Hemolysis Associated With 25% Human Albumin Diluted With Sterile Water—United States, 1994-1998

Since 1994, a shortage of 5% human albumin, a product used off-label during therapeutic plasma exchange (TPE), has existed in the United States. Because of this shortage, hospital pharmacists may prepare 5% solution of human albumin by diluting 25% human albumin with 0.9% NaCl or, when sodium load is a concern, 5% dextrose. However, if sterile water alone is used as the diluent, the osmolarity (tonicity) of the albumin solution is reduced and may cause hemolysis in recipients. This report describes two of 10 episodes of hemolysis in recipients. This report describes two of 10 episodes of hemolysis in recipients. This report describes two of 10 episodes of hemolysis in recipients. This report describes two of 10 episodes of hemolysis in recipients. This report describes two of 10 episodes of hemolysis in recipients.

**Case 1**

In January 1998, a 44-year-old patient in a Maine hospital underwent TPE with 5% human albumin prepared by diluting 25% human albumin 1:5 with sterile water to treat cryoglobulinemia. After an infusion of 270 mL of the solution, the fluid in the plasma exchange device tubing became tinged red, and the procedure was stopped. The patient reported no symptoms; however, the patient's hematocrit decreased within 24 hours from 36% to 29% (normal: 37%-48%) and 48 hours later, serum creatinine increased from 0.9 mg/dL to 3.5 mg/dL (normal: <1.5 mg/dL). During the next 2 weeks, the patient's renal function recovered, and the patient subsequently underwent TPE with 5% human albumin without complication.

**Case 2**

In July 1998, a 76-year-old patient with multiple myeloma, chronic renal insufficiency, anemia, and thrombocytopenia was hospitalized in Pennsylvania for hip replacement. Two days after surgery, the patient underwent TPE for the multiple myeloma with 5% human albumin prepared by diluting 25% human albumin 1:5 with sterile water. After 750 mL were infused, red-tinged plasma was observed in the exchange tubing and red-tinged urine in the catheter bag, and the procedure was discontinued. The patient reported no symptoms.

Within 4 hours, hematocrit, blood urea nitrogen, and creatinine had not changed from baseline values, but the serum lactate dehydrogenase had increased from 149 IU/L to 734 IU/L (normal: 100 IU/L-225 IU/L). Eight hours after TPE, the patient went into shock and had a cardiac arrest. The hematocrit had decreased from 22% to 19%. Shortly after resuscitation, the patient developed disseminated intravascular coagulation (DIC) and bled from multiple sites. During the next 48 hours, progressive renal insufficiency developed; creatinine levels increased from 2.8 mg/dL to 3.9 mg/dL, and bleeding continued. The patient died 72 hours after TPE.

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**CDC Editorial Note:** When a 5% albumin solution is prepared by diluting 25% human albumin with sterile water, its osmolarity is approximately one fifth that of plasma. Hemolysis and the consequent acute renal insufficiency in case 1 probably resulted from the hypotonicity of the 5% albumin solution used during TPE. In case 2, the DIC and the accompanying renal insufficiency probably also were triggered by TPE-induced hemolysis. The large volumes used in the procedure may have aggravated the hemolysis in these cases, because the hypotonic plasma replacement mixture accounted for a significant fraction of the patients' blood volume. In addition, the shearing force of the plasma exchange device, in association with hypotonic stress, may have damaged RBCs and contributed to the hemolysis.

Since 1994, FDA has received 10 reports of hemolysis associated with infusion of 25% albumin diluted with sterile water. Eight of the 10 occurred after 1996. Four of the 10 patients had no hemolysis-associated complications; five developed acute renal insufficiency. Two patients died: one from the underlying disease, and the other was described in case 2 of this report.

In five cases, including case 2, the hospital pharmacists relied on the seventh or eighth editions of Trissel's *Handbook on Injectable Drugs*, both of which give incorrect instructions on diluting 25% albumin. In another case, the pharmacist relied on the ninth edition, in which the entry is ambiguous. In case 1 of this report, the pharmacist failed to follow the pharmacy's standard procedure of using 0.9% NaCl as the diluent. In the other three cases, the references used are not known.

