

The Promise of Novel Technology for the Prevention of Intravascular Device–Related Bloodstream Infection. I. Pathogenesis and Short-Term Devices

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Intravascular devices (IVDs) are widely used for vascular access but are associated with substantial risk of development of IVD-related bloodstream infection (BSI). The development of novel technologies, which are based on an understanding of pathogenesis, promises a quantum reduction in IVD-related infections in an era of growing nursing shortages. Infections of short-term IVDs (that is, those in place <10 days), including peripheral venous catheters, noncuffed and nontunneled central venous catheters (CVCs), and arterial catheters, derive mainly from microorganisms colonizing the skin around the insertion site, which most often gain access extraluminally. More-effective cutaneous antiseptics, such as chlorhexidine, a chlorhexidine-impregnated sponge dressing, CVCs with an anti-infective coating, anti-infective CVC hubs, and novel needleless connectors, have all been shown to reduce the risk of IVD-related BSI in prospective randomized trials. The challenge for the future will be to identify new preventative technologies and to begin to adapt more widely those technologies already shown to be efficacious and cost-effective.

Reliable vascular access is one of the most essential features of modern medical care. Unfortunately, the intravascular devices (IVDs) needed to establish reliable access are associated with a significant potential for producing iatrogenic disease, particularly bacteremia and candidemia [1–3]. More than 250,000 IVD-related (IVDR) bloodstream infections (BSIs) occur in the United States each year [1], each associated with attributable mortality rates of 12%–25% [4, 5], prolongation of hospital stay [4–7], and an added health care cost of \$33,000–\$35,000 [4–7].

By drawing on the growing knowledge of the pathogenesis and epidemiology of these infections, effective guidelines for the prevention of BSIs can be formulated. This review will first

examine the pathogenesis and magnitude of IVDR BSIs and discuss the use of novel technology for the prevention of IVDR BSIs involving short-term IVDs. A subsequent article will review technologic advances for the prevention of IVDR BSI involving long-term IVDs.

NATURE OF THE PROBLEM

Prospective studies in which every IVD was cultured at the time of removal show that every type of device carries some risk of causing BSI, but that the magnitude of risk varies greatly [8]. The device that poses the greatest risk of IVDR BSI today is the central venous catheter (CVC) in its many forms: up to 75% of IVDR BSIs originate from CVCs of various types [4–10], and CVCs are the most important risk factor for nosocomial candidemia [11]. Short-term, noncuffed, single-lumen or multilumen catheters inserted percutaneously into the subclavian or internal jugular vein have been shown to have rates of catheter-related BSI in the range of 3%–5% (table 1) [1, 2, 8]. Contrary to common belief, arterial catheters used for hemodynamic monitoring pose a risk of catheter-related BSI comparable to that of short-term CVCs [8].

Received 31 July 2001; revised 21 January 2002; electronically published 2 April 2002.

This is the first part of a 2-part article. Part 2, subtitled "Long-Term Devices," will appear in the next issue of *Clinical Infectious Diseases*.

Financial support for the writing of this manuscript was provided by an unrestricted research grant from the Oscar Rennebaum Foundation.

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Clinical Infectious Diseases 2002;34:1232–42

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1058-4838/2002/3409-0011\$03.00

Table 1. Rates of bloodstream infection (BSI) caused by various types of devices used for vascular access.

Device	No. of prospective studies	No. of device-related BSIs			
		Per 100 catheters		Per 1000 catheter-days	
		Pooled mean	95% CI	Pooled mean	95% CI
Peripheral venous catheter	13	0.2	0.1–0.3	0.6	0.3–1.2
Arterial catheter	6	1.5	0.9–2.4	2.9	1.8–4.5
Short-term, nonmedicated CVC	61	3.3	3.3–4.0	2.3	2.0–2.4
Pulmonary-artery catheter	12	1.9	1.1–2.5	5.5	3.2–12.4
Hemodialysis catheter					
Noncuffed	15	16.2	13.5–18.3	2.8	2.3–3.1
Cuffed	6	6.3	4.2–9.2	1.1	0.7–1.6
Peripherally inserted central catheter	8	1.2	0.5–2.2	0.4	0.2–0.7
Long-term tunneled and cuffed CVC	18	20.9	18.2–21.9	1.2	1.0–1.3
Subcutaneous central venous port	13	5.1	4.0–6.3	0.2	0.1–0.2

NOTE. Adapted from Kluger and Maki [8] based on 206 published prospective studies in which every device was evaluated for infection. CVC, central venous catheter.

