

Presentation

Evidence-Based Practice in the Management of Vascular Access Devices for Home Parenteral Nutrition Therapy

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ABSTRACT. Catheter-related bloodstream infection and catheter occlusion are potential significant complications of parenteral nutrition therapy. The increased incidence and associated morbidity, mortality, increased costs, and quality-of-life issues experienced with these adverse events necessitate specialized management of vascular access devices. The host coagulation response to biomaterials and the associated development of biofilm on vascular devices are complex phenomena. Multiple interventions are required to prevent

access of bacteria to both intraluminal and extraluminal catheter surfaces, and the occurrence of catheter occlusion. The discovery of the biofilm form of microbial life and the associated recalcitrance of biofilm bacteria to antimicrobials has provided insight into the failure of current prevention, diagnostic, and treatment protocols. Critical interventions are presented correlating current evidence with new discoveries in pathogenesis. (*Journal of Parenteral and Enteral Nutrition* 30:S82–S93, 2006)

The revolution in health-care delivery systems over the last 2 decades has shifted the care of patients from the acute care setting to alternate sites. Provision of healthcare in the home has become the fastest-growing segment of the healthcare system to the extent that nearly as many patients are receiving care in the home as in the hospital setting.¹

Nearly eight million people in the United States received medical care at home in 1996,² of which 774,113 (10%) were estimated to have at least 1 indwelling medical device.³ The use of a medical device is the greatest predictor (exogenous) of healthcare-associated infection.³ Complications related to vascular access devices (VADs) have reportedly been the primary cause of morbidity, mortality, and rehospitalization related to parenteral nutrition therapy in hospitalized patients,^{4,5} home patients—including adults^{6–8} and pediatrics^{9,10}—in the United States and abroad.^{11–13} Unfortunately, the transfer of care to alternate sites was not accompanied by the development of national surveillance systems to monitor outcomes and adverse events or with the establishment of formal infection control programs for standardization in the prevention, diagnosis, and treatment of complications.^{3,14}

The safe administration of parenteral nutrition (PN) requires the use of a central venous catheter (CVC) due to the hypertonic and acidic properties of the solution. CVCs most appropriate for PN therapy in the home include peripherally inserted central catheters (PICC),

tunneled catheters, and implanted ports^{15,16} (see Ryder Appendix). However, the use of these devices is not without serious risk. Thrombotic catheter occlusion and catheter-related infections are the most frequently reported catheter complications for all types of CVCs in all healthcare settings. In an analysis of data from the Strategic Health Care Programs National Database (April 1999 to September 2000) that included 50,470 patients receiving home infusion care (2.83 million catheter-days), the rate of CVC complication was 1.5 per 1000 catheter-days.¹⁷ The most common events (per 1000 catheter-days) were catheter dysfunction (0.83; nonthrombotic 0.6, thrombotic 0.23), catheter-site infections (0.26), and bloodstream infections (0.19). In the face of the increasing shift of care for the more acutely ill and immunocompromised patients to the nonhospital setting, an increase in the rate of these complications might be expected.

Prevention of complications remains the cornerstone of quality patient care and improved outcomes. Harbarth et al¹⁸ conducted a systematic review of the literature published in the last decade to generate a crude estimate of the proportion of potentially preventable nosocomial infections under current healthcare conditions. The evaluation of 30 reports suggests that at least 20%, ranging from 10% to 70%, of all nosocomial infections are preventable. The most important reduction effect was discovered for catheter-related bloodstream infection (CRBSI). Little is known about the proportion of preventable infections in the home-care setting.

With continued concern for the increased morbidity, mortality, and risk of device-related complications and the lack of standardization of care in alternate sites, it is prudent to identify key evidence-based strategies applicable to home PN patients for the care and man-

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agement of VADs. The purpose of this paper is to review the evidence for implementation of critical preventative strategies linked to the pathogenesis of the most common VAD complications, catheter-related infections and thrombotic catheter occlusion.

CATHETER-RELATED INFECTIONS

The estimated 20% prevention rate for nosocomial infections raises the question of why 80% are not preventable. Recent discoveries related to microbial survival strategies and antimicrobial resistance provide insight into the pathogenesis of CRBSIs. Understanding pathogenesis gives clear direction to prevention.

Pathogenesis of Catheter-Related Infections

IV catheters inserted into the bloodstream are subject to the hydrodynamics of 2 flow systems. The external surface of the catheter interfaces with the circulating blood, whereas the internal surface interacts with a variety of infusates, including crystalloid solutions, drug admixtures, blood and blood products, and nutritive solutions. The rate of blood flow is dependent on the diameter of the catheterized vessel and the patient's physiologic status. The rate of flow within the catheter is highly variable, depending on the infusion therapy, or there may be no flow when the catheter is "locked." Both Silastic and polyurethane are negatively charged, and hydrophobic biomaterials that promote adherence of various contacting particles in solutions and host products form a "conditioning film" on the catheter surface.

Under any circumstance, the external and internal catheter luminal surfaces are not mirror images. Microorganisms in contact with either surface interact with the biomaterial under very different conditions. The pathogenesis of infection at each surface must be considered independently in order to develop effective measures for prevention. Catheter-related infections occur as the result of a complex series of events: (a) microbial contamination of the internal or external surface of the catheter or add-on devices, (b) microbial adherence, (c) biofilm development, and (d) dispersal and dissemination of biofilm bacteria into the bloodstream.¹⁹

