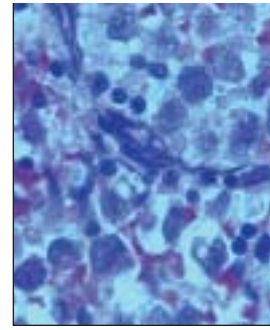


## CATHETER-RELATED BLOODSTREAM INFECTIONS, PART II: SPECIFIC PATHOGENS AND PREVENTION

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### SPECIFIC PATHOGENS

#### *Coagulase-Negative Staphylococci*

Coagulase-negative staphylococci, such as *Staphylococcus epidermidis*, are the most common cause of catheter-related bloodstream infections (CRBIs).<sup>1,2</sup> Most patients have a benign clinical course and rarely develop frank sepsis with a poor outcome.<sup>3</sup> To date, there have been no randomized trials that have evaluated any treatment modality for CRBIs due to coagulase-negative staphylococci. Coagulase-negative staphylococcal CRBIs may resolve with removal of the catheter and no antibiotic therapy, yet many experts believe that such infections should be treated with antibiotics. Although patients with catheter-related coagulase-negative staphylococcal bacteremia can be treated successfully while the catheter remains in place, with the majority remaining free of recurrence, catheter retention could result in a significantly higher risk for the recurrence of the bacteremia.<sup>4</sup>

#### *Staphylococcus Aureus*

There are no data from randomized trials with adequate sample size and statistical power to show an optimal duration for the treatment of catheter-related *S aureus* bloodstream infection (BSI). In the past, *S aureus* bac-

teremia was treated for 1 month due to greater concern about the risk of endocarditis than would be expected.<sup>5,6</sup> However, several recent studies have suggested that the risk of endocarditis or other deep tissue infection related to *S aureus* bacteremia may be sufficiently low to recommend a shorter course of therapy (10 to 14 days) for patients with apparently uncomplicated CRBI.<sup>7-12</sup>

Removal of vascular catheters that are infected with *S aureus* has been associated with a more rapid response to therapy and/or a higher cure rate in three observational studies.<sup>13-15</sup> However, none of these studies was a randomized, controlled trial, so definitive data are unavailable. It appears reasonable that removable nontunneled catheters that can be easily replaced should be removed immediately when they are found to be the source of *S aureus* bacteremia, even for mild to moderate cases. By contrast, with long-term tunneled or hemodialysis catheters, which are more expensive and more difficult to replace, this recommendation is more controversial (except in the setting of tunnel infection), despite the fact that two of the three aforementioned studies suggested a higher rate of failure when catheters were not immediately removed.<sup>13,15</sup>

In a recent study that used the antibiotic lock technique in addi-

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tion to standard parenteral therapy for patients with hemodialysis CRBI, all 40 cases of CRBIs (including all 12 cases reported to involve *S aureus*) were cured and the catheters were salvaged.<sup>16</sup> These results suggest that, in some cases, uncomplicated *S aureus* infection of tunneled catheters may be managed without catheter removal in the absence of tunnel or exit-site infection (ie, when infection is confined to the lumen of the catheter) by means of standard parenteral therapy combined with antibiotic lock therapy.

For patients who remain febrile and/or have bacteremia for more than 3 days following catheter removal and/or initiation of antibiotic therapy, a longer course of therapy has been recommended due to an increased risk for underlying endocarditis.<sup>17,18</sup> AIDS has been reported to be an adverse prognostic factor in patients with catheter-related *S aureus* bacteremia.<sup>19</sup> For this reason, a longer course of therapy has also been recommended for patients with HIV infection who develop catheter-related *S aureus* BSI.<sup>20</sup> A randomized trial suggested that treating severe *S aureus* infections with rifampin and a fluoroquinolone was as effective as the use of standard parenteral therapy with a  $\beta$ -lactam antibiotic or vancomycin in patients who are allergic to  $\beta$ -lactam antibiotics.<sup>21</sup> These results are credible because of the excellent results achieved with oral rifampin and quinolone for the treatment of right-side endocarditis due to *S aureus*.<sup>22,23</sup> If rifampin is used to treat such infections, a single daily dose results in higher area-

under-the-curve values for rifampin than do divided doses that total to the same amount.<sup>24,25</sup>

