



## Chronology of Public Health Concerns With Propofol Administration<sup>1/</sup>

- DIPRIVAN® (propofol) Injectable Emulsion is a sterile intravenous sedative/hypnotic agent that is used to induce and maintain general anesthesia; supplement regional anesthetic techniques; sedate ventilated patients receiving intensive care; and induce conscious sedation for surgical and diagnostic procedures in and outside of operating theaters.<sup>2/</sup>
- The product is formulated in a carrier consisting in large part of a soybean oil-in-water emulsion that contains 1% propofol. Propofol injectable emulsion is a nonpyrogenic anesthetic that is administered by single or repeated intravenous bolus injections or by continuous infusions.
- The original formulation of DIPRIVAN, which did not contain the antimicrobial additive disodium edetate, was initially approved for marketing on October 2, 1989 through an NDA (No. 19-627) for use as an anesthetic in outpatient and inpatient procedures based upon adequate and well-controlled studies demonstrating its safety and efficacy.
- DIPRIVAN is terminally sterilized in vials, ampules, and prefilled syringes prior to labeling, packaging, and distribution, and, when used under the conditions prescribed in the labeling, including adherence to appropriate aseptic handling techniques, it is safe and effective. Because the DIPRIVAN propofol formulation is a fat-based (soybean oil-based) product, however, it is susceptible to extrinsic microbial contamination if used improperly.
- Accordingly, the original formulation of DIPRIVAN was marketed in the United States as a single-use parenteral product and users were advised to observe strict aseptic techniques and to discard unused portions of the product within the required time limits.
- Following the launch of the original formulation of DIPRIVAN, however, ICI Pharmaceuticals (which later became Zeneca Pharmaceuticals) and the FDA began to receive reports of infections associated with the failure of health care providers in the United States to use appropriate aseptic techniques when handling DIPRIVAN. The reports included descriptions of serious infections in multiple patients, raising the concern of Zeneca, the FDA and the Centers for Disease Control and Prevention (“the

---

<sup>1/</sup> Excerpted in part from Citizen Petition concerning a request to withdraw approval of certain portions of NDA 19-627 that provide for the formulation of DIPRIVAN® (propofol) Injectable Emulsion which does not contain disodium edetate, submitted on behalf of Zeneca Inc. to Food and Drug Administration (April 7, 1998).

<sup>2/</sup> See DIPRIVAN labeling.

CDC"). These public health authorities also raised concerns about the potential for multi-dosing and the potential effect it could have on microbial growth.

- Between June 1990 and February 1993, the CDC conducted investigations at seven hospitals with unusual outbreaks of bloodstream infections, surgical site infections and acute febrile episodes after surgical procedures using DIPRIVAN. The study focused on the description of four clusters of post operative infections in four states and concluded, in each case, that contamination occurring from propofol administration was caused by extrinsic contamination arising from mishandling of the product.<sup>3/</sup> Specifically, the investigations conducted by the CDC indicated that misuse of the product included the failure of physicians to change lines appropriately, the retention beyond recommended time periods of syringes containing DIPRIVAN, and failure to observe other aseptic techniques. In addition, the CDC concluded that DIPRIVAN had not been contaminated at the time of manufacture and that the adverse experiences were the result of improper handling of the drug.
- In response to adverse event reports, Zeneca, with guidance from the FDA and the CDC, issued revised labeling,<sup>4/</sup> and successive "Dear Doctor" letters,<sup>5/</sup> and launched an extensive, continuous educational campaign to warn health care professionals of the risks associated with failure to maintain aseptic handling techniques.
- As a result of concerted educational efforts by Zeneca, which were encouraged by the CDC and the FDA, there was a reduction in the number of clusters of fever and infection that had been seen in association with the mishandling of DIPRIVAN in the

---

<sup>3/</sup> See CDC, Postsurgical Infections Associated with an Extrinsically Contaminated Intravenous Anesthetic Agent -- California, Illinois, Maine, and Michigan, 39 Morbidity & Mortality Weekly Report 1990, 426 (describing initial CDC investigation); Shri N. Bennett, M.D., et al., Postoperative Infections Traced to Contamination of an Intravenous Anesthetic, Propofol, 333 New England J. Med. 147 (1995) (describing CDC investigation).

<sup>4/</sup> Zeneca incorporated several changes to the labeling of the original formulation of DIPRIVAN to address the concerns associated with the mishandling of the drug which were communicated by press releases as well as direct mailings to health care personnel. The Company also issued revised package inserts to accompany the "Dear Doctor" letters, which included more specific directions regarding proper handling techniques and renewed reminders regarding the maintenance of aseptic techniques in the package insert.

<sup>5/</sup> See Letter from Nancy E. Nazari, M.D., Medical Communications, Stuart Pharmaceuticals, to Medical Colleagues (July 6, 1990); Letter from Nancy E. Nazari, M.D., Professional Communications, Stuart Pharmaceuticals, to Medical Colleagues (Feb. 5, 1991) (warning health care personnel of postoperative infections caused by failure to observe proper aseptic techniques and subsequent contamination of the original formulation of DIPRIVAN).

U.S. However, this mishandling was not completely eradicated, and clusters of serious adverse events continued to be reported.<sup>6/</sup>

- In meetings with the FDA, Zeneca presented information regarding its extensive safety efforts, including labeling changes and educational activities; although the FDA agreed that Zeneca had made substantial efforts and had achieved some success, the Agency remained concerned that the misuse by practitioners would continue and encouraged Zeneca to conduct research to determine whether an excipient could be added to the drug's formulation to address these risks.
- Zeneca therefore conducted a number of clinical studies that ultimately showed that the antimicrobial, EDTA, could be added to propofol without affecting its safety and efficacy. Based on these studies, FDA approved an sNDA for a new formulation of DIPRIVAN with EDTA on June 11, 1996.

---

<sup>6/</sup> See Shri N. Bennett, M.D., et al., Postoperative Infections Traced to Contamination of an Intravenous Anesthetic, Propofol, 333 New England J. Med. 147 (1995).

# **Postsurgical Infections Associated with an Extrinsicly Contaminated Intravenous Anesthetic Agent -- California, Illinois, Maine, and Michigan, 1990**

In May and June 1990, the Hospital Infections Program in CDC's Center for Infectious Diseases received reports of four clusters of postsurgical infections and/or hyperthermic reactions occurring in patients after a variety of clean or clean-contaminated surgical procedures. These infections/reactions have been reported from four states and have been associated with three different pathogens. This report summarizes the preliminary results of investigations conducted at four hospitals.

**California.** During an 8-day period, five patients at one hospital developed *Staphylococcus aureus* surgical wound infections (SWI) following clean surgical procedures. All patients developed fever and surgical wound infection within 12-72 hours of surgery. All *S. aureus* isolates had the same phage type. An epidemiologic investigation identified use of an intravenous anesthetic, propofol (DiprivanPr\*), delivered by an infusion pump and attendance by one anesthesiologist as risk factors. A throat culture of the implicated anesthesiologist grew *S. aureus*; the isolate had the same phage type as that recovered from the patients' wounds.

**Illinois.** During a 5-day period, four patients who underwent different surgical procedures at one hospital developed *Candida albicans* bloodstream infections and/or endophthalmitis. An epidemiologic investigation identified receipt of propofol by infusion pump and preparation of the infusion by one anesthesiologist as risk factors for infection. A review of anesthesia practices revealed numerous breaks in aseptic technique during preparation of the anesthetic. Cultures of unopened ampules of propofol from the same lots being used at the hospital were negative. Further studies to identify the source of *C. albicans* are ongoing.