The patient's skin is the primary source of contamination of the external catheter surface. During insertion, bacteria are impacted on the tip and external catheter surface as the catheter transcends the epidermis. Thus, the catheter arrives in the bloodstream with a specific quantity of adherent bacteria. Elliott et al²⁰ verified this phenomenon in a study of 30 cardiac surgical patients requiring central venous catheterization. After insertion, the skin at the insertion site and all devices used during the procedure were cultured. The tip of each catheter was cultured *in situ* within 90 minutes of the insertion during surgery. Sixty-seven percent of cultures from the insertion site were positive, as well as 50% of guidewires, 4% of skin dilators, 36% of insertion needles, and 17% of the catheter tips. Within 3 days, 11% of catheters had >15 colony forming units (cfu) on the external surface despite rigorous skin antisepsis and aseptic technique. These results

are further substantiated in 2 subsequent studies using pulsed gel electrophoresis techniques to match organisms attached to the tip of the catheter with organisms at the insertion site.^{21,22}

Arrival of the catheter into the bloodstream triggers a well-defined host response.²³ Plasma proteins instantly adhere to the catheter surface upon contact with the blood. Attachment of arriving platelets, neutrophils, and fibrin(ogen) forms a "conditioning layer" on the catheter surface over the next few hours. Thrombus may then form to a variable extent over the fibrin sheath. After approximately 1 week, migratory fibroblasts and smooth muscle cells from the injured vessel wall cover the fibrin sheath/pericatheter thrombus. By 2 weeks, a layer of migratory endothelial cells that may then be protective against microbial attachment encases the host-derived sheath. Planktonic bacteria "free floating" in the bloodstream from distant sources may attach to the developing conditioning layer or pericatheter thrombus and further colonize the catheter.^{24–26} The preattached bacteria immediately develop a biofilm for survival in a new hostile environment.

Concurrently, contamination and colonization of the skin tract or subcutaneous tunnel may continue to occur during the inflammatory phase of wound healing within the first few days of catheterization. Microorganisms from the skin surface at the insertion site are passively transported within the edematous skin tract by capillary action.²⁷ The arriving microorganisms attach to the catheter surface or surrounding traumatized tissue and form colonizing biofilm. The progression from colonization to infection depends on the bacterial count, the species present, the virulence of the organisms, and the host immune response.²⁸

Microorganisms gain entrance to the internal lumen of the catheter at any entry point, anywhere along the fluid path where the system is manipulated (ie, IV solution connection sites, administration tubing junctions, access portals, and needleless connectors). The source of contamination is primarily the hands of medical personnel and the patient's own skin or body fluids in contact with the access sites. Bacteria flowing through any of the administration devices that come in direct contact with the inner lumen attach to surface and form colonizing biofilms. The same process of protein attachment, fibrin deposition, and clotting occurs within the lumen when used for blood sampling and blood product administration or when blood is allowed to remain within the lumen. The host conditioned surface then provides attachment sites for arriving bacteria.^{25,28}

Biofilm: Microbial Life on Surfaces

The initial event in the formation of biofilm is the attachment of microbes to the surface of the biomaterial or conditioned surface. Within 10–20 minutes of direct contact, phenotypic changes within the microbial cell wall initiate the production of species-dependent adhesins and accumulation proteins.^{29,30} Self-produced exopolymer saccharides embed the proliferating cells into cell clusters or microcolonies.

Although each biofilm is unique in structure, most biofilms develop as multilayered cell clusters with a complex architecture of towers and flow channels for the delivery of nutrients and removal of waste. This structure sustains an environment heterogeneous to oxygen level, nutrient availability, and metabolic state, depending on the location of the cell within the biofilm. The parent cells adherent to the biomaterial surface are the most deprived of nutrient availability and are the most metabolically altered into a slow-growing or nongrowing, dormant lifestyle. Development of the biofilm evolves according to the local microenvironment conditions and is often incorporated structurally within host conditioning layers or tissue matrices. The rate of growth is influenced by flow rate, nutrient composition of the liquid (blood or infusate), and temperature.³¹ The bloodstream provides ideal conditions to support biofilm growth on indwelling devices. Depending on the location and number of attached or "sessile" bacteria, the biofilm forms in patchy sections or develops in a contiguous layer completely covering the surface.

Biofilms harbor large numbers of organisms within a small scale, and pathogen cell densities can reach as many as 10^7 cells/cm² on a surface.³² Increasing cellular density within the biofilm triggers an elaborate cell-to-cell communication that regulates biofilm structure and progeny cell dispersal.³³ Dissemination of biofilm cells is species dependent but typically occurs by the shedding of single daughter cells or detachment of clumps of biofilm cells by hydrodynamic shear forces or by cell-cell signaling that directs the production of substances that lyse the biofilm matrix.³⁴ Cells dispersed as single planktonic cells are readily killed by normal host defense mechanisms, and the biofilm remains nonpathogenic. However, when the dissemination becomes extensive or if the host becomes immunosuppressed, colonization develops into overt infection.³⁰ Dispersal in clumps, particularly *Staphylococcus aureus*, containing hundreds of resistant cells may result in metastatic infections.³⁵

Biofilms mature at variable rates dependent on the microbial species. *Staphylococcus* biofilms mature within 7 days, whereas *Pseudomonas* biofilms mature later, around 10–12 days.^{36,37} Extraluminal catheter-related infections are typically evidenced within the first week of catheterization.³⁸ This correlates well with heavy initial colonization of the external catheter surface that was most likely inserted through poorly disinfected skin. Infection from the internal lumen typically occurs after 1 week as the number of manipulations increase; however, more recently the internal lumen has been shown to be the primary source of bloodstream infection as early as 3 and 6 days in short-term catheters.³⁹ The mean time to infection in long-term catheters is >10 days and implicates the internal lumen as the major site of CRBSI.⁴⁰

It has been estimated that as many as 65% of bacterial infections treated by physicians in the developed world are related to biofilms.³⁴ Clinical implications for prevention, diagnosis, and treatment of vascular catheter-related infections can be derived from understanding the pathogenesis of biofilm infections. The follow-

ing characteristics of biofilm infections should be considered in the management of CVCs^{25,29,35,41}:

- virtually any organism in contact with a biomaterial can form a biofilm;
- microbial attachment to surfaces results in extensive phenotypic changes profoundly different from unattached cells;
- bacteria growing in biofilm may be in a dormant but viable state and initially may fail to grow in culture;
- biofilm infections are inherently resistant to all antimicrobial agents (by 10–1000 times) and to the host's immune system;
- aging biofilms become increasingly more difficult to treat;
- in general, exposure of biofilm to prolonged and elevated concentrations of antibiotic agents kills approximately 90% of biofilm cells; the persisting cells survive and regenerate the biofilm after cessation of antibiotic therapy.