### *Gram-Negative Bacilli*

The incidence of intravascular CRBI due to Gram-negative bacilli may also be increasing. These microorganisms are commonly associated with contaminated infusate and are a common cause of BSI in immunocompromised patients with tunneled catheters or devices.<sup>26,27</sup> Successful treatment of tunneled catheter-related Gram-negative bacteremia has been reported by antimicrobial therapy without catheter removal, especially in studies of pediatric patients.<sup>16</sup> Other studies have demonstrated that catheter removal in cases of catheter-related bacteremia with *Pseudomonas* species other than *P aeruginosa*, *B cepacia*, *Acinetobacter baumannii*, and *Stenotrophomonas* species reduced the rate of treatment failure and improved survival.<sup>28</sup>

An antimicrobial agent with activity against aerobic Gram-negative bacilli should be added to the empiric coverage of CRBIs in neutropenic patients and in those presenting with severe sepsis or septic shock. It should also be considered in cases of nosocomial outbreaks due to specific Gram-negative organisms (eg, an *A baumannii* outbreak in an intensive care unit [ICU]) and whenever a contaminated infusate is suspected as the source of the infection. Several antimicrobial agents might be included in the empiric antimicrobial regimen: aminoglycosides,

aztreonam, third-generation cephalosporins with antipseudomonal activity, fourth-generation cephalosporins, piperacillin/tazobactam, and the quinolones. No data are available to guide the duration of therapy with intravenous (IV) antibiotics vs oral antibiotics for Gram-negative BSIs. For some antibiotics, such as the quinolones (eg, ciprofloxacin) or trimethoprim-sulfamethoxazole, blood levels after oral administration differ minimally from levels after IV administration. Extended-spectrum  $\beta$ -lactamase-producing *Klebsiella pneumoniae* bacteremia occurring in an epidemic ICU setting is mainly catheter-related. Because of high rates of resistance to  $\beta$ -lactam/ $\beta$ -lactamase inhibitors and the variable activity of aminoglycosides, carbapenems should be the treatment of choice since they are uniformly active against these strains.<sup>29</sup>

The clinical characteristics and outcome of bacteremia caused by non-glucose-fermenting Gram-negative bacilli and *Aeromonas* species were examined by Martino et al<sup>30</sup> in 115 adults with hematologic malignancies or solid tumors. The most aggressive pathogens were *P aeruginosa*, *Stenotrophomonas maltophilia*, *Aeromonas* species, *Acinetobacter* species, and *B cepacia*, all of which caused either septic syndrome or pneumonia in more than 40% of cases. *P aeruginosa* was involved less often in catheter-related bacteremia than other species. Polymicrobial bacteremia (n = 28) was catheter related more often than monomicrobial bacteremia and more often

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required catheter removal for definitive cure. *S maltophilia* is an important pathogen, especially in the highly compromised host. Isolation of this organism from a blood culture should prompt a careful review of the patient with particular emphasis on removal of indwelling CVCs and commencement of appropriate antibiotic therapy. In a retrospective analysis of BSIs due to *S maltophilia* at a tertiary care hospital in Melbourne, Australia, 80% of episodes were nosocomial. The most common characteristics in cases of bacteremia were the presence of an indwelling central venous catheter (CVC) (84%) and previous antibiotic therapy (73%). A significant correlation was found between deaths and a failure to remove the CVC ( $P=.01$ ) or treat with appropriate antimicrobials ( $P=.01$ ).<sup>31</sup>

To compare the characteristics of bacteremic infections by different aerobic Gram-negative bacilli in patients with hematologic malignancies, Martino and colleagues<sup>32</sup> studied 54 consecutive monomicrobial bacteremias by Enterobacteriaceae (EB), 15 by *P aeruginosa*, 43 by other non-glucose-fermenting Gram-negative bacilli (NGF-GNB), and 11 by other GNB. A significant proportion of bacteremias by EB (37%) and *P aeruginosa* (40%) were accompanied by severe morbidity (septic shock, pneumonia, or deep-seated organ infections) vs only 7% of other NGF-GNB ( $P<.01$ ). Most infections by these latter bacteria were catheter-related bacteremias (80% vs 2% of EB,  $P<.005$ ), while most EB infections (61%) were uncomplicated

bacteremias of unknown source vs 14% of other NGF-GNB ( $P<.005$ ). Appropriate antibiotics alone cured 98% of EB and 73% of *P aeruginosa* bacteremias but only 26% of other NGF-GNB ( $P<.005$  for both differences), which were cured by catheter removal in 70%, usually after failure of antibiotic treatment.

