Preventing Infection in Intravenous Therapy

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Reprinted from Hospital Practice
April, 1976 Vol. 11 No. 4 Pp. 95-104
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Any part of an infusion system—not just the cannula, its most distal portion—may be at fault when sepsis complicates IV therapy. Detailed here are both intrinsic and extrinsic mechanisms by which contamination may occur; recommendations such as more widespread use of steel scalp needles and early termination of infusions are given. The special requirements of total parenteral nutrition systems are defined.

Without question, intravenous infusion therapy has become an indispensable therapeutic modality in present-day medicine. It has probably saved more lives than all the antibiotics ever developed. At least 10 million of the more than 40 million Americans hospitalized each year receive some form of IV therapy—be it blood transfusion, fluid and electrolyte replacement, drug administration, or total parenteral nutrition. Yet IV therapy also carries a tremendous and, in my view, generally vastly underrated potential for iatrogeny. Virtually, anything one can think might go wrong with IV systems has, in fact, gone wrong (see Table on next page): mixing of incompatible drugs, use of the wrong drug or the wrong dose, and even inadvertent intrarteral injection leading to severe arterial spasm and distal gangrene. Other disastrous complications, many of which are well known and all of which have been reported, include: fluid overload and pulmonary edema, transfusion reactions, profound electrolyte imbalance, catheter embolus, air embolus, hemorhorax and pneumothorax, and possibly even pulmonary hypertension related to high concentrations of particulate matter in IV solutions. And near the top of the list is sepsis.

For all intents and purposes, the patient receiving IV therapy has a hollow conduit directly connecting his bloodstream with the outside world and its abundant microflora. One of the patient's most important host defenses is totally abrogated—the intact skin. IV therapy almost seems to comprise a diabolical experimental model for producing systemic infection. Indeed, the current most popular animal model for studying bacterial endocarditis consists of guiding a plastic catheter into the left heart of a rabbit and transiently superimposing a bacteremia; endocarditis develops almost uniformly.

Fortunately, sepsis, like virtually all of the other IV therapy-related problems mentioned above, is largely preventable. This fact provides the basis and is the motive for the discussion that follows, for we do not want to treat iatrogenic infections but to prevent them. In this regard it is important to realize that despite the often spectacular advances medicine has made in the last few decades, the greatest reduction in mortality (and prolongation of life expectancy) occurred around the turn of the century, when the value of preventive medicine, with its stress on elementary public health measures, including antisepsis, began fully to be appreciated and widely and systematically applied. This fact, I think, still has great relevance to events in hospitals today.

Infusion therapy has been in use in this country for over 45 years and plastic venous catheters have been widely employed since 1945, yet as recently as 1962 the idea that infusion-related infections might constitute a significant nosocomial hazard was largely ignored. The American Hospital Association's monograph of that year, Control of Infections in Hospitals, for example, did not even mention IV therapy as a potential source of infection. In the decade following 1963, when the first prospective study of catheter-related infection was published, more than 40 groups of investigators focused attention on this long-neglected area. Recent outbreaks of sepsis traced to contaminated IV fluids in this country and Great Britain have brought about even greater awareness of the iatrogenic perils of infusion therapy. In the discussion that follows, the terms "infusion-related infection" and "IV-related infection" are used to designate infections caused by any part of the infusion system, including the venous cannula or IV fluid. Cannula

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is a general term that includes all types of plastic catheters – from 2 inches to 24 inches in length – and also steel needles (see figure on page 99).

### Catheter-Related Sepsis

Most of the studies in this area have focused on the most distal portion of the delivery system, the cannula, particularly the plastic catheter, which is now used in about half of all IV infusions. None, however, rigorously examined the possibility that fluid flowing through the catheter might be contaminated. In addition, not all studies cultured catheters under optimal conditions of local asepsis. However, nearly all employed qualitative bacteriology. The amputated catheter tip was immersed in liquid media and growth of microorganisms was variably categorized as “contamination,” “colonization,” or “infection” (which designation was most appropriate is unknown). Some investigators elected to exclude positive cultures with such skin commensals as bacillus species, diphtheroids, Staphylococcus albus, and Streptococcus viridans. This judgment may not have been justified, since such organisms probably reach the catheter tip by the same mechanisms as more virulent ones, and, while relatively avirulent, such skin flora can occasionally cause life-threatening systemic infection, particularly in the presence of implanted foreign materials.

