INTRODUCTION

Intravenous (iv) catheters are used frequently in hospitalized patients today. The most common complication of iv therapy is infection. Several studies (1–3) have reported the incidence of bacterial colonization of iv devices to range from 30 to 78%. In these reports, the local application of neomycin–polymyxin–bacitracin ointment to the insertion site did not produce uniform results in preventing infection. Moran (3) showed a significant decrease in the incidence of organisms recovered from surgically placed iv cutdowns to which this ointment had been applied. In the other studies by Norden (4) and Zinner et al. (5), there was no overall reduction in colonization of iv catheters using the same antibiotic ointment. Paradoxically, the high frequency of bacterial isolation from iv devices cited in the literature, yields low rates of bacteremia (2–4%) and correlate poorly with phlebitis. Despite the high incidence of recovery of organisms, the source and significance of bacteria isolated from the iv catheter tip have not been established.

The purpose of this study is to establish via a double-blind trial, the efficacy of the local application of gentamicin cream in preventing colonization and infection of iv catheters. Unlike previous experimental protocols, organisms recovered from iv devices were compared to cultures of skin flora before insertion and at the time of removal of the catheter. This procedure was employed for two reasons: (1) In order to determine the frequency of local skin flora as a source of bacteria leading to subsequent colonization and infection of the iv catheter, and (2) the potential of preventing infection from this source with local gentamicin. Finally,
an effort was made to establish the significance of organisms isolated from iv catheters and their correlation with clinical signs of phlebitis.

**METHODS**

The study was divided into three parts.

*Part I. Pretrial Survey*

For 5 mo prior to the start of the double-blind trial iv catheters were randomly cultured in order to define the frequency of organisms isolated from iv catheter tips under nontrial conditions. The culture technique was the same as that described below and no local antibiotics were used.

*Part II. Double-Blind Trial of Gentamicin Cream vs Placebo Cream*

All iv catheters and needles inserted in patients on the Georgetown Medical Service during the period from January 7, 1969 to April 20, 1969 were eligible for study. A protocol calling for the house officer to initiate the experimental procedure was as follows: Upon starting iv therapy, a skin culture (pre-skin) was taken from the prospective site before any antiseptic was applied and the swab dropped into a tube of thioglycollate broth. Each house officer maintained his usual procedure in preparing the skin site for venipuncture. Alcohol sponges, tincture of benzalkonium, and aqueous benzalkonium (Zephiran) were used. Polyethylene plastic catheters (Inracath, C. R. Bard, Inc., Murray Hill, NJ) or butterfly needles (Abbott Laboratories, No. Chicago, IL) were the iv systems employed. A tube of cream identified only by number was selected at random for each patient. The placebo cream was identical in color and physical consistency to the gentamicin cream. Tube number, time of starting the iv, type of iv system, and antiseptic solution were all recorded on a form kept at the patient’s bedside. The cream was applied to the iv skin juncture after insertion and then daily by a group of nurses. Clinical signs of phlebitis at the iv site were recorded on the bedside data sheet by the nurse. When the iv was to be discontinued, a skin culture (post-skin) was taken from the skin–iv system juncture and dropped into thioglycollate broth. The iv catheter or needle was then removed aseptically (Tomac Suture Removal Set, American Hospital Supply/Div. of AHSC, Evanston, IL). The tip of the iv system catheter or needle was first streaked across a blood agar plate (BAP). Then, approximately 2 cm of the catheter tip was severed using sterile forceps and scissors, and placed in thioglycollate broth. Butterfly needles were first streaked across a BAP; then, a moistened sterile swab was touched to the needle tip and placed in thioglycollate media. All bacteria were identified by antibiotic disc sensitivity patterns including gentamicin. Population parameters of age, sex, hospital duration, presence of diabetes, neoplastic disease, or infection other than at the iv site were recorded.

*Part III. Double-Blind Study plus Sterile Technique*

After completion of most of the double-blind study, a sterile insertion technique was adopted by two of the investigators on a small series of patients. In addition to the above protocol, the prospective iv site was scrubbed with tincture of benzalkonium and sterile gloves were used when inserting the iv system.

