Pathogenesis of Infections Related to Intravascular Catheterization

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EPIDEMIOLOGY

Just a few decades ago, every venous cannulation was something of an adventure for hospitalized patients. Steel "butterfly" needles posed little infection risk but provided relatively insecure venous access and had to be changed frequently. Short plastic cannulae were more reliable, but these stiff, thick-walled polyvinyl chloride devices were associated with high rates of phlebitis, local infection, and bacteremia (62, 69, 105, 107, 108, 112, 130). When peripheral veins in the arm were exhausted, physicians often resorted to a venous "cut down" or femoral venous catheterization, both of which were associated with infection risks that would be considered intolerable today (8, 129). Patients were also at risk for septicemia caused by contaminated intravenous fluids, although the medical community was largely unaware of this problem until the early 1970s, when a nationwide epidemic of infusion-related infection was traced to contamination of fluids at the time of manufacture (58, 103, 114, 115, 149, 166).

The past decade has witnessed impressive technological advances in intravenous therapy. Improved manufacturing practices for large-volume parenteral fluids have substantially reduced the risk of contamination. There have also been remarkable improvements in catheter design and materials. Stiff, relatively thrombogenic and infection-prone materials, such as polyvinyl chloride, have been largely replaced by smoother, more pliable, considerably less reactive plastics such as Teflon and silicon elastomer. Central venous catheters can be left in place for months and even years with acceptable complication rates (see below). Thus, patients who would have died of malnutrition in years past can now be supported indefinitely by intravenous infusions. Conditions that used to require lengthy hospitalizations for intravenous therapy can now be treated safely in the home. It is in this context that the current risk of infusion-related infection must be judged. Lives are being saved by aggres-sive, prolonged use of intravascular devices, but the increasing use of these catheters in patients who are older, sicker, and more immunosuppressed has led to serious infectious and noninfectious complications and substantial morbidity and mortality. Although the noninfectious complications have received scant attention in the literature, particularly compared with the many hundreds of papers devoted to infusion-related infection, the risk of perforation of the heart or great veins, pneumo- or hemothorax, and central venous thrombosis is well known to intensivists and surgeons.

It has been estimated that 50,000 to 120,000 patients in the United States develop nosocomial infusion-related bacteremia annually (107, 159). Data from the National Nosocomial Infections Surveillance (NNIS) System of the Centers for Disease Control (CDC) indicate that primary (not secondary to infection at another anatomical site) bloodstream infections, which usually are attributable to intravenous therapy, account for 8% of all nosocomial infections and rival nosocomial pneumonia in terms of cost and morbidity (68, 85, 106, 162, 181, 192). The incidence of nosocomial primary bloodstream infection, expressed as the number of infections per 1,000 discharged patients, increased steadily throughout the 1980s in all types of U.S. hospitals (Fig. 1) (11). Recognizing that only patients with catheters could be at risk for catheter-related infection and that the magnitude of this risk was associated with the duration of vascular cannulation, CDC investigators decided to express infection rates in terms of days of catheterization instead of the number of discharged patients. Using this refined measurement technique, intensive care unit (ICU) patients were found to be at particularly high risk for infection, and not surprisingly, the vast majority of ICU bacteremias were associated with central venous catheters. The infection rate varied dramatically depending on the type of ICU in which patients were hospitalized, ranging from a median of 2.1 per 1,000 central-catheter days in respiratory ICUs to 30.2 per 1,000 central-catheter days in burn units (Fig. 2) (134). In patients without central catheters, median rates ranged from 0 to 2.0 bacteremias per 1,000 days, a highly significant difference.

The incidence of bacteremia also varied considerably from
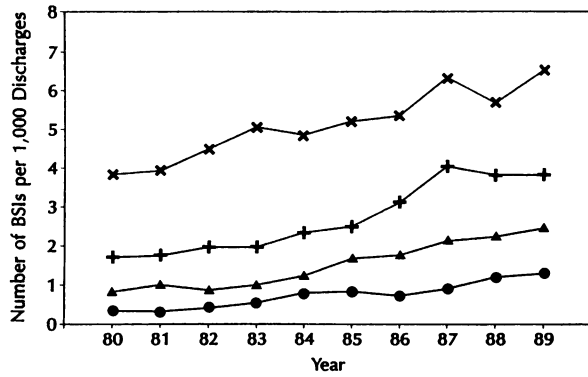
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FIG. 1. Secular trends in the primary bloodstream infection (BSI) rate for all pathogens by hospital stratum. Symbols: ●, small nonteaching hospitals; ▲, large nonteaching hospitals; +, small teaching hospitals; ×, large teaching hospitals. Reproduced from reference 11 with permission.

hospital to hospital (134). For example, among 21 pediatric ICUs, incidence ranged from <3 to 27 central line-associated bacteremias per 1,000 central-line days. Adequate studies to determine whether these remarkable statistics reflect differences in the severity of illness of patients cared for in these units or variations in infection control practices and quality of care have not been performed. In fact, such interhospital comparisons of nosocomial infection rates, which have been advocated and pilot tested by the Joint Commission on Accreditation of Health Care Organizations (91), must be interpreted with extreme caution because existing surveillance data are inadequate to permit adjustment for potential confounding variables. The significance of failing to adjust infection rates for confounding variables, such as severity of illness, catheter type, and the specific infusion therapy being administered, is discussed in greater detail below.

There has been a gradual change in the spectrum of pathogens isolated from patients with infusion-related bacteremia. The incidence of infection caused by gram-negative rods has remained relatively stable over the past decade, but the incidence of primary bacteremia due to gram-positive bacteria, particularly *Staphylococcus aureus*, coagulase-

FIG. 2. Median central line- and non-central line-associated bloodstream infection rates by ICU type, October 1986 through December 1990. Reprinted from reference 134 with permission.

negative staphylococci (principally *Staphylococcus epidermidis*), and enterococci, has increased significantly. For example, in large NNIS teaching hospitals, the incidence of bacteremia caused by coagulase-negative staphylococci increased by 754% between 1980 and 1989, and the incidence of *S. aureus* and enterococcal bacteremia increased by 176 and 120%, respectively (11). In addition, the incidence of primary bloodstream infection caused by *Candida* spp. increased in all hospital types, with the greatest increase (487%) occurring in large teaching hospitals. This trend is particularly alarming since hospital-acquired candidemia is associated with an attributable mortality rate of 38% and an excess length of hospital stay of 30 days (193). In contrast, the incidence of primary gram-negative rod bacteremia in teaching hospitals has been virtually unchanged over the 10-year period. Although these trends have been attributed to increased use of intravascular catheters and decreased contamination of parenteral fluids, the explanation probably is much more complex, with changes in the patient population, hospital environment, and medical practice as well as in the microbes themselves all playing a role.

