www.medscape.com

Authors and Disclosures

From the Department of Pharmacy Practice, Wayne State University College of Pharmacy, Detroit, Michigan (**Dr. Bestul**); and the Department of Pharmacy Practice, Ferris State University College of Pharmacy, Kalamazoo, Michigan (**Dr. VandenBussche**).

From Pharmacotherapy > Review of Therapeutics

Antibiotic Lock Technique: Review of the Literature

Megan B. Bestul, PharmD; Heather L. VandenBussche, PharmD

Posted: 03/22/2005; Pharmacotherapy. 2005;25(2):211-227.

Abstract and Introduction

Abstract

Central venous catheters (CVCs) are frequently used for patients requiring long-term venous access. Catheter-related infection is a serious complication associated with extended use of a CVC and can result in catheter removal. The antibiotic lock technique, a controversial method for sterilizing the catheter lumen, involves instilling high concentrations of antibiotics with or without heparin into the catheter lumen for extended periods of time. Studies differ regarding the choice and concentrations of antibiotics, dwell times in the catheter lumen, presence of heparin in the antibiotic lock technique solution, use of systemic antibiotics with the technique, and use of the technique for prevention or treatment of catheter-related infections. Results of in vitro studies demonstrate that many antibiotic combinations are stable and maintain high drug concentrations for prolonged periods of time. In vivo studies report the success of multiple combinations for both prevention and treatment with antibiotic lock technique in salvaging these catheters.

Introduction

Central venous catheters (CVCs) have become an integral part of medical management for a variety of patients, including those requiring long-term total parenteral nutrition, chemotherapy, or hemodialysis. Infection of the catheter or catheter hub and catheter-related septicemia are major complications for patients with permanent or semipermanent indwelling catheters. For many patients, venous access is limited, and continuous removal and replacement of catheters is usually not feasible when these devices become infected. Systemic and/or local antibiotic therapy is often used to prevent catheter removal in these patients who rely on indwelling devices for long-term medical management.

Despite efforts to improve and use proper aseptic techniques, 1 of every 20 CVCs inserted results in at least one systemic infection.[1] These infections are associated with up to 25% mortality, an estimated cost of $28,690 for each episode of catheter-related sepsis, and an average increase of 6.5 days in hospitalization for critically ill patients.[2] The number of catheter-related bacteremia cases is estimated to be more than 35,000/year.[3] With this number rising annually due to the increased use of CVCs for long-term medical management, a variety of methods have been developed to prevent and treat CVC infections and avoid catheter removal.

The antibiotic lock technique is a controversial method used to prevent and treat catheter-related infections. This technique involves instilling an antibiotic solution into the catheter hub and allowing the solution to dwell for a particular length of time, with the goal of eradicating organisms from an infected line or preventing a line from becoming colonized and at risk for infection. The concepts behind antibiotic lock technique are to prolong the life of the catheter while reducing morbidity and costs of managing catheter-related infections. In addition, the use

of antibiotic lock technique may spare patients from certain toxic effects of systemic antibiotic administration, and the risk of bacterial resistance may be reduced.[3,4]

Studies that evaluated antibiotic lock technique vary in the types of antibiotics and concentrations used, the addition of heparin to the solutions, dwell times in the catheter lumen, and use of the technique for prevention or treatment of CVC infection. Making evidence-based decisions regarding antibiotic lock technique recommendations is difficult for health care professionals because of differences in study methods and outcomes measured in small observational studies, as well as lack of large randomized clinical trials to assess effectiveness.

Information on antibiotic lock technique was obtained through a literature search of the PubMed database from January 1972-January 2004 and a manual review of reference lists from identified studies.

Catheter-Related Infection

Catheter-related infections are reported to occur in 2-40% of patients with indwelling devices.[5-16] Of these infections, 45-70% are caused by gram-positive bacteria, most commonly *Staphylococcus aureus* and coagulase-negative staphylococci, whereas gram-negative organisms account for approximately 28%.[17-22] Catheter-related infections may be classified as intraluminal or extraluminal (or outer surface contamination), including soft-tissue infections in tunneled CVCs. Endogenous microorganisms residing on the skin or in the catheter hub are the major causes of catheter infections (Table 1).[23-33] Normal skin flora are usually responsible for infecting catheters that have been in place for less than 10 days, whereas organisms residing in catheter hubs are most likely to cause infection in catheters that have been in place longer.[34,35]

Table 1. Organisms That Cause Catheter-Related Infections[23-33]

Skin Organism	Organisms Spread by Contaminated Hands or Intravenous Fluids	Pathogens Emerging as Sources of Infection
Staphylococcus aureus [a]	*Pseudomonas aeruginosa*	*Micrococcus* sp
Coagulase-negative staphylococci [a, b]	*Stenotrophomonas maltophilia*	*Achromobacter* sp
	Acinetobacter sp	*Mycobacterium* sp
Bacillus sp	*Candida albicans*	*Malassezia furfur*
Corynebacterium sp	*Candida parapsilosis* [b]	*Rhodotorula* sp
		Fusarium sp
		Trichosporon sp
		Hansenula anomala

[a]Leading pathogens that cause catheter-related infections.

[b]Organisms that produce extracellular slime.

The ability of microorganisms to attach to catheters depends on properties of the catheter surface, organism, and host. Factors that determine catheter adherence include the physical irregularities and charge differences of the catheter surface, the presence of host proteins (i.e., fibronectin, fibrinogen, fibrin, laminin, thrombospondin, and collagen) that act as adhesins, the ability of organisms to form "slime" or a biofilm, and the organism's hydrophobicity.[36,37]

Once a catheter is inserted into the vasculature, host proteins coat the interior and exterior surfaces of the

device and serve as a site to which certain organisms bind. For example, coagulase-negative staphylococci bind to fibronectin, *S. aureus* binds to fibronectin and fibrinogen, and *Candida albicans* binds to fibrin.[38-40] Micro-organisms that are bound within these complex matrixes of host proteins are difficult to eradicate since antimicrobials do not penetrate well into areas surrounded by fibrin or similar complex proteins. Microorganisms that infect catheter surfaces may produce slime consisting of fibrous glycocalyx or microbial biofilm composed of exopolysaccharides, or they may "free-float" over the catheter surface. Bacteria that produce a biofilm are more resistant to antibiotics, in particular glycopeptides, because of the relative inability of drugs to penetrate this film.[23-25,41,42] In addition, these organisms are not affected by phagocytes or antibodies produced by the host.[36,37]

When medical management is selected for the treatment of catheter-related infections as opposed to device removal, therapy usually consists of systemic antimicrobial administration through the infected line. Systemic treatment alone is often not sufficient to eradicate organisms from infected catheters and may lead to eventual device removal. In an attempt to improve organism eradication rates and prevent removal of permanent and semipermanent indwelling vascular devices, antibiotic lock technique has been used alone and in conjunction with systemic antibiotics for the prevention and treatment of intraluminal infections of a CVC. Guidelines from the Infectious Diseases Society of America and the Centers for Disease Control and Prevention- Healthcare Infection Control Practices Advisory Committee include use of antibiotic lock technique as a therapeutic option for intraluminal infections where the device is not removed and, although not routine, as prophylaxis for CVC infection in select patient populations.[43,44]

Antibiotic Lock Technique

The concept of antibiotic lock technique was developed in the late 1980s as a derivation of the heparin lock technique. This method involves instilling a highly concentrated antibiotic solution into a catheter lumen and allowing the solution to dwell for a specified time period for the purpose of sterilizing the lumen. One group of researchers hypothesized that using high concentrations of bactericidal antibiotics with activity against common catheter-related bacteria could effectively sterilize a catheter and reduce catheter-related sepsis from intraluminal line infections.[45,46] They determined that the vancomycin and amikacin concentrations used in the first antibiotic lock technique experiments were 40-80 times and 60-120 times greater, respectively, than the peak blood concentrations attained when the antibiotics were administered systemically with conventional dosing. Other studies documented that concentrations of vancomycin and amikacin in a catheter lumen maintained high levels for at least 8-12 hours and were stable and microbiologically active over a 12-hour dwell time within a lumen.[46,47]

Antimicrobial choices for use in the antibiotic lock technique are dependent on the different pathogens suspected to infect the catheter lumen (Table 1), characteristics of the organisms (i.e., ability to produce slime, adherence to host proteins), and the pharmacodynamic properties of the antimicrobial agent. For antibiotics such as aminoglycosides and fluoroquinolones, known as concentration-dependent killers, optimal and rapid bacterial killing occurs at high concen-trations (peak concentrations of at least 8-10 times the minimum inhibitory concentration [MIC] of a targeted organism or, for fluoro-quinolones, a 24-hour area under the concen-tration-time curve:MIC ratio of ≥ 125 for gram-negative organisms).[48] As a result of the postantibiotic effect of these drugs, maintaining high concentrations throughout a dosing interval or dwell time within a catheter may not be necessary. In comparison, b-lactams and vancomycin require maintenance of a concen-tration above the targeted organism's MIC for most of the dosing interval for optimal killing and are, therefore, known as time-dependent killers. Ideally, antibiotics used in antibiotic lock technique may be most effective if high drug concentrations are maintained for an extended period of time to maximize killing ability since high antibiotic concentrations may be needed in order to penetrate the microbial biofilm.[3] As a result of these stipulations, stability and compatibility become important factors to consider when selecting an antibiotic. The antibiotic(s) must be stable within the catheter lumen for the dosing interval or dwell time, as well as be compatible with the type of catheter used and any other component present in the lumen, such as heparin or other antimicrobials.

Table 1. Organisms That Cause Catheter-Related Infections[23-33]

Skin Organism	Organisms Spread by Contaminated Hands or Intravenous Fluids	Pathogens Emerging as Sources of Infection
Staphylococcus aureus [a]	*Pseudomonas aeruginosa*	*Micrococcus* sp
Coagulase-negative staphylococci [a, b]	*Stenotrophomonas maltophilia*	*Achromobacter* sp
	Acinetobacter sp	*Mycobacterium* sp
Bacillus sp	*Candida albicans*	*Malassezia furfur*
Corynebacterium sp	*Candida parapsilosis* [b]	*Rhodotorula* sp
		Fusarium sp
		Trichosporon sp
		Hansenula anomala

[a]Leading pathogens that cause catheter-related infections.

[b]Organisms that produce extracellular slime.

Nonheparinized Versus Heparinized Technique

Secondary to the presence of certain host proteins in the catheter lumen, such as fibronectin, fibrinogen, and fibrin, heparin may increase the efficacy of antibiotics used in antibiotic lock technique to treat catheter-related infections.[36] However, the concept of combining heparin with antibiotics in lock solutions is as controversial as the use of the antibiotic lock technique. Physical compatibility and chemical stability of the components of the antibiotic lock solution, as well as heparin use in certain patient populations (i.e., hypocoagulable states, documented heparin-induced thrombocytopenia), are limiting factors that need to be considered when adding heparin to an antibiotic lock solution. Numerous studies have been conducted that include heparin as a component of antibiotic lock technique solutions.[49-55] One group of investigators who are considered pioneers in the development of the antibiotic lock technique in the 1980s primarily studied heparinized antibiotic lock solutions, whereas another group conducted research by using nonheparinized antibiotic lock therapy.[45,46,50,52,56-59] Subsequent studies have cited the original work regarding specific antibiotics and study methodology for conducting antibiotic lock research.[47,49,51,53,55,58,60-65]

In Vitro Studies

Numerous in vitro studies have evaluated different concentrations of various antibiotics and their activity against common bacteria that infect catheter lumina (Table 2).[49,50,52,53,60,65] Data from these studies have provided information regarding effective antibiotics, dosages and concentrations, and dwell times that have been used in clinical trials.