**Maine.** During a 2-day period, two patients who each underwent different surgical procedures at one hospital developed fever (temperature greater than or equal to 40.4 C (greater than or equal to 104.8 F)) and hypertension (systolic blood pressure (BP) greater than or equal to 226 mm Hg, diastolic BP greater than or equal to 108 mm Hg) within 2 hours following surgery. Both patients recovered after aggressive supportive therapy. An epidemiologic investigation

identified receipt of propofol by infusion pump and preparation of the infusion pump by one nurse anesthetist as risk factors for the reactions. The same infusion pump, syringe, and propofol preparation were used in the two patients; cultures of the propofol solution infusing at the time of the second patient's reactions grew *Moraxella osloensis*, and endotoxin assays using the *Limulus* amoebocyte lysate assay method detected 3900-5000 ng/mL of endotoxin. Cultures and endotoxin assays of unopened ampules of propofol from the same lot being used at the hospital were negative.

Michigan. During a 2-week period, 13 (23%) of 56 patients at one hospital in which clean or clean-contaminated procedures were performed developed postoperative *S. aureus* bacteremia and/or SWI; all patient isolates had the same phage type. Epidemiologic studies identified receipt of propofol by infusion pump and preparation of the infusion pump by one nurse anesthetist as risk factors for infection. The risk of infection was not increased when propofol was given as a single bolus injection without the infusion pump. Cultures of unopened ampules of propofol from the same lot being used at the hospital were negative. Cultures of the hands of the implicated nurse anesthetist grew *S. aureus*; phage typing is pending. A review of anesthesia procedures revealed that when propofol remained in the infusion pump at the completion of one surgery it was used during the next surgical procedure. Reported by: S Carr, S Waterman, MD, Los Angeles County Dept of Health Svcs; G Rutherford, MD, California Dept of Health Svcs. R Martin, DVM, B Francis, MD, State Epidemiologist, Illinois Dept of Public Health. K Gensheimer, MD, State Epidemiologist, Maine Dept of Human Svcs. J Altamirano, MD, W Hall, MD, B Robinson, PhD, S Shah, MS, R Wilcox, MD, State Epidemiologist, Michigan Dept of Public Health. Center for Drug Evaluation and Research, Food and Drug Administration. Div of Field Svcs, Epidemiology Program Office; Hospital Infections Program and Div of Mycotic Diseases, Center for Infectious Diseases, CDC.

### **Editorial Note**

Editorial Note: The simultaneous and sudden onset of clusters of postoperative infections following clean or clean-contaminated surgical procedures in multiple states is unusual. All cases at all four hospitals were associated with the use of propofol, a newly introduced intravenous hypnotic anesthetic agent that received Food and Drug Administration (FDA) approval in October 1989. Propofol is a sterile, nonpyrogenic, white, soybean oil-in-water emulsion to be used by intravenous delivery for induction (by bolus administration) and/or maintenance (by drip infusion) anesthesia. The product has no preservative and refrigeration is not recommended by the manufacturer.

For at least four reasons, the preliminary results of these investigations suggest that contamination of propofol was extrinsic (i.e., contaminated during manipulation after receipt from the manufacturer) and not intrinsic (i.e., contaminated at the time of manufacture). First, at each of the hospitals investigated, different lots of propofol were used, and cultures of previously unopened ampules from each hospital were sterile. Second, at each hospital, cases were associated only with propofol that was administered by infusion, using a 60 cc syringe in a pump, and prepared by a specific anesthetist/anesthesiologist. Third, aseptic technique was not observed during preparation of the propofol for use during infusion; syringes used for bolus administration of propofol were used only on single patients, whereas those used in the infusion pump were usually used on multiple patients. Fourth, since infusions are delivered

over a longer period of time, extrinsically contaminating microorganisms could proliferate during the infusion interval and between use in different patients. Growth studies performed at CDC show that when propofol is inoculated with low numbers (101-102 cfu/mL) of *S. aureus*, the organisms rapidly proliferate to high numbers (105-106 cfu/mL) within 24 hours at 33 C (91.4 F).

Two recent surveys of anesthesia personnel show that aseptic technique and infection control practices are frequently not implemented during administration of anesthesia (1,2). In these surveys, from 48% to 90% of respondents reused syringes to administer drugs to multiple patients. The investigation of the current clusters suggests that severe, life-threatening complications may occur in patients as a consequence of breaks in health-care workers' aseptic technique in combination with the use of a drug that is capable of supporting the rapid growth of microorganisms. These outbreaks underscore the importance of aseptic technique and infection control in anesthesia practice. The manufacturer of propofol, in conjunction with the FDA, is revising the label and package inserts and notifying all anesthesiologists and nurse anesthetists in the United States to emphasize the importance of using aseptic technique in the preparation and administration of propofol.

Physicians are requested to report clusters of infections in postoperative patients suspected to be associated with the use of propofol through state health departments to the Epidemiology Branch, Hospital Infections Program, Center for Infectious Diseases, CDC; telephone (404) 639-3406.

## References

1. Kemper PM, Learned DW. Anesthesia practice: a vector of infection? (Abstract). *Anesthesiology* 1989;71:A948.
2. Rosenberg AD, Bernstein RL, Ramanathan S, Albert DB, Marshall MH. Do anesthesiologists practice proper infection control precautions? (Abstract). *Anesthesiology* 1989;71:A949. \*Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

**Disclaimer** All *MMWR* HTML documents published before January 1993 electronic conversions from ASCII text into HTML. This conversion may have resulted in character translation or format errors in the HTML version. Users should not rely on this HTML document, but are referred to the original *MMWR* paper copy for the official text, figures, and tables. An original paper copy of this issue can be obtained from the Superintendent of Documents, U.S. Government Printing Office (GPO), Washington, DC 20402-9371; telephone: (202) 512-1800. Contact GPO for current prices.

\*\*Questions or messages regarding errors in formatting should be addressed to [mmwrq@cdc.gov](mailto:mmwrq@cdc.gov).

## POSTOPERATIVE INFECTIONS TRACED TO CONTAMINATION OF AN INTRAVENOUS ANESTHETIC, PROPOFOL

SHIRI N. BENNETT, M.D., MICHAEL M. McNEIL, M.B., B.S., M.P.H., LEE A. BLAND, M.A., M.P.H., MATTHEW J. ARDUINO, M.S., DR.P.H., M. ELSA VILLARINO, M.D., M.P.H., DENNIS M. PERROTTA, PH.D., DALE R. BURWEN, M.D., SHARON F. WELBEL, M.D., DAVID A. PEGUES, M.D., LEONARDO STROUD, M.D., M.P.H., PAUL S. ZEITZ, D.O., M.P.H., AND WILLIAM R. JARVIS, M.D.

**Abstract Background.** Between June 1990 and February 1993, the Centers for Disease Control and Prevention conducted investigations at seven hospitals because of unusual outbreaks of bloodstream infections, surgical-site infections, and acute febrile episodes after surgical procedures.

**Methods.** We conducted case-control or cohort studies, or both, to identify risk factors. A case patient was defined as any patient who had an organism-specific infection or acute febrile episode after a surgical procedure during the study period in that hospital. The investigations also included reviews of procedures, cultures, and microbiologic studies of infecting, contaminating, and colonizing strains.

**Results.** Sixty-two case patients were identified, 49 (79 percent) of whom underwent surgery during an epidemic period. Postoperative complications were more frequent during the epidemic period than before it. Only exposure to propofol, a lipid-based anesthetic agent, was

significantly associated with the postoperative complications at all seven hospitals. In six of the outbreaks, an etiologic agent (*Staphylococcus aureus*, *Candida albicans*, *Moraxella osloensis*, *Enterobacter agglomerans*, or *Serratia marcescens*) was identified, and the same strains were isolated from the case patients. Although cultures of unopened containers of propofol were negative, at two hospitals cultures of propofol from syringes currently in use were positive. At one hospital, the recovered organism was identical to the organism isolated from the case patients. Interviews with and observation of anesthesiology personnel documented a wide variety of lapses in aseptic techniques.