Despite these limitations, rates of positive catheter cultures observed in these studies ranged from 3.8% to 57%; rates of associated sepsis ranged from zero to as high as 8%. As to the type of catheter, some investigators noted particularly high rates of positive cultures and sepsis in association with surgical cutdowns or percutaneously placed subclavian catheters; the highest rates were found in association with umbilical catheters in neonates. In general, although incidence of culture positivity with percutaneously inserted plastic catheters varied widely from institution to institution, there was striking unanimity that the longer catheters were left in place, the higher the rates of positive catheter cultures and associated sepsis (see graph on page 98). Specifically, when percutaneous plastic catheters were left in longer than 48 hours, the incidence of catheter-related sepsis generally ranged between 5% and 7%, and in some hospitals it was as high as 8%. This observation is the basis of the most important measure for prevention of catheter-related sepsis: remove IV catheters whenever possible within 48 to 72 hours of insertion.

The most common isolates from catheters were Staphylococcus epidermidis, Staphylococcus aureus, gram-negative bacilli like klebsiella-enterobacter, serratia, and enterococci. These are all organisms that are commonly found on the skin of hospitalized patients, an observation that brings us to pathophysiologic considerations and the first of the routes by which IV components can become contaminated and patients infected.

We all normally harbor a luxuriant and predominantly gram-positive pop-

### Potential Hazards of IV Therapy

<table>
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<tr>
<th>Septicemia</th>
<th>Catheter-related</th>
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<td>Contaminated IV fluid or drugs</td>
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<td>Fluid overload leading to pulmonary edema</td>
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<td>Electrolyte imbalance syndromes</td>
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<td>Drug-related problems</td>
<td>Adverse reactions (hypersensitivity, toxicity)</td>
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<td>Incompatibilities</td>
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<td>User errors (drug, dose, route)</td>
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### Adverse reactions to blood products

- Infusion thrombophlebitis
- Catheter embolus

### Complications of central venous catheters

- Air embolus
- Pneumothorax
- Hemothorax
- IV fluid hydrothorax
- Brachial plexus injuries
- Vascular injuries
- Cardiac perforation, tamponade
- Thromboembolism

### Foreign materials in fluid from the IV apparatus

- Particulate matter
- Leached plasticizers

### Metabolic aberrations associated with total parenteral nutrition

- Hyperosmotic hyperglycemic coma
- Hyperchloremic acidosis
- Hyperammonemia
- Azotemia
- Hypovitaminosis and trace metal deficiencies
- Hypophosphatemic anemic anemia
- Hepatic cellular derangements
- Fatty acid deficiencies

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*Health hazards posed by particulate matter (phlebitis, pulmonary hypertension) and accumulation of plasticizers in tissues (oncogenesis) are suspected but not yet proved.

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96
ulation of skin flora. But that population can turn predominantly gram-negative under conditions that increase skin humidity, as is often the case with bedridden patients. Accordingly, the failure of rigorous disinfection at the infusion site increases the risk that either gram-positive or gram-negative skin organisms may be introduced into the catheter wound at the time the catheter is being inserted or later, when organisms may migrate along the interface between catheter and tissue.

The patient, however, is not the only possible human reservoir of skin organisms that can contaminate an IV site. Studies in several hospitals have shown that besides carrying the usual skin flora, the hands of over 46% of hospital personnel randomly sampled also had gram-negative bacilli, suggesting that routine handwashing before and after every patient contact is often neglected or carried out in only the most perfunctory fashion. In a number of hospitals now, outbreaks of hospital-associated infection, primarily with S. aureus or gram-negative bacilli, have been directly linked to organisms carried on the hands of hospital personnel. In addition, an outbreak of klebsiella sepsisemia was traced to heavily contaminated hand lotion used by nurses; other investigators have found that such lotions may be heavily contaminated with candida and gram-negative bacilli.

Another factor to consider is whether the patient already has an infection elsewhere. A number of investigators have found that catheters inserted in infected patients became culture-positive and initiated sepsisemia much more frequently than did catheters in noninfected patients. Often the organism responsible for the infection was the same one later isolated from the catheter. By what mechanisms might this occur? One possibility is that a transient, clinically undetected bacteremia spawned by a distant infection seeds the catheter with pathogenic organisms. Perhaps they are trapped within the loosely organized clot that almost uniformly forms around the plastic catheter within 24 hours. However, these organisms may also enter the catheter wound from without in the process of manipulation of the apparatus, primarily by hospital personnel but perhaps also by patients themselves. One study found that catheters removed because of phlebitis, leakage, or infiltration had high rates of culture-positivity. It may be that the practice of irrigating or otherwise manipulating occluded, leaking, or infiltrated catheters provides an opportunity not only for introducing contaminants but also for perpetuating infections.