Table 2. In Vitro Studies of Antimicrobial Combinations Used for the Antibiotic Lock Technique

Drug Concentration	Study Conditions	Antibiotic Lock Technique Dwell Time	Outcomes	Results
Vancomycin 25 µg/ml-heparin 9.75 U/ml	Vials of parent solutions and dilutions stored at	NA	Vancomycin and heparin stability; vancomycin MIC and	Vancomycin concentration was stable over 40 days;

Vancomycin 25 µg/ml Heparin 9.75 U/ml[50]	~23°C or 4°C for 85 days		MBC for *Staphylococcus aureus* and *S. epidermidis*	vancomycin MIC for both strains similar over 85 days; vancomycin-heparin not bactericidal against S. aureus at vancomycin concentration of 12.5 µg/ml; vancomycin-heparin bactericidal against S. epidermidis at vancomycin concentration 1.56-6.25 µg/ml; heparin activity retained over study period.
Vancomycin 5 mg/ml (antibiotic lock technique) Vancomycin 0.45 mg/ml (continuous) Vancomycin 150 mg q8h (intermittent dose) alone or in combination with rifampin 25 mg q8h, netilmicin 150 mg q12h, or fosfomycin 500 mg q6h Control nutrition solution[65]	Polyvinyl chloride catheters colonized with *S. epidermidis* and treated with 1 of 7 therapies for 3 days at room temperature (n=5 each)	12 hrs	Sterilization of inner surface catheter colonization with slime-producing *S. epidermidis*	Sterilization: 0/5 (vancomycin intermittent, vancomycin continuous, or control), 3/5 (vancomycin-netilmicin or vancomycin-fosfomycin), 2/5 (vancomycin-rifampin), 5/5 (vancomycin antibiotic lock technique); mean $\log_{10}$ cfu/catheter: 5.75 (control), 2.56 (vancomycin intermittent), 2.46 (vancomycin continuous), 0.92 (vancomycin-rifampin), 0.83 (vancomycin-fosfomycin), 0.7 (vancomycin-netilmicin), 0.00 (vancomycin antibiotic lock technique).
Vancomycin 25 µg/ml-heparin 9.73	Vials stored at ~23°C for 60 days	NA	Vancomycin and heparin stability;	Vancomycin-heparin-ciprofloxacin as

U/ml-ciprofloxacin 2 µg/ml			vancomycin MIC and MBC for *S. aureus* and *S. epidermidis* ; ciprofloxacin MIC and MBC for *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*	effective as vancomycin and ciprofloxacin controls with similar MICs and MBCs against all organisms tested; vancomycin concentration was stable over 60 days; heparin activity retained over at least 3 mo.
Vancomycin 50 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml	Vancomycin 50 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml also stored at 4°C			
Vancomycin 25 µg/ml				
Ciprofloxacin 2 µg/ml				
Vancomycin 50 µg/ml-heparin 9.75 U/ml				
Heparin 10 U/ml[52]				
Ceftriaxone 83.3 mg/ml	Silicone catheter lumina inoculated with *S. aureus, S. epidermidis* (3 strains), *K. pneumoniae, Enterobacter aerogenes, Candida albicans, Candida tropicalis* and treated with antibiotic lock technique for 7 days	12 hrs (alternated with TPN and incubated at 35°C for 12 hrs)	Elimination or reduction in intraluminal colonization; stability of antimicrobials over 12 hrs determined by bioassay; catheter microbial adherence determined by electron microscopy at 4, 8, and 12 hrs	All antiinfectives stable for 12 hrs with < 10% loss of activity; significant reductions in intraluminal colonization with all antimicrobials by day 7; all gram-positive strains significantly reduced or eliminated at day 1 by nafcillin and vancomycin; gram-negative strains reduced or eliminated at day 1 by ceftriaxone and aztreonam.
Vancomycin 83.3 mg/ml				
Nafcillin 83.3 mg/ml				
Gentamicin 13.3 mg/ml				
Aztreonam 83.3 mg/ml				
Amphotericin B 1 mg/ml or				
Fluconazole 2 mg/ml[60]				
Vancomycin-heparin	Sterile polystyrene test tubes incubated at 25°C and 37°C for 10 days	NA	Antibiotic stability in presence of heparin over 10 days; also assessed separately in presence of *S. epidermidis, K. pneumoniae, E. coli,* or *P. aeruginosa*	Ceftazidime activity declined by 28-36% after 7 days and ~50% after 10 days (at 37°C); all others had ≤ 10% reduction in activity over 10 days.
Cefazolin-heparin				
Ticarcillin-clavulanic acid-heparin				
Ceftazidime-heparin	One tube of each solution also assessed in presence of microorganisms			
Ciprofloxacin-heparin (all antibiotic concentrations 500 µg/ml except ciprofloxacin 125 µg/ml; heparin 100 U/ml in all combinations)[53]				

Cefazolin Cefazolin-heparin Vancomycin Vancomycin-heparin Ceftazidime Ceftazidime-heparin Ciprofloxacin Ciprofloxacin-heparin Gentamicin Gentamicin-heparin (all antibiotic concentrations 10 mg/ml except gentamicin 5 mg/ml; heparin 5000 U/ml in all combinations)[49]	Glass test tubes stored in the dark at 37°C for 72 hrs; heparin combinations also stored in dual-lumen polyurethane CVCs	NA	Stability using spectrophotometry; heparin combination stability also assessed using HPLC	Ciprofloxacin, ciprofloxacin-heparin not studied due to immediate precipitate formation; cefazolin, ceftazidime, and gentamicin had significant absorbance changes after 72 hrs ($p<0.05$) in test tubes; adding heparin further reduced only cefazolin absorbance ($p<0.05$); in CVCs, significant absorbance changes with cefazolin, ceftazidime, vancomycin, and gentamicin ($p<0.001$).

NA = not applicable; MIC = minimum inhibitory concentration; MBC = minimum bactericidal concentration; cfu = colony-forming units; TPN = total parenteral nutrition; CVC = central venous catheter; HPLC = high-performance liquid chromatography.

One group examined the stability of a vancomycin and heparin solution and its antibacterial activity against staphylococcal isolates.[50] Vancomycin stability over time was measured directly by fluorescent polarization immunoassay and indirectly by determining the MIC and minimum bactericidal concentration (MBC) against *S. aureus* and *Staphylococcus epidermidis* on days 1, 12, 26, and 40. On day 85, MICs were measured again for all solutions. In addition, the authors studied heparin stability in the vancomycin-heparin and control solutions by measuring the activated partial thromboplastin time (aPTT) at 0, 3, and 6 weeks. The vancomycin concentrations and the *S. aureus* MICs were similar for all solutions throughout the study period. However, the vancomycin-heparin solution was not bactericidal against *S. aureus* at vancomycin concentrations of 12.5 µg/ml, whereas the control solution MBCs were between 3.12 and 12.5 µg/ml. Against *S. epidermidis,* all vancomycin-heparin and control solutions were bactericidal at concentrations of 1.56-6.25 µg/ml. Prolongation of the aPTT was similar at all time periods and was maintained up to 5.5 months. The authors concluded that the vancomycin-heparin solution maintained antistaphylococcal and anticoagulant activity for at least 85 days whether stored at 4°C or room temperature. This study is limited by its lack of evaluation using a true model of catheter infection.

Another group reported the effectiveness of vancomycin antibiotic lock therapy versus conventional systemic vancomycin therapy in treating polyvinylchloride catheter surfaces that were colonized with *S. epidermidis.* [65] After induced colonization, a parenteral nutrition solution was infused through each catheter at room temperature for 9 hours/day for 3 days. After each infusion, the catheters were clamped and incubated at 37°C for 15 hours. Catheters were then randomly treated with vancomycin alone or in combination with netilmicin, fosfomycin, or rifampin for 3 days, whereas control catheters were infused with only nutrition solution (five of each type). Vancomycin was administered by either intermittent administration (1-hr infusion alone or

sequentially in combination with another antibiotic every 8 hrs with continuous nutrition solution infusion at Y-site), by 24-hour continuous administration (vancomycin added to the nutrition solution), or by antibiotic lock technique (2.5 mg/0.5 ml injected twice/day and locked until the next antibiotic administration). After the 3-day antibiotic therapy, each catheter lumen was rinsed with 50 ml of parenteral nutrition solution, clamped, and incubated at 37°C for 15 hours to allow bacterial replication before colony counts. Catheters were flushed with tryptic soy broth that was placed on tryptic soy agar plates and incubated for 24-48 hours. A catheter was considered sterile if the broth did not contain any colony-forming units (cfu).

When intermittently infused, vancomycin had a statistically significant effect on bacterial growth ($p<0.001$) but did not sterilize any of the catheters. Vancomycin in combination with other antibiotics reduced bacterial growth compared with vancomycin alone ($p<0.05$), but sterilization of the catheter lumina was inconsistent within each combination and was variable among antibiotic combinations. Continuous infusion of vancomycin also reduced bacterial growth but failed to sterilize the catheters. Vancomycin antibiotic lock therapy sterilized all five of the catheter lumina but did not produce a statistically significant decrease in bacterial growth compared with vancomycin administration in combination with the other antibiotics. In a separate time-kill experiment, high concentrations of vancomycin (450 or 5000 mg/L) resulted in rapid bactericidal activity versus a slower kill rate with a lower concentration (7.5 mg/L) alone and in combination. The authors concluded that high antibiotic concentrations in close contact with pathogens for extended periods of time provide more effective bactericidal treatment than that of lower concentrations in solutions that flow over bacteria during intermittent or continuous infusions. They stated that systemic antibiotics were required if there was evidence of extraluminal infection since antibiotics do not significantly enter the bloodstream when using the antibiotic lock technique. This study compared antibiotic locks with conventional modes of therapy by using an appropriate catheter infection model but is limited by its small sample and evaluation of only *S. epidermidis* colonization.

Researchers also evaluated a vancomycin-heparin-ciprofloxacin solution for its stability and activity against gram-negative and gram-positive organisms.[52] Preparation of the vancomycin-heparin portion was identical to that of a previous study[50] with the exception of a small decrease in the heparin concentration (9.75 vs 9.73 U/mL). In addition, ciprofloxacin 2 µg/ml was added. Vancomycin concentrations were measured directly by fluorescent polarization immunoassay, and aPTT was measured to determine indirectly the stability of heparin. In addition, the MICs and MBCs of vancomycin (for *S. aureus* and *S. epidermidis*) and ciprofloxacin (for *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*) were determined to evaluate indirectly the stability of the antibiotics in the various preparations.

The combination solutions were as effective as vancomycin or ciprofloxacin alone in inhibiting or killing all bacteria tested. Doubling the vancomycin concentration to 50 µg/ml did not result in a lower MIC for either *S. aureus* or *S. epidermidis.* Ciprofloxacin did not appear to have a synergistic or additive effect with vancomycin against gram-positive bacteria. For gram-negative bacteria, the ciprofloxacin activity in all antibiotic lock combinations was identical to the activity of the ciprofloxacin control. The addition of ciprofloxacin and/or vancomycin to heparin did not affect anticoagulant activity when compared with the standard heparin lock solution. The solutions maintained anticoagulant activity for at least 3 months and were not affected by storage temperature. The researchers concluded that both antibiotics maintained full antimicrobial activity and were appropriate concentrations for prophylaxis of catheter-related sepsis when combined with heparin. This study is limited by its lack of evaluation using a catheter infection model.

Another group examined the ability of various antibiotics to reduce or eradicate bacterial colonization in a silicone catheter lumen.[60] Strains of *S. aureus, S. epidermidis* (three different strains, one that produced a highly adherent biofilm), *K. pneumoniae, Enterobacter aerogenes, C. albicans,* and *Candida tropicalis* were used to infect the catheters. The catheters were filled with total parenteral nutrition solution and incubated for 12 hours at 35°C followed by instillation of the antibiotic lock technique for 12 hours and repeated for 7 days. The antimicrobials used are shown in Table 2 . Catheter microbial adherence was assessed over 12 hours, and catheter segments were analyzed for quantitative microbial counts on days 1, 4, and 7.

Table 2. In Vitro Studies of Antimicrobial Combinations Used for the Antibiotic Lock

Technique

Drug Concentration	Study Conditions	Antibiotic Lock Technique Dwell Time	Outcomes	Results
Vancomycin 25 µg/ml-heparin 9.75 U/ml	Vials of parent solutions and dilutions stored at ~23°C or 4°C for 85 days	NA	Vancomycin and heparin stability; vancomycin MIC and MBC for *Staphylococcus aureus* and *S. epidermidis*	Vancomycin concentration was stable over 40 days; vancomycin MIC for both strains similar over 85 days; vancomycin-heparin not bactericidal against S. aureus at vancomycin concentration of 12.5 µg/ml; vancomycin-heparin bactericidal against S. epidermidis at vancomycin concentration 1.56-6.25 µg/ml; heparin activity retained over study period.
Vancomycin 25 µg/ml				
Heparin 9.75 U/ml[50]				
Vancomycin 5 mg/ml (antibiotic lock technique)	Polyvinyl chloride catheters colonized with *S. epidermidis* and treated with 1 of 7 therapies for 3 days at room temperature (n=5 each)	12 hrs	Sterilization of inner surface catheter colonization with slime-producing *S. epidermidis*	Sterilization: 0/5 (vancomycin intermittent, vancomycin continuous, or control), 3/5 (vancomycin-netilmicin or vancomycin-fosfomycin), 2/5 (vancomycin-rifampin), 5/5 (vancomycin antibiotic lock technique); mean $\log_{10}$ cfu/catheter: 5.75 (control), 2.56 (vancomycin intermittent), 2.46 (vancomycin continuous), 0.92 (vancomycin-rifampin), 0.83 (vancomycin-
Vancomycin 0.45 mg/ml (continuous)				
Vancomycin 150 mg q8h (intermittent dose) alone or in combination with rifampin 25 mg q8h, netilmicin 150 mg q12h, or fosfomycin 500 mg q6h				

				fosfomycin), 0.7 (vancomycin-netilmicin), 0.00 (vancomycin antibiotic lock technique).
Control nutrition solution[65]				
Vancomycin 25 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml	Vials stored at ~23°C for 60 days	NA	Vancomycin and heparin stability; vancomycin MIC and MBC for *S. aureus* and *S. epidermidis* ; ciprofloxacin MIC and MBC for *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*	Vancomycin-heparin-ciprofloxacin as effective as vancomycin and ciprofloxacin controls with similar MICs and MBCs against all organisms tested; vancomycin concentration was stable over 60 days; heparin activity retained over at least 3 mo.
Vancomycin 50 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml	Vancomycin 50 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml also stored at 4°C			
Vancomycin 25 µg/ml				
Ciprofloxacin 2 µg/ml				
Vancomycin 50 µg/ml-heparin 9.75 U/ml				
Heparin 10 U/ml[52]				
Ceftriaxone 83.3 mg/ml	Silicone catheter lumina inoculated with *S. aureus, S. epidermidis* (3 strains), *K. pneumoniae, Enterobacter aerogenes, Candida albicans, Candida tropicalis* and treated with antibiotic lock technique for 7 days	12 hrs (alternated with TPN and incubated at 35°C for 12 hrs)	Elimination or reduction in intraluminal colonization; stability of antimicrobials over 12 hrs determined by bioassay; catheter microbial adherence determined by electron microscopy at 4, 8, and 12 hrs	All antiinfectives stable for 12 hrs with < 10% loss of activity; significant reductions in intraluminal colonization with all antimicrobials by day 7; all gram-positive strains significantly reduced or eliminated at day 1 by nafcillin and vancomycin; gram-negative strains reduced or eliminated at day 1 by ceftriaxone and aztreonam.
Vancomycin 83.3 mg/ml				
Nafcillin 83.3 mg/ml				
Gentamicin 13.3 mg/ml				
Aztreonam 83.3 mg/ml				
Amphotericin B 1 mg/ml or				
Fluconazole 2 mg/ml[60]				
Vancomycin-heparin	Sterile polystyrene test tubes incubated at 25°C and 37°C for 10 days	NA	Antibiotic stability in presence of heparin over 10 days; also assessed separately in presence of *S. epidermidis, K. pneumoniae, E. coli,*	Ceftazidime activity declined by 28-36% after 7 days and ~50% after 10 days (at 37°C); all others had ≤ 10% reduction in activity over 10
Cefazolin-heparin				
Ticarcillin-clavulanic acid-heparin				
Ceftazidime-heparin	One tube of each			