**Conclusions.** With the increasing use of lipid-based medications, which support rapid bacterial growth at room temperature, strict aseptic techniques are essential during the handling of these agents to prevent extrinsic contamination and dangerous infectious complications. (*N Engl J Med* 1995;333:147-54.)

OUTBREAKS of postoperative surgical-site infections or bloodstream infections are usually thought to be related to the surgeon or the surgical procedure. In May and June 1990, the Centers for Disease Control (CDC) were notified of the simultaneous and sudden onset of postoperative infections of the bloodstream, surgical sites, or other sites involving a variety of organisms at hospitals in four states. These outbreaks were investigated and traced to the use of a newly introduced anesthetic agent, propofol (Diprivan, Stuart Pharmaceuticals, Wilmington, Del.).<sup>1</sup> Propofol is a sterile, white, nonpyrogenic, oil-based anesthetic agent that is given intravenously; approved by the Food and Drug Administration (FDA) and marketed in the United States since November 1989, propofol is used in the induction (by bolus administration) and maintenance (by drip infusion) of anesthesia. In this paper, we describe seven independent investigations that traced the outbreaks to extrinsic contamination of propofol associated with lapses in aseptic techniques by anesthesia personnel.

### METHODS

#### Definition and Ascertainment of Cases

We reviewed microbiologic, surgical, infection-control, and medical records to identify case patients. In each investigation, a case patient was defined as any patient with an organism-specific infectious complication or acute febrile episode after a surgical procedure dur-

ing the hospital-specific study period (Table 1). Infections of the bloodstream, surgical sites, or other sites were defined according to CDC criteria.<sup>2,3</sup> An acute febrile episode was defined as the occurrence of fever (temperature,  $>39^{\circ}\text{C}$  [ $101.5^{\circ}\text{F}$ ]) with no apparent cause after a surgical procedure and during the study period. For each hospital the study period encompassed the interval before the epidemic period and the epidemic period itself.

#### Comparative Studies

To determine whether an outbreak was occurring, we compared the rates of hospital-specific cases of postoperative infections meeting our definition that occurred before the epidemic period with those occurring during the epidemic. At each hospital, a case-control or cohort study was performed; in some instances, both kinds of studies were performed. In the case-control studies, the case patients were compared with randomly selected patients in the same hospital who underwent surgery during the epidemic period (Table 1). In the cohort studies, the case patients were compared with all other patients in the same hospital who underwent surgery during the epidemic period. Follow-up case-control or cohort studies were conducted to define exposures and associations further.

All medical records for the case patients and the control patients were reviewed to determine the patients' characteristics and potential preoperative, perioperative, and postoperative risk factors.

#### Procedural Review

To evaluate the role of procedural factors, we reviewed operating-room and anesthesia practices by interviewing personnel, observing surgical and anesthesia procedures, administering written questionnaires, and reviewing infection-control policies.

#### Microbiologic Studies

All available isolates from the case patients, the environment, and hospital personnel were sent to the CDC and were identified according to standard methods. All *Staphylococcus aureus* isolates were phage-typed.<sup>4</sup> Strains of *Candida albicans* were compared by means of pulsed-field gel electrophoresis<sup>5</sup> and DNA fingerprinting followed by Southern blot transfer and hybridization with the CARE-2 probe.<sup>6</sup> All *Enterobacter agglomerans* isolates were examined by plasmid and restriction-endonuclease analysis.<sup>7</sup> All *Serratia marcescens* isolates were serotyped with Edwards and Ewing's O antigen tests and Le Minor's H-immu-

From the Hospital Infections Program, National Center for Infectious Diseases (S.N.B., L.A.B., M.J.A., M.E.V., D.R.B., S.F.W., D.A.P., L.S., W.R.J.), the Division of Bacterial and Mycotic Diseases (M.M.M.), and the Division of Field Epidemiology, Epidemiology Program Office (P.S.Z.), Centers for Disease Control and Prevention, Atlanta; and the Texas Department of Health, Austin (D.M.P.). Address reprint requests to Dr. Jarvis at the Hospital Infections Program, MS E-69, Centers for Disease Control and Prevention, 1600 Clifton Rd., NE, Atlanta, GA 30333.

Table 1. Characteristics of the Epidemics, Attack Rates, and Type of Study Conducted at Each Hospital.

HOSPITAL No.	ORGANISM	STUDY PERIOD		ATTACK RATE*		FIRST STUDY		SECOND STUDY	
		BEFORE EPIDEMIC	DURING EPIDEMIC	BEFORE EPIDEMIC	DURING EPIDEMIC	TYPE	COMPARISON GROUP	TYPE	COMPARISON GROUPS
1	<i>S. aureus</i>	10/1/89-4/16/90	4/17/90-6/20/90	0/2112	16/668	Case-control	Patients who had surgery on same day as the case patients but had no infection or reaction (2 per case patient)	Case-control	Case patients and controls from first study who had general anesthesia
2	<i>C. albicans</i>	1/1/90-4/15/90	4/16/90-4/30/90	0/2555	4/364	Cohort	All other patients who had surgery during the epidemic period	Cohort	Case patients and all other patients from first study who had surgery on the 2 days the case patients had surgery
3	<i>S. aureus</i>	1/1/90-5/14/90	5/15/90-5/31/90	0/574	13/56	Cohort	All other patients who had surgery during the epidemic period	Cohort	Case patients and all other patients from first study who had general anesthesia
4	<i>Moraxella osloensis</i> †	1/1/90-5/9/90	5/10/90-5/11/90	Not done	Not done	Cohort	All other patients who had surgery during the epidemic period	None	—
5	<i>E. agglomerans</i> ‡	9/3/89-8/16/90	8/17/90-8/27/90	0/239§	4/18§	Cohort	All other patients who had surgery during the epidemic period	None	—
6	<i>Serratia marcescens</i>	1/1/91-9/27/92	9/28/92-10/13/92	1/15,046	6/360	Case-control	Patients who had surgery during the epidemic period with no infection or reaction (3 per case patient)	Case-control	Case patients and controls from first study who had orthopedic surgery
7¶	None identified Facility A Facility B	1/1/92-12/12/92	12/13/92-12/19/92	11/16,000 1/3000	3/463 1/50	Case-control	Patients >18 yr old who had nonobstetrical surgery at either facility during the epidemic period with no infection or reaction (3 per case patient)	Cohort	Case patients and all other patients from first study who received anesthesia from Anesthesiologist A for nonobstetrical surgery

\*The rates are for all hospitals except hospital 5. The numerator is the number of case patients, and the denominator the number of patients undergoing surgery. The attack rates before and during epidemic periods were significantly different:  $P < 0.001$  (hospitals 1, 2, 3, 5, and 6);  $P = 0.006$  (hospital 7, facility A); and  $P = 0.03$  (hospital 7, facility B).

†This was isolated only from syringes containing propofol, not from cultures of specimens obtained from case patients. The isolation of *M. osloensis* was not part of the case definition.

‡Case patients whose blood cultures grew *E. agglomerans* were classified as definitely meeting the case definition. One patient with sepsis whose blood culture did not grow *E. agglomerans* was classified as a probable case patient. One patient in whom sepsis did not develop and who did not have blood drawn for culture but had a white-cell count exceeding 30,000 cells per cubic millimeter was classified as a possible case patient.

§The numerator is the number of *E. agglomerans* blood cultures, and the denominator the total number of blood cultures that grew any organism.