PATHOGENESIS OF IVDR BSI

There are 2 major sources of IVDR BSI: (1) colonization of the IVD, or “catheter-related infection,” and (2) contamination of the fluid administered through the device, or “infusate-related infection” [12]. Contaminated infusate is the cause of most epidemic IVDR BSIs; this source has been reviewed elsewhere [1]. In contrast, catheter-related infections are responsible for most endemic IVDR BSIs and constitute the focus of this review.

For microorganisms to cause catheter-related infection, they must first gain access to the extraluminal or intraluminal surface of the device, where they can adhere and become incorporated into a biofilm that allows sustained infection and hematogenous dissemination [13]. Microorganisms gain access by 1 of the 3 following mechanisms: (1) skin organisms invade the percutaneous tract, probably facilitated by capillary action [14], at the time of insertion or in the days afterward; (2) microorganisms contaminate the catheter hub (and lumen) when the catheter is inserted over a percutaneous guidewire or when it is later manipulated [15]; or (3) organisms are carried hematogenously to the implanted IVD from remote sources of local infection, such as a pneumonia (figure 1) [16, 17].

With short-term IVDs (i.e., those in place <10 days)—peripheral intravenous catheters, arterial catheters, and noncuffed, nontunneled CVCs—most device-related BSIs are of cutaneous origin, are from the insertion site, and gain access extraluminally [18–20] and, occasionally, intraluminally. In contrast, contamination of the catheter hub and lumen appears to be the predominant mode of BSI with long-term, permanent IVDs (i.e., those in place ≥10 days), such

as cuffed Hickman- and Broviac-type catheters, cuffed hemodialysis CVCs, subcutaneous central venous ports, and peripherally inserted central catheters [21–24].

STRATEGIES FOR PREVENTION OF IVDR BSI

Detailed recommendations for the prevention of IVDR BSI were first published in 1973 [12], then by the Hospital Infection Control Practices Advisory Committee (HICPAC) in 1981 and again in 1996, and are being updated again [25]. With more consistent implementation of preventative measures (table 2), during the past decade, the incidence of primary IVD-associated BSI has decreased by nearly 40% [26]. Given a growing and critical shortage of nursing staff [27] and the growing evidence that nursing understaffing, especially in intensive care units (ICUs), greatly increases the risk of IVDR BSI [28], we believe that a further reduction in risk will require wider adoption of novel preventative technologies.

NOVEL TECHNOLOGY FOR PREVENTION OF SHORT-TERM IVDR BSI

During the past 2 decades, many investigators have examined the utility of novel technologies for prevention of IVDR BSI, with greater progress than has been achieved for any other type of nosocomial infection. Table 3 lists the results of a meta-analysis [29] of all of the clinical trials of each novel technology for short-term IVDs that could be found; the data given are only for prospective, randomized trials that used IVDR BSI as an outcome measure.