Ciprofloxacin-heparin (all antibiotic concentrations 500 µg/ml except ciprofloxacin 125 µg/ml; heparin 100 U/ml in all combinations)[53]	solution also assessed in presence of microorganisms		or *P. aeruginosa*	days.
Cefazolin Cefazolin-heparin Vancomycin Vancomycin-heparin Ceftazidime Ceftazidime-heparin Ciprofloxacin Ciprofloxacin-heparin Gentamicin Gentamicin-heparin (all antibiotic concentrations 10 mg/ml except gentamicin 5 mg/ml; heparin 5000 U/ml in all combinations)[49]	Glass test tubes stored in the dark at 37°C for 72 hrs; heparin combinations also stored in dual-lumen polyurethane CVCs	NA	Stability using spectrophotometry; heparin combination stability also assessed using HPLC	Ciprofloxacin, ciprofloxacin-heparin not studied due to immediate precipitate formation; cefazolin, ceftazidime, and gentamicin had significant absorbance changes after 72 hrs ($p<0.05$) in test tubes; adding heparin further reduced only cefazolin absorbance ($p<0.05$); in CVCs, significant absorbance changes with cefazolin, ceftazidime, vancomycin, and gentamicin ($p<0.001$).

NA = not applicable; MIC = minimum inhibitory concentration; MBC = minimum bactericidal concentration; cfu = colony-forming units; TPN = total parenteral nutrition; CVC = central venous catheter; HPLC = high-performance liquid chromatography.

In a separate experiment, the antibiotic lock solutions were bioassayed after 4, 8, and 12 hours of incubation to determine the intraluminal antimicrobial concentrations over time. Each antiinfective was stable, retaining greater than 90% activity over the 12-hour incubation period. All test strains were sensitive to the appropriate antibiotics. Microscopy revealed that *E. aerogenes* was less adherent to the catheters than were *S. epidermidis* and *K. pneumoniae,* which produced biofilm. After an antibiotic lock with gentamicin, nafcillin, ceftriaxone, or vancomycin, a statistically significant decrease was noted in *S. aureus* and *S. epidermidis* (the biofilm-producing strain and one strain without biofilm) colonization or elimination by day 1 ($p<0.001$). Colonization with the third *S. epidermidis* strain (a nonslime producer) was reduced by day 1 when treated with nafcillin or vancomycin and by day 7 when treated with ceftriaxone or gentamicin. The *K. pneumoniae* colonization was eradicated by day 1 with aztreonam, ceftriaxone, and gentamicin ($p<0.001$). Aztreonam and ceftriaxone reduced *E. aerogenes* colonization by day 1 as compared with day 4 with gentamicin. Both yeast strains were successfully eradicated by day 7 with the use of amphotericin B, whereas fluconazole eradicated *C. albicans* and significantly reduced

C. tropicalis colonization by day 7. The researchers concluded that the reduction in microorganism colonization was statistically significant for gram-positive and gram-negative bacteria and yeasts after 7 days of appropriate antibiotic lock therapy. Although the study involved a catheter infection model using multiple antimicrobials and microorganisms, it used only high drug concentrations without heparin in the study solutions and assessed stability by using bioassay rather than chemical assay.

In 1999, another group reported the stability of vancomycin, cefazolin, ticarcillin-clavulanic acid, ceftazidime, or ciprofloxacin combined with heparin in test tubes for use in port infections (Table 2).[53] All antibiotic concentrations were 500 µg/ml, except ciprofloxacin owing to macroscopic precipitation observed at higher concentrations. Heparin stability was not assessed in this study. In separate test tubes, 10^4 cfu/ml of susceptible bacteria (*S. epidermidis, K. pneumoniae, E. coli, or P. aeruginosa*) were added to each combination to assess if stability was altered in the presence of microorganisms. Antibiotic concentrations were determined by bioassay on days 1, 3, 7, and 10. After 1 day, antibiotic activity remained constant for all solutions, regardless of bacterial presence. There was a 28-36% decline in ceftazidime activity after 7 days and up to 50% loss of activity after 10 days for samples stored at 37°C. There was 10% or less reduction in antibiotic activity of all other agents at both temperatures. The authors concluded that the antibiotic solutions were stable since the concentrations remaining after 10 days were significantly above the MICs of common line pathogens, including that of ceftazidime which may be adequate for dwell times of up to 7 days. However, this study did not evaluate chemical drug stability or heparin activity over time and did not use a true port infection model.

Table 2. In Vitro Studies of Antimicrobial Combinations Used for the Antibiotic Lock Technique

Drug Concentration	Study Conditions	Antibiotic Lock Technique Dwell Time	Outcomes	Results
Vancomycin 25 µg/ml-heparin 9.75 U/ml	Vials of parent solutions and dilutions stored at ~23°C or 4°C for 85 days	NA	Vancomycin and heparin stability; vancomycin MIC and MBC for *Staphylococcus aureus* and *S. epidermidis*	Vancomycin concentration was stable over 40 days; vancomycin MIC for both strains similar over 85 days; vancomycin-heparin not bactericidal against S. aureus at vancomycin concentration of 12.5 µg/ml; vancomycin-heparin bactericidal against S. epidermidis at vancomycin concentration 1.56-6.25 µg/ml; heparin activity retained over study period.
Vancomycin 25 µg/ml				
Heparin 9.75 U/ml[50]				
Vancomycin 5 mg/ml (antibiotic lock technique)	Polyvinyl chloride catheters colonized with *S. epidermidis*	12 hrs	Sterilization of inner surface catheter colonization with	Sterilization: 0/5 (vancomycin intermittent,

	and treated with 1 of 7 therapies for 3 days at room temperature (n=5 each)		slime-producing *S. epidermidis*	vancomycin continuous, or control), 3/5 (vancomycin-netilmicin or vancomycin-fosfomycin), 2/5 (vancomycin-rifampin), 5/5 (vancomycin antibiotic lock technique); mean log_{10} cfu/catheter: 5.75 (control), 2.56 (vancomycin intermittent), 2.46 (vancomycin continuous), 0.92 (vancomycin-rifampin), 0.83 (vancomycin-fosfomycin), 0.7 (vancomycin-netilmicin), 0.00 (vancomycin antibiotic lock technique).
Vancomycin 0.45 mg/ml (continuous)				
Vancomycin 150 mg q8h (intermittent dose) alone or in combination with rifampin 25 mg q8h, netilmicin 150 mg q12h, or fosfomycin 500 mg q6h				
Control nutrition solution[65]				
Vancomycin 25 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml	Vials stored at ~23°C for 60 days	NA	Vancomycin and heparin stability; vancomycin MIC and MBC for *S. aureus* and *S. epidermidis* ; ciprofloxacin MIC and MBC for *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*	Vancomycin-heparin-ciprofloxacin as effective as vancomycin and ciprofloxacin controls with similar MICs and MBCs against all organisms tested; vancomycin concentration was stable over 60 days; heparin activity retained over at least 3 mo.
Vancomycin 50 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml	Vancomycin 50 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml also stored at 4°C			
Vancomycin 25 µg/ml				
Ciprofloxacin 2 µg/ml				
Vancomycin 50 µg/ml-heparin 9.75 U/ml				
Heparin 10 U/ml[52]				
Ceftriaxone 83.3 mg/ml	Silicone catheter lumina inoculated with *S. aureus, S. epidermidis* (3	12 hrs (alternated with TPN and	Elimination or reduction in intraluminal colonization; stability	All antiinfectives stable for 12 hrs with < 10% loss of activity; significant reductions
Vancomycin 83.3 mg/ml				

Nafcillin 83.3 mg/ml Gentamicin 13.3 mg/ml Aztreonam 83.3 mg/ml Amphotericin B 1 mg/ml or Fluconazole 2 mg/ml[60]	strains), *K. pneumoniae, Enterobacter aerogenes, Candida albicans, Candida tropicalis* and treated with antibiotic lock technique for 7 days	incubated at 35°C for 12 hrs)	of antimicrobials over 12 hrs determined by bioassay; catheter microbial adherence determined by electron microscopy at 4, 8, and 12 hrs	in intraluminal colonization with all antimicrobials by day 7; all gram-positive strains significantly reduced or eliminated at day 1 by nafcillin and vancomycin; gram-negative strains reduced or eliminated at day 1 by ceftriaxone and aztreonam.
Vancomycin-heparin Cefazolin-heparin Ticarcillin-clavulanic acid-heparin	Sterile polystyrene test tubes incubated at 25°C and 37°C for 10 days	NA	Antibiotic stability in presence of heparin over 10 days; also assessed separately in presence of *S. epidermidis, K. pneumoniae, E. coli,* or *P. aeruginosa*	Ceftazidime activity declined by 28-36% after 7 days and ~50% after 10 days (at 37°C); all others had ≤ 10% reduction in activity over 10 days.
Ceftazidime-heparin Ciprofloxacin-heparin (all antibiotic concentrations 500 µg/ml except ciprofloxacin 125 µg/ml; heparin 100 U/ml in all combinations)[53]	One tube of each solution also assessed in presence of microorganisms			
Cefazolin Cefazolin-heparin Vancomycin Vancomycin-heparin Ceftazidime Ceftazidime-heparin Ciprofloxacin Ciprofloxacin-heparin Gentamicin Gentamicin-heparin (all antibiotic concentrations 10 mg/ml except	Glass test tubes stored in the dark at 37°C for 72 hrs; heparin combinations also stored in dual-lumen polyurethane CVCs	NA	Stability using spectrophotometry; heparin combination stability also assessed using HPLC	Ciprofloxacin, ciprofloxacin-heparin not studied due to immediate precipitate formation; cefazolin, ceftazidime, and gentamicin had significant absorbance changes after 72 hrs ($p<0.05$) in test tubes; adding heparin further reduced only cefazolin absorbance ($p<0.05$); in CVCs, significant absorbance changes with cefazolin, ceftazidime, vancomycin, and

gentamicin 5 mg/ml; heparin 5000 U/ml in all combinations)[49]		gentamicin (p<0.001).

NA = not applicable; MIC = minimum inhibitory concentration; MBC = minimum bactericidal concentration; cfu = colony-forming units; TPN = total parenteral nutrition; CVC = central venous catheter; HPLC = high-performance liquid chromatography.

Another group assessed the stability of cefazolin, vancomycin, ceftazidime, ciprofloxacin, and gentamicin for use in an antibiotic-heparin lock solution (Table 2).[49] Each antibiotic was stored alone in separate glass test tubes for 72 hours and was analyzed at 24-hour intervals for stability by using spectrophotometry. Antibiotic-heparin solutions were then prepared and stored in both glass test tubes and dual-lumen polyurethane CVCs for 72 hours, analyzed for stability with spectrophotometry, and confirmed with high-performance liquid chromatography.