¶When the initial investigation at facility A implicated an anesthesiology group that also worked at facility B, facility B was included as part of this investigation. The two facilities were considered together for all analyses except for attack rate.

bilization tests.<sup>8,9</sup> Endotoxin assays were performed on selected serum and environmental samples with the turbidimetric limulus amoebocyte lysate assay (LAL-5,000, Associates of Cape Cod, Woods Hole, Mass.)<sup>10</sup> or gel clot assay.<sup>11</sup>

Material for culture was obtained from products and personnel thought to be involved in the epidemics as well as from selected products and personnel not implicated in the epidemics. Cultures of the hands of personnel were obtained with use of a previously described method.<sup>12</sup> In some instances, direct impressions of obvious hand lesions were made onto tryptic-soy-agar plates; other lesions were swabbed with premoistened cotton-tipped applicators that were then streaked on tryptic-soy-agar plates. Water, fluids, and medications were cultured on tryptic soy agar according to the membrane-filtration technique.<sup>13</sup>

### Statistical Analysis

All data were collected with the use of standardized forms and analyzed with Epi Info version 5.<sup>14</sup> Odds ratios, relative risks, and 95 percent confidence intervals were calculated. Fisher's exact test or the chi-square test was used to compare categorical variables, and Student's t-test or Wilcoxon's test was used to compare continuous variables.

## RESULTS

### Comparative Studies

Sixty-two patients met the case definitions, 49 of whom underwent surgery during the hospital-specific

epidemic periods. In all six hospitals in which it was evaluated, the attack rate was significantly greater during the epidemic period than in the period preceding it (Table 1). The epidemic periods lasted from 2 to 65 days (median, 11) (Fig. 1).

Next, the investigation focused on the 49 case patients who became ill during an epidemic period. These patients ranged in age from 22 to 90 years. Forty-one (84 percent) had infectious complications in which an etiologic agent was isolated, and 8 (16 percent) had acute febrile episodes. Thirty-two (65 percent) were women. Twenty-two of the 49 case patients had undergone orthopedic surgery (45 percent), 10 gynecologic surgery (20 percent), 9 general surgery (18 percent), 2 urologic surgery (4 percent), 1 ophthalmologic surgery (2 percent), 3 biopsy (6 percent), and 2 other surgical procedures (4 percent) (Table 2). Of the 41 case patients from whom an etiologic agent was isolated, 12 (29 percent) had only bloodstream infections, 18 (44 percent) only surgical-site infections, and 6 (15 percent) both surgical-site and bloodstream infections. One case patient had a surgical-site infection and an endocardial infection. Four case patients had other infections (urinary tract infection or endophthalmitis).

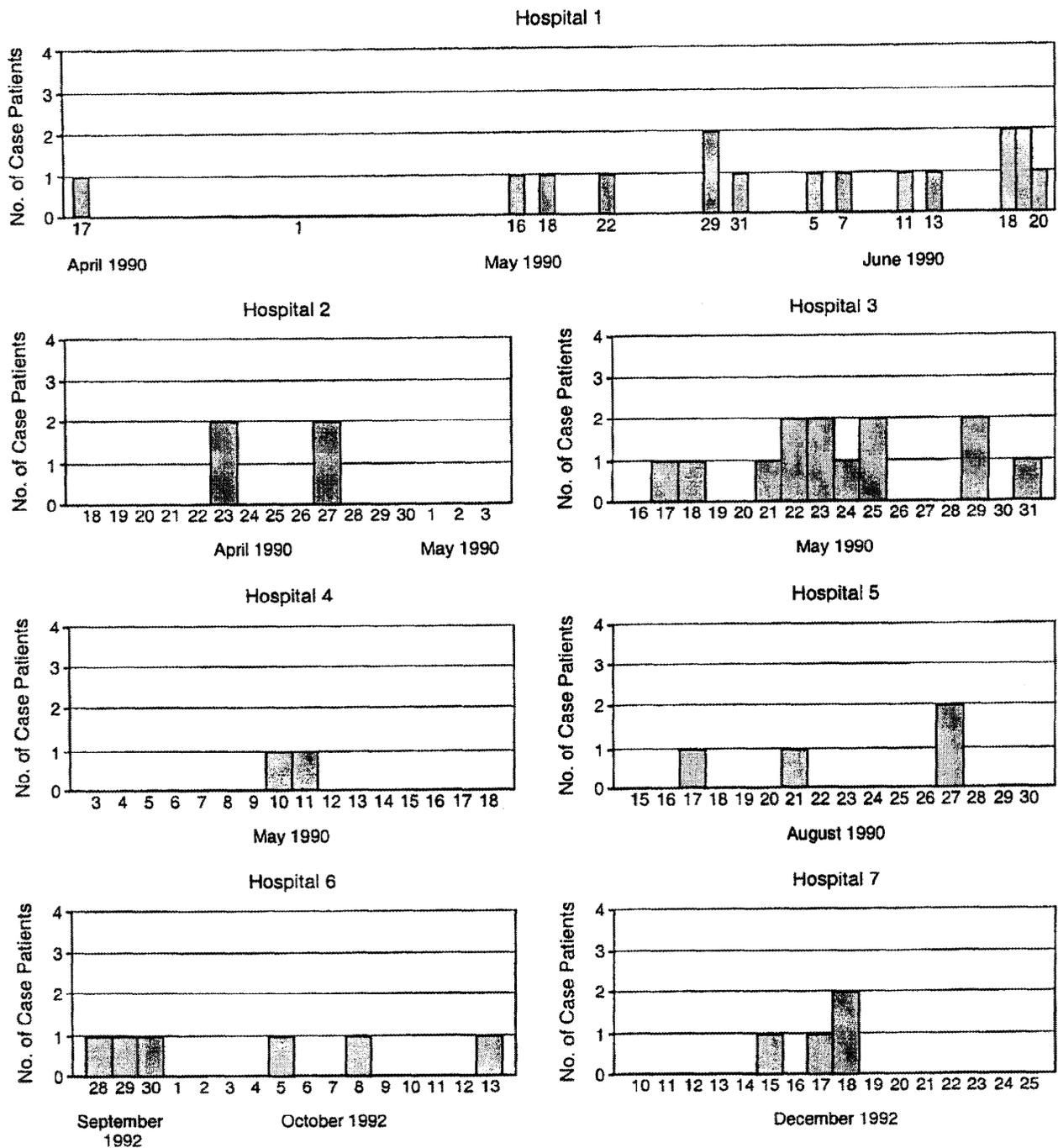


Figure 1. Distribution of Case Patients According to the Date of Surgery and Hospital.

The interval from the time of surgery to the first positive culture ranged from less than 1 day to 51 days. Eight case patients had their hospitalization prolonged because of their infections, 20 required rehospitalization, and 11 required surgical intervention. Eighteen had infectious complications distant from the surgical site.