SOURCES OF MICROORGANISMS CAUSING INFUSION-RELATED INFECTIONS

Contaminated Infusion Systems

The infusion system is vulnerable to microbial invasion via numerous routes: intrinsic contamination of infusate during manufacture; contamination of additives, piggyback infusions (including blood products), or in-line injectables; cracks in intravenous bottles or punctures in intravenous bags; attachment of bags or bottles to administration sets; changes of administration sets; manipulation of stop cocks, connections, and filters; retrograde contamination of fluid from contaminated catheters; and violation of system integrity to obtain blood or to irrigate occluded cannulae (70, 105, 112). Fastidious technique must be used when setting up or manipulating intravenous systems or preparing intravenous solutions for administration. Introduction of even small numbers of microorganisms can have dire consequences, because intravenous fluids provide a surprisingly hospitable environment for the growth of many pathogens. Knowledge of which solutions support the growth of which specific pathogens is crucial for epidemiological investigations and clinical decisions. For example, *Klebsiella*, *Enterobacter*, and *Citrobacter* species proliferate rapidly in 5% dextrose in water at room temperature despite this solution's acidic pH and lack of nutrients, whereas staphylococci, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Candida* spp. do not (114). Pseudomonads are able to grow in particularly adverse environments, including distilled water, normal (0.9%) sodium chloride, and even iodophor antiseptics (12, 60, 84, 104). *Candida* spp. grow well in protein hydrolysate solutions but much less vigorously in the synthetic amino acid mixtures used for hyperalimentation today (61); bacterial growth generally is suppressed in synthetic amino acid solutions. Lipid emulsion supports the rapid growth of a wide variety of bacterial and fungal pathogens, including *Candida* (35, 55, 126) and *Malassezia* spp., especially *Malassezia furfur* (6, 100, 155).

Except for a few little publicized clusters of infection, the dangers of intravenous fluid contamination were largely ignored until 1970 to 1971, when a massive nationwide epidemic of infusion-related septicemia was traced to 5% dextrose in water produced by a single manufacturer (103,
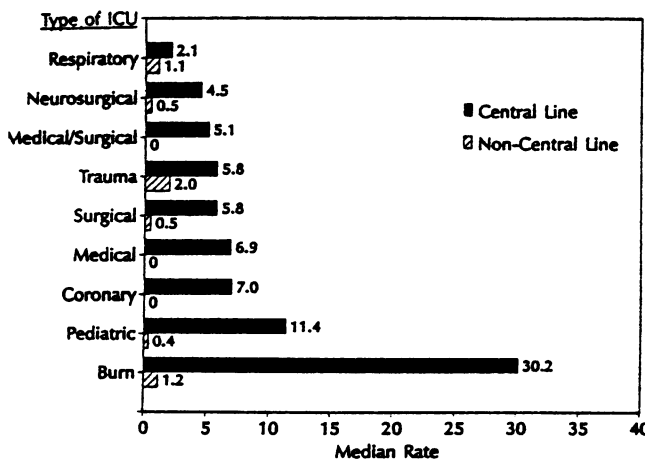
114, 115). The true extent of the outbreak still is unknown, but 25 hospitals in CDC's NNIS system reported approximately 400 cases of bacteremia caused by *Enterobacter agglomerans* and *Enterobacter cloacae* (115). The predominance of *E. agglomerans*, a sugar cane pathogen, in this outbreak was particularly noteworthy. Investigation by the CDC revealed that the onset of the epidemic coincided with introduction of a new elastomer-lined, screw-cap closure system. Bacterial strains implicated in the epidemic were found throughout the manufacturing plant and gained access to the interior of the screw-cap via cooling condensate after autoclaving (103). Hospital personnel inoculated these bacteria into intravenous fluid bottles while inserting ("spiking") administration sets. Within 24 h, concentrations of bacteria in the bottles exceeded 10^6/ml, causing fulminant septicemia even in patients with no serious underlying condition. It is interesting to note how few young physicians and nurses are familiar with this outbreak, which had a profound effect on manufacturing practices and hospital infection control at the time. Presumably, the absence of major outbreaks in the United States for almost 2 decades coupled with stricter manufacturing standards have led to justifiable complacency. On the other hand, lessons learned in the United States are not always absorbed worldwide. A decade after the U.S. outbreak, a virtually identical problem was reported from Aghia Sophia Children's Hospital in Athens, Greece (125). The cast of characters was the same: 63 children with unexpected *E. agglomerans* and *E. cloacae* bacteremias, the screw-cap bottle, and a contaminated manufacturing plant.

Whether intravenous fluid manufacturers have immunized themselves against future contamination problems remains to be seen, but in-use contamination of infusion systems remains a threat. Fortunately, careful handling of infusion systems is so well integrated into standard nursing practice that contamination of in-use fluids occurs very rarely (7, 17). When contaminants are detected, they tend to be microorganisms of low virulence that do not proliferate readily in intravenous solutions. Accordingly, expensive recommendations that intravenous administration sets should be changed every 24 h to preclude excessive buildup of contaminants have been relaxed to permit changes every 48 to 72 h (7, 17, 18, 63, 110, 177). Since every manipulation of the system provides an opportunity for contamination, it is reasonable to consider even longer intervals between changes.

Scrupulous attention to aseptic technique can reduce the risk of infusion contamination substantially, but on the basis of recent experience, hospital epidemiologists may still be in for occasional surprises. A fascinating example of creative sleuthing was reported recently by Maki et al. (113). The investigation was launched after three patients developed postoperative bacteremia due to *Pseudomonas pickettii*. Serendipitously, nearly 1,000 cultures of in-use intravenous fluid had been performed during this period as part of an unrelated study. *P. pickettii* was recovered from fluids given to two of the three bacteremic patients as well as from infusions administered to six patients who did not become ill. All nine patients had received intravenous fentanyl during surgery, and it was discovered that the fentanyl had been contaminated when a drug-abusing pharmacy technician removed the drug from predrawn syringes and replaced it with distilled water contaminated with *P. pickettii*. Infusion-related outbreaks can be caused by technical problems as well as mischief. For example, a cluster of *Candida parapsilosis* bloodstream infections was attributed to back-

flow of yeast cells into total parenteral nutrition solutions when a vacuum pump was used inappropriately (180).

Catheter Contamination

While sporadic epidemics due to contaminated infusions undoubtedly will continue to occur, the vast majority of endemic infusion-related infections are caused by catheter contamination (62, 69, 105, 107, 108, 112). Despite the passage of time, a much reproduced drawing by Maki still serves to summarize the principal routes by which microorganisms are believed to reach the catheter (Fig. 3) (107). However, investigators from Barcelona, Spain, have suggested that this figure omits an additional route of catheter-related infection: contamination of the catheter hub (45, 99, 175). In one study of 135 subclavian catheters, 14 (70%) of 20 episodes of bacteremia were thought to have originated from a contaminated hub, with secondary colonization of the catheter tip (99). In an earlier report, an outbreak of bacteremia caused by coagulase-negative staphylococci was attributed to manipulation of colonized hubs by the nursing staff (175). Problems at the junction of the administration tubing and catheter hub may have contributed to two other clusters of bacteremia caused by coagulase-negative staphylococci (39, 142). Most recently, Fan et al. found the positive and negative predictive values of hub surveillance cultures for catheter-related bacteremia to be slightly better than those of skin cultures at the catheter site (45), and Sitges-Serra and Linares have advocated obtaining a swab of the inner surface of the catheter hub for Gram stain and culture to identify patients infected via this route (174).

Since catheter hubs have been cultured systematically in very few studies, the relative importance of hub contamination is unclear. However, Maki's group has suggested that hub contamination plays a minor role. In an investigation of pulmonary artery Swan-Ganz catheters, positive hub cultures were found in only 7% of catheters (127). In another study of central venous and arterial catheters, the rate of hub colonization ranged from 1.9 to 5.7% (117).