Table 2. In Vitro Studies of Antimicrobial Combinations Used for the Antibiotic Lock Technique

Drug Concentration	Study Conditions	Antibiotic Lock Technique Dwell Time	Outcomes	Results
Vancomycin 25 µg/ml-heparin 9.75 U/ml	Vials of parent solutions and dilutions stored at ~23°C or 4°C for 85 days	NA	Vancomycin and heparin stability; vancomycin MIC and MBC for *Staphylococcus aureus* and *S. epidermidis*	Vancomycin concentration was stable over 40 days; vancomycin MIC for both strains similar over 85 days; vancomycin-heparin not bactericidal against S. aureus at vancomycin concentration of 12.5 µg/ml; vancomycin-heparin bactericidal against S. epidermidis at vancomycin concentration 1.56-6.25 µg/ml; heparin activity retained over study period.
Vancomycin 25 µg/ml				
Heparin 9.75 U/ml[50]				
Vancomycin 5 mg/ml (antibiotic lock technique)	Polyvinyl chloride catheters colonized with *S. epidermidis* and treated with 1 of 7 therapies for 3	12 hrs	Sterilization of inner surface catheter colonization with slime-producing *S. epidermidis*	Sterilization: 0/5 (vancomycin intermittent, vancomycin continuous, or

	days at room temperature (n=5 each)			control), 3/5 (vancomycin-netilmicin or vancomycin-fosfomycin), 2/5 (vancomycin-rifampin), 5/5 (vancomycin antibiotic lock technique); mean log_{10} cfu/catheter: 5.75 (control), 2.56 (vancomycin intermittent), 2.46 (vancomycin continuous), 0.92 (vancomycin-rifampin), 0.83 (vancomycin-fosfomycin), 0.7 (vancomycin-netilmicin), 0.00 (vancomycin antibiotic lock technique).
Vancomycin 0.45 mg/ml (continuous)				
Vancomycin 150 mg q8h (intermittent dose) alone or in combination with rifampin 25 mg q8h, netilmicin 150 mg q12h, or fosfomycin 500 mg q6h				
Control nutrition solution[65]				
Vancomycin 25 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml	Vials stored at ~23°C for 60 days	NA	Vancomycin and heparin stability; vancomycin MIC and MBC for *S. aureus* and *S. epidermidis* ; ciprofloxacin MIC and MBC for *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*	Vancomycin-heparin-ciprofloxacin as effective as vancomycin and ciprofloxacin controls with similar MICs and MBCs against all organisms tested; vancomycin concentration was stable over 60 days; heparin activity retained over at least 3 mo.
Vancomycin 50 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml	Vancomycin 50 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml also stored at 4°C			
Vancomycin 25 µg/ml				
Ciprofloxacin 2 µg/ml				
Vancomycin 50 µg/ml-heparin 9.75 U/ml				
Heparin 10 U/ml[52]				
Ceftriaxone 83.3 mg/ml	Silicone catheter lumina inoculated with *S. aureus, S. epidermidis* (3 strains), *K. pneumoniae,*	12 hrs (alternated with TPN and incubated at 35°C for	Elimination or reduction in intraluminal colonization; stability of antimicrobials over 12 hrs determined by	All antiinfectives stable for 12 hrs with < 10% loss of activity; significant reductions in intraluminal colonization with all
Vancomycin 83.3 mg/ml				
Nafcillin 83.3 mg/ml				

Gentamicin 13.3 mg/ml Aztreonam 83.3 mg/ml Amphotericin B 1 mg/ml or Fluconazole 2 mg/ml[60]	*Enterobacter aerogenes, Candida albicans, Candida tropicalis* and treated with antibiotic lock technique for 7 days	12 hrs)	bioassay; catheter microbial adherence determined by electron microscopy at 4, 8, and 12 hrs	antimicrobials by day 7; all gram-positive strains significantly reduced or eliminated at day 1 by nafcillin and vancomycin; gram-negative strains reduced or eliminated at day 1 by ceftriaxone and aztreonam.
Vancomycin-heparin Cefazolin-heparin Ticarcillin-clavulanic acid-heparin	Sterile polystyrene test tubes incubated at 25°C and 37°C for 10 days	NA	Antibiotic stability in presence of heparin over 10 days; also assessed separately in presence of *S. epidermidis, K. pneumoniae, E. coli,* or *P. aeruginosa*	Ceftazidime activity declined by 28-36% after 7 days and ~50% after 10 days (at 37°C); all others had ≤ 10% reduction in activity over 10 days.
Ceftazidime-heparin Ciprofloxacin-heparin (all antibiotic concentrations 500 µg/ml except ciprofloxacin 125 µg/ml; heparin 100 U/ml in all combinations)[53]	One tube of each solution also assessed in presence of microorganisms			
Cefazolin Cefazolin-heparin Vancomycin Vancomycin-heparin Ceftazidime Ceftazidime-heparin Ciprofloxacin Ciprofloxacin-heparin Gentamicin Gentamicin-heparin (all antibiotic concentrations 10 mg/ml except gentamicin 5 mg/ml; heparin 5000 U/ml	Glass test tubes stored in the dark at 37°C for 72 hrs; heparin combinations also stored in dual-lumen polyurethane CVCs	NA	Stability using spectrophotometry; heparin combination stability also assessed using HPLC	Ciprofloxacin, ciprofloxacin-heparin not studied due to immediate precipitate formation; cefazolin, ceftazidime, and gentamicin had significant absorbance changes after 72 hrs ($p<0.05$) in test tubes; adding heparin further reduced only cefazolin absorbance ($p<0.05$); in CVCs, significant absorbance changes with cefazolin, ceftazidime, vancomycin, and gentamicin ($p<0.001$).

in all combinations)[49]	

NA = not applicable; MIC = minimum inhibitory concentration; MBC = minimum bactericidal concentration; cfu = colony-forming units; TPN = total parenteral nutrition; CVC = central venous catheter; HPLC = high-performance liquid chromatography.

For antibiotics stored alone, absorbance was reduced for cefazolin (6.7%, $p<0.05$), ceftazidime (13.4%, $p<0.05$), gentamicin (3%, $p<0.05$), and vancomycin (0.7%, NS). After heparin was added, cefazolin was the only agent with an additional significant decrease in absorbance of 2.4% ($p<0.05$). Ciprofloxacin was removed from the study because a precipitate formed immediately with the addition of heparin. The most significant absorbance reductions were seen with combinations stored in CVCs: 27.4% with cefazolin, 29.7% for vancomycin, 40.2% for ceftazidime, and 8% for gentamicin ($p<0.001$), suggesting adsorption to the catheter surface. The authors stated that these reductions may not be clinically significant because the concentrations remaining in the catheter lumen were approxi-mately 5 mg/ml (substantially greater than the usual MICs of organisms involved in causing catheter-related infections). They concluded that high antibiotic and heparin concentrations were stable inside CVCs over 72 hours. This study is limited by its use of only high drug concen-trations, no evaluation of heparin activity, and its lack of assessment of antimicrobial activity against microorganisms and effects with use of a true catheter infection model.

These in vitro trials provide information regarding the stability of antibiotics when used alone, in combination with other antibiotics and/or heparin, and in different catheter devices for antibiotic lock treatment. In addition, antimicrobial efficacy was demonstrated in some studies by reduction of bacterial colonization and stable bactericidal activity over time. Most of the antibiotics evaluated maintained stability and/or efficacy in polyurethane CVCs for at least 7 days. However, ciprofloxacin stability in antibiotic lock solutions was dependent on its concentration, which must be considered in any therapy that includes its use.

These studies differed significantly in the antibiotic concentrations used, varying as much as 1000-fold, and did not always include an anticoagulant, which may be a desirable component of antibiotic lock therapy. In addition, the study models used variable drug stability assessment methods and catheter infection models. They also inconsistently evaluated the effects of bacteria (including biofilm producers) in the study models. Despite these differences, these studies have served as guides for antibiotic selection and concentrations used in human trials of the antibiotic lock technique.

Clinical Studies

The clinical studies can be separated into two categories based on the use of antibiotic lock technique for prevention or treatment of catheter infections (Table 3 and Table 4).[45,47,51,54,55,57-59,61-64,66] In comparison to the laboratory studies, most of the treatment studies do not include heparin as a component of the antibiotic lock solutions.

Table 3. Catheter-Related Bacteremia Prevention Trials

Population	Treatment	Catheter Type	Dwell Time	Outcomes
45 pediatric hematology-oncology patients undergoing chemotherapy or	Vancomycin 25 µg/ml-heparin 9.75 U/ml (n=21)	Tunneled, central venous	Daily flush solution (5 ml) with additional flushes	Average of 247 ± 140 catheter-days/patient; 0 episodes of vancomycin-susceptible bacteremia in the vancomycin-heparin group vs 6 episodes in

who were neutropenic (median age 46 mo, range 2-227 mo)[58]	Heparin 10 U/ml (n=24)		after blood sampling or infusions	the heparin group (p=0.035); no reported adverse effects with vancomycin- heparin; no vancomycin-resistant organisms isolated.
117 adult neutropenic oncology patients (mean age 43 yrs)[51]	Vancomycin 25 µg/ml-heparin 10 U/ml (n=60)	Nontunneled, multilumen, central venous	2.5 ml for 1 hr q 2 days; solutions removed and discarded after dwell time	Colonization of catheter hubs: 0 episodes in the vancomycin-heparin group vs 9 in the heparin group (p=0.001); catheter-related bacteremia: 0 episodes in the vancomycin-heparin group vs 4 in the heparin group (p=0.05); proportion of patients free of catheter hub colonization and bacteremia: 74.6% and 88% in the heparin group vs 100% for both in the vancomycin- heparin group (p=0.004 and 0.06, respectively).
	Heparin 10 U/ml (n=57)			
83 oncology patients (median age 6 yrs, range 2-55 yrs)[66]	Vancomycin 25 µg/ml-heparin 25 U/ml (n=39)	Single lumen, central venous	Daily flush solution (5 ml)	Average CVC placement was 200 days; more CVC-related bacteremia cases occurred in the nonneutropenic heparin group compared with the vancomycin-heparin group (p=0.019); no difference between groups in neutropenic patients.
	Heparin 25 U/ml (n=44)			
126 pediatric oncology patients with 153 CVCs[59]	Vancomycin 25 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml (n=38)	Tunneled, central venous	Flush solution	Median number of line-days/patient: 200-247; 58 blood- stream infections in 42-mo study (43 gram-positive, 14 gram-negative, 1 fungal); infection rate was higher in the heparin group compared with the vancomycin- heparin and vancomycin-heparin-ciprofloxacin groups (p=0.004 and 0.005, respectively); time to infection significantly increased with vancomycin-heparin and vancomycin-heparin-ciprofloxacin (p=0.011 and 0.036, respectively); catheter occlusion significantly reduced only by vancomycin-heparin-ciprofloxacin (p=0.005).
	Vancomycin 25 µg/ml-heparin 9.73 U/ml (n=35)			
	Heparin 9.73 U/ml (n=80)			
10 pediatric hematology-oncology patients (median age 5	Vancomycin 2 mg/ml-heparin 100 U/ml (22 samples)	Implantable venous access devices	3 ml locked for 2-34 days	Median dwell time: 17 days vancomycin-heparin (range 4-28 days) and 17 days ceftazidime-heparin (range 2-34 days);

yrs, range 2.5-9 yrs)[55]	Ceftazidime 2 mg/ml-heparin 100 U/ml (18 samples)	(ports)		antibiotic concentrations remained > 100 µg/ml for 21 days; concentration/MIC for susceptible organisms was > 100 for ≥ 21 days with vancomycin and > 29 for 15 days with ceftazidime.

CVC = central venous catheter.

Table 4. Catheter-Related Bacteremia Treatment Trials

Population	Treatment	Antimicrobials Used	Catheter Type for Antibiotic Lock Technique	Dwell Time	Outcomes
11 patients receiving home-parenteral nutrition (24 cases of catheter-related sepsis)[45]	Antibiotic lock technique x 16 days (range 12-27 days [11 cases]) or systemic antibiotics x 3 days (range 2-10 days) followed by antibiotic lock technique x 12 days (range 6-16 days [11 cases]); 2 cases managed with systemic antibiotics only x 3 wks	Amikacin 1.5 mg/ml or minocycline 0.2 mg/ml or vancomycin 1.0 mg/ml	Subcutaneously tunneled, silicone	2 ml locked for 12 hrs/day between nutrition cycles	90% were treated successfully with antibiotic lock technique or systemic therapy followed by antibiotic lock technique; hospital stay was shorter for patients treated with antibiotic lock technique alone (p<0.02).
19 patients receiving home-parenteral nutrition (27 cases of catheter-related sepsis)[57]	Antibiotic lock technique x 15 days (range 7-20 days [20 cases]); systemic	Amikacin 1.5 mg/ml or minocycline 0.2 mg/ml or vancomycin 1.0 mg/ml	Silicone	2 ml locked for 12 hrs/day between nutrition cycles	Combining data with results from 1988 trial[45]: no significant difference in cure rates between

	antibiotics x 3 days (range 2-5 days) followed by antibiotic lock technique x 15 days (7 cases)				antibiotic lock technique alone and systemic therapy + antibiotic lock technique.
36 patients with chronic renal failure requiring hemodialysis[54]	Systemic treatment in combination with antibiotic lock technique (injected between the 2 hemodialysis sessions) x 15 days	Vancomycin or ciprofloxacin 100 µg/ml in 5% heparin	Double-lumen central venous	Between hemodialysis sessions	11/36 patients had 13 episodes of catheter-related sepsis; mean onset for the first episode was 73.5 days (range 7-180 days); no patients required catheter removal for cure.
11 pediatric patients (12 CVC infections)[62]	Antibiotic lock technique x 10-14 days	Vancomycin, mezlocillin, amphotericin B, ampicillin + gentamicin, or amikacin 2 mg/ml	Various central venous (Hickman, Quinten, or Portacath)	3-4 ml locked for 12 hrs/day	10/12 episodes of CVC infections were successfully treated with antibiotic lock technique (2 failures suspected to be secondary to blood clots or slime from *Staphylococcus epidermidis*).
9 episodes of catheter-related sepsis[47]	Antibiotic lock technique x 1-2 wks (systemic antibiotics were allowed for 1 wk); fungal infections were treated	Gentamicin 5 mg/ml, vancomycin 5 mg/ml, or amphotericin B 2.5 mg/ml (ampicillin 2 mg/ml + vancomycin used in one episode for *Enterococcus faecalis* ; ciprofloxacin 1	Subcutaneously tunneled, central venous	3 ml locked for 8-12 hrs/day	All 7 episodes of bacterial infections were cured with antibiotic lock technique (4 required an average of 2.1 days of systemic antibiotics);

	for ≥ 15 days	mg/ml used in one episode for *Stenotrophomonas maltophilia*)			average length of antibiotic lock technique to cure bacterial infections was 8.6 days; 2 Candida infections were initially cleared but relapsed 6 wks-7 mo later.
16 patients with human immunodeficiency virus or cancer[63]	Antibiotic lock technique + systemic antibiotics	Vancomycin 5 mg/ml or teicoplanin 5 mg/ml (± amikacin)	Venous access ports	1-2 times/day	Treatment was successful in 5 patients without port removal; partial response occurred in 2 patients; 9 patients failed therapy, requiring port removal.
42 patients receiving home parenteral nutrition[64]	Antibiotic lock technique x 10-15 days	Antibiotics selected based on organisms identified and sensitivity of the organisms	Single-cuffed silicone CVCs and implantable ports	NA	Antibiotic lock technique was more effective in treating infections in CVCs than implantable ports ($p<0.05$).

