dextran) and crystalloid (e.g., lactated Ringer's and saline) solutions.

The incidence of adverse events per albumin treatment is estimated to be <0.01% [4]; they may result from reactions to constituents of the albumin solution and to unstandardized clinical uses of albumin [4, 5]. Examples of adverse events attributed to albumin and reported to the US Food and Drug Administration (FDA, Rockville, MD) include pyrexia, hypotension, dyspnea, dermatitis, rigors, and urticaria (FDA, unpublished data).

Background and Case Reports

Case 1. On 23 August 1996, a 50-year-old man (patient 1) recovering from abdominal surgery at Via Christi Regional Medical Center–St. Francis (VCSF), in Wichita, Kansas, received an iv infusion of 25 g of 25% Albuminar (lot P61205; Centeon, L.L.C., King of Prussia, PA), a brand of human albumin. The patient complained of rigors and chills during the infusion and subsequently developed a fever (temperatures to 40.6°C). He became progressively hypotensive (systolic blood pressure, 62 mm Hg) and required transfer to the intensive care unit for hemodynamic support.

The patient's complaints at the time of the infusion and the dramatic clinical course caused clinicians to suspect that the albumin was the culprit. Cultures of the opened Albuminar vial and of the patient's blood obbtained ~2 h after the administration of albumin yielded *E. cloacae.* A MedWatch report was

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filed with the FDA. On 20 September 1996 the manufacturer, in collaboration with the FDA, issued a voluntary market withdrawal of Albuminar lot P61205. This lot of ~17,000 vials of Albuminar had been manufactured on 12 May 1996 and was released for distribution in late June 1996.

Case 2. The blood bank supervisor at Bellin Memorial Hospital, in Green Bay, Wisconsin, was notified by Centeon of the voluntary market withdrawal of Albuminar. Reviewing the hospital's use of Albuminar, the supervisor identified a 64-year-old man (patient 2) who had undergone abdominal and spinal surgery on 4 September 1996 and, over a 13-day postoperative period, had received 37 vials of 25% Albuminar, also from lot P61205. A culture of blood obtained from patient 2 on 16 September 1996 yielded *E. cloacae.*

At the FDA, cultures of previously unopened vials of Albuminar lot P61205 yielded *E. cloacae, Stenotrophomonas maltophilia,* and *Enterococcus gallinarum.* We describe an investigation undertaken to determine (1) the association between receiving Albuminar and developing an *E. cloacae* bloodstream infection (BSI) at VCSF, (2) the extent of Albuminar-associated infections in the United States, and (3) the likely mechanism of Albuminar contamination.

Methods

Assessments at VCSF. In a preliminary study to determine the extent of the outbreak at VCSF, we compared the number of primary nosocomial BSIs due to *E. cloacae, S. maltophilia,* or *E. gallinarum* that occurred from 1 January through 30 June 1996 (the pre-epidemic period) with the number of primary nosocomial BSIs due to the same organisms that occurred from 1 July through 30 September 1996 (i.e., the epidemic period). Microbiology and pharmacy records were cross-referenced to identify all patients with BSIs due to these organisms who had received Albuminar after 1 July 1996.

On the basis of the results of the preliminary study, we performed a case-control study to determine whether Albuminar was associated with *E. cloacae* BSI. A case patient was defined as any VCSF patient with a primary (i.e., not secondary to infection at another site) nosocomial *E. cloacae* BSI during the epidemic period. A control patient was defined as any VCSF patient with a primary BSI due to gram-negative organisms other than *E. cloacae* during the epidemic period. Case and control patients were identified by review of VCSF microbiology records from the epidemic period.

Both case patients and control patients were excluded if positive blood cultures were obtained <48 h after admission. To meet our definition of Albuminar exposure, administration of Albuminar must have occurred within 2 weeks before the onset of BSI. Albuminar exposure was ascertained by review of pharmacy, billing, and medical records. Demographic and clinical data were obtained from medical records.

Assessments at other hospitals. Extensive efforts to assess Albuminar use and to identify patients with Albuminar-related *E. cloacae* BSIs were made at 2 other hospitals in Wichita and at Bellin Memorial Hospital.

Efforts were also made to inform the health care community of the contaminated albumin product and to identify other cases. State health departments, pharmacists, and physicians were notified. Notices were published on the Internet website of the Centers for Disease Control and Prevention (CDC) and in the Morbidity and Mortality Weekly Report [6, 7]. In addition, a notice was issued to ~210 hospitals belonging to the National Nosocomial Infections Surveillance system and to >340 hospitals belonging to a single private hospital chain that had been purchasing and using this brand of human albumin exclusively.

