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Pseudomonas Species Bacteremia Caused by Contaminated Normal Human Serum Albumin

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In May and June 1973, 11 patients on the surgical service at the University of Maryland Hospital had bacteremia caused by *Pseudomonas* species. Seven of the isolates recovered from blood cultures had the same antibiogram (sensitive only to chloramphenicol and tetracycline). Ten of the 11 patients were given 25% normal serum albumin (human) shortly before the onset of symptoms. In contrast, only two of seven patients with bacteremia due to *Pseudomonas aeruginosa* in May and June ($P = 0.013$) and only nine of 20 patients located in surgical special care units during these months ($P = 0.014$) were given this product. When cultured, the albumin in one of 54 previously unopened vials from the implicated lot yielded *Pseudomonas cepacia* sensitive only to chloramphenicol, tetracycline, and nalidixic acid. Subsequent investigation showed that five more patients in four other hospitals had symptoms of bacteremia shortly after the infusion of different lots of albumin from the same manufacturer, and in four cases *P. cepacia* was cultured from the suspect albumin. Since sterility testing by manufacturers may not detect low-frequency contamination, surveillance of nosocomial infections, investigation of unusual disease clusters, and prompt reporting of suspect reactions are essential in the control of such outbreaks.

Normal serum albumin (human) is an excellent growth medium for certain microorganisms [1], but contamination of this product seems to be a rare cause of nosocomial infections. In two previous reports of bacteremia resulting from contaminated albumin, contamination occurred in the hospital [2, 3]. We report an outbreak of bacteremia due to *Pseudomonas* species that was caused by 25% normal serum albumin (human) contaminated apparently during manufacture.

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Materials and Methods

Epidemiologic methods. In May and June 1973, 11 blood culture isolates of *Pseudomonas* species, most with the same unusual antibiogram, were recovered at the University of Maryland Hospital. During this period, the hospital laboratory had been testing two methods for blood culture, the Bactec (Johnston Laboratories, Inc., Cockeysville, Md.) method and the B-D vacutainer (Becton-Dickinson Co., Rutherford, N.J.) method,[1] and had asked that blood culture specimens be drawn with use of both methods. Isolates of *Pseudomonas* were identified as either *Pseudomonas aeruginosa* or *Pseudomonas* spe-

[1] Names of products and manufacturers are provided for the purpose of identification only, and inclusion does not imply endorsement by the Public Health Service of the U.S. Department of Health, Education, and Welfare.

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cies, and antibiotic sensitivities of the isolates to ampicillin, carbenicillin, cephalothin, chloramphenicol, colistin, gentamicin, kanamycin, and tetracycline were determined by the method of Bauer et al. [4].

The cluster of isolates of *Pseudomonas* species prompted an epidemiologic investigation. Bacteriology records were reviewed for identification of all blood culture isolates of *Pseudomonas* that were recovered from July 1972 through June 1973 and of all sputum and urine culture isolates of *Pseudomonas* that were recovered from May through June 1973. The medical records of all patients with blood culture isolates of *Pseudomonas* species in May and June 1973 (case patients) were then reviewed, and common factors and exposures were noted. These patients were compared with patients in two control groups: one consisting of patients with blood culture isolates of *P. aeruginosa* recovered in May and June and the other consisting of a random group of patients who, in May and June, were located in surgical special care units where the majority of case patients were located. The investigation suggested that the bacteremias were caused by contaminated normal serum albumin.

Culture methods. Each unit of normal serum albumin is packaged in a box containing a 50-ml vial of albumin with a rubber stopper closure, administration tubing, an infusion needle, and an airway needle. The individual components were cultured under laminar air-flow hoods by personnel who wore gowns, masks, and gloves. Open petri dishes containing trypticase soy agar with 5% sheep blood (TSAB) were exposed in the hoods to monitor the sterility of the air environment.