Based on these considerations, it is most prudent to view the insertion of an IV catheter as a surgical (albeit minor) procedure, in some situations (e.g., total parenteral nutrition) to the extent of performing it only with sterile gloves and drapes and in a treatment room away from hospital traffic. Since one obviously cannot autoclave
As data combined from four published studies involving a total of 916 catheters show, there may not only be a positive correlation of culture positivity with duration of catheterization but a dramatic leap on the fourth day in the rate of associated septicemia.

A cannula insertion site, this means that chemical disinfection must be relied upon for effective degemming. As much, strict adherence to the first tenet of chemical disinfection is imperative: all organic material must first be removed, which in the case of IV therapy means that every bit of dead skin, dirt, blood, and mucus must first be scrubbed off vigorously before applying the disinfectant. Even the best of disinfectants will be ineffective against microorganisms lying beneath such debris. On the other hand, most IV sites are relatively hairless, and the proposal that the IV site routinely be shaved prior to catheter insertion can probably be regarded as unnecessary and possibly even self-defeating. In the first place, a relationship between the presence of hair and counts of bacterial skin flora has not been demonstrated. In the second place, there is evidence that local microecologic alterations resulting from shaving (i.e., abrasions) can influence the skin microflora. As to the consequences of such a change, a controlled study of surgical wound infection showed a 10-fold reduction in infections when hair was removed with a depilatory instead of a razor; several other studies have also confirmed the fact that shaving has an adverse influence on surgical wounds.

Of the variety of disinfectants to choose from, iodine-containing agents are preferred. In vitro studies and clinical trials have shown that they are rapid-acting and highly effective bactericidal, fungicidal, and sporadicidal agents. Occasional patients may be allergic to iodine, but iodine burns, which were used to be fairly common when 5% to 7% solutions were in use, are infrequent with the 1% to 2% solutions currently employed. A solution of 1% iodine in water or in 70% alcohol (tincture of iodine) is inexpensive, highly effective, and seldom causes discomfort or burns, especially when washed off 30 seconds after applica-

[Diagram of data]
examined for signs of inflammation. A positive finding in any of these areas constitutes a "suspect infection," which must be immediately discontinued in toto.

When local inflammation or unexplained fever is noted—and with all catheters that have been left in place longer than 48 hours—the catheter should routinely be cultured at removal. We have found that rolling the amputated segment across a blood agar plate, in contrast to the conventional technique of culture in broth, provides an accurate assessment of local infection. Ninety percent of 250 catheters in our institution recently sampled by this method yielded no growth or only several colonies on the plate, whereas all catheters causing septicemia gave heavy growth, 1,000 colonies or greater.

Sepsis would almost certainly be greatly minimized if all catheters were removed without fail after 48 hours, but this is simply not always possible in patients with few peripheral veins and who medically must have a stable route for venous access. Another approach is to try to lessen local contamination by applying a combination antibiotic or an antibiotic ointment to the catheter site at the time of insertion and at periodic intervals thereafter. The effect of such topical agents on decreasing the risk of infection is not conclusively known. Only a handful of studies have been done and the number of patients in each with catheter-related septicemia was relatively few. But taken together, the results of five studies (which all used the same agent) suggest that a topical antimicrobial is protective; ointment containing polymyxin, neomycin, and bacitracin significantly reduced the incidence of catheter-related septicemia. On the other hand, these studies also suggest that topical antibiotics can alter the population of organisms found on catheters, selecting for drug-resistant, gram-negative bacilli or yeasts. The frequency with which candida was recovered increased with the use of the antibiotic combination, especially when catheters were left in longer than 72 hours. Conceivably, use of topical iodine-containing antiseptics that are active against all bacteria and fungi could obviate the hazard of superinfection. Clearly, large-scale studies are needed in this area.

### Steel Needles

Steel needles, such as the popular "scalp-vein needles" widely used in pediatric services, generally have a smaller bore than most widely used plastic catheters, are usually easier to insert, and seem to cause substantially less phlebitis and infection than plastic catheters. There are, to be sure, many unanswered questions here. For example: How much safer, if at all, are the newer small-bore plastic catheters? What is the influence of such catheter materials as polystyrene, polyvinyl chloride, silicone, or Teflon on culture positivity, septicemia, and phlebitis? Nevertheless, there is substantial evidence to indicate that scalp-vein needles should be used much more frequently than they currently are.