For surveillance purposes, a definite case was defined as a primary BSI or surgical site infection due to *E. cloacae* or *S. maltophilia* that occurred after 1 July 1996 in a patient who had received Centeon Albuminar within 2 weeks before the infection and whose isolate matched an isolate from an Albuminar vial, as determined by pulsed-field gel electrophoresis (PFGE). A probable case was the same as a definite case, except that the patient's isolate either was not available to be tested by PFGE or did not match by PFGE. A patient was excluded from the group of case patients if they had a polymicrobial infection or if there was a likely source of infection other than Albuminar.

Microbiological studies. Isolates of *E. cloacae* from case patients and from Albuminar vials were sent to the CDC for confirmation and for DNA typing by means of PFGE [8].

Statistical methods. Data were collected on standardized forms, entered into a computer, and analyzed with use of Epi Info version 6.02 software (CDC). Categorical variables were compared with the Yates corrected χ^2 or Fisher's exact test. Continuous variables were compared by means of the Kruskal-Wallis test.

Investigation of Albuminar production. The FDA conducted an on-site investigation of the manufacturer's Albuminar production facilities, in Kankakee, Illinois. Albuminar vials were examined and tested in FDA laboratories.

Results

Albumin use and BSI rate at VCSF. During the pre-epidemic period, there was only 1 patient with a primary nosocomial BSI due to *E. cloacae.* During the epidemic period, 5 patients with primary nosocomial *E. cloacae* BSIs were identified. The primary nosocomial *E. cloacae* BSI rate per hospital discharge was significantly higher during the epidemic period than in the pre-epidemic period (5 of 5806 vs. 1 of 12,046; $P = .02$). There were no episodes of *S. maltophilia* or *E. gallinarum* BSI during either the epidemic period or the pre-epidemic period.

During the epidemic period, 451 patients at VCSF received either Centeon or Alpha Therapeutic (Albutein, Los Angeles, CA) albumin. A total of 691 vials of Centeon Albuminar, lot P61205, were used during this period. The number of patients who received Albuminar from this lot is uncertain, since other lots of Albuminar were also used during the epidemic period and lot numbers were not consistently recorded in the patient medical records or pharmacy records.

Case-control study. Five patients met the definition of a case patient (table 1), and 9 met the definition of a control patient. Underlying diagnoses of control patients (end-stage

Table 1. Characteristics of case patients at Via Christi Regional Medical Center–St. Francis Campus (Wichita, Kansas), from 1 July through 30 September 1996.

Age (y), sex	Time (d) from admission to BSI	Underlying condition	Albuminar received?	Time to positive blood culture[a]	Outcome of BSI
50, M[b]	11	ESRD, prior bowel perforation	Y	2 h	Survived
3, M	15	Trauma	Y	3 d	Survived
36, F	7	Trauma	Y	1 d	Survived
1.5, M	4	Cancer	N	—	Survived
49, M	18	Cancer	N	—	Survived

NOTE. BSI, bloodstream infection; ESRD, end-stage renal disease; N, no; Y, yes.
[a] Interval between last Albuminar dose and positive blood culture.
[b] Patient 1 (in Case Reports).

renal disease, $n = 4$; cancer, $n = 3$; myocardial infarction, $n = 1$; and AIDS, $n = 1$) were similar to those of the case patients except for the absence of any trauma. Organisms causing the BSIs in the control patients included *Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Providencia rettgeri, Klebsiella pneumoniae, Pseudomonas stutzeri, Bacteroides gracilis, Campylobacter species,* and *Serratia marcescens.*

Case patients and control patients were similar in terms of sex (male, 4 of 5 vs. 7 of 9, respectively; $P = 1$) and age (median age, 36 vs. 60 years; $P = .12$). In contrast, the interval between admission and onset of BSI was significantly longer among case patients than among control patients (median, 11 days vs. 3 days; $P = .02$). Case patients were significantly more likely than control patients to have received Albuminar within 3 days prior to the onset of BSI (3 of 5 vs. 0 of 9; OR, undefined; $P = .03$).

Other hospitals. At 1 of the additional Wichita hospitals, there had been only 1 patient with *E. cloacae* BSI during the epidemic period, but the patient had not received Albuminar. At the other Wichita hospital, 1 patient was identified as having received Albuminar on 12 occasions, with subsequent development of *E. cloacae* BSI. No infections due to *S. maltophilia* or *E. gallinarum* occurred at either of these 2 hospitals.

At Bellin Memorial Hospital, 40 vials of possibly contaminated Albuminar were used during the epidemic period; 37 of these vials were given to patient 2, who subsequently developed *E. cloacae* BSI; the remaining 3 vials were given to 2 other patients, who did not develop BSI. No episodes of infection due to *S. maltophilia* or *E. gallinarum* were identified at Bellin Memorial Hospital.

