Infection Control in

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Infection is a significant hazard, and disseminated fungal infection has been a particularly frequent and dread complication of total parenteral nutrition. Rates of septicemia as high as 27% have been reported. A survey by the Center for Disease Control and a review of the literature indicate that the risk of infection can be substantially reduced if stringent infection control measures are practiced. Accordingly, the Center's Hospital Infections Section has developed infection control guidelines for total parenteral nutrition programs.

During the past few years, total parenteral nutrition (TPN) has become increasingly popular as a means of achieving an anabolic state in patients otherwise unable to maintain normal nitrogen balance. The essential components of commonly used TPN solutions are dextrose and protein hydrolysates or synthetic amino acids. Trace elements, essential fatty acids, vitamins, and electrolytes are provided as required. Dudrick and co-workers\textsuperscript{1,2} refined and popularized the techniques for administering such a concentrated form of parenteral nutrition to humans in the late 1960s.

See also page 1344.

Total parenteral nutrition subsequently has been demonstrated to be a valuable adjunct in the care of critically ill infants and adults with a variety of conditions.\textsuperscript{1-12}

Unfortunately, the hypertonic solutions used in TPN rapidly thrombose peripheral veins; therefore, administration catheters must be placed in regions of high blood flow. Although arteriovenous shunts and fistulae have been used for this purpose,\textsuperscript{13} the greatest experience has been with central venous catheters. In adults, the superior vena cava or right atrium may be reached via percutaneous catheterization of the subclavian or internal jugular veins.\textsuperscript{14,15} Infants have such small subclavian veins that it is considerably safer to catheterize the external jugular vein. To facilitate aseptic catheter maintenance in infants, the proximal end of the catheter is usually brought out through a subcutaneous tunnel to the parietal scalp.\textsuperscript{16}

Although TPN can be life-saving, it is potentially dangerous, especially in the hands of personnel not thoroughly versed in its proper use. The most frequently noted complication has been sepsis, and the remainder of this report will discuss the occurrence and prevention of sepsis in patients receiving TPN.

Infectious Complications of TPN

A report from the University of Minnesota\textsuperscript{17} emphasizes the risk of sepsis complicating TPN. A retrospective review of 33 cases of fungal septicemia occurring during an 18-month period showed that 22 patients had developed infection while receiv-
Total Parenteral Nutrition

ing TPN. Even more alarming was the observation that 18 of the 22 TPN patients with fungal septicemia died, and that this complication was the primary cause of death in 15. These startling findings prompted a prospective study in which it was found that septicemia developed in 13 of 49 (27%) patients receiving TPN; in eight cases the septicemia was fungal.

In evaluating the Minnesota experience, it is extremely important to note that no firm guidelines for the administration of TPN existed at that institution. Concerning the cases in the retrospective study:

No uniform protocol was followed regarding techniques of solution preparation or administration. Addition of dextrose, vitamins, etc., was usually done by personnel on the nursing stations. Albumin and blood were frequently administered through the same catheter as the protein hydrolysate solution, and this intravenous line was often used to monitor central venous pressure as well.

Micropore filters and antibiotic cream were used sporadically. No uniform changes in technique were instituted for the prospective study.

When meticulous technique, such as that described by Dudrick and coworkers, is employed, what is the risk of infection? In an attempt to obtain an overview of the problem, the Center for Disease Control (CDC) solicited TPN data from hospitals cooperating with CDC in a nosocomial infection surveillance project (National Nosocomial Infections Study), and from additional selected medical centers. Thirty-one institutions were found to employ sound infection control practices when preparing and administering TPN. These hospitals reported treating 2,078 patients with an associated septicemia rate of 7%. Fifty-four percent of the septicemias reported were fungal.