CVC = central venous catheter; NA = not available.

Prevention Trials. One group performed a randomized, double-blind study in pediatric hematology or oncology patients to evaluate the effects of a vancomycin-heparin flush solution on the occurrence of bacteremia resulting from CVC colonization with vancomycin-susceptible bacteria (Table 3).[58] Children were randomly assigned to receive either vancomycin-heparin or heparin alone for all catheter flushes. Episodes of fever or sepsis were evaluated to determine if systemic antibiotics were warranted. Children remained in the study until either the CVC was permanently removed or when study solutions could no longer be administered.

Table 3. Catheter-Related Bacteremia Prevention Trials

Population	Treatment	Catheter Type	Dwell Time	Outcomes
45 pediatric hematology-oncology patients undergoing chemotherapy or	Vancomycin 25 µg/ml-heparin 9.75 U/ml (n=21)	Tunneled, central venous	Daily flush solution (5 ml) with additional flushes	Average of 247 ± 140 catheter-days/patient; 0 episodes of vancomycin-susceptible bacteremia in the vancomycin-heparin group vs 6 episodes in

who were neutropenic (median age 46 mo, range 2-227 mo)[58]	Heparin 10 U/ml (n=24)		after blood sampling or infusions	the heparin group (p=0.035); no reported adverse effects with vancomycin- heparin; no vancomycin-resistant organisms isolated.
117 adult neutropenic oncology patients (mean age 43 yrs)[51]	Vancomycin 25 µg/ml-heparin 10 U/ml (n=60)	Nontunneled, multilumen, central venous	2.5 ml for 1 hr q 2 days; solutions removed and discarded after dwell time	Colonization of catheter hubs: 0 episodes in the vancomycin-heparin group vs 9 in the heparin group (p=0.001); catheter-related bacteremia: 0 episodes in the vancomycin-heparin group vs 4 in the heparin group (p=0.05); proportion of patients free of catheter hub colonization and bacteremia: 74.6% and 88% in the heparin group vs 100% for both in the vancomycin- heparin group (p=0.004 and 0.06, respectively).
	Heparin 10 U/ml (n=57)			
83 oncology patients (median age 6 yrs, range 2-55 yrs)[66]	Vancomycin 25 µg/ml-heparin 25 U/ml (n=39)	Single lumen, central venous	Daily flush solution (5 ml)	Average CVC placement was 200 days; more CVC-related bacteremia cases occurred in the nonneutropenic heparin group compared with the vancomycin-heparin group (p=0.019); no difference between groups in neutropenic patients.
	Heparin 25 U/ml (n=44)			
126 pediatric oncology patients with 153 CVCs[59]	Vancomycin 25 µg/ml-heparin 9.73 U/ml-ciprofloxacin 2 µg/ml (n=38)	Tunneled, central venous	Flush solution	Median number of line-days/patient: 200-247; 58 blood- stream infections in 42-mo study (43 gram-positive, 14 gram-negative, 1 fungal); infection rate was higher in the heparin group compared with the vancomycin- heparin and vancomycin-heparin-ciprofloxacin groups (p=0.004 and 0.005, respectively); time to infection significantly increased with vancomycin-heparin and vancomycin-heparin-ciprofloxacin (p=0.011 and 0.036, respectively); catheter occlusion significantly reduced only by vancomycin-heparin-ciprofloxacin (p=0.005).
	Vancomycin 25 µg/ml-heparin 9.73 U/ml (n=35)			
	Heparin 9.73 U/ml (n=80)			
10 pediatric hematology-oncology patients (median age 5	Vancomycin 2 mg/ml-heparin 100 U/ml (22 samples)	Implantable venous access devices	3 ml locked for 2-34 days	Median dwell time: 17 days vancomycin-heparin (range 4-28 days) and 17 days ceftazidime-heparin (range 2-34 days);

yrs, range 2.5-9 yrs)[55]	Ceftazidime 2 mg/ml-heparin 100 U/ml (18 samples)	(ports)		antibiotic concentrations remained > 100 µg/ml for 21 days; concentration/MIC for susceptible organisms was > 100 for ≥ 21 days with vancomycin and > 29 for 15 days with ceftazidime.

CVC = central venous catheter.

There were 45 children enrolled, with 52 catheters placed: 21 patients received vancomycin-heparin and 24 received heparin alone. Six episodes of bacteremia related to luminal colonization with vancomycin-susceptible bacteria were reported in the heparin group compared with no episodes in the vancomycin-heparin group (p=0.035). This was defined as a peripheral vein culture with 10% or less of the organisms obtained when drawn through the CVC and with no evidence of exit-site infection. Cultures from one patient in the vancomycin-heparin group grew *K. pneumoniae,* whereas all six cultures in the heparin group grew vancomycin-susceptible organisms (five coagulase-negative staphylococci and one *Corynebacterium* sp; in addition, one culture also grew *E. coli*). There was a significantly longer time to the first episode of vancomycin-susceptible bacteremia in the vancomycin-heparin group compared with the heparin alone group (p=0.04). No vancomycin-resistant organisms were isolated during the study. Peripheral blood vancomycin levels were undetectable, but when the blood specimens were drawn in relation to flush solution administration is not clear. The authors concluded that use of vancomycin-heparin flush solution in immunocompromised children with indwelling CVCs may reduce the frequency of vancomycin-susceptible bacteremia related to catheter colonization. One limitation of this study is the variability in dwell time between patients since the use of catheters depended on individual patient needs.

In a double-blind, randomized trial, the effectiveness of antibiotic lock technique in preventing catheter lumen colonization and subsequent gram-positive bacteremia was evaluated in 117 adult patients with chemotherapy-induced neutropenia (neutrophil count < 500 cells/mm^3).[51] Patients with nontunneled, multilumen, polyurethane CVCs were randomly assigned to receive heparin (57 patients) or vancomycin-heparin (60 patients) lock solutions for an average of 10-11 days. Exclusion criteria were patients with clinical or microbiologic evidence of infection, vancomycin allergy, or need for antibiotics or parenteral nutrition. Catheter hub and insertion site cultures were collected at baseline and twice/week and were repeated along with blood cultures before starting systemic antibiotics for those who developed febrile neutropenia. Catheter tip cultures were also performed for any removed catheters.

Significant catheter hub colonization (≥ 15 cfu/ml) occurred in 9 (15.8%) of the 57 patients in the heparin-only group compared with none in the vancomycin-heparin group (p=0.001). Colonizing organisms were *S. epidermidis* (7 patients), *Staphylococcus capitis* (1 patient), and *Corynebacterium* sp (1 patient). Catheter-related bacteremia occurred in 4 (7%) of 57 patients receiving heparin (*S. epidermidis* in 3 patients and *S. capitis* in 1) compared with none of the patients in the vancomycin-heparin group (p=0.05). One patient with *S. epidermidis* colonization required catheter removal because of breakthrough bacteremia. None of the isolated organisms were vancomycin resistant. The proportions of patients who remained free of catheter hub colonization and catheter-related bacteremia at study end were 74.6% and 88%, respectively, in the heparin group compared with 100% for both in the vancomycin-heparin group (p=0.004 and 0.06, respectively).

The authors concluded that vancomycin-heparin antibiotic lock therapy is successful in decreasing the frequency of catheter hub colonization with gram-positive bacteria in neutropenic patients. They also concluded that the local administration of vancomycin during periods of chemotherapy-induced neutropenia decreases the risk of resistant bacterial growth compared with systemic antibiotic administration. However, it is important to note the short treatment duration used in this study, making the probability low for selecting or producing resistant organisms.

Another group reported on the efficacy of a vancomycin-heparin flush solution for prevention of CVC-related bacteremia in 83 oncology patients with a single-lumen CVC.[66] The patients were randomly assigned to receive a daily flush with vancomycin-heparin (39 patients) or heparin alone (44 patients). Febrile episodes were evaluated, and central and peripheral blood cultures were drawn before starting systemic antibiotics.

Sixty-four patients experienced 143 febrile episodes (82 episodes in the heparin-alone group and 61 in the vancomycin-heparin group). More episodes occurred in nonneutropenic patients receiving heparin alone (35 episodes) than in those receiving vancomycin-heparin (14 episodes, p=0.014). In neutropenic patients, there were 47 episodes in both groups. Bacteremia was documented in 44 cases in which 23 were gram-positive organisms, 20 were gram-negative organisms, and 1 was *Candida.* Bacteremia with vancomycin-sensitive organisms was reported in 16 episodes in the heparin-alone group compared with 7 episodes in the vancomycin-heparin group (p=0.19). No episodes were reported in the vancomycin-heparin group of nonneutropenic patients, whereas 9 of the 16 episodes in the heparin-alone group were in nonneutropenic patients (p=0.019). No vancomycin-resistant organisms were found during the study period.

The authors concluded that vancomycin-heparin flush solutions effectively prevented bacteremia with vancomycin-susceptible organisms in nonneutropenic patients but had limited value in patients with neutropenia. Limitations of this study include a small sample and lack of distinction between catheter-related bacteremia and bacteremia due to other causes, including contamination.

In another study, the authors evaluated the effects of a broad-spectrum antibiotic flush solution on prevention of central line infections in 126 pediatric oncology patients.[59] Children were excluded if they had totally implanted catheters, were critically ill, or had continuous fluids running through the CVC. Children were randomly assigned in a double-blind fashion to receive vancomycin-heparin-ciprofloxacin (34 patients with 38 lines), vancomycin-heparin (28 patients with 35 lines), or heparin alone (64 patients with 80 lines). Flushes were used for the entire study or the life of the CVC. Once a patient became febrile, each febrile episode was evaluated and treated according to criteria that included assessment of neutrophil count, presence of sepsis, and evidence of CVC infection.

The line infection rate (possible, probable, or definite) was significantly higher in the heparin group (1.72/1000 line-days) than in both the vancomycin-heparin group (0.37/1000 line-days) and the vancomycin-heparin-ciprofloxacin group (0.55/1000 line-days, p=0.004 and 0.005, respectively). The time to infection was also increased by using an antibiotic flush solution compared with heparin alone (p=0.011 and 0.036 for vancomycin-heparin and vancomycin-heparin-ciprofloxacin, respectively). In addition, of 11 gram-negative infections, 10 occurred in the heparin flush group and 1 occurred in the vancomycin-heparin-ciprofloxacin group.

There were no cases of vancomycin-resistant organisms recovered from sterile sites during the study period. Peripheral ciprofloxacin blood levels drawn randomly in seven patients after vancomycin-heparin-ciprofloxacin flush were lower than the assay sensitivity limit (< 0.05 µg/ml). Nonneutropenic patients developed significantly fewer catheter-related infections with preventive antibiotic flush solutions than with heparin alone; this protective effect was less dramatic in neutropenic patients. The authors concluded that the use of a vancomycin-heparin-ciprofloxacin or a vancomycin-heparin flush solution significantly reduced the complications associated with tunneled CVCs in immuno-compromised children and could save significant health care resources by reducing the number of catheter-related infections by approximately 70%. Although this was a well-designed study, it is limited by its applicability to patients with totally implantable port devices.

Another group evaluated the antibiotic stability of lock solutions used for prolonged dwell times in 10 pediatric oncology patients with implantable ports.[55] Children were excluded if they required an infusion sooner than 48 hours after antibiotic lock therapy, had a port infection or acute illness, or had current or anticipated antibiotic therapy. Vancomycin or ceftazidime was combined with heparin and locked in each port for 2-34 days, depending on the need for port access. When the port was accessed, up to 1 ml of fluid was aspirated and assayed for antibiotic concentration (40 samples). All measured vancomycin concentrations were greater than 130 µg/ml, and no correlation was noted between concentration and dwell time for vancomycin. However, an

inverse correlation was noted between the ceftazidime dwell time and concentration ($p<0.0001$), which most likely reflects loss of ceftazidime activity. Overall, the concentrations of both antibiotics remained above the MIC_{90} of susceptible organisms for prolonged periods of time. The authors concluded that the high antibiotic concentrations used in lock solutions were stable for at least 2 weeks in an implantable port lumen and may allow for treatment of port infections. However, this study did not evaluate the effect of antibiotic lock solutions on preventing or treating port infections and was small in nature.