While a controlled comparison of needles and plastic catheters has not been done, combined data from eight prospective studies of scalp-vein needles revealed only one associated bacteremia in more than 700 patients, an incidence less than 0.2%. In contrast, more than 30 published studies of plastic catheters have reported rates of septicemia ranging, as previously noted, from 0 to 8%. Scalp-vein needles do have to be replaced more frequently because they tend to infiltrate rather quickly. Thus, plastic catheters are indicated when a secure IV route is needed in critically ill patients. For elective IV infusion, however, scalp-vein needles should be used in perhaps 80% of instances rather than the prevailing 50%. Whether the crucial factor is that the smaller bore is less traumatic to veins, or that steel is less thrombogenic, or that the more frequent changes they require are responsible for their apparent greater safety is not known and should be investigated. The few reported cases of septicemia linked to scalp-vein needles have occurred primarily in patients with cancer or who were otherwise significantly immunocompromised.

### Suppurative Phlebitis

Suppurative phlebitis, also known as septic thrombophlebitis, is the

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One way to reduce risk of IV-related sepsis is to increase use of the steel scalp-vein needle (left, in center with anchoring flange, contrasted with 24-, 3-, and 24-inch plastic catheters) in routine infusions. Although studies directly comparing use of plastic catheters are lacking, the risk of septicemia may be as much as 40 times higher with the latter. Photo at right shows Klebsiella pneumoniae-positive culture of plastic catheter tip that was removed from septicemic patient.
most dreaded and extreme form of catheter-related infection, where the vein becomes a bag of pus discharging massive numbers of microorganisms into the bloodstream. Most reports have been from burn centers, since patients with full-thickness burns seem particularly vulnerable. Suppurative phlebitis is now among the leading causes of septic death in burn patients, superseding infections of the burn wound. Coagulase-positive S. aureus and, in recent years, multiply resistant gram-negative bacilli, especially klebsiella-enterobacter, pseudomonas, and serratia, have been most frequently implicated. Recent studies have shown that in burn patients the process commonly also affects the great central veins, particularly the subclavian, iecofemoral, and superior vena cava, and is related to centrally placed catheters. Central venous suppuration was found in 18% of burn patient autopsies in one series; in this location such suppuration was almost uniformly lethal. Fortunately, in recent years, the frequency of suppurative phlebitis in burn patients has been cut significantly by widespread and stringent adherence to the practice of changing plastic catheters at frequent intervals.

Suppurative phlebitis probably occurs to a significant degree, for the most part unrecognized, in nonburn patients, particularly in cannulations of the lower extremity. We have seen five cases in the past one and a half years in nonburn patients all of whom either were suffering from cancer or were receiving corticosteroids. Three cases occurred in association with lower extremity cannulations, providing further evidence of a substantially greater risk of catheter-related infection in this area, compared with arm vein cannulations.

Clinical recognition of suppurative phlebitis may be very difficult, since local signs of inflammation—particularly in burn patients—are absent in as many as 50% of cases. The usual manifestation is refractory and often overwhelming septicemia, commonly first presenting several days after catheter removal. Perhaps the best way to diagnose venous suppuration is to routinely milk the vein from above outward, toward the catheter site, whenever a catheter is removed. If pus is expressed (and in my experience it usually is if suppuration is present) and the patient appears to be septic—or when the diagnosis is suspected but external examination is nonyielding—representative sections of the vein should be taken for bacteriologic and histopathologic examination. If suppurative phlebitis is proved, the best hope for cure lies in total resection of the purulent segment and all its involved tributaries.

**Infusion Phlebitis**

Infusion phlebitis—infammation of the cannulated vein, often associated with secondary thrombosis—is an extremely common sequela of IV therapy. Multiple studies have implicated a number of contributory factors. These include: 1) anatomic location—veins of the lower extremities, with their relatively sluggish blood flow, are more vulnerable than more cephalad vessels; 2) length of time the cannula is in place—the longer the cannulation, the greater the risk; 3) position of the catheter tip—one study showed that central venous catheters, inserted in the arm, that fed directly into the superior vena cava caused phlebitis less often than did the conventional catheters that terminated in the arm vein; 4) type of cannula material—steel needles and certain polymers such as polyethylene or silicone are substantially less phlebitogenic than polyvinyl chloride; 5) cannula diameter—large-bore catheters tend to cause more phlebitis; and 6) type of infusate—glucose-containing solutions (especially when hypertonic) and certain drugs, such as methicillin, the cephalosporins, barbiturates, and cytotoxic agents, are very irritating to the vein.