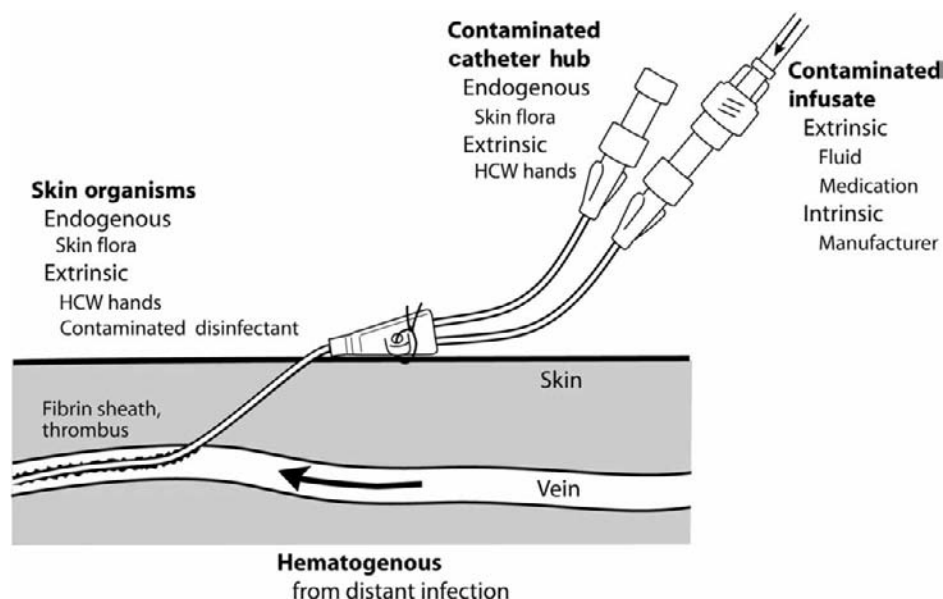


Figure 1. Potential sources of infection of a percutaneous intravascular device (IVD): the contiguous skin flora, contamination of the catheter hub and lumen, contamination of infusate, and hematogenous colonization of the IVD from distant, unrelated sites of infection [1]. HCW, health care worker.

Cutaneous Antisepsis

Given the evidence of the importance of cutaneous microorganisms in the pathogenesis of short-term IVDR infection, measures to reduce colonization of the insertion site would seem to be of the highest priority, particularly the choice of the chemical antiseptic for disinfection of the insertion site. In the United States, iodophors, such as 10% povidone-iodine, are used most widely [30]. Eight randomized, prospective trials have compared a chlorhexidine-containing antiseptic with either povidone-iodine or alcohol for preparation of the skin before insertion of IVDs [31–38], 5 of which specifically examined the antiseptic's role in the prevention of IVDR BSI involving CVCs and arterial catheters [31–35].

The agents were well tolerated in every trial. Seven of 8 trials [31–33, 35–38] found lower rates of catheter colonization in the chlorhexidine-containing antiseptic group, and 3 of 5 of the trials involving CVCs and arterial catheters showed a significant reduction in CVC-related BSIs [31, 33, 35]. A meta-analysis of the 5 trials of CVCs and arterial catheters (table 3) suggests that a chlorhexidine-containing antiseptic is superior to iodophors and indicates that, at the present time, it should be the antiseptic of first choice for vascular access sites [25].

Topical Anti-infective Creams or Ointments

Periodic application of a polyantibiotic ointment containing polymyxin, neomycin, and bacitracin was perhaps the first technologic innovation aimed at prevention of IVDR BSI. Five prospective randomized trials involving peripheral iv catheters

conducted during 1969–1986, in aggregate, showed no clear-cut benefit for prevention of IVDR BSI [39–43], but they did show a 5-fold increased risk of catheter colonization by *Candida* species [44].

Three subsequent trials of povidone-iodine ointment applied onto CVC insertion sites yielded discrepant results (table 3). A small trial that used povidone-iodine ointment with hemodialysis catheters showed a marked reduction in the rate of catheter-related BSIs caused by *Staphylococcus aureus* (2% vs. 17%; $P < .01$) [45]. Conversely, 2 larger trials involving all-purpose CVCs, primarily in an ICU patient population, showed no benefit whatsoever [43, 46].

More recently, the novel antistaphylococcal topical agent mupirocin was shown to be effective for preventing colonization of short-term noncuffed CVCs in a randomized trial [47], and a recent study involving patients undergoing hemodialysis demonstrated a significant reduction in the incidence of *S. aureus* BSIs (3% vs. 22% of catheters; $P < .001$; table 3) [48]. However, the routine use of topical mupirocin for the prevention of CVC-related BSI in a large European neonatal unit resulted in a 42% prevalence of mupirocin resistance among clinical isolates of coagulase-negative staphylococci [49]. Furthermore, heavy use of this agent for the control of an outbreak of infection with methicillin-resistant *S. aureus* in another center led to high-level mupirocin resistance in clinical *S. aureus* isolates [50]. Mupirocin is a valuable agent for decolonization of methicillin-resistant *S. aureus* carriers [51]. We believe that its routine use on vascular catheter sites will promote resistance. Routine use

Table 2. General recommendations for the prevention of intravascular device–related (IVDR) bloodstream infections (BSIs).