Treatment Trials. In one observational study, researchers evaluated antibiotic lock solutions to treat catheter-related sepsis in 11 patients receiving home parenteral nutrition (Table 4).[45] A total of 24 cases of catheter-related sepsis occurred in 18 catheters over a cumulated 286-month period. After meeting specified criteria for catheter-related sepsis, patients were treated with antibiotic lock alone (group 1, 11 cases) or with a short course of systemic antibiotics followed by an antibiotic lock (group 2, 11 cases). Treatment was chosen according to physician judgment and was not randomly selected. Lock solutions used depended on the infecting organism. The first two cases of catheter-related sepsis were treated with only systemic antibiotics for 3 weeks and served as a basis for comparison.

Table 4. Catheter-Related Bacteremia Treatment Trials

Population	Treatment	Antimicrobials Used	Catheter Type for Antibiotic Lock Technique	Dwell Time	Outcomes
11 patients receiving home-parenteral nutrition (24 cases of catheter-related sepsis)[45]	Antibiotic lock technique x 16 days (range 12-27 days [11 cases]) or systemic antibiotics x 3 days (range 2-10 days) followed by antibiotic lock technique x 12 days (range 6-16 days [11 cases]); 2 cases managed with systemic antibiotics only x 3 wks	Amikacin 1.5 mg/ml or minocycline 0.2 mg/ml or vancomycin 1.0 mg/ml	Subcutaneously tunneled, silicone	2 ml locked for 12 hrs/day between nutrition cycles	90% were treated successfully with antibiotic lock technique or systemic therapy followed by antibiotic lock technique; hospital stay was shorter for patients treated with antibiotic lock technique alone ($p<0.02$).
19 patients receiving home-parenteral	Antibiotic lock technique x	Amikacin 1.5 mg/ml or minocycline 0.2	Silicone	2 ml locked for 12 hrs/day	Combining data with results from 1988

nutrition (27 cases of catheter-related sepsis)[57]	15 days (range 7-20 days [20 cases]); systemic antibiotics x 3 days (range 2-5 days) followed by antibiotic lock technique x 15 days (7 cases)	mg/ml or vancomycin 1.0 mg/ml		between nutrition cycles	trial[45]: no significant difference in cure rates between antibiotic lock technique alone and systemic therapy + antibiotic lock technique.
36 patients with chronic renal failure requiring hemodialysis[54]	Systemic treatment in combination with antibiotic lock technique (injected between the 2 hemodialysis sessions) x 15 days	Vancomycin or ciprofloxacin 100 µg/ml in 5% heparin	Double-lumen central venous	Between hemodialysis sessions	11/36 patients had 13 episodes of catheter-related sepsis; mean onset for the first episode was 73.5 days (range 7-180 days); no patients required catheter removal for cure.
11 pediatric patients (12 CVC infections)[62]	Antibiotic lock technique x 10-14 days	Vancomycin, mezlocillin, amphotericin B, ampicillin + gentamicin, or amikacin 2 mg/ml	Various central venous (Hickman, Quinten, or Portacath)	3-4 ml locked for 12 hrs/day	10/12 episodes of CVC infections were successfully treated with antibiotic lock technique (2 failures suspected to be secondary to blood clots or slime from *Staphylococcus epidermidis*).
9 episodes of catheter-related sepsis[47]	Antibiotic lock technique x 1-2 wks (systemic antibiotics	Gentamicin 5 mg/ml, vancomycin 5 mg/ml, or amphotericin B 2.5 mg/ml (ampicillin 2 mg/ml +	Subcutaneously tunneled, central venous	3 ml locked for 8-12 hrs/day	All 7 episodes of bacterial infections were cured with antibiotic lock technique (4

	were allowed for 1 wk); fungal infections were treated for ≥ 15 days	vancomycin used in one episode for *Enterococcus faecalis* ; ciprofloxacin 1 mg/ml used in one episode for *Stenotrophomonas maltophilia*)			required an average of 2.1 days of systemic antibiotics); average length of antibiotic lock technique to cure bacterial infections was 8.6 days; 2 Candida infections were initially cleared but relapsed 6 wks-7 mo later.
16 patients with human immunodeficiency virus or cancer[63]	Antibiotic lock technique + systemic antibiotics	Vancomycin 5 mg/ml or teicoplanin 5 mg/ml (± amikacin)	Venous access ports	1-2 times/day	Treatment was successful in 5 patients without port removal; partial response occurred in 2 patients; 9 patients failed therapy, requiring port removal.
42 patients receiving home parenteral nutrition[64]	Antibiotic lock technique x 10-15 days	Antibiotics selected based on organisms identified and sensitivity of the organisms	Single-cuffed silicone CVCs and implantable ports	NA	Antibiotic lock technique was more effective in treating infections in CVCs than implantable ports ($p<0.05$).

CVC = central venous catheter; NA = not available.

Of the 18 catheters inserted, 7 catheters were removed owing to migration or blockage (four catheters), septicemia (one catheter), or failed therapy (two catheters, one patient in each group both due to *Candida* infections after primary bacterial eradication). Successful treatment occurred in 90% of cases of catheter-related sepsis in groups 1 and 2 without catheter removal. Hospital stay was significantly shorter for patients in group 1 than for those in group 2 (average of 4.4 and 7.2 days, respectively, $p<0.02$) and was approximately 3 times shorter than for patients treated with systemic therapy alone. In addition, negative in-line blood cultures were obtained after 3.8 days in group 1 compared with 4.2 days in group 2. The researchers concluded that antibiotic lock therapy alone can success-fully treat catheter-related sepsis. This study is severely limited by its small sample size, lack of treatment randomization and standardization, and discontinuation of parenteral feeding while the patient was febrile.

In 1990, the same researchers published a second observational study involving antibiotic lock use in 19

patients receiving parenteral nutrition, with 27 episodes of catheter-related sepsis.[57] The study methods were similar to those of their previous study.[45] In this study, however, antibacterial activity of the solutions against *E. coli* and *S. epidermidis* was determined with a daily bioassay after storage in syringes at 4°C. Amikacin maintained antibacterial activity for 17 days, whereas vancomycin and minocycline retained activity for 3 and 4 days, respectively. In 20 cases of catheter-related sepsis, antibiotic lock was used alone compared with 7 episodes of catheter-related sepsis treated initially with systemic antibiotics followed by an antibiotic lock. As a result of previously documented incompatibilities between antibiotics (specifically aminoglycosides) and heparin,[67,68] heparin was given as a daily injection in all patients before each nutrition infusion. Gram-positive bacteria were the infecting pathogens in 22 cases, whereas gram-negative organisms were isolated in 5 cases. Two catheters were removed during the study period: one due to *S. epidermidis* after lock therapy alone and the other due to *Enterobacter agglomerans* after systemic and antibiotic lock treatment.

The average infection-free time for the remaining 25 episodes was 152 days (range 7-570 days). Of these episodes, 15 were recurrent infections of the same catheter that became reinfected an average of 2 times (range 1-3 times). However, 7 of the 15 recurrent episodes were caused by a different bacterial strain than previously isolated. The average time between recurrent episodes was 2 months.

Combining these results with those from the researchers' previous trial,[45] no significant difference was noted in cure rates between using systemic antibiotics before lock therapy (16/18, 89%) and antibiotic lock technique alone (29/31, 94%). The researchers concluded that antibiotic lock technique was an effective treatment for bacterial catheter-related sepsis not associated with infection of the entry point or the subcutaneous tunnel site. However, it must be kept in mind that these were not randomized trials and physician bias in selecting lock therapy alone versus antibiotic lock plus systemic therapy may have influenced success rates.

Another group studied the use of antibiotic locks for catheter-related sepsis in 36 adult patients with renal failure requiring hemodialysis.[54] Patients were prospectively studied for 12 months after placement of double-lumen central venous catheters. Patients who appeared to be septic were treated empirically with intravenous vancomycin 1 g/week. If blood cultures grew gram-negative organisms, therapy was changed to intravenous ciprofloxacin 200 mg admin-istered at the end of each hemodialysis session.

Half of each antibiotic dose was infused through each catheter lumen for a 15-day treatment period. Patients were excluded if they required catheter removal for phlebitis and/or insertion-site infection, deteriorated clinically, were suspected to have pulmonary embolism or bacterial endocarditis, had persistent bacteremia after 48-72 hours of antibiotic therapy, or were fungemic. In between hemodialysis sessions, either vancomycin or ciprofloxacin 100 µg/ml in 5% sodium heparin was injected into each catheter lumen and allowed to dwell until the following hemodialysis session.

Only 30% of patients developed catheter-related sepsis (13 episodes in 11 patients), and none required catheter removal as a result of persistent infection. The causative organisms were *S. epidermidis* and *P. aeruginosa* in 77% of the cases, whereas *S. aureus* was isolated in 15.4%. The researchers speculated that success could be attributed to the "high concentration of the antibiotic in the endoluminal perfusion," or antibiotic lock technique. However, this was a small, observational study with no control group to fully assess the effectiveness of antibiotic locks compared with systemic therapy alone.

In another study, 11 pediatric patients with 12 CVC infections were treated with antibiotic lock therapy.[62] Patients received antibiotic locks if bacteria were isolated from blood cultures drawn through a catheter after 96 hours of systemic treatment, if blood cultures were sterile from a peripheral venous site, or if they had no acute illness and no focus of infection other than the catheter. The choice of antimicrobial used for the lock solution was based on the isolated organism and was used for 10-14 days. Systemic administration of antibiotics and the use of heparin were prohibited during the antibiotic lock treatment period. Blood cultures were obtained on a daily basis from the catheter to determine the efficacy of the antibiotic lock.

Of the 12 episodes, 10 cases of catheter-related sepsis were cured with antibiotic lock technique. The two

treatment failures occurred because of catheter occlusion by a blood clot and/or slime produced by *S. epidermidis.* The authors stated that antibiotic lock therapy is possibly a better choice for first-line therapy than are systemic antibiotics for treating a catheter infection that has not progressed to systemic infection. However, this was another small, observational, uncontrolled trial in which it is unclear if CVCs were simply colonized or infected.

An open, uncontrolled study of antibiotic lock technique and systemic antibiotics for catheter-related sepsis was performed in patients receiving home parenteral nutrition.[47] Patients were excluded if they were 18 years or younger or if any of the following were present: sepsis, infection with *S. aureus,* metastatic infection, or catheter tunnel infection. After exclusion due to sepsis or *S. aureus* infection (three patients), there were nine episodes of catheter-related bacteremia or fungemia treated with intraluminal antimicrobials (Table 4). Antibiotic lock therapy was used for 1-2 weeks with or without up to 1 week of systemic antibiotic therapy. Fungal infections were treated with intraluminal amphotericin B for 15 or more days.

Table 4. Catheter-Related Bacteremia Treatment Trials

Population	Treatment	Antimicrobials Used	Catheter Type for Antibiotic Lock Technique	Dwell Time	Outcomes
11 patients receiving home-parenteral nutrition (24 cases of catheter-related sepsis)[45]	Antibiotic lock technique x 16 days (range 12-27 days [11 cases]) or systemic antibiotics x 3 days (range 2-10 days) followed by antibiotic lock technique x 12 days (range 6-16 days [11 cases]); 2 cases managed with systemic antibiotics only x 3 wks	Amikacin 1.5 mg/ml or minocycline 0.2 mg/ml or vancomycin 1.0 mg/ml	Subcutaneously tunneled, silicone	2 ml locked for 12 hrs/day between nutrition cycles	90% were treated successfully with antibiotic lock technique or systemic therapy followed by antibiotic lock technique; hospital stay was shorter for patients treated with antibiotic lock technique alone ($p<0.02$).
19 patients receiving home-parenteral nutrition (27 cases of catheter-	Antibiotic lock technique x 15 days (range 7-20	Amikacin 1.5 mg/ml or minocycline 0.2 mg/ml or vancomycin 1.0	Silicone	2 ml locked for 12 hrs/day between nutrition	Combining data with results from 1988 trial[45]: no significant

related sepsis)[57]	days [20 cases]); systemic antibiotics x 3 days (range 2-5 days) followed by antibiotic lock technique x 15 days (7 cases)	mg/ml		cycles	difference in cure rates between antibiotic lock technique alone and systemic therapy + antibiotic lock technique.
36 patients with chronic renal failure requiring hemodialysis[54]	Systemic treatment in combination with antibiotic lock technique (injected between the 2 hemodialysis sessions) x 15 days	Vancomycin or ciprofloxacin 100 µg/ml in 5% heparin	Double-lumen central venous	Between hemodialysis sessions	11/36 patients had 13 episodes of catheter-related sepsis; mean onset for the first episode was 73.5 days (range 7-180 days); no patients required catheter removal for cure.
11 pediatric patients (12 CVC infections)[62]	Antibiotic lock technique x 10-14 days	Vancomycin, mezlocillin, amphotericin B, ampicillin + gentamicin, or amikacin 2 mg/ml	Various central venous (Hickman, Quinten, or Portacath)	3-4 ml locked for 12 hrs/day	10/12 episodes of CVC infections were successfully treated with antibiotic lock technique (2 failures suspected to be secondary to blood clots or slime from *Staphylococcus epidermidis*).
9 episodes of catheter-related sepsis[47]	Antibiotic lock technique x 1-2 wks (systemic antibiotics were allowed for 1 wk);	Gentamicin 5 mg/ml, vancomycin 5 mg/ml, or amphotericin B 2.5 mg/ml (ampicillin 2 mg/ml + vancomycin used in one episode for	Subcutaneously tunneled, central venous	3 ml locked for 8-12 hrs/day	All 7 episodes of bacterial infections were cured with antibiotic lock technique (4 required an average of 2.1

	fungal infections were treated for ≥ 15 days	*Enterococcus faecalis* ; ciprofloxacin 1 mg/ml used in one episode for *Stenotrophomonas maltophilia*)			days of systemic antibiotics); average length of antibiotic lock technique to cure bacterial infections was 8.6 days; 2 Candida infections were initially cleared but relapsed 6 wks-7 mo later.
16 patients with human immunodeficiency virus or cancer[63]	Antibiotic lock technique + systemic antibiotics	Vancomycin 5 mg/ml or teicoplanin 5 mg/ml (± amikacin)	Venous access ports	1-2 times/day	Treatment was successful in 5 patients without port removal; partial response occurred in 2 patients; 9 patients failed therapy, requiring port removal.
42 patients receiving home parenteral nutrition[64]	Antibiotic lock technique x 10-15 days	Antibiotics selected based on organisms identified and sensitivity of the organisms	Single-cuffed silicone CVCs and implantable ports	NA	Antibiotic lock technique was more effective in treating infections in CVCs than implantable ports ($p<0.05$).