**RESULTS**

Data from iv systems used in 211 patients were analyzed with regard to the incidence, etiology, significance, and prevention of colonization or infection of the iv device. These results are recorded for the three parts of this study as follows.
Incidence and Significance of Bacteriologically Positive IV Devices

The incidence of bacteriologically positive iv systems as determined by growth of bacteria in thioglycollate media and/or on BAP was: (Part I) Pretrial Survey patients 47.6% (20/42). (Part II) Trial patients placebo 32.1% (26/81). Trial patients gentamicin 33.3% (22/66). (Part III) Sterile technique, trial patients placebo, 33% (4/12). Sterile technique, trial patients, gentamicin 10% (1/10).

In evaluating the significance of positive iv systems, infection of the iv device was considered probable if both BAP and thioglycollate cultures revealed growth of the same organism. Possible infection, or simply colonization of the iv, was applied to cultures of the iv tips which produced growth in either BAP or thioglycollate cultures alone. Isolations in thioglycollate media outnumbered those on BAP by a ratio of 2 to 1.

Using this revised classification, the incidence of probable infection was: Part I. 26.1% (11/42) patients. Part II. Trial patients, placebo, 13.5% (11/81) and trial patients, gentamicin 6.1% (4/66). Part III. Sterile technique, trial patients, placebo, 0% (0/12) and sterile technique, trial patients, gentamicin 0% (0/10) [see Fig. 1]. Two observations tended to support this arbitrary classification of probable infection vs possible infection or colonization of the iv catheter. Most possible (90%) infections lacked clinical signs of phlebitis while 50% of probable infections had gross evidence of inflammation (P < 0.01). Phlebitis was more frequent in probable infections than in noninfected iv devices when intravenous antibiotics, a common cause of chemical phlebitis, had been excluded (P < 0.05).

Etiology

The etiology of the probably infected iv catheter was determined by comparing the pre-skin culture before installation and the post-skin culture at time of removal. The following correlations suggest the skin flora as the source of infection: Infected iv devices matched patients’ pre-skin flora in: Part I, 48%. Part II, placebo, 36% and gentamicin, 0%. Part III, sterile technique, placebo, 0% and sterile technique, gentamicin, 0%. The remaining infected iv devices where there was no correlation with pre-skin cultures were considered to be secondary to contamination on insertion. The percentage of probable infections attributed to the contamination factor

![Fig. 1. Incidence of patients with bacteriologically positive iv devices. Probable infection means growth of the same organism from the catheter tip streaked on BAP as well as in thioglycollate medium. Possible infection signifies growth in only one culture medium and of little consequence.](image-url)
listed accordingly: Part I, 52%. Part II, placebo, 64%, and gentamicin, 100%. Part III, sterile technique, placebo 0% and sterile technique gentamicin, 0% (see Fig. 2).

Other sources of infected iv devices not correlating with skin flora were the theoretical possibilities of seeding the catheter tip by coincidental bacteremia and the use of contaminated iv devices or solutions. (6,7) None of the iv devices in the patients who had bacteremia from another focus were infected in this study. No organisms were recovered by culturing random samples of iv solutions or unused iv catheters immersed in thioglycollate media for 5 days.

**Prevention**

The above findings bear a direct relation to the efficacy of the local application of gentamicin cream to iv systems. Since the local application of gentamicin could only be expected to prevent iv infection secondary to skin flora and not that due to contamination on insertion, it was observed that no probable infections occurred in the gentamicin group due to skin flora. However, 36% of the probable infections in the placebo iv devices were infected with organisms matching the skin flora culture prior to starting the iv. These infections occurred over a 1- to 5-day range of iv catheterization.

Generally, there was no overall statistically significant difference between placebo or gentamicin-treated groups. However, even if etiology of infection is disregarded, there was a trend toward $P$ values which approached significance in the gentamicin-trial patients. When probable infection rates for trial patients were analyzed according to duration of iv catheterization a significant difference was found. Trial patients, placebo group, developed 10/72 probable infections when iv devices were left in place from 0 to 5 days as compared with 1/56 probable infections in the trial patients, gentamicin group. ($P < 0.05$) [see Fig. 3].