Evidence-Based Prevention Strategies

The Centers for Disease Control and Prevention's (CDC) *Guidelines for the Prevention of Intravascular Catheter-Related Infections* offers 113 recommendations for implementation in all healthcare settings.¹⁵ This extensive set of guidelines represents the complexity of effort required for the safe use of these devices. Harbarth et al¹⁸ found that the most effective approach to the reduction of nosocomial infections includes the implementation of a multimodal quality improvement program applying standardized policies and, if necessary, mandatory practice changes. Considering the pathogenesis of catheter-related infections, interventions should be designed to prevent microbial contact with the external catheter surface and microbial entry to the internal surfaces of the entire delivery system. Given that the major sources of microorganisms are the patient's own skin and the hands of medical personnel, a multimodal intervention package must be implemented to prevent microbial access from these sources.

Extraluminal contamination: skin antisepsis. Contamination of the external lumen during insertion and throughout the duration of use is most effectively minimized by systematic skin antisepsis and the use of an antimicrobial dressing (Table I). Preoperative skin preparation is probably the most important intervention for the prevention of CRBSI. Protocol development for effective skin antisepsis requires an understanding of the anatomy, physiology, and microbiology of the skin at the chosen site of insertion.

The basic structure of the skin from outer- to innermost layer includes the superficial horny cell layer of the stratum corneum (1–2 mm thick), the viable or stratified cell layer of epidermis (50–100 μ m thick), the dermis (1–2 mm thick), and the hypodermis (1–2 mm thick).⁴² The stratum corneum is composed of approximately 15 layers of corneocytes that provide the barrier function of the skin. The corneocytes are remnants of terminally differentiated keratinocytes generated by the stratified epidermis positioned directly under the stratum corneum. The stratified epidermis is

TABLE I
Evidence-based recommendations for the prevention of contamination of the external lumen of central venous catheters

Intervention	Recommendation: Guidelines for Prevention of Intravascular Catheter-Related Infections ¹⁵	CDC category	Cochrane level
Skin antisepsis	Disinfect clean skin with an appropriate antiseptic before catheter insertion and during dressing changes. Although a 2% chlorhexidine-based preparation is preferred, tincture of iodine, an iodophor, or 70% alcohol can be used.	IA	
	New evidence: Chalyakunapruk N, Veenstra DL, Lipsky BA, et al. Chlorhexidine compared with povidone iodine solution for vascular catheter-site care: a meta-analysis. <i>Ann Intern Med.</i> 2002;136:792–801. Conclusion: Results suggest that the incidence of bloodstream infections is significantly reduced in patients with central venous lines who receive chlorhexidine gluconate vs povidone iodine. For insertion-site skin disinfection.		I
Site dressing	Seal LA, Paul-Cheadle D. A systems approach to preoperative surgical patient skin preparation. <i>AJIC.</i> 2004;32:57–62. Conclusion: These data support the need for a systems approach to preoperative surgical skin preparation and reinforce the CDC guidelines. This approach has a positive impact on infection rates and may reduce the additional costs associated with this preventable event.	IA	IV
	Use either sterile gauze or sterile, transparent, semipermeable dressing to cover the catheter site.		
	New evidence: Gillies D, O'Riordan L, Car D, et al. Gauze and tape and transparent polyurethane dressings for central venous catheters. <i>Cochrane Database Syst Rev.</i> 2003;4:CD003827. Conclusion: There was no evidence of any difference in the incidence of infectious complications between any of the dressing types compared in the review. There is a high level of uncertainty regarding the risk of infectious complications with the compared dressings. Further research is necessary using rigorously performed randomized controlled trials. No recommendation can be made for the use of chlorhexidine sponge dressings to reduce the incidence of infection		I
	New evidence: Hanazaki K, Shingu K, Adachi W, et al. Chlorhexidine dressing for the reduction in microbial colonization of the skin with central venous catheters: a prospective randomized controlled trial. <i>J Hosp Infect.</i> 1999; 42:165–167. Conclusion: The use of the chlorhexidine sponge significantly reduces colonization of the insertion site as compared to use of the transparent dressing alone.		Unresolved issue
	Maki DG, Mermel LA, Kluger D, et al. The Efficacy of a Chlorhexidine-Impregnated Sponge for the Prevention of Intravascular-Related Infections: A Prospective, Randomized, Controlled, Multicenter Study. Washington, DC: American Society for Microbiology; 2000. Conclusion: The use of the chlorhexidine-impregnated sponge resulted in significant reductions in the incidence of local catheter-related infections and catheter-related bloodstream infections.		II

composed of 10–20 layers of keratinized epithelial cells. The stratum corneum receives a new basal layer of cells to replace the outermost surface layer of dead cells (squames) shed from the skin surface each day. The stratum corneum is replaced in total approximately every 2 weeks.⁴³ Healthy skin disseminates approximately 10^7 squames daily, 10% of which contain viable bacteria.