CVC = central venous catheter; NA = not available.

All seven episodes of bacterial catheter-related sepsis were cured by using antibiotic lock solutions for an average of 8.6 days without catheter removal, but four episodes were also treated with an average of 2.1 days of systemic antibiotics. Two *Candida* infections initially cleared with use of lock therapy and systemic antifungals, but both episodes relapsed 6 weeks to 7 months later, one of which required catheter removal. In six patients being treated with antibiotic locks, vancomycin and gentamicin levels were assessed after dwelling for 8-12 hours in the catheters. Both drug concentrations remained above the MICs of commonly infecting organisms (3.822 ± 1.017 µg/ml for vancomycin [five patients] and 3.33 µg/ml for gentamicin [one patient]). The authors concluded that antibiotic locks used for 7-8 days were as effective as standard systemic antibiotic treatment periods of 10-16 days for clearing catheter-related bacteremia. They also stated that vancomycin and gentamicin lock concentrations remained elevated for at least 8-12 hours after being instilled in the catheter. In addition, daily use of amphotericin B lock technique was effective in suppressing *Candida* infection and extending the catheter life for months.

This study is limited by the small number of episodes of catheter-related sepsis and the lack of a comparison

group to assess antibiotic lock technique monotherapy versus systemic therapy. The authors did not elaborate on the decrease in antibiotic lock concentrations found in a small subanalysis in this study.

In another small study, 16 patients with venous access ports who had human immunodeficiency virus or cancer were treated with antibiotic locks for febrile CVC-related bacteremia.[63] Patients were excluded if they had localized insertion- or tunnel-site infection. The antibiotic lock was used in combination with systemic antibiotics (Table 4) directed against the isolated organisms.

Table 4. Catheter-Related Bacteremia Treatment Trials

Population	Treatment	Antimicrobials Used	Catheter Type for Antibiotic Lock Technique	Dwell Time	Outcomes
11 patients receiving home-parenteral nutrition (24 cases of catheter-related sepsis)[45]	Antibiotic lock technique x 16 days (range 12-27 days [11 cases]) or systemic antibiotics x 3 days (range 2-10 days) followed by antibiotic lock technique x 12 days (range 6-16 days [11 cases]); 2 cases managed with systemic antibiotics only x 3 wks	Amikacin 1.5 mg/ml or minocycline 0.2 mg/ml or vancomycin 1.0 mg/ml	Subcutaneously tunneled, silicone	2 ml locked for 12 hrs/day between nutrition cycles	90% were treated successfully with antibiotic lock technique or systemic therapy followed by antibiotic lock technique; hospital stay was shorter for patients treated with antibiotic lock technique alone ($p<0.02$).
19 patients receiving home-parenteral nutrition (27 cases of catheter-related sepsis)[57]	Antibiotic lock technique x 15 days (range 7-20 days [20 cases]); systemic antibiotics x 3 days (range 2-5	Amikacin 1.5 mg/ml or minocycline 0.2 mg/ml or vancomycin 1.0 mg/ml	Silicone	2 ml locked for 12 hrs/day between nutrition cycles	Combining data with results from 1988 trial[45]: no significant difference in cure rates between antibiotic lock technique alone and systemic

	days) followed by antibiotic lock technique x 15 days (7 cases)				therapy + antibiotic lock technique.
36 patients with chronic renal failure requiring hemodialysis[54]	Systemic treatment in combination with antibiotic lock technique (injected between the 2 hemodialysis sessions) x 15 days	Vancomycin or ciprofloxacin 100 µg/ml in 5% heparin	Double-lumen central venous	Between hemodialysis sessions	11/36 patients had 13 episodes of catheter-related sepsis; mean onset for the first episode was 73.5 days (range 7-180 days); no patients required catheter removal for cure.
11 pediatric patients (12 CVC infections)[62]	Antibiotic lock technique x 10-14 days	Vancomycin, mezlocillin, amphotericin B, ampicillin + gentamicin, or amikacin 2 mg/ml	Various central venous (Hickman, Quinten, or Portacath)	3-4 ml locked for 12 hrs/day	10/12 episodes of CVC infections were successfully treated with antibiotic lock technique (2 failures suspected to be secondary to blood clots or slime from *Staphylococcus epidermidis*).
9 episodes of catheter-related sepsis[47]	Antibiotic lock technique x 1-2 wks (systemic antibiotics were allowed for 1 wk); fungal infections were treated for ≥ 15 days	Gentamicin 5 mg/ml, vancomycin 5 mg/ml, or amphotericin B 2.5 mg/ml (ampicillin 2 mg/ml + vancomycin used in one episode for *Enterococcus faecalis* ; ciprofloxacin 1 mg/ml used in one episode for *Stenotrophomonas*	Subcutaneously tunneled, central venous	3 ml locked for 8-12 hrs/day	All 7 episodes of bacterial infections were cured with antibiotic lock technique (4 required an average of 2.1 days of systemic antibiotics); average length of antibiotic lock technique to

		maltophilia)			cure bacterial infections was 8.6 days; 2 Candida infections were initially cleared but relapsed 6 wks-7 mo later.
16 patients with human immunodeficiency virus or cancer[63]	Antibiotic lock technique + systemic antibiotics	Vancomycin 5 mg/ml or teicoplanin 5 mg/ml (± amikacin)	Venous access ports	1-2 times/day	Treatment was successful in 5 patients without port removal; partial response occurred in 2 patients; 9 patients failed therapy, requiring port removal.
42 patients receiving home parenteral nutrition[64]	Antibiotic lock technique x 10-15 days	Antibiotics selected based on organisms identified and sensitivity of the organisms	Single-cuffed silicone CVCs and implantable ports	NA	Antibiotic lock technique was more effective in treating infections in CVCs than implantable ports ($p<0.05$).

CVC = central venous catheter; NA = not available.

Treatment without port removal was successful in five patients (31%), whereas partial response (defined as cure of the initial infection followed by a recurrent infection with a different microorganism) occurred in two patients. Nine patients (56%) failed therapy and required port removal. Although this was a small observational study, it involved patients with venous access ports that contain a reservoir connected to the catheter. The presence of this reservoir can affect the success of an antibiotic lock secondary to the size of the reservoir and presence of "residue," such as fibrin or other proteins, in the lumen. The residue can serve as a harbor for bacteria, limiting the efficacy of antibiotics, which may explain the high rate of failure found in this study.

Another group of investigators examined the use of antibiotic locks to treat catheter-related sepsis in 42 patients receiving home parenteral nutrition through either single-lumen cuffed silicone CVCs (64%) or implantable ports (26%).[64] Based on specific diagnostic criteria, 39 episodes of catheter-related sepsis occurred during the study. The most frequently isolated organism was *S. epidermidis,* and patients were treated with the appropriate antibiotics for the organism(s) isolated (antibiotics not specified in study). The lock technique was more effective in treating infections of CVCs than implanted ports ($p<0.05$), reinforcing the results of the above-mentioned study.[63] The investigators concluded that antibiotic lock therapy can be an effective method for salvaging and sterilizing CVCs, but this study is limited by its small, uncontrolled, observational nature and lack of detail regarding the methodology of its antibiotic lock technique.

Discussion

Clinical trials have evaluated the use of antibiotic lock technique for prevention and treatment of catheter infections, but most of the prevention trials used antibiotic flush solutions rather than true antibiotic lock therapy. Although preventive therapy appears to be successful in inhibiting catheter colonization and, therefore, development of catheter infections, these flush solutions may predispose patients to antibiotic resistance since the solutions are infused systemically as opposed to being contained within a catheter lumen and withdrawn before utilization of the catheter for drug administration. Comparatively, vancomycin used as true lock therapy may select for resistance if CVCs are colonized with intrinsically resistant strains that could overgrow when vancomycin-susceptible organisms are suppressed. In addition, using flush solutions may not result in a high concentration of antibiotic in contact with the catheter lumen for an extended period of time, depending on the frequency of infusions given through the catheter.

In trials evaluating antibiotic lock technique for the treatment of catheter infections, the lock technique resulted in significantly shorter hospital stays compared with systemic antibiotics alone. In addition, no differences were noted in cure rates between antibiotic lock monotherapy and systemic therapy administered before antibiotic lock technique.[43,55] In these small trials, most catheter infections were cured with antibiotic lock technique (with or without systemic antibiotics), but failures were reported, mainly due to infections with other organisms, catheter occlusion or blockage (heparin not included in most trials), or persistence of *Candida* colonization.[45,47,54,57,62-64] In addition, the use of antibiotic lock therapy resulted in average subsequent infection-free periods of 74-152 days.[45,57] The antibiotic lock technique appeared to be less effective in treating infections of implantable ports than infections of other types of CVCs.[61,62]

Limitations of these trials need to be considered when making conclusions regarding antibiotic lock technique in catheter-related sepsis. Data are lacking from large, randomized, controlled trials to determine if antibiotic lock technique is more effective than systemic antibiotics for treatment of line infections. The treatment studies vary in the selection of antibiotics used for the lock technique, as well as in the concentrations and dwell times. In addition, some studies included lock technique in combination with or after systemic antibiotic treatment, which were not randomized; furthermore, the study populations differed significantly and various definitions of catheter-related sepsis were used. None of these studies evaluated antimicrobial blood levels with the lock technique to determine if systemic exposure occurred with this treatment modality.

Based on the available evidence, antibiotic lock technique monotherapy appears effective when treating certain catheter-related infections and can prolong catheter life. Also, antibiotic lock monotherapy may result in shorter hospital stays compared with systemic antibiotic therapy for treatment of line infections. For patients with a catheter-related infection that has not progressed to septicemia and does not involve tissue infection at the insertion or tunnel site, antibiotic lock technique could be considered as an option to salvage venous access when such salvage is a high priority in a patient with limited venous access sites or to avoid adverse effects from systemic antibiotics.

Conclusion

The antibiotic lock technique provides an alternative method to treat catheter-related sepsis or colonization, without the administration of systemic antibiotics or removal of the indwelling vascular device. It may also be useful in pre-venting CVC infection in certain patient populations, although development of resistance remains a concern with daily use of these solutions; however, the concern for resistance may be less with antibiotic lock technique than with systemic antibiotics and possibly flush solutions. Many antimicrobial combinations have been evaluated for stability (with or without heparin) and effectiveness for prevention and treatment of CVC infection. To prevent catheter-related sepsis, evidence supports the use of vancomycin 25 µg/ml in combination with heparin 9.75 U/ml to prevent gram-positive infections, with the possible addition of cipro-floxacin 2 µg/ml to prevent gram-negative infections when such therapy is considered appropriate based on patient characteristics. Preventive therapy may involve daily flush solu-tions or use of 1-hour dwell times every 1-2 days.

Use of antibiotic lock solutions to treat catheter-related sepsis remains controversial, although evidence is mounting that antibiotic lock technique may be used successfully to avoid catheter removal in certain patients.

High intraluminal antibiotic concentrations may be needed, particularly if biofilm and fibrous material are present, in order to achieve bacterial eradication. Multiple antibiotic combinations with heparin have been studied and are stable for at least 12-24 hours. The antibiotic lock technique is well tolerated and generally effective in treating CVC-related infections that do not involve soft tissue at the insertion or tunnel site or that are not fungal in origin. Catheter clearance may be achieved after 1-2 weeks of antibiotic lock therapy alone or in combination with systemic antibiotics. The frequency of antibiotic locks and appropriate dwell time are not well established and must be individualized based on drug stability and frequency of intravenous drugs or fluids that are infused with use of the infected line. Large, prospective, randomized trials are needed to determine the most appropriate concentration of antibiotics, duration of therapy, and role of concomitant systemic antibiotics with antibiotic lock therapy for catheter-related sepsis.