### *Candida Species*

Antifungal therapy is necessary in all cases of vascular catheter-related candidemia. In one study, 4 of 26 patients with catheter-associated candidemia who were treated with catheter removal but without systemic antifungal therapy developed endophthalmitis, resulting in loss of vision in 3 patients.<sup>33</sup> A prospective, randomized study of 206 patients with candidemia (72% of whom were considered to have vascular catheter-associated candidemia) but without neutropenia showed that fluconazole (400 mg per day given for at least 14 days) was as effective as, but less toxic than, amphotericin B (0.5 mg/kg per day) given for the same length of time.<sup>34</sup> Considering lower toxicity and the potential for oral administration, fluconazole is a better choice than amphotericin B if the organism is susceptible.<sup>35</sup>

The impact of CVC removal on the outcome of candidemia has been evaluated in several studies.<sup>36,37</sup> In a multicenter, prospective, observational study that assessed the efficacy of amphotericin B and fluconazole in the treatment of candidemia, vascular catheter retention was a signifi-

cant, independent prognostic factor for persistence of candidemia after 72 hours of antifungal therapy and for mortality.<sup>37</sup> For a patient who has candidemia and a nontunneled CVC, initial management should include an attempt to exchange the catheter and perform semiquantitative or quantitative catheter cultures. If the catheter is colonized with the same species of *Candida* as is the blood, the CVC should be removed. If the culture of blood samples from a patient with a tunneled catheter or implantable port yields a *Candida* species, the decision regarding catheter removal should be based on the likelihood of catheter-related candidemia rather than on candidemia from another source, such as the gastrointestinal tract. Predictors of tunneled CVC-related candidemia include isolation of *C parapsilosis* from blood samples, quantitative blood cultures that suggest catheter-related candidemia, differential time to positivity (>2 hours) for blood samples drawn from a percutaneous site compared with those drawn through the CVC, candidemia in a patient without neutropenia who has a CVC and no other apparent source for the BSI (with the exception of the vascular catheter), candidemia in a patient who is receiving hyperalimentation through the catheter, and persistent candidemia in a patient who is not responding to systemic antifungal therapy.<sup>38</sup> Any of these situations should cause the clinician to consider the possibility of CRBI and the need to remove the CVC. Management of infections caused by *C albicans* and other fungi is summarized in

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the recent Infectious Diseases Society of America guidelines for the management of candidiasis.<sup>39</sup>

Nucci and Anaissie<sup>40</sup> conducted a literature review to select studies that evaluated CVC removal as a prognostic factor of mortality in candidemia, performing a multivariate analysis with odds ratio (OR) and 95% confidence interval (CI) and including a validated severity of illness score. Of 203 studies of candidemia, only 4 fulfilled these criteria. One study showed a benefit from CVC removal in a subset of 21 neutropenic patients,<sup>41</sup> another study showed no benefit,<sup>42</sup> and the remaining 2 studies showed a marginal benefit from this strategy.<sup>43,44</sup>

In a prospective observational study of 145 cases of candidemia in patients with different underlying conditions, Nucci et al<sup>41</sup> evaluated risk factors for death. The Karnofsky performance status scale was used to evaluate severity of illness. The median performance status score was significantly higher in patients who had the catheter removed (40 vs 30;  $P=.002$ ). Nevertheless, catheter retention was the only variable associated with increased risk of death on multivariate analysis (OR, 4.22; 95% CI, 2.0–11.6). In another prospective observational study, Nucci et al<sup>42</sup> evaluated 54 patients with cancer with fungemia (43 of whom had candidemia). The scoring system used to evaluate severity of illness was the Karnofsky performance status scale. Retention of the CVC was associated with higher mortality rates by univariate analysis. However, multivariate