Recommendation	Strength of evidence ^a
General measures	
Educate all health care workers involved with vascular access regarding indications for use, proper insertion technique, and maintenance of IVDs	IA
Surveillance	
Routinely monitor institutional rates of IVDR BSI	IA
Determine rates of CVC-related BSI, using standardized definitions and denominators, expressed per 1000 CVC-days	IB
At insertion	
Use aseptic technique	
Wash hands before insertion or manipulation of any IVD	IA
Wear clean or sterile gloves during insertion or manipulation of noncentral IVD	IC
Use maximal barrier precautions (mask, cap, long-sleeved sterile gown, sterile gloves, and sterile sheet drape) during insertion of CVCs	IA
Use dedicated intravenous-device teams strongly recommended	IA
Use cutaneous antisepsis (chlorhexidine is preferred; however, an iodophor, such as 10% povidone-iodine, tincture of iodine, or 70% alcohol are also acceptable)	IA
Use of sterile gauze or a sterile semipermeable polyurethane film dressing	IA
Use of systemic antibiotics at insertion strongly discouraged	IA
Maintenance	
Remove IVDs as soon as their use is no longer essential	IA
Monitor the IVD site on regular basis—ideally, daily	IB
Change dressing of CVC insertion site at least weekly	II
Use of topical antibiotic ointments not recommended	IA
Perform systemic anticoagulation with low-dose warfarin (1 mg daily) for patients with long-term IVDs and no contraindication	IA
Replace PIVCs every 96 h	IA
Replace administration sets every 96 h, unless lipid-containing admixture or blood products given, in which case administration sets should be replaced every 24 h	IA
Technology	
Consider use of chlorhexidine-impregnated sponge dressing for adolescent and adult patients who have non-cuffed CVCs or arterial catheters expected to remain in place for ≥ 4 days	NR
If, after consistent application of basic infection-control precautions, the institutional rate of IVDR BSI is still high for short-term CVCs (i.e., ≥ 3.3 BSIs per 1000 IVD-days), consider the use of a CVC coated with an anti-infective agent (i.e., chlorhexidine–silver sulfadiazine or minocycline–rifampin)	IB
For individual patients with long-term IVDs in place who have had recurrent IVDR BSIs, despite consistent application of infection-control practices, consider the use of a prophylactic antibiotic lock solution (i.e., heparin with vancomycin [25 μ g/mL] with or without ciprofloxacin [2 μ g/mL])	II

NOTE. Adapted from the Healthcare Infection Control Practices Advisory Committee (HICPAC) draft guideline for the prevention of intravascular catheter–related infections [25]. CVC, central venous catheter; IVD, iv device; PIVC, peripheral iv catheter.

^a Adapted from the Centers for Disease Control/HICPAC system for weighting recommendations based on the quality of scientific evidence. IA, strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiological studies; IB, strongly recommended for implementation and supported by some experimental, clinical, or epidemiological studies and a strong theoretical rationale; II, suggested for implementation and supported by suggestive clinical or epidemiological studies or theoretical rationale; NR, no recommendation for or against use at this time.

of mupirocin and other topical anti-infectives on IVD insertion sites is discouraged in the new HICPAC guideline [25].

Novel Dressings

IVDs can be dressed with sterile gauze and tape or with a sterile, transparent, semipermeable polyurethane film dressing. The available data suggest that the 2 types of dressings are equivalent in terms of their effect on IVDR BSIs, including those involving short-term CVCs (table 3) [52–58].