Interestingly, most studies of catheter-related infection were able to demonstrate little correlation between positive cultures of catheter tips and phlebitis and most investigators have thus concluded that phlebitis is primarily a physiological phenomenon. However, we found that half of the patients with sepsis related to contaminated IV fluids in a recent nationwide outbreak manifested infusion phlebitis. This phlebitis-related phlebitis was often far more severe than the phlebitis that is not uncommon when plastic catheters are used, and it occurred even in patients who had only scalp-vein needles. Moreover, by using a semi-quantitative technique of culturing catheters, which identified local infection, we recently found that infection of the catheter wound is strongly associated with local inflammation. In all likelihood, phlebitis is a multiorgan system, and infection is only one—but an obviously important one clinically—of the many causative factors. Most patients with phlebitis obviously do not have systemic infection, but the presence of phlebitis connotes an 8-fold increased risk of related sepsis as compared with no phlebitis: approximately one half of the patients with catheter-related septicemia will have phlebitis.

**Sepsis-Related to Contamination of Infusion Fluid**

Another major consideration in the development of infusion-related sepsis is the fluid itself, which may become contaminated either through a breakdown of asepsis during manufacture (intrinsically contamination) or during use in the hospital (extrinsic contamination).

*Intrinsic contamination:* A historic example of intrinsic contamination began in the summer of 1970 shortly after one manufacturer began distributing fluids in bottles with a new elastomer-lined screw-cap closure. By December, reports began to accumulate at the Center for Disease Control from U.S. hospitals of excessive numbers of cases of IV-associated septicemia. The major causative organisms were *Enterobacter cloacae* and *Enterobacter agglomerans* (formerly known as erwinia); the latter organism had been a very rare cause of septicemia in human beings and was better known as a plant pathogen. (Just as the clinical rarity of these strains helped to expose the problem in the first place, so the possible pathogenic role of other more common organisms in causing IV-related septicemia is obscured by their clinical frequency.)

In a significant number of cases in which cultures had been done, the infecting organisms were found in large numbers within the patient’s running IV fluid at the time of positive blood
culture. When in-use IV systems of two other major suppliers were sampled, about 5% to 10% were found to be contaminated with a variety of organisms, but not by either E. cloacae or E. agglomerans. The cause of the epidemic was uncovered when frequent microbial contamination was shown to be present within the depths of the new closures. Forty percent of cap assemblies sampled from several thousand bottles of the involved manufacturer's stock were found to be contaminated by a wide variety of microorganisms, including the epidemic strains. As expected, these strains were subsequently found throughout the inanimate environment of the manufacturing plant.

As a result of the investigation it was concluded that when the cap was removed, microorganisms in the cap liner or thread areas were afforded access into the fluid. Simply loosening the cap and shaking the bottle briefly — as was commonly done in hospitals at that time during introduction of additives into fluids — transferred contaminants from the cap to fluid over half of the time in a laboratory study (see “How the Septicemia Trail Led to the IV-Bottle Cap,” HP, August 1971). By March 1971 the situation was perceived as a nationwide outbreak involving at least 25 hospitals and approximately 400 patients. The epidemic peaked in February and March of 1971 and was abruptly curtailed, but only after a nationwide recall of the affected product.

Since this epidemic, three further outbreaks have occurred, two in England — one involving seven cases and the other 40 cases — and one in the U.S. The lesson of the first U.S. epidemic proved extremely valuable: although the implicated products were distributed nationally, the second U.S. outbreak was detected and a recall put in effect so rapidly that only five cases were identified. It can be anticipated that outbreaks of infection due to intrinsically contaminated infusion products will continue to occur in the future. However, continued efforts to increase the sensitivity of quality control practices in industry, expanded nationwide programs of surveillance of nosocomial infection that can reliably detect events of low frequency in widely scattered hospitals, and greater awareness of the part of hospitals and physicians can lessen their frequency and impact.

Extrinsic contamination: A pertinent fallout of our investigation during the first U.S. outbreak was the realization that microorganisms of extrinsic origin are commonly present in all manufacturers' in-use IV fluids. Their presence is related to the many manipulations of the system, such as the addition of medications to the bottle or line, changing bottles or bags, and the use of stopcocks and pressure monitors. We found that the IV fluid of approximately 4% to 10% of in-use infusions contained culturable microorganisms. Usually these were only very low concentrations (<1 organisms/ml) of relatively avirulent organisms (primarily skin commensals such as Staphylococcus epidermidis and bacillus species). Presence of contamination was directly related to the duration of uninterrupted infusion. With rare exceptions, only members of the tribe klebsiellae (TK) — klebsiella, enterobactor, and serratia — were found in concentrations exceeding 10 organisms/ml. Moreover, the major pathogens in the ongoing nationwide outbreak and in the few prior published reports of septicemia attributed to extrinsic contamination of IV fluid were members of TK. The question was: Why these organisms?