analysis found that catheter retention was not significantly associated with death, while severity of illness, persistent neutropenia, and older age were. Anaissie et al<sup>43</sup> retrospectively evaluated 491 episodes of candidemia in patients with cancer. The authors used two severity of illness scores, the Simplified Acute Physiologic Score (SAPS) and the Acute Physiology and Chronic Health Evaluation (APACHE) III score. The influence of the removal of a CVC on outcome was analyzed in 363 patients who had also received antifungal therapy. The CVC exchange was associated with higher cure rate, and earlier exchanges had greater effects. Patients who had the catheters retained had higher APACHE III scores ( $P=.001$ ) and were more likely to have neutropenia ( $P<.001$ ). However, by multivariate analysis, only severity of illness, visceral dissemination, persistent neutropenia, and treatment with antifungal therapy were found to be important predictors of death. Luzzati et al<sup>44</sup> retrospectively analyzed 189 adult nonneutropenic patients with candidemia. The authors used the McCabe scale for severity of illness, which has been shown to correlate with the mortality rate in patients with infectious diseases.<sup>45,46</sup> Catheter removal had a modest impact on mortality by multivariate analysis ( $P=.047$ ).

These four studies had important differences, including patient population (eg, patients had cancer or other underlying diseases), inclusion criteria (all patients vs only those who received antifungal ther-

apy), sample size (as few as 54 patients and as many as 476), and severity of illness score used (APACHE, SAPS, Karnofsky, and McCabe scores). It is notable that, unlike the SAPS or APACHE scores, which are based on objective parameters, the McCabe and the Karnofsky performance scores include an element of subjectivity. In the three studies for which data are available, patients whose CVC was retained had significantly higher severity of illness scores. Even the most sophisticated statistical analyses cannot control for all confounding variables, including those that are known (such as the tendency of doctors to remove CVCs in healthier subsets of patients and in patients whose life expectancy is considered acceptable) and those that are unknown. Although it is possible — even likely — that removal of CVCs may reduce the rate of complications caused by candidemia, including death, the published literature could not substantiate this widely held consensus.

Because of the limited data on duration of candidemia and its complication, the reviews by Nucci and colleagues focused on survival as the only objective endpoint for evaluation. However, death is not a good endpoint, since most patients with candidemia have major underlying disease. Speculating that candidemia could be primarily of gastrointestinal origin in patients with cancer who have severe neutropenia and mucositis (acute leukemia, stem cell transplant), as suggested by Nucci and Anaissie<sup>47</sup> and supported by fulfillment of Koch's postulates, removal of CVCs is least

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likely to have an impact on outcome in this setting. The Infectious Diseases Society of America has recently provided practice guidelines for the treatment of candidiasis that include removal of all existing vascular catheters in patients with candidemia while acknowledging the moderate supportive evidence (BII level of evidence, ie, moderate evidence to support the recommendation with data from cohort or case-control studies).<sup>40</sup>

## PREVENTION

### Short-Term Catheters

Short-term, noncuffed, single-lumen or multilumen catheters inserted percutaneously into the subclavian or internal jugular vein have been shown to have rates of CRBIs in the range of 3% to 5%.<sup>26</sup> With short-term intravascular devices (IVDs) — those in place for less than 10 days (peripheral intravenous catheters, arterial catheters, and noncuffed, nontunneled CVCs) — most device-related CRBIs are of cutaneous origin, from the insertion site, and gain access extraluminally<sup>48-50</sup> and, occasionally, intraluminally. During the past two decades, greater progress than has been achieved for any other type of nosocomial infection has been achieved by the use of novel technologies for prevention of IVD-related BSI.

#### *Cutaneous Antisepsis*

The chemical antiseptic for disinfection of the insertion site could reduce colonization. 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.<sup>51-58</sup> The agents were well tolerated in every trial. Only three of the five trials involving CVCs and arterial catheters showed a significant reduction in CVC-related BSIs.<sup>51,53,55</sup>

#### *Topical Anti-Infective Creams or Ointments*

In a study involving patients undergoing hemodialysis, the novel antistaphylococcal topical agent mupirocin caused a significant reduction in the incidence of *S aureus* BSIs (3% vs 22% of catheters;  $P<.001$ ).<sup>59</sup> However, the routine use of topical mupirocin for the prevention of VC-related BSI resulted in a 42% prevalence of mupirocin resistance among clinical isolates of coagulase-negative staphylococci.<sup>60</sup> It is a common belief that routine use of mupirocin on vascular catheter sites will promote resistance. Routine use of mupirocin and other topical anti-infectives on IVD insertion sites is discouraged in the new guidelines of the Hospital Infection Control Practices Advisory Committee (HICPAC).<sup>61</sup>