After the protective metal overseal of the vial was disinfected with 70% alcohol, it was removed with sterile forceps and placed in a tube containing brain-heart infusion broth enriched with 0.5% beef extract (EBHIB). The top of the rubber stopper was sampled with a sterile cotton-tipped swab moistened with EBHIB, and the swab was placed in a tube containing EBHIB. The stopper was then removed with sterile forceps and placed in a jar containing EBHIB, and the albumin was poured into a jar containing 150 ml of EBHIB. After the infusion needle was removed aseptically from the tubing and the needle end was placed firmly into the lumen of the tubing, the infusion line was filled with 30 ml of EBHIB with use of a sterile syringe. The tubing was then clamped, the protective guard around the needle was replaced, and the line was hung in an incubator at 35 C. After the protective sleeves of the airway needle were removed, both the sleeves and the needle were placed in a jar containing 150 ml of EBHIB.

All cultures were incubated at 35 C for 14 days. If turbidity developed, the cultures were streaked on TSAB and MacConkey's agar and incubated at 35 C for an additional 18–48 hr. Colonies were then inoculated on triple sugar iron slants, appropriate biochemical tests were performed for identification of species, and antibiotic sensitivities were determined by the method of Bauer et al. [4].

Results

From July 1972 through April 1973, the University of Maryland Hospital had no more than three patients per month with blood culture isolates of *Pseudomonas* (figure 1). All isolates were identified as *P. aeruginosa* except for one that was identified as *Pseudomonas* species. Although the number of blood culture isolates of *P. aeruginosa* increased in May and June 1973, the number of blood culture isolates of *Pseudomonas* species increased markedly and became as common as isolates of *P. aeruginosa*. Of the 11 isolates of *Pseudomonas* species recovered in May and June, seven were sensitive only to chloramphenicol and tetracycline; one was sensitive to carbenicillin, colistin, gentamicin, chloramphenicol, and tetracycline; and three had unknown antibiograms because the organisms died during sensitivity testing. In seven patients from whom isolates of *Pseudomonas* species were recovered, blood was drawn with use of both the Bactec and the B-D vacutainer methods: organisms were isolated from all seven patients with use of the Bactec method but only from two patients with use of the B-D vacutainer method ($P = 0.01$). During the same two months, only 10 (4%) of 261 isolates of *Pseudomonas* obtained from urine and sputum cultures were identified as *Pseudomonas* species. Only one of the isolates from sputum had the same antibiogram as most of the isolates from

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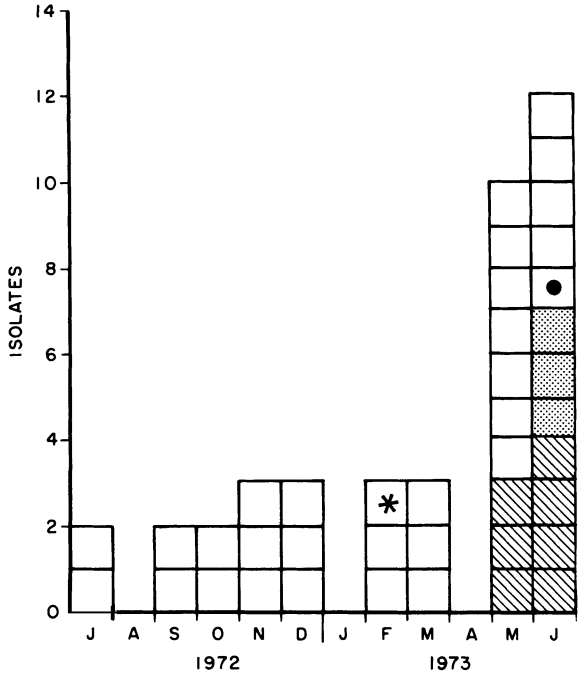

Figure 1. Isolates of *Pseudomonas* recovered from blood cultures performed at the University of Maryland Hospital from July 1972 through June 1973. Only the first isolate from any one patient is recorded according to month recovered. (□) = *Pseudomonas aeruginosa*; (▣) = *Pseudomonas* species, no antibiogram performed; (▨) = *Pseudomonas* species sensitive only to chloramphenicol and tetracyline; (▩) = *Pseudomonas* species with growth characteristics that did not permit sensitivity determination; and (▣) = *Pseudomonas* species sensitive to carbenicillin, colistin, gentamicin, chloramphenicol, and tetracycline.