Studies directly comparing different types of polyurethane dressings have not found differences in rates of catheter col-

onization or IVDR infection between standard polyurethane dressings and new hyperpermeable polyurethane dressings (OpSite IV3000, Smith and Nephew; Tegaderm Plus, 3M) (table 3) [59, 60]. A small study found that use of a novel hydrocolloid dressing (Visiband; Convatec-Squibb) was associated with reduced cutaneous colonization, compared with standard polyurethane dressings [61]; however, a larger randomized trial failed to show any benefit, finding a higher rate of catheter colonization and BSI in the hydrocolloid dressing group (table 3) [62].

The results of trials of polyurethane dressings, which contain

Table 3. Meta-analyses of prospective, randomized, clinical trials of novel technologies for prevention of intravenous device-related bloodstream infections in patients with short-term central venous catheters (CVCs) in place.

Technology	No. of trials	No. of CRBSIs/ no. of CVCs studied		RR (95% CI)	P
		Study technology	Control device		
Chlorhexidine (vs. povidone-iodine) cutaneous antisepsis	5	14/931	33/1213	0.55 (0.22–1.15)	.07
Topical anti-infective cream/ointment					
Povidone-iodine ointment	3	10/212	23/228	0.47 (0.14–1.21)	.04
Mupirocin ointment	1	1/69	10/67	0.10 (0.00–1.24)	<.01
Dressings					
Polyurethane (vs. gauze)	7	27/1070	20/725	0.97 (0.43–1.89)	.76
Hydrocolloid	1	5/77	1/78	5.06 (0.38 to >50)	.12
Hyperpermeable polyurethane	2	3/259	4/206	0.60 (0.02–8.73)	.70
Chlorhexidine sponge	1	8/665	24/736	0.37 (0.17–0.81)	.01
Silver-impregnated cuff	5	10/283	14/247	0.62 (0.28–1.38)	.30
Anti-infective-coated or -impregnated CVC					
Benzalkonium chloride	2	1/131	3/123	0.31 (0.00–22.90)	.36
Chlorhexidine-silver sulfadiazine	15	68/2100	107/2135	0.65 (0.45–0.90)	<.01
Minocycline-rifampin	1	0/130	7/136	0.00 (0.00–2.80)	.02
Minocycline-rifampin (vs. chlorhexidine-silver sulfadiazine)	2	1/394	14/418	0.08 (0.00–0.81)	<.01
Silver impregnated	4	18/260	42/246	0.40 (0.24–0.68)	<.01
Silver iontophoretic	3	8/275	21/295	0.41 (0.18–0.91)	.02
Anti-infective hub connector					
Antiseptic hub	2	9/144	15/137	0.57 (0.15–1.61)	.20
Povidone-iodine sponge wrap	1	0/22	6/25	0.00 (0.00–3.69)	.02
Needleless connectors	2	4/245	21/263	0.20 (0.07–0.59)	<.01

NOTE. Data are only from prospective, randomized trials that involved short-term centrally placed central venous catheters (CVCs) and that reported intravenous device-related bloodstream infection as an outcome. CRBSI, catheter-related bloodstream infection.

an antiseptic, such as povidone-iodine [63] or ionized silver [64], have also been disappointing. However, on the basis of the superiority of chlorhexidine for cutaneous disinfection of vascular access sites, a novel chlorhexidine-impregnated sponge dressing has been developed (Biopatch; Johnson & Johnson Medical) and evaluated in 3 trials to date (table 3) [65–67].

In a randomized trial by Hanazaki et al. [65], use of the chlorhexidine dressing was associated with significantly lower rates of cutaneous colonization of the catheter insertion site (0% vs. 10.9%; $P < .01$); however, no efforts were made to identify colonization of catheters or catheter-related BSI. A large, prospective, randomized trial comparing the use of the chlorhexidine dressing to a standard polyurethane dressing with short-term CVCs and arterial catheters in adults admitted to 2 teaching hospital ICUs showed a 60% reduction in the rate of catheter-related BSIs (RR, 0.37; $P = .01$; table 3) with use of the chlorhexidine sponge dressing, and no adverse reactions were associated with its use [67]. Moreover, testing of the in

vitro susceptibility of isolates recovered from infected catheters in both groups showed no evidence that the antiseptic dressing promoted resistance to chlorhexidine.