To begin to answer the question we must first consider that IV therapy is virtually synonymous with 5% dextrose (glucose) in water (D5%/W); it and other glucose-containing solutions are by far the most frequently used infusion products in hospitals. In the 1970-71 epidemic, for instance, more than 90% of affected patients received glucose-containing solutions.

Commercially available D5%/W might be characterized at first glance as a relatively minimal microbiologic media. It is acidic and its only possible nitrogen source is dissolved atmospheric nitrogen, while glucose and a dissolved CO2 comprise the only car-
bon sources. Theoretically, the absence of organic nitrogen should be sufficient to prevent microbial growth. For most organisms this is probably true, yet it has long been known that many TK members are able to fix atmospheric nitrogen. As to another seeming impediment to microbial growth, the relatively low (room) temperature of the medium, it had been shown that TK organisms are facultative psychrophiles, i.e., they grow well at or below room temperature.

With these observations in mind, I studied the growth properties of 51 strains of TK, five strains of Candida albicans, and 49 strains of non-TK bacteria, including E. coli, herellea species (new nomenclature, acinetobacter), Pseudomonas aeruginosa, proteus species, and staphylococci, in the four major commercial brands of D5%W at 25°C. All strains, clinical isolates from human infections, were first washed to remove organic sources of nitrogen. We found that 95 of the 51 TK strains proliferated rapidly in all four brands, going from normalized zero-time concentrations of 4 organisms/ml to 100,000 organisms/ml in only 24 hours. In contrast, 48 of the 49 non-TK strains either failed to grow or died over 48 hours. The five strains of C. albicans grew only very slowly, reaching a mean normalized 24-hour concentration of about 50 organisms/ml. Turbidity or other evidence of microbial growth visible to the unaided eye could not be detected at any time, even at 48 hours when many strains of TK had attained concentrations exceeding 10^5/ml. (Of note, molds, usually entering through minute cracks in the bottles, may cause faint turbidity or filmy precipitates.) Attempts to demonstrate significant growth with representatives of the same cast of organisms in normal saline were unsuccessful. Recent evidence from other laboratories suggests that P. aeruginosa grows well in distilled water and Pseudomonas cepacia may be one of the rare non-TK species able to proliferate in D5%W.

The import of these findings, I think, is that now, in addition to the cannula, IV fluid itself may be recognized as a significant potential source of nosocomial sepsis, in which tribe klebsielleae organisms may be expected to predominate. The available evidence suggests that sepsis caused by contamination of IV fluid—whether extrinsic or intrinsic—is a low-frequency event, and as such is usually unrecognized as due to the infusion or is attributed to the cannula. Over the last 10 to 15 years the incidence of septicemia caused by members of TK, especially Klebsiella pneumoniae, Enterobacter aerogenes, and Serratia marcescens, has risen dramatically. In the main this trend has been attributed to changing patterns of bacterial resistance related to ever-increasing use of antimicrobials. It should be recognized, however, that in recent years the use of IV therapy has also increased dramatically.

Recognizing the cumulative nature of in-use contamination of IV fluid and the explosive growth potential of tribe klebsielleae organisms, the simplest and most logical way to reduce the incidence and impact of either intrinsic or extrinsic contamination of IV fluid is to routinely change all bottles or bags and delivery apparatus every 24 hours (at the maximum every 48 hours), and at each change of cannula to totally replace all infusion equipment. I do not accept the proposal that in order to reduce the risk of infusion phlebitis, intrinsically acidic solutions such as D5%W should be routinely buffered with sodium bicarbonate before use. This act adds one more point to which intravenous organisms can be introduced by hospital personnel. Moreover, we have found that neutralization broadens the spectrum of organisms capable of proliferating in glucose-containing fluid, adding pseudomonads and acinetobacter as potential pathogens. In addition, minute quantities of blood buffer IV fluid and also provide organic nutrients for more fastidious organisms that would otherwise be incapable of growth. Accordingly, we have recommended that following administration of blood products, the entire delivery system be replaced.