Table 1. Comparison of characteristics of case patients and control patients.

Characteristic	*Pseudomonas* species group (cases)	Controls: *Pseudomonas aeruginosa* group	Controls: Surgical special care group
Total patients	11	7	20
Age (median years)	49	64	34
Sex			
Male	7	3	12
Female	4	4	8
Length of hospitalization (median days)	18	37	4
Location in hospital			
Shock-trauma unit	5	1	12
Surgical intensive care unit	3	1	8
Surgical floors	3	2	0
Other	0	3	0
Invasive procedure before bacteremia			
Operation	10	2	18
Intravenous therapy	11	7	20
Urinary catheter	8	4	17
Respiratory therapy	9	2	14
Blood product given (interval in hr)*			
Whole blood	6 (>24)	3 (>24)	15
Packed cells	7 (12)	4 (>24)	15
Fresh frozen plasma	6 (9)	4 (>24)	13
Normal serum albumin†	10 (2)	2 (>24)	9

NOTE. The charts on four of the 11 patients in the *P. aeruginosa* group were never located. Numbers given are numbers of patients unless noted otherwise.

*Intervals are given as medians and represent the time between the most recent administration of the solution and the onset of bacteremia.

†The *Pseudomonas* species group was compared with the other groups: $P = 0.013$ for the *P. aeruginosa* group, and $P = 0.014$ for the surgical special care group.

blood (sensitive only to chloramphenicol and tetracycline).

In the 11 case patients with *Pseudomonas* species isolated from blood cultures in May and June, the onset of bacteremia occurred at least 24 hr after admission, and no other sites of infection with *Pseudomonas* species were revealed to explain the portal of entry of the organisms. At the time blood was obtained for culture, all 11 patients had temperatures of ≥101 F, and seven had symptoms suggesting endotoxic shock (blood pressures that dropped below 90/60). Six patients received antibiotics, but none were given chloramphenicol or tetracycline, to which the organisms were sensitive. Two patients died, but the deaths may have been caused by their underlying diseases. In the others, temperatures and blood pressures returned to normal within 24 hr.

All 11 case patients were cared for on the surgical service (most were located in either the shock-trauma unit or the surgical intensive care unit), and all were given iv therapy (table 1). Since the shock-trauma unit had its own surgeons, anesthesiologists, nurses, and operating rooms, and since interns were responsible for the insertion and care of iv catheters in their patients, it seemed unlikely that a single person could have been involved in the care of all case patients or

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that a single technique or bottle of antiseptic solution could have been used for catheter insertion and care of these patients. Although records of the type of catheter inserted were not usually kept, it was known that only four patients had central venous pressure catheters, and only three had arterial lines connected to pressure transducers. Although the patients had not been given a single crystalloid iv solution or additive within 12 hr before the onset of bacteremia, 10 of the 11 patients received normal serum albumin at a median time of 2 hr (range, 0.25–6 hr) before onset of bacteremia. The organisms from the patient who did not receive albumin had an antibiogram different from that of the others (sensitive to carbenicillin, colistin, gentamicin, chloramphenicol, and tetracycline). Furthermore, the medical record of one of the patients showed that his physicians had considered albumin contamination as a possible cause of bacteremia when the patient developed endotoxic shock 15 min after albumin infusion began. Therefore, the physicians removed the infusion apparatus, noted the lot number on the vial (lot no. 75A), and cultured the patient's blood with use of the Bactec method and the remaining albumin with use of the B-D vacutainer method. The blood culture yielded *Pseudomonas* species but the albumin culture was negative.

Since the hospital did not keep records of the lot number on the vial of albumin administered to each patient, the other patients who received albumin from this lot could not be traced, and a control group of patients who received albumin from other lots could not be identified. However, case patients were compared with a control group of patients who had *P. aeruginosa* isolated from blood cultures in May and June and with a random control group of 20 of 93 patients located in surgical special care units during the same period (table 1). Ten (91%) of 11 case patients received albumin compared with only two (29%) of seven patients in the *P. aeruginosa* group ($P = 0.013$) and only nine (45%) of 20 in the surgical unit group ($P = 0.014$). The groups did not differ significantly in the receipt of any other blood products.