#### *Novel Dressings*

Studies directly comparing different types of polyurethane dressings have not found differences in rates of catheter colonization or IVD-related infection between standard polyurethane dressings and new hyperpermeable polyurethane dressings (OpSite IV3000, Smith &

Nephew Medical Ltd, Hull, UK; Tegaderm Plus, 3M Co, St. Paul, Minn).<sup>62</sup> The results of trials of polyurethane dressings that contain an antiseptic such as povidone-iodine<sup>63</sup> or ionized silver<sup>64</sup> have been disappointing. A novel chlorhexidine-impregnated sponge dressing has been developed (Biopatch, Johnson & Johnson Medical, Arlington, Tex) and evaluated in three trials to date.<sup>65-67</sup> In the randomized trial by Hanazaki et al,<sup>65</sup> use of the chlorhexidine dressing was associated with significantly lower rates of cutaneous colonization of the catheter insertion site (0% vs 10.9%;  $P<.01$ ). A large prospective, randomized trial by Maki et al<sup>67</sup> comparing the use of the chlorhexidine dressing to a standard polyurethane dressing with short-term CVCs and arterial catheters in adults admitted to two teaching hospital ICUs showed a 60% reduction in the rate of CRBIs (RR, 0.37;  $P=.01$ ) with use of the chlorhexidine sponge dressing.

#### *Attachable Silver-Impregnated Cuff*

A silver-impregnated subcutaneous collagen cuff has been developed and is usually placed at the interface of the skin insertion site and the proximal subcutaneous space. 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. This cuff decreases the risk of colonization associated with short-term catheters (with a mean duration of placement of less than 10 days).<sup>68,69</sup>

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However, out of five studies,<sup>68-72</sup> only one was able to show a significant reduction in the number of CVC-related BSIs.<sup>68</sup>

### *Benzalkonium-Impregnated CVCs*

Heparin is commonly bonded to the external surface of pulmonary-artery Swan-Ganz catheters. Benzalkonium chloride, the surfactant used to bind the heparin, has antimicrobial activity; thus, heparin-bonded catheters exhibit surface antimicrobial activity in vitro.<sup>73</sup> Neither of the randomized trials of a benzalkonium-impregnated, short-term multilumen CVC showed benefit for the prevention of BSIs.<sup>74,75</sup> However, the catheter colonization was significantly reduced in one of these two trials.

### *Chlorhexidine-Silver Sulfadiazine-Impregnated Catheters*

A novel CVC made of polyurethane impregnated with minute quantities of silver sulfadiazine and chlorhexidine (Arrow-Gard, Arrow International Inc, Reading, Pa) became available 12 years ago. Two recent meta-analyses have shown that chlorhexidine-silver sulfadiazine-impregnated CVCs reduce rates of CVC-related BSI by at least 40%. The meta-analysis of 12 studies by Veenstra et al<sup>76</sup> showed that these catheters coated with chlorhexidine-silver sulfadiazine decrease the risk of CRBIs associated with short-term CVCs. Using the Mantel-Haenszel method, it was demonstrated that the short-term use (less than 2 weeks) of

these catheters is associated with a decrease in CRBIs. The lack of efficacy of chlorhexidine-silver sulfadiazine-impregnated catheters in situations requiring long-term catheterization of longer than 3 weeks was attributed to the reduced antimicrobial activity of the catheter over time and lack of luminal protection.<sup>77</sup> These studies confirm that the chlorhexidine-silver sulfadiazine-impregnated CVC is effective for reducing rates of CRBI in patients at high risk of infection who require short-term central venous access.

### *Antibiotic-Coated Catheters*

Catheters impregnated with minocycline and rifampin have the advantage of coating the internal and external surface of the catheter. Raad et al<sup>78</sup> proposed the use of a catheter coated with minocycline and rifampin on the basis of in vitro and animal data demonstrating potent activity of this novel combination against Gram-positive organisms, Gram-negative organisms, and *C albicans*. In a prospective, randomized, multicenter clinical trial,<sup>79</sup> these catheters were shown to be 12-fold less likely to be associated with CRBIs when compared with catheters externally impregnated with chlorhexidine-silver sulfadiazine. Concerns related to the potential for emergence of antibiotic resistance (especially to rifampin) with the use of this catheter were raised. Two large prospective, randomized trials<sup>79,80</sup> failed to demonstrate the emergence of antibiotic resistance. In addition, the use of such catheters

in the ICU of a cancer center resulted in a significant decrease in the frequency of nosocomial vancomycin-resistant enterococci-related bacteremia.<sup>81</sup> Although induction of resistance to this antimicrobial combination has not been identified in the three clinical trials reported to date,<sup>82</sup> an in vitro study has shown that resistance to the minocycline-rifampin combination can develop.<sup>83</sup>