Two case patients (4 percent) who became ill during the epidemic period died. At hospital 5, three of the

four case patients had signs of sepsis and required vasopressor support; disseminated intravascular coagulation, acute renal failure, and symptoms of the adult respiratory distress syndrome developed in all three. At hospital 7, all case patients had hypotension (systolic blood pressure,  $\leq 90$  mm Hg; mean systolic blood pressure, 82 mm Hg), required vasopressor support, had thrombocytopenia (platelet count,  $< 100,000$  per cubic millimeter; mean, 74,000 per cubic millimeter) within

Table 2. Characteristics of the 49 Case Patients Who Became Ill during an Epidemic Period.\*

HOSPITAL No.	No. OF CASE PATIENTS	TYPE OF INFECTION				TYPE OF SURGERY						TIME FROM SURGERY TO 1ST POSITIVE CULTURE (DAYS) OR ONSET OF SYMPTOMS (HR)	DEATHS
		BS	SS	BS AND SS	OTHER	ORTH	CYNE	GENL	UROL	OPHTH	OTHER		
1	16	5	8	2	1†	11	1	2	1	1	0	1-40 (4.5) days	2
2	4	0	0	1	3‡	1	1	1§	0	0	1¶	1-46 (11.5) days	0
3	13	3	6	3	1	4	4	2	0	0	3**	1-14 days	0
4	2	Not applicable††				0	0	2	0	0	0	≤2 hr	0
5	4	2‡‡	0	0	0	0	1	2	1	0	0	3-9 hr	0
6	6	2	4	0	0	6	0	0	0	0	0	2-51 (8.5) days	0
7	4	Not applicable§§				0	3	0	0	0	1¶¶	≤24 hr	0

\*BS denotes bloodstream, SS surgical site, orth orthopedic, cyne gynecologic, genl general, urol urologic, and ophth ophthalmologic. †Urinary tract infection.  
 ‡Ophthalmologic infection. §Vascular surgery. ¶Plastic surgery. ||Surgical-site and endocardial infections. \*\*Biopsy.  
 ††The two case patients had acute febrile episodes consisting of fever (temperature, >40.4°C [104.8°F]) and hypertension (systolic blood pressure, ≥226 mm Hg; diastolic blood pressure, ≥108 mm Hg) in the two hours after surgery.  
 ‡‡The etiologic agent was isolated from only two case patients.  
 §§The four case patients had acute febrile episodes (temperature, 39.0°C) with no apparent cause in the 24 hours after a surgical procedure at either facility A or facility B.  
 ¶¶Debridement of foot ulcer.

48 hours after surgery, and had elevated concentrations of fibrin-split products (mean, >10 µg per milliliter) within 24 hours after surgery.

At each hospital, there were no significant differences between case patients and controls or unaffected surgical patients in sex, age, inpatient or outpatient status, preoperative American Society of Anesthesiologists score, preoperative skin preparation, surgical-wound

class, receipt of prophylactic antimicrobial therapy, or duration of surgery.

Although a number of potential risk factors were identified, including the use of certain intravenous anesthetic agents or other intravenous agents, only the receipt of propofol was significantly associated with postoperative infectious complications at all hospitals (Table 3). At six hospitals, exposure to a single anes-

Table 3. Comparison of Potential Risk Factors among Case Patients and Controls or Other Surgical Patients without Postoperative Infections.\*

POTENTIAL RISK FACTOR	HOSPITAL 1†		HOSPITAL 2		HOSPITAL 3†		HOSPITAL 4		HOSPITAL 5		HOSPITAL 6		HOSPITAL 7	
	CASE PATIENTS VS. CONTROLS‡	OR	CASE PATIENTS VS. OTHER SURGICAL PATIENTS‡	RR	CASE PATIENTS VS. OTHER SURGICAL PATIENTS‡	RR	CASE PATIENTS VS. OTHER SURGICAL PATIENTS‡	RR	CASE PATIENTS VS. OTHER SURGICAL PATIENTS‡	RR	CASE PATIENTS VS. CONTROLS‡	OR	CASE PATIENTS VS. OTHER SURGICAL PATIENTS‡	RR
IV anesthetic agents														
Sufentanil	NS		NS		NS		NS		4/4 vs. 35/76	Undef	NS		—	
Midazolam (Versed)	NS		NS		NS		NS		—		NS		4/4 vs. 4/13	Undef
Alfentanil (Alfenta)	14/14 vs. 10/14	Undef	—		NS		NS		—		—		—	
Propofol	—		—		—		—		4/4 vs. 30/76	Undef	—		—	
Induction	14/14 vs. 9/14	Undef	NS		NS		—		—		5/6 vs. 2/10	20§	NS	
Maintenance	14/14 vs. 7/14	Undef	3/4 vs. 15/67	8.8	11/12 vs. 11/19	4.5	2/2 vs. 5/17	Undef	—		5/6 vs. 2/10	20§	3/4 vs. 2/13	16
Mean dose	NS		NS		NS		NS		—		NS		¶	
Personnel														
Anesthesiologist A	14/14 vs. 3/14	Undef	4/4 vs. 5/67	Undef	—		2/2 vs. 10/37	Undef	—		6/6 vs. 1/10	Undef	4/4 vs. 0/13	Undef
Nurse-anesthetist A	NS		—		11/12 vs. 10/19	5.2	—		4/4 vs. 15/76	Undef	—		NS	
Surgeon A	NS		NS		—		—		—		5/6 vs. 1/10	45**	NS	

\*Results are from the follow-up studies performed for all hospitals except hospitals 4 and 5. OR denotes odds ratio, RR relative risk, IV intravenous, NS not a significant difference (for the comparison between groups), and Undef undefined.

†For hospitals 1 and 3, the number of case patients shown is the number in the follow-up study.

‡The number of case patients with exposure to the potential risk factor divided by the total number of case patients as compared with the number of controls or other surgical patients with exposure to the potential risk factor divided by the total number of controls or other surgical patients.

§The first case patient identified during the epidemic period did not receive propofol but was noted before surgery to have two skin lesions present on the limb undergoing surgery. Four days after surgery a fever and thick serosanguineous drainage from the surgical site developed. Blood cultures were negative, but wound cultures grew *S. marcescens*.

¶The mean induction dose of propofol was 200 mg for the case patients and 120 mg for the other surgical patients (P=0.02).

||The potential risk factor was the preparation of a propofol infusion pump by Nurse-anesthetist A; the presence of Nurse-anesthetist A alone was not significantly associated with illness.

\*\*Anesthesiologist A induced anesthesia in all patients operated on by Surgeon A; therefore, it was not possible to assess them independently.

thesiologist or nurse-anesthetist was a risk factor. At the seventh facility, the preparation of a propofol-infusion pump by a specific nurse-anesthetist was found to be a risk factor.

#### Procedural Review

In general, the practices of anesthesia personnel who were implicated in the outbreaks did not differ from those of other personnel. However, they were found to have done at least one of the following: prepare multiple syringes of propofol at one time for use throughout the day; reuse syringes or infusion-pump lines, or both, on different patients; use syringes of propofol that had been prepared up to 24 hours beforehand; transfer prepared syringes of propofol between operating rooms or facilities; sometimes fail to wear gloves during the insertion of intravenous catheters; and sometimes fail to wear gloves during procedures that involved touching mucous membranes or preparing or administering propofol. At hospital 7, anesthesia personnel were also

found not to disinfect the rubber stoppers of 50-ml propofol vials before use.

#### Microbiologic Studies

At five of seven hospitals, an etiologic agent was isolated from the case patients (Table 4). In four of those five hospitals, all available isolates from the case patients were found to be identical by phage-typing (hospitals 1 and 3), plasmid analysis (hospital 5), or serotyping (hospital 6). At the remaining hospital (hospital 2), pulsed-field gel electrophoresis, DNA fingerprinting, and CARE-2 hybridization patterns of *C. albicans* isolates revealed two distinct karyotypic patterns, each of which was isolated from two case patients.

At hospital 1, the same strain of *S. aureus* was recovered from the case patients and from a lesion on the scalp of the anesthesiologist implicated in the outbreak. At hospital 3, the same strain of *S. aureus* was recovered from the case patients and the hands of the nurse-anesthetist implicated in the outbreak. At hospital 2,

Table 4. Results of Cultures of Samples from Hospital Personnel and Propofol and Results of Typing of the Isolates Obtained from Case Patients, Personnel, and Propofol.