The microbiology of the skin varies widely, depending on body location and nutrient and water availability. Normal colony count of the skin at the subclavian and jugular insertion sites is approximately 1000–10,000 cfu/cm² compared with approximately 10 cfu per cm² at the antecubital space.⁴⁴ The transient skin flora arrives from the environment and may include bacteria, fungi, and virus. The resident flora is found mainly in the stratum corneum, 80% of which are located within the first 5 layers.⁴⁵ The remaining 20% inhabit the deeper reservoirs of sebaceous glands and

hair follicles sustained within biofilms that provide added protection against antiseptic agents.^{29,46,47} The dominant species of resident flora is the coagulase negative staphylococci (CNS; mostly *Staphylococcus epidermidis*). *S epidermidis* grows in prolific biofilms between the squamous cells of the outer 3–10 layers of the stratified epithelium and colonize the hair follicles and sebaceous glands quite successfully.³²

Topical application of antimicrobial agents eliminates CNS on the skin surface but does not sterilize the underlying stratum corneum, sebaceous glands, or hair follicles.⁴⁸ The bacterial concentration of the skin is most effectively reduced by the combination of physical removal, along with antimicrobial activity by antiseptic exposure.⁴⁹ The CDC guidelines¹⁵ and the 2004 AORN (*Association of Operating Room Nurses*) *Standards, Recommended Practices, and Guidelines*⁵⁰ recommend a 2-step process for preoperative skin preparation and continued catheter insertion site care. The 2

steps include skin cleansing, followed by application of an antiseptic. The CDC guidelines recommend specific antiseptics for use on clean skin but do not address methods for cleansing the skin. The AORN guidelines provide specific recommended practice techniques for both skin cleansing and surgical site preparation. Recommendations for skin cleansing include (a) patient showering before arrival at the practice setting, (b) washing the surgical site before arrival in the practice setting, and (c) washing the surgical site immediately before applying the antiseptic agent.⁵⁰

Data presented by Seal and Paul-Cheadle⁵¹ further support the utility of a systems approach to surgical-site preparation. Use of a combination of antiseptic shower(s) or bath(s), followed by antiseptic surgical site preparation with alcohol-based antiseptics resulted in a positive impact on the incidence of surgical-site infections.

Substantial evidence indicates that chlorhexidine gluconate (CHG) solutions are the superior agents for use in vascular catheter insertion care for the reduction of CRBSIs. The CDC guidelines recommend 2% CHG as the preferred antiseptic for skin preparation and designate its use as a performance indicator for reducing CRBSI. The economic benefits of CHG use for vascular catheter site care have been compared with povidone iodine use in a decision analysis model.⁵² The model estimates that the use of CHG compared with povidone iodine results in a 1.6% decrease in the incidence of CRBSI, a 0.23% decrease in the incidence of death, and a cost savings of \$113 per catheter used.

CHG in combination with alcohol increases the potential activity of the antiseptics. The alcohol provides rapid reduction in bacterial counts but has minimal persistence. The CHG remains active for at least 6 hours and is minimally affected by the presence of organic material.^{53,54} Repeated use of CHG increases effectiveness over time due to the binding and retention of active antiseptic to the surface epithelial cell walls.⁵⁵ A preoperative 4% CHG skin scrub (Hibiclens scrub sponge, Regent Medical Ltd, Irlam, UK) followed by the application of a 2% CHG/70% alcohol antiseptic (ChloraPrep, Medi-Flex Inc., Kansas City, KS) is suggested for maximum physical and chemical reduction of transient and resident flora before passage of the catheter through the skin.

Within 18 hours of antiseptic application, resident bacteria surface from the deeper reservoirs and recolonize the skin surface, regardless of the type of sterile dressing applied over the insertion site.^{45,48,53} Repeated skin antisepsis may be important within the first 24–48 hours of insertion to remove repopulating bacteria from the insertion site avoiding migration into the skin tract by capillary action. Postinsertion site care is accomplished by using the same 2-step process. Skin cleansing with gentle mechanical friction accomplishes removal of desquamed epithelial cells, repopulating bacteria, inactive antiseptic, oils, sweat, and any drainage if present. The antiseptic is then applied to clean skin. A multidirectional, back-and-forth cleansing using alcohol saturated swab sticks, followed by circular application of a 2% CHG/70% alcohol combination, is suggested.⁵⁶

Extraluminal contamination: antimicrobial dressing. Considerable debate over the role of gauze and tape dressings vs transparent polyurethane film dressings in the prevention of catheter-related infections has been observed in the literature. Gillies et al⁵⁷ recently completed a Cochran database systematic review to identify by meta-analysis any differences between gauze and tape dressings and transparent polyurethane film dressings in the incidence of CVC-related local infection or CRBSI, catheter security, dressing condition, tolerance to the material, and ease of application in hospitalized patients. There was no evidence of any difference in the incidence of infectious complications between any of the dressing types compared in the review. Traditional sterile gauze and tape dressings and transparent polyurethane film dressings provide protection for the catheter site from trauma and transient bacteria and prevent the accumulation of moisture; however, neither have any antimicrobial properties. This illustrates the critical importance of effective skin antisepsis as the major intervention in the prevention of catheter site infection, tunnel and port pocket infection, and CRBSI from the extraluminal source.

The use of a CHG-impregnated polyurethane foam disc applied around the catheter and in direct contact with the skin surface at the insertion site has demonstrated the ability to maintain a sterile skin surface at the insertion site over the lifetime of the catheter.⁵⁸ In a randomized clinical trial, 50 patients undergoing abdominal surgery had a CVC placed for PN and received either a transparent polyurethane film dressing (Bioclusive, Johnson & Johnson, Inc, New Brunswick, NJ) or a CHG-impregnated disc (Biopatch, Johnson & Johnson) covered with a transparent film dressing. Two skin cultures were taken once a week during the dressing change, 1 from under the CHG disc and 1 from a distant site under the transparent dressing. Contamination was detected under the transparent dressing in 14 of 60 cases (23.3%), whereas no bacterial contamination was observed under the CHG disc ($p < .0001$). In the control group (transparent dressing alone), bacterial contamination was detected in 7 of 64 cases (10.9%) at the insertion site and in 17 of 64 cases (26.6%) at the distant site under the dressing ($p < .0001$). The difference in contamination at the insertion site between the CHG disc and control was significant in favor of the CHG disc ($p < .01$). There was no difference in contamination under the dressing at the distant site between the 2 groups.