Available reports of the incidence of sepsis complicating TPN are summarized in the Table. The rate of sepsis due to all pathogens ranged from 6% to 27%. Although none of the studies listed was controlled, sepsis was attributed to fungi in a surprisingly large number of cases; Candida was the chief offender. Total parenteral nutrition-associated fungal infection has also been documented in several case reports. This is in marked contrast to the rarity of fungal septicemia in patients receiving conventional intravenous infusions, although one French study did report a significant incidence of this complication. Several factors may be involved in the development of fungal sepsis in patients receiving TPN:

1. Broad-spectrum antibiotics, radiation, steroids, and immunosuppressants all predispose patients to fungal septicemia. It is also a well-documented observation that fungal infections frequently occur in debilitated patients, especially when there is a compromised immunologic response. Disseminated fungal disease sometimes complicates the course of newborn infants with severe illnesses of all types. Although patients receiving other forms of intravenous therapy are exposed to the same predisposing factors and develop bacteria rather than fungal sepsis, it is possible that prolonged catheterization, coupled with other variables mentioned below, favors fungal proliferation.

2. *Candida* proliferates more rapidly than most common bacterial pathogens in TPN solutions. The importance of actually testing the growth properties of various organisms in intravenous fluid was demonstrated during the recent epidemic of septicemia resulting from intrinsically contaminated intravenous products. Members of the tribe Klebsiella proliferated when inoculated into D5W, but *Candida* grew slowly. Total parenteral nutrition fluid is extremely hypertonic and rather acidic, and it would be surprising if all organisms grew equally well in it.
study concerning this subject demonstrated that Candida albicans proliferates exuberantly, while "Klebsiella Enterobacter," Pseudomonas aeruginosa, and Staphylococcus aureus grow poorly in TPN solutions. Another study found that C albicans grows well in a solution of protein hydrolysates and 6% dextrose (TPN solutions generally include 20% to 25% dextrose) at 30 C and 37 C, but growth is suppressed at 4 C. Growth at room temperature was not evaluated. Preliminary studies conducted at CDC indicate that Candida grows rapidly at room temperature in TPN solution prepared with a protein hydrolysate injection (Hypotrogen), the number of organisms increasing by one log in 12 hours and three logs in 24 hours. Klebsiella and some strains of S aureus grow as rapidly as Candida, but E coli, Serratia, Proteus, and Enterobacter grow more slowly, and Pseudomonas does not grow at all. Candida does not proliferate quite as rapidly in TPN solution prepared with amino acid, synthetic solution (Freamine), while the bacterial pathogens tested show minimal growth.

3. Several clinical trials have suggested that an ointment containing polymyxin B sulfate, bacitracin, and neomycin sulfate (Neosporin ointment) applied to polyethylene catheter sites predisposes patients to colonization with Candida. Since this ointment has been used liberally in the maintenance of TPN catheters, it is conceivable that it has contributed to the increased incidence of fungal septicemia. Moreover, the occlusive dressings conventionally employed in the care of such catheters may alter the microbiologic flora of the skin and foster proliferation of Candida. Some TPN programs are now switching from ointment containing polymyxin B, bacitracin, and neomycin to topical iodophor ointment; it will be important to assess by controlled clinical trials whether this agent diminishes the frequency of fungal sepsis. Clinical trials with nonocclusive sterile dressings should also be considered.

Comment

Enthusiasm for the therapeutic potential of TPN must be tempered by a sobering awareness of the incidence of sepsis associated with such therapy. We believe that the incidence of infection secondary to TPN can be reduced if sound infection control measures are employed. The Hospital Infections Section of CDC previously has issued recommendations for the insertion and care of polyethylene catheters used for the delivery of conventional intravenous solutions. These recommendations provide a rational basis for developing guidelines for the care of TPN delivery systems. However, because of the length of time TPN catheters are left in place and the debility of patients receiving TPN, this therapy requires even more stringent measures to reduce the infection hazard. Hospital Infections Section guidelines for infection control in TPN therapy follow.

Infection Control Guidelines for TPN Programs

1. Total parenteral nutrition should be initiated only when indicated by the patient's clinical requirements. The need for TPN should be balanced against the significant risks inherent in such therapy. The premature infants and critically ill patients for whom TPN is generally prescribed are especially prone to serious infection, and TPN should be administered under the supervision of a physician who is thoroughly versed in the techniques and complications of this therapeutic modality.