Additional studies of hub contamination clearly are warranted, but the data presented so far have done little to alter the consensus that most infusion-related infections result from contamination of the catheter itself during insertion and subsequent care. A considerable body of epidemiological and microbiological data suggests that microorganisms at the insertion site track into the catheter wound and quickly colonize the intravascular segment of the catheter. Migration of bacteria down the external surface of the catheter can occur with startling speed (33), suggesting that the fate of many catheters is sealed the moment they are inserted. The origins of these microorganisms are diverse (Fig. 3). In some cases, the organisms are inoculated directly onto the insertion site by the application of contaminated antiseptic. As noted previously, pseudomonads can survive in the iodophor antiseptics that are in widespread use today (12, 60, 84), but contamination of antiseptics was an even greater problem in the past, when insertion sites were prepared with agents such as aqueous benzalkonium chloride, which supported the growth of many gram-negative pathogens (41, 51). Microorganisms can also be transported to the catheter wound by the contaminated hands of hospital personnel, who often fail to stop at the sink even when caring for high-risk patients in ICUs (1, 64). In addition, the catheter wound may be contaminated endogenously by microorgan-

CONTAMINATED
DISINFECTANTS

HANDS OF
MEDICAL PERSONNEL

AUTOINFECTION

CONTAMINATED
HUB

External
Spread

Hematogenous
Seeding

PATIENT'S
MICROFLORA

SKIN

VEIN

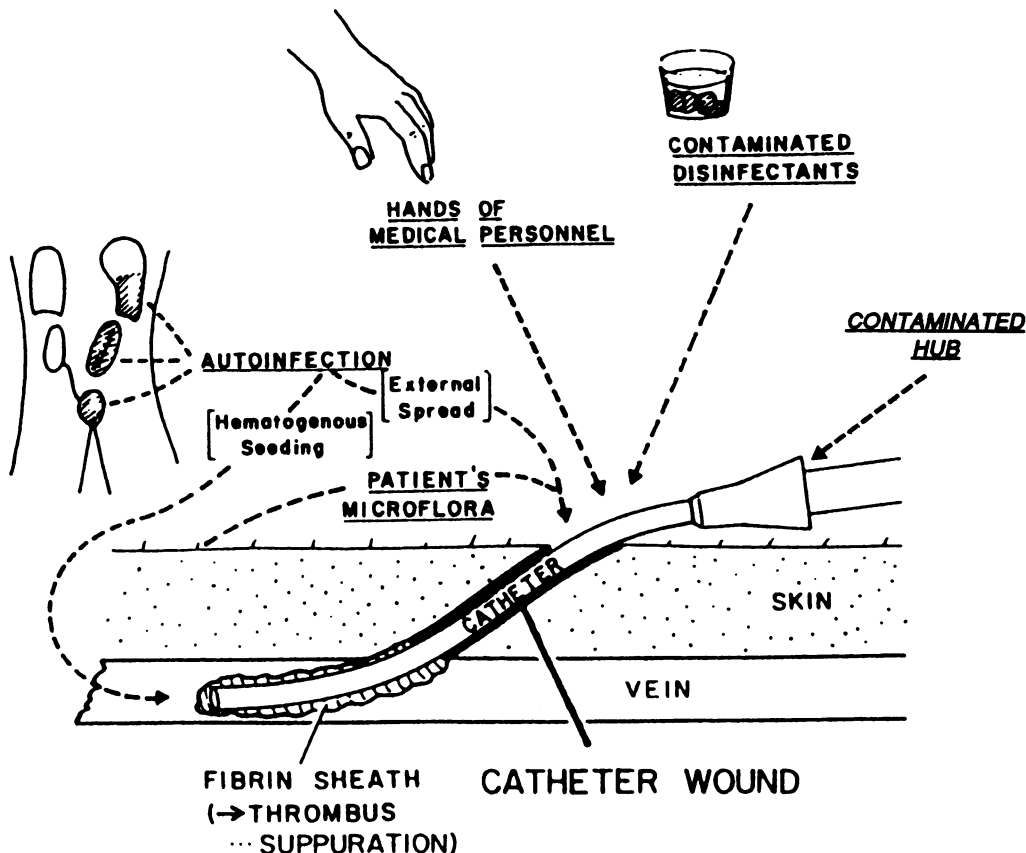FIBRIN SHEATH   CATHETER WOUND
(→THROMBUS
··· SUPPURATION)

FIG. 3. Sources of catheter-related infections. Adapted from reference 107 with permission.

isms colonizing other body sites, such as the respiratory and gastrointestinal tracts. This is particularly likely to occur when personnel neglect to interrupt their routine patient care activities to wash their hands before touching the catheter site. It is sobering to recall how heavily patients are colonized with nosocomial pathogens. For example, the stool of ICU patients frequently contains $>10^8$ CFU of hospital-acquired gram-negative bacilli per g (57). Even if personnel are careful, the risk of infection is sometimes, but not inevitably (90, 135, 194), higher when catheters are placed in skin sites that are prone to heavy contamination, such as the neck of a patient with a tracheostomy or the groin (8, 128, 129). An extraordinary level of care is required to isolate the catheter site from the adjacent sea of microorganisms in such cases.

While all of these routes of catheter contamination are noteworthy, none rivals the importance of the patient's own cutaneous flora at the catheter insertion site. It is no accident that coagulase-negative staphylococci, the principal components of normal skin flora, are recovered so frequently from colonized catheters and patients with catheter-related bloodstream infections. Most investigators have found an excellent correlation between the results of cultures of insertion sites and cultures of catheters (5, 13, 178, 195). For example, Snydman et al. found that the results of skin cultures taken within 1 week prior to removal of catheters used for total parenteral nutrition were highly predictive of the results of semiquantitative catheter cultures (predictive value of a negative skin culture = 98%; predictive value of a positive culture = 61%) (178). In every case of significant catheter

colonization, at least one of the organisms found on the catheter was also present at the skin site. Similarly, Armstrong et al. reported that catheter infection (defined by semiquantitative catheter culture) was highly correlated with a positive insertion site culture (relative risk = 4.5) (5), and Bjornson et al. documented an association between catheter colonization and growth of $>10^3$ CFU from cultures of the insertion site (13). By using stepwise logistic regression (120), Maki and Will found that heavy skin colonization was associated with both central venous catheter infection (odds ratio = 9.5) and bacteremia (odds ratio = 9.2). Positive skin cultures also are associated with colonization of peripheral intravenous catheters (116). Although none of these investigators used the molecular techniques required to prove that strains isolated from skin and catheter were identical, plasmid profiles of S. epidermidis isolates from the skin and bloodstream of critically ill neonates were similar in one study (189).

Additional support for the theory that microorganisms generally contaminate the intravascular catheter segment by migrating from the skin into the catheter wound comes from microbiological studies of the surface of colonized cannulae. If this hypothesis is correct, then the microorganisms responsible for catheter infection and bacteremia should be found primarily on the external surface of the catheter. Quantitative cultures of the catheter surface might be expected to predict which catheters are truly infected and are likely to spawn bloodstream infections. Indeed, Maki et al. have demonstrated that catheter-associated infections can be diagnosed relatively simply by rolling the intravascular or

intracutaneous segment of the catheter across an agar plate and counting the resulting number of colonies (118). In Maki's studies, growth of >15 colonies was associated with bacteremia in 10 to 14% of cases (118), whereas growth of <15 colonies or isolation of microorganisms only by non-quantitative broth culture of catheters rarely indicated that the catheter was responsible for bacteremia. Numerous investigators have studied more cumbersome catheter culture techniques, including quantitative cultures of sonicated, vortexed, rinsed, or flushed catheters and Gram stain of impression smears (16, 27–30, 148, 170), but Maki's method remains in wide use because of its simplicity and relatively good predictive values. However, one novel approach deserves mention. Cooper and Hopkins noted that catheters colonized with significant numbers of organisms by Maki's criteria could be identified expeditiously by Gram staining the external surface of the catheter (sensitivity = 100%; specificity = 97%) (32). In only 4 of 41 colonized catheters were microorganisms visualized on the internal surface of the catheter by Gram stain, and in all of these cases, far greater numbers of microorganisms were present on the external surface. Acridine orange staining of catheter tips may also be used to detect catheter colonization directly (34, 198).