In a second, randomized, blinded, controlled, multicenter trial by Maki et al,⁵⁹ use of a CHG-impregnated foam disc (Biopatch) was compared with a control transparent polyurethane film dressing in 589 hospitalized patients receiving short- and medium-term CVCs and arterial catheters.^{59,60} All CRBSIs were confirmed by concordance between microorganisms isolated from peripheral blood and the catheter tip, hub, or infusate demonstrated by DNA subtyping. The CHG dressing significantly reduced the risk of local catheter-related infection (CHG disc, 28.14%; and control, 45.24%; $p < .001$) and CRBSI (CHG disc, 2.37%; and control, 6.12%; $p < .05$). Not surprisingly, the greatest

TABLE II
Evidence-based recommendations for the prevention of contamination of the internal lumen of central venous catheters

Intervention	Recommendation: Guidelines for Prevention of Intravascular Catheter-related Infections ¹⁵	CDC category	Cochrane level
Hand hygiene	Observe proper hand hygiene procedures by washing hands with either conventional antiseptic-containing soap and water or with waterless alcohol-based gels or foams. Observe hand hygiene before and after palpating catheter insertion sites, as well as before and after inserting, replacing, accessing, repairing, or dressing an intravascular catheter.	IA	
	New evidence: Boyce JM, Pittett D. HICPAC Committee and HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force: guideline for hand hygiene in health-care settings. <i>MMWR Recommend Rep.</i> 2002;51(RR16):1–44.	IB	
	Recommendation: Decontaminate hands before having direct contact with patients.		
	When decontaminating hands with an alcohol-based hand rub, apply product to palm of one hand and rub hands together, covering all surfaces of hands and fingers, until hands are dry. Follow manufacturer's recommendations regarding the volume of product to use.	IB	
Access-site disinfection	When washing hands with soap and water, wet hands first with water, apply the amount of product recommended by the manufacturer to hands, and rub hands vigorously for at least 15 seconds, covering all surfaces of the hands and fingers. Rinse hands with water and dry thoroughly with a disposable towel.	IB	
	Clean injection ports with 70% alcohol or an iodophor before accessing the system.	IA	
	Minimize contamination risk by wiping the access port with an appropriate antiseptic and accessing the port with only sterile devices.	IB	
	New evidence: Casey AL, Worthington T, Lambert PA, Quinn D, Farouqi MH, Elliott TS. A randomized, prospective clinical trial to assess the potential infection risk associated with the PosiFlow needleless connector. <i>J Hosp Infect.</i> 2003;54:288–293.		I
Prophylactic flush solution	Conclusion: Disinfection of needleless connectors with either chlorhexidine/alcohol or povidone iodine significantly reduced external microbial contamination.		
	Do not routinely use antibiotic lock solutions to prevent CRBSI. Use prophylactic antibiotic solution only in special circumstances (eg, in the treating a patient with long-term cuffed or tunneled catheter or port who has a history of multiple CRBSIs despite optimal maximal adherence to antiseptic technique).	II	
	New evidence: Chatzinikolaou I, Zipf TF, Hanna H, et al. Minocycline-ethylenediamine-tetraacetate lock solution for the prevention of implantable port infections in children with cancer. <i>Clin Infect Dis.</i> 2003;36:116–119.		III
	Conclusion: M-EDTA lock solution was efficacious in preventing port-related infections in children with cancer, without causing any adverse events. Large prospective, randomized trials are needed to further test the ability of M-EDTA to prevent long-term catheter-related infections.		
	Kite P, Eastwood K, Sugden S, Percival SL. Use of <i>in vivo</i> generated biofilms from hemodialysis catheters to test the efficacy of a novel antimicrobial catheter lock for biofilm eradication <i>in vitro</i> . <i>J Clin Microbiol.</i> 2004;42:3073–3076.		IV
	Conclusion: The efficacy of tetrasodium EDTA as a catheter lock potentially shows that this agent could substantially reduce catheter-related infections and be used to treat patients with limited access.		

benefit was the prevention of local infection and the extraluminal source of CRBSI.

The cost benefit and impact on CRBSI mortality has also been assessed. A cost-benefit sensitivity analysis estimates potential US net benefits from CHG dressing use to range from \$275 million to approximately \$1.97 billion, and a preventable mortality between 329 and 3906 deaths annually.⁶⁰

The combination of the 2-step protocol of cleansing and antiseptic site preparation for both preoperative and insertion site preparation using 2% CHG and 70% alcohol combinations along with application of the CHG-impregnated disc appears to be very powerful and cost-effective for the prevention of catheter-related infections in short-term transcutaneous catheters. This combination may be beneficial for prevention of tunnel infections in cuffed catheters, particularly

within the first 2 weeks until adhesion of the cuff to the subcutaneous tissue is complete.

Intraluminal contamination: hand hygiene. Entry of microorganisms through contaminated access sites of the infusion system is the major source of intraluminal contamination and the major source of CRBSI in long-term catheters. Interventions should be focused on prevention of touch contamination, access-site disinfection, and use of prophylactic flush solutions (Table II).

As early as 1 week after admission, hospitalized patients become colonized with antimicrobial-resistant pathogens that may be transferred into the home on hospital discharge.⁶¹ Fundamental to developing infection-control policies for the delivery of medical care in the home is the need to recognize that people live in an environment where all types of human activities are ongoing and that pathogens are continually introduced

into the home on people, food and water, pets, insects, and by air transmission.⁶² Hand hygiene is intended to decrease contamination of the hands with transient organisms from the local environment.

The term *hand hygiene* includes handwashing, antiseptic hand wash, antiseptic hand rub, or surgical hand antisepsis. In both the CDC *Guidelines for the Prevention of Intravascular Device-Related Infections*¹⁵ and the CDC *Guideline for Hand Hygiene in Health-Care Settings*,⁴² decontamination of hands is recommended before and after providing care procedures for intravascular devices. An antiseptic hand rub or antiseptic hand wash is recommended for hand decontamination.