### *Silver-Impregnated Catheters*

A silver-coated or -impregnated catheter is the only other surface modification that has been evaluated in clinical trials. In a randomized clinical trial involving patients in the oncology ward, Goldschmidt et al<sup>84</sup> found that CRBIs developed in 21.2% of the patients with uncoated catheters compared with 10.2% of the patients silver-coated catheters ( $P=.011$ ). A subsequent trial of the same technology failed to find any difference in the rate of CRBIs of silver-coated CVCs vs control catheters.<sup>85</sup> To overcome the inadequate release of silver ions at the catheter surface, 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 two trials.<sup>86,87</sup> In the study by Boswald et al,<sup>86</sup> catheter-associated infections were diagnosed in the silver group in 5.26 of 1,000 catheter-days and in 18.34 of 1,000 catheter-days in the control group, indicating a reduction rate of 71.3% ( $P<.05$ ,  $\chi^2$  test).<sup>86</sup>

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More recently, a silver iontophoretic device has been developed, whereby silver ions are released through a low-voltage current going through silver wires that are attached to the intercutaneous proximal segment of the catheter connected to a small electric power source. Three small randomized clinical trials have failed to demonstrate a statistically significant reduction in the risk of infection by the silver iontophoretic catheter.<sup>88-90</sup>

## Long-Term Catheters

Long-term IVDs, such as cuffed Hickman- and Broviac-type catheters, cuffed hemodialysis CVCs, subcutaneous central venous ports, and peripherally inserted central catheters, are indispensable for the care of patients who require prolonged parenteral nutrition or frequent transfusion of blood products or intravenous medications. Contamination of the catheter hub and lumen appears to be the principal mode of BSI with long-term, permanent IVDs (ie, those in place 10 days). In general, the use of maximal sterile barrier precautions at IVD insertion and more effective cutaneous antiseptics, together with technology that reduces intraluminal colonization, are likely to be effective for the prevention of IVD-related BSIs associated with long-term devices.

### *Subcutaneous Cuffs for Long-Term CVCs*

Surgically implanted Hickman and Broviac catheters incorporate a subcutaneous Dacron cuff that cre-

ates a mechanical barrier against invasion of the tract by skin organisms. Rates of BSIs per 1,000 IVD days for these catheters are far lower than those for short-term, percutaneously inserted, noncuffed CVCs inserted in the ICU.<sup>26</sup> The use of Dacron cuffs on large dual-lumen hemodialysis catheters has substantially reduced the risk of IVD-related BSIs in patients who require long-term central access for dialysis. The Quinton Permcath (Quinton Instrument Co, Seattle, Wash) is a tunneled, double-lumen, flexible silastic catheter with a Dacron cuff and is reported to be associated with a low rate of infection.<sup>91,92</sup>

### *Subcutaneous Central Venous Ports*

Surgically implanted subcutaneous central venous ports that can be accessed intermittently with a steel needle have been associated with the lowest rates of IVD-related BSI. A prospective observational study of Hickman catheters and central ports involving patients in an oncology ward showed that, for patients who require intermittent central access, the incidence of infections per device-day was 12 times greater with catheters than with ports. Patients with solid tumors were the least likely to have device-related infectious morbidity compared with patients with hematologic cancers. The reasons for the difference in infectious complications may be attributable to type of disease, intensity of therapy, frequency with which devices are accessed, or duration of neutropenia.<sup>93</sup> Subcutaneous central venous ports are preferred for peri-

odic chemotherapy, while a cuffed, tunneled catheter or a peripherally inserted CVC is preferred for parenteral nutrition.<sup>94</sup>

### *Attachable Silver-Impregnated Cuffs*

Because the cuff cannot prevent luminal colonization, attachable cuffs would not be expected to significantly impact the rates of IVD-related BSI associated with long-term Dacron-cuffed catheters. A study by Groeger et al<sup>95</sup> indicated that a silver-impregnated cuff had no effect in decreasing the incidence of catheter-related bacteremias/fungemias, tunnel infections, or the spectrum of causative microorganisms involved in cancer patients with tunneled chronic venous access catheters.