**Bacteremia**

Bacteremia occurred in eight patients; only one infection was secondary to the iv catheter. The organism was *Aerobacter aerogenes*, and the bacteremia occurred in a patient receiving gentamicin cream. This patient had a central venous catheter in place for 5 days and gentamicin cream was applied only on the first day by mistake. *Streptococcus faecalis* was obtained on the pre-skin culture.
Fig. 3. Effect of duration of catheterization vs percentage of patients with bacterial colonization of iv systems and type of infection, i.e., possible or probable.
**Bacteriology**

All organisms isolated from the iv devices except one case of *Candida albicans* infection were sensitive to gentamicin. Of the 66 organisms recovered, 21 were "classical" pathogens, nine accounting for probable infections and 12 for possible infections. Coagulase-negative *Staphylococcus albus* was the most common organism isolated from skin flora although the entire spectrum of gram-positive cocci and gram-negative rods was encountered.

**Population Parameters**

Analysis of the trial patients showed that the gentamicin and placebo groups were comparable with regard to age, sex, hospital duration, hematocrit, WBC, count, and blood urea nitrogen (BUN) in the study. The presence of diabetes, neoplastic disease, or another focus of infection (pneumonia, urinary tract infection, etc.) did not significantly influence the iv device colonization rate. No probable infections were found with butterfly needles which remained in place an average of 36 hr. The use of either alcohol or benzalkonium chloride (Zephran) did not significantly alter respective infection rates.

**DISCUSSION**

By using new approaches in experimental design an attempt was made to study not only the efficacy of a locally applied antibiotic in preventing iv catheter colonization and infection, but also the source and significance of organisms recovered from the iv catheter tips. Using a semiquantitative culturing technique consisting of first streaking the removed iv catheter across a BAP and then placing the tip in thioglycollate broth, an estimate of the number or significance of organisms isolated in relation to clinical phlebitis was determined. All previous studies have cultured catheter tips initially in broth alone.

No study has identified the frequency of local skin flora as the source of organisms found on the iv tip. Therefore, the skin at the iv site was cultured before starting and stopping the iv system. The role of the person starting the iv as a source of infection was evaluated by using sterile gloves at the time of iv insertion. These new approaches to the problem of iv catheter infection support the results reported in this study and possibly explain some of the paradoxical data in the literature.

**Incidence and Significance**

Using the semi-quantitative technique described above, a bacterial isolate from an iv catheter tip was considered to indicate probable infection if both BAP and thioglycollate media yielded growth of the same organism. Possible infection, or more likely, contamination-colonization, was indicated when only one of the two cultures produced bacteria. This arbitrary classification had a profound effect on the incidence of infection in the three parts of this study. In Part I (Pretrial Survey of the incidence of infection of iv catheters used without the application of local biotics), bacteria were found on 48% of iv catheter tips. This figure is in the range reported by several authors (1–3) of 30–78%. When infection rates were examined according to the criteria of probable vs possible infection, it was found that probable infections were present in 26.2% of the patients.

Similarly, there was a significant reduction in overall infection rates of 33% and 32.1% in Part II of this study (double-blind trial of gentamicin cream vs placebo cream) to 6.1% and 13.5%. In Part III (double-blind trial plus sterile technique on insertion) possible infection rates were 10% and 33% for gentamicin.
vs placebo-treated catheters while no probable infections were found in both groups. Of particular importance to this arbitrary classification of probable vs possible infection, was the observation that clinical phlebitis was associated with predominantly probable infections ($P < 0.01$) after iv antibiotics, a common source of chemical phlebitis, had been excluded. Although phlebitis, in this study, was found to be statistically related to probable infection, 50% of probable infections lacked evidence of phlebitis. Therefore, it would appear that even though phlebitis indicates infection, its absence empirically does not rule out the iv catheter as a site of significant numbers of bacteria.

