As advances have been made in the care of very low-birth-weight infants, some techniques or practices have caused unexpected complications. One such practice is umbilical vessel catheterization to monitor an infant's arterial blood pressure, infuse fluids and medications, and obtain blood specimens for laboratory examinations. The catheters frequently are flushed with sterile isotonic saline or a 5% solution of dextrose in water, with the flush solution frequently being obtained from a multidose vial. The United States Pharmacopeia requires all medications or solutions marketed in a multidose vial to contain an antimicrobial preservative. Benzyl alcohol, an aromatic alcohol, is used for this purpose in a wide variety of medications and fluids for parenteral therapy, usually in a concentration of 0.9%.

Two groups of investigators, Gershanik et al\(^1\) (New Orleans) and Brown et al\(^2\) (Portland), independently concluded that an intravascular infusion of flush solutions containing 0.9% benzyl alcohol caused severe metabolic acidosis, encephalopathy, respiratory depression with gasping, and perhaps other abnormalities leading to the death of a total of 16 infants. Blood and urine from several affected infants had high levels of both benzoic and hippuric acids, known metabolites of benzyl alcohol. Both groups stated that no additional cases occurred after solutions with benzyl alcohol preservative were banned in their nurseries.

Subsequently, in May 1982, the Food and Drug Administration\(^3\) with the concurrence of the American Academy of Pediatrics and the Centers for Disease Control,\(^4\) urged pediatricians and other personnel in hospitals not to use fluids preserved with benzyl alcohol (or other antimicrobial agents) as intravascular flush solutions for newborn infants and not to use diluents with this preservative to reconstitute or dilute medications for infants.

Metabolically, benzyl alcohol is oxidized to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. This metabolic pathway may not be functional in premature infants and may allow accumulation of benzoic acid (and perhaps unmetabolized benzyl alcohol) with resulting metabolic acidosis and toxicity. Known toxic effects on benzyl alcohol include respiratory failure, vasodilation, hypotension, convulsions, and paralysis; little is known specifically about toxicity of the compound in newborn infants. Most studies of benzyl alcohol toxicity in animals\(^5\) have evaluated a single-rapid or slow infusion into adult animals of various species; none has evaluated multiple infusions over a prolonged period into a newborn or immature animal. Thus, benzyl alcohol appears to be a safe preservative for small-volume parenteral medications for adults; data are not available to justify the same conclusion for newborn infants.

Pharmacologically, administration of preserved flush solutions to newborn infants and adults is considerably different. Infants receive a much larger flush relative to body weight than do adults, reducing considerably the therapeutic-toxic ratio for any substance infused. The increasingly aggressive treatment of tiny newborn infants over the last several years may have contributed both to the occurrence of the problem and to its recent recognition. In two studies,
\(^{1,2}\) the volumes of flush solution received by the infants were estimated; and, from this, the amount of benzyl alcohol infused was calculated. A daily administration of benzyl alcohol approaching levels known to be toxic for a single infusion in adult rats, the most sensitive of the animals tested, was found.\(^5\) Unfortunately, the actual amounts of benzyl alcohol received by the infants probably will remain unknown because precise information about the frequency and volume of flush solutions administered is not recorded in
most neonatal intensive care units. Without this precise information, calculation of a dose-response effect in the infants is not possible.

The data reported by Gershanik et al and Brown et al are striking and warrant the action taken by the FDA, even though both studies were uncontrolled and the clinical information reported is not totally consistent. Preliminary data from other neonatal units suggest that the mortality for small premature infants (those weighing <1.1 kg) has declined after the preserved solutions were no longer used. These data must be confirmed. Additional laboratory and animal studies are needed to assess the significance and pathophysiology of the problem, especially since benzyl alcohol continues to be administered to newborn infants in small amounts in a variety of medications. To define pathologic changes in different organ systems that might be attributable to benzyl alcohol poisoning, histologic studies of tissues from infants who died after receiving solutions preserved with benzyl alcohol should be conducted and the sections carefully compared with specimens from matched infants who died but had not received preserved solutions.

The impact of eliminating benzyl alcohol as a preservative in flush solutions for infants also requires assessment. If the toxicity of the preserved solutions has been as great as the initial studies indicate, a significant decrease in mortality of small premature infants should be observed. Conversely, if the preservatives have been important in preventing solution contamination, an increase in neonatal septicemia with selected organisms such as Pseudomonas, Klebsiella, Enterobacter, and Serratia may ensue.

As an emergency measure, manufacturers of commonly used solutions packaged in multiple-dose vials with benzyl alcohol preservative have agreed with the FDA request to include a warning, “Not for Use in Newborns,” on the labels of these products. The FDA, USP, and others are reviewing the need for permanent changes in products, labels, and package inserts. At the hospital level, each neonatal unit should assess its patterns and needs in providing flush solutions for infants and should establish a system with its hospital pharmacy to assure a satisfactory and safe means of providing sterile, unpreserved solutions. Vials of normal saline and 5% dextrose solution are available without preservatives, although by USP standard these are labeled for single use only. Alternatively, unit-dose flushes in syringes or a single, large-volume container of a flush solution could be dispensed several times each day to the nursery area; unused syringes or fluid remaining in the container should be discarded when the new supply is received. Preparation of solutions, including addition of heparin if this is used, should be carried out in the pharmacy. Refrigeration will retard growth of most bacteria that inadvertently contaminate the solutions during preparation. Cold fluids should not be administered to infants; therefore, refrigerated solutions will need to be brought to room temperature before use. These flush solutions at room temperature should be used within a few hours or be discarded, a function that could coincide with the beginning of each nursing shift. These alternative methods of providing flush solutions have not been evaluated in clinical trials.

Other sources of benzyl alcohol should be identified in solutions and medications administered to infants. Many medications also contain benzyl alcohol as a preservative. In general, the volume of benzyl alcohol received by this route is negligible compared with the amount received in flush solutions. For newborn infants, it may be preferable to avoid use of medications with preservatives whenever possible. However, the presence of benzyl alcohol as a preservative should not preclude use of medications indicated for treatment of an infant. Another potential source of exposure of infants to benzyl alcohol is through instillation of an isotonic solution into endotracheal tubes. Although pulmonary absorption of some pharmacologic agents is significant, information about absorption of benzyl alcohol by this route is unknown.

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### Benzyl Alcohol: Toxic Agent in Neonatal Units

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