### *Peripherally Inserted Central Venous Catheters*

Peripherally inserted central venous catheters (PICCs), utilizing a cephalic or basilic venous approach, may provide a safe alternative to the standard catheter approach. Also, since non-physician providers can insert the PICC, this approach may introduce a potential cost savings to health-care institutions. Some authors report that PICCs are associated with a lower risk of IVD-related BSI than standard, nontunneled, noncuffed CVCs in the outpatient setting.<sup>96,97</sup> However, the prospective studies in which PICCs were used in hospitalized patients suggest that the risk of IVD-related BSI is similar to that seen with cuffed and tunneled CVCs.<sup>98,99</sup>

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### *Novel Securement Devices*

A novel sutureless device for securing noncuffed vascular catheters has recently become available (StatLock, Venetec International Inc, San Diego, Calif). Yamamoto et al<sup>100</sup> evaluated the performance of this sutureless, adhesive-backed device for securement of PICCs. One hundred seventy patients requiring PICCs were randomized to suture (n = 85) or StatLock securement (n = 85). Average securement time with StatLock was significantly shorter (4.7 minutes vs 2.7 minutes;  $P < .001$ ). Although StatLock was associated with fewer total complications (42 vs 61), this difference did not achieve significance. However, there were significantly fewer PICC-related BSIs in the StatLock group (2 vs 10;  $P = .032$ ). Further investigation is needed to determine how StatLock helps to reduce CRBIs.

### *Novel Dressings*

In a multicenter trial involving six neonatal ICUs, Garland and colleagues<sup>66</sup> examined the utility of the chlorhexidine sponge dressing. The majority of catheters (75%) were PICCs. In critically ill neonates requiring prolonged central venous access, the chlorhexidine-impregnated dressing, replaced weekly, was as effective as cutaneous disinfection with 10% povidone-iodine and redressing the site every 3 to 7 days for preventing CRBI and BSI without a source. The risk of local contact dermatitis under the chlorhexidine dressing limits its use in low-birth-

weight infants who require prolonged central access during the first 2 weeks of life. Additional studies are required before the chlorhexidine sponge dressing can be recommended for routine use with long-term IVDs.

### *Silver-Coated Catheters*

In contrast to the extensive research related to the study of novel surfaces for short-term devices, little has been published on novel surfaces for long-term devices. In a single study of long-term, tunneled hemodialysis catheters, Trerotola et al<sup>101</sup> found that silver coating did not confer a benefit against clinical infection or colonization.

### *Antibiotic Lock Therapy*

The antibiotic lock is a new form of local antibiotic prophylaxis in which an antibiotic solution is instilled into the catheter lumen, allowed to dwell for a defined period of time, usually 6 to 12 hours, and then removed. The prophylactic use of systemic antibiotics at the time of IVD insertion or implantation has not proven to be effective in reducing the incidence of IVD-related BSI and is strongly discouraged in the new HICPAC draft guideline.<sup>102</sup> Vancomycin incorporated into total parenteral nutrition admixtures have shown reduced rates of coagulase-negative staphylococcal BSI in low-birth-weight infants, but it results in prolonged low levels of vancomycin in blood and tissue, which is conducive to promoting vancomycin resistance.

Among six prospective, randomized trials on the use of antibiotic lock solutions for the prevention of BSIs associated with long-term IVDs, two studies lacked statistical power to detect a significant difference in BSI,<sup>103,104</sup> while the four remaining studies found a statistically significant benefit.<sup>105-108</sup> The largest trial<sup>107</sup> randomized 126 pediatric oncology patients with a recently placed tunneled CVC to three prophylactic lock regimens: heparin, vancomycin and heparin (VH), and vancomycin, heparin and ciprofloxacin (VHC). The time to develop a line infection was significantly increased using either antibiotic flush. The rate of total line infections, Gram-positive line infections, and Gram-negative line infections was significantly reduced by either VH or VHC. Sixty-two lines (41%) developed 119 occlusion episodes (heparin, 3.99 per 1,000 line-days; VHC, 1.75 per 1,000 line-days;  $P = .0005$ ). No adverse events were detected, including increased incidence of vancomycin-resistant *Enterococcus* colonization or disease. Unfortunately, the investigators did not distinguish local infections from true IVD-related BSIs in the final data and did not assess the impact of an antibiotic lock solution on nosocomial colonization with vancomycin-resistant enterococci, methicillin-resistant *S aureus*, and fluoroquinolone-resistant Gram-negative bacilli in the study population. A subsequent randomized trial involving a neonatal population showed an 80% reduction in PICC-related BSIs (RR, 0.20;  $P = .03$ ).<sup>108</sup> This study, using a vancomycin lock solution for 20 or 60 minutes twice per day, found

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no colonization or infection with vancomycin-resistant organisms in exposed infants.