Hand hygiene is the simplest, most effective measure for preventing healthcare-acquired infections.^{53,54} However, it is well known that compliance with hand hygiene by medical and nurse clinicians has historically been dismal.^{42,54} Hand hygiene protocols for home patients should be incorporated into the provider's infection control program and should include education and compliance monitoring of the nursing staff, education and compliance monitoring of the patient/caregiver, provision of appropriate hand hygiene products, and routine observation and feedback of technique to patients and caregivers.^{62,63}

Intraluminal contamination: access-site disinfection. Access-site disinfection is probably the most important step in prevention of CRBSI in long-term catheters. The CDC guidelines strongly recommend cleaning access ports with 70% alcohol or an iodophor before accessing the system; however, no recommendation regarding the duration or method for cleaning is provided (Table II). Three studies were cited in support of the Category IA recommendation. The study by Salzman et al⁶⁴ compared the efficacy of CHG (1% with and without 70% alcohol), ethanol (70% and 97%), and normal saline in eradicating microorganisms in an *in vitro* model of catheter hub contamination. They found that 70% ethanol was more effective than 1% CHG and concluded that ethanol is likely to be the safest treatment.

In the second *in vitro* study by Luebke et al,⁶⁵ the septum of 2 devices, one a conventional latex injection port and the other a split-septum injection system (Interlink, Baxter Healthcare Corp, Deerfield, IL), was inoculated with an *Enterococcus faecium* suspension of 10^4 – 10^5 cfu/mL. Each system was swabbed with a 70% alcohol-saturated pad using either a single-motion wipe or a 5-second wipe followed by a 1-minute drying period before puncture for flushing. The control group had no cleansing before puncture and flushing. The devices were accessed by either a needle (injection port) or blunt cannula (Interlink).

When 1 single-motion wipe was performed, the recovery fluid from the needleless device was positive in 6%, and 4% were positive in the conventional system. In the 5-second wipe/1-minute drying group, the recovery fluid was positive in 4% of needleless devices, whereas none of the conventional system cultures were positive. When no disinfection was performed, the transfer of organisms into the fluid path of the split septum was positive in 31%–80% of the needleless

devices and 72%–90% of the conventional injection ports. The authors concluded that the needleless system performed like the conventional system, but reinforced the need for an appropriate disinfection procedure before accessing either system.

The third cited study documented the potential spread of iatrogenic infection through contaminated multidose vials but did not examine the effect of antiseptics for disinfection before entry into the vial.⁶⁶

Casey et al,⁶⁷ in a more recent randomized, prospective, controlled trial, compared the microbial contamination rate of standard injection caps and a needleless positive-pressure valve. Seventy-seven patients undergoing cardiac surgery and requiring a CVC were randomly allocated to receive either needleless connectors (BD PosiFlow, BD Medical, Sandy, UT) or standard injection caps attached to stopcock entry points at the catheter hub. The microbial contamination rate of the external compression seals of 274 needleless connectors and 306 standard caps was assessed to compare the efficacy of 3 disinfectants: 70% isopropyl alcohol, 0.5% CHG gluconate in 70% isopropyl alcohol, and 10% povidone iodine. Each device was cleaned before and after each manipulation, allowing the disinfectant to dry for 2 minutes on each occasion. Each device was exchanged after 72 hours.

Forty-one percent of the needleless valves were externally contaminated at exchange. Contamination of the external compression seals was significantly lower when disinfected with CHG ($p < .0001$) and povidone iodine ($p < .0001$). There was no statistically significant difference in contamination rates between the CHG and povidone iodine group ($p = .4$). Seven percent of the needleless-valve stopcock entry points were internally contaminated, with no statistical difference between any of the disinfectants.

In the standard-cap group, 18% of the septa were externally contaminated, with no significant difference between the rate and extent of microbial contamination after swabbing with each of the disinfectants. Eighteen percent of the stopcock entry points were contaminated. Disinfection of the entry ports with either CHG or povidone iodine resulted in a reduced rate of internal contamination compared with alcohol. Overall, the use of 0.5% CHG gluconate in 70% isopropyl alcohol before and after each manipulation resulted in the lowest contamination rates.

These results are comparable to the results in a trial by Maki et al,⁶⁸ who compared the use of 2% aqueous CHG, 10% povidone iodine, and 70% alcohol for preinsertion skin antisepsis and access-site disinfection. The use of 2% CHG was associated with the lowest rates of localized infection and bacteremia.

Intraluminal contamination: prophylactic flush solution. The third critical intervention for prevention of intraluminal contamination is the instillation of an anti-infective locking solution when the catheter is not in use. The current standard includes normal saline or heparinized saline for maintaining catheter patency. Neither of these solutions inhibit microbial growth. To the contrary, heparin has been shown to support microbial growth in solution and in biofilm.^{69–72} Preliminary findings by Hostetler et al have raised concern that

heparin used in intravascular catheters may play a role in triggering a series of events that result in the production of a life-threatening toxic shock–like reaction with fungal (*Candida*) infections.⁷³

In at least 3 studies, prophylactic antibiotic catheter locking has demonstrated efficacy in the prevention of CRBSI^{74–76}; however, with the rapid emergence of Gram-positive, Gram-negative, and fungal antibiotic resistant strains, frontline antibiotics such as vancomycin, quinolones, β lactams and aminoglycosides should be reserved for treatment of systemic infections.^{40,77} Thus, the strong recommendation of the CDC is to not routinely use antibiotic lock solutions to prevent CRBSI.¹⁵

The efficacy of a combination solution of minocycline (Wyeth-Ayerst, Pearl River, NY) and disodium EDTA (Endrate; Abbott Laboratories, Chicago, IL) (M-EDTA) as a broad-spectrum antimicrobial/antibiofilm and antithrombotic agent has been thoroughly studied *in vitro*.^{69–71} Raad et al⁷⁰ investigated the prophylactic use of minocycline (3 mg/mL) and disodium EDTA (30 mg/mL) in 14 children with cancer for whom the solution was used to lock their ports. They found that M-EDTA significantly decreased the risk of CRBSI in comparison to the control group of 48 children using heparin ($p = .05$). These results are promising; however, IV minocycline has recently been discontinued by the manufacturer and is no longer available.