Since growth of microorganisms on the skin is so critical to the pathogenesis of catheter-associated infection, it is hardly surprising that so many new products and techniques have been designed either to reduce the microbial burden at the insertion site or to interdict the migration of microorganisms into the catheter wound. Many of the studies that have tested the efficacy of these innovations have provided additional evidence of the role of skin flora in catheter colonization and infection.

At least one of these technological "advances" apparently has misfired. Semipermeable transparent dressings, although considerably more expensive than gauze, were thought to be worth the cost because they would facilitate frequent inspection of the catheter site for signs of inflammation without removal of the dressing. Although initial trials suggested that transparent dressings could be left in place for a week or more if no inflammation was detected, most studies have found that transparent dressings promote microbial growth on the underlying skin, which in turn is associated with an increased risk of catheter colonization (75, 186). In one randomized trial (31), 7 (16.6%) of 42 patients with transparent dressings developed catheter-associated bacteremia compared with 0 of 34 patients with gauze dressings ($P = 0.015$). These findings have been supported by a recent meta-analysis (75).

If proliferation of organisms on the skin leads to catheter contamination, then use of effective skin antiseptics or antimicrobial ointments would be expected to reduce the risk of infection. Given the frequency, morbidity, and cost of catheter-associated infections, it is surprising how few careful studies of these simple interventions have been performed. Most studies of antimicrobial ointments were performed more than 20 years ago and are virtually irrelevant in light of subsequent changes in intravenous infusion technology. At best, these studies suggest that ointment containing polymyxin, bacitracin, and neomycin delays but does not prevent contamination of peripheral cannulae (109, 138, 197). However, there has been concern that such topical antibiotics might encourage the overgrowth of Candida spp. Povidone-iodine, which remains in widespread use, was marginally effective in one study (109) but ineffective in another small trial (156). Recently, mupirocin (pseudomonic

acid) ointment, which has excellent antistaphylococcal activity, was shown to have a beneficial effect on central venous catheter colonization when applied to the insertion site (73, 74). In control patients, ≥15 CFU were found on 17% of catheters removed within 24 h, on 35% removed within 48 h, and on 66% removed within 120 h. Colonization rates in patients treated with mupirocin were 3, 10, and 0%, respectively. Unfortunately, a sterile preparation of mupirocin is not yet available in the United States.

An important recent study demonstrated that the antiseptic used to prepare the skin for catheter insertion and to clean the catheter site can have a profound effect on the risk of subsequent infection. Maki's group randomized 668 central venous and arterial catheters into three antiseptic treatment groups: 10% povidone-iodine, 70% alcohol, and 2% aqueous chlorhexidine gluconate (a preparation that is not available in the United States) (117). Antiseptic was used at the time of insertion and every 48 h thereafter when gauze dressings were changed. Chlorhexidine was associated with the lowest rate of catheter colonization (2.3% compared with 7.1% for alcohol and 9.3% for iodophor) and catheter-associated bacteremia (0.5, 2.3, and 2.6% respectively) (117). The superiority of the chlorhexidine preparation was attributed to its broad-spectrum antimicrobial properties and its prolonged residual activity on the skin.

For many years, central venous catheter design has emphasized physical barriers to microbial penetration of the catheter wound. Both the Broviac catheter, which was introduced in 1973 (15), and the Hickman catheter (introduced in 1979) (72) were designed to impede migration of bacteria toward the intravascular catheter segment by a combination of subcutaneous tunnelling of the catheter and use of a built-in catheter cuff. In addition, both catheters were made of silicon elastomer in the hope that this smooth, flexible material would be less irritating to the veins, less thrombogenic, and less likely to provide a nidus for colonization and infection. Although the relative roles of catheter material, catheter cuff, and subcutaneous tunnelling are unknown, there is no doubt that these catheters revolutionized intravascular therapy by providing secure, prolonged venous access with an acceptable risk of infection, especially when considered in terms of risk of infection per day of catheterization (37, 186).

If tunnels and cuffs provide good protection against catheter contamination, total implantation of the catheter system, including the injection port, beneath the skin should be even safer. Several commercial products are available, each with an injection reservoir that is implanted surgically into a subcutaneous pouch in the thoracic wall. The injection port is attached to a silicon elastomer catheter that is tunnelled into a large vessel. Infusions are administered by percutaneous insertion of a needle through the silicon membrane of the port. Theoretically, skin microorganisms might track along the needle into the port while the system is in use, setting up a difficult-to-treat reservoir infection. However, if the needle is inserted with aseptic technique and removed as soon as the infusion has been completed, infection occurs infrequently. A recent review of 10 studies of totally implantable catheters by one of us (D.A.G.) (186) revealed infection rates ranging from 0 to 0.10 infection per 100 catheter days, with several investigators reporting rates as low as 0.04 to 0.06/100 days. These rates are approximately one-third those reported for externalized tunnelled lines. In one study that directly compared the two types of catheter systems, there were 0.13 exit site infection and 0.03 episode of bacteremia per 100 catheter days in patients with externalized lines

versus 0.06 pocket infection per 100 days and no bacteremias in patients with totally implantable lines (163).

Tunnelled catheters such as those described above are suitable for patients who need chronic venous access, but since surgery is required, they are not appropriate for patients who need only short-term therapy via a central line. Since percutaneous central venous catheters have been associated with high rates of infection, particularly in ICU patients, there has been an effort to incorporate some of the features of tunnelled lines into the design of these catheters. For example, one manufacturer has developed a silver-impregnated collagen cuff that can be attached to a percutaneous central venous catheter at the time of insertion. This cuff not only forms a physical barrier to skin organisms, similar to the cuffs of Hickman and Broviac catheters, but also provides an antimicrobial barrier because of the broad-spectrum antimicrobial activity of silver. Two groups of investigators demonstrated an impressive, statistically significant reduction in catheter colonization when cuffed catheters were compared with conventional lines (50, 111). There was also a trend toward fewer bacteremias in the patients who received cuffed catheters.

Some investigators have advocated a last-ditch defense should all of these strategies fail to halt the entry of microorganisms into the catheter wound: impregnation of the catheter itself with antimicrobial agents. Noncovalent bonding of antibiotics to plastic catheters has been associated with reduced risk of catheter colonization in laboratory animals (187), and loading of polyurethane catheters with a hydrophilic coating with teichoplanin has eliminated adherent bacteria from the catheter surface in vitro (86). In a recent randomized trial in humans, Kamal et al. found that catheters treated with a cationic surfactant and then dipped in cefazolin (an anionic antibiotic) were associated with a 2% rate of colonization compared with a 14% rate of colonization with untreated catheters (89). Unfortunately, the control catheters were not treated with surfactant, so the independent effect of the cefazolin is unclear. Moreover, cefazolin would be ineffective against oxacillin-resistant staphylococci, which are prevalent in many ICUs. Maki et al. have attempted to overcome the disadvantage of using a narrow-spectrum antibiotic by testing a catheter impregnated with silver sulfadiazine and chlorhexidine gluconate (119). Although antiseptic-treated catheters were twofold less likely to be colonized and fourfold less likely to be associated with bacteremia, further study is needed before the general use of such catheters can be endorsed. Alternative technologies for bonding antimicrobial agents to catheter materials are being explored (83). Some investigators have suggested the simpler approach of dripping low concentrations of antibiotics, such as vancomycin (169), through the catheter, but this strategy seems foolhardy, since it would provide selective pressure for the further emergence of vancomycin resistance among nosocomial gram-positive cocci.