On February 18, 1973, the hospital began receiving normal serum albumin from Lederle Laboratories Division, American Cyanamid Company, Pearl River, N.Y. From that time until the investigation, the hospital received 7,482 vials from eight different lots, 750 of which were from lot no. 75A. During the investigation, a prevalence survey of normal serum albumin in the Central Supply Department and on the wards showed that 70 vials of this lot remained; none were visibly turbid.

Fifty-four of these vials and their components were cultured. *Pseudomonas cepacia* sensitive only to chloramphenicol, tetracycline, and nalidixic acid (the isolates recovered from patients had not been tested against nalidixic acid) was recovered from one of the 54 vials (from the fluid and rubber stopper but not the swab specimen taken from the top of the stopper). Fungi were recovered from one of the other rubber stoppers, and *Staphylococcus epidermidis, Bacillus* species, and fungi were recovered from 21 (39%) of 54 of the airway needles. No organisms were isolated from the infusion needles or from the administration tubing.

Because of the epidemiologic and laboratory evidence of contamination, the manufacturer recalled lot no. 75A on August 12, 1973 from the 20 other hospitals to which it had been distributed. In addition, personnel in these hospitals were telephoned to gain information on their experiences with albumin from this lot. None were aware of any reactions caused by albumin, none kept records that would allow the tracing of those patients who had been given albumin from the implicated lot, and none of the hospitals' laboratories had recovered *P. cepacia* from blood cultures performed during the preceding year.

Investigators then reviewed the manufacturer's records of complaints about the product and the records of all blood culture isolates sent to the Center for Disease Control (CDC; Atlanta, Ga.) from January 1972 to August 1973 and subsequently identified as *P. cepacia*. From these reviews, five patients who had developed endotoxic shock during the infusion of the same manufacturer's normal serum albumin were identified in four other hospitals. In four of the five cases, *P. cepacia* was recovered from the albumin but not from the blood cultures. In the fifth case, *P. cepacia* was recovered only from the blood culture. The contaminated vials were from four other lots (lots no. 56A, 67A, 70A, and 93A) and had

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been administered from October 1972 to August 1973. Because vials in any of the 36 lots between no. 56A and no. 93A could conceivably have been contaminated, the manufacturer recalled all of its normal serum albumin.

Discussion

Infection control personnel discovered the contamination of normal serum albumin described here because of a marked increase, during a two-month period, in blood culture isolates of *Pseudomonas* species that had the same unusual antibiogram (sensitive only to chloramphenicol and tetracycline). Since *P. cepacia* with the same antibiogram was recovered from the implicated albumin, we assume that the blood culture isolates from these patients were also *P. cepacia*. In the past, this organism has caused nosocomial outbreaks of urinary or respiratory tract infections, surgical wound infections, bacteremias, and pseudobacteremias (contaminated blood cultures) [5–19]. In most instances, these outbreaks were attributed to contaminated aqueous disinfectants (usually chlorhexidine or benzalkonium chloride) used for antisepsis of the skin or for disinfection of invasive devices [7–14], decontamination of topical anesthetics used before insertion of endotracheal tubes [15], or decontamination of sterile water used for irrigation of solutions and humidifiers or for the cooling of iv solutions prepared in the hospital pharmacy [16–19]. In the outbreak reported here, the affected patients showed no evidence of such exposures.