Attachable Silver-Impregnated Cuff

A tissue-interface barrier (Vitacuff; Vitaphore Corporation) incorporates the technology of Hickman catheters with an attachable cuff made of biodegradable collagen to which silver ion is chelated. The cuff can be attached to any short-term CVC or Swan-Ganz introducer at the time of insertion. Released silver ions provide an additional chemical barrier against introduced contamination.

Clinical trials of the attachable cuff involving short-term CVCs have had conflicting results (table 3) [44, 68–71]. Two of 5 studies demonstrated a significant reduction in the proportion of devices colonized with the use of an attachable cuff, but only 1 study was able to show a significant reduction in

the number of CVC-related BSIs [68]. The tendency of the cuff to be extruded has been offered as an explanation for its limited utility in preventing infections involving short-term CVCs.

Anti-infective Catheter Surfaces

Given the multiplicity of potential sources for infection of an IVD and the importance of adherence of microorganisms to the catheter surface in the pathogenesis of infection, the most effective strategy for prevention might be to develop a catheter with a surface material that is intrinsically resistant to colonization. Coating the catheter surface with a nontoxic antiseptic or antimicrobial drug, or incorporating such a substance into the catheter material itself, might prove to be an important technologic innovation for the prevention of IVDR infection.

Benzalkonium-impregnated CVCs. Heparin is now commonly bonded to the external surface of pulmonary-artery Swan-Ganz catheters during their manufacture [72]. Because the surfactant used to bind the heparin, benzalkonium chloride, has antimicrobial activity, heparin-bonded catheters exhibit surface antimicrobial activity in vitro [73]. Although no randomized clinical trial has specifically examined this issue for catheters in situ, an analysis of prospective studies of Swan-Ganz catheter-related infection suggests that heparin bonding leads to reduced rates of infection [73].

This serendipitous discovery prompted 2 randomized trials of a benzalkonium-impregnated, short-term multilumen CVC [74, 75]. Although the impregnated catheter was well tolerated and catheter colonization was significantly reduced in one of the trials [74], neither trial showed benefit for the prevention of BSIs (table 3).

Chlorhexidine–silver sulfadiazine–impregnated catheters. A novel CVC made of polyurethane impregnated with minute quantities of silver sulfadiazine and chlorhexidine (ArrowGard; Arrow International) became available ~10 years ago. There have now been 15 randomized trials of this catheter for prevention of CVC-related infection [76–90]. Most of the trials have demonstrated a reduction in the rate of CVC colonization, but only 2 were able to show a significant reduction in the number of CVC-related BSIs [82, 89]. In the most rigorous study to date [82], which used molecular subtyping to conclusively identify CVC-related BSIs, use of the antiseptic catheter was associated with a 2-fold reduction in the incidence of catheter colonization and a 5-fold reduction in the rate of catheter-related BSIs (RR, 0.21; $P = .03$). In vitro analysis of 58 isolates recovered from infected catheters from the 2 groups showed no evidence that use of the antiseptic catheter induced resistance to chlorhexidine and silver sulfadiazine. Use of the antiseptic catheter was shown to be highly cost-effective when baseline rates of CVC-related BSI exceeded 2% (i.e., 3.3 cases per 1000 IVD-days).

Recent meta-analyses by Veenstra et al. [91] and Mermel [3]

have shown that chlorhexidine–silver sulfadiazine–impregnated CVCs reduce rates of CVC-related BSI by at least 40% (OR, 0.40–0.56). Veenstra et al. [91] have also published cost analyses suggesting that use of the antiseptic CVC is cost-effective when the incidence of CVC-related BSI is greater than 0.4 BSIs per 1000 IVD-days [92, 93]; they project that, for every 300 antiseptic catheters used, \$59,000 will be saved, 7 cases of BSIs will be avoided, and 1 death will be prevented.