As shown in Fig. 3, one additional mechanism of catheter colonization requires consideration: hematogenous seeding of the catheter tip by bacteremia from a distant site of infection. Catheter colonization is thought to be facilitated by the presence of a fibrin sheath that develops on the intravascular surface of the catheter shortly after insertion (79, 95, 105, 120, 147, 148, 182, 190). Hematogenous seeding almost certainly occurs, but far less frequently than contamination via the catheter wound.

FACTORS INVOLVED IN THE PATHOGENESIS OF CATHETER-RELATED INFECTION

The Host

The underlying condition of the patient influences the risk of infusion-related infection. Malignancy, immunodeficiency, severe burns, and malnutrition, all problems that compromise host defenses, lead to a higher rate of infection. For example, a number of recent reports have emphasized the relatively high rate of infection in AIDS patients with long-term central venous catheterization (56, 157, 176). However, studies to quantify the precise magnitude of the risk associated with specific host impairments have not been performed, and the relative contributions of the patient's condition, type of catheter, duration of catheterization, preexisting infections, and concomitant therapies remain to be elucidated.

Some progress in developing measures of underlying illness severity, particularly in ICU patients, has been made, and it will be important for investigators of catheter-associated infections to consider these developments when designing future studies. Interpretation of nosocomial infection rates is difficult without information concerning the nature of the ICU population under study, and comparison of rates among ICUs is simply impossible without controlling for confounding due to underlying severity of illness. Severity scoring systems are available for patients of all ages. The APACHE (Acute Physiology and Chronic Health Evaluation) score, which is now in its third version, is used internationally and has proved to be quite reliable in estimating the risk of mortality under most circumstances (92). PSI (Physiologic Stability Index) (154) and its streamlined revision, PRISM (Pediatric Risk of Mortality) (153), are suitable for routine use in pediatric ICUs. For example, Pollack's group used PSI to demonstrate that large differences in mortality rates among pediatric ICUs could be attributed almost entirely to differences in the severity of illness of patients in these units (152). Recently, our group has developed two scales for use in neonatal ICUs. One of these scoring systems (SNAP [Score for Neonatal Acute Physiology]) measures physiologic derangements present within 24 h of birth (161). The other (NTISS [Neonatal Therapeutic Intervention Scoring System]) measures the intensity of therapies required by babies in the first day of life (67). Both SNAP and NTISS predict mortality risk very well, and both improve prediction models based on birth weight alone.

Although the utility of these severity scoring systems in predicting mortality is widely acknowledged, it is important to recognize that their abilities to predict other adverse outcomes of hospitalization, such as catheter-associated infection, remain virtually unknown. Only one published study has examined the correlation between a severity scoring system and nosocomial infection risk (151). Pollack et al., in Toronto, Ontario, Canada, demonstrated that pediatric ICU patients with a PRISM score of >10 on admission were three times more likely to develop a nosocomial infection than children with lower scores (10.8 versus 3.4%). The hazard of comparing hospital infection rates without adjusting for severity of illness is all too clear, as demonstrated by the NNIS data on catheter-associated bacteremias mentioned above (134). For example, the NNIS investigators suggested that the wide disparity in ICU bacteremia rates that they documented required a careful examination of practices and procedures in individual units. However, these infection rates were not adjusted for under-

lying severity of illness or even for specific types of central catheters. Neonatal ICU infection rates were only crudely stratified by birth weight (1,500 g) despite abundant evidence that risk increases dramatically and progressively only at birth weights below 1,500 g (54, 59).

While concentrating on the role of the catheter itself in the pathogenesis of infusion-related infection, investigators have tended to overlook the influence of the therapy delivered through the catheter on the risk of infection. Sometimes the effect is so dramatic that it is recognized with ease. For example, when 12 of 107 patients receiving interleukin-2 therapy for cancer developed central venous catheter-associated bacteremia, Snydman's group quickly realized that this rate of infection was considerably greater than the incidence of bacteremia in the ICU (4.1%), among patients with solid tumors (1.9%), or among patients receiving total parenteral nutrition (2.8%) (179). A strong association of S. aureus bacteremia with preceding S. aureus colonization of the catheter site and interleukin-2-associated skin desquamation was noted. Other investigators have confirmed the increased risk of infection in patients receiving interleukin-2 via central venous catheters (14, 173).

The effect of concomitant therapy is not always so dramatic. For example, many investigators have maintained that the use of intravascular catheters, particularly central venous lines, is the major risk factor for bacteremia caused by coagulase-negative staphylococci in neonates (42, 96, 133). However, central catheters are used primarily in very low-birth-weight babies with prolonged hospitalizations in neonatal ICUs. After adjusting for these potential confounding variables, some groups could not confirm that the catheters themselves were independently associated with coagulase-negative staphylococcal bacteremia (48, 167). Instead, they demonstrated that the types of intravenous fluids administered to the babies were associated with infection. Recently, our own group performed a case control study in infants in our neonatal ICU, matching infants by birth weight and duration of exposure to the unit (53). We found that central venous catheters indeed were associated with coagulase-negative staphylococcal bacteremia (odds ratio = 3.5), but since central lines were used infrequently in the ICU, only 15% of bacteremias could be attributed directly to these catheters. In addition, we noted that intravenous infusions of lipid were independently associated with coagulase-negative staphylococcal bacteremia (odds ratio = 5.8), and since many babies received lipids, the attributable risk for lipids was 57%. Moreover, the risk of bacteremia was constant regardless of when lipids were administered during hospitalization, and the risk increased linearly with increasing duration of lipid infusion. Since pharmacy and ICU practices virtually precluded frequent contamination of the lipid, we hypothesized that infusion of lipid ignited the proliferation of bacteria that had already been deposited on the catheter, ultimately leading to bacteremia. The risk of bacteremia may also have been potentiated by the tendency of lipids to block flow through the catheter (143) and to impair the functions of neutrophils and macrophages (47).

An analogous situation may be found in the high rate of Malassezia furfur fungemia in neonates and older patients receiving lipids (6, 100, 155). M. furfur is known principally for its association with a relatively innocuous skin condition, pityriasis (tinea) versicolor, and for its strict growth requirement for fatty acids. This yeast grows exuberantly on the skin of hospitalized babies and can spread rapidly in a neonatal ICU (10). When lipids are infused through a con-taminated catheter, M. furfur fluorishes, leading to bloodstream invasion and even catheter occlusion (6).

Catheter Composition

A thorough review of catheter materials is beyond the scope of this paper. In general, manufacturers have tried to design catheters that do not provoke a host response, are not thrombogenic, do not irritate blood vessels, and have few surface irregularities in which microorganisms can lodge (see below). Catheters must be supple so that they can pass freely through the vasculature but not so flexible that they tend to kink. They should be easy to insert and hard to break.