Instead, epidemiologic evidence suggested that a contaminated iv blood product, normal serum albumin, was responsible for the outbreak. However, at the time of bacteremia, physicians at the University of Maryland Hospital considered this possibility in only one patient who developed endotoxic shock 15 min after albumin infusion began. Bacterial contamination of albumin, however, may be difficult to recognize because a high concentration of organisms is required to cause turbidity [3, 20] and because albumin is often administered to postsurgical or seriously ill patients who commonly develop fever or even endotoxic shock because of their underlying conditions. Thus, personnel may not associate these symptoms with albumin infusion. Furthermore, even if one suspects contamination of the iv fluid, contamination may be intrinsic or extrinsic (occurring in the hospital), and the latter is more likely. A short period between the start of an infusion and the onset of symptoms, as observed in the patient mentioned above, is somewhat suggestive of intrinsic contamination, but proof requires documentation of iv-associated bacteremia in patients in more than one hospital and isolation of the same organism from the patients and from unused iv fluid. In this outbreak, patients in five hospitals had albumin-associated bacteremia, and *P. cepacia* was recovered from the suspect albumin in four of these hospitals. It was therefore assumed that contamination had occurred sporadically during the filling of individual vials at the manufacturing plant since albumin is sterilized by membrane filtration before the final filling of vials rather than by autoclaving after filling, as is done with crystalloid iv solutions. However, *P. cepacia* was not recovered from cultures taken at the manufacturing plant (performed by Dr. Paul D. Parkman, Bureau of Biologics, Food and Drug Administration, Bethesda, Md.).

Three findings that initially argued against albumin contamination require an explanation. First, the only time that the suspect albumin was cultured at the University of Maryland Hospital, no organisms were recovered. This result was probably due to the culture method used, since only 2 ml of fluid was inoculated into a B-D vacutainer. Second, one patient who had bacteremia due to *Pseudomonas* species in May and June did not receive albumin. However, the isolate recovered from her blood had an antibiogram different from that of the other isolates. Furthermore, she was later found to have subacute bacterial endocarditis, and her subsequent blood culture isolates, which had the same antibiogram as the previous isolate, were identified at the CDC as *P. aeruginosa* and *Pseudomonas fluorescens*. Finally, one patient with a tracheostomy who did not receive albumin had a sputum specimen from which *Pseudomonas* species sensitive only to chloramphenicol and tetracycline were cultured. We do not know how this patient acquired the organisms. However, he was located in the shock-trauma unit at the same time as were two patients from whom blood culture isolates of

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Pseudomonas species were recovered, and it is possible that personnel transmitted the organisms on their hands from contaminated albumin to this patient's tracheostomy.

Although this outbreak was recognized at the University of Maryland Hospital because *P. cepacia* is an unusual pathogen in nosocomial infections, we suspect that recognition in many hospitals was hindered because of the difficulty in isolation or identification of this organism. In January 1973, the Bureau of Laboratories of the CDC included *P. cepacia* as an "unknown" in its proficiency testing program. Of 432 laboratories, only 42% identified the genus and the species correctly, 43% identified the genus only, and 15% could not identify either the genus or the species [21]. Apparently, the problems that are usually associated with isolation of *P. cepacia* are its tendency to die on artificial solid media and its marked aerobic growth requirements. As shown at the University of Maryland Hospital, where two methods of blood culture were being tested at the time of the outbreak, *Pseudomonas* species was recovered significantly more often by the method allowing more aeration, the Bactec method, than by the B-D vacutainer method [22]. Indeed, if contamination had occurred six months eariler, before the Bactec method was used at that hospital, the outbreak might not have been recognized there either.

Two other epidemics caused by contaminated, commercially prepared iv products have been reported in the United States since 1971 [23–25]. In those episodes and in the one reported here, only a few vials in a given lot were contaminated (low-frequency contamination), but multiple lots were affected. The manufacturers' sterility testing may not detect such low-frequency contamination since Federal regulations require them to culture only 20 of the 1,500–2,000 vials in each lot [26]. At a contamination rate of 1% in one lot (approximately 10 of 680 vials from lot no. 75A administered at the University of Maryland Hospital probably caused reactions), 300 vials rather than 20 would have to be cultured to be 95% certain of detecting one contaminated vial. Although routine sterility testing of this magnitude is not feasible, statistically determined, sequential sampling of a small number of vials may prove better than the present method of sampling [27].

Currently, recognition of bacterial contamination of normal serum albumin depends greatly on hospital surveillance and the reporting of reactions. If physicians suspect albumin contamination, we encourage the reporting of this information to public health authorities, but we discourage the sampling of unused vials by individual hospital laboratories since so many vials must usually be cultured to identify one contaminated vial. The Hospital Infections Branch at the CDC is available for consultation in evaluation of such problems.

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