Terminal in-line 0.22- to 0.45-micron membrane filters have been developed and advocated to reduce the risk of sepsis from contaminated fluids. A 0.45-micron filter permits the passage of pseudomonads and occasional other gram-negative bacilli, and thus a 0.22-micron filter is necessary to remove all bacteria; however, a pump is usually then required to assure continuous flow. Although promising on a theoretical basis, no controlled study in a sufficiently large population to assess the efficacy of filters in preventing sepsis has been reported. Moreover, the manual manipulation of the delivery system needed to install the filter for use adds one more opportunity for extrinsic contamination. A recent uncontrolled study found a fourfold increased rate of sepsis in patients on total parenteral nutrition in whom filters were used. Although filters may ultimately prove of greater value in removing particulate matter and reducing infusion phlebitis, further studies are needed.

Preparation and compounding of parenteral solutions are probably best done under optimal conditions of asepsis in a central pharmacy rather than by a heterogeneous population of nurses on the ward. Without question, airborne contamination can be virtu-
ally eliminated in laminar flow hoods in such an area. Since touch contamination is probably a much greater source of fluid contamination, however, there remains the nagging fear that a break in aseptic technique in the pharmacy could expose a large number of patients to contaminated products. The interval between preparation and use of pharmacy-prepared solutions also provides opportunity for multiplication of any introduced organisms. Nonetheless, these hypothetical concerns are probably greatly outweighed by the inherent benefits of a more standardized approach to asepsis and quality control. A marked reduction in drug incompatibilities and medication errors can also be expected with central preparation of solutions. For such reasons, the USP's National Coordinating Committee on Large Volume Parenterals recently went on record as recommending that all parenteral solutions (except in medical emergencies) be prepared by pharmacists in a designated central area of the hospital (Am J Hosp Pharm 31:261, 1974).

Sepsis and Total Parenteral Nutrition

In 1966, Dudrick and his coworkers demonstrated the feasibility of maintaining positive nitrogen balance by a totally parenteral route of alimentation, using hypertonic glucose solutions (see "Long-Term Parenteral Feeding," HP, October 1968). In the past five years, this therapeutic modality has proved highly effective and often lifesaving for patients with severe and prolonged but reversible states of gastrointestinal compromise. The iatrogenic complications associated with this therapeutic modality have been many; but, except for sepsis, generally not of life-threatening consequence.

In most respects, the problems with sepsis encountered in total parenteral nutrition (TPN) are the same ones associated with conventional IV therapy but greatly magnified. In the early years, from 1960-73, the rate of sepsis associated with TPN was as high as 15% to 22% in some hospitals. Even centers with formal training programs and presumable special expertise had rates as high as 33%. Approximately 50% of septicemias were caused by C. albicans, and many were "fatal." More recent studies have now shown convincingly that TPN may be delivered with only a 1% to 2% risk of sepsis (see S.J. Dudrick et al., "Long-Term Parenteral Nutrition: Its Current Status," HP, May 1975). However, the history of this TPN reveals a grimly documented potential for disastrous infectious complications that must be recognized.

One reason, of course, is that by definition, TPN patients are critically ill and malnourished, and many are also on immunosuppressive drugs. Moreover, the solutions themselves can induce abnormalities in neutrophil number and function, related to folic acid and phosphate depletion respectively. Another reason is that TPN catheters must be left in place in these debilitated patients for prolonged periods of time. Because the hyperoncotic solutions involved are highly irritating to peripheral veins, the procedure requires cannulation of the central circulation, an undertaking with its own complications (pneumothorax and vascular injuries, in the main) and not to be repeated unnecessarily in the same patient.

Here again, however, we find ourselves addressing the question of the nature of the fluid. For our studies of the growth of microorganisms in conventional IV fluid have been extended to TPN solutions by Goldmann. The results show that C. albicans, T. glabrata, S. marcescens, and K. pneumoniae, and some strains of S. aureus proliferate exuberantly in a commercial solution prepared from casein hydrolysates and 50% dextrose; among these; organisms; however, only candida and toxiplasmosis were able to grow in a commercial synthetic amino acid-dextrose solution (albeit more slowly than in the first medium). The ability of candida to proliferate well in these solutions is particularly intriguing, since the organism has been a major pathogen in TPN; it is perhaps all the more suggestive in light of the demonstrated slow growth of candida in conventional IV fluid (D5W) and the relative rarity of candidiasis in patients receiving conventional IV therapy. The evidence, however, is not yet conclusive and these other points must be raised: patients with compromised immune states are known to be particularly susceptible to fungal infection; antibiotic treatments (as noted) may alter the microbiologic flora of the skin and may predispose to fungal colonization; and occlusive dressings used in the care of TPN catheters may do the same, probably by increasing local humidity, thereby favoring proliferation of fungi.