None of the catheters now available commercially approaches perfection. However, enormous strides have been made, and today's catheter materials are far superior to the stiff plastics that dominated the market only a couple of decades ago. The profound decrease in the risk of infection associated with peripheral percutaneous intravenous cannulae provides a vivid example of the progress that has been made in a relatively short period. Twenty years ago, a review of infusion-related infection by one of us (D.A.G.) noted that peripheral catheters were associated with a high risk of phlebitis and infection, with infection rates ranging from 2 to 5% for catheters left in place for longer than 48 h (112). Just 10 years later, we reported that Teflon catheters were associated with a negligible rate of catheter colonization and no bacteremia if removed within 48 to 72 h and cared for by an intravenous therapy team (188). In a recent study of more than 2,000 short peripheral Teflon and polyurethane catheters, Maki and Ringer found no cases of catheter-related bacteremia even when catheters were left in place for more than 72 h (116). This improved safety profile may be explained not only by the smooth, pliable, relatively inert surface of these catheters but also by the fact that coagulase-negative staphylococci adhere less avidly to Teflon than to older catheter plastics such as polyvinyl chloride (171, 172). Even percutaneous midline catheters that are inserted in the arm but are long enough to reach the great veins appear to have a rather low infection risk and are now used extensively for home intravenous therapy, although rigorous studies of the safety of these catheters have not appeared in the literature.

Interaction between Microorganisms and Catheters

An astonishing array of microorganisms can cause catheter-related infections. In just the past 2 years, our clinical microbiology laboratory has identified catheter infections due to Rhodococcus spp., Mycobacterium avium-Mycobacterium intracellulare, Corynebacterium aquaticum, Corynebacterium sp. group D-2, Pseudomonas mesophilica, Pseudomonas putida, and Agrobacterium radiobacter, to name just a few of the more unusual pathogens.

By definition, all of these infections have one thing in common: the presence of a plastic intravenous catheter. Of course, a wide variety of plastics is used in catheter construction. Given this broad spectrum of pathogens and biomaterials, a unifying hypothesis for the pathogenesis of catheter colonization is likely to prove elusive. It seems safe to assume that the microbe-catheter interaction involves a series of interrelated steps, including adherence, persistence (colonization), and dissemination. In this paper, we illustrate these basic principles by reviewing the pathogenesis of catheter infections due to coagulase-negative staphylococci. The special properties of coagulase-negative staphylococci

FIG. 4. Scanning electron micrograph of coagulase-negative staphylococci adhering in vitro to imperfections in a polyvinyl chloride intravenous catheter (magnification, ×10,000). Reprinted from reference 52 with permission.

that allow them to adhere to, colonize, and infect plastic biomaterials have been the focus of intense study in recent years. Investigation of coagulase-negative staphylococci is particularly likely to be fruitful because these microorganisms, which are found universally in large numbers on normal human skin, almost never cause infection in the absence of a foreign body.

Adherence. Attachment of coagulase-negative staphylococci to plastic catheter materials occurs very rapidly. Within minutes of dipping a catheter into a broth culture of staphylococci, microorganisms clinging to the catheter surface can be visualized by electron microscopy (52, 146). Seen under the electron microscope, the surfaces of commercial catheters are far from perfect, and staphylococci tend to nestle in pits and crevices (Fig. 4) (52). Many investigators have postulated that extracellular slime is the specific adhesin responsible for this attachment of coagulase-negative staphylococci to plastic biomaterials. However, slime is not seen in electron micrographs taken very early in the colonization process and is more likely to be involved in persistence of staphylococci on the catheter surface than in initial adherence (see below). Other investigators have stressed the importance of nonspecific factors in attachment. Cell surface hydrophobicity has been evaluated extensively (40, 76–78, 97, 139, 144, 160). One group has claimed that measurement of hydrophobicity can predict the clinical significance of coagulase-negative staphylococcal clinical isolates better than any other laboratory test (124). While hydrophobicity may play a role in adherence, there is marked variation in hydrophobicity, not only among different strains of coagulase-negative staphylococci (including slime-producing strains) but even over the surfaces of individual bacteria (77, 97, 160). Moreover, hydrophobic strains vary considerably in their abilities to adhere to plastics (78).

Other nonspecific determinants of the interaction between coagulase-negative staphylococci and the catheter surface

may include long-range forces (London-van der Waal's electromagnetic forces of attraction), the free energy of bacterial surfaces, and the hydrophobicity ("wetability") of the catheter surface (40). The theory that hydrophilic catheters might be less prone to bacterial attachment has been particularly attractive to some manufacturers, although evidence that such plastics preserve their wetability in vivo or reduce the risk of infection is lacking.

Of course, any in vitro study of staphylococcal adherence to plastic catheters taken directly from the manufacturer's carton may not be relevant to the in vivo situation. Indeed, catheters are rapidly coated with host proteins such as fibrin, fibrinogen, and fibronectin once they are inserted into the vasculature (79, 145, 190). *S. aureus* binds avidly to fibronectin (49, 71, 190, 191), and there is considerable evidence that *S. aureus* infections of implanted foreign bodies are mediated by fibronectin. Thus, it has been tempting to speculate that adherence of coagulase-negative staphylococci also might be enhanced by proteins coating the catheter surface. Russell et al. found a modest increase in adherence of coagulase-negative staphylococci to polyvinyl chloride catheters that had been preincubated with fibronectin (165), and Vaudaux noted slightly enhanced adherence to intravenous catheters of unspecified material that had been removed from patients. They attributed this enhanced adherence to fibronectin (191). However, Pascual et al. detected no increased attachment to fibronectin-coated catheters (139). Moreover, recent studies by our group demonstrated that adherence of coagulase-negative staphylococci was inhibited by coating silicon elastomer catheters with fresh blood, plasma, and serum and with purified fibrin, fibrinogen, and fibronectin (Fig. 5) (131). The adherence of these coagulase-negative staphylococcal strains to Teflon catheters that had been inserted into volunteers for 5 min or 24 h was not significantly different from adherence to uninserted catheters; adherence of one of these three strains to

COATING OF
CATHETERS
WITH:

| | 0 50 100 150 200 | 0 50 100 150 200 |

TSB

Blood

Plasma

Serum

Albumin

Fibrinogen

Fibronectin

Fibrin
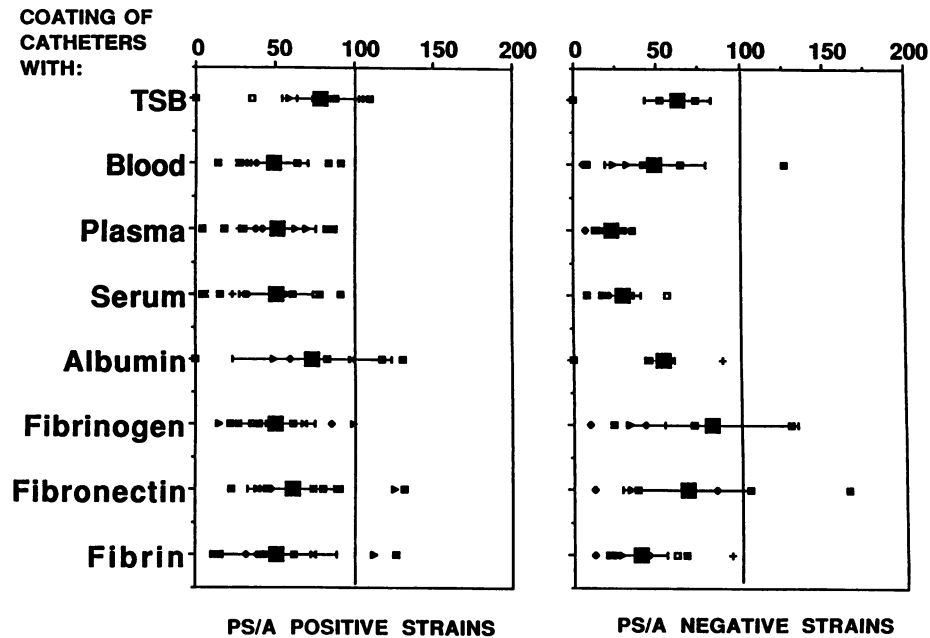
PS/A POSITIVE STRAINS   PS/A NEGATIVE STRAINS