Microbiological studies. The *E. cloacae* isolates obtained from cultures of 3 previously unopened Albuminar vials yielded 2 different PFGE patterns (table 2). The *E. cloacae* PFGE pattern of 1 of these isolates was unique and did not match with any other *E. cloacae* PFGE pattern. *E. cloacae* isolates obtained from cultures of the other 2 previously unopened Albuminar vials, from the blood of patient 1, from patient 1's opened Albuminar vial, and from the blood of patient 2 had identical PFGE patterns.

Albuminar-associated infections in the United States. As a result of national publicity, we identified 6 additional patients who developed *E. cloacae* infection following receipt of Albuminar, bringing the total number of patients identified to 8. The 6 additional patients had been hospitalized in California, Kansas, Missouri, and Ohio; 5 of the 6 patients had undergone surgery before receiving Albuminar. No isolates were available for PFGE typing for 3 of these additional patients, and the isolates from the other 3 patients did not match the 2 available *E. cloacae* isolates from the Albuminar vials (table 2).

Investigation of Albuminar production. On 27 September 1996, upon learning of the second case report (patient 2), the FDA directed Centeon L.L.C. to issue a class I recall of lot P61205 of Albuminar. An investigation by the FDA at the manufacturing site in early October 1996 revealed that on >1 occasion, pallets containing Albuminar vials fell while being moved by forklift from one location to another within the plant. As a result, small cracks apparently developed in some vials.

In addition, water in a cooling bath into which Albuminar vials were placed following pasteurization was found to contain >700,000 gram-negative rods (*Sphingomonas paucimobilis* and *Sphingobacterium multivorum*) per milliliter at the time of the FDA investigation. Furthermore, at one step in the process, tap water was sprayed on the vials to cool them after pasteurization.

The FDA laboratory received 628 Albuminar vials from multiple distribution sites and selected 276 vials representing 31 different lots for closer examination. Of the 276 vials, 152 (55%)

Table 2. Summary of pulsed-field gel electrophoresis (PFGE) results for *Enterobacter cloacae* isolates from Albuminar vials and from patients who received Albuminar.

Hospital	Source of isolate	Albuminar lot no.	PFGE type
VCSF	Blood, patient 1	P61205	a
VCSF	Opened Albuminar vial, patient 1	P61205	a
BMH	Blood, patient 2	P61205	a
—	Unopened Albuminar vial	P61205	a
—	Unopened Albuminar vial	P61205	a
—	Unopened Albuminar vial	P61205	b
VCSF	Blood, patient 3	NR	c
Hospital X	Blood, patient 4	NR	d
Hospital Y	Blood, patient 5	NR	e

NOTE. BMH, Bellin Memorial Hospital, Green Bay, Wisconsin; NR, not recorded; VCSF, Via Christi Regional Medical Center–St. Francis Campus, Wichita, Kansas.

Figure 1. Albuminar vial with small crack. Of 276 Albuminar vials examined at the FDA, 152 (55%) had chips, dents, or scratches measuring 1–5 mm, as seen here.

had chips, dents, or scratches measuring 1–5 mm (figure 1). Four (1.5%) of the vials examined had visible cracks measuring ⩾6 mm (figure 2). Vials from only 1 lot, P61205, tested positive in sterility tests. All previously unopened vials that were shown to harbor organisms had cracks.

Because of evidence of repeated accidents and absence of adequate quality control at this later stage in the manufacturing process for Albuminar and another Centeon product (Plasma-Plex), Centeon, L.L.C., in cooperation with the FDA, announced a worldwide recall of all lots of Centeon Albuminar (albumin [human], 5%, 20%, and 25%) and Centeon Plasma-Plex (plasma protein fraction [human], 5%) on 9 October 1996. At the time, Centeon had ~20% of the United States market share of albumin, and the Albuminar recall involved ~116,000 vials. Of the ~17,000 vials in lot P61205, Centeon recovered 6525.

Discussion

Enterobacter species are enteric pathogens that commonly colonize and infect hospitalized patients [9, 10]. They have been implicated in both point-source outbreaks and outbreaks caused by patient-to-patient transmission via the hands of hospital personnel [11]. Nosocomial *E. cloacae* outbreaks have occurred in neonatal intensive care units [12–14], burn units, and postsurgical cardiac intensive care units. *Enterobacter* species can survive in nutritionally poor fluids; contaminated iv fluids such as saline and 5% dextrose have caused several outbreaks [15–19]. This is the first documented outbreak of *E. cloacae* associated with contamination of a plasma derivative.