The most recent experience with TPN has shown that in a stringent program of asepsis—in which, for example, TPN catheters were used exclusively for TPN and not also to infuse drugs or to draw or dissect blood—the risk of associated infection can be reduced to less than 1%, optimally, as noted, to 1% to 2%. A corollary of this experience might be advanced: hospitals that administer total parenteral nutrition with rates of sepsis substantially exceeding 3% ought seriously to reassess their program or even consider discontinuing it.

How can infection control be implemented most effectively here? It now appears that crucial to the success of any TPN program is formation of a TPN team. At the very least, this means one or more nurses, a physician, a pharmacist or other staff member trained in the preparation of TPN solutions, and, if possible, a surgeon, a bacteriologist, and a physician with an interest in infectious diseases. The TPN team is solely responsible for teaching the "principles and techniques of infection control to physicians and nurses charged with administering TPN solutions. It is an operation best run, according to a detailed written protocol that spells out all control measures. Solutions for TPN must be prepared by a centralized pharmacy admixture service in a laminar-flow hood rather than by a mixed group of nurses on the ward.

IV Teams

In my view, this kind of thinking is directly transferrable to infection control in conventional IV therapy. The first step is recognition by all medical personnel that IVs are potentially dangerous. The second step is the institution of surveillance procedures. This takes us to the concept of the
Selected Reading


Goldmann DA, Maki DG. Infection control in total parenteral nutrition. JAMA 223: 1360, 1973

Maki DG, Anderson RL, Shulman JA. In-use contamination of intravenous infusion fluid. Appl Microbiol 28: 775, 1974


Received and Management of Infusion-Related Sepsis

Although the stringent program of prevention and most fervent compliance will substantially reduce the incidence of infusion-related sepsis, sporadic infections, albeit rare, will undoubtedly continue to occur. A favorable clinical outcome hinges upon early recognition and prompt institution of appropriate therapy (obviously most important is removal of the indwelling infusion).

Clinically, infusion-related sepsis is indistinguishable from sepsis of other etiologies: abrupt onset with extreme fever, bedshaking rigors, and hypotension are often dramatic, but non-specific gastrointestinal and neurologic symptoms can easily divert attention away from the infection. Glucose intolerance in patients receiving TPN, particularly in infants or when it is progressive, must be regarded as a harbinger of occult TPN-related sepsis until proved otherwise. When present, phlebitis is very suggestive of an IV-related origin of infection, but it is actually absent half of the time. Ironical-

ly, this is especially the case with venous suppurative. Sometimes one is aided in diagnosis by the fact that there is no other obvious site of infection and the patient is an unlikely candidate for sepsis (often young or in good health). However, we have found in a recent study that catheter-related sepsis in an intensive care unit population can be extremely occult.

Often it is attributed to pneumonia, urinary tract or surgical wound infection, or simply considered cryptogenic and treated empirically. Very characteristic of infusion-related sepsis is its refractoriness, despite intensive antimicrobial therapy, until the offending infusion has been removed. In the 1970-71 nationwide outbreak, 17 of 19 patients in one hospital continued to have positive blood cultures after 24 hours or more of gentamicin therapy, until their infusions were fortuitously or intentionally removed.

If infusion-related sepsis is suspected, besides obtaining blood from a separate vein for culture, discontinuation of the entire infusion including all delivery apparatus and the cannula is mandatory, and the cannula and samples of infusion fluid should be cultured. The site should be examined for purulence, which is present should be gram-stained and cultured, and in such instances, exploratory venotomy should also be considered. Although infusion-related sepsis often resolves without antimicrobial therapy following removal of the entire offending infusion, systemic antimicrobials should be administered to seriously ill patients. Drug selection is occasionally guided by the results of prior blood cultures or gram-stained smears of purulence, however, if these are unavailable — and they usually are — antimicrobial combinations effective against microorganisms known to be commonly associated with both catheter- and infusion-related infection are indicated. A combination of a penicillinase resistant semisynthetic penicillin (e.g., methicillin) or a cephalosporin (e.g., cephalothin) and an aminoglycoside, such as gentamicin, is effective against the most frequently implicated bacterial pathogens. In general, empiric antifungal therapy in the initial regimen is rarely necessary or desirable objective evidence of systemic infection (based on positive blood cultures, presence of candida in pleural, ascitic, joint, or cerebrospinal fluid, histopathologic confirmation, ophthalmoscopic signs of retinitis, repeated recovery of candida from multiple anatomic sites, or positive serologic tests) is usually required before initiating therapy with amphotericin B or 5-fluorocytosine.