References

1. Maki DG, Cobb L, Garman JK, Shapiro JM, Ringer M, Helgerson RB. An attachable silver-impregnated cuff for prevention of infection with central venous catheters: a prospective randomized multicenter trial. Am J Med 1988;85:307-14.
2. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. JAMA 1994;271:1598-601.
3. Capdevila JA, Gavalda J, Pahissa A. Antibiotic-lock technique: usefulness and controversies. Antimicrobics Infect Dis Newsletter 1996;15:9-13.
4. Oppenheim BA. Optimal management of central venous catheter-related infections: what is the evidence? J Infect 2000;40:26-30.
5. Vanherweghem JL, Dhaene M, Goldman M, et al. Infections associated with subclavian dialysis catheters: the key role of nurse training. Nephron 1986;42:116-19.
6. Cheesbrough JS, Finch RG, Burden RP. A prospective study of the mechanisms of infection associated with hemodialysis catheters. J Infect Dis 1986;154:579-89.
7. Hoen B, Kessler M, Hestin D, Mayeux D. Risk factors for bacterial infections in chronic haemodialysis adult patients: a multicentre prospective survey. Nephrol Dial Transplant 1995;10:377-81.
8. Schwab SJ, Buller GL, McCann RL, Bollinger RR, Stickel DL. Prospective evaluation of a Dacron cuffed hemodialysis catheter for prolonged use. Am J Kidney Dis 1988;11:166-9.
9. Cappello M, De Pauw L, Bastin G, et al. Central venous access for haemodialysis using the Hickman catheter. Nephol Dial Transplant 1989;4:988-92.
10. Vanherweghem JL, Cabolet P, Dhaene M, et al. Complications related to subclavian catheters for hemodialysis: report and review. Am J Nephrol 1986;6:339-45.
11. Moss AH, Vasilakis C, Holley JL, Foulks CJ, Pillai K, McDowell DE. Use of a silicone dual-lumen catheter with a Dacron cuff as a long-term vascular access for hemodialysis patients. Am J Kidney Dis 1990:16:211-15.
12. 12. Marr KA, Sexton DJ, Conlon PJ, Corey GR, Schwab SJ, KirklandKB. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. Ann Intern Med 1997;127:275-80.
13. Huraib S, Askar A, Abu-Aisha H, al-Wakeel J. Prevalence of infection from subclavian dialysis catheters with two different postinsertion catheter cares: a randomized comparative study. Angiology 1994;45:1047-51.
14. Levin A, Mason AJ, Jindal KK, Fong IW, Goldstein MB. Prevention of hemodialysis subclavian vein catheter infections by topical povidone-iodine. Kidney Int 1991;40:934-8.
15. Fong IW. Prevention of haemodialysis and peritoneal dialysis catheter-related infection by topical povidone-iodine. Postgrad Med J 1993;69(suppl 3):S15-17.
16. Chazan JA, London MR, Pono LM. Long-term survival of vascular accesses in a large chronic hemodialysis population. Nephron 1995;69:228-33.
17. Cairo MS, Spooner S, Sowden L, Bennetts GA, Towne B, Hodder F. Long-term use of indwelling multipurpose silastic catheters in pediatric cancer patients treated with aggressive chemotherapy. J Clin Oncol 1986;4:784-8.
18. Darbyshire PJ, Weightman NC, Speller DC. Problems associated with indwelling central venous

catheters. Arch Dis Child 1985;60:129-34.
19. Lowder JN, Lazarus HM, Herzig RH. Bacteremias and fungemias in oncologic patients with central venous catheters: changing spectrum of infection. Arch Intern Med 1982;142:1456-9.
20. Raucher HS, Hyatt AC, Barzilai A, et al. Quantitative blood cultures in the evaluation of septicemia in children with Broviac catheters. J Pediatr 1984;104:29-33.
21. Winston DJ, Dudnick DV, Chapin M, Ho WG, Gale RP, Martin WJ. Coagulase-negative staphylococcal bacteremia in patients receiving immunosuppressive therapy. Arch Intern Med 1983;143:32-6.
22. Flynn PM. Vascular access device infections. In: Patrick CC, ed. Clinical management of infections in immunocompromised infants and children. Philadelphia: Lippincott, Williams & Wilkins, 2001:212-23.
23. Costerton JW, Irvin RT, Cheng KJ. The bacterial glycocalyx in nature and disease. Annu Rev Microbiol 1981;35:299-324.
24. Pfaller MA, Messer SA, Hollis RJ. Variations in DNA subtype, antifungal susceptibility, and slime production among clinical isolates of Candida parapsilosis. Diagn Microbiol Infect Dis 1995;21:9-14.
25. Farber BF, Kaplan MH, Clogston AG. Staphylococcus epidermidis extracted slime inhibits the antimicrobial action of glycopeptide antibiotics. J Infect Dis 1990;161:37-40.
26. Raad II, Darouiche RO. Catheter-related septicemia: risk reduction. Infect Med 1996;3:807-23.
27. Sherertz RJ, Raad II, Belani A, et al. Three-year experience with sonicated vascular catheter cultures in a clinical microbiology laboratory. J Clin Microbiol 1990;28:76-82.
28. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med 1977;296:1305-9.
29. Kiehn TE, Armstrong D. Changes in the spectrum of organisms causing bacteremia and fungemia in immuno-compromised patients due to venous access devices. Euro J Clin Microbiol Infect Dis 1990;9:869-72.
30. Raad II, Bodey GP. Infectious complications of indwelling vascular catheters. Clin Infect Dis 1992;15:197-208.
31. Maki DG. Infections due to infusion therapy. In: Bennett JV, Brachman PS, eds. Hospital infections. Boston: Little Brown, 1992;849-98.
32. Strausbaugh LJ, Sewell DL, Ward TT, Pfaller MA, Heitzman T, Tjoelker R. High frequency of yeast carriage on hands of hospital personnel. J Clin Microbiol 1994;32:2299-300.
33. Plouffe JF, Brown DG, Silva J Jr, Eck T, Stricof RL, Fekety FR Jr. Nosocomial outbreak of Candida parapsilosis fungemia related to intravenous infusions. Arch Intern Med 1977;137:1686-9.
34. Mermel LA, McCormick RD, Springman SR, Maki DG. The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: a prospective study utilizing molecular subtyping. Am J Med 1991;91: S197-205.
35. Maki DG, Stolz SM, Wheeler S, Mermel LA. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: a randomized, controlled trial. Ann Intern Med 1997;127:257-66.
36. Hanna H, Raad I, Darouiche R. New approaches for prevention of intravascular catheter-related infections. Infect Med 2001;18:38-48.
37. Raad I. Intravascular-catheter-related infections. Lancet 1998;351:893-8.
38. Hawiger J, Timmons S, Strong DD, Cottrell BA, Riley M, Doolittle RF. Identification of a region of human fibrinogen interacting with staphylococcal clumping factor. Biochem J 1982;21:1407-13.
39. Kuusela P. Fibronectin binds to Staphylococcus aureus. Nature 1978;276:718-20.
40. Bouali A, Robert R, Tronchin G, Senet JM. Characterization of binding of human fibrinogen to the surface of germ-tubes and mycelium of Candida albicans. J Gen Microbiol 1987;133(pt 3):545-51.
41. Sheth NK, Franson TR, Sohnle PG. Influence of bacterial adherence to intravascular catheters on in-vitro antibiotic susceptibility. Lancet 1985;2:1266-8.
42. Deretic V, Schurr MJ, Boucher JC, Martin DW. Conversion of Pseudomonas aeruginosa to mucoidy in cystic fibrosis: environmental stress and regulation of bacterial virulence by alternative sigma factors. J Bacteriol 1994;176:2773-80.
43. Mermel LA, Farr BM, Sheretz RJ, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 2001;32:1249-72.

44. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. MMWR Recomm Rep 2002;51(RR-10):1-29.
45. Messing B, Peitra-Cohen S, Debure A, Beliah M, Bernier JJ. Antibiotic-lock technique: a new approach to optimal therapy for catheter-related sepsis in home-parenteral nutrition patients. J Parenter Enteral Nutr 1988;12:185-9.
46. Messing B. Catheter-sepsis during home parenteral nutrition: use of the antibiotic-lock technique. Nutrition 1998;4:466-8.
47. Benoit JL, Carandang G, Sitrin M, Arnow PM. Intraluminal antibiotic treatment of central venous catheter infections in patients receiving parenteral nutrition at home. Clin Infect Dis 1995;21:2186-8.
48. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1-12.
49. Vercaigne LM, Sitar DS, Penner B, Bernstein K, Wang GQ, Burczynski FJ. Antibiotic-heparin lock: in vitro antibiotic stability combined with heparin in a central venous catheter. Pharmacotherapy 2000;20:394-9.
50. Henrickson KJ, Powell KR, Schwartz CL. A dilute solution of vancomycin and heparin retains antibacterial and anticoagulant activities. J Infect Dis 1988;157:600-1.
51. Carratala J, Niubo J, Fernandez-Sevilla A, et al. Randomized, double-blind trial of an antibiotic-lock technique for prevention of gram-positive central venous catheter-related infection in neutropenic patients with cancer. Antimicrob Agents Chemother 1999;43:2200-4.
52. Henrickson KJ, Dunne WM. Modification of central venous catheter flush solution improves in vitro antimicrobial activity. J Infect Dis 1992;166:544-6.
53. Anthony TU, Rubin LG. Stability of antibiotics used for antibiotic-lock treatment of infections of implantable venous devices (ports). Antimicrob Agents Chemother 1999;43:2074-6.
54. Capdevila JA, Segarra A, Planes AM, et al. Successful treatment of haemodialysis catheter-related sepsis without catheter removal. Nephrol Dial Transplant 1993;8:231-4.
55. Haimi-Cohen Y, Husain N, Meenan J, Karayalcin G, Lehrer M, Rubin LG. Vancomycin and ceftazidime bioactivities persist for at least 2 weeks in the lumen in ports: simplifying treatment of port-associated bloodstream infections by using the antibiotic lock technique. Antimicrob Agents Chemother 2001;45: 1565-7.
56. Henrickson KJ, Powell KR, Schwartz CL. A dilute solution of vancomycin and heparin retains antibacterial and anticoagulant activities. J Infect Dis 1988;157:600-1.
57. Messing B, Man F, Colimon R, Thuillier F, Beliah M. Antibiotic-lock technique is an effective treatment of bacterial catheter-related sepsis during parenteral nutrition. Clin Nutr 1990;9:220-5.
58. Schwartz C, Henrickson KJ, Roghmann K, Powell K. Prevention of bacteremia attributed to luminal colonization of tunneled central venous catheters with vancomycin-susceptible organisms. J Clin Oncol 1990;8:1591-7.
59. Henrickson KJ, Axtell RA, Hoover SM, et al. Prevention of central venous catheter-related infections and thrombotic events in immunocompromised children by the use of vancomycin/ciprofloxacin/heparin flush solution: a randomized, multicenter, double-blind trial. J Clin Oncol 2000;18:1269-78.
60. Andris DA, Krzywda EA, Edmiston CE, Krepel CJ, Gohr CM. Elimination of intraluminal colonization by antibiotic lock in silicone vascular catheters. Nutrition 1998;14:427-32.
61. Douard MC, Arlet G, Leverger G, et al. Quantitative blood cultures for diagnosis and management of catheter-related sepsis in pediatric hematology and oncology patients. Intensive Care Med 1991;17:30-5.
62. Johnson DC, Johnson FL, Goldman S. Preliminary results treating persistent central venous catheter infections with the antibiotic lock technique in pediatric patients. Pediatr Infect Dis J 1994;13:930-1.
63. Longuet P, Douard MC, Arlet G, Molina JM, Benoit C, Leport C. Venous access port-related bacteremia in patients with acquired immunodeficiency syndrome or cancer: the reservoir as a diagnostic and therapeutic tool. Clin Infect Dis 2001; 32:1776-83.
64. Reimund JM, Arondel Y, Finck G, Zimmermann F, Duclos B, Baumann R. Catheter-related infection in patients on home parenteral nutrition: results of a prospective survey. Clin Nutr 2002;21:33-8.
65. Gaillard JL, Merlino R, Pajot N, et al. Conventional and nonconventional modes of vancomycin administration to decontaminate the internal surface of catheters colonized with coagulase-negative staphylococci. J Parenter Enteral Nutr 1990;14:593-7.

66. Barriga FJ, Varas M, Potin M, et al. Efficacy of a vancomycin solution to prevent bacteremia associated with an indwelling central venous catheter in neutropenic and non-neutropenic cancer patients. Med Pediatr Oncol 1997;28:196-200.
67. Reynolds JEF, Parfitt K, Parsons AV, et al. Martindale: the extra pharmacopoeia, 31st ed. London: Pharmaceutical Press; 1996.
68. Nilsson L, Naller R, Ansehn S. Inhibition of aminoglycoside activity by heparin. Antimicrob Agents Chemother 1981;26: 155-8.

Reprint Address
Heather L. VandenBussche, Pharm.D., Department of Pharmacy Practice, Ferris State University, Bronson Methodist Hospital, 601 John Street, Kalamazoo, MI 49007; E-mail: vandenbh@bronsonhg.org .

Pharmacotherapy. 2005;25(2):211-227.