HOSPITAL No.	ORGANISM CAUSING OUTBREAK	ISOLATES* FROM CASE PATIENTS	OPERATING ROOM AND ANESTHESIA PERSONNEL		PROPOFOL	
			CULTURES FROM HANDS	OTHER CULTURES	UNOPENED VIAL	OPENED VIAL
1	<i>S. aureus</i>	16/16 had identical antimicrobial-susceptibility patterns; 9/9 had the same phage type†	‡	Culture of scalp lesion from Anesthesiologist A had the same antimicrobial susceptibility pattern and phage type as isolates from the case patients	Negative	Not available for testing
2	<i>C. albicans</i>	2/4 had pattern A; 2/4 had pattern B§	4 candida species were isolated from 8/14 anesthesiologists¶: <i>C. parapsilosis</i> (5/14), <i>C. lipolytica</i> (3/14), <i>C. laurenti</i> (1/14), <i>C. albicans</i> (1/14)	Not done	Negative	Negative
3	<i>S. aureus</i>	10/10 had the same phage type**	<i>S. aureus</i> was isolated from 2/3 surgeons, 1/7 operating room nurses or staff members, 1/2 nurse-anesthetists; only <i>S. aureus</i> from Nurse-anesthetist A had the same phage type as isolates from case patients††	<i>S. aureus</i> was isolated from anterior nares of 3/6 surgeons, 1/7 operating room nurses or staff members, 0/2 nurse-anesthetists, 2/3 housekeeping staff; no isolate had the same phage type as isolates from case patients	Negative	Not available for testing
4	<i>M. osloensis</i>	No organism isolated	Not done	Not done	Negative	<i>M. osloensis</i> isolated; 3900–5000 ng/ml endotoxin‡‡
5	<i>E. agglomerans</i>	2/2 had identical plasmid banding patterns	<i>E. agglomerans</i> from Nurse-anesthetist D had a plasmid banding pattern that differed from those of case-patient and propofol isolates	Not done	Negative	<i>E. agglomerans</i> isolated; banding patterns identical to those of case-patient isolates§§
6	<i>S. marcescens</i>	6/6 had serotype O12:H15	Surgeon A and Anesthesiologist A had negative cultures	Rectal cultures from Surgeon A and Anesthesiologist A were negative	Not done	Not available for testing
7	None identified	No organism isolated; endotoxin levels within normal limits	Anesthesiologist A had negative cultures	Nasopharyngeal cultures from Anesthesiologist A were negative	Not done	Not available for testing

\*The numbers shown are the number of case-patient isolates with positive results divided by the total number of case-patient isolates tested.

†Only 9 of 16 isolates from case patients were available for typing; at that time, analysis by pulsed-field gel electrophoresis was not routinely performed on strains isolated during outbreaks.

‡Could not be assessed because of overgrowth caused by delays in mailing.

§One case patient with karyotype, DNA-fingerprint, and CARE-2 probe pattern A and one case patient with karyotype, DNA-fingerprint, and CARE-2 probe pattern B had surgery on day 1 of the outbreak; similarly, one case patient with karyotype, DNA-fingerprint and CARE-2 probe pattern A and one case patient with karyotype, DNA-fingerprint, and CARE-2 probe pattern B had surgery four days later, on day 2 of the outbreak.

¶Cultures from two anesthesiologists grew more than one candida species.

||The isolate was not available for later analysis by pulsed-field gel electrophoresis.

\*\*Only 10 of 13 isolates from case patients were available for typing.

††Nurse-anesthetist A was the only operating room or anesthesia staff member noted to have lesions on hands (active eczema).

‡‡Propofol left over in the infusion-pump syringe was tested.

§§Two syringes containing propofol were prepared by Nurse-anesthetist A the day before they were cultured. One syringe was used to administer propofol to a patient who was not a case patient; the other syringe was not used.

*C. albicans* was the infecting strain and a variety of candida species were isolated from the hands of a number of anesthesiology personnel. Candida species were not commonly recovered from the handwashings of anesthesia personnel at other hospitals. Only one anesthesiologist was colonized with *C. albicans*; this anesthesiologist was not implicated in the epidemic, and the isolate was not typed. At hospital 5, *E. agglomerans* was isolated from the hands of a nurse-anesthetist who was not implicated in the epidemic; this isolate had a plasmid banding pattern that was different from the pattern of the isolates from the case patients and the propofol samples.

Cultures of unopened ampules of propofol from lots in use at hospitals 1 through 5 were negative. Ampules of propofol in use at the time of the outbreaks were not available for analysis at most hospitals. At two hospitals, syringes of propofol in use at the time of the outbreaks were available for analysis. At hospital 4, cultures of propofol from the syringes were positive for endotoxin and grew *Moraxella osloensis*; only the case patients had received propofol from these syringes. At hospital 5, cultures of propofol from the syringes grew the same organism as that isolated from the case patients (*E. agglomerans*).

#### DISCUSSION

Between June 1990 and February 1993, we investigated seven outbreaks of perioperative or postoperative infectious complications in which epidemiologic and laboratory evidence documented extrinsically contaminated propofol as the cause. Extrinsic contamination, contamination that occurs during the handling of propofol after its manufacture, was suggested because different lots of propofol were used in each outbreak; cultures of unopened vials of propofol from the same lots as the implicated vials were negative; the presence of specific nurse-anesthetists and anesthesiologists and the receipt of propofol, particularly by infusion, were epidemiologically associated with postoperative infectious complications; and lapses in aseptic technique by anesthesia personnel were observed or reported.

Viruses and bacteria have been associated with extrinsic contamination of intravenous agents.<sup>15-17</sup> Extrinsically contaminated infusates have also been associated with pyrogenic reactions without bacteremia.<sup>18,19</sup> However, no other single intravenous agent has been associated with such widespread outbreaks of extrinsic contamination or has been contaminated by such a wide variety of organisms.

Several properties inherent to propofol contribute to its extrinsic contamination. The active ingredient, 2,6-diisopropylphenol, is formulated in an emulsion of soybean oil, glycerol, and egg lecithin. Lipid emulsions, lipid-based anesthetic agents, and propofol support rapid microbial growth at room temperatures,<sup>20-24</sup> whereas most intravenously administered anesthetic or sedative agents are not lipid-based and do not support rapid microbial growth.<sup>24-26</sup> Unlike most other intravenous

anesthetics, propofol contains no preservatives or antimicrobial agents to retard bacterial growth, and refrigeration is not recommended by the manufacturer.<sup>27</sup>

Before 1991, propofol was available only in 20-ml glass ampules, and anesthesia personnel drew up the contents of several ampules into a single syringe for use in an infusion pump. In 1991, propofol became available in 50-ml and 100-ml rubber-topped vials. Use of the larger vials was intended to decrease the risk of extrinsic contamination by obviating the need to use multiple ampules of propofol during the assembly of an infusion pump. However, the larger vials look like multidose vials, and our investigations revealed that the vials are sometimes being used for an extended period of time, for more than one patient or procedure, and to refill syringes meant to be used only once.

Our investigations revealed a number of anesthesia practices that could contribute to the extrinsic contamination of propofol. Despite the written recommendations of professional associations, such as the American Society of Anesthesiologists<sup>28</sup> and the American Association of Nurse Anesthetists,<sup>29</sup> which specifically advocate the use of aseptic techniques during the handling of medications, several authors have reported poor compliance with aseptic techniques and infection-control practices by anesthesia personnel.<sup>30-36</sup> Contamination of multidose vials,<sup>15,37,38</sup> use of a single syringe to administer medication to different patients,<sup>39</sup> assembling infusion equipment far in advance of use,<sup>40</sup> and contamination of syringes and catheters<sup>38</sup> have all been implicated in other outbreaks. Studies show that reuse of multidose vials can cause contamination of the medication in the vial<sup>15</sup> and that contamination can occur during the opening of a glass vial whose surface has not been disinfected.<sup>41</sup> Injecting medications into intravenous catheters can cause syringes to become contaminated even if the needle is changed,<sup>42-46</sup> so that using common syringes to administer medication to different patients can transmit infectious agents. In other outbreaks unrelated to the use of propofol, anesthesia personnel have been identified as the carriers or source of the outbreak.<sup>47-49</sup>

The contamination of intravenous agents as a result of the anesthesia practices noted above may not always result in the appearance of clinical disease because many intravenous agents do not support bacterial growth. With propofol, however, and potentially other lipid-based intravenous agents, contamination of the agent with even very small numbers of organisms may result in clinical disease. Therefore, the manufacturer's recommendations for the use of propofol must be carefully followed, including appropriate disinfection of the surface of the neck of the ampule or the rubber stopper in a vial before use, preparation of propofol just before use, use of aseptic handling procedures, and restriction of the use of an ampule or vial to a single patient.<sup>27</sup>

After the first report in 1990 of four CDC investigations demonstrating the risks of propofol use and the

necessity for strict aseptic techniques in the handling of this anesthetic,<sup>1</sup> the manufacturer sent letters to all registered anesthesiologists, nurse-anesthetists, and chief pharmacists in the United States informing them of these outbreaks and the risks of extrinsic contamination of propofol. The manufacturer also revised the product label and package insert to stress the importance of the use of aseptic techniques and to warn users that propofol can support rapid microbial growth.<sup>27</sup> It also broadly advertised the requirement for aseptic techniques in promotional and instructional materials. Despite these efforts, in June 1993 we were informed of another outbreak in which two deaths occurred. This outbreak was linked to the use of propofol from the recently introduced 50-ml rubber-topped vial. In March 1994, we were informed of two more propofol-associated outbreaks in different states.

We continue to receive reports of sporadic episodes of fever, infection, or sepsis thought to be associated with extrinsically contaminated propofol. Between July 1989 and May 1994, the FDA received reports of 38 clusters of fever or infection (or both) involving 155 patients in 20 states that were thought to be associated with propofol use (FDA: unpublished data). At least four patients who received propofol have died.

The magnitude of the problem has probably been underestimated. Most infections in surgical patients are thought to be related to the surgeon, surgical procedure, or postoperative care. The association of infection with the use of an agent such as propofol or a procedure such as anesthesia may not be appreciated. Propofol-associated outbreaks may remain unidentified unless an unusual organism is isolated from one or more patients; the infections occur in unusual settings, such as among patients undergoing clean, uncomplicated surgical procedures; the infections are clustered among a group of patients; signs of infection occur during or soon after surgery; unusual endotoxin reactions occur perioperatively; or the index of suspicion is high. The receipt of smaller doses of infective organisms may lead to milder illness or a delayed onset of symptoms that go undetected. We suspect that only larger outbreaks or those associated with serious or life-threatening outcomes have been identified, whereas smaller or less severe outbreaks or single episodes of illness associated with contaminated propofol may not have been identified.

Despite the initial reports of propofol-associated outbreaks and the education efforts by the manufacturer, the number of clusters of infection or fever associated with propofol use reported to the FDA rose steadily from 1991 through 1993 (FDA: unpublished data). In 1993, propofol was approved for use as a sedative in intensive care units. The availability of propofol in larger vials and the approval of its use in the intensive care setting, coupled with continued outbreaks and the recurrent linkage of such outbreaks with the non-aseptic handling of propofol by anesthesia personnel, suggest that further efforts are required.

Studies suggest that attempts to educate anesthesia personnel and revise their infection-control practices have not always been successful.<sup>50</sup> However, we strongly recommend increased efforts to educate anesthesia personnel about the need for aseptic techniques and basic infection-control practices. With the introduction of propofol into busy inpatient and outpatient settings where aseptic practices may be less rigorous and multidrug-resistant organisms are common,<sup>51,52</sup> the risk of extrinsic contamination may be higher than in the operating room. Access to propofol in these settings should be restricted to those educated in its unique properties and handling requirements.

Infection-control practitioners, anesthesia personnel, and others must maintain a high index of suspicion for episodes of infection or fever in patients who receive propofol for general anesthesia or sedation. Infections or acute febrile episodes thought to be associated with propofol use should be reported through state health departments to the Hospital Infections Program of the CDC at (404) 639-6413 and to the FDA's MedWatch medical-products reporting program at 1-800-FDA-1088.

We are indebted to Sonia M. Aguero, Roger L. Anderson, Ph.D., Loretta A. Carson, Gary A. Hancock, Sigrid K. McAllister, Conrardine Riddle, and Barbara A. Schable of the Hospital Infections Program, CDC; to Brent A. Lasker, Ph.D., and Timothy Lott, Ph.D., of the Division of Bacterial and Mycotic Diseases, CDC; to Diane M. Simpson, M.D., Ph.D., Texas Department of Health; to Byron J. Francis, M.D., Illinois Department of Public Health; to William N. Hall, M.D., M.P.H., James Altamirano, M.D., M.P.H., Barbara Robinson-Dunn, Ph.D., and Kenneth R. Wilcox, M.D., M.P.H., Michigan Department of Public Health; to Edward B. Hayes, M.D., and Kathleen F. Gensheimer, M.D., M.P.H., Maine Bureau of Health; to Charles H. Woernle, M.D., M.P.H., Alabama Department of Public Health; to Lawrence K. Sands, D.O., M.P.H., Arizona Department of Health Services; to Raymond J. Alderfer, M.D., M.P.H., FDA; and to the many persons at the seven hospitals who contributed to these investigations.

## REFERENCES

1. Postsurgical infections associated with an extrinsically contaminated intravenous anesthetic agent — California, Illinois, Maine, and Michigan, 1990. *MMWR Morb Mortal Wkly Rep* 1990;39:426-7, 433.
2. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;16:128-40. [Erratum. *Am J Infect Control* 1988;16:177.]
3. Garner JS. Guideline for prevention of surgical wound infections. 1985. Atlanta: Centers for Disease Control, 1985.
4. Blair JE, Williams REO. Phage typing of Staphylococci. *Bull World Health Organ* 1961;24:771-84.
5. Lasker BA, Carle GF, Kobayashi GS, Medoff G. Comparison of the separation of *Candida albicans* chromosome-sized DNA by pulsed-field gel electrophoresis techniques. *Nucleic Acids Res* 1989;17:3783-93.
6. Mason MM, Lasker BA, Riggsby WS. Molecular probe for identification of medically important *Candida* species and *Torulopsis glabrata*. *J Clin Microbiol* 1987;25:563-6.
7. Maniatis T, Fritsch EF, Sambrook J. Molecular cloning: a laboratory manual. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1982.
8. Edwards PR, Ewing WH. Identification of enterobacteriaceae. 4th ed. New York: Elsevier Science Publishing, 1986:431-40.
9. Traub WH, Kleber I. Serotyping of *Serratia marcescens*: evaluation of Le Minor's H-immobilization test and description of three new flagellar H antigens. *J Clin Microbiol* 1977;5:115-21.
10. Remillard JF, Gould MC, Roslansky PF, Novitsky TJ. Quantitation of endotoxin in products using the LAL kinetic turbidimetric assay. In: Watson SW, Levin J, Novitsky TJ, eds. Detection of bacterial endotoxins with the Limulus amoebocyte lysate test: proceedings of an international conference held in Woods Hole, Massachusetts, September 8-11, 1985. Vol. 231 of Progress in clinical and biological research. New York: Alan R. Liss, 1987:197-210.

11. Bacterial endotoxins test. In: United States Pharmacopeia. 21st rev. Rockville, Md.: United States Pharmacopeial Convention, 1985:1165-7.
12. Petersen NJ, Collins DE, Marshall JH. A microbiological assay technique for hands. *Health Lab Sci* 1973;10:18-22.
13. Membrane filtration method. In: Franson MA, Greenberg AE, Trussell RR, Clesceri LS, eds. *Standard methods for the examination of water and wastewater*. Washington, D.C.: American Public Health Association, 1985:869-70.
14. Dean AD, Dean JA, Burton JH, Dicker RC. Epi Info, version 5: a word processing, database, and statistics program for epidemiology on microcomputers. Atlanta: Centers for Disease Control, 1990.
15. Alter MJ, Ahtone J, Maynard JE. Hepatitis B virus transmission associated with a multiple-dose vial in a hemodialysis unit. *Ann Intern Med* 1983;99:330-3.
16. Jackson PG, Keen H, Noble CJ, Simmons NA. Injection abscesses due to *Mycobacterium chelonae* occurring in a diabetic patient. *Tubercle* 1981;62:277-9.
17. Maki DG, Anderson RL, Shulman JA. In-use contamination of intravenous infusion fluid. *Appl Microbiol* 1974;28:778-84.
18. Kantor RJ, Carson LA, Graham DR, Petersen NJ, Favero MS. Outbreak of pyrogenic reactions at a dialysis center: association with infusion of heparinized saline solution. *Am J Med* 1983;74:449-56.
19. Steere AC, Rifaat MK, Seligmann EB Jr, et al. Pyrogen reactions associated with the infusion of normal serum albumin (human). *Transfusion* 1978;18:102-7.
20. Crocker KS, Noga R, Filibeck DJ, Krey SH, Markovic M, Steffee WP. Microbial growth comparisons of five commercial parenteral lipid emulsions. *J Parenter Enteral Nutr* 1984;8:391-5.
21. Jarvis WR, Highsmith AK. Bacterial growth and endotoxin production in lipid emulsion. *J Clin Microbiol* 1984;19:17-20.
22. Tessler M, Dascal A, Gioseffini S, Miller M, Mendelson J. Growth curves of *Staphylococcus aureus*, *Candida albicans*, and *Moraxella osloensis* in propofol and other media. *Can J Anaesth* 1992;39:509-11.
23. Arduino MJ, Bland LA, McAllister SK, et al. Microbial growth and endotoxin production in the intravenous anesthetic propofol. *Infect Control Hosp Epidemiol* 1991;12:535-9.
24. Berry CB, Gillespie T, Hood J, Scott NB. Growth of micro-organisms in solutions of intravenous anaesthetic agents. *Anaesthesia* 1993;48:30-2.
25. Sosis MB, Braverman B. Growth of *Staphylococcus aureus* in four intravenous anesthetics. *Anesth Analg* 1993;77:766-8.
26. Thomas DV. Propofol supports bacterial growth. *Br J Anaesth* 1991;66:274.
27. Diprivan injection. Wilmington, Del.: Stuart Pharmaceuticals, 1993 (package insert).
28. Recommendations for infection control for the practice of anesthesiology. Park Ridge, Ill.: American Society of Anesthesiologists, 1993.
29. Infection control guide. Park Ridge, Ill.: American Association of Nurse Anesthetists, 1993.
30. Greene ES. Quality assurance in infection control. *Anesthesiology* 1990;73:Suppl:A1061. abstract.
31. Harrison CA, Rogers DW, Rosen M. Blood contamination of anaesthetic and related staff. *Anaesthesia* 1990;45:831-3.
32. Kempen PM, Learned DW. Anesthesia practice — a vector of infection? *Anesthesiology* 1989;71:Suppl:A948. abstract.
33. Kempen PM. Contamination of syringes. *Can J Anaesth* 1989;36:730-1.
34. O'Donnell NG, Asbury AJ. The occupational hazard of human immunodeficiency virus and hepatitis B virus infection. I. Perceived risks and preventive measures adopted by anaesthetists: a postal survey. *Anaesthesia* 1992;47:923-8.
35. Rosenberg AD, Bernstein D, Skovron ML, Ramanathan S, Turndorf H. Are anesthesiologists practicing proper infection control precautions? *Anesth Analg* 1991;72:Suppl:S228. abstract.
36. Rosenberg AD, Bernstein RL, Ramanathan S, Albert DB, Marshall MH. Do anesthesiologists practice proper infection control precautions? *Anesthesiology* 1989;71:Suppl:A949. abstract.
37. Corbett JJ, Rosenstein BJ. *Pseudomonas* meningitis related to spinal anesthesia: report of three cases with a common source of infection. *Neurology* 1971;21:946-50.
38. North JB, Brophy BP. Epidural abscess: a hazard of spinal epidural anaesthesia. *Aust N Z J Surg* 1979;49:484-5.
39. Froggatt JW, Dwyer DM, Stephens MA. Hospital outbreak of hepatitis B in patients undergoing electroconvulsive therapy. In: Program and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, September 29–October 2, 1991. Washington, D.C.: American Society for Microbiology, 1991. abstract.
40. Rudnick JR, Beck-Sague C, Anderson R, Schable B, Miller M, Jarvis W. Post-operative gram-negative bacteremia due to environmental contamination, Washington. In: Program and abstracts of the 2nd Annual Meeting of the Society for Hospital Epidemiology of America, Baltimore, April 12–14, 1992. West Deptford, N.J.: Society of Hospital Epidemiology of America, 1992. abstract.
41. Zacher AN, Zornow MH, Evans G. Drug contamination from opening glass ampules. *Anesthesiology* 1991;75:893-5.
42. Koepke JW, Selner JC. Allergy testing of multiple patients with a common syringe. *N Engl J Med* 1984;311:1188.
43. Koepke JW, Reller LB, Masters HA, Selner JC. Viral contamination of intradermal skin test syringes. *Ann Allergy* 1985;55:776-8.
44. Lutz CT, Bell CE Jr, Wedner HJ, Krogstad DJ. Allergy testing of multiple patients should no longer be performed with a common syringe. *N Engl J Med* 1984;310:1335-7.
45. Parlow JL. Blood contamination of drug syringes used in anaesthesia. *Can J Anaesth* 1989;36:Suppl:S61-S62. abstract.
46. Trepanier CA, Lessard MR, Brochu JG, Denault PH. Risk of cross-infection related to the multiple use of disposable syringes. *Can J Anaesth* 1990;37:156-9.
47. Mastro TD, Farley TA, Elliott JA, et al. An outbreak of surgical-wound infections due to group A streptococcus carried on the scalp. *N Engl J Med* 1990;323:968-72.
48. Hospital outbreak of streptococcal wound infection — Utah. *MMWR Morb Mortal Wkly Rep* 1976;25:141.
49. Schaffner W, Lefkowitz LB, Goodman JS, Koenig MG. Hospital outbreak of infections with group A streptococci traced to an asymptomatic anal carrier. *N Engl J Med* 1969;280:1224-5.
50. Kempen PM, Treiber H. Teaching hygienic practices or practicing hygiene as teaching? *Anesth Analg* 1990;70:Suppl:S199. abstract.
51. Jarvis WR, Edwards JR, Culver DH, et al. Nosocomial infection rates in adult and pediatric intensive care units in the United States. *Am J Med* 1991;91:185S-191S.
52. Weinstein RA. Epidemiology and control of nosocomial infections in adult intensive care units. *Am J Med* 1991;91:179S-184S.

Because the great majority of television and radio news programs now begin at 5 p.m. Eastern time, the *Journal's* embargo time for these media has been changed from 6 to 5 p.m. Wednesday, beginning with the July 6 issue. The embargo time for the print media will continue to be Thursday morning, the day of publication.