FIG. 5. Inhibition of adherence of PS/A-positive and PS/A-negative strains of *S. epidermidis* to Teflon intravenous catheters by fresh blood, plasma, and serum proteins. Individual symbols represent individual strains, and large boxes represent the means for all strains. Error bars indicate 95% confidence intervals. TSB, tryptic soy broth. Reprinted from reference 131 with permission.

catheters removed from patients was enhanced slightly (131).

While acknowledging that coagulase-negative staphylococci may have nonspecific surface properties that promote adherence to plastics, our group has been interested in defining specific components of the cell surface that mediate initial adherence to catheter materials. As we explored the role of slime in the pathogenesis of catheter colonization, we discovered that a slime-producing strain of *S. epidermidis* (RP62A) widely used to study staphylococcal adherence expresses a specific polysaccharide capsular adhesin (PS/A) (185). PS/A purified from strain RP62A and polyclonal and monoclonal antibodies raised against PS/A inhibited adherence of both the homologous strain and heterologous coagulase-negative staphylococcal strains to silicon elastomer tubing in a dose-response fashion (185). Screening of a large number of *S. epidermidis* clinical isolates revealed that almost all expressed a serologically related PS/A and that adhesin expression correlated poorly with slime production (185). Recently, Mack and his colleagues also described an *S. epidermidis*-associated polysaccharide that appears to mediate adherence and accumulation of cells on polymer surfaces (102).

These observations suggested that immunotherapy directed specifically against PS/A might be of value in the prevention of infection caused by coagulase-negative staphylococci by inhibiting adherence to foreign bodies (93). To investigate this possibility, we developed a rabbit model of intravenous catheter infection and bacteremia. Silicon elastomer catheters that had been dipped in an inoculum of PS/A-positive coagulase-negative staphylococci were inserted into the right jugular vein and kept open with heparin via a subcutaneous osmotic pump. Blood cultures were obtained for 8 days until the heparin in the pump was depleted. Nonimmune rabbits were bacteremic throughout the study period and had a strong immune response to

teichoic acid but not to PS/A. PS/A immunization (in complete Freund's adjuvant), but not teichoic acid immunization, reduced bacteremia significantly and prevented the immune response to teichoic acid seen in infected animals. Passive infusion of PS/A-specific polyclonal and monoclonal antibodies via a separate, uncontaminated catheter in the left jugular vein protected against both bacteremia and hematogenous colonization of the contralateral catheter. Protection was also seen when rabbits were challenged with a heterologous strain. In subsequent experiments, we also found that active and passive immunoprophylaxis against PS/A prevented *S. epidermidis* endocarditis in a rabbit model (183).

In these animal models, we were unable to determine whether protection was due to the antiadhesive properties of PS/A-specific antibody or to the opsonophagocytic effect of antibody on blood-borne coagulase-negative staphylococci. We speculated that PS/A might serve not only as a staphylococcal adhesin but also as a typical bacterial capsule, impairing host defense by interfering with phagocytic killing.

Although most investigators have lavished their attention on coagulase-negative staphylococcal slime and polysaccharide adhesins, some have started to explore the surface proteins of staphylococci. Patrick's group, for example, has identified 20 to 30 distinct proteins on the surface of coagulase-negative staphylococci; 5 to 10 of these proteins were immunogenic and were recognized by normal human sera (141). More to the point, Plaunt and Patrick demonstrated that pretreatment of coagulase-negative staphylococci with protease reduced adherence to plastic (150). Timmerman et al. described a 220-kDa protein antigen on the surface of a strain of *S. epidermidis* (strain 354, an isolate from a patient with catheter-related bacteremia) that appeared to be involved in adherence to polystyrene spheres (184). Monoclonal antibodies to the 220-kDa protein partially inhibited adherence, as did Fab fragments of monoclonal antibodies. Pretreatment of bacterial cells with protease and rifampin

also reduced adherence. Immunogold electron microscopy suggested that this protein antigen projects from the cell surface, but the information presented to date is insufficient to conclude that the protein is a fimbrial structure. Rupp and Archer (164) found that *S. epidermidis* isolates obtained from intravascular catheters and patients with prosthetic valve endocarditis were much more likely to cause hemagglutination of a panel of human and animal erythrocytes than isolates from the skin of preoperative patients. The ability of strains of *S. epidermidis* to cause hemagglutination also correlated with their ability to adhere to polystyrene. These investigators speculated that a protein on the surface of staphylococci is involved in hemagglutination and adherence, as has been observed in numerous bacterial interactions with mucosal surfaces.

One additional adherence mechanism of *S. epidermidis* also deserves mention, although it probably is of minimal importance in catheter-related infections. When there is a preexisting fibrin-platelet clot (for example, on a prosthetic heart valve), *S. epidermidis* adherence may be mediated by lipoteichoic acid (27). Conceivably, hematogenous seeding of the tips of indwelling intravascular catheters could be facilitated in this fashion.

Persistence, infection, and dissemination. As noted previously, many investigators have been intrigued by the abilities of some coagulase-negative staphylococcal strains, particularly those isolated from infected medical devices, to elaborate copious amounts of an extracellular material generally referred to as slime (20, 21, 24–26, 36, 38, 40, 52, 82, 94, 101, 105, 124, 144, 146, 158, 196). Credit for the discovery of the importance of slime in the pathogenesis of coagulase-negative staphylococcal foreign-body infection probably should go to Bayston and Penny, who examined infected cerebrospinal fluid shunts under the microscope and noted that microcolonies of staphylococci imbedded in a mucoid layer adherent to the surface of shunt valves could be visualized (9). Coagulase-negative staphylococci from these shunts produced a mucoid, slimy material that was thought to be a polysaccharide because it stained with alcian blue.

After a brief hiatus, investigation of the significance of slime production began in earnest, led by Christensen and his colleagues. These studies were facilitated by development of a simple macroscopic method for measuring slime production that was based on Christensen's observation that slime-producing strains left a film on the surfaces of plastic tubes that could be stained with alcian blue or safranin (24). A more quantitative measurement of slime production has been obtained by using spectrophotometry to measure slime deposition in tissue culture wells (26, 38) or by measuring cell-associated urease activity (43). Slime production can be influenced by the media and environmental conditions in which staphylococci are grown (81). Some investigators have claimed that phenotypic expression of slime can also be determined by growing coagulase-negative staphylococci on Memphis agar, which contains bromcresol purple (21), but we have found this technique to be unreliable for most strains.