2. Total parenteral nutrition therapy should be the responsibility of a team of individuals with a particular interest and expertise in the field. At the very least, such a team should include a nurse, a physician, and a pharmacist or other staff member trained in the preparation of TPN solution. If possible, a surgeon, a bacteriologist, and a physician with an interest in infectious disease should participate. This team should be responsible for teaching principles and techniques of infection control to physicians and nurses charged with the care of TPN systems. Hospitals unable to assemble such a team of experts probably should not use TPN.

3. Total parenteral nutrition solutions should be prepared, catheters placed, delivery systems maintained, and fluid administered according to a detailed protocol incorporating adequate infection control measures. This protocol should be approved by the hospital administration, infection control committee, nursing service, and pharmacy standards committee.

4. All TPN components and additives should be mixed by a trained member of the hospital staff using aseptic technique. Optimally, a properly maintained laminar flow hood should be utilized. However, even scrupulous technique will not completely eliminate contamination during preparation, and recent experience indicates that intrinsic contamination of intravenous fluid products is possible. Since some microorganisms can proliferate in TPN fluid stored at room temperature, the fluid should be used immediately. If the fluid must be stored, it should be kept at 4 C and used as soon as possible.

5. The insertion of a TPN catheter should be considered a surgical procedure and ideally should be performed in an operating theater or treatment room. Persons involved in the placement of a catheter should wash, gown, mask, and glove as they would for any other surgical procedure.

6. The site of catheter placement should be chosen as indicated in the preceding text. The skin may be shaved, or hair may be removed with a depilatory. Sterile drapes must be used to ensure preservation of the sterile field. The site should be thoroughly disinfected. An excellent method utilizes 1% iodine in 70% alcohol. After 30 seconds drying time, the iodine solution should be washed off with 70% isopropyl alcohol. Both agents should be applied with friction, working from the center of the field to the periphery. An iodophor disinfectant may be substituted in patients with sensitive skin, but should not be washed off with alcohol, as its antibacterial action may depend in part on the sustained release of free iodine. In the rare case in which these preparations cannot be tolerated by the patient, vigorous, prolonged (greater than one minute) washing with 70% isopropyl alcohol is acceptable.

7. After the intravenous administration route is established, the catheter should be securely anchored to prevent irritating to-and-fro motion and to avoid potential transport of cutaneous bacteria into the puncture wound. Although evidence is not con-
clusive, topical antimicrobial applications may afford added protection against infectious complications. Since studies have suggested that antibiotic ointments may actually favor the selective growth of fungi, the junction of the skin and catheter may be covered with a topical antibacterial, antifungal, iodophor ointment. The site of intravenous administration should be covered with a sterile dressing.

8. With an aseptic technique (gown, mask, gloves, sterile field), the catheter site should be inspected and disinfected periodically. Antimicrobial ointment should be reapplied and the dressing changed on these occasions. Most physicians perform these procedures every two to three days, although controlled studies have not been performed to determine the optimal interval.

9. Administration of fluid at a site should be discontinued immediately if signs of inflammation, purulence, thrombosis, or extravasation of fluid are observed. It must be borne in mind, however, that catheters may be responsible for septicemia even if local signs of inflammation are not present.

10. No controlled studies have been performed to determine how frequently TPN catheters should be routinely changed. Some investigators remove catheters and initiate therapy at another site every 30 days, even if there have been no complications.

11. To avoid unnecessary contamination, the TPN system should not be used to measure the central venous pressure, administer blood products or "piggy-back" medications, or obtain blood samples. Some physicians wash the intravenous tubing with an iodophor solution and apply iodophor ointment to all joints in the circuit to inhibit the entry of microorganisms.