Tetrasodium EDTA (tEDTA) has been investigated as an antimicrobial agent in both *in vitro* and *ex vivo* studies. Ryder et al⁷⁸ compared ciprofloxacin 10, 100, 1000, and 5000 $\times$ MIC to tEDTA 40 mg/mL for the eradication of coagulase negative staphylococcus and *Pseudomonas aeruginosa* (PA) biofilm bacteria grown on glass fiber membranes. The mean log reduction (MLR) of CNS after 6 hours of exposure to ciprofloxacin was 7% at 10 $\times$ MIC, 15% at 100 $\times$ MIC, 26% at 1000 $\times$ MIC, and 35% for 5000 $\times$ MIC. The MLR of PA at 6 hours was 58% at 10 $\times$ MIC, 74% at 100 $\times$ MIC, 68% at 1000 $\times$ MIC, and 82% for 5000 $\times$ MIC. The MLR of the tEDTA at 6 hours was 100%, a statistically significant reduction against all other tested concentrations of ciprofloxacin ($p \leq .001$), except for CNS at 100 $\times$ MIC at 6 hours ($p = .06$).

Kite et al⁷⁹ investigated the effect of tEDTA in an *ex vivo* study of 20 clinically infected hemodialysis catheters. The explanted catheters were screened by a culture of through-catheter flush technique. Bacteria identified in the biofilms were Gram-positive, Gram-negative, and mixed species. The initial biofilm cell count levels averaged above 10^5 cfu/1 cm of intraluminal catheter surface. tEDTA 40 mg was instilled into equal catheter sections and remained “locked” for 24 hours. tEDTA was effective at complete eradication of the total viable count in almost all cases. tEDTA appears to be a very promising agent for the prophylaxis and treatment of vascular catheters, but randomized clinical trials are needed.

THROMBOTIC CATHETER OCCLUSIONS

Pathogenesis of Intraluminal Thrombotic Catheter Occlusions

Catheter occlusion may be partial or complete and is typically evidenced by inability to infuse or aspirate,

sluggish flow, or frequent pump alarms. Thrombotic catheter occlusion occurs as a result of clotted blood within the lumen or from the buildup of fibrin on the intraluminal surface over time. Plasma proteins and fibrin(ogen) are deposited during aspiration or administration of blood or blood products. Clotting of whole blood within the lumen is usually a consequence of an inadequate volume of flush solution, inadequate flushing technique, or retrograde blood flow on disconnect from needless connectors. Clotting directly at and slightly within the tip of the catheter may result from convex blood flow and fluid displacement that occurs while the catheter is locked, regardless of flushing method or needless connector design.⁸⁰

The correlation between thrombosis and infection has been well described.⁸¹ Some microbial species quickly attach directly to polymer surfaces, whereas others more readily adhere to a fibrin/platelet matrix. The biofilm/fibrin matrix formation may become thick enough to cause partial or complete occlusion. Sherertz et al⁸² investigated the sensitivity of various culture methods in the diagnosis of triple-lumen catheter infections. A strong correlation was identified between failed blood aspiration and the titer of microorganisms cultured from each lumen ($r = .85$). The inability to aspirate blood for culture was experienced in 51% of aspiration attempts, a likely indicator of partial or complete occlusion. The frequency of failed blood aspiration was 91% in catheters with significantly positive lumen cultures (100 cfu) compared to 58% when the cultures were negative (<100 cfu; $p = .001$).

Evidence-Based Prevention Strategies

Strategies for prevention of thrombotic occlusion should be focused on methods to maintain patency by keeping blood out of the catheter (Table III). The prevention of thrombotic catheter occlusion is centered primarily on 2 interventions: catheter flushing and the use of antireflux needless connectors and valves (Table III).

Intraluminal thrombotic occlusion: prophylactic flush solutions. There are 3 components important to the flushing protocol for maintaining patency of vascular catheters: the flush solution, the volume of solution, and the flushing technique. The use of normal saline and heparin has been studied extensively over the last 2 decades. Two meta-analyses published in the early 1990s set the current standard specifically for peripheral IV catheters. The results of the analysis by Peterson and Kirchhoff⁸³ found no significant difference in duration of patency between IV catheters flushed with saline solution and those flushed with a heparinized solution. Goode et al⁸⁴ concluded that saline is as effective as heparin in maintaining patency, preventing phlebitis, and increasing duration of use in peripheral IV locks. Saline has been used successfully in maintaining patency of CVCs as well.⁸⁵

Despite these findings, the rate of catheter occlusion,¹⁵ the incidence of intraluminal clots,^{86–88} the risk of heparin-induced thrombocytopenia,⁸⁹ and the lack of antimicrobial activity of saline and heparin continue to

TABLE III
Evidence-based recommendations for the prevention of thrombotic catheter occlusion