Although the duration of antibiotic lock therapy has varied among studies, it most often is 2 weeks. Because the purpose of antibiotic lock therapy is to sterilize the lumen of the catheter, patients should be selected to receive such treatment on the basis of a high likelihood of intraluminal infection. Two studies have suggested that 2 weeks of antibiotic lock therapy alone may be as effective for intraluminal infection, in terms of time taken for obtaining negative in-line blood cultures and failure of antibiotic treatment, as a few days of systemic therapy followed by 2 weeks of antibiotic lock therapy.<sup>109,110</sup> However, with some pathogens (eg, *S aureus*) or situations (eg, positive peripheral blood culture, neutropenia), most clinicians would not choose to provide antibiotic lock therapy without a full course of parenteral therapy.<sup>111</sup>

The importance of patient selection for antibiotic lock therapy was supported by the results of 2 studies in which 15 of 17 patients were treated for 20 episodes of CRBI with no relapse of the same species.<sup>110,112</sup> In one of these studies, 22 episodes of catheter sepsis were identified, involving coagulase-negative staphylococci (11), Gram-negative bacilli (3), Gram-positive bacilli (1), yeast (4), and mixed bacteria or fungi (3). In a selected group of patients, treatment was successful 92% of the time.<sup>112</sup> With extraluminal infection (eg, inflammation over the tun-

nel or exit site or pocket of a totally implanted port), antibiotic lock therapy alone could be inadequate, even though parenteral therapy plus antibiotic lock therapy would not be much better than parenteral therapy alone. In a recent study in which parenteral antibiotic therapy administered through the catheter was used in addition to antibiotic lock therapy for apparent intraluminal infection, cures were reported in all 40 patients with catheter-related bacteremia.<sup>16</sup> Each of these patients had salvage of the tunneled catheter, with a mean follow-up of 20.5 months. By contrast, another study found that only 31% of patients with AIDS or cancer and chamber infections with venous access port-related bacteremia were cured by antibiotic lock therapy with parenteral therapy.<sup>113</sup> Limited efficacy of the antibiotic lock therapy might be explained by the presence of deposits of fibrin that include clusters of bacteria inside the reservoir of the port. A subsequent study found that ports in patients with AIDS and chamber infections with or without associated bacteremia were more likely to be salvaged when antibiotic lock therapy with or without parenteral therapy was used (22 of 27 cases) than when standard parenteral therapy without antibiotic lock therapy was used (1 of 6 cases;  $P=.005$ ).<sup>114</sup>

The Centers for Disease Control and Prevention guidelines recommend against the use of vancomycin as a prophylactic agent in the prevention of CRBIs because it is an independent risk factor for the acquisition of vancomycin-

resistant enterococci.<sup>115</sup> In addition, prolonged use of vancomycin could lead to the emergence of staphylococci with intermediate resistance to vancomycin.<sup>116-120</sup> A flush solution combining minocycline hydrochloride and ethylenediaminetetra acetic acid (EDTA) was synergistic against resistant Gram-positive and -negative bacteria and *C albicans* and was efficacious in preventing the recurrence of staphylococcal infections in short- and long-term catheters.<sup>121</sup> A more recent prospective, randomized study demonstrated the efficacy of this combination in preventing CRSIs in patients undergoing hemodialysis with a long-term indwelling CVC.<sup>122</sup> However, because antibiotic lock solutions clearly reduce the risk of IVD-related BSI associated with long-term IVDs, the new HICPAC draft guideline<sup>102</sup> considers their use acceptable in individual cases in which a patient who requires indefinite vascular access (eg, a patient with short-bowel syndrome or who is undergoing hemodialysis) continues to experience IVD-related BSIs despite stringent compliance with infection-control guidelines.

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