These studies confirm that the chlorhexidine–silver sulfadiazine–impregnated CVC is effective for reducing rates of catheter-related BSI in patients at high risk of infection who require short-term central venous access. Studies involving CVCs left in place for >1 week have generally found less benefit [76, 77, 79, 81, 83], probably because the antiseptic catheter begins to lose surface antimicrobial activity during the first 72 h after placement [78], decreasing to 25% of its baseline value within 10 days in situ [83].

In vivo resistance to the chlorhexidine–silver sulfadiazine combination has not been reported; however, chlorhexidine resistance was inducible in vitro in an isolate of *Pseudomonas stutzeri* [94]. Although clinical trials in the United States have not reported adverse effects from use of the catheter, 12 cases of anaphylactoid reactions have been reported from Japan (~1 case per 8300 catheters placed) [95], and a case of anaphylactic shock has been reported from the United Kingdom [96]. There have been no reports of reactions from the United States, where >3 million catheters have been sold through the year 2000; suspected adverse reactions should be reported to the US Food and Drug Administration [95].

Antibiotic-coated catheters. In a randomized clinical trial involving use of CVCs and arterial catheters in a surgical ICU, catheters with cefazolin bonded to the surface with benzalkonium chloride were associated with a 7-fold reduction in the rate of catheter colonization; however, there were no catheter-related BSIs identified in the study [97]. A subsequent historical analysis in their ICU found that routine use of cefazolin-coated catheters was associated with a marked reduction in the rate of catheter-related BSI (from 11.5 to 5.1 cases per 1000 IVD-days; $P < .01$) [98]. In these studies, no data were provided on whether the antibiotic-coated catheters promoted infection by cefazolin- or other antibiotic-resistant organisms or yeasts.

Raad et al. [99, 100] proposed the use of a minocycline-rifampin-coated catheter on the basis of in vitro and animal data demonstrating potent activity of this novel combination against gram-positive organisms, gram-negative organisms, and *Candida albicans*. A randomized clinical trial involving nearly 300 short-term CVCs found that minocycline-rifampin-coated catheters were associated with greatly reduced rates of catheter colonization (8% of patients with coated catheters vs. 26% of those without coated catheters; $P < .001$; table 3) and CVC-

related BSIs (0% vs. 5%, respectively; $P < .01$) [101]. No resistance to the minocycline-rifampin combination was detected.

A multicenter trial comparing minocycline-rifampin-coated and chlorhexidine-silver sulfadiazine-impregnated CVCs found that antibiotic-coated catheters were far less likely to be colonized at removal (RR, 0.34; $P < .001$) [102]. Although Kaplan-Meier analysis showed that the 2 catheters are equivalent with regard to the risk of catheter-related BSI until day 7, overall rates of BSI were much lower among patients who had the minocycline-rifampin-coated catheter placed (0.3 vs. 4.1 cases per 1000 IVD-days; $P < .001$; table 3).

The superiority of this catheter may lie in the fact that both the external and internal surfaces of the catheter are coated, whereas only the external surface of the antiseptic catheter was coated. Moreover, the combination of minocycline and rifampin exhibits surface activity against staphylococci that is far superior to that of chlorhexidine-silver sulfadiazine [103], and the antibiotic-coated catheter appears to retain surface antimicrobial activity for longer periods in situ [100–104]. A new CVC (ArrowGard Plus; Arrow International), which has a higher level of chlorhexidine-silver sulfadiazine in the catheter material and coating the external and internal surfaces as well as the catheter hub, is now available, and its efficacy is being evaluated in a multicenter randomized trial.

The major theoretical deterrents to the use of antibiotics for coating percutaneous intravascular catheters are the ineffectiveness of antibiotics against antibiotic-resistant nosocomial bacteria and yeasts, the risk of promoting bacterial resistance with long-term topical use [49, 105, 106], and the potential for hypersensitization [107]. Although induction of resistance to this antimicrobial combination has not been identified in the 3 clinical trials done to date [101, 102, 108], an in vitro study has shown that resistance to the minocycline-rifampin combination can develop [109]. Future studies should carefully evaluate the long-term effect of anti-infective agent-coated catheters on nosocomial microbial resistance.