Intervention	Standard: Intravenous nursing society: infusion nursing standards of practice ⁹¹	Cochrane level
Prophylactic flush solutions	Flushing with 0.9% sodium chloride solution to ensure and maintain patency of an intermittently used CVC with a 3-position pressure-activated valve or a closed distal tip should be performed at established intervals. Flushing with heparin flush solution to ensure and maintain patency of an intermittently used CVC should be performed at regular intervals; the concentration of heparin should not interfere with the patient's clotting factors. The volume of the flush solution should be equal to at least twice the volume capacity of the catheter and add-on devices. New evidence: Chatzinikolaou I, Zipf TF, Hanna H, et al. Minocycline-ethylenediamine-tetraacetate lock solution for the prevention of implantable port infections in children with cancer. <i>Clin Infect Dis</i>. 2003;36:116–119. Results: No port infections, thrombotic events, or other adverse events were observed, compared with 10 port infections and 2 thrombotic events in 48 control patients whose ports were flushed with heparin. Kite P, Eastwood K, Sugden S, Percival SL. Use of <i>in vivo</i> generated biofilms from hemodialysis catheters to test the efficacy of a novel antimicrobial catheter lock for biofilm eradication <i>in vitro</i>. <i>J Clin Microbiol</i>. 2004;42:3073–3076. Conclusion: The efficacy of tetrasodium EDTA as a catheter lock potentially shows that this agent could substantially reduce catheter-related infections and be used to treat patients with limited access. EDTA is a calcium and iron chelator with anticoagulant activity. Polaschegg HD, Shah C. Overspill of catheter locking solution: safety and efficacy aspects. <i>ASAIO J</i>. 2003;49:713–715. Conclusion: The injection volume must exceed 120% of the catheter lumen to achieve the full strength of the locking solution at the tip.	I
Antireflux valves	No published standard or formal recommendations available for the use of needleless devices for the prevention of catheter occlusion. New evidence: Jacobs BR, Schilling S, Doellman D, et al. Central venous catheter occlusion: a prospective, controlled trial examining the impact of a positive-pressure valve device. <i>JPEN J Parenter Enteral Nutr</i>. 2004;28:113–118. Conclusion: CVCs with a positive-pressure valve device have a lower incidence of complete catheter occlusion than those with a standard cap.	III

be of great concern. EDTA has been explored as a potential agent for protection against catheter infection. EDTA is a calcium and iron chelator with very effective anticoagulation activity. Along with infection rates, Chatzinikolaou et al also compared occlusion rates of implanted vascular ports in the pediatric cancer patients using either a heparin lock or M-EDTA.⁹⁰ Two thrombotic episodes occurred in 48 patients in the heparin group, whereas no thrombotic events occurred in the M-EDTA group of 14 patients. tEDTA also appears to be a promising agent with dual application for both antimicrobial and anticoagulant capability.⁷⁹

The volume of flush solution is an important factor not only to prevent intraluminal clotting but also catheter tip occlusion, a phenomenon that occurs as a result of laminar flow and the flow distribution as predicted by the Hagen-Poiseuille law when the catheter is locked.⁹¹ The *IV Nursing Society's Standards of Practice* recommend that the volume of flush solution be equal to at least twice the volume capacity of the catheter.⁹¹ The findings of Polaschegg and Shah⁹² support this standard. In an *in vitro* study using dye and saline dilution, the investigators demonstrated that approximately 14% of the injected flush solution spills from the catheter when the exact priming volume is injected, resulting in a mean concentration of approximately 90% of the locking solution's concentration remaining in the fluid at the tip of the catheter. They concluded that the injection volume must exceed 120% of the

catheter lumen to achieve the full strength of the locking solution at the tip.

Intraluminal thrombotic occlusion: antireflux needleless connectors. Needleless connectors are important devices in the reduction of needlestick injuries in healthcare workers. However, the net benefit of these devices has been called into question as a result of several reports of associated increased infection risk.^{93,94} Early device designs also reportedly increased the incidence of catheter occlusion, particularly in the smaller-lumen catheters where a longer length of catheter is filled by a reflux displacement volume of blood on disconnection of the syringe.⁹⁵

Currently, at least 5 needleless connectors redesigned with an end positive-pressure mechanism and 2 devices incorporating a neutral displacement valve exist in the marketplace; however, evidence-based literature involving each of these devices is limited. Four randomized or prospective controlled trials investigating 3 antireflux devices—2 testing a neutral valve and 2 a positive-end-pressure valve—report a reduced incidence of catheter occlusion with the use of these devices.^{96–99} Reduced occlusion rates were also reported in 3 clinical studies evaluating use of 2 positive-end-pressure needleless connectors.^{95,100,101}

Currently, at least 2 marketed devices have not been validated in well-designed clinical trials or descriptive clinical investigations regarding infection risk or efficacy in the reduction of occlusion rates. Clinicians

should be cautious when using these devices without implementation of strict protocols and close monitoring of clinical outcomes. Access-site disinfection and timely changes of the devices has been stressed as a safety measure in the prevention of needleless device-associated CRBSI.^{67,94,102–106} The use of well-designed anti-reflux devices is an effective strategy for the prevention of CRBSI when appropriately disinfected before use and replaced at recommended intervals.

In summary, the prevention of catheter-related infections and thrombotic intraluminal occlusion requires strict adherence to evidence-based protocols. The development of effective protocols for the prevention, diagnosis, and treatment of CRI requires an understanding of the pathogenic mechanisms of microbial access to both the external and internal catheter lumen and the subsequent development of biofilm. A multimodal intervention strategy is required to address the multiple potential sources of microbial access to the catheter and delivery system. Recommended strategies critical in the prevention of extraluminal contamination include skin antisepsis and antimicrobial dressings. Hand hygiene, access-site disinfection, and antimicrobial flush solutions address prevention of intraluminal contamination. Although some of these are based on strong evidence, others are based on best practice theory and clinical evaluation.

Interventions to reduce the incidence of thrombotic catheter occlusions improve outcomes related to infection, delayed therapy, cost of treatment, and loss of access. Although not well studied, needleless devices designed to eliminate the presence of blood within the catheter while not increasing the risk of infection should be used with active outcome monitoring and quality-improvement controls. The use of normal saline as a flush solution may be a prudent choice in the face of the current concerns with heparin use. Continued investigation regarding the efficacy of new and promising flush solutions is urgently needed.

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