12. Considerable attention has been given recently to the possibility of using micropore filters to diminish the risk of infection secondary to contaminated intravenous solutions. It has been suggested that these filters be placed terminally—that is, between catheter and tubing. The 0.45μ filter is designed to block the passage of fungi and most bacteria (except some types of Pseudomonas and aberrant bacterial forms). The 0.22μ filter will block virtually all bacteria, but a pump is usually necessary to insure sufficiently rapid flow of viscous TPN solutions (such pumps are often used anyway to regulate the amount of fluid administered to infants). Both filters are effective in inhibiting the passage of air emboli and large particles, but they will not prevent the passage of endotoxin. Theoretically, these filters should reduce the hazard of infection from intrinsically contaminated solutions. Filters could also conceivably reduce the risk of infection from extrinsic contaminants entering secondary to the use of additives or manipulation of the system above the filter, but they would have little effect on organisms gaining access to the system from points below the filter. It must be stressed that there have been no controlled clinical trials performed to demonstrate the ultimate utility of these filters in reducing infection. The manual insertion of any device into the intravenous system increases the likelihood of contaminating the system, although incorporation of the filters into intravenous tubing during manufacture would greatly reduce this problem. The potential value of micropore filters is recognized, and controlled clinical trials to verify their efficacy are encouraged.

13. Studies have demonstrated that even if TPN fluid is sterile when it arrives from the pharmacy, intravenous systems may become contaminated from extrinsic sources. Preliminary studies at CDC indicate that Candida proliferates very rapidly in TPN fluid prepared with casein hydrolysates. To reduce the hazard from proliferation of contaminants, this type of TPN fluid should not be left in use for more than 12 hours after preparation. Since administration sets serve as a reservoir for fluid, they should be changed approximately every 12 hours. Candida proliferates less rapidly in TPN solution prepared with synthetic amino acids; therefore, this type of solution may remain in use 24 hours after preparation and administration sets changed accordingly. Bottles of TPN fluid should be closely inspected for cracks since extrinsic fungal or bacterial contamination of fluid can occur through cracks so small that fluid does not leak out. Bottles should also be discarded if turbidity or precipitate is detected (TPN fluid normally looks slightly milky, but not cloudy). The absence of turbidity or precipitate does not guarantee freedom from contamination; in fact, bacterial contamination may not be visible even with 10 organisms/ml present. Every bottle should be labeled clearly with the patient's name, the date, time of preparation, and additives.

14. The TPN system should be considered immediately in the differential diagnosis of fever. Should infections of septicemia develop in a patient receiving TPN, certain measures should be taken in addition to the usual cultures of the patient's blood and other possible sites of infection. The TPN administration set and bottle should be discontinued immediately. Twenty milliliters of TPN fluid should be withdrawn aseptically from the intravenous tubing, 1 ml used to prepare a pour plate, and the rest placed in a blood culture bottle. The nature of the solution and the lot number of the bottle should be recorded on the laboratory requisition. Some physicians retain blood cultures through the catheter to increase the likelihood of documenting the presence of infected thrombi adjacent to the catheter tip. The presence of systemic Candida infection may be confirmed sometimes by examination of blood smears for intraleukocytic fungal forms or by the results of serological tests. Unless another obvious source of sepsis can be quickly documented, the TPN catheter should also be removed. The skin at the catheter site should be disinfected to eliminate skin contaminants, the catheter aseptically removed, and the tip of the catheter clipped off with sterile technique and cultured in appropriate media, such as brain heart infusion broth, enriched with 0.5% beef extract. If indicated, therapy should be reestablished at another site. Fungal septicemia and bacteremia may resolve spontaneously, without specific antimicrobial therapy, when the offending infusion system is removed; however, appropriate antifungal or antibacterial therapy should be administered if clinical signs or positive cultures indicate persistent infection. Relatively silent foci of infection may be established by even the most transient septicemia.
References


CORRECTION

Serum Cholesterol Level—An error occurred in the brief report, "Dissecting Hernoma of the Coronary Artery: A Possible Complication of Oral Contraceptive Therapy," published in the Jan 29 issue (222:550-551, 1973). On page 550, in column 2, in the second to the last line, the serum cholesterol level should have been 234 mg/100 ml, not 434 mg/100 ml.