The national shortage of 5% human albumin occurred during the same period as most of the hemolysis episodes. This shortage may be partially attributed to changes in production capacity. In 1997, two of the five manufacturers suspended or slowed production to bring their operations into compliance with Food and Drug Administration (FDA) good manufacturing practice regulations (Center for Biologics Evaluation and Research, FDA, personal communication, 1999). These manufacturers shared 20%-40% of the 5% human albumin market.
To stop the potentially life-threatening error that can occur when incorrectly preparing replacement albumin solution for TPE, FDA has recommended safety measures to manufacturers (revise package inserts with a warning about the risk for hemolysis), and to hospital pharmacists (a "drug warning" appeared in the FDA medical bulletin in 1998 and two alerts were issued through the Institute for Safe Medication Practices). FDA also has published letters in peer-reviewed journals, and has worked with the American Society of Health-Systems Pharmacists, publisher of Trissel’s handbooks, to revise the ambiguous entry. In addition, FDA has notified manufacturers of plasma exchange devices of this serious but preventable error.

Pharmacists and clinicians who encounter hemolysis associated with 25% human albumin diluted to 5% with sterile water for infusion are encouraged to report it to MEDWATCH, HF-2, FDA, 5600 Fishers Lane, Rockville, MD, 20852-9787; telephone (800) 332-1088; fax (800) 332-0178; World Wide Web site <http://www.fda.gov/medwatch>; to CDC’s Hospital Infections Program, National Center for Infectious Diseases, telephone (404) 639-6413; or to the product manufacturer.

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Nosocomial Group A Streptococcal Infections Associated With Asymptomatic Health-Care Workers—Maryland and California, 1997

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GROUP A STREPTOCOCCUS (GAS), A COMMON cause of pharyngitis and uncomplicated skin and soft tissue infections, can cause serious invasive infections (including necrotizing fasciitis and streptococcal toxic-shock syndrome [STSS]) and death. Since 1965, at least 15 postoperative or postpartum GAS outbreaks attributed to asymptomatic carriage in health-care workers (HCWs) have been reported. This report describes two nosocomial outbreaks of GAS infection in Maryland and California during 1996-1997; the findings suggest that early infection-control measures that include active surveillance may interrupt transmission and prevent morbidity and mortality.

Maryland
During July 1996-August 1997, seven patients with postpartum GAS infections were identified by hospital A. A case of GAS infection was defined as GAS isolated from any nonpharyngeal site in a patient whose symptoms began >12 hours after admission to hospital A during January 1996-September 1997. Review of the hospital’s microbiology records for all nonpharyngitis GAS cultures during the study period identified two additional postpartum cases. No cases were identified on other wards. Of nine case-patients, seven had endometritis; two of these had sepsis; one developed hypotension and required admission to the intensive-care unit (ICU). One patient developed postcesarean delivery wound infection, and another had a urinary tract infection. No patients died.

Each of the nine case-patients was compared with five controls. Controls were selected randomly from patients on the obstetric ward during the study period. Exposure to one HCW (HCW A) was associated strongly with infection (odds ratio = 25; 95% confidence interval = 2.8-1200.0).

Swab specimens were collected and cultured from the throat, rectum, vagina, and skin of 198 HCWs who worked on the labor and delivery or postpartum wards during the outbreak period. GAS isolates from the HCWs and a patient isolate were typed by sequencing the variable portion of the M-protein gene (emm typing). Three HCWs had positive cultures for GAS. Only the rectal isolate from HCW A was identical to that of the case-patient (emm type 77). HCW A’s wife, who was asymptomatic, had positive rectal and vaginal cultures for the same strain. HCW A and his wife were treated with oral vancomycin and rifampin. Surveillance cultures of HCW A have remained negative, and hospital A has had no additional cases.

California
During December 23, 1996-January 1, 1997, three patients who had surgery at hospital B developed STSS. On December 23, a previously healthy 28-year-old woman underwent a parathyroidectomy performed by surgeon A. The day before surgery, surgeon B performed direct laryngoscopy on the patient. She developed chest pain and hypotension on December 24. On December 26, she was transferred to the ICU because of respiratory distress, then developed cardiopulmonary arrest. Cultures taken December 23 from the neck wound and pleural fluid grew GAS. She went into shock and developed renal failure, coagulopathy, and purpura and died on December 29.