**Etiology**

The observation, however, that most isolates from iv catheters are of little clinical importance may explain the paradoxical impression conveyed in the literature of the high frequency of organisms recovered from iv catheters and the low rate of bacteremia. Of particular clinical importance with regard to etiology of iv catheter infection were the following observations: no probable infections due to skin flora occurred in the gentamicin-treated patients; and the use of sterile technique, consisting of scrubbing the skin with tincture of benzalkonium and using sterile gloves while starting the iv system, eliminated all probable infections. If the majority of iv catheter infections are not related to the patient's preexisting skin flora, and all significant infection can be prevented by the use of sterile technique (particularly sterile gloves), it would appear that contamination on insertion is the major source of infection. Thus, since most iv infections are not due to migration of skin flora down the course of the iv catheter, then, as reported in the literature, the local application of antibiotics will not and have not been efficacious. Two publications (8,9) in which the incidence of organisms recovered from iv devices were 3.8% and 5.2%, as opposed to the 30–78% range found in the antibiotic trial literature, were remarkable because these studies were conducted in hospitals in which an iv team started and maintained all iv systems. No antibiotics were applied in these two studies and contamination obviously was minimized.

In hospitals lacking iv teams where iv therapy is relegated to busy house officers and medical students, the importance of using aseptic technique in this procedure should be stressed.

**Prevention**

Only by identifying the role of the skin flora in producing infection, could conclusive results regarding the efficacy of local gentamicin in preventing iv infection be obtained. As in other studies, there was no overall statistically significant difference in infection rates between the gentamicin-treated group and the placebo group (Part II). However, with the opportunity in this study to compare etiology of probable infections as to the source of iv isolates, it was noted that infections due to skin flora were 36% and 0% for placebo vs gentamicin groups, respectively. Therefore, local gentamicin appeared to do the job of eliminating skin flora. Yet, the more important contamination factor would have concealed this effect if skin cultures were not taken.

There are three major trials of neomycin–polymyxin–bacitracin ointment to prevent iv infection in the literature. Norden (4) found that the daily application of this ointment increased the duration of iv catheterization but not the ultimate incidence of infection. There was a significant reduction in coagulase-negative *Staphylococcus albus* in the antibiotic group. Zinner *et al.* (5) studied the application of the same ointment every second day with no reduction in the rate of iv coloniza-
tion in the treated group. However isolates of Staphylococcus aureus and gram-negative rods "pathogens" appeared to be significantly decreased. Most disturbing, however, was the finding that 30% of the organisms isolated were resistant to the ointment in vitro.

Moran (3) demonstrated that the application of the same ointment to surgical iv cut-downs significantly reduced the infection rate from 78% to 18%. With the concepts derived from the present study, it may be possible to explain some of the contradictory data reported. The studies of Norden (4) and Zinner et al. (5) failed to identify the source of organisms isolated on iv catheter tips. Therefore, if it is assumed that contamination on insertion is a major factor in the ultimate recovery of organisms from iv catheters, and since all the studies were conducted in large, busy hospitals where the house staffs were responsible for iv therapy, it is likely that contamination of the iv system on insertion made the effect of local antibiotics negligible in preventing infection by skin flora. Similarly, the positive effect of Moran, Atwood, and Rowe (3) possibly can be explained by noting that the study was conducted on surgical iv cut-downs. According to their protocol, the prospective iv site was thoroughly shaved, scrubbed, and draped. The iv was inserted with sterile gloves. This surgical approach to the iv cut-down most likely eliminated the contamination factor on insertion. Therefore, local antibiotics were effective in decreasing skin flora as a source of iv catheter infection.

The crucial unanswered question from this report is the relative importance of possible or probable infection as a source of bacteremia, a recognized complication of prolonged iv catheterization (10). Only one case of bacteremia occurred in this study from a probable infection of a central venous catheter. In order to document statistically a significant difference in bacteremia as the result of probable vs possible infection, a much larger study is needed.

In conclusion, it can be stated that the majority of bacteriological isolates from the iv catheters are of little consequence. The single most important factor in preventing infection is sterile technique on insertion. Local antibiotics, in this case gentamicin cream, and possibly other ointments, if resistant organisms are not prevalent in a given hospital, will prevent only the minority of infections which are due to local skin flora. All iv devices should be removed as soon as possible, especially at the first sign of phlebitis. However, if prolonged iv catheterization is unavoidable, the local application of gentamicin will prevent the few infections of iv catheters due to skin flora.

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