Because cultures of previously unopened Albuminar vials were positive for *E. cloacae, S. maltophilia,* and *E. gallinarum,* we first looked for BSI due to any of these organisms in patients at VCSF; we found only *E. cloacae* BSIs. Since albumin recipients frequently have undergone invasive procedures or have multiple serious medical problems, they are more likely to develop nosocomial infections, regardless of albumin exposure. Therefore, we performed a case-control study to assess the association between Albuminar and *E. cloacae* BSI at VCSF.

Receipt of Albuminar within 72 h of onset of BSI was statistically significant and associated with the development of *E.*

Figure 2. Albuminar vial with large crack. Four (1.5%) of the 276 Albuminar vials examined at the FDA had readily visible cracks measuring ≥6 mm, as seen here.

cloacae BSI. Isolates were available from 2 of the 3 VCSF case patients who received Albuminar; these 2 isolates did not match by PFGE. However, the *E. cloacae* isolate from patient 1 was identical by PFGE to the isolate from patient 1's opened Albuminar vial, to isolates from 2 previously unopened Albuminar vials, and to the isolate from patient 2. These epidemiological and laboratory data confirm that the Albuminar was contaminated by *E. cloacae.* It is not certain whether Albuminar was the cause of the *E. cloacae* BSIs that occurred in the 2 other VCSF case patients who had received Albuminar.

Results of the FDA investigation of the Kankakee manufacturing site suggest that vials of Albuminar may have been externally contaminated with bacteria from the cooling bath or the rinse water. When pallets of the vials were dropped, some vials cracked, which allowed the bacteria on their external surfaces to enter and multiply in the Albuminar.

Nationally, we identified 8 patients who had *E. cloacae* infections after receiving Albuminar. *E. cloacae* isolates were not available from 3 patients. Of the 5 *E. cloacae* isolates from patients that were available for typing by PFGE at the CDC, 2 (from patients 1 and 2) matched isolates from 3 Albuminar vials (patient 1's opened vial and 2 previously unopened vials); the 3 remaining patient isolates had distinct PFGE patterns. One of the previously unopened Albuminar vials yielded an additional *E. cloacae* isolate with a unique PFGE pattern that did not match that of any available patient isolate. Had more Albuminar vials been cultured, it is possible that more PFGE patterns of *E. cloacae* would have been identified and that more PFGE patterns from patient and albuminar isolates would have matched.

Difficulties in tracking Albuminar distribution and the small numbers of Albuminar recipients at many institutions precluded ready assessment of the morbidity caused by the contaminated Albuminar. Case finding was difficult. First, there was a low attack rate, as was demonstrated by our preliminary study, which uncovered only 3 cases among 451 patients who received albumin at VCSF. Thus, any single health care facility was unlikely to have a large number of infected patients.

Second, because patients who receive albumin are frequently severely ill, they are often being treated with antimicrobials when albumin is administered. This circumstance could obscure an infection associated with Albuminar. The *E. cloacae* isolated from patient 1's blood culture and Albuminar vial was not multidrug-resistant and did not form extended-spectrum β-lactamase.

Third, even when cases of *E. cloacae* BSI were identified, it often was not clear whether they were attributable to Albuminar. Albumin recipients are frequently patients who have multiple risk factors for infection because they have many medical problems and have undergone multiple invasive procedures. Since *E. cloacae* is a common nosocomial pathogen, it was difficult to implicate Albuminar as the source of infection, especially if an isolate was not available for genotyping.

Fourth, recording of the albumin brand name and lot number in patients' medical records often was inconsistent, so even when it was known that a patient had received albumin, the records often were inadequate for review. Albumin was occasionally given to a patient as part of another treatment; for example, via parenteral nutrition or as a result of priming a cardiac bypass pump for cardiac surgery. These alternative methods of albumin administration generally were not identified on the routine medication sheets, so these recipients might be missed.

Finally, some cases patients received Albuminar and developed *E. cloacae* BSIs or wound infections, but their *E. cloacae* isolates were no longer available for PFGE testing.

In summary, we report a multistate outbreak of *E. cloacae* BSI caused by a contaminated albumin product. The outbreak was quickly recognized by clinicians caring for the index patient and reported to the CDC and FDA. A national surveillance effort identified 6 additional cases that were probably associated with administration of Albuminar. Epidemiological and laboratory data confirmed the intrinsic contamination of Albuminar by *E. cloacae.* The resulting worldwide recall of Albuminar and related products may have prevented further cases of *E. cloacae* bacteremia.

Before administering intravenous fluids, drugs, or biologics to patients, health care workers should examine the product vial or bag for any evidence of impaired integrity [20]. If damage to the product container is evident, the product should not be administered.

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