Using its quantitative assay, Christensen's group found that slime producers constituted nearly two-thirds of clinically significant strains in an "outbreak" of *S. epidermidis* intravenous catheter-related infections but only one-third of alleged blood culture contaminants and skin isolates (23). Investigators at the University of Virginia noted that 91% of clinically significant blood isolates of coagulase-negative staphylococci elaborated slime. In conjunction with identi-

fication of an organism as *S. epidermidis*, slime production had a sensitivity of 93%, a specificity of 85%, and a positive predictive value of 87% (82). Similar results have been obtained elsewhere (36). It should be noted, however, that the decision as to whether a given isolate of coagulase-negative staphylococci is clinically significant remains somewhat arbitrary.

In an effort to provide more direct evidence that slime enhances the virulence of coagulase-negative staphylococci, some investigators have turned to animal models. Christensen's group, for example, found that strains of coagulase-negative staphylococci that produce copious amounts of slime are more likely than poor slime producers to cause catheter-associated tunnel infections in the flank of a mouse (25), although recent work has failed to confirm these findings (140). If slime is a true virulence factor, then when and how it has its effect were not clarified by these animal experiments.

In vitro and in vivo work has been hindered by a lack of isogenic mutants with stable expression or lack of expression of the virulence factors of interest. Christensen et al., for example, used a phenotypically weak slime producer rather than an isogenic slime-negative strain of coagulase-negative staphylococci in his experiments (25). More recently, Christensen et al. reported a spontaneous mutant and an acriflavin mutant of *S. epidermidis* RP62A that did not produce slime and appeared to accumulate more slowly on plastic surfaces (22). Our group has used transposon mutagenesis to obtain a slime-negative, PS/A-negative strain of *S. epidermidis* that adheres poorly to silicon elastomer in comparison with its parent strain (132).

If slime is involved in the pathogenesis of catheter-related infection, what, precisely, is its role? Examination of catheters exposed to slime-producing strains in vitro or removed from patients with catheter-associated infections suggests strongly that slime facilitates bacterial persistence and catheter colonization. Scanning electron micrographs of catheters dipped in suspensions of slime-producing strains of coagulase-negative staphylococci reveal that adherent staphylococci are coated with slime within a matter of hours (146). Eighteen hours later, microcolonies of staphylococci are virtually invisible beneath a thick blanket of slime (Fig. 6). Scanning electron micrographs of catheters removed from patients are equally compelling (52, 122), although it is unclear whether the biofilm (sometimes referred to as glycocalyx) enveloping the staphylococci is derived primarily from the bacteria or from the host's bloodstream. Exuberant biofilm formation has also been seen on infected cardiac pacemaker leads and power packs (121) and on peritoneal dialysis catheters (123).

Once *S. epidermidis* has taken up residence on the catheter surface, slime may play a role in helping the bacteria evade host defenses. Presumably, biofilm provides a nonspecific physical barrier to cellular and humoral defense mechanisms, but there may be more specific effects of slime as well. Johnson et al. demonstrated that pretreatment of human neutrophils with extracellular slime substance interfered with chemotaxis (88), although slime itself was chemotactic to neutrophils. It was also noted that slime stimulated the release of lactoferrin from neutrophil granules, leading Johnson et al. to speculate that degranulation might compromise the ability of neutrophils to kill catheter-associated staphylococci. However, the effect on lactoferrin release was modest and seen only with the highest concentrations of slime tested, while myeloperoxidase release was minimal. Despite these somewhat unconvincing results, Johnson's

FIG. 6. Scanning electron micrograph of coagulase-negative staphylococci adhering to a polyvinyl chloride intravenous catheter after incubation of the catheter for 18 h in vitro (magnification, ×10,000). Reprinted from reference 52 with permission.

group did find that *S. epidermidis* incubated for 18 h on a catheter surface to promote elaboration of slime was more resistant to phagocytosis than organisms grown for 2 h in broth (88), confirming the general principle that bacteria on a solid surface are more resistant to phagocytosis than freely suspended or planktonic organisms (87, 144). Noble et al. have also described slime factors that appear to be inhibitory to the bactericidal activities of neutrophils (136, 137).

In addition to its effect on neutrophil function, slime may interfere with lymphocyte activity (65, 66, 145). For example, slime has been reported to inhibit T- and B-cell blastogenesis and immunoglobulin production. However, crude slime preparations were used in these experiments, and it is not clear whether the observed effects were due to slime itself or to the well-known immunomodulating properties of teichoic acid (19), a prominent constituent of crude slime (80, 185).

Slime also may impair the abilities of antibiotics to kill coagulase-negative staphylococci, particularly when microcolonies of staphylococci are imbedded in a thick biofilm on a catheter surface (2, 3, 4, 44, 46, 98). A combination of factors may contribute to this reduced antibiotic effect. Biofilm may act as a diffusion barrier, reducing the effective concentration of some antibiotics at their sites of action. In addition, antibiotics that have excellent MBCs when tested against log-phase broth cultures in the clinical laboratory may be much less active when faced with sessile, slowly growing, nutritionally deprived bacteria on a catheter surface. Accordingly, Costerton and others have suggested that routine laboratory testing is inappropriate for foreign-body infections and have proposed alternative testing systems that more closely mimic the interaction of antibiotics and bacteria in a biofilm (2, 4). However, despite these theoretical considerations and some supporting experimental data, most bacterial intravascular catheter infections, especially if

caused by coagulase-negative staphylococci, can be eradicated with a 10- to 14-day course of an antibiotic chosen on the basis of conventional susceptibility testing (186).

Little is known about effective host defenses against catheter-associated infections caused by coagulase-negative staphylococci. As noted above, immunocompromised patients such as those with AIDS are at increased risk of infection. Schutze et al. suggested that premature neonates might be more susceptible to bacteremia caused by coagulase-negative staphylococci than term infants or adults because their neutrophils are less efficient at phagocytic killing (168). Those investigators also demonstrated a role for antibody and complement in opsonic killing of coagulase-negative staphylococci. Antibody to Fc receptors blocked phagocytosis of coagulase-negative staphylococci, whereas antibody to complement receptors 1 and 3 did not. However, complement was required for opsonophagocytosis, since its destruction resulted in complete elimination of bacterial killing. Thus, premature neonates might be more susceptible to coagulase-negative staphylococcal infection because of their deficiencies in antibody and complement.

Specific immunity to coagulase-negative staphylococci has not been well defined. One might expect that skin colonization with coagulase-negative staphylococci over a lifetime would result in high titers of serum antibody, but such titers have not been documented. Preliminary data from our laboratory suggest that only about 10% of healthy humans have opsonic antibodies at titers greater than 10. As noted previously, antibody against PS/A was protective in our rabbit models of catheter infection and endocarditis (93, 183). Interestingly, nonimmune animals that developed *S. epidermidis* infection had large increases in antibody to teichoic acid but not to PS/A (93). Moreover, purified PS/A was more immunogenic in rabbits and mice than was PS/A present on the bacterial cell (93). These findings raise the

possibility that natural exposure to PS/A on bacterial surfaces may not result in high titers of antibody to this antigen, which appears to be a major target of protective antibody.

CONCLUSIONS

Despite major advances in the design of intravenous catheters, catheter-related infection remains a major problem. Since most catheter infections are caused by the patient's cutaneous microflora, efforts to prevent microorganisms at the insertion site from reaching the intravascular segment of the catheter can reduce the risk of infection substantially. Improved catheter materials or catheters with antimicrobial agents bound to their surfaces may provide additional protection. Current studies of the pathogenesis of catheter infection, including the factors that mediate adherence, persistence, and dissemination, may lead to new preventive strategies.

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