Silver-impregnated catheters. A silver-coated or -impregnated catheter is the only other surface modification that has been evaluated in clinical trials (table 3) [110–115]. In a randomized clinical trial involving patients in the oncology ward, Goldschmidt et al. [110] found that a noncuffed silver-coated CVC was one-half as likely as a control catheter to cause CVC-related BSI (10.2% vs. 21.2% of catheters; $P = .01$). A subsequent trial of the same technology failed to find any difference in the rate of colonization of silver-coated CVCs, as compared with that of control catheters, and there were no differences in the rates of catheter-related BSI [112].

The equivocal efficacy of these first-generation silver catheters has been ascribed to inadequate release of silver ions at the catheter surface [116]. Two second-generation silver-impregnated catheters have been studied clinically. The Erlanger

catheter uses a microdispersed silver technology to greatly increase the quantity of available ionized silver and has been evaluated in 2 trials [113, 114]. Patients in an adult study randomized to the Erlanger catheter group had lower rates of catheter colonization and rates of “catheter-associated sepsis” than did patients in the control catheter arm (5.3 vs. 18.3 cases per 1000 IVD-days; $P < .05$).

A novel silver-impregnated CVC that uses oligodynamic iontophoresis technology has been developed and studied in 3 randomized trials. This technology incorporates both silver and platinum into the polyurethane, promoting the local release of silver ions. A large cohort study that used historical controls demonstrated that rates of CVC-related BSI in the year that the silver-platinum catheter was used exclusively were markedly lower than rates seen in the years in which standard polyurethane CVCs were used (0% vs. 4%; $P < .001$) [115]. Three small, randomized clinical trials have examined the efficacy of the silver iontophoretic catheter [111, 117, 118]. Individually, these trials failed to demonstrate a statistically significant reduction in the risk of infection; however, pooled analysis of the results suggests that this catheter can reduce the risk of IVDR BSI (RR, 0.41; $P = .02$; table 3).

Active iontophoresis. Active iontophoresis is the newest CVC technology to be developed. The application of a low-amperage electrical current to carbon-impregnated CVCs [119] or through silver wires wrapped around the proximal segment of silicone CVCs [120] has been studied in vitro, with successful results. Building on these results, a novel silver CVC through which a low-level electrical current is passed has been developed. In vitro experiments with this technology suggest that active iontophoresis can sterilize an established biofilm and can prevent secondary biofilm formation on top of a dead biofilm, a theoretical limitation of the passive anti-infective surface technologies. Although promising, this CVC technology has yet to be evaluated in a clinical trial.

Anti-infective Hubs and Connectors

A novel CVC hub developed by Segura et al. [121] (Segur-Lock; Inibsa Laboratories) contains a connecting chamber filled with iodinated alcohol and was shown in a randomized clinical trial to be associated with greatly reduced rates of catheter colonization and CVC-related BSI (4% vs. 16%; $P < .01$), although a subsequent trial failed to show benefit with the use of this hub (table 3) [122]. Another model, which used a povidone-iodine-saturated sponge to encase the hub, also showed significant reductions in CVC-related BSIs, as compared with a control hub (0% vs. 24%; $P < .05$; table 3) [123]. Although noncuffed CVCs were studied in these trials, the catheters remained in place for a considerably longer duration than usual (14–21 days) in ICUs in the United States, which emphasizes the importance of the intraluminal route of CVC-related BSI.

The design of these trials and the definitions used for catheter-related BSI and device colonization were not as rigorous as those used in the trials of antiseptic- and antimicrobial-coated catheters.

Needleless connectors have been shown to reduce the risk of needlestick injuries in health care workers [124]; however, their net benefit has been called into question by reports of paradoxically increased rates of primary BSI [125]. Inappropriate use of these devices may have been responsible in some instances [126]. Recent randomized clinical trials that compared 2 novel needleless connectors with standard hub connectors have shown a reduced risk of IVDR BSI (RR, 0.20; $P = .001$; table 3) [127, 128].

Part 2 of this review, which will appear in the next issue of *Clinical Infectious Diseases*, will discuss the utility of novel technology in preventing IVDR BSI with long-term IVDs.

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