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On December 30, a previously healthy 56-year-old woman underwent a subtotal thyroidectomy performed by surgeon A with the assistance of surgeon B. She was discharged December 31. Later that day, she was found dead in her home. Postmortem cultures of blood and tissue grew GAS. The cause of death was attributed to septicemia and GAS.

On December 30, a previously healthy 57-year-old woman underwent a subtotal thyroidectomy performed by surgeon A with surgeon B assisting. The next day she was discharged. On January 1, 1997, she sought care at the emergency department and was admitted to the ICU in shock, with acidosis, respiratory failure, renal impairment, and bilateral pleural effusions. Cultures from the surgical wound, pleural fluid, and blood grew GAS. After a hospital course including sepsis, global myocardial hypokinesis, and lower gastrointestinal bleeding, she was discharged on February 4.

Review of hospital B’s microbiology records revealed no episodes of postoperative GAS infection during the 6 months before the outbreak. Surgeon A was the only HCW who had contact in the operating room with all three patients. Nasopharyngeal, throat, rectal, and vaginal cultures were obtained from the 41 staff members who worked in the operating room and the pre- or postoperative areas on the days of surgery for the patients. All cultures were negative except a throat culture from one orderly that grew GAS. Surgeon A received self-initiated penicillin on January 2, before adequate cultures were obtained. Rifampin was added following adequate culturing. Throat cultures from surgeon A’s household contacts were negative.

GAS isolates from all three patients were emm type 1 and had indistinguishable restriction fragment length polymorphism patterns. The orderly’s GAS isolate was emm type STNS5.

Surgeons A and B were restricted from patient care until each had completed a 10-day course of penicillin and rifampin. No further postoperative GAS infection has occurred in hospital B.

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CDC Editorial Note: GAS is an unusual cause of surgical site or postpartum infections. The bacterium is isolated from <1% of surgical-site infections and 3% of infections after vaginal delivery (CDC, unpublished data, 1986-1997). The most common site of asymptomatic carriage among HCWs is the anus, but vaginal, skin, and pharyngeal carriage have been implicated. GAS carriers can shed the organism into the immediate environment despite proper gowning and gloving. The mode of transmission is presumed to be airborne.

Surgical and obstetric patients are particularly vulnerable to infection because broken cutaneous or mucosal barriers facilitate invasive infection after exposure. In Toronto, Ontario, Canada, three of eight investigations following an episode of nosocomial GAS on surgical or obstetric wards identified an asymptomatic HCW.

To prevent additional nosocomial GAS infections, enhanced surveillance and limited epidemiologic investigation are warranted following one episode of nosocomial GAS infection on a surgical or obstetric ward. After identification of a patient with postoperative or postpartum GAS, medical and laboratory records should be reviewed to identify other infections, and isolates from infected patients should be stored and surveillance heightened to identify additional episodes.

When an episode of postoperative or postpartum GAS is identified, limited HCW screening should be undertaken. Most nosocomial transmission is traced to carriers involved in direct patient care. For a postpartum GAS-infected patient, screening should include all HCWs present at the delivery and those who performed vaginal examinations before delivery. For a postoperative GAS-infected patient, screening should include all HCWs present in the operating room during the procedure and those who changed dressings on open wounds. Screening of HCWs should include culture of the nares, throat, vagina, rectum, and skin. HCWs may return to work pending culture results. Any HCW culture-positive for GAS should refrain from patient care for the first 24 hours of antimicrobial treatment. The regimen should be tailored to the carriage site; previous reports have indicated anal carriage may be difficult to eradicate. For example, appropriate treatment for a positive rectal culture may be vancomycin 250 mg orally four times a day and rifampin 600 mg orally twice a day for 10 days. For a positive throat, vaginal, or skin culture, appropriate treatment may be penicillin 500 mg four times a day for 10 days with rifampin 600 mg orally twice a day for the last 4 days of the 10-day course.

If surveillance identifies additional patients or HCWs with positive cultures for GAS, the isolates should be typed by emm, serologic, or other molecular methods to identify the strain. When the isolates are the same and a carrier has not been identified, screening should be expanded to include HCWs who had less direct patient care. CDC also recommends obtaining cultures from household contacts of implicated carriers to identify and treat potential reservoirs for reinfection. Because carriage may recur, implicated carriers should be monitored with periodic surveillance cultures